

## Cardiogenic shock

### Etiology

The most common cause of cardiogenic shock is LV dysfunction and necrosis as a result of acute myocardial infarction (AMI) (1).

Acute valvular insufficiency or stenosis prevents the normal ejection of blood. Besides ventricular septal or free wall rupture (1).

### Pathophysiology

Compensatory mechanism to decrease in COP, include an increase in sympathetic tone (seen clinically as increased HR and peripheral vasoconstriction) which initially serve to increase CO and maintain central arterial pressure. Decrease in CO result in a decreased perfusion to vital tissues and organs, also the decrease in CO leads to a reduction in the flow of blood through the coronary arteries, which can lead to infarct extension and a further worsening of cardiac performance (1).

### Clinical manifestation of cardiogenic shock

Sign and symptoms similar to that of hypovolemic shock (hypotension, tachypnea and tachycardia, oliguria and cold extremities) but patients frequently have signs of volume overload because the heart cannot move blood through the circulation. Peripheral edema can be seen in the extremities; lung sounds are diminished, and rales may be present as pulmonary edema develops. These findings are particularly evident in patients with severe HF (1). Hypovolemia occurs in up to 20% of patients in cardiogenic shock (1)

There is Reduced CO, BP, but elevated PCWP and SVR(systemic vascular resistance) (1).

**PCWP (pulmonary artery wedge pressure) is usually low in hypovolemic shock and high in cardiogenic shock** (1)

**Useful diagnostic measures:** chest x ray to check pulmonary edema, ECG and ECHO to detect cardiac abnormalities (1).

### Treatment options of cardiogenic shock

Fluids, vasodilators and inotropes (1)

#### A. Fluids

Augmentation of preload with a fluid to improve CO is the first option. However, if there is pulmonary edema or if PCWP is more than 18 mmHg, or If the PCWP rises but the CO does not improve, fluid challenges should be discontinued since there is no benefit from fluid therapy instead they may worsen pulmonary edema (1).

Additionally elevating the preload without appreciably improving CO also can increase LV wall tension, which is a major determinant of myocardial (oxygen consumption)  $\dot{V}O_2$  ; consequently, myocardial ischemia could develop (1).

## B. VASODILATORS (PRELOAD AND AFTERLOAD REDUCTION)

A peripheral vasodilator acts to decrease pulmonary venous congestion by reducing preload (PCWP). It will improve CO by decreasing the resistance to ventricular ejection (afterload) as well.

In patients with myocardial ischemia, vasodilators improve subendocardial blood flow, reduce the myocardial wall tension, and reduce the LV radius. The resultant decrease in myocardial  $\dot{V}O_2$  will help prevent further depression of cardiac function (1).

Vasodilators in patients with LV failure (HF), lower elevated SVR, that occur due to reflex increase in sympathetic tone in response to a fall in systemic arterial pressure, so vasodilators improve ventricular function (1). One of major limitation of using vasodilators is blood pressure reduction, so Vasodilators should be reserved for situations in which hemodynamic monitoring shows the patient to have LV failure with elevations in PCWP and SVR, and a SBP greater than 90 mm Hg (1).

## C. INOTROPIC SUPPORT

A rapid-acting inotropic agent (e.g., dopamine, dobutamine, epinephrine) also can be used to increase myocardial contractility and CO. The disadvantage of this intervention is that improved CO is accompanied by an increased myocardial oxygen demand (1).

So if PCWP elevated, while BP is low the inotropes are the best choice to improve COP and BP. If the BP stabilized vasodilators can be tried.

If there is concomitant pulmonary edema, diuretics can be started when BP elevated to normal values (1).

Note: evidence suggests that inotropic agents can be associated with an increased risk of mortality in patients with HF despite the improvement of symptoms and hemodynamic indices (1).

### **Inotropic agents**

**Dopamine:** is a precursor of norepinephrine, has inotropic (contractility), chronotropic, and vasoactive properties, all of which are dose dependent (1).

At low doses 0.5 to 2 mcg/kg/minute, dopamine stimulates dopaminergic receptors primarily in the splanchnic, renal, and coronary vascular beds. Low dosages of dopamine may slightly increase myocardial contractility,

but usually will not alter HR or systemic vascular resistance (SVR) significantly (1). Low-dose dopamine increases urine output but has not been shown to be able to reduce the incidence or degree of renal dysfunction (1).

At 2 to 5 mcg/kg/minute, the improved cardiac performance produced by dopamine is through direct stimulation of  $\beta_1$ -adrenergic receptors and indirectly through release of norepinephrine from nerve terminals (1). At these doses dopamine increases stroke volume (SV) (inotropic effect), HR (chronotropic effect), and consequently CO (1).

At infusion rates of 5 to 10 mcg/kg/minute, the  $\alpha$ -adrenergic receptors are activated. At this dosage, the vasoactive effects on peripheral blood vessels are unpredictable and depend on the net effect of  $\beta_1$ -adrenergic stimulation,  $\alpha$ -adrenergic stimulation, and reflex mechanisms. MAP and PCWP usually will rise (1).

At doses greater than 15 to 20 mcg/kg/minute, dopamine primarily stimulates peripheral  $\alpha$ -adrenergic receptors, causing peripheral arterial vasoconstriction (increase SVR) that leads to increases in afterload, preload, and myocardial oxygen demand as well as Ischemia (1).

The increase in SVR limits CO; thus, infusion rates should be limited to less than 10 to 15 mcg/kg/minute in patients with cardiac failure (1).

#### **Dosing of dopamine:**

Start at low doses, and if there is no response, titration of doses by 1-2 mcg/kg can be done every 10 min. (1)

#### **Adverse effects encountered with dopamine infusion**

It includes increased HR, anginal pain, arrhythmias, headache, hypertension, vasoconstriction, nausea, and vomiting. Extravasation of large amounts of dopamine during infusion can cause ischemic necrosis and sloughing (1).

#### **How to check if the increase in Cardiac output due to inotropic or chronotropic effect?**

Depend on stroke volume since  $COP = SV(\text{stroke vol}) * HR$

If the COP increased and HR highly increased while SV slightly increased mean that chronotropic effect is predominant (1). Increase in HR, mean increase in myocardial O<sub>2</sub> demand & may worsen the IHD (1)

#### **DOBUTAMINE**

Dobutamine is a strong positive inotropic drug with predominant direct  $\beta_1$  agonist effects and weak  $\beta_2$ - and  $\alpha_1$ -adrenergic effects, with greater  $\beta_2$ -vasodilatory than  $\alpha_1$ -vasoconstrictive actions (1). Dobutamine produces a larger increase in CO and is less arrhythmogenic than dopamine (3). Unlike dopamine, dobutamine does not release endogenous norepinephrine or stimulate renal dopaminergic receptors (1). Compared

with dopamine, dobutamine has equal or greater inotropic action. Dobutamine lowers PCWP and SVR with increasing doses, whereas dopamine may increase PCWP and SVR with increasing doses (1). In the clinical setting, dobutamine may be preferred in patients with depressed CO, elevated PCWP, and increased SVR with mild hypotension (1).

### **Dobutamine side effects**

Arrhythmias, nausea, anxiety, and tremors. The increases in contractility and HR caused by dobutamine can cause an increase in myocardial  $\dot{V}O_2$  and can lead to ischemia in patients with coronary artery disease (1).

**Another limiting factor to dobutamine is tolerance to its hemodynamic effects with long-term continuous use. A decline in CO and HR has been seen after prolonged infusion and is most likely caused by downregulation of  $\beta_1$ -receptors (1).**

### **Dosing للاطلاع**

Dobutamine should be started at a low dosage (i.e., 2.5 mcg/ kg/minute). Maximum 10 – 20 mcg/ min. Dose titration every 10 minutes based on patient tolerance (1).

If patient stabilized then an acceptable method frequently used is to taper Dobutamine by 2 mcg/kg/minute every 30 to 60 minutes (1).

### **Switching from dopamine to dobutamine**

This usually is done if the patient suffers from tachycardia with dopamine usage. Once the dobutamine has been started, a reduction in the dose of dopamine should be attempted. A decrease of 20% of the current infusion rate every 10 to 15 minutes is reasonable (1).

### **Epinephrine**

Epinephrine has dose-dependent hemodynamic effects (1).

At lower infusion ranges (0.01– 0.1 mcg/kg/minute) epinephrine stimulates  $\beta_1$ -adrenergic receptors, causing increases in HR and contractility. As the dose increases, more  $\alpha_1$ -receptor stimulation occurs, resulting in vasoconstriction and corresponding increases in SVR (1).

Epinephrine is frequently used in the cardiac surgery setting, because of its favorable hemodynamic effects (increased CO and BP) (1).

### **Side effects**

Epinephrine can induce hyperglycemia through gluconeogenesis and has been shown to increase lactate levels compared with other vasopressors and inotropic agents (1). So epinephrine should be reserved for patients with a markedly depressed CO in conjunction with severe hypotension (1).

## **Acute MI with cardiogenic shock**

Cardiogenic shock after AMI occurs in only a small percentage of patients, but carries a high mortality rate (1).

Treatment of these critically ill patients involves two components: stabilization and definitive treatment. Reperfusion of the occluded artery is of paramount importance in these patients (1).

The goals are to maintain adequate oxygen delivery ( $Do_2$ ) to the tissues and to prevent further hemodynamic compromise. Stabilization includes: (a) establishing ventilation and oxygenation (arterial  $Po_2$  should be greater than 70 mm Hg); (b) restoring central arterial BP and CO with vasopressors and inotropic agents, if needed; (c) infusing fluids, if hypovolemic; and (d) treating pain, arrhythmias, and acid–base abnormalities, if present (1).

A. Administration of oxygen either by face mask or by mechanical ventilation which enhances the myocardial oxygen supply and may contribute to improved ventricular performance (1).

B. The arterial pressure must be increased to provide adequate coronary and systemic perfusion to meet oxygen requirements. Otherwise myocardial tissue necrosis will expand into the area of ischemia. This results in further hemodynamic impairment and initiates a vicious feedback cycle that can lead to intractable pump failure and irreversible shock (1).

The use of vasoactive agents is not without risk, however, because they can exacerbate ventricular arrhythmias and increase  $\dot{V}o_2$  in ischemic myocardium. Therefore, the minimal dose that will provide adequate perfusion pressure should be used (1). Exclusive use of these measures does not improve survival (1).

The combination regimen (7.5 mcg of dopamine and 7.5 of dobutamine) offered hemodynamic superiority compared with either agent alone in this group of patients (1).

PDEI like milrinone are not preferred because of their vasodilating properties which further reduce blood pressure in these patients (1).

C. Optimizing preload to improve CO and systemic perfusion is crucial, especially in patients with RV infarction. In patients with severe LV impairment caused by cardiogenic shock, increasing intravascular volume (especially by IV fluids) can worsen pulmonary congestion (1).

Thrombolytic therapy in AMI may reduce the incidence of subsequent cardiogenic shock, but its value may be limited in patients who have already experienced shock possibly because of reduced delivery of the

agent to the coronary artery thrombus as a result of hypotension. Early PCI may be of more benefit than thrombolytic agents in patients with cardiogenic shock complicating AMI (1).

### **Treatment of lactic acidosis**

The use of sodium bicarbonate to correct lactic acidosis in cardiogenic shock and other critically ill patients is controversial. Sodium bicarbonate can have numerous adverse effects, such as hypernatremia, paradoxical intracellular acidosis, and hypercapnia; therefore, Bicarbonate is recommended only, if at all, when severe acidemia (pH <7.2 or HCO<sub>3</sub> – <10 to 12 mEq/L) is present (1).

### **Norepinephrine**

It is a potent  $\alpha$ -adrenergic agonist that vasoconstricts arterioles at all infusion rates, thereby increasing SVR, it has a slight effect on B1 receptor to increase heart contractility (1). Worsening of ventricular function can occur because of increased afterload as a side effect for NE (1). Although coronary perfusion pressure is enhanced as a result of the elevation in diastolic pressure, myocardial  $\dot{V}O_2$  also is increased. Consequently, myocardial ischemia and arrhythmias may be exacerbated and LV function further compromised (1).

### **SEPTIC SHOCK**

Septic shock is associated with a high mortality rate, reflecting the limited therapeutic options available at this time (1). Septic shock is characterized initially by a normal or high CO and a low SVR (1).

#### **Definitions according to Society of Critical Care Medicine**

Sepsis syndrome: a systemic inflammatory response resulting from infection. When associated organ dysfunction, hypoperfusion, or hypotension is present, it is termed *severe sepsis*; when hypotension persists despite adequate fluid resuscitation and requires inotropic or vasopressor support, it is termed *septic shock* (1).

### **Etiology of sepsis**

Systemic infection caused by either aerobic or anaerobic bacteria is the leading cause of septic shock. Fungal, mycobacterial, rickettsial, protozoal, or viral infections can also be encountered. However Gram negative bacteria like *Enterobacteriaceae*, *Pseudomonas*, and *Haemophilus*, (in decreasing order of frequency) responsible for septic shock slightly more than G+ bacteria (1).

Immunocompromised patients, neonate, AIDS, cancer patients, DM, alcoholics, those with renal or hepatic failure are at high risk for septic shock (1).



## **Pathophysiology of septic shock**

Immunologic host response to infection involves inflammatory and immunodepressive (anti-inflammatory) phases (1). It has been thought that circulating inflammatory mediators, such as cytokines, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), platelet activating factor, may cause myocardial dysfunction (1). The presence of these inflammatory cytokines promotes inflammation and vascular endothelial injury (fluid extravasations), and also causes an overwhelming activation in coagulation (1), which may be caused by increase in thrombin by sepsis. A coagulopathic state promotes formation of microvascular thrombi leading to hypoperfusion, ischemia, and, ultimately, organ failure (1).

In late septic shock, the body is no longer able to compensate because of the cardiac effects of the inflammatory mediators and resultant myocardial edema, thus resulting in a decreased CO (1).

## **The clinical features of septic shock**

Fever, chills, nausea, vomiting, and diarrhea are common symptoms (1). While Hemodynamic signs of septic shock include hypotension, tachycardia, elevated CO, low SVR, and a low PCWP. There is also low (oxygen delivery)  $\dot{V}O_2$  and (oxygen consumption)  $\dot{V}O_2$ .

Additionally metabolic acidosis indicating anaerobic metabolism most likely caused by decreased perfusion causing lactic acidosis (1). Furthermore urine output is reduced, and cerebral perfusion declined causing confusion and disorientation (1).

**Characteristic laboratory findings** include leukocytosis or leukopenia, thrombocytopenia with or without coagulation abnormalities, and, often, hyperbilirubinemia (1). Also CRP is highly elevated (4)

These features are usually readily detectable and occur within 24 hours after bacteremia develops, particularly if the bacteremia is caused by gram-negative organisms (1).

## **Therapeutic Approach of septic shock (1)**

The management of septic shock is directed toward three primary areas:

- (a) Eradication of the source of infection,
- (b) Hemodynamic support and control of tissue hypoxia, and
- (c) Inhibition or attenuation of the initiators and mediators of sepsis.

Additional issues should be considered like glucose control, and stress ulcer prophylaxis (1).

**Blood glucose management** should occur with insulin when 2 consecutive blood glucose levels are  $>180\text{mg/dL}$  rather than an upper target blood glucose  $\leq 110\text{mg/dL}$  (4).

**DVT prophylaxis:** done using subcutaneous LMWH, if creatinine clearance is less than 30ml/min then use dalteparin (4).

**Stress ulcer prophylaxis** using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (4).

**A. Eradicating the source of infection involves the early administration of antimicrobial therapy, and, if indicated, surgical drainage. The use of an appropriate antibiotic regimen is associated with a significant increase in survival (1).**

Recommended empiric regimens typically include an anti pseudomonal penicillin or third- or fourth-generation cephalosporin plus vancomycin or a similar broad-spectrum agent to cover for gram positive cocci, aerobic gram-negative bacilli, and anaerobes (1).

Duration of therapy is typically 7 to 10 days; longer courses may be appropriate in patients who have undrainable foci of infection, bacteremia with *S. aureus*; or if patient has neutropenia (4).

However When combination therapy used empirically it should not be administered for longer than 3 to 5 days (4).

**B. The 2<sup>nd</sup> goal in treating septic shock is to optimize  $\dot{V}O_2$  to the tissues and to control abnormal use of oxygen and anaerobic metabolism by reducing the tissue oxygen demand (1).** This can be achieved if we reach the following goals (3). MAP(mean arterial pressure) 65mmHg or more, ScVO<sub>2</sub> (oxygen saturation) equal or more than 70% and Cardiac index = 3L/min/m<sup>2</sup> or more (3). [The MAP is a better reflection of systemic arterial pressure because it considers the diastolic pressure (1)]

Note: raising arterial BP and CO with inotropic agents or vasopressors before restoring adequate blood volume actually can worsen tissue perfusion (1)

#### **Algorithm for hemodynamic support during septic shock treatment**

Firstly start with IV fluids, then check MAP if it is below the goal, check PCWP if within the range continue fluids but if PCWP = 18 or more (3), [if fluids not correct hypoxia or filling pressure (PCWP) is increased or CI still low and patient still hypotensive (1)], then use vasopressor or inotropes: use either norepinephrine 0.02 – 3 mcg/kg/min or dopamine at 2 – 20 mcg / kg /min. If dysrhythmia is present then use phenylephrine. If Hypotension still present use hydrocortisone 300mg/ day for 1 week (3) Now check SVO<sub>2</sub> if not reach goal check PCV if lower than 30 use blood but if it is 30 or more use dobutamine (3). [Blood transfusions should be



used if the hematocrit is less than 21% unless there is an active source of bleeding or a history of cardiac disease (1)].

If MAP and SVO<sub>2</sub> reach the goal check CI, if CI below the goal use dobutamine (or increase its dose if it is already used).

After all these measures if MAP still low use vasopressin 0.01 – 0.04 unit/min (3)

#### **IV Fluids**

Crystalloids are preferred but albumin can be used when patients require substantial amounts of crystalloids (4).

Usually crystalloids are given as 500 – 1000ml/30min as bolus doses.

Patients in septic shock are susceptible to experiencing noncardiogenic pulmonary edema. Therefore, fluid boluses should be given with ongoing monitoring to determine the CVP and PCWP at which CO is maximal (1). The elevation of PCWP to 18mmHg without a significant increase in CO suggests that an optimal PCWP has been reached. Therefore, additional fluid therapy to maintain his BP may worsen his pulmonary edema and further compromise his pulmonary gas exchange. Additional fluid boluses at this time should be used only to maintain the current level of intravascular volume status (1).

#### **Inotropes and Vasopressors**

Norepinephrine was found to be superior to dopamine, with improvement in arterial BP, urine flow,  $\dot{V}O_2$ ,  $\dot{V}O_2$ , and lactate levels (1).

**Dopamine** as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (4). Dopamine is an appropriate choice if MAP, CO and SVR low because of its combined  $\alpha$ -adrenergic vasoconstrictive actions and  $\beta$ -adrenergic inotropic effects will increase SVR and CO, and thus MAP (1).

**Phenylephrine** may be beneficial in septic shock because of its selective  $\alpha$ -agonism, vascular effects, rapid onset, and short duration. Phenylephrine may be a useful alternative in patients who cannot tolerate the tachycardia or tachydysrhythmias with use of dopamine or norepinephrine, in patients with known underlying myocardial dysfunction, and in patients refractory to dopamine or norepinephrine (because of  $\beta$ -receptor desensitization). It is generally initiated at dosages of 0.5 mcg/kg/min and may be titrated every 5 to 15 minutes to desired effects (3).

Potent vasoconstrictors such as norepinephrine and phenylephrine should be given through central veins due to the possibility of extravasation and tissue damage with peripheral administration (3).

**Dobutamine** produces a larger increase in CO and is less arrhythmogenic than dopamine (3).

The addition of dobutamine to epinephrine (3) (or norepinephrine (1)) regimens can improve gastric mucosal perfusion (3).

Clinically, dobutamine leads to a decrease in SVR. So dobutamine in contrast to dopamine lowers PCWP and causes less pulmonary shunting. Because of that volume status must be monitored closely to avoid the development of hypotension and reduced MAP. Fluids should be administered as needed to maintain the PCWP at maximal tolerated levels of 16 to 18 mm Hg. Dobutamine does increase  $\dot{V}O_2$  and CI when given concurrently with or after volume resuscitation (1).

### **Epinephrine**

At the high infusion rates used in septic shock,  $\alpha$ -adrenergic effects are predominantly seen, and SVR and MAP are increased. It is an acceptable single agent in septic shock due to its combined vasoconstrictor and inotropic effects. Epinephrine may be particularly useful when used earlier in the course of septic shock in young patients and those without known cardiac abnormalities (3).

Lactate concentrations may rise during the first few hours of epinephrine therapy but normalize over the ensuing 24 hours in survivors (3).

### **Vasopressin**

Sepsis can cause a decrease in responsiveness to catecholamines resulting in refractory hypotension, possibly because of down regulation of adrenergic receptors. Septic patients exhibit an increased sensitivity to vasopressin (1). Additionally patients in septic shock have decreased endogenous levels of vasopressin (1). Vasopressin is an endogenous hormone that has very little effect on BP under normal conditions, but becomes very important in maintaining BP when the baroreceptor reflex is impaired, such as in shock states (1). It causes vasoconstrictive effects that, unlike adrenergic receptor agonists, are preserved during hypoxia and severe acidosis. It also causes vasodilation in the pulmonary, coronary, and selected renal vascular beds that may reduce PAP and preserve cardiac and renal function. However, vasopressin is not recommended as a replacement for norepinephrine or dopamine in patients with septic shock but may be considered in patients who are refractory to catecholamine vasopressors despite adequate fluid resuscitation. If used, the dose should not exceed .04 unit/min (3).

### **Corticosteroids**

There is a controversy to use of steroids in septic shock, however, corticosteroids were originally proposed as a treatment option because of their anti inflammatory properties with the hope of attenuating the body's response to infection (1).

Steroids can be initiated in septic shock when adrenal insufficiency is present or when weaning of vasopressor therapy proves futile. A daily dose equivalent to 200 to 300 mg hydrocortisone should be continued for 7 days. Adverse events are few because of the short duration of therapy (3). In treated patients hydrocortisone tapered when vasopressors are no longer required (4).

#### Reference

1. Applied therapeutics
2. Davidson
3. Handbook of pharmacotherapy
4. International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

Further Reading: للاطلاع

#### **Last line treatment for acute MI and cardiogenic shock**

Patients who cannot be stabilized with pharmacologic intervention, and in whom systemic or myocardial perfusion is becoming compromised, may require further support through insertion of a mechanical circulatory assist device (1). Like Intra-aortic balloon counterpulsation IABP, which augments coronary arterial perfusion pressure during diastole and reduces LV impedance during systole. (1), although its use lack of evidence but it is still used. One of its serious side effects is thrombocytopenia and limb ischemia (1). Heparin anticoagulation is usually used with IABP because the device has a large surface area that can be thrombogenic (1).

Newer devices have been developed (TandemHeart, Impella) that augment CO directly and decrease the load on the LV. These small pumps are placed percutaneously in the cardiac catheterization laboratory, so do not require major cardiac surgery. They are best used for temporary circulatory support until more definitive therapy is available. Systemic anticoagulation is required with these devices, and adverse effects include bleeding and thrombosis (1).

#### **Controversial therapies for septic shock**

Other therapies with controversy like statin with their pleiotropic effects as anti inflammatory , immunomodulator, and reducing vascular endothelial injury(1), while drotrecogin alpha which is the activated protein C is now withdrawn from market since it don't improve survival ( which act to enhances fibrinolysis and has potent inhibitory effects on

thrombin, which possesses thrombotic as well as inflammatory effects )  
(1).

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