# Pathophysiology of Shock

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## Definition

- *Shock* is the clinical syndrome that results from inadequate tissue perfusion. Irrespective of cause the hypoperfusion-induced imbalance between the delivery of and requirements for oxygen and substrate leads to cellular dysfunction.
- The cellular injury created by the inadequate delivery of oxygen and substrates also induces the production and release of inflammatory mediators that further compromise perfusion through functional and structural changes within the microvasculature.
- This leads to a vicious cycle in which impaired perfusion is responsible for cellular injury which causes maldistribution of blood flow. Further compromising cellular perfusion; the latter causes multiple organ failure and if the process is not interrupted, leads to the death of the patient.

## Definition

- Shock occurs when very severe and/or persistent, inadequate oxygen delivery leads to irreversible cell injury; thus, only rapid restoration of oxygen delivery can reverse the progression of the shock state.
- The fundamental approach to management, therefore is to recognize overt and impending shock in a timely fashion and to intervene emergently to restore perfusion.
- Clinical shock is usually accompanied by hypotension. i.e.. a mean arterial pressure <60 mmHg in previously normotensive persons.

## Pathophysiology

- Normally when cardiac output falls, systemic vascular resistance rises to maintain a level of systemic pressure that is adequate for perfusion of the heart and brain at the expense of other tissues such as muscle, skin, and especially the gastrointestinal tract.
- Systemic vascular resistance is determined primarily by the luminal diameter of arterioles. The metabolic rates of the heart and brain are high. and their stores of energy substrate are low. These organs are critically dependent on a continuous supply of oxygen and nutrients and neither tolerates severe ischemia for more than brief periods.

## Pathophysiology

- Autoregulation, i.e.. the maintenance of blood flow over a wide range of perfusion pressures. is critical in sustaining cerebral and coronary perfusion despite significant hypotension.
- when mean arterial pressure drops to <60 mmHg, flow to these organs falls and their function deteriorates.

## Pathophysiology: Cellular responses

- Interstitial transport of nutrients is impaired, leading to a decline of intracellular high-energy phosphate stores. Mitochondrial dysfunction and uncoupling of oxidative phosphorylation are the most likely causes for decreased amounts of ATP.
- As a consequence there is an accumulation of hydrogen ions, lactate, and other products of anaerobic metabolism. As shock progresses, these vasodilator metabolites override vasomotor tone, causing further hypotension and hypoperfusion.
- Dysfunction of cell membranes is thought to represent a common end-stage pathophysiologic pathway in the various forms of shock. Normal cellular transmembrane potential falls, and there is an associated increase in intracellular sodium and water, leading to cell swelling, which interferes further with microvascular perfusion.

## Pathophysiology

- Hypovolemia, hypotension, and hypoxia are sensed by baroreceptors and chemoreceptors, which contribute to an autonomic response that attempts to restore blood volume, maintain central perfusion, and mobilize metabolic substrates.
- Hypotension disinhibits the vasomotor center, resulting in increased adrenergic output and reduced vagal activity. Release of norepinephrine induces peripheral and splanchnic vasoconstriction, a major contributor to the maintenance of central organ perfusion, while reduced vagal activity increases the heart rate and cardiac output.

## Pathophysiology: Renal responses

- Renin release is increased in response to adrenergic discharge and reduced perfusion of the juxtaglomerular apparatus in the kidney.
- Renin induces the formation of angiotensin I, which is then converted to angiotensin II, an extremely potent vasoconstrictor and stimulator of aldosterone release by the adrenal cortex and of vasopressin by the posterior pituitary.
- Aldosterone contributes to the maintainance of intravascular volume by enhancing renal tubular reabsorption of sodium, resulting in the excretion of a low-volume, concentrated, sodium-free urine.
- Vasopressin has a direct action on vascular smooth muscle, contributing to vasoconstriction, and acts on the distal renal tubules to enhance water reabsorption.

## Pathophysiology: Renal responses

- Acute renal failure , a serious complication of shock and hypoperfusion, occurs less frequently than before because of early aggressive volume repletion. Acute tubular necrosis is now more frequently seen as a result of the interactions of shock, sepsis, the administration of nephrotoxic agents (such as aminoglycosides and angiographic contrast media), and rhabdomyolysis; the latter may be particularly severe in skeletal muscle trauma.
- The physiologic response of the kidney to hypoperfusion is to conserve salt and water. In addition to decreased renal blood flow, increased afferent arteriolar resistance accounts for diminished glomerular filtration rate, which together with increased aldosterone and vasopressin is responsible for reduced urine formation. Toxic injury causes necrosis of tubular epithelium and tubular obstruction by cellular debris with back-leak of filtrate. The depletion of renal ATP stores that occurs with prolonged renal hypoperfusion contributes to subsequent impairment of renal function. There is no convincing evidence that low-dose dopamine protects against acute renal failure.

## Classification of Shock

| | |
|---|---|
| Hypovolemic | Septic |
| Traumatic | Hyperdynamic |
| Cardiogenic | Hypodynamic |
| Intrinsic | Neurogenic |
| Compressive | Hypoadrenal |

## Hypovolemic shock

| *Mild* (<20% Blood Volume) | *Moderate* (20–40% Blood Volume) | *Severe* (>40% Blood Volume) |
|---|---|---|
| Cool extremities | Same, plus: | Same, plus: |
| Increased capillary refill time | Tachycardia | Hemodynamic instability |
| Diaphoresis | Tachypnea | Marked tachycardia |
| Collapsed veins | Oliguria | Hypotension |
| Anxiety | Postural changes | Mental status deterioration (coma) |

## Hypovolemic shock

- Volume resuscitation is initiated with the rapid infusion of isotonic saline or Ringer's lactate through large-bore intravenous lines. No distinct benefit from the use of colloid has heen demonstrated and, in trauma patients it is associated with a higher mortality.
- The infusion of 2 to 3 L over 20 to 30 min should restore normal hemodynamic parameters. Continued hemodynamic instability implies that shock has not been reversed and/or that there are significant ongoing blood or volume losses.
- Continuing blood loss, with hemoglobin concentrations declining to <10 g/dL should initiate blood transfusion.
- In the presence of severe and/or prolonged hypovolemia, inotropic support with dopamine, vasopressin, or dobutamine may be required to maintain adequate ventricular performance.

- Successful resuscitation also requires support of respiratory function. Supplemental oxygen should be provided, and endotracheal intubation may be necessary to maintain arterial oxygenation.
- Following resuscitation from isolated hemorrhagic shock, end-organ damage is frequently less than following septic or traumatic shock. This may be due to the absence of the massive activation of inflammatory mediator response systems and the consequent nonspecific organ injury seen in the latter conditions.

## Septic shock

- The clinical findings in septic shock are a consequence of the combination of metabolic and circulatory derangements driven by the systemic infection and the release of toxic components of the infectious organisms, e.g., the endotoxin of gram-negative bacteria or the exotoxins and enterotoxins of gram-positive bacteria.
- Organism toxins lead to the release of cytokines, including IL-1 and TNF-a, from tissue macrophages. Tissue factor expression and fibrin deposition are increased, and disseminated intravascular coagulation may develop.
- The inducible form of NO synthase is stimulated and NO, a powerful vasodilator, is released.

## hyperdynamic septic shock

- Tachycardia is present, the cardiac output is normal or elevated, and the systemic vascular resistance is reduced while the pulmonary vascular resistance is elevated.
- The extremities are usually warm. However splanchnic vasoconstriction with decreased visceral flow is present.
- The venous capacitance is increased, which decreases venous return. With volume expansion cardiac output becomes supranormal.
- Myocardial contractility is depressed in septic shock by mediators including NO, IL-I, and/or TNF-a. Inflammatory mediator-induced processes include increased capillary permeability and continued loss of intravascular volume.

## hypodynamic septic shock

- As sepsis progresses, vasoconstriction occurs and the cardiac output declines.
- The patient usually becomes markedly tachypneic, febrile, diaphoretic, and obtunded, with cool, mottled, and often cyanotic extremities.
- Oliguria, renal failure, and hypothermia develop.
- there may be striking increases in serum lactate.

## Neurogenic shock

- Interruption of sympathetic vasomotor input after a high cervical spinal cord injury, inadvertent cephalad migration of spinal anesthesia, or severe head injury may result in neurogenic shock.
- In addition to arteriolar dilatation, venodilation causes pooling in the venous system, which decreases venous return and cardiac output.
- The extremities are often warm in contrast to the usual vasoconstriction- induced coolness in hypovolemic or cardiogenic shock.
- Treatment involves a simultaneous approach to the relative hypovolemia and to the loss of vasomotor tone. Excessive volumes of fluid may be required to restore normal hemodynamics.
- Once hemorrhage has been ruled out, norepinephrine may be necessary to augment vascular resistance.

## Hypoadrenal shock

- The normal host response to the stress of illness, operation, or trauma requires that the adrenal glands hypersecrete cortisol in excess of that normally required.
- Hypoadrenal shock occurs in settings in which unrecognized adrenal insufficiency complicates the host response to the stress induced by acute illness or major surgery.
- Adrenocortical insufficiency may occur as a consequence of the chronic administration of high doses of exogenous glucocorticoids. Critical illness, including trauma and sepsis may also induce a relative hypoadrenal state. Other less common causes include adrenal insufficiency secondary to idiopathic atrophy, tuberculosis, metastatic disease, bilateral hemorrhage, and amyloidosis.
- The shock produced by adrenal insufficiency is characterized by reductions in systemic vascular resistance, hypovolemia, and reduced cardiac output.

## Hypoadrenal shock

- The diagnosis of adrenal insufficiency may be established by means of an ACTH stimulation test.
- In the hemodynamically unstable patient, dexamethasone sodium 4 mg should be given intravenously. This agent is preferred because unlike hydrocortisone it does not interfere with the ACTH stimulation test.
- Simultaneous volume resuscitation and pressor support are required.

## Cardiogenic shock (CS)

- CS is characterized by systemic hypoperfusion due to severe depression of the cardiac index [<2.2 *(L/min)/m2)* and sustained systolic arterial hypotension «90 mmHg), despite an elevated filling pressure [pulmonary capillary wedge pressure (PCWP) >18 mmHg].
- It is associated with in-hospital mortality rates >50%.
- Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute myocardial infarction (MI) and less frequently by cardiomyopathy or myocarditis or cardiac tamponade .

## Incidence

- CS is the leading cause of death of patients hospitalized with MI.
- Early reperfusion therapy for acute MI decreases the incidence of CS.
- Shock is typically associated with ST elevation MI and is less common with non-ST elevation MI .
- Typically, at least 40% of the LV myocardium should be damaged for establishment of CS.

**ETIOLOGIES OF CARDIOGENIC SHOCK OR PULMONARY EDEMA**

Acute myocardial infarction/ischemia
- LV failure
- VSR
- Papillary muscle/chordal rupture—severe MR
- Ventricular free wall rupture with subacute tamponade
- Other conditions complicating large MIs
  - Hemorrhage
  - Infection
  - Excess negative inotropic or vasodilator medications
  - Prior valvular heart disease
  - Hyperglycemia/ketoacidosis

Post-cardiac arrest
Post-cardiotomy
Refractory sustained tachyarrhythmias
Acute fulminant myocarditis
End-stage cardiomyopathy
Hypertrophic cardiomyopathy with severe outflow obstruction
Aortic dissection with aortic insufficiency or tamponade
Pulmonary embolus
Severe valvular heart disease
- Critical aortic or mitral stenosis
- Acute severe aortic or MR

Toxic-metabolic
- Beta-blocker or calcium channel antagonist overdose

**OTHER ETIOLOGIES OF CARDIOGENIC SHOCK[a]**

RV failure due to:
- Acute myocardial infarction
- Acute coronary pulmonale

Refractory sustained bradyarrhythmias
Pericardial tamponade
Toxic/metabolic
- Severe acidosis, severe hypoxemia

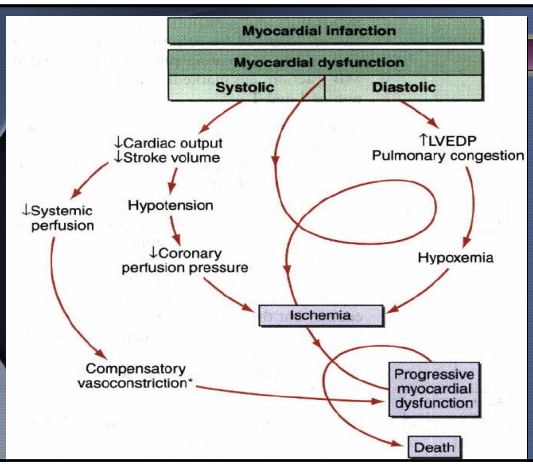


**TABLE 253-4** *Physiologic Characteristics of the Various Forms of Shock*

| Type of Shock | CVP and PCWP | Cardiac Output | Systemic Vascular Resistance | Venous $O_2$ Saturation |
|---|---|---|---|---|
| Hypovolemic | ↓ | ↓ | ↑ | ↓ |
| Cardiogenic | ↑ | ↓ | ↑ | ↓ |
| Septic | | | | |
| Hyperdynamic | ↓↑ | ↑ | ↓ | ↑ |
| Hypodynamic | ↓↑ | ↓ | ↑ | ↑↓ |
| Traumatic | ↓ | ↓↑ | ↑↓ | ↓ |
| Neurogenic | ↓ | ↓ | ↓ | ↓ |
| Hypoadrenal | ↓↑ | ↓ | =↓ | ↓ |

## Patient profile

In patients with acute MI, older age, female sex, prior MI, diabetes, and anterior MI location are all associated with increased risk of CS

- In patients with non-ST elevation MI, prior heart failure (HF), coronary artery bypass graft (CABG) surgery, and peripheral vascular disease are additional important risk factors.
- Severe and extensive coronary artery atherosclerotic lesions are typically present in MI patients who develop shock.
- Two thirds of patients with CS have flow-limiting stenoses in all three major coronary arteries, and 20% have left main coronary artery stenosis.

## Timing

- CS is present on admission in only 10 to 15% of patients who develop CS complicating MI.
- one-half develop it rapidly thereafter, within 6 h of MI onset.
- Another quarter develop shock later on the first day.
- Subsequent onset of CS may be due to reinfarction, marked infarct expansion, or a mechanical complication.

## Clinical findings

- Most patients have continuing chest pain and dyspnea and appear pale, apprehensive, cyanotic, and diaphoretic. Mentation may be altered, with varying degrees of somnolence, confusion, and agitation.
- The pulse is typically weak and rapid, or severe bradycardia due to high-grade heart block may be present.
- Systolic arterial pressure is reduced «90 mmHg) with a narrow pulse pressure «30 mmHg).
- Tachypnea, Cheyne-Stokes respirations, and jugular venous distention may be present.
- The precordium is typically quiet, with a weak apical pulse. SI is usually soft, and an S3 gallop may be audible.

## ECG

CS due to acute MI with LV failure, Q waves and/or >2-mm ST elevation in multiple leads or left bundle branchblock are usually present.

More than one-half of all infarcts associated with shock are anterior.

- Global ischemia due to severe left main stenosis is usually accompanied by severe (e.g., >3 mm) ST depressions in multiple leads.

## CXR

- The chest x-ray typically shows pulmonary vascular congestion and often pulmonary edema, but these findings may be absent in up to a third of patients. The heart size is usually normal when CS results from a first MI but is enlarged when it occurs in a patient with a previous MI.

## Echocardiography

- A two-dimensional echocardiogram with color flow Doppler should be obtained promptly in patients with suspected CS to help define its etiology. Doppler mapping demonstrates a left-to-right shunt in patients with VSR and the severity of MR
- when the latter is present. Proximal aortic dissection with aortic regurgitation or tamponade may be visualized or evidence for pulmonary embolism obtained

## Pulmonary artery balloon flotation catheters

- given the ominous prognosis, their use is generally recommended for measurement of filling pressures and cardiac output to confirm the diagnosis and help optimize use of intravenous fluids, inotropic agents, and vasopressors . Blood samples for O2 saturation measurement should be obtained from the right atrium, right ventricle, and pulmonary artery to rule out a left-to-right shunt. Mixed venous O2saturations are low and arterial-venous O2 differences are elevated, reflecting increased O2extraction and low cardiac index, and the PCWP is elevated. However. these measurements, as well as systemic arterial pressure, may have returned toward normal in the presence of sympathomimetic amines. Systemic vascular resistance may be normal or elevated in CS. Equalization of right- and left-sided filling pressures (right atrial and PCWP) suggests cardiac tamponade as the cause of CS
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## Left Heart Catheterization & Coronary Angiography

- Measurement of LV pressure, definition of the coronary anatomy, and left ventriculography provide useful information and are indicated in most patients with CS complicating MI.
- Because of the procedural risk in this critically ill population, cardiac catheterization should be performed when there is a plan and capability for immediate coronary intervention or when a definitive diagnosis has not been made by other tests.

- In addition to the usual treatment of acute MI initial therapy is aimed at maintaining systemic and coronary perfusion by raising systolic blood pressure to -90 mmHg with vasopressors and adjusting volume status to a level that ensures optimum LV filling pressure (PCWP - 20 mmHg). Hypoxemia and acidosis must be corrected; most patients require endotracheal intubation to correct these abnormalities.
- Negative inotropic agents should be discontinued and the doses of renally cleared medication adjusted.
- Hyperglycemia should be corrected with continuous infusion of insulin.
- Bradyarrhythmias may require transvenous pacing. Recurrent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment.

## Inotropic Agents and Vasodilators

- **Vasoactive drugs are an important pharmacologic defense in the treatment of shock.**
- **May be required to support BP in the early stages of shock.**
- **These agents may be needed to**:
  - Enhance CO through the use of inotropic agents
  - Increase SVR through the use of vasopressors

## Effects of Inotropic Agents and Vasodilators 1

| Drug | Receptor | CO | SVR | Dose Range |
|---|---|---|---|---|
| Epinephrine | $\alpha_1$ ,$\beta_1$, ($\beta_2$) | ↑↑ | ↑ | 0.02 - 0.5 |
| Norepinephrine | $\alpha_1$, $\beta_1$ | 0 - ↑ | ↑↑↑ | 0.05 - 0.5 |
| Dopamine | $\beta_2$, DR, ($\alpha$) | ↑ | ↑ | 2 -12 |
| Dobutamine | $\beta_1$, $\beta_2$ | ↑↑ | ↑ | 2 - 12 |
| Dopexamine | $\beta_1$, $\beta_2$, DR | ↑↑ | 0 - ↑ | 0.9 - 5 |
| Vasopressin | Angiotensin III | 0 - ↓ | ↑↑↑ | 5 - 20 |
| Amrinone | PDI | ↑↑ | ↓↓ | 5 -10 |

(µg/kg/min)

## Effects of Inotropic Agents and Vasodilators 2

| Drug | CO | SVR | Dose Range |
|---|---|---|---|
| Nifedipine | 0 - ↑ | ↓ | 0.5 - 10 |
| Nitroglycerin | 0 - ↑ | ↓ | 3 - 5 |
| Nitroprusside | 0 - ↑ | ↓ | 0.5 - 5 |
| Prostacyclin | ↑ | ↓ | 10 - 40 |

(µg/kg/min)