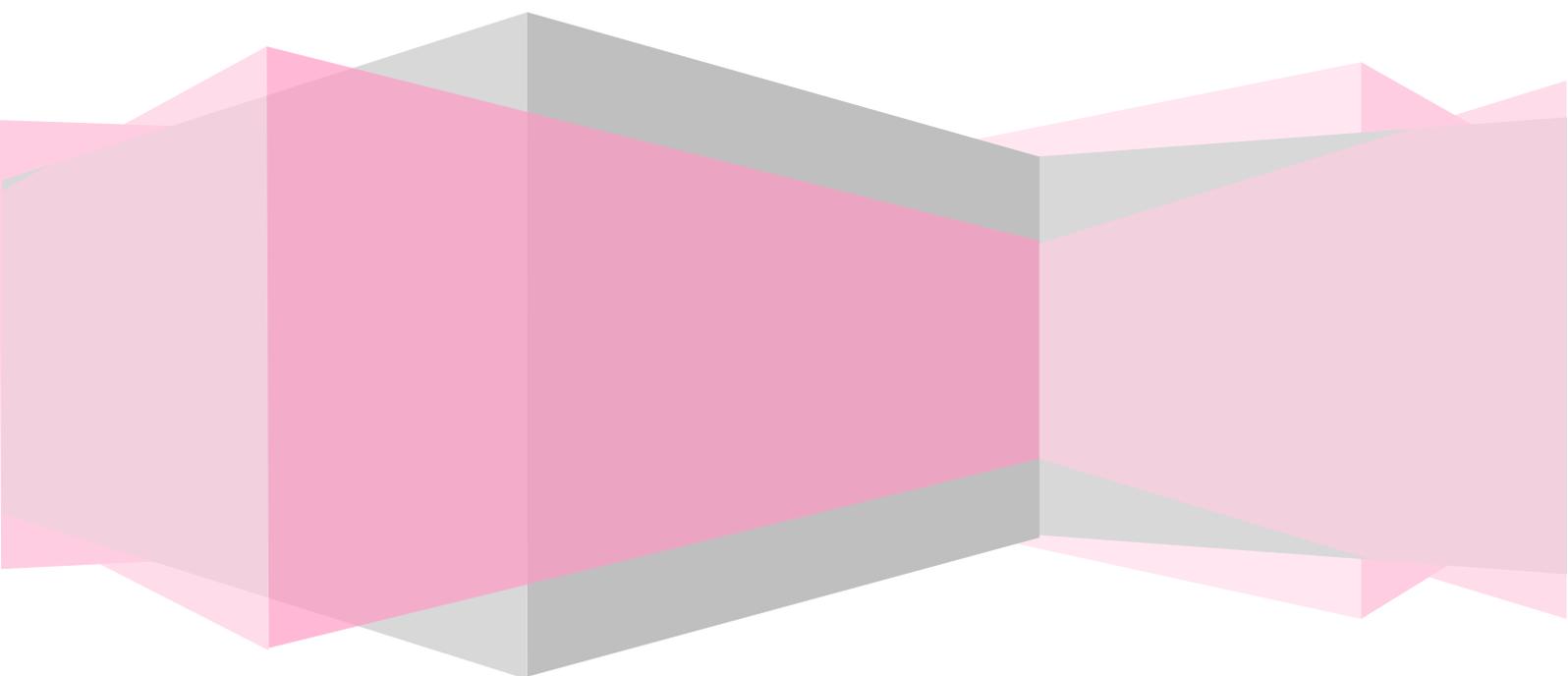


INOTROPE LEARNING PACKAGE

LIVERPOOL ICU

Sharon-Ann Shunker 2014



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Cardiac output & its determinants

CARDIAC OUTPUT (C.O)

Cardiac output

- Is the amount of blood ejected from the heart in litres/minute
- NORMAL CARDIAC OUTPUT = 4 - 8 L/min

The determinants of cardiac output are:

- Heart Rate, and
- Stroke Volume

The determinants of **stroke volume** are:

- Preload
- Afterload
- Contractility

CARDIAC OUTPUT (CO) = HEART RATE (HR) x STROKE VOLUME (SV)

Cardiac Index (CI):

- Is a more accurate determinant of heart function as it takes into account the patient's body surface area (m²).
- It is determined by HR, SV, Height and Weight. (Hudak, et al, 1990).

Heart Rate:

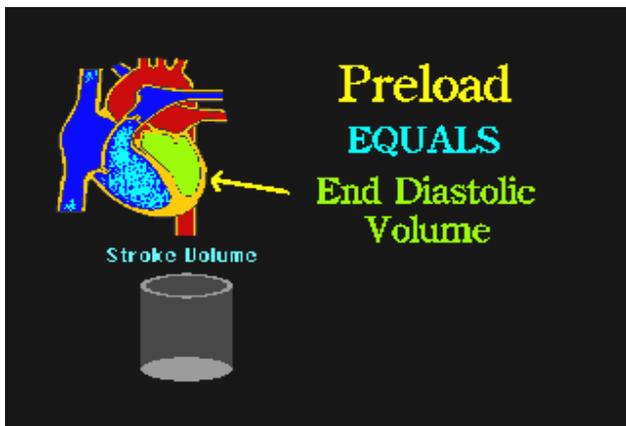
- No. of beats per minute.
- Optimal heart rate balances coronary blood flow (which takes place mainly during diastole) with cardiac output and is usually between 80 and 100 beats per minute.
- Normal sinus rhythm ensures atrioventricular synchrony and maximises cardiac efficiency (Salenger et al 2003).

Stroke volume:

- The amount of blood which is ejected from the heart with each beat.
- It is determined by preload, afterload and myocardial contractility.
- It can be manipulated by fluids, inotropes, vasopressors and vasodilators.

Preload:

- Pressure or stretch exerted on the walls of the ventricle by blood filling at end diastole.
- “The heart will pump what it receives” Starling’s law of the heart.
- The Frank-Starling mechanism describes the ability of the heart to change its force of contraction (and hence stroke volume) in response to changes in venous return.
- In other words, if the end diastolic volume increases, there is a corresponding increase in stroke volume.



PRELOAD = reflects volume status

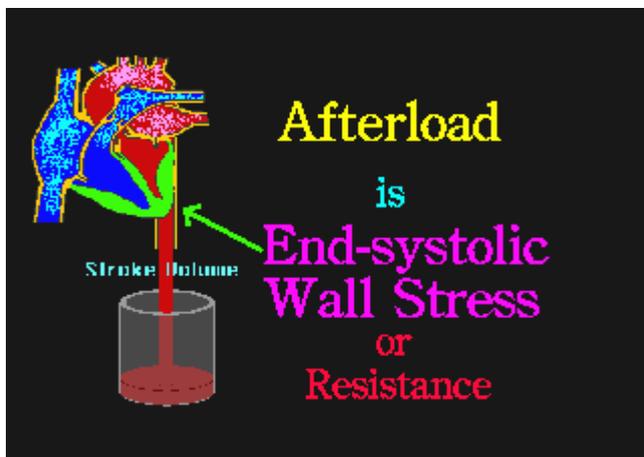
Increases with ~ hypervolaemia

Decreases in ~ hypovolaemia – may result from bleeding, fluid loss or vasodilation.

Effect of preload and afterload: www.chinohills.anunico.us

Afterload:

- Resistance to left ventricular contraction
- It is assessed by measuring systemic vascular resistance (SVR).
- It is the degree of constriction or dilatation of the arterial circulation.
- High afterload increases myocardial work load and oxygen demand and decreases cardiac output



AFTERLOAD = resistance L ventricle must overcome to circulate blood.

Increases with ~ hypothermia

~ history of hypertension

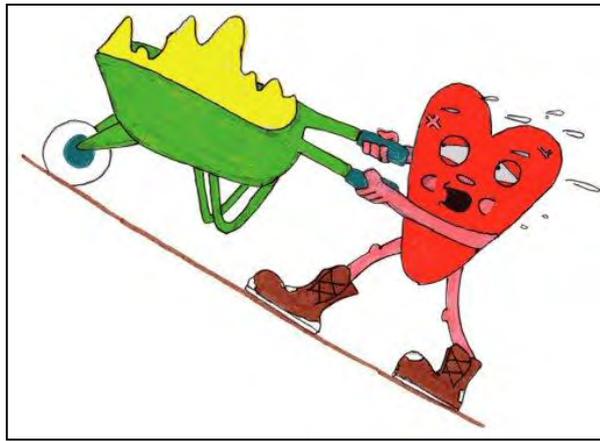
~ vasoconstriction

~ aortic valve stenosis

~ increase in SVR

Contractility:

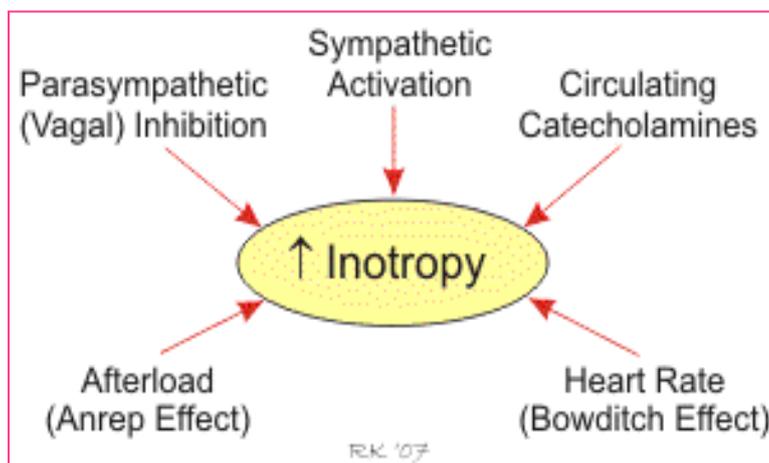
- Is the ability of the myocardial muscle fibres to shorten independent of preload and afterload.
- It is the ability of the heart to contract and the force at which it does so.
- The force of contraction is determined by the concentration of calcium ions in the cells
- Increase contractility can be increased by flooding cell with more calcium (beta agonist) or by keeping more calcium in the cell and not letting it escape.
- Myocardial contractility is enhanced if necessary by using inotrope pharmacological agents, such as adrenaline, dobutamine, milronone and levosimendan. The choice of agent is individualised to the specific clinical situation.



learnhaemodynamics.com

Mechanisms that regulate cardiac output are:

- The autonomic nervous system by altering the heart rate, contractility, preload and afterload.
- The parasympathetic nervous system by slowing down the heart rate.
- The sympathetic nervous system innervates the conduction system of the heart, the arterioles and veins.
- Stimulation produces an increase in heart rate, contractility, preload (venous constriction) and afterload (arterial vasoconstriction).



cvphysiology.com

Definitions/Indications for inotropes

Definitions:

Inotropes:

- These are agents that alter the force and strength of myocardial contractility.
- powerful drugs used to regulate a patient's heart rate, blood pressure and the force of contraction of the heart



Vasopressors:

- These are sympathomimetic drugs that mimic the effects of the sympathetic nervous system.
- They cause vascular smooth muscle vasoconstriction

Vasodilators

- Relax the smooth muscle in blood vessels, which causes the vessels to dilate.
- Dilation of arterial (resistance) vessels leads to a reduction in systemic vascular resistance, which leads to a fall in arterial blood pressure.
- Dilation of venous vessels decreases venous blood pressure.

Indications:

- Inotropes are indicated to increase cardiac output by increasing the force of contraction in patients with cardiogenic and distributive shock.
- Vasopressors are indicated to increase cardiac output in shock associated with reduced afterload
- Shock states with low blood pressure that is not responding to fluid boluses

Shock

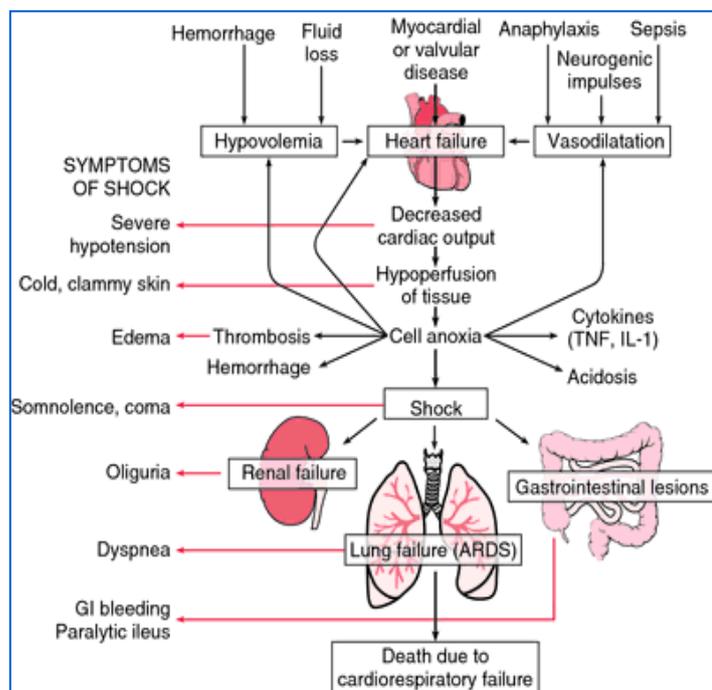
- Shock is a condition that develops from failure of the cardiovascular system to maintain adequate CO, which results in low blood flow and inadequate nutrient and O2 delivery to body tissues and organs.
- It ultimately results in tissue hypoxia, cellular dysfunction and organ failure.
- Many of the patients in intensive care present with or develop different types of shock.

Classification of shock:

1. Hypovolaemic
2. Cardiogenic
3. Vasogenic/
Distributive: includes neurogenic, anaphylactic and septic shock

Shock is a dynamic process, and more than one classification can contribute at any one time

Medical-dictionary.thefreedictionary.com



Clinical Signs of Shock

Using a system approach to assessment the following are some of the clinical manifestations of shock:

- *CNS* - agitation, confusion, altered LOC, convulsions, permanent cerebral damage in the presence of severe, prolonged hypoxia.
- *Resp* - ↑ RR, ↑ respiratory effort, cyanosis, pulmonary edema.
- *CVS* - ↑ HR, ↓ BP, ↓ pulse pressure, ↓ capillary return, cool shut down peripheries, pallor, diaphoresis, ↓JVP.
- *Renal* - ↓ urine output <0.5ml/kg/hr, which may result in Acute Renal Failure.

- *GIT* - stress ulcers, ileus and *GIT* ischemia
- *Liver* - ↑ hepatic transaminases and bilirubin
- Other features - metabolic acidosis which is a lactic acidosis 2° to tissue hypoxia

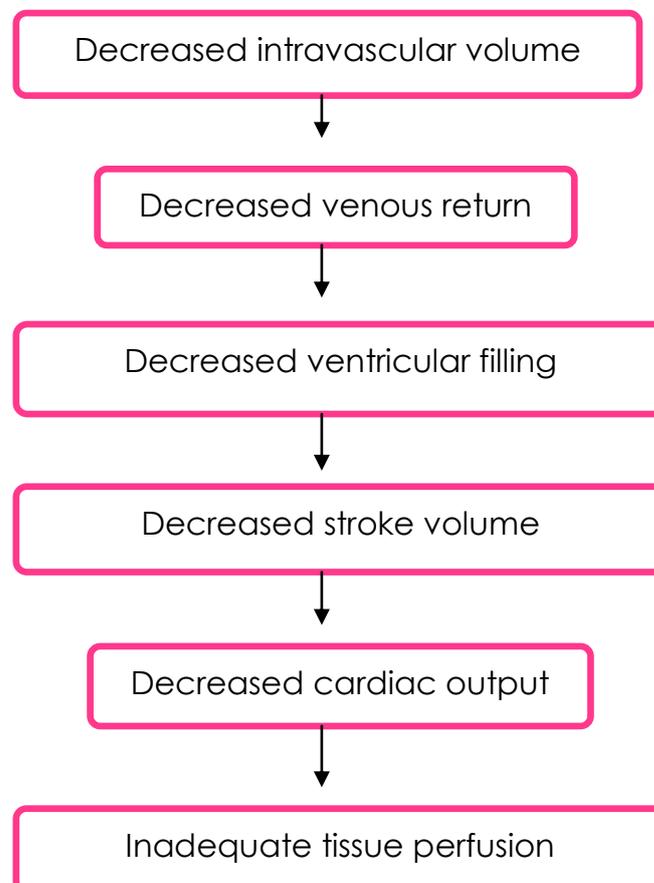
1. Hypovolemic shock

Causes

Hypovolaemic Shock results from intravascular fluid loss, which may be caused by:

- blood loss
- gastrointestinal (, vomiting, diarrhoea, pancreatitis, peritonitis, etc)
- renal (diuretics, Na⁺ losing nephropathy, etc)
- “surface losses” (burns, sweat, respiration)
- maldistribution (anaphylaxis, sepsis, crush syndrome, etc)

Pathophysiology of hypovolemic shock



Management of hypovolemic shock

A - Maintain AIRWAY.

B - Optimize BREATHING & Oxygenation.

C - Restore & maintain CIRCULATION.

- Insert 2 large bore cannulas.
- Fluid boluses to resuscitate IVS.
- Whole blood, packed cells, FFP, platelets if indicated and patient is bleeding or has lost blood.
- Ongoing fluid therapy to maintain circulating volume.

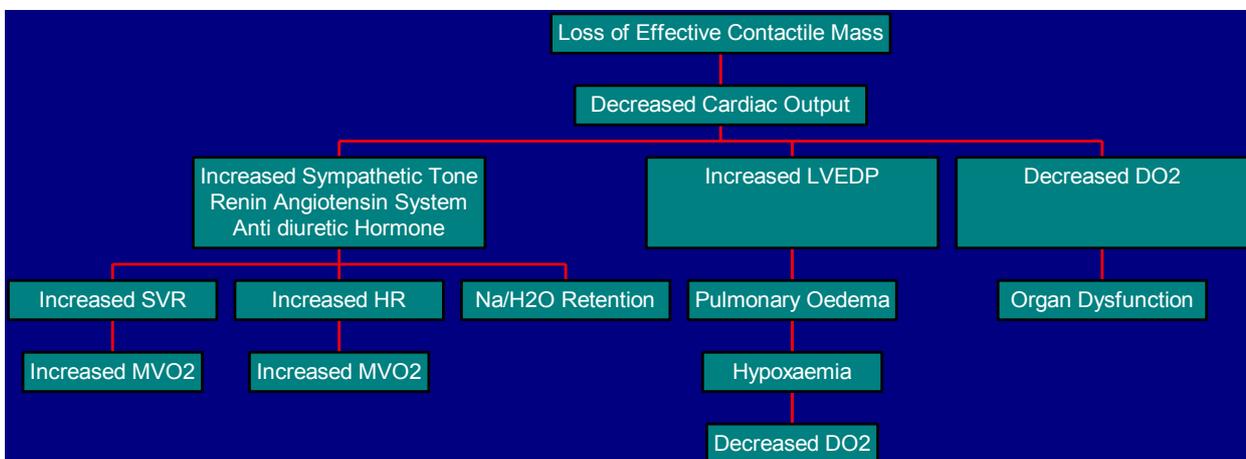
2. Cardiogenic Shock

Causes

- Myocardial infarction / ischaemia
- Trauma (including tamponade)
- Cardiomyopathy
- Myocarditis
- Dysrhythmia
- Valvular / Septal defects
- Post Cardiac surgery / Transplantation
- Drugs / Poisons

Pathophysiology of cardiogenic shock

- There is myocardial dysfunction that leads to decreased cardiac output because of impaired contractility and stroke volume.
- The compensatory mechanisms put further strain on the impaired myocardium and can increase the workload of the heart and worsen existing myocardial ischemia.



DO₂ is oxygen delivery; VO₂ is oxygen consumption

Management of cardiogenic shock

- A- Maintain airway
- B – Optimize breathing and give high flow oxygen. NIV with CPAP will assist alleviate respiratory distress and treat cardiogenic pulmonary edema.
- C – Ensure that there is good access, assess and aim to treat / reverse the cause of shock (e.g.: the patient may require thrombolysis for a stenosis LCA infarct).
- Administer vasodilating agents and inotropes such as dobutamine that improve contractility without increasing heart rate and SVR.
- Administer diuretics if there are signs of heart failure and fluid overload.
- Aim is to reduce myocardial workload & O₂ demand & improve O₂ supply.

Vasogenic/Distributive Shock

- This is caused by vasodilation, reduction in afterload and decreased circulatory volume.
- It includes septic shock, anaphylactic shock and neurogenic shock.
- Of these we are going to focus on **septic shock** as there is still a high mortality rate associated with septic shock in critically ill patients.

Sepsis Definitions:

SIRS criteria: 2 of the following + suspected or confirmed infection = Sepsis

- Core temp >38°C or <36°C
- Elevated heart rate (>90 bpm)
- Respiratory rate > 20 bpm or PaCO₂ <32mmHg or IPPV for acute respiratory process
- WBC count >12,000/mm³ or <4,000/mm³ or >10% immature neutrophils

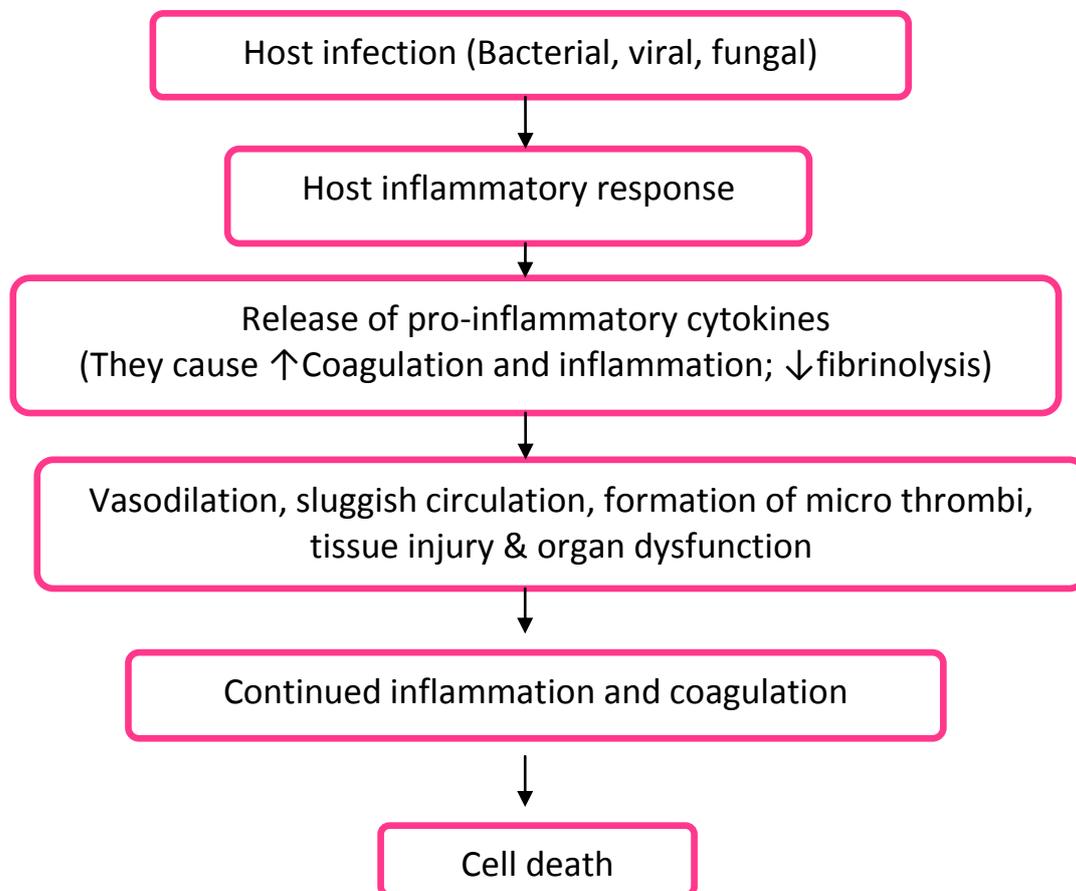
Severe Sepsis:

- Sepsis plus organ dysfunction

Septic Shock:

- Sepsis with BP <90mmHg for 1 hour despite adequate fluid resuscitation or the need for inotropes to maintain BP >90mmHg

Sepsis Pathophysiology



Management of Septic Shock

- A – maintain airway
- B – Optimize breathing and oxygenation (including strategies to optimize oxygen delivery and match this to consumption)
- C - Ensure there is good access. Administer fluid boluses to compensate for vasodilation and decreased circulatory volume
- Source control – remove and treat the source of infection. Administer antibiotic therapy early and in a timely manner (within one hour, as per the sepsis bundle guidelines). Culture to determine the causative organism.
- For blood pressure not responding to fluid therapy – commence inotropic support and administer infusion of vasopressors to maintain SBP and MAP and hence prevent organ ischemia and injury.

Key points to remember when managing a patient with shock

- ❖ Time is of the essence, intensive therapy and monitoring is essential
- ❖ Identify cause, treat and prevent further losses
- ❖ Assess extent of physiological disturbance
- ❖ Identify “deficiency” and “replenish”
 - intravascular volume
 - contractility
 - capillary permeability

- ❖ Monitor therapy and adjust accordingly

Inotropes and Vasopressors

Inotropes and **vasopressors** have excitatory and inhibitory actions on the heart and vascular smooth muscle, as well as important metabolic, central nervous system and presynaptic autonomic nervous system effects.

They are powerful drugs that are used in Intensive Care to regulate a patient's heart rate, blood pressure and the force of contraction of the heart. They do this by working on specific receptors throughout the body

(Overguard & Vladimir, 2008).

Small changes in the rate of infusions of these agents may produce a rapid response in patients' heart rate and blood pressure.

In some of the ICU patients the maintenance of blood pressure is extremely dependant on the inotropes and vasopressor infusions and hence careful titration and continuous monitoring is essential.

It is imperative that nurses caring for patients who are receiving these drugs are aware of the specific dosage ranges and the receptors activated, the desired effects of the drugs and the complications associated with their administration

Receptors, agonists and antagonists

Drugs commonly used in the management of the critically ill patient are:

- **Adrenaline, noradrenaline and dobutamine**

These drugs will have varying effects on

- vascular resistance,
- myocardial contractility and
- heart rate

depending on the dose used and the receptor that is activated by the drug.

Receptors relevant to this group of drugs include:

- **alpha1, beta1 and beta2 receptors.**

Due to the frequency with which these drugs are used and the effects they can exert on the cardiovascular system, knowledge of their action is essential to provide safe and effective care to the critically ill patient.

Most drugs produce their effects by acting on specific protein molecules known as **receptors**.

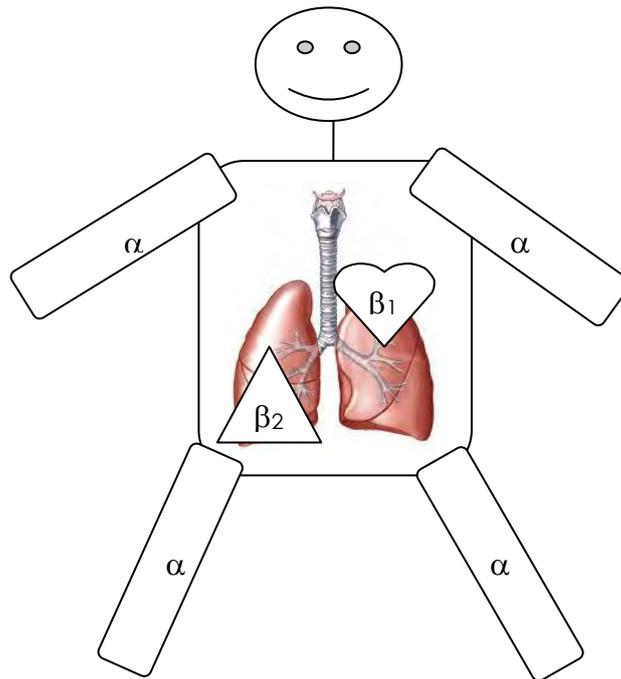
These receptors are activated by transmitter substances or hormones. Transmitter substances that activate a receptor and produce a response are called **agonists**.

Drugs that combine with receptors but do not activate them are called **antagonists**.

By combining with receptors, antagonists reduce the probability of transmitter substances or hormones from combining with the receptor and therefore are often used to block the action of other drugs.

Receptor locations and actions

Receptor Type	Location	Primary action(s) when stimulated
Alpha₁	Found primarily in vascular smooth muscle.	<ul style="list-style-type: none"> ▪ Vasoconstriction. ▪ Activation of α_1 adrenergic receptors on arterial vascular smooth muscle cells results in smooth muscle contraction and increase in systemic vascular resistance (SVR). ▪ It results in peripheral vasoconstriction.
Beta₁	Found in the heart and intestinal smooth muscle.	<ul style="list-style-type: none"> ▪ Increased contractility automaticity, AV conduction and heart rate. ▪ Stimulation of β_1 adrenergic receptors results in enhanced myocardial contractility through Ca^{+} mediated facilitation of the actin-myosin complex binding with troponin C. ▪ It also enhances chronicity through Ca^{+} channel activation. ▪ It results in an increase in heart rate and contractility
Beta₂	Bronchial vascular and uterine smooth muscle.	<ul style="list-style-type: none"> ▪ Vasodilation and bronchial dilation. ▪ Stimulation of β_2 adrenergic receptors on vascular smooth muscle cells through a different intracellular mechanism results in increased Ca^{+} uptake by the sarcoplasmic reticulum and vasodilation. ▪ This causes bronchodilation and dilation of coronary arteries.
Dopaminergic receptors	Found in the renal and mesenteric vessels.	<ul style="list-style-type: none"> ▪ Increased blood flow to the kidneys and mesentery. ▪ Stimulation of dopaminergic receptors in the kidney and splanchnic vasculature results in renal and mesenteric vasodilation.
V₁ & V₂ receptors	<p>V₁ – found in vascular smooth muscle.</p> <p>V₂ – found in renal collecting duct</p>	<ul style="list-style-type: none"> ▪ Stimulation of V₁ receptors in the vascular smooth muscle mediates constriction. ▪ Stimulation of V₂ receptors in the renal collecting duct, enhances the permeability of the collecting duct and mediates water reabsorption

Receptor Location: (β_1 , β_2 , α)

Adrenaline: sympathomimetic amine with

- high affinity for β_1 , β_2 and α_1
- β effects are more pronounced at a small dose
- α_1 effects at a higher dose.

Noradrenaline: sympathomimetic amine with

- Potent α_1 effects and modest β -agonist activity.

Dobutamine: synthetic catecholamine with

- Strong β_1 and β_2 effects.
- Its cardiac β_1 effect makes it a potent inotrope
- It has weak chronotropic activity.
- Vascular smooth muscle binding results in combined α_1 adrenergic agonism and antagonism
- β_2 stimulation with a net vascular effect of mild vasodilation.

Vasopressin: exerts its circulatory effect on

- V_1 receptors causing constriction of vascular smooth muscle
- Its V_2 effects increase renal collecting duct permeability and mediate water reabsorption.

The above drugs must always be administered via a Central Venous Catheter (the only exception being during an emergency situation).

Table: Inotrope / vasopressor, clinical indication, receptor binding (Overguard & Vladimir, 2008).

Drug	Clinical Indication	α_1	β_1	β_2	DA	V ₁ / V ₂
Adrenaline	Shock (cardiogenic, vasodilatory), cardiac arrest, bronchospasm / anaphylaxis, symptomatic bradycardia	+++++	+++++	+++	N/A	N/A
Noradrenaline	Shock (cardiogenic, vasodilatory), low cardiac output with low SVR	+++++	+++	++	N/A	N/A
Dobutamine	Low cardiac output (decompensated HF, cardiogenic shock, sepsis induced myocardial dysfunction)	+	+++++	+++	N/A	N/A
Isoprenaline	Heart block & Brady arrhythmias	0	+++++	+++++	N/A	N/A
Metaraminol	Acute Hypotension	+++++	+	0	N/A	N/A
Vasopressin	Shock (cardiogenic, vasodilatory), cardiac arrest	N/A	N/A	N/A	N/A	+++++

- **α and β receptor activity:**
 ⇒ + To +++++ is minimal to maximal.

Milrinone

- is a positive inotrope and vasodilator and is used in ICU to enhance cardiac function
- Unlike catecholamines, milrinone is a phosphodiesterase inhibitor (PDI) that does not affect the adrenergic receptors.
- The inhibition of phosphodiesterase leads to the inhibition of the breakdown of cyclic adenosine monophosphate. This results in increase in myocardial contractility (increase CI) and venous and arterial dilation (decrease preload and SVR).
- The resulting vasodilation may lead to a slight increase in heart rate.

Glyceryl Trinitrate (GTN):

- Is a vasodilator that produces a dose-related dilatation of both arterial and venous beds with venous dilatation more predominant.
- It is used to reduce systolic, diastolic, and mean arterial pressures and myocardial oxygen consumption.
- Peripheral pooling may reduce venous return to the heart, reducing left ventricular end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP, preload).
- Arterial relaxation reduces systemic vascular resistance and arterial pressure (afterload) and there is dilatation of the coronary arteries.
- Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or an increased heart rate decreases diastolic filling time. It is used for:
 - The control of hypertension
 - Congestive heart failure associated with acute myocardial infarction.
 - Treatment of angina pectoris in patients who have not responded to recommended doses of organic nitrates and/or a beta-blocker.

Clinical Considerations.

- A tachycardia produced by the **beta-1** effects of inotropes will increase the amount of workload and myocardial oxygen requirement of the heart.
 - In patients who have cardiac disease, the myocardial oxygen demands may exceed the myocardial oxygen supply and myocardial ischemia may result.
- **Alpha** effects cause vasoconstriction and the SVR or afterload increases.
 - This will improve blood pressure but it also means the heart will have to work a lot harder in order to eject the blood from the ventricle.
 - Increased heart workload means increased myocardial oxygen demands.
 - If this exceeds myocardial oxygen supply, then ischemia may occur.
 - This could have a significant impact on patients with a cardiac history.
- Dobutamine is often a good drug to use in myocardial infarction as it doesn't increase HR (beta 1) and myocardial oxygen demands or increase SVR (alpha effects) and myocardial workload.
 - As it does not have any alpha properties, BP is supported by increased myocardial contractility only; therefore if hypotension persists an alpha stimulant may be required.

Inotropes and vasopressors should never be purged.

Purging results in uneven doses of the drug being given to the patient and as a result the patient can have huge changes in their haemodynamic parameters.

Inotropes and vasopressors need to be regulated by continuous infusion to maintain a consistent dose delivery and haemodynamic control. Continuous monitoring of blood pressure with arterial lines is necessary to help close monitoring and titration of therapy.

Drug Calculations

Drug calculation formulae:

To calculate mcg/kg/min for a given infusion rate:

$$\text{mcg/kg/min} = \frac{\text{rate (ml/hr)} \times \text{concentration (mcg/ml)}}{\text{Weight (kg)} \times 60}$$

For example:

A patient receiving an adrenaline infusion at 5mls/hr.

The infusion is 4mg in 50mls (80mcg/ml)

Patient weighs 90kgs

To calculate dose in mcg/kg/min:

$\text{Mcg/kg/min} = 5 \times 80 \text{ divided by } 90 \text{ divided by } 60$

$= 0.07 \text{mcg/kg/min}$

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Learning Activities

1. Discuss the response elicited when the following receptors are activated:
 - Alpha
 - Beta 1
 - Beta 2
 - V₁ & V₂
2. Why is dobutamine a useful inotrope for patients in cardiogenic shock?
3. List the actions and usages for adrenaline
4. Why is noradrenaline useful drug for septic shock?
5. What is the dose in mcg/kg/min of a noradrenaline infusion running at 10mls/hr for a 70kg patient?
6. What is the maximum infusion rate for vasopressin when used for shock?
7. What are some of the safety considerations when caring for patients with inotrope and vasopressor or vasodilator infusions?
8. Define shock. How is shock classified into 3 different types?
9. For each of the types of shock, give a definition and state the main mechanisms involved. Give some clinical examples.

TYPE	MECHANISM	CLINICAL EXAMPLE
<p>Hypovolemic Shock</p>		
<p>Cardiogenic Shock</p>		
<p>Septic shock</p>		
<p>Anaphylactic shock</p>		
<p>Neurogenic Shock</p>		

Worksheet

