Shock (休克)

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Clinical Manifestation

- Hypotension
- Narrowed pulse pressure
- Cold and clammy skin
- Oliguria
- Dulled sensorium
A young man is brought to the emergency department by ambulance on the next day after a severe traffic accident. He is unconscious. His blood pressure is 78/48 mm Hg, heart rate is 130 beats per minute. There is no evidence of head trauma. The pupils are 2 mm and reactive. He withdraws to pain. Cardiac examination reveals no murmurs, gallops, or rubs. The lungs are clear to auscultation. The abdomen is tense, with decreased bowel sounds. The patient shows cyanosis, with thready pulses.

Question:

What are the three major pathophysiologic causes of shock? Which was likely in this patient? Why?

What are the three general stages of shock according to the different changes in microcirculation? Which was likely in this patient? Why?

What pathogenetic mechanism accounts for this patient’s unresponsiveness and cyanosis?

What therapeutic measures are essential for this patient?
What is shock?

Shock refers to a dangerous systemic pathological process under the effect of various drastic etiological factors, characterized by acute circulatory failure including decreased effective circulatory volume, inadequate tissue perfusion, cellular metabolism impediment and multiple organs.
Four stages of shock research

- Describing symptom
- Acute circulatory failure
- Microcirculation theory
- Cellular and molecular levels
Teaching contents

- Etiology and classification of shock
- Pathogenesis of shock
- Alterations of metabolism and function
- Features of several common types of shock
- Pathophysiologic basis of prevention and treatment
- Case presentation
Etiology and classification

1. Classification according to cause

① **Loss of blood or fluid:**
   - Blood loss: hemorrhagic shock; Fluid loss: dehydration shock (collapse); Burn: burn shock

② **Trauma:** traumatic shock

③ **Infection:** infectious shock; endotoxic shock; septic shock

④ **Anaphylaxis:** anaphylactic shock

⑤ **Heart failure:** cardiogenic shock

⑥ **Strong stimulation on nerve system:** nerogetic shock
Etiology and classification

2. Classification according to the initial changes

① Hypovolemic shock
② Vasogenic shock
③ Cardiogenic shock
Etiology and classification

3. Classification by hemodynamic characteristics

① Hyperdynamic shock: warm shock

- high cardiac output, low vascular resistance, warm skin

② Hypodynamic shock: cold shock

- low cardiac output, high vascular resistance, cold skin
Pathogenesis of shock

- Microcirculatory mechanisms
  - Ischemic hypoxia stage
  - Stagnant hypoxia stage
  - Refractory stage
- Cellular and molecular mechanisms
Presented by Lillehei in 1964.

Shock is a syndrome mainly of **microcirculation impairment**.

The **sympathetic-adrenal system** is consecutive excited all time during shock development, leading to decreased tissue perfusion by **vasoconstriction**.
“Microcirculation Theory” of Shock

The common pathogenic link is microcirculation impairment caused by intensive excitation of sympathetic-adrenal system.

The pathogenic key point is blood flow rather than blood pressure.

The mechanism is intensive excitation rather than failure or numbness of sympathetic-adrenal system.
Microcirculation
Microcirculatory mechanisms

1. Ischemic hypoxia stage (compensatory stage)
   - Microcirculatory changes
   - Mechanism of microcirculatory changes
   - Compensatory significances
   - Clinical manifestations
Microcirculatory changes

Normal

Ischemic hypoxia stage
Microcirculatory changes

- Small blood vessel constriction.
- Precapillary resistance↑↑ > postcapillary resistance↑
- Closed capillary↑.
- Blood inflows vein by straightforward pathway and A-V shunt.
- Characteristics of inflow and outflow: inflow and outflow↓↓; inflow < outflow.
Mechanism of microcirculatory changes

Blood lose, Traumar etc. →
Activation of sympathetic-adrenal system →
Vasoconstrictive substance ↑↑
(catecholamine, angiotension II, vasopressin, TAX₂, endothelin)

↓
Activation of α-receptors

↓
Constriction of micrangiun

↓
Activation of β-receptors

↓
Opening of A-V shunts
Compensatory significances

① Venous constriction → stored blood return to circulation (self blood transfusion) (60~70%)

② Capillary pressure↓ → fluid transfer from interstitial space to circulation (self fluid infusion) (1500ml)
  Catecholamines, AII ↑ → cardiac contractility ↑
  peripheral vascular resistance ↑

③ Redistribution of blood → Decrease blood flow to the skin, skeletal muscle, kidneys and abdominal organs
  → maintain blood supplying to heart and brain
Clinical manifestations

- Heart rate $\uparrow$
- Cardiac contractility $\uparrow$
- Thready pulse and narrowing of pulse pressure
- Vasoconstriction and ischemia of abdominal organs
- Urine $\downarrow$
- Anus temperature $\downarrow$
- Ischemia of skin
- Pale face, cool limbs
- Sweat gland secretion $\uparrow$
- Sweating, clamminess
- Excitation of senior region of CNS
- Agitate, restless
  (awake but somewhat anxious)
Microcirculatory mechanisms

2. Stagnant hypoxia stage (reversible decompensated stage)

- Microcirculatory changes
- Mechanism of microcirculatory stasis
- Effect of microcirculatory stasis
- Clinical manifestations
Microcirculatory changes

Normal

Stagnant hypoxia stage
Microcirculatory changes

- Precapillary resistance $\downarrow \downarrow >$ postcapillary resistance(-) or $\downarrow$.
- Opened capillary $\uparrow$.
- Characteristics of inflow and outflow: inflow $\uparrow$ and outflow $\downarrow$; inflow $>$ outflow.
Mechanism of microcirculatory stasis

- Acidosis
- Local accumulation of metabolic products
- Alteration of hemorheology
- Endotoxin
- Effects of humoral factors
Effect of microcirculatory stasis

- Effective circulating blood volume ↓↓
- Blood flow resistance ↑↑
- Blood pressure ↓↓
- Blood supply for vitals ↓↓ and dysfunctional
Clinical manifestations

- Microcirculation stasis
  - Returned blood volume ↓
    - Cardiac output ↓
      - Renal blood flow ↓
        - Stasis in kidney
          - Stasis in skin
            - Cyanosis or maculation
        - Oliguria or anuria
          - Brain ischemia
            - Blood pressure ↓
              - Dull or coma
Microcirculatory mechanisms

3. Refractory stage (microcirculatory failure stage)

- Microcirculatory changes
- Mechanism of microcirculatory failure
- Effect of microcirculatory failure
- Clinical manifestations
Microcirculatory changes

Normal

Characteristic: neither inflow or outflow; inflow = outflow

DIC stage
Disseminated intravascular coagulation formation

The mechanisms of **DIC** in this stage:

1) blood concentrated, fibrinogen↑, RBC and platelet aggregation, 
   blood viscosity↑ → blood flow slow down

2) Severe acidosis → vascular ECs injury.

3) Septic Shock: bacteria and toxin → mono/macrophage secreting 
   cytokines → monocyte and endothelium releasing tissue factor

4) Traumatic shock: tissue factor release
   → initiating the extrinsic clotting pathway

5) Hetero-type blood transfusion → hemolysis
   → erythrocytin release
The consequences of DIC:

1) The microcirculation pathway completely blocked by microthrombi → blood return to heart reduced sharply

2) Fibrinopeptide, fibrin degradation product (FDP) and complement↑→vascular permeability↑
   → aggravating microcirculation impairment

3) Bleeding → ECBV further decreased.

4) Embolism and infarction of organs
   → aggravating acute organ failure
Cellular and molecular mechanisms

- Alteration of cellular metabolism
- Cell injury and apoptosis
- Humoral factors
  - Vasoactive amines
  - Endothelium-derived vasoactive mediators
  - Regulation peptides
- Inflammatory mediator and inappropriate inflammatory response
Alteration of Cell Metabolism and Multiple Organ Dysfunction

In the microcirculation impairment theory, impairment of cell metabolism is thought to be secondly to the microcirculation impairment and is caused by hypoxia and acidosis.

However, several facts was found recently, which suggest the primary cause of shock may also damage cells directly. Afterwards, the understanding for shock has been involved to the cellular and molecular levels.
1. Impairment of cell metabolism

(1) Oxygen deficiency and glycolysis enhancement

$\Rightarrow$ ATP↓, Lactic acid↑

(2) Energy deficient, sodium pump dysfunction and Na$^+$, H$_2$O inflow

$\Rightarrow$ Cellular edema, Hyperkalemia

(3) Lactic acid and CO$_2$↑

$\Rightarrow$ Local acidosis
2. Cell injury and apoptosis

(1) **Cell Injury**

1) *Cell membrane damage*
2) *Mitochondria damage*
3) *Lysosome damage*
(2) **Cell apoptosis**

The activated inflammatory cells secrete or release cytokines, inflammatory mediators and oxygen free radicals which attack vascular endotheliums, PMNs, mono/macrophages, lymphocytes and parenchymal cells of various organs. This results in denaturing, apoptosis or necrosis.
3. Multiple organ dysfunction syndrome

MODS: More than 2 organs dysfunction occur successively in patients without pre-exit organ dysfunction

(1) Causes and category

1) Causes
   ① Infectious causes (severe infection in abdominal cavity, bile duct)
   ② Non-infectious cause (severe trauma, operation, shock)

2) Clinical types
   ① Rapid single-phase (directly caused by injurious factors) 1~3 weeks
   ② Delayed two-phase (first hit second hit)
(2) **Common MODS**

1) *Pulmonary dysfunction (83%~100%)*

Acute lung injury (ALI)

→ acute respiratory distress syndrome (ARDS)

**Clinical manifestation:**

Acute respiratory failure characterized by

1. progressive dyspnea,
2. hypoxia, cyanosis,
3. pulmonary edema,
4. decreased pulmonary compliance.
**Pathogenesis:**

Activated PMN $\rightarrow$ cytokines $\rightarrow$ Mφ $\rightarrow$ inflammatory cascade, OFR

1. EC injury
2. Pulmonary microcirculation dysfunction
   - Pulmonary stasis, edema, bleeding
   - Transparent membrane formation
   - Embolism or thrombosis in micro circulation
   - Local atelectasis

3. Diffusion disorder
4. Ventilation/perfusion mismatching
Clinical manifestation:
Jaundice occurred in 5 days, bilirubin↑.

2) Hepatic dysfunction (95%)

1. Bacteria and toxin from intestine

2. Kupffer’s cells activated
   →IL8 →PMN attracted and adhesion
   →TNF, IL-1, OFR

3. Xanthine Oxydase (rich in liver)→OFR

Clinical manifestation:
Jaundice occurred in 5 days, bilirubin↑.
3) **Renal dysfunction (40% – 55%)**

Acute renal failure (shock kidney)

1. Sympathetic, Ang II
   → Renal vasoconstriction, RBF↓ → Functional renal failure

2. ALD, ADH↑
   → Tubular reabsorption of H₂O and Na⁺↑

3. Persistent ischemia, toxin, OFR, microthrombosis
   → acute tubular necrosis (ATN)

   → parenchymal renal failure (persistent shock)
4) *Gastrointestinal dysfunction*

Mucosa edema, stress ulcer, intestinal ischemia → necrosis, bleeding

5) *Cardial dysfunction*

Heart dysfunction may occur at late stage.

6) *Others*

Immune inhibition, coagulation dysfunction, CNS dysfunction
4. Systemic inflammatory response syndrome

SIRS is defined as auto-magnified and destroyed inflammation, characterized by disseminated activation of inflammatory cells and inflammatory mediator spillover.

1) Causes

1) Severe infection (septicemia)
2) Non- infectious hit (necrosis, ischemia, trauma, burn)
(2) **Pathogenesis**

1. Activation and diffusion of inflammatory cells
   - Mφ, PMN, EC and platelet

2. Proinflammatory mediators spillover
   - TNF, ILs(1,2,6,8), IFN, LTB4, PAF, TXA2
     → **Shock & multiple organ dysfunction**

3. Compensatory anti-inflammatory response syndrome (CARS)
   - sTNFR, IL-1ra, IL-4, IL-10, IL-13, PGE2, PGI2
     → **Immune inhibition**
Alterations of metabolism and function

- Disturbance of microcirculation
- Inappropriate inflammatory response

**Metabolic alteration**
- Negative Nitrogen balance
  - ATP↓
  - Na+-K+-ATPase↓
  - Cell swelling
- Anaerobic glycolysis
  - Metabolic acidosis
  - Respiratory acidosis
  - ARDS
- Metabolic acidosis
- Respiratory acidosis
  - vasodilation

**Multiple organ dysfunction**
- Lung
- Kidney
- Liver
- GI
- Heart
- Brain
- Acute renal failure
- Bleeding endotoxin translocation
- Dull coma
- Jundice enzymes↑
- Cardiac dysfunction
Cardiogenic shock

- Compensatory renin-aldosterone, ADH*
- Adequate or ↑ blood volume
- ↑ SVR
- Catecholamine compensatory release

- Systemic and pulmonary edema
- Dyspnea

- ↑ Preload, stroke volume, and heart rate
- ↑ Myocardial oxygen requirements

- ↓ Cardiac output, ↓ ejection fraction
- ↓ Blood pressure

- ↓ Tissue perfusion
- Impaired cellular metabolism
- Myocardial dysfunction

- Ischemia
Neurogenic shock

- Imbalance between sympathetic and parasympathetic stimulation
  - Massive vasodilation
    - ↓ Vascular tone
      - ↓ SVR
        - Inadequate cardiac output
          - ↓ Tissue perfusion
            - Impaired cellular metabolism
Hypovolemic shock

- Decreased intravascular volume
  - ↓ Cardiac output
    - ↑ Heart rate, contractility
    - Catecholamine release
      - ↑ SVR
    - ↑ Volume
      - ↑ Cardiac output
      - More volume loss
        - ↓ Cardiac output
          - ↓ Systemic and pulmonary pressures
            - ↓ Tissue perfusion
              - Impaired cellular metabolism
Anaphylactic shock

Antigen (allergen)

- Antigen (allergen)
- Antibody (IgE)

Complement, histamine, kinins, prostaglandins

- ↑ Capillary permeability
- Extravasation of intravascular fluids
- Edema
- ↓ SVR
- Relative hypovolemia
- ↓ Cardiac output
- ↓ Tissue perfusion
- Impaired cellular metabolism

Peripheral vasodilation

- Constriction of extravascular smooth muscle (bronchoconstriction, laryngospasm, gastrointestinal cramps)
Pathophysiologic basis of shock prevention and treatment

1. Etiological prevention and treatment
2. Pathogenetic treatment

(1) Correction of acidosis.
(2) Expansion of blood volume
(3) Application of vasoactive drugs reasonably
(4) Treatment of cell damage
(5) Application of proinflammatory mediator antagonists.
(6) Prevention of organ function failure
Shock is a dangerous general pathogenic process caused by various drastic etiological factors, characterized by acute circulatory failure including microcirculation impairment, inadequate perfusion of vital organs, cellular metabolism impediment and dysfunction of organs.

Microcirculation impairment caused by intensive excitation of sympathetic-adrenal system is the common pathogenic link of shock.

According to the different changes of microcirculation, shock can divided into 3 stages:

- Ischemic hypoxia phase (compensatory stage)
- Stagnant hypoxia phase (reversible decompensatory stage)
- Refractory phase (microcirculatory failure stage).
The compensatory effects in ischemic hypoxia stage include: Auto-blood transfusion (venous constriction), auto-fluid infusion (capillary pressure ↓), peripheral resistance ↑ and redistribution of blood.

The mechanisms for microcirculation stasis in stagnant hypoxia stage are vasodilation (mainly by prolonged tissue ischemia and hypoxia) and changes of hemorheology.

The mechanisms of DIC in refractory stage include blood flow slow down, vascular ECs injury (severe acidosis) and TF release (septic or traumatic shock and hemolysis). Its consequences are blood return to heart reduced sharply, ECBV further decreased, aggravating microcirculation impairment and acute organ failure.
Besides microcirculation impairment, the primary cause of shock may also damage cells directly, including impairment of cell metabolism, cell injury (membrane, mitochondria, lysosome) and apoptosis.

Infectious or non-infectious causes may leading to MODS. The common multiple organ dysfunction syndrome include:

- Pulmonary dysfunction—Adult Respiratory Distress Syndrome
- Hepatic dysfunction—hepatocyte injury and jaundice
- Renal dysfunction—Acute Renal Failure
- Gastrointestinal dysfunction—mucosa edema, stress ulcer, etc.
- Cardiac dysfunction and others (immune, coagulation, CNS)
Case presentation

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