Drug Therapy for Shock

Disclaimer

All the content material provided here is only made for teaching purpose.

Definition

- Shock is a physiologic state in which significant, systemic reduction in tissue perfusion results in decreased tissue oxygen delivery.

- Can lead to irreversible cell and tissue injury ultimately resulting in:
  - end-organ damage
  - multi-system organ failure
  - death
- Mortality from shock remains high:
  - cardiogenic shock from AMI - 60-90%
  - septic shock - 35-40%
  - hypovolemic shock - varies depending on disease state

Physiologic Determinants

$$CO = HR * SV$$

CO = cardiac output

HR = heart rate

SV = stroke volume

Classification of Shock

- Hypovolemic
- Cardiogenic
- Distributive

Hypovolemic Shock

- Results from decreased preload
- Preload is one of the determinants of stroke volume
- When preload drops, cardiac output drops

Hypovolemic Shock

- Hemorrhage – examples include:
  - Trauma
  - GI bleed
  - Ruptured aneurysm

- Fluid losses – examples include:
  - Diarrhea
  - Vomiting
  - Burns
  - Third spacing of fluid

Cardiogenic Shock

- Results from pump failure
- Manifested as decreased cardiac output
- Four broad categories (examples given):
  - Cardiomyopathies
    - Myocardial infarction
    - Dilated cardiomyopathy
  - Arrhythmias
    - Both tachycardic and bradycardic

Cardiogenic Shock

- Mechanical
  - Valvular stenoses or insufficiencies
- Obstructive/extracardiac
  - Pulmonary embolism
  - Tension pneumothorax
  - Pericardial tamponade

Distributive Shock

- Also referred to as vasodilatory shock
- Results from a severe decrease in SVR
- Examples include:
  - septic shock
  - systemic inflammatory response syndrome (SIRS)
  - anaphylaxis
  - neurogenic shock

Shock States

Physiologic Variable	Preload	Pump Function	Afterload	Tissue Perfusion
Clinical Measurement	PCWP	CO	SVR	SvO_2
Hypovolemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Distributive	↓ or ↔	↑	↓	↑

Common Features of Shock

- Hypotension
- Cool, clammy skin
- Oliguria
- Altered mental status
- Metabolic acidosis

Evaluation of the Patient in Shock

- Primary
  - History
  - Physical Examination
  - Laboratory
  - Radiographic
- Secondary
  - pulmonary artery catheterization
  - echocardiography

Management in Shock

- Shock is an emergency state:
  - initial focus is on ABC's of resuscitation
    - airway, breathing, circulation
- Adequate venous access
  - central venous access not always required, but often necessary
- Optimization of volume status
- Identification of cause of shock and directed therapy

Management of Hypovolemic Shock

- Volume replacement key for all causes of hypovolemic shock
  - nonhemorrhagic: crystalloid fluid replacement
  - hemorrhagic: crystalloid fluid replacement and blood product replacement
- Directed therapy to correct the cause of hypovolemic shock

Management of Cardiogenic Shock

- PA catheter commonly used
- vasopressor support (specific discussion later) often needed
- may need intra-aortic balloon pump
- hypotension may or may not be present
- identification of type of cardiogenic shock critical for optimal management

Management of Cardiogenic Shock

- Myocardial infarction
  - most common cause of cardiogenic shock
  - directed therapy for MI
    - aspirin, heparin, glycoprotein IIb/IIIa inhibitors, revascularization
- Pulmonary embolism
  - most common cause of obstructive shock
  - avenues available to rapidly resolve clot burden
    - thrombolysis, interventional radiology directed clot extraction, surgical embolectomy

Management of Distributive Shock

- Identification of cause and directed therapy
  - e.g. Addisionian crisis - steroid replacement
- Septic shock
  - most common form of distributive (vasodilatory) shock
  - early and aggressive fluid replacement is important and often underutilized
  - vasopressor support often required

Septic shock (continued)

- identification of infectious site/source and guided therapy (antibiotics and drainage)
- steroid replacement with concomitant relative adrenal insufficiency
- optimal glucose control
- recombinant human activated protein C
- attention to support of each organ system

Pharmacological management of Shock

- Goals:
  - Increase CO to restore normal hemodynamics
  - Increase blood pressure and redistribute blood flow to vital organs (brain).

- Pharmacological agents used depend on clinical and physiological parameters of shock and type of shock.
  - Agents used are primarily adrenergic receptor agonists

Physiological actions of adrenergic receptors

Receptor type	**Receptor action (relative to hemodynamics)**
α_1	Arterial vasoconstriction Increased myocardial contractility (minor)
α_2	Constriction of venous capacitance (major) Feedback inhibition of norepinephrine release at sympathetic fibers
β_1	Increased myocardial contractility (inotropy) Increased heart rate (chronotropy)
β_2	Relaxation of vascular smooth muscle (skeletal muscle) (Relaxation of bronchial smooth muscle)
D_1	Relaxation of splanchnic vascular smooth muscle Relaxation of renal vascular smooth muscle
D_2	Inhibition of norephinephrine uptake at sympathetic fibers

Receptor pharmacology

	Activity at receptors			
	α	β_1	β_2	D
Dopamine	++/+++	++++	++	++++
Dobutamine	+	++++	++	0
Epinephrine	++++	++++	+++	0
Isoproteronol	0	+++	+++	0
Norepinephrine	+++	+++	+	0
Phenylephrine	++/+++	0	0	0

Dopamine

- Pharmacodynamics
  - Low and moderate doses – primarily binds dopaminergic and β_1 receptors
  - Higher doses – α_1 receptors stimulated

- Clinical effects
  - Increase heart rate (chronotropy) and contractility (inotropy)
  - Increase SVR by arteriolar vasoconstriction (higher doses).

Contd….

- Clinical application
  - Most commonly used vasopressor
    - common starting dose – 5 µg/kg/min
  - Cardiogenic or distributive shock (shock of any etiology)

- Adverse effects
  - Tachyarrhythmias, excessive tachycardia
  - Precipitate myocardial ischemia
  - Excessive vasoconstriction (digital ischemia)
  - Nausea and vomiting (central effects)

Contd….

- Pharmocodynamics
  - Primarily stimulates β_1 receptors
  - Lesser binding to β_2 and α receptors

- Clinical effects
  - Increase CO (primarily inotropic effect)
  - SVR without significant change or a decline
  - Starting dose – 2-5 µg/kg/min

Dobutamine

- Clinical application
  - Cardiogenic shock and congestive heart failure
    - Common starting dose – 2-5 µg/kg/min
  - Sometimes used in distributive shock (when CO is normal or low which can occur in septic shock)

- Adverse effects
  - Tachycardia and tachyarrhythmias
  - Myocardial ischemia

Epinephrine

- Pharmacodynamics
  - Extremely potent, high affinity binding of all α and β receptors.

- Clinical effects
  - Increase CO
  - Increase SVR by vasoconstriction
    - High doses cause prominent vasoconstriction

Contd….

- Clinical applications
  - Refractory shock of all types – starting at 0.2 µg/kg/min
  - Cardiopulmonary resuscitation – 1 mg IV push
  - Anaphylaxis – 0.2-0.5 ml of 1:1000 dilution subcutaneously

- Adverse effects
  - Excessive vasoconstriction
  - Tachycardia and tachyarrhythmias
  - Myocardial ischemia
  - Hyperglycemia

Isoproteronol

- Pharmacodynamics
  - β_1 and β_2 receptor agonist
  - No α effects

- Clinical effects
  - Increased CO
  - Decreased SVR
  - Variable effect on blood pressure

Contd….

- Clinical application
  - Not useful for shock because of prominent β_2 effect and lack of α – may decrease MAP
  - Rare uses to increase heart rate (as in Torsade de Pointes)

Norepinephrine

- Pharmacodynamics
  - β_1, α_1, α_2 receptor agonist
  - Low doses (< 0.03 µg/kg/min) have prominent β_1 effect
  - Higher doses (> 0.06 µg/kg/min) stimulate α receptors

- Clinical effects
  - Increase CO
  - Increase SVR

Contd….

- Clinical applications
  - Distributive shock
  - Profound, refractory shock of any type

- Adverse effects
  - Excessive vasoconstriction
  - Arrhythmia
  - Myocardial ischemia

Phenylephrine

- Pharmacodynamics
  - α_1 and α_2 receptor agonist
  - Lacks β effect

- Clinical effects
  - Increased SVR
  - Starting dose - 30 µg/min

Contd….

- Clinical application
  - Distributive shock (especially if very high heart rate or history of tachyarrhythmia)
  - Less commonly used than norepinephrine

- Adverse effects
  - Excessive vasoconstriction
  - Reflex bradycardia

Nonadrenergic Vasopressors and Inotropes

- Vasopressin
  - antidiuretic hormone (ADH) analoge
  - can be used as a second line pressor agent
  - recent studies suggest a relative deficiency of ADH in sepsis
  - often added at a fixed rate of 0.04 units/min

Contd…

- Phosphodiesterase inhibitors
  - amrinone and milrinone
  - have inotropic and vasodilatory actions
  - effects are similar to dobutamine
  - used in cardiac failure

References

1. Tripathi KD. ‘Essentials of Medical Pharmacology’, 6th edition, Jaypee Brothers Medical publications (P) Ltd., New Delhi, 2003.
2. Dale M M, Rang H P, and Dale M M. Rang & Dale's Pharmacology’, 7th edition. Edinburgh: Churchill Livingstone, 2007.
3. Guyton, A. C. and Hall, J. E. 2006. Textbook of Medical Physiology. 11th Edition. Saunders, Philadelphia.