**Paparella: Volume I: Basic Sciences and Related Principles**

**Section 7: General Surgical Principles**

# Chapter 33: Physiology and Treatment of Shock due to Volume Loss (Trauma), Sepsis, or Myocardial Damage

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Few subjects in medicine stimulate as much controversy as the cause and treatment of shock, whether the insult be trauma, infection, or cardiac failure. Much of the controversy could probably be eliminated if all physicians could agree on a suitable definition. Early definitions emphasized the clinical description, and none did this better than Gross in 1872 who stated that shock was "a manifestation of the rude unhinging of life". At present, it is generally believed that shock occurs when the blood flow to an area, tissue, or organ is sufficient to maintain the normal activity of its cells.

Usually, shock is associated with a lowered blood pressure. But low blood pressure does not always indicate inadequate blood flow, just as a normal or even a high blood pressure does not always ensure an adequate nutritional blood flow. Perhaps this overemphasis on the importance of blood pressure in the pathophysiology of shock grew out of the original observations on blood pressure made more than two centuries ago by the English clergyman Steven Hales (1733). It was Hales, using glass tubing, who observed that in the horse the arterial side of the circulation supported a column of blood equivalent in height to the arterial blood pressure. He also observed that the length of the column fell when he bled the horse. Most remember Hales for these observations on arterial blood pressure, but few remember his equally important observations that the lowered blood pressure was associated with cold skin and constriction of the veins. Now, 250 years later, we are just beginning to appreciate the great importance of these observations in understanding the pathophysiology of shock. The observations of Hales in 1733 were confirmed by similar studies of LeDran, whose work was first translated into English from the original French in 1743. LeDran noted that vasoconstriction occurred in shock due to gunshot wounds "as if surrounded with a ligature and hence, the stream of animal spirits becomes intercepted or entirely suspended with a universal coldness due to interception of fluids". The first use in English of the word "shock" was in this translation of LeDran's work in describing the clinical picture of a boy who died from gunshot wounds (LeDran, 1743). It should also be noted that the term "choc" had been used in France for many years before this, usually to describe a clinical picture resulting from collisions involving people in horsedrawn carriages.

The frequent wars of the 19th century, including the United States Civil War, provided many opportunities for the observation of shock but stimulated little in the way of investigation with the exception of the work of Bernard in 1852. By the beginning of the 20th century, knowledge of the physiology of circulation had been begun by Starling (1895-1896), Bayliss (1919), Cannon (1923), and others. This information, coupled with advances in clinical medicine and surgery, formed a basis for our present knowledge of shock. In 1917, Archibald and MacLean emphasized that low blood pressure is one of the more constant signs of shock; however, it is not an essential finding.

Several authors made clinical and physiologic observations indicating that the sympathoadrenal system was activated in shock and that the usual clinical signs of shock were related to increased circulating levels of epinephrine and increased activity of the sympathetic nervous system. By the early 1990s, it was accepted that shock results from a decrease in blood volume. By 1930, Blalock had conclusively shown that traumatic shock was due to hypovolemia.

Blalock went on to develop a classification of shock that remains clinically useful today and includes four major categories: (1) hypovolemic shock; (2) cardiogenic shock; (3) neurogenic shock; and (4) vasogenic or septic shock (Table 1).

Table 1. Classification of Shock

Hypovolemic shock

- Blood loss
- Plasma loss
- Water loss

Cardiogenic shock

- Myocardial infarction
- Tamponade
- Arrhythmia

Neurogenic shock

- Spinal shock
- Spinal anesthesia

Vasogenic or septic shock

- Gram-negative bacteremia
- Gram-positive bacteremia

## Pathophysiology of Shock

Circulatory and metabolic changes occur when a patient is in shock. Vasoconstriction is the major circulatory change and is greatest in cutaneous, muscle, and visceral vascular beds. If the vasoconstriction continues unabated, local tissue hypoxia occurs, disrupting cellular function. Compensatory changes occur in this sequence, but it represents a common pathophysiologic pathway for hypovolemic, cardiogenic, neurogenic, and septic shock.

The inciting events of shock may be different for the various classes of shock, but the progression and outcome of untreated cases follow the course outlined. Hypovolemic shock is most commonly caused by acute blood loss secondary to accidental injury, surgery, or external fluid loss such as in diarrhea. The defect is an actual reduction in circulating blood volume. Cardiogenic shock is seen after myocardial infarction, arrhythmias, cardiac contusion,

or cardiac tamponade. The primary problem is pump failure, and blood volume may be normal or expanded. Neurogenic shock is associated with high spinal cord injuries or spinal anesthesia with release of sympathetic tone to the vascular system. This causes a relative hypovolemia to occur because of the sudden vasodilatation. Septic shock is the most complex of the shock types. Many different problems can exist, but an important one is the inability of the cells to metabolize oxygen and nutrients correctly. This stimulates a hyperdynamic cardiac state when the body attempts to deliver more nutrients and oxygen to the cells.

## Circulatory Response

How is it that such seemingly diverse stimuli as bleeding, infection, and cardiac damage can lead to this common microcirculatory response? The response is initiated by the baroreceptors of the aorta and great vessels and probably also by baroreceptors that are present throughout the vascular system. When blood volume is depleted from any cause, venous return to the heart decreases and cardiac output falls, followed by a fall in blood pressure. Baroreceptors respond to decreased arterial pressure by decreasing tone and signal the sympathetic nerve center in the brain stem. Increased sympathetic nerve center activity causes an outpouring of epinephrine from the adrenal medulla and norepinephrine from the postganglionic sympathetic nerve endings. The microcirculations of the skin and viscera are supplied with alpha receptors, which respond to epinephrine and norepinephrine by vasoconstriction in arterioles and venules. The microcirculations of the heart and voluntary muscles do not have alpha receptors and do not constrict; consequently, these organs receive a greater percentage of the reduced cardiac output. The heart and voluntary muscles do have beta receptors, however, which are also stimulated by epinephrine and norepinephrine. This results in an increased rate and force of contraction of the heart (inotropic and chronotropic effect) and dilatation of arterioles and venules in the voluntary muscles. The cerebral circulation has neither alpha nor beta receptors that cause vasoconstriction in the viscera during shock and, hence, receives a greater portion of the reduced cardiac output, since no vasoconstriction occurs within the cerebral circulation. The vasoconstriction that does occur eventually deprives cells of oxygen (ischemic anoxia). If this state continues, hypoxemia causes stagnant anoxia. Stagnant anoxia is due to a combination of persisting venular constriction, aggregation of blood cells within the stagnant circulation, and probably microthrombosis as a terminal event.

These vascular responses, apparently evolutionary in nature, are designed for the preservation of life. This response to stress was labeled the "fight or flight reaction" by Cannon, more than half a century ago (Cannon, 1923). An equally descriptive term might be "nature's first aid". This latter descriptive title should remind physicians that persistent "first aid" measures involving synthetic catecholamines should not be employed. This course of action only accelerates the progression from ischemic to stagnant shock.

## Metabolic Consequences

The importance of cellular anoxia is its metabolic consequences. Anoxia, to paraphrase Haldane, "wrecks" the cell. We can best understand how this damage occurs by reviewing normal cell function. Figure illustrates some basic concepts of intracellular function. Glucose crosses the cell membrane with the aid of insulin to form glucose-6-phosphate. Within the cytoplasm, anaerobic glycolysis occurs, releasing 15 to 20 per cent of the energy of the

glucose molecule in the form of high energy phosphate bonds, adenosine triphosphate (ATP), and pyruvate. The remainder of the ATP from the glucose molecule is released by the metabolism of pyruvate, which occurs within the mitochondria in the aerobic, or Krebs', cycle. The end products of aerobic glycolysis, which are carbon dioxide and water, are then excreted across the cell membrane. ATP is needed to fuel the many parts of the cell including the cell membrane, the mitochondria, and the endoplasmic reticulum, at which site plasma proteins are synthesized. ATP is also required for maintaining the integrity of the lysosomal membrane, which contains potent hydrolytic enzymes.

If the cellular perfusion is not restored and anoxia continues, cell damage begins to occur. One of the earliest signs of cell damage is the influx of water into the cell and the passage of potassium out of the cell into the extracellular fluid. This is due to a declining integrity of the cell membrane so that the "sodium pump" is no longer able to maintain the differential concentrations of electrolytes and water within and without the cell. Within the cell, there is edema in the mitochondria where aerobic glycolysis occurs, slowing of synthesis of plasma proteins within the endoplasmic reticulum, and, in the later stages, a breakdown of the lysosomal membrane. This allows the potent hydrolytic enzymes within the lysosomal "envelope" to escape and begin to digest the cell itself. This interaction produces toxic polypeptides that cause additional cell damage. The extent of intracellular damage from the tissue anoxia primarily determines whether or not resuscitation of the patient will be successful.

The loss of fluid to the cells and surrounding tissues is reflected as decreased venous return as the effective circulating blood volume falls. Effective blood volume is reduced by the early passage of plasma albumin through microcirculatory endothelium whose integrity has been breached by anoxia. Loss of albumin into the extravascular space is usually thought to be a late manifestation of shock, but more accurate methods of measuring oncotic pressures of plasma and of tissue fluid indicate that plasma albumin loss occurs early in shock. The end result of these changes is cell death in the visceral organs. The skin, lung, liver, gut, and kidney of patients dying of severe or prolonged shock may show varying manifestations of this process, which is now popularly referred to as "multiple organ failure". It should be noted that the organ or organs most severely damaged by shock vary among the mammalian species. Thus, in humans, the lung and kidney appear to be the organs most sensitive to the effects of shock. In contrast, the canine gut is more sensitive than the kidney, but the lung of the dog is also easily damaged in shock. The rabbit lung is similar to the canine organ in its sensitivity, whereas the gut of the rat is extensively damaged in shock. Among primates, i.e. chimpanzees and baboons, the lung and perhaps the liver seem to be the most sensitive organs in shock.

## Types of Shock

### Hypovolemic-Hemorrhagic Shock

The homeostatic mechanisms that support perfusion to vital organs are simulated when an acute blood loss occurs. The hypovolemia is sensed by the baroreceptors, and the events already discussed are set in motion. Hypovolemic shock can be graded in relationship to its physiologic insult (Table 2).

## Neurogenic Shock

A discrepancy between peripheral vasoconstriction and vasodilatation as compared with the effective blood volume is the circumstance that produces neurogenic shock. The increase in peripheral capacitance, usually because of a decreased vascular tone, causes a decrease in venous return, producing decreased cardiac output. Vasomotor or vasovagal hypotension is one clinical example of this phenomenon that is usually short lived and mild. Transection of the spinal cord in the cervical region can produce severe hypotension by this mechanism. The resulting hypotension once again stimulates the compensatory changes through the baroreceptors.

## Septic Shock

Most patients suffering from septic shock have a gram-negative infection. All gram-negative aerobic and anaerobic bacteria (the most common being *Escherichia coli, Klebsiella, Aerobacter, Pseudomonas, Proteus,* coliform species, and *Bacteroides*) contain a complex lipopolysaccharide in the cell wall called endotoxin. Endotoxin is released by the death of the bacteria and combines with elements in the blood (complement, antibody, and probably other factors as well) to become a potent sympathomimetic substance that causes intense spasm in the viscerocutaneous microcirculation. Lewis Thomas (1974) best described this phenomenon as follows:

"When we sense lipopolysaccharide, we are likely to turn on every defense at out disposal; we will bomb, defoliate, blockade, seal off and destroy all the tissues in the area ... There is nothing intrinsically poisonous about endotoxin, but it must look awful, or feel awful, when sensed by cells ... Sometimes, the mechanisms used for overkill are immunologic, but often ... they are more primitive kinds of memory. We tear ourselves to pieces because of symbols, and we are more vulnerable to this than to any host of our predators. We are, in effect, at the mercy of our own pentagons most of the time".

The integrity of the microcirculation is lost, and the effective circulating blood volume decreases, reducing the venous return, cardiac output, and blood pressure. Once again, the baroreceptor response is brought into play, and the increased sympathetic activity, which is mediated through the sympathetic nerve centers, further decreases flow in the viscerocutaneous microcirculation.

There is also some evidence that the activated endotoxin acts directly on the central nervous system to cause disorientation, coma, tachypnea, and tachycardia. A principal characteristic of septic shock that differentiates it from other types is the accelerated deterioration of the microcirculation following exposure to endotoxin and the concomitant cell disruption. There also may be some direct cellular effects of the activated endotoxins. The organs principally damaged in dogs are the lung and gut, and in primates, the lung, liver, and kidney. The picture in humans is similar, but there are important differences that have troubled investigators, such as the normal or high cardiac output, and normal or low total peripheral resistance usually seen early in the course of the disorder. Only later in septic shock does the cardiac output fall and the clinical signs of late septic shock in humans become similar to those found in the other types of shock: hypotension; cold, pale, or cyanotic skin of the extremities; and oliguria or anuria.

When seen in the early stages, patients with septic shock present with low arterial pressure, oliguria, high cardiac index, and a very low peripheral resistance. Central venous pressure or pulmonary capillary wedge pressure is often normal or low unless cardiac failure has occurred. In the past, there was much controversy about the hemodynamic picture of patients suffering from septic shock. Some investigators maintained that patients suffering from gram-negative sepsis showed a low cardiac index and high total peripheral resistance. Others observed a high cardiac index and low total peripheral resistance. It is now clear that these apparently opposite views depend on how early in the course of the shock the hemodynamics of the patient are measured. Almost all patients with early gram-negative septic shock show a hyperdynamic state with high cardiac index and low resistance. With time, cardiac failure occurs, even in those patients with previously normal hearts. Hence, the finding of a low cardiac output and high peripheral resistance is an ominous sign of late septic shock.

## Cardiogenic Shock

Why should myocardial damage and shock, whether acute or chronic, result in a peripheral response similar to that caused by bleeding or endotoxins of the gram-negative bacteria? Again, the baroreceptors are involved. With cardiac damage, cardiac output falls, causing a fall in blood pressure, and baroreceptors pass this information on to sympathetic nerve centers within the brain stem. The sympathoadrenal response initiated by these sympathetic centers is identical in every way with that occurring following a decrease in venous return caused by blood loss or sepsis. Moreover, when cardiac damage occurs over a prolonged period of time, the same peripheral changes are called "congestive heart failure". There is increased afterload due to arteriolar constriction, and increased preload due to venular constriction. The decreased cardiac output further reduces coronary blood flow as well as peripheral flow. Pulmonary edema, hepatic congestion, low cardiac output, cold and poorly perfused extremities, and oliguria are characteristics of both acute cardiogenic shock and chronic congestive heart failure. The only significant difference is in time: acute cardiogenic shock occurs in minutes or hours, whereas chronic congestive heart failure may take years to develop.

## General Treatment Principles

In summary, the response to the stress of trauma, sepsis, or cardiac damage is mediated through the sympathoadrenal system and is reflected in a clinical picture of decreased viscerocutaneous perfusion, oliguria, and, in a varying period of time, hypotension. How can this information be used in the treatment of shock in humans, if indeed the common forms of shock are related by a common response? Some general treatment principles can be outlined (Table 3).

The volume status of the patient must be an initial determination in treatment. In the majority of patients, fluid is required, although occasionally a patient in cardiogenic shock needs diuresis, not volume expansion. The type of fluid resuscitation in patients with this condition remains controversial. Crystalloids are our choice. Numerous studies document the need to replace extracellular deficits with a crystalloid solution. It has been suggested that liberal use of crystalloids contributes to or causes pulmonary insufficiency because of a decrease in colloid oncotic pressure. Pulmonary failure is not simply correlated with fluid

resuscitation but is usually associated with multiple systemic insults. The most common of these insults is sepsis. Neither a lowered plasma oncotic pressure nor massive crystalloid replacement produces pulmonary insufficiency consistent with the adult respiratory distress syndrome. When given inappropriately, both colloids and crystalloids can cause pulmonary edema. The data suggest that albumin or colloid solution is not necessary for shock resuscitation except in the patient with a chronically low serum albumin. An additional reason to use crystalloids is their lower cost.

Table 3. General Treatment Principles for Shock

Volume assessment and adjustment

- Preload
- Crystalloid, colloid, blood

Pump assessment and support

- Cardiac output
- Systemic vascular resistance-afterload
- Inotropes
- Vasoactive agents

Metabolic assessment

- Oxygenation
- Infection control for septic shock
- Metabolic agents

Assessment of the volume status can take place during clinical examination or by intravascular monitoring. The central venous pressure or pulmonary artery pressure can be used as guides to preload. Neither is completely accurate, but their response to fluid administration is often helpful. Central venous pressure is often used for initial assessment. When patient response is inadequate or unexplained, further sophisticated monitoring, such as the pulmonary artery catheter, is used.

## Central Venous Pressure

Central venous pressure (CVP) monitoring became popular in the early 1960s and continues to be widely used as a measure of right-sided filling pressures or right-sided preload. CVP monitoring provides adequate data for appropriate fluid management, especially in the young patient with normal cardiac function. Four variables control the pressure measured in the central veins: (1) the volume of blood; (2) the distensibility and contractility of the right side of the heart; (3) venomotor activity; and (4) intrathoracic pressure. The CVP measurement is the result of these factors and does not necessarily reflect the competence of right- or left-sided ventricular function of the adequacy of the circulating blood volume.

The validity of CVP measurement depends on accurate catheter placement in the superior vena cava. The placement should be documented radiographically. Respiratory

fluctuations confirm catheter patency and placement in an intrathoracic vessel. Placement may be through an antebrachial vein puncture, although a subclavian vein or internal jugular vein is more commonly used. The manometer zero point is usually chosen as one-half the anterior posterior diameter of the chest at the fourth intercostal space. One- or two- to eight-cm of water pressure is considered normal. Trends in the pressure response to fluid administration are much more important than the absolute value.

In general, a low CVP suggests that hypovolemia may exist and that a fluid challenge is not likely to be detrimental. The rate of infusion should be gauged by the CVP response. A minimal response confirms the likelihood of hypovolemia. A rapid rise in pressure suggests an adequate blood volume or poor right-sided ventricular reserve. Positive pressure ventilation, pneumothorax, abdominal distention, and pericardial tamponade are conditions that falsely elevate CVP values. Thus, CVP monitoring can be useful in many patients if its limitations are recognized, but in severely ill patients or when CVP monitoring does not reflect the clinical situation, Swan-Ganz catheter should be performed.

## Pulmonary Artery Catheter

Monitoring of the pulmonary artery pressure and pulmonary capillary wedge pressure is a relatively recent innovation. In 1953, Latagolia and Ronn described a balloon-tipped catheter for use in dogs to catheterize the pulmonary artery without thoracotomy. In 1970, Swan and Ganz reported the use of such a catheter in humans. The major advantage provided by the pulmonary artery catheter is closer approximation of left-sided cardiac pressures. Proper catheter insertion places the catheter tip in the pulmonary artery. Inflation of the balloon causes occlusion of arterial pressure and free communication between the catheter tip and the capillary venous compartment of the lung. This pressure is referred to as the pulmonary wedge pressure (PWP). Synonymous terms are pulmonary capillary wedge pressure (PCWP), pulmonary artery wedge pressure (PAWP), and pulmonary artery occlusion pressure (PAOP). Normal pressure values are listed in Table 4.

Table 4. Direct Circulatory Measurements

| | |
|---|---|
| Aortic pressure | 110 to 130/79 to 85 mm Hg |
| Mean arterial pressure (MAP) | 82 to 102 mm Hg |
| Pulmonary arterial pressure | 25/10 mm Hg |
| Mean pulmonary arterial pressure (MPAP) | 12 to 15 mm Hg |
| Left ventricular pressure | 120/0 to 4 mm Hg |
| Right ventricular pressure | 25/0 to 4 mm Hg |
| Left atrial pressure | 0 to 5 cm water |
| Pulmonary arterial wedge pressure (PCWP) | 0 to 5 cm water |
| Right atrial pressure | 0 to 4 cm water |
| Central venous pressure (CVP) | 0 to 4 cm water |
| Heart rate (HR) | 60 to 80 beats/min |

## Left-Ventricular End-Diastolic Pressure

Good correlation between pulmonary capillary wedge pressure, left atrial pressure, and left ventricular end-diastolic pressure (LVEDP) is usually accepted. However, the

measurement of LVEDP does not always provide an adequate measure of left ventricular end-diastolic volume (LVEDV), which is a more reliable index of left ventricular preload. A number of reports show lack of correlation between PCWP, LVEDP, and LVEDV. The reason for this poor correlation are technical and are related to abnormal physiology.

PCWP may not reflect LVEDP because of incorrect catheter placement, improper transducer placement, faulty transducer calibration, pressure damping, respiratory pressure artifact, eccentric balloon occlusion, pulmonary venous obstruction, valvular heart disease, increased pericardial pressure, and altered left ventricular compliance. LVEDP, but not LVEDV, may be reflected by PCWP. This discrepancy exists because of variations in left ventricular compliance, the pressure surrounding the cardiac chambers, and the diastolic volume of the right ventricle. It is obvious that pressure measurements can be misleading as a single guide to left ventricular preload. However, no more clinically feasible measurement is yet available.

## Selective Clinical Application

The clinical challenge of pulmonary artery catheter use is to properly interpret the information it provides. It should be used with an understanding of its assumptions and limitations. Defining therapeutic goals for patient groups and monitoring therapy while attempting to achieve these goals are helpful. In general terms, pulmonary artery pressure monitoring may be useful in any patient in whom tissue perfusion is less than optimal when the imbalance between intravascular volume and cardiac competence is considered a possible cause. Several general categories of such patients are listed in Table 5.

Table 5. Clinical Conditions in which Pulmonary Artery Catheterization may be useful

| |
|---|
| Primary or secondary operative procedures when significant cardiovascular disease is present |
| Perioperative myocardial infarction or congestive heart failure |
| Massive fluid resuscitation, especially if cardiovascular pharmacologic support is required |
| Perioperative pulmonary deterioration requiring constant volume ventilation, with or without positive end-expiratory pressure |
| Perioperative renal failure, with or without the need for hemodialysis |
| Progressive multiple organ failure |

A cardiovascular disaster should not be considered the necessary prerequisite for pulmonary pressure monitoring. The appropriate augmentation of preload, the pharmacologic reduction of afterload, and inotropic support are practical and effective concepts that often require rather strict control. Frequent changes in the amount and type of therapy are possible only if pulmonary artery pressure and cardiac monitoring are available.

Once fluid balance has been adjusted, cardiac response must be evaluated. If cardiac response to fluid administration is not adequate, then further support of cardiac function is needed. The most common therapy at this time is inotropic support of the myocardium. In patients with cardiogenic shock, a high systemic vascular resistance may be present and afterload reduction with a vasodilator may be necessary. This type of therapy should not be

used unless the patient is being monitored with a pulmonary artery catheter and his response measured against hemodynamic calculations. Another case in which this therapy would be used is in the patient in neurogenic shock who needs peripheral vascular support with a vasoconstrictive agent.

Metabolic support includes providing adequate inspired oxygen concentrations. Glucose is not usually provided in the solution used for fluid resuscitation because one compensatory response is hyperglycemia. Still, it is important to make sure that hypoglycemia is not present. Control of infection is obviously of importance to the patient in septic shock. Proper cultures should be obtained and broad-spectrum antibiotics begun empirically. If necessary, surgical drainage should be performed as soon as the patient is prepared for surgery.

Finally, what should be done if all support mechanisms fail? A number of treatments are classified as potentially beneficial or are used in only specific circumstances. Some of these treatments include glucocorticoids, GIK solution (glucose, insulin, and potassium), beta-blockade, and mechanical cardiac support. Each treatment is discussed under its specific area of use.

Table 6. Critical Hemodynamic and Metabolic Measurements in Shock

| **Primary Measurements** | **Normal Values** | **Secondary Measurements** | **Normal Values in Adults** |
|---|---|---|---|
| Arterial BP | 120/80 mm Hg | Pulse pressure | 40 mm Hg |
| | | Position change | 0 mm Hg |
| Pulse rate | 70/min | EKG | Sinus rhythm |
| CVP | 5 +/- 2 cm saline | PAWP | 5 +/- 2 cm |
| CI | 3.20 +/- 0.20 L/min/$m^2$ | Stroke index | 46.0 +/- 5.0 mL/$m^2$ |
| | | Systemic vascular resistance | 2100 +/- 200 dyne-sec/cm/$cm^5$/$m^2$ |
| | | Left ventricular stroke work index | 56.0 +/- 6.0 gm/m/$m^2$ |
| | | Starling performance curves | |
| Urine flow | 50 mL/hour | Specific gravity | 1.003-1.030 |
| | | Urine to plasma creatinine ratio | > 20 |
| | | Urine sodium concentration | < 20 mEq/L |
| Arterial $pO_2$ | 100 torr | Arterial $O_2$ | 19.0 +/- 1.0 mL/100 mL |
| Arterial $pCO_2$ | 40 torr | A-V $O_2$ diff | 4.60 +/- 0.40 mL/100 mL |
| Arterial pH | 7.4 | $O_2$ consumption | 140.0 +/- 25.0 mL/min/$m^2$ |
| | | Alv-art $O_2$ diff | < 100 torr |
| Arterial lactate | 1 mM/L | | |
| Hct | 35 to 45 % | $P_{50}$ | 27 +/- 1.5 mm Hg. |

## Treatment Goals

Once treatment has begun, certain goals should be sought as indicators of successful therapy. MacLean (1977) has described critical hemodynamic and metabolic measurements in shock, and some of these are useful goals for treatment. These measurements are listed in Table 6.

The general goal of treatment is an oriented patient with warm skin, systolic blood pressure 90 mm Hg or above, heart rate of 100 or less, urine output 30-50 mL/hr, CVP of 12 cm water or a PCWP of 10 mm Hg, normal arterial lactate, arterial pH of 7.40, $PaO_2$ of 75 mm Hg or greater, and $PaCO_2$ of 35 to 45 mm Hg.

## Treatment

### Traumatic (Hemorrhagic) Shock

A typical reaction to traumatic shock due to blood loss is illustrated. Blood pressure, CVP, cardiac index, and urine output are usually low. PAWP, if measured, is also usually low if cardiac function has been previously normal. The skin of the peripheral extremities is cool and pale, and the total peripheral resistance is high.

When blood is given, the cardiac index rises and the total peripheral resistance falls. Blood pressure increases, indicating that the pressure increase was due to increased flow rather than to increased resistance. The urinary output is increased, and the skin becomes warm. Almost all patients suffering from hypovolemic shock respond to volume expansion alone if treatment is prompt, the source of blood loss is eliminated, and other complications such as infection or cardiac failure do not occur.

A graded physiologic response to blood loss is found, which is helpful in guiding therapy. A class I hemorrhage is an acute loss of blood volume of 10 to 15 per cent. This blood loss induces minimal clinical symptoms similar to those seen after blood donation. Usually no treatment is indicated, and if any is given, it is limited to crystalloid replacement. Class II hemorrhage is a blood loss of 15 to 30 per cent and is indicated by tachycardia and a decrease in pulse pressure. This change in pulse pressure is secondary to the increased diastolic pressure caused by the catecholamine release. If no further blood loss occurs, most patients can be treated with up to 2 liters of crystalloid replacement. A class III hemorrhage is a blood loss of 30 to 40 per cent that causes classic signs of hypovolemia. Patients with this level of shock require crystalloid and blood replacement. Patients who do not stabilize with approximately 2 liters of lactated Ringer's solution have suffered at least a class III hemorrhage, and blood products should be given early in the course of the disorder. A class IV hemorrhage is a blood loss of greater than 40 per cent. In these patients, shock is life threatening, and treatment should include rapid crystalloid and blood administration.

### Cardiogenic Shock

Myocardial infarction is a frequent cause of severe shock and is usually characterized by a high central venous pressure and high PAWP, high total peripheral resistance, low cardiac index, and low arterial pressure. Metabolically, oxygen consumption increases

markedly as the cardiac index increases. Careful fluid administration, using the PAWP as a guide, can save patients in cardiogenic shock. Digitalis often has little beneficial effect. Approximately 50 per cent of patients selected by a cardiac index of 2 L/min/$m^2$ for treatment despite a normal arterial blood pressure respond favorably. The probability that infarct size can be reduced is an added advantage of this aggressive program.

Treatment of cardiogenic shock depends on manipulating preload, contractility, and afterload (Table 7). Preload is the volume returning to the heart, contractility is the strength of contraction, and afterload is the resistance the heart is pumping against. Most drugs that are commonly used for cardiovascular support affect cardiac output by altering contractility or afterload. Fluid administration is out usual means of changing preload. *No inotropic agent* should be given until the blood volume is adequate - in other words, preload requirements must be filled first. In general, blood or plasma expanders are given until the central venous pressure is 10 to 15 cm of water or the pulmonary artery wedge pressure is 12 to 18 mm Hg. Pharmacologic support of the myocardium is considered next. A number of drugs are used for their effect on contractility and afterload. These include dopamine, dobutamine, nitroprusside, nitroglycerin, and digitalis.

## Dopamine

Dopamine is 3-hydroxytyramine, which is a precursor of noradrenaline. Dopamine stimulates both alpha and beta adrenergic receptors, and its actions are highly dose dependent. At low doses (1 to 5 microg/kg/min), dopamine has a direct renal vasodilating effect. At moderate doses (5 to 10 microg/kg/min), dopamine has an inotropic effect that is mediated through beta-1 receptors. At large doses (> 10 microg/kg/min), the predominant effect of dopamine is alpha-vasoconstriction. The renal and mesenteric vasodilatation that occurs at low doses are the result of a specific vascular dopamine receptor.

Dopamine raises the cardiac index at low to moderate doses with no significant change in the heart rate or oxygen consumption. Systemic vascular resistance and pulmonary vascular resistance decreases if they are elevated prior to the dopamine infusion. In general, this is secondary to the increased cardiac index. In general, this is secondary to the increased cardiac index. Patients respond to a wide range of dopamine dosages. Infusion rates should begin at 2 to 5 microg/kg/min, with gradual increases until the desired hemodynamic and renal effects are obtained. Most patients respond to dopamine infusions below 20 microg/kg/min. As the effective dose is reached, the lowest infusion rate consistent with adequate organ perfusion should be maintained. The most serious adverse effect produced by dopamine is ventricular arrhythmias. This complication usually occurs at high doses and is preceded by tachycardia.

## Dobutamine

Dobutamine is predominantly a beta-1 receptor agonist. It was synthesized to minimize the chronotropic and cardiac side effects of dopamine and isoproterenol. Dobutamine causes an increase in myocardial contractility without increasing afterload. Its inotropic effects usually are not limited by excessive chronotropic effects. Dobutamine may actually decrease total peripheral resistance. Its favorable actions are an increase in contractility and a decrease in afterload. The agent is of most use when the patient has a low cardiac output, moderate heart rate, and a high peripheral vascular resistance. The dosage schedule is similar to that

of dopamine.

## Afterload Reduction

Reduction of afterload is another component of cardiac manipulation. The therapeutic benefit of afterload reduction relates to the concept that the quantity of flow per unit of time in blood vessels is equal to the pressure within the vessels, divided by the peripheral resistance:

**Flow = Pressure/Resistance**

Proper amounts of vasodilators reduce arterial pressure, maintain blood pressure, and improve cardiac output. It is emphasized that the increase in cardiac output with vasodilator treatment does not occur unless adequate preload is present. If adequate preload is not present, vasodilators cause hypotension and decrease cardiac output. It is necessary to monitor pulmonary wedge pressure, cardiac output, systemic blood pressure, and systemic vascular resistance closely in patients receiving vasodilator treatment. If this is not done, there is the risk of reducing cardiac output instead of increasing it.

### Nitroprusside

Nitroprusside is an ideal agent for the reduction of afterload because it relaxes arterial and venous smooth muscle. The effect of this vasodilator is remarkably specific for vascular smooth muscle because, in therapeutic doses, it has no effect on uterine or intestinal smooth muscle, or on myocardial contractility. The drug is potent, and low doses are usually effective in reducing afterload. Intravenous infusion usually is started at 10 microg/min or less. Nitroprusside is potentially toxic. The drug is converted to cyanide in the blood, and the cyanide is converted rapidly to thiocyanate, which is excreted in the urine. The cyanide ion can combine with cytochrome c of the respiratory chain and inhibit aerobic metabolism. Toxicity is best detected by measuring blood levels of thiocyanate. At infusion rates of less than 3 microg/kg/min, toxicity is almost never observed. The earliest sign of cyanide toxicity is metabolic acidosis. Recognition of metabolic acidosis is easier than performing routine measurements of thiocyanate levels. Treatment of nitroprusside toxicity is with infusions of thiosulfate, sodium nitrate, or hydroxycobalamin (vitamin $B_{12}$), either separately or together.

### Nitroglycerin

Nitroglycerin is another agent used for afterload reduction. Nitroglycerin relaxes various smooth muscles, including vascular, ureteral, uterine, gastrointestinal, and bronchial muscles. Routes of administration for various products include sublingual tablets, cutaneous ointments, sustained release oral forms, and inhalation aerosol. Intravenous solutions are given at a rate of 10 to 20 microg/min. This dose is increased by 5 to 10 microg/min every 5 to 10 minutes until the desired hemodynamic or clinical response occurs.

The pharmacologic effects of nitroglycerin first become manifested by arteriolar dilatation. This dilatation increases cardiac output, stroke volume, and coronary blood flow. Venous capacitance increases with marked reductions in left ventricular filling pressures and cardiac work. When the administration is sustained, nitroglycerin causes prominent venous

dilatation, in contrast to nitroprusside, which causes relatively balanced venous and arteriolar dilatation. This pronounced venodilatation results in a greater reduction of preload than afterload, with minimal augmentation or even lowering of the cardiac output. In comparison with nitroglycerin, several studies show greater augmentation of cardiac output by nitroprusside for equal reductions in afterload, making nitroprusside the preferred drug for afterload reduction. Nitroglycerin is most useful in patients with coronary artery disease. Nitroglycerin decreases ventricular volume and systolic wall tension, leading to diminished myocardial oxygen consumption and lower metabolic demands of the myocardium. Perfusion of the endocardium is preserved. Similar changes do not accompany nitroprusside administration. In patients with severe coronary artery disease who require afterload reduction therapy, nitroglycerin has the theoretic advantage of preserving endocardial blood flow.

Indications for intravenous nitroglycerin in surgical patients, either in the treatment of hypertension or for afterload reduction, have been suggested. Ten to fifteen microg/min is the recommended dosage, with increases of 5 to 10 microg/min every 3 to 5 minutes until headache occurs or mean arterial pressure drops more than 20 mm Hg. The usual dose of intravenous nitroglycerin required for afterload reduction or hypertension control in the surgical patient is at least 50 to 100 microg/min.

## Digitalis

Digitalis, or digoxin, is used primarily for congestive heart failure. The chief physiologic effects of digitalis are (1) increased force of myocardial contractions; (2) changes in myocardial conduction; and (3) increased refractory period to the AV node. Digitalis increases oxygen consumption while increasing the work efficiency of the failing heart. The increased efficiency then decreases oxygen consumption as cardiac compensation occurs. The net effect causes oxygen consumption to fall. In a nonfailing heart, digitalis causes an increased force of contraction, but since there is no improvement in mechanical efficiency, only increased myocardial oxygen consumption results. The most common reason to give digitalis to the surgical patient is to treat cardiac failure or to produce sustained atrial ventricular block in rapid atrial arrhythmias, which controls the ventricular response. The loading dose is usually 0.75 to 1 mg, administered in two to three equivalent doses 6 hours apart. Effects are maximal by 6 hours.

Toxic effects are seen in 18 per cent of patients receiving digitalis. It is especially important to protect the patient against hypokalemia and hypomagnesemia. The interpretation of serum digoxin levels is a major aid in the diagnosis of digitalis toxicity. The serum sample should be obtained 6 to 8 hours after the last dose to ensure that equilibrium has been achieved between the myocardial and serum levels of digitalis. Normal serum values for digitalis are as follows: subtherapeutic, less than 0.4 nanog/mL; optimal, 0.5 to 2.5 nanog/mL; and toxic, more than 3 nanog/mL. Treatment for toxicity begins by stopping the administration of the digitalis compound and any potassium-wasting drug. Dilantin is often helpful at an intravenous dose of 25 to 50 mg/min until the arrhythmia disappears or a maximum of 1 gm is given. Lidocaine can also be used for ventricular irritability. Propranolol is used to treat ventricular arrhythmias, junctional arrhythmias, and atrial tachycardia with block.

## Septic Shock

Septic shock is a more complex condition than either traumatic or cardiogenic shock because of the inflammatory effect of living bacteria on tissue and the probable production of local hormones that lead to arteriovenous admixture or "physiologic shunting". The effect of this admixture is decreased oxygen utilization. Thus, we have the paradox of patients suffering profound shock with oliguria, acidosis, and hypotension in the face of normal or high cardiac indices and low total peripheral resistances.

The first step in the management of septic shock is fluid replacement, as in the other types of shock. Most patients require crystalloid and colloid resuscitation. Often, colloid resuscitation is needed because the coagulation system is adversely affected by endotoxin produced by the bacteria. Clotting factors are often given early in resuscitation, based on abnormalities in prothrombin time. Cardiovascular support is often needed, and the same drugs used for cardiogenic shock are useful. A specific principle for treating septic shock is the control of infection by elimination of the source of continued bacterial contamination of the blood. Surgical drainage and antibiotics are the treatments directed at the elimination of the causative microorganism. When feasible, surgical drainage usually produces the most dramatic results, but antibiotic therapy can be as effective. Antibiotics are used alone or in combination with surgical drainage. Before starting administration of antibiotics, however, cultures of all suspected fluids should be taken. These include cultures of the blood, urine, sputum, wound drainage, and intravenous catheter tips.

The choice of antibiotics is of extreme importance. Proper selection depends on the site of infection, the circumstances surrounding the infection, the state of host immunity, and the prevailing antibiotic susceptibilities of bacteria. Polymicrobial infections with gram-negative organisms are a common finding. Multiple organisms were reported in 6 per cent of bacteremias in 1970, 13 per cent in 1975, and 30 per cent in 1980. An increase in anaerobic isolates may account for some of this increase, because approximately 90 per cent occur as polymicrobial infections.

Antibiotic therapy must be sufficiently broad to be effective against multiple organisms. Empiric therapy for the surgical patient requires two drugs: an aminoglycoside and penicillin derivative. This combination covers a broad spectrum of gram-negative, gram-positive, and anaerobic organisms. If penicillin-resistant *Staphylococcus* is a problem, then a cephalosporin or vancomycin may be appropriate. Anaerobic coverage should be added especially if *Bacteroides fragilis* infection is suspected. Anaerobic coverage with chloramphenicol, metronidazole, or clindamycin is acceptable. Currently, empiric therapy with second and third generation cephalosporins *alone* is not considered adequate for the septic patient.

## Corticosteroids

The use of steroids in septic shock or other shock states remains controversial. Steroids can produce vasodilatation, preserve capillary membranes, decrease complement activation, stabilize lysosomal membranes, and act as a positive inotrope. These and other effects listed in Table 8 may be helpful in treating shock. One of the most important actions of the early use of glucocorticosteroids in treating septic shock is probably their ability to stop the

"cascade", whereby endotoxin liberated from the cell wall of gram-negative bacteria becomes activated by combining with complement and antibody to become activated endotoxin or anaphylatoxin. Without access to complement and antibody, endotoxin is a harmless substance. The hemodynamic effects of corticosteroids include increased cardiac output but are variable and inconsistent. We have not been able to demonstrate any difference in hemodynamic response between septic patients receiving 48 hours of methylprednisolone and those receiving placebo. This same dose of methylprednisolone has been associated with a statistically significant increase in infectious complications. In septic shock, the best results with steroids are found when the drug is given early in the clinical syndrome. Currently, the best recommendation regarding steroid use would be to use them before bacterial infection develops. This is extremely difficult in most situations. However, in some clinical settings, bacteremia can be predicted. The most common clinical situation is before draining a cavity containing a large abscess. It is important to stress that the corticosteroids are a part of a total program to treat shock and that early, aggressive treatment is the key to increasing survival. When corticosteroids are used, a dose of methylprednisolone, 30 mg/kg, or dexamethasone, 3 to 6 mg/kg, is given intravenously. Their use is then stopped without tapering of dosage.

## Metabolic Support

Occasionally, patient response is not adequate despite complete therapy, as outlined earlier, and other support mechanisms may be helpful. Many of these mechanisms provide substrates for metabolism. It is rare that these methods would be tried clinically unless more standard therapies failed. Patients who do not respond to a program of fluids, vasodilators, and inotropic agents are usually suffering from a massive myocardial infarction or some unrecognized abdominal catastrophe such as splenic, hepatic, or pancreatic rupture or a gangrenous or perforated bowel.

## GIK Solution

Glucose-containing solutions can support the anoxic myocardium and improve myocardial performance. This glucose-insulin-potassium (GIK) solution contains 1 gm/kg of glucose, 0.5 units/kg of regular insulin, and 20 mEq of potassium chloride. The infusion is given over a 10-minute period. The GIK solution has improved myocardial performance in animals and humans. It increases contractility independent of preload. Both right and left ventricular function is improved. Glucose yields a 40 per cent higher cardiac index than does mannitol, and the effect lasts for at least 45 minutes. An increase in oxygen consumption is measurable during GIK infusion, which is secondary to the increased cardiac output and oxygen availability and not to any improvements in oxygen unloading. This solution causes a fall in serum potassium, so the solution should not be used in hypokalemic patients. Use of GIK solution is especially helpful in patients who are receiving maximal inotropic therapy but who show minimal response.

## ATP Solutions

Another substrate for energy production is adenosine triphosphate (ATP). Infusion of solutions of ATP-$MgCl_2$ has been used to treat hemorrhagic and endotoxic shock. Cellular ATP levels are depressed after a period of shock but are elevated during early septic shock. This elevated level could result from increased production or decreased use of ATP.

Myocardial adenosine triphosphatase (ATPase) is depressed by exposure to endotoxin, which could explain the elevated myocardial ATP levels and depressed myocardial function. The infusion of ATP magnesium chloride in septic rats has not improved survival, but a combination of ATP magnesium chloride and 50 per cent glucose in saline has improved survival in septic shock. Benefits in hemorrhagic shock have not been established. Clinical uses of ATP solutions are not yet defined, but these investigations must be viewed as out crude attempts to correct the cellular damage produced by various shock states.

## Glucagon

Glucagon is a polypeptide hormone produced in the alpha-cells of the pancreatic islets. It is important in maintaining plasma glucose levels during fasting and stress. Glucagon has been shown to have inotropic and chronotropic cardiac effects in animals and humans. The inotropic effects are more pronounced that the chronotropic effects, but both are independent of the beta-adrenergic receptor. Glucagon has been used to treat cardiogenic shock and propranolol overdose. The dose used is intravenous bolus, 1 to 5 mg, every 30 to 60 minutes, or intravenous infusion, 1 to 20 mg/hr.

## Intra-Aortic Balloon Pump

The use of the intra-aortic balloon pump (IABP) has proved useful in saving some patients with myocardial damage. The principle of the IABP is the same as for the vasodilators, i.e. reduced cardiac work (Table 9). During diastole, the inflation of the balloon empties the aorta centrally into the coronary and cerebral circulations and peripherally into the abdominal viscera. During systole, the left ventricle then ejects blood into the "empty" aorta. This decreased afterload reduces the work of the left ventricle in emptying itself. More complete emptying also occurs, which reduces wall tension and oxygen demand. As a result, the heart rate also decreases. Hence, the three principal determinations of oxygen demand of the myocardium are favorably affected. Afterload is reduced, myocardial fiber length is shortened, and heart rate falls. The result is a 15 to 20 per cent decrease in cardiac work and oxygen demand. Although previously used only in cardiogenic shock, the IABP is now being used in severe traumatic and septic shock.

## Efficacy of Therapy

For patients treated with the protocol of volume and cardiac support plus other adjunctive measures, survival from shock is now greater than 70 per cent. This is much improved from management plans using vasoconstrictors as the primary treatment. It should be emphasized that the number of patients in hemorrhagic or traumatic shock who need drugs in addition to volume is small if the source of bleeding is promptly controlled and treatment is started early.

With a regimen of fluids, drugs, and devices, the majority of patients can also be resuscitated from septic and cardiogenic shock with restoration of good nutritional blood flow as evidenced by clinical observations of skin temperature, urinary output, and hemodynamic and metabolic measurements. In addition, if the offending agent or source of the problem, such as infection or continued cardiac damage, can also be eliminated, the ultimate goal, discharge from the hospital, is also achieved.