**Shock**

**Introduction**

* Shock is defined as **a syndrome of impaired tissue perfusion** **accompanied by hypotension**. This impairment of tissue perfusion eventually leads to **cellular dysfunction**, followed by **organ damage and death** if untreated.
* **Causes of shock** are situations that result in a

reduction of intravascular volume (hypovolemic shock),

myocardial pump failure (cardiogenic shock),

increased vascular capacitance (distributive shock, sepsis).

* ***The type of treatment required depends on the etiology.***

**Classification of Shock and Precipitating Events**

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| ***Hypovolemic Shock*** |
| ***Hemorrhagic*** |
| Gastrointestinal bleeding |
| Trauma |
| Internal bleeding: ruptured aortic aneurysm, retroperitoneal bleeding |
| ***Nonhemorrhagic*** |
| Dehydration: vomiting, diarrhea, diabetes mellitus, diabetes insipidus, overuse of diuretics |
| Sequestration: ascites, third-space accumulation |
| Cutaneous: burns, nonreplaced perspiration and insensible water losses |
| ***Cardiogenic Shock*** |
| ***Nonmechanical*** *Causes* |
| Acute myocardial infarction |
| Low cardiac output syndrome |
| Right ventricular infarction |
| End-stage cardiomyopathy |
| ***Mechanical*** *Causes* |
| Rupture of septum or free wall |
| Mitral or aortic insufficiency |
| Papillary muscle rupture or dysfunction |
| Critical aortic stenosis |
| Pericardial tamponade |
| ***Distributive Shock*** |
| *Septic Shock* |
| Anaphylaxis |
| *Neurogenic* |
| Spinal injury, cerebral damage, severe dysautonomia |
| *Drug-Induced* |
| Anesthesia, ganglionic and adrenergic blockers, and over-doses of barbiturates, narcotics |
| *Acute Adrenal Insufficiency* |

* **The distinctions** **among subtypes** of shock only apply in the relatively **early stages**.
* As the syndrome evolves and **compensatory mechanisms** are overwhelmed, it becomes increasingly **difficult to determine** the subtypes because the clinical and **pathophysiologic features of advanced shock are the same for all.**
* Also, **different types of shock can occur at the same time** (e.g., a patient with septic shock who is also hypovolemic).

**Pathophysiology**

* **Tissue perfusion** is a complex process of oxygen and nutrient delivery as well as waste removal.
* When perfusion is impaired, it sets up a cascade of events that can eventually end in death
* Although the etiology of shock is varied, the **eventual progression (if untreated)** results from a common pathway of **ischemia**, **endogenous inflammatory cytokine** release, and the **generation of oxygen radicals**.

1. When cells are subjected to a **prolonged period** of ischemia, anaerobic metabolism begins.
2. This inefficient process results in a decrease of **adenosine triphosphate** (ATP) stores and causes the buildup of lactic acid and other toxic substances that can alter the cellular machinery and eventually result in cell death.
3. In the advanced stages of shock, irreversible cellular damage leads to **multiple organ system failure (MOSF)**, also known as **multiple organ dysfunction syndrome (MODS).**
4. **Inflammatory cytokines** are produced by the body in response to ischemia, injury, or infection.
5. The phrase **systemic inflammatory response syndrome** **(SIRS)** is the recommended umbrella term to **describe any acute, overwhelming inflammatory response, independent of the cause**.

SIRS is usually a late manifestation of hypovolemic forms of shock. It is ***uncommon in cardiogenic shock***, but ***is the hallmark of septic shock***.

**SIRS is clinically characterized by profound vasodilation, which impairs perfusion, and increased capillary permeability, which can lead to reduced intravascular volume.**

1. The following mediators have been identified as possible causes of the **proinflammatory reaction** underlying sepsis and multiple organ failure3:

* Macrophages and their products
* Cytokines: tumor necrosis factor (TNF), interleukin-1(IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8)
* Neutrophils and products of degranulation
* Platelets and the coagulation factors formed on their surfaces
* Derivatives of arachidonic acid
* T and B lymphocytes and their products

**Clinical Presentation**

* **Clinical syndrome of shock progresses through several stages**.
* During each step, the body uses and exhausts various compensatory mechanisms to ***balance oxygen delivery (DO2) and oxygen consumption (VO2) in an effort to maintain perfusion of vital organs.***
* **A major determinant of tissue perfusion** is the systemic or mean arterial pressure. Mean arterial pressure (MAP) is a function of the product of blood flow (cardiac output [CO]) and systemic vascular resistance (SVR).
* Cardiac output is the product of heart rate (HR) and stroke volume (SV)
* Vascular resistance is determined primarily by vascular smooth muscle tone, modulated by the sympathoadrenal system and by circulating humoral and local metabolic factors.
* These interacting factors are what contribute to the clinical syndrome seen in patients with shock.

**The classic findings observed with shock include the following**:

* Systolic blood pressure (SBP) <90 mmHg (or >60 mmHg decrease from baseline in a hypertensive patient)
* Tachycardia (HR >90 beats/minute)
* Tachypnea (respiratory rate [RR] >20 breaths/minute)
* Cutaneous vasoconstriction: cold, clammy, mottled skin (although not typical of distributive shock)
* Mental confusion (agitation, stupor, or coma)
* Oliguria: urine output <20 mL/hour
* Metabolic acidosis (lactic acidosis secondary to anaerobic glycolysis)

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| **Hemodynamic Findings in Various Shock States** |
| |  |  |  |  | | --- | --- | --- | --- | |  | ***Hypovolemic*** | ***Cardiogenic*** | ***Distributive (Septic)*** | | Heart Rate | ↑ | ↑ | ↑ | | Blood Pressurea | ↓ | ↑/↓ | ↓ | | Cardiac Output | ↓ | ↓ | ↓b | | Preload (PCWP) | ↓ | ↑ | ↑/↓ | | Afterload (SVR) | ↑ | ↑ | ↓ | |

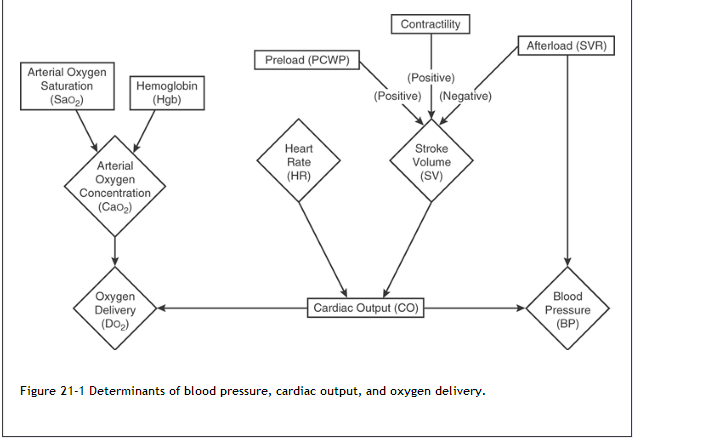
**Hemodynamic Monitoring**

***Noninvasive Monitoring***

Clinical examination and ***vital signs*** (temperature, HR, BP, RR) provide valuable information regarding the cardiovascular system and organ perfusion.

***Invasive Monitoring***

Arterial Pressure Line (APL)Central Venous Catheter (CVC) Pulmonary Artery Catheter(PAC)



**Determinants of Cardiac Function and Hemodynamic Indices**

* Assuming oxygen content of blood is adequate, CO and SVR are the ultimate determinants of oxygen delivery and adequate arterial pressure, and thus overall tissue perfusion.

**Hypovolemic Shock**

* **Shock secondary to a *reduction in intravascular volume***.

Whether the primary insult is the external **loss of fluid volume** (e.g., blood, plasma, or free water) or the **internal sequestration** of these fluids into body cavities (**third spacing**),

* the overall result is **reduced venous return** (decreases in CVP and PCWP) and decreased CO .
* **The severity of hypovolemic shock** depends on the **amount** and **rate** of intravascular volume loss and each person's capacity for compensation.
* Although responses vary, a healthy person may **tolerate an acute loss** of **as much as 30%** of his or her intravascular volume with minimal clinical signs and symptoms.
* Compensatory mechanisms such as increases in HR, myocardial contractility, and SVR, are sufficiently effective for this loss in volume such that measurable falls in systolic BP are not detected.
* **Losses in excess of 80%** generally overwhelm compensatory mechanisms and the patient's condition can deteriorate to overt shock with hypotension and signs of hypoperfusion.
* If **restorative measures** are not taken immediately, **irreversible shock** and **death** may result.

**The most common and dramatic cause of hypovolemic shock** is

1. **hemorrhagic shock** in which intravascular volume depletion occurs as a result of bleeding. Trauma is responsible for most cases of acute hemorrhagic shock; other significant causes are rupture of vascular aneurysms, acute gastrointestinal bleeding, ruptured ectopic pregnancy, and postoperative bleeding.
2. **Other mechanisms** for hypovolemic shock are conditions associated with

(a) excess fluid losses from gastrointestinal or renal sources or

(b) plasma loss caused by burns or sequestration (also known as third-space accumulation).

**Acute Hemorrhagic Shock**

* The major hemodynamic abnormality in hypovolemic shock is ***decreased venous return (preload)*** to the heart, resulting in a decrease in CO. Oxygen delivery to the tissues is reduced from this and from the loss of oxygen-carrying hemoglobin.
* The physiologic response of the body to a sudden decrease in volume (preload) is

1. *A release of catecholamines* (epinephrine, norepinephrine). The subsequent increase in HR and contractility help maintain CO.
2. *The peripheral vasoconstriction* caused by the sympathomimetic response serves to maintain arterial pressure.
3. *fluid shifts from the interstitial spaces* into the vasculature to increase preload.

These responses are effective at maintaining BP in patients with a loss of up to approximately ***30% of the total blood volume***.

**The goals of treatment = Resuscitation**

1. Correction of inadequate tissue perfusion and oxygenation,

2. Limiting secondary insults, such as reperfusion injury or compartment syndrome.

* **HR, BP, and urine output** have been traditional markers for the adequacy of resuscitation, but reliance on these end points alone is acceptable only in the initial management of hemorrhagic shock.
* Ongoing deficiencies in oxygen delivery to vital organs may progress and, if left untreated, organ dysfunction and death may result.
* Measurement of base (bicarbonate) deficit and **lactate levels** can be used to assess the global adequacy of perfusion. ***Metabolic acidosis can signal that resuscitation is incomplete despite normal vital signs.***

**Treatment**

* Adequate airway is established
* Initial vital signs are obtained,
* Infusion of IV fluids initially, **crystalloids** or **colloids** are used to restore blood volume *as blood products may not be immediately available and are frequently unnecessary to manage mild shock (10%–20% blood loss).*

**Crystalloids** are **isotonic solutions** that contain either saline (0.9% sodium chloride; “normal saline”) or a saline equivalent (lactated Ringer's [LR] solution).

**Colloidal** solutions contain **large oncotically active** molecules that are derived from natural products such as proteins (albumin), carbohydrates (dextrans, starches), and animal collagen (gelatin)

* Isotonic solutions (normal saline or RL solution) freely distribute within the extracellular fluid compartment, which is divided between the interstitial and intravascular spaces at a ratio of 3:1.
* This distribution is determined by the net forces of colloid oncotic pressure (COP) and hydrostatic pressure, both inside and outside the capillary vascular space.
* `*Consequently, large volumes of crystalloid fluid are required to expand the intravascular space during resuscitation.*
* In contrast, *colloids effectively expand the intravascular space with little loss into the interstitium.*
* Comparatively smaller volumes of colloids than of crystalloids are thus required for resuscitation, and because these large molecules persist intravascularly, their duration of action is longer.
* It is often thought that three to four times as much volume of crystalloid is necessary to provide the same degree of volume expansion as obtained from a colloid.
* Many of the colloidal agents, however, can cause allergic or hypersensitivity reactions as well as coagulopathic effects and colloids are much more expensive than crystalloids.

**Crystalloids--Volume Requirements**

* Isotonic crystalloids equilibrate rapidly between the interstitial and intravascular spaces at a ratio of 3:1.
* For every liter of fluid infused, approximately 750 mL will pass into the interstitium, whereas 250 mL will remain in the plasma.
* Based on estimated blood loss,

*the “three-to-one rule” may be applied as a general guideline: for each 1 mL of blood loss, 3 mL of crystalloid is infused.*

**A safe and effective approach is**

1. give 1 to 2 L of fluid as an initial bolus as rapidly as possible for an adult or 20 mL/kg for a pediatric patient.
2. Between boluses, fluids are slowed to maintenance rates  (150–200 mL/hour), with ongoing evaluation of the patient's physiologic response for signs of continued blood loss or inadequate perfusion that would indicate the need for additional volume replacement.

Indications that circulation is improving include

* Normalization of BP, pulse pressure, and HR.
* Signs that actual organ perfusion is normalizing and that fluid resuscitation is adequate include improvements in *mental status, warmth and color of skin, improved acid-base balance, and increased urinary output. The minimal acceptable urine output for a patient is 0.5 mL/kg*.
* Persistent metabolic acidosis in a normothermic shock patient usually indicates the need for additional fluid resuscitation; sodium bicarbonate is not recommended unless the pH is <7.2.

**Lactated Ringer's Versus Normal Saline**

* Ringer's solution is the fluid of choice for the initial resuscitation of trauma patients and normal saline as the second choice.
* Because normal saline has a high chloride content (45 mEq more than LR), it can cause hyperchloremic acidosis, thereby worsening the tissue acidosis that occurs in the setting of hypovolemic shock.

**Hypertonic Saline**

* The advantage of HS as a resuscitative fluid is the *smaller volume of fluid required This could be a particular advantage in the prehospital setting*
* Consequently, plasma volume is rapidly expanded to a greater extent than similar volumes of crystalloid solutions, and systemic BP, CO, and oxygen transport are readily increased.
* HS also improves myocardial contractility, causes peripheral vasodilation, and redistributes blood flow preferentially to the splanchnic and renal circulation.
* Hypertonic saline-dextran (7.5% sodium chloride in 6% dextran 70 [HSD])

**Blood Replacement**

* The prior conventional approach to the transfusion of critically ill patients was to maintain the hemoglobin above 10 g/dL or the hematocrit above 30%.
* **In acute hemorrhage**, the *actual degree of blood loss is not accurately reflected by the hemoglobin and hematocrit values****,***

Because it takes at least 24 hours for all fluid compartments to come to equilibrium, a normal hematocrit (or Hgb concentration) in the setting of hemorrhagic shock does not rule out significant blood loss or indicate adequacy of transfusion***.***

**Adverse Effects of Transfusion**

1. Banked blood is stored with citrate anticoagulant additive. With multiple transfusions, the large amount of citrate can cause hypocalcemia and acid-base abnormalities.
2. Hyperkalemia also can occur because transfusion of stored blood causes the release of potassium from hemolyzed (ruptured) red blood cells (RBC).
3. Hemolytic transfusion reactions are the most common cause of acute fatalities from blood transfusions. Astute recognition of the signs and symptoms of a transfusion reaction, such as anxiety, pain at infusion site, fever, hypotension, tachycardia, hemolysis, and hemoglobinuria, can prevent unnecessary morbidity and mortality.
4. Transfusions can also cause acute lung injury owing to recipient neutrophil priming by reactive lipid products from the red blood cell membrane, which causes capillary endothelial damage in the lungs.
5. Blood products and donors are screened for disease, thus transmission of viral illness is a small risk
6. Hemostatic abnormalities, specifically coagulopathies and thrombocytopenia, may be transiently related to dilution from administration of large volumes of crystalloids, colloids, or banked blood, but are more likely caused by the extent of injury and the development of disseminated intravascular coagulopathy.
7. Immunosuppression has also been associated with blood transfusions as evidenced by enhanced graft survival in renal transplant recipients, tumor recurrence in patients with colorectal carcinoma, and in postoperative infections.

**Albumin and Hetastarch**

* **Albumin,** the predominant protein in the plasma, accounts for approximately 80% of the colloid *oncotic pressure*,the force that maintains fluid in the intravascular space.
* Human serum albumin is the colloidal agent.
* Side effects primarily involve transient clotting abnormalities and anaphylactic reactions (0.5%)
* Albumin is available as a 5% solution that is isotonic with the plasma and a 25% solution that is hypertonic.
* **Hetastarch** or hydroxyethyl starch (HES) is a synthetic colloid made from amylopectin, which closely resembles human serum albumin, but is considerably less expensive.
* Available as a 6% solution in normal saline,
* *HES expands the plasma volume by an amount greater than the volume infused because the high oncotic pressure draws water from the interstitial spaces.*
* Hetastarch with a low incidence of side effects and allergic reactions. Dose-related reductions in platelet count and transient increases in PT and PTT.HES can also cause elevation in serum amylase levels up to three times the normal level.

**Postoperative Hypovolemia**

Common causes of hypovolemia in surgical patients are

1. postoperative bleeding,
2. Third spacing, The bowel walls and interstitial space can sequester large amounts of fluids, and this can produce a state of relative hypovolemia
3. Temperature-related vasodilation.
4. Inadequate fluid administration during the operative procedure
5. Systemic vasodilatory properties of drugs given in the operating room or in the immediate postoperative period (e.g., morphine sulfate and other narcotics)

***References***

*- Roger Walker, Clive Edwards (eds), Clinical Pharmacy & Therapeutics.2012*

*-Barbara G.Wells & Joseph T. Diriro, Pharmacotherapy hand book 7th Edition*