ACS with cardiogenic shock
Need for pharmacologic supportive therapy !

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Agenda

1- Hemodynamic Support

2- Vasopressor supportive therapy
- **Dopamine**
- **Norepinephrine**
- **Epinephrine**
- **Levosimendan**

3- Inotropic supportive therapy
- **Dobutamine**
- **Phosphodiesterase III inhibitors**

Cardiogenic Shock

- Is a state of inadequate tissue perfusion due to cardiac failure
- Is associated with the highest rate of early and late mortality in patients with AMI
- Occurs in up to 8% of patients hospitalized for STEMI
- Has a mortality rate of 50% to 60% within 30 days

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Hemodynamic Support

- Dopamine, norepinephrine, and epinephrine are vasoconstricting drugs that help to maintain adequate blood pressure during life-threatening hypotension and help to preserve perfusion pressure for optimizing flow in various organs. *(Ascheim DD, et al.Circulation. 2013) .*
- The mean blood pressure required for adequate splanchnic and renal perfusion [MAP] of 60 or 65 mm Hg.

- In patients with inadequate tissue perfusion and adequate intravascular volume, initiation of inotropic and/or vasopressor drug therapy may be necessary.
- Dopamine increases myocardial contractility and supports the blood pressure; however, it may increase myocardial oxygen demand.
- Dobutamine may be preferable if the systolic blood pressure is higher than 80 mm Hg; it has the advantage of not affecting myocardial oxygen demand as much as dopamine does.

- Dopamine is usually initiated and the infusion rate is adjusted according to the blood pressure and other hemodynamic parameters.
- If the patient remains hypotensive despite moderate doses of dopamine, a direct vasoconstrictor (eg, norepinephrine) should be started.

- The potent vasoconstrictors (eg, norepinephrine) are best reserved for situations of refractory hypotension and organ hypoperfusion because of their unfavorable role in increasing afterload, cardiac filling pressure and impairing cardiac output.
- However, one study of patients with shock found no difference in outcome between treatment with norepinephrine and treatment with dopamine. *(Devriendt J, et al. N Engl J Med. 2010)*
- There is no consensus regarding the first-line choice of vasopressor in cardiogenic shock.

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Vasopressor supportive therapy

- There is little in the way of randomized clinical trial data to guide the use of inotropic or pressor therapy in patients with cardiogenic shock.
- The use of these agents is indicated in patients with cardiogenic shock, but it is important to note that a survival benefit has not been established.
- Indeed, routine use of these agents in patients with hemodynamically stable, decompensated HF was associated with greater morbidity and no clinical benefit.

(Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure [OPTIME-CHF] 2003).

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Dopamine

- Dopamine is a precursor of norepinephrine and epinephrine and has varying effects according to the doses infused.

- A dosage of less than 5 mcg/kg/min, causes vasodilation of renal, mesenteric, and coronary beds.

- At a dosage of 5-10 mcg/kg/min, beta1-adrenergic effects induce an increase in cardiac contractility and heart rate.

- At dosages higher than 10 mcg/kg/min, predominant alpha-adrenergic effects lead to arterial vasoconstriction and an elevation in blood pressure.

- The blood pressure increases as a result of its inotropic effect.
- The undesirable effects are tachycardia and increased pulmonary shunting, as well as the potential for decreased splanchnic perfusion and increased pulmonary arterial wedge pressure.

Adverse Effects

- CVS : Ventricular arrhythmia, AF(at very high doses), ectopic beats, anginal pain, cardiac conduction abnormalities, widened QRS complex, bradycardia, hypotension, hypertension, vasoconstriction.
- Respiratory: Dyspnea
- GIT: Nausea, vomiting
- Metabolic/nutritional: Azotemia
- CNS: Headache, anxiety
- Endocrine: Piloerection
- Ocular: Increased intraocular pressure; dilated pupils
- Gangrene of extremities

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Norepinephrine

- Norepinephrine is a potent alpha-adrenergic agonist with only minor beta1-adrenergic agonist effects.
- Norepinephrine can increase blood pressure successfully in patients who remain hypotensive following dopamine.
- The dosage of norepinephrine may vary from 0.2 to 1.5 mcg/kg/min, and high dosages (up to 3.3 mcg/kg/min) have been used because of the alpha-receptor down-regulation in persons with sepsis.

Adverse Effects

- Bradycardia
- Hypertension
- Arrhythmias
- Confusion
- Anxiety
- Dyspnea, with or without respiratory difficulty
- Headache
- Nausea and vomiting
- Sweating
- Tremor
- Restlessness
- Urinary retention
- Extravasation
- Gangrene

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Epinephrine

- Epinephrine is an strong alpha1, beta1, and moderate beta2 adrenergic effect.
- It can increase the MAP by increasing the stroke volume, as well as systemic vascular resistance (SVR) and heart rate.
- Epinephrine decreases the splanchnic blood flow and may increase oxygen delivery and consumption.

- Administration of this agent may be associated with an increase in systemic and regional lactate concentrations.
- The use of epinephrine is recommended only in patients who are unresponsive to traditional agents.
- Other undesirable effects include an increase in lactate concentration, a potential to produce myocardial ischemia, the development of arrhythmias, and a reduction in splanchnic flow.

Adverse Effects

- Angina
- Anxiety
- Apprehensiveness
- Cardiac arrhythmias
- Dizziness
- Flusing
- Dyspnea
- Headache
- Nausea
- Pallor
- Sweating
- Tremor

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Levosimendan

- Levosimendan, widely used in Europe.
- can be considered for use in conjunction with vasopressors to improve coronary blood flow. *(Rauwolf T, et al. Crit Care Med. 2008).*
- This agent acts by increasing the sensitivity of the cardiac myofilament to calcium, rather than increasing intracellular concentrations of free calcium.

- Levosimendan stabilises troponin C and the kinetics of actin-myosin cross-bridges without increasing myocardial consumption of adenosine triphosphate (ATP).
- Levosimendan is a potent inotrope and also a vasodilator of the arterial, venous, and coronary circulation.
- It should be used with caution, however, in that it can cause hypotension.

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Dobutamine

- Dobutamine (sympathomimetic agent) is a beta1-receptor agonist, though it has some beta2-receptor and minimal alpha-receptor activity.
- It is used in a dosage range of 2 to 20 mcg/kg/min and has a half-life of approximately 2 minutes.

- IV dobutamine induces significant positive inotropic effects, with mild chronotropic effects through activation of adenyl cyclase, an increase in intracellular cyclic adenosine monophosphate (cAMP) and, therefore, calcium levels.
- It also induces mild peripheral vasodilation (decrease in afterload).
- The combined effect of increased inotropy and decreased afterload induces a significant increase in cardiac output.

- In the setting of acute MI, dobutamine use could increase the size of the infarct because of the increase in myocardial oxygen consumption.
- In general, caution should be exercised when administering dobutamine in patients with moderate or severe hypotension (eg, systolic blood pressure <80 mm Hg), because the peripheral vasodilation, in some cases, may cause a further fall in blood pressure.

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Phosphodiesterase III inhibitors

- Phosphodiesterase III inhibitors (PDIs), which include inamrinone (formerly amrinone) and milrinone, are inotropic agents with vasodilating properties and long half-lives.
- Milrinone is used in a dosage range of 0.3 to 0.75 mcg/kg/min and has a long half-life of 1.5 to 3 hours, with the longer half-life in patients with renal impairment.

- The mechanism of action of PDIs is distinct from dobutamine in that they prevent breakdown of cAMP, thereby increasing intracellular cAMP levels.

- The hemodynamic properties of PDIs are :

(1) A positive inotropic effect on the myocardium and peripheral vasodilation (decreased afterload)

(2) A reduction in pulmonary vascular resistance (decreased preload).

- PDIs may be beneficial in persons with cardiac pump failure who require more concomitant pulmonary and systemic vasodilation than is typically achieved by dobutamine.

- Unlike catecholamine inotropes, these drugs are not dependent on adrenoreceptor activity; therefore, patients are less likely to develop tolerance to these medications.

- PDIs are less likely than catecholamines to cause adverse effects known to be associated with adrenoreceptor activity (eg, increased myocardial oxygen demand, myocardial ischemia).

- They are also associated with less tachycardia and myocardial oxygen consumption. However, the incidence of tachyarrhythmias is greater with PDIs than with dobutamine.

Table 3: Summary of Shock Treatments

Treatment goal	Management
Correct mechanical problem (e.g. tamponade, surgical bleeding)	Immediate surgical correction
Optimise preload	1. Start with crystalloid infusion 5–10 ml/kg and continue up to 20 ml/kg 2. Continue with colloid infusion up to 20ml/kg (gelatine if GFR > 35 ml/min or albumin 5 % if GFR < 35 ml/min)
Optimise vascular tone and perfusion pressure	1. NA infusion 0.1-1 µg/kg/min 2. Vasopressin infusion 0.01-0.04 U/min if NA >0.5 µg/kg/min 3. Consider methylene blue 1 x 2 mg/kg iv if < 24 hours after cardiac surgery and if NA >0.5 µg/kg/min
Optimise myocardial contractility	1. Dobutamine infusion up to 5 µg/kg/min 2. Milrinone infusion 0.01–0.25 µg/kg/min (particularly useful in patients under β blockers) 3. Adrenaline infusion up to 0.3 µg/kg/min infusion in case of life threatening shock 4. Consider ECLS in non-responders to pharmacological inotropic support
Optimise heart rate and rhythm: Bradycardia – Atrial fibrillation, VES, ventricular tachycardia	Consider external/internal pacing1. Optimise magnesium and potassium levels 2. Amiodaron 2x 150 mg over 30min iv, followed by an infusion of 400-1200 mg/d (total of 0.1g/kg) 3. Synchronised electrical cardioversion (biphasic 2x200 joule)
Optimise oxygen delivery	Deliver oxygen via face mask (goal SaO_2 92-98 %) Early intubation and mechanical ventilation to reduce oxygen expenditure Haematocrit goal >27 % in the acute shock phase
Sepsis/SIRS	SIRS: Hydrocortisone 100 mg loading dose iv, followed by 50 mg qid iv for 5 days, when NA >0.3 µg/kg/min Sepsis: Begin empiric antibiotic therapy within one hour after suspicion of septic shock (after sampling for microbiology)

CVVHD = continuous veno-venous haemodiafiltration; ECLS = extracorporeal life support; NA = noradrenalin; qid quarter in die (for 4times a day);
SaO_2 = oxygen saturation; SIRS = systemic inflammatory response syndrome; VES = ventricular extra systoles.