Vasoactive agents in the ICU

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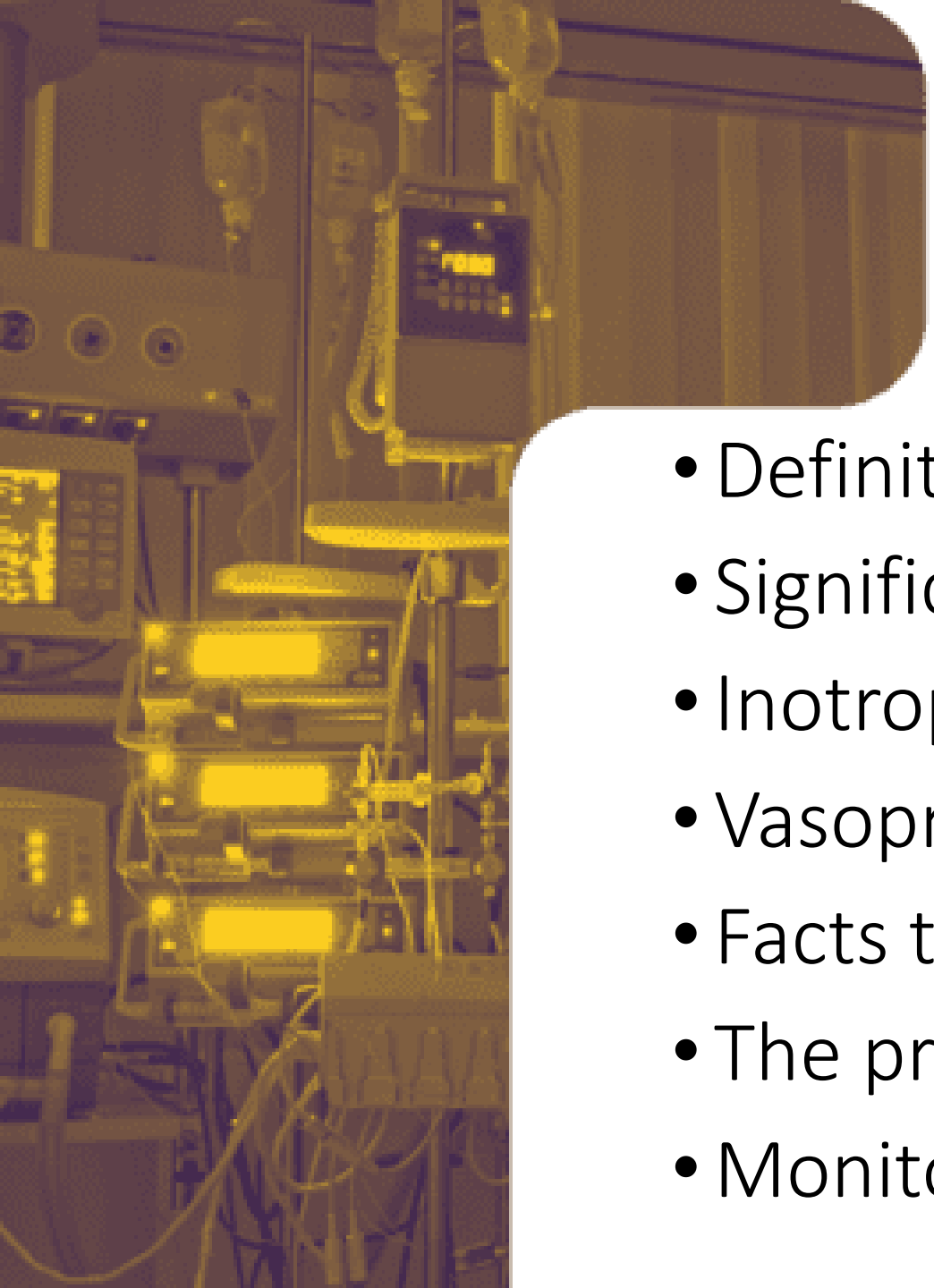


Content

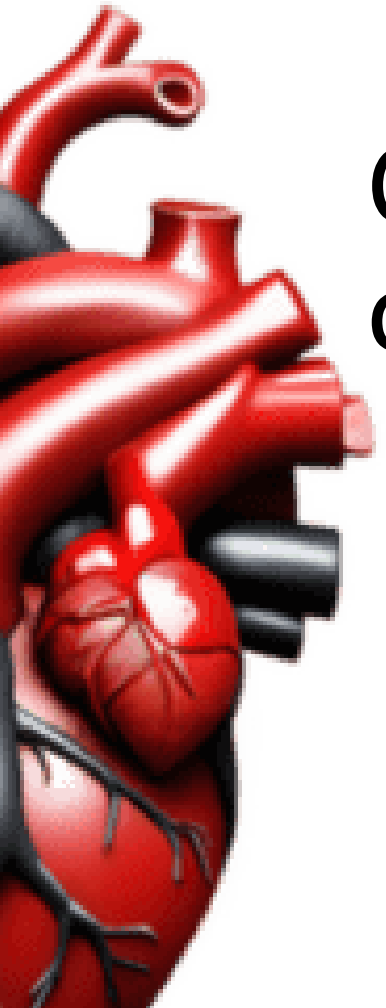
- Definition/Classifications
- Significant receptors in vasoactive therapy
- Inotropes
- Vasopressors
- Facts to consider about vasoactive therapy.
- The principles of vasoactive therapy
- Monitoring patients on vasoactive therapy.

Definition

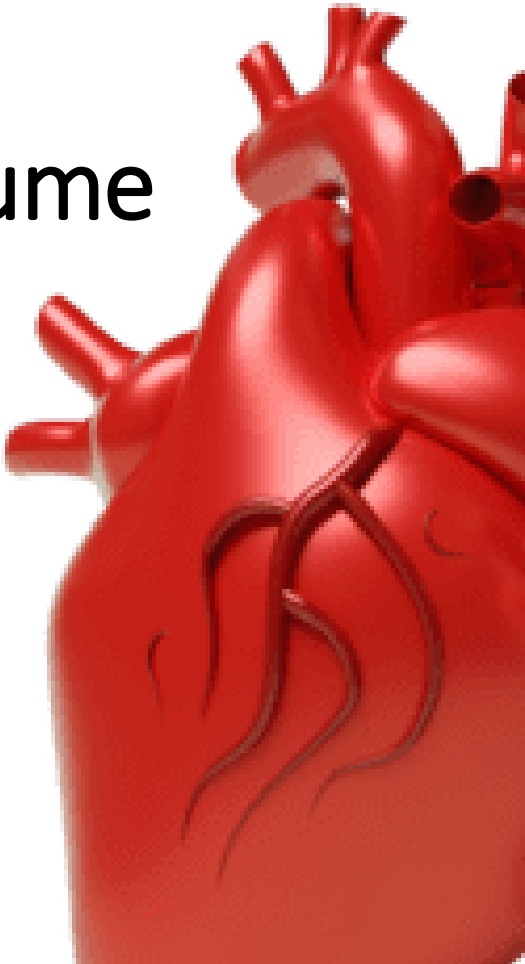
- Vasoactive agents are drugs used in the intensive care units and operating rooms to maintain patients' key hemodynamic variables such as **blood pressure**, **heart rate**, **cardiac output**, and **end-organ perfusion** within normal ranges.
- They have been classified based on their relative effects on the heart and vascular tone into inotropes and vasopressors.

Inotropic effect:
Increased contractile function of the heart leading to increased cardiac output.

Vasopressor effect :
Increased vascular tone leading to increased peripheral vascular resistance, and by extension increased arterial blood pressure.



Cardiac output = heart rate (beats/min) × stroke volume (mL/beat)



Significant receptors of vasoactive agents

Alpha 1 receptor:
located in the smooth muscle of blood vessels. They cause constriction and increase vascular resistance (vasoconstriction).

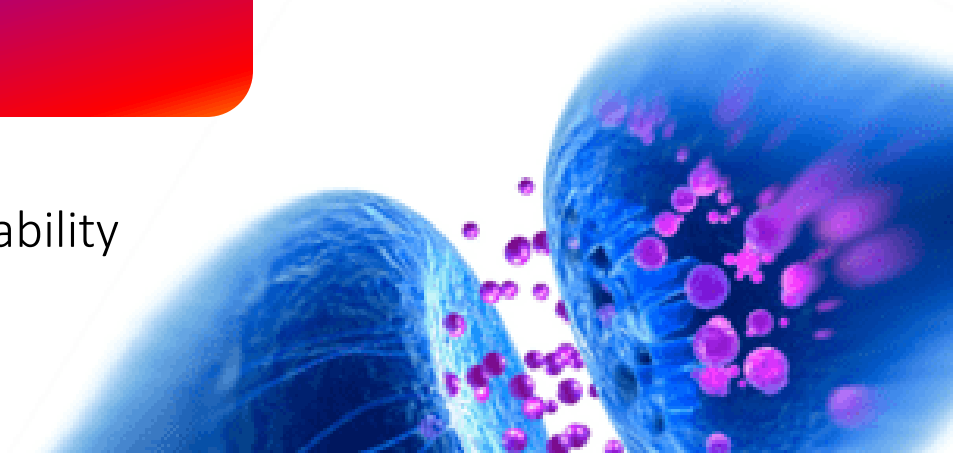
Beta 1 receptor:
located in the heart. Stimulation primarily causes increase in heart rate (chronotropy) and contractility of the myocardium (inotropy), leading to increased cardiac output.

Beta 2 receptor:
located in the vascular and bronchial smooth muscles. Stimulation primarily causes relaxation of vascular and bronchial smooth muscles causing vasodilation and bronchodilation.

Dopamine receptor:
In the myocardium, stimulation causes increased contractility, heart rate, and cardiac output. In the kidneys, dopamine receptor D1 and D2 stimulation causes diuresis.

Vasopressin 1 receptor:
causes moderate vasoconstriction in the peripheral arterioles.

Vasopressin 2 receptor:
causes increased water permeability at the renal tubules.



Norepinephrine

- Norepinephrine is a potent agonist of α-1 and β-1 adrenergic receptors commonly used in distributive shock to induce **vasoconstriction** and increase MAP, with minimal impact on heart rate.
- As a result of its dual effects, it can increase systemic vascular resistance without significant increase in heart or decrease in cardiac output.
- It is recommended as the **first-line drug** for treating septic shock, according to the Surviving Sepsis guideline 2021. Studies have shown that after adequate volume resuscitation, noradrenaline increases urine output and creatinine clearance in septic patients.
- Studies comparing norepinephrine with dopamine and epinephrine for shock reversal have demonstrated similar outcomes in terms of shock reversal, with norepinephrine potentially with fewer adverse side effects. Thus making a case for its use as **first-line vasoactive medication** of choice in all shock types.

Norepinephrine

- Unstable in alkaline solutions; should be diluted in dextrose or half-saline solution.

Doses:

Continuous IV/IO infusion: 0.05–0.1 mcg/kg/min

Titrate to desired effect

Usual maximum dose: 2 mcg/ kg/min

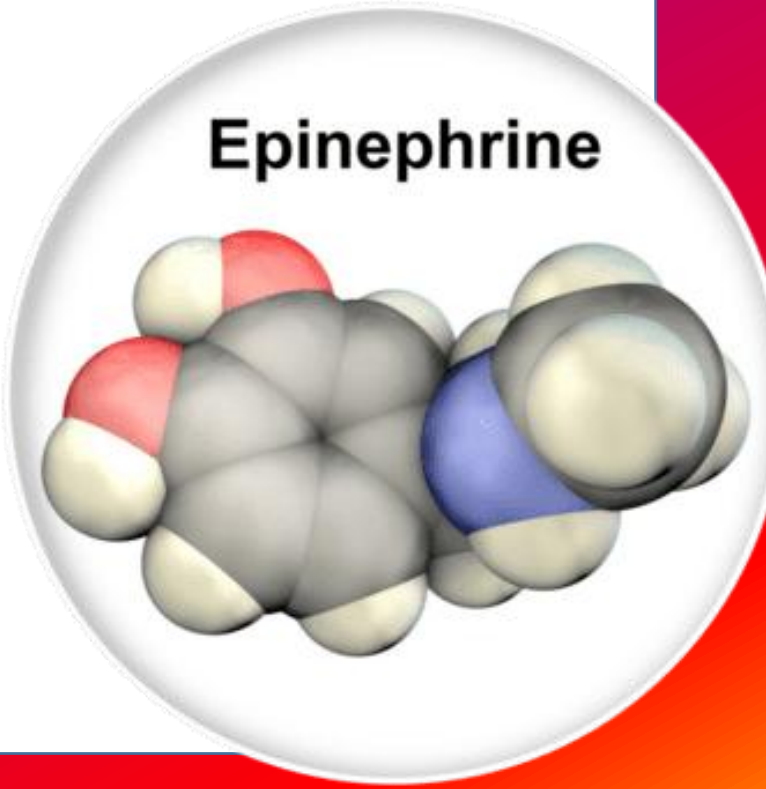
Higher doses have been also reported

Epinephrine

- Epinephrine has dose-dependent receptor affinities for α and β adrenergic receptors. At low-to-moderate doses, β effects predominate, leading to inotropic support in addition to vasoconstriction. Epinephrine will **increase heart rate** and blood pressure as a result.
- Historically, this mechanism makes epinephrine a preferred agent in the treatment of cardiogenic shock syndromes, particularly when inotropy or cardiac "squeeze" is needed in addition to blood pressure support or in the treatment of **symptomatic bradycardia**.
- Additionally, because epinephrine affects β-1 and β-2, it is the drug of choice for **anaphylactic shock**.
- Some adverse effects unique to epinephrine include **induction of a type B lactic acidosis**, **increased insulin resistance**, and **tachycardia**.

Epinephrine

- Has dose-dependent activity:
- Low doses (<0.05–0.1 mg/kg/min) produce vasodi_x0002_latation (β2 receptors).
- High doses (>0.1 mg/kg/min) produce vasocon_x0002_striction (α receptors) of the skeletal and vascular smooth muscles with a subsequent increase in myocardial oxygen consumption.



Phenylephrine

- Phenylephrine acts as a selective agonist of α-1 receptors, exerting minimal or no activity on β receptors. This pharmacological profile makes it an optimal choice for elevating MAP through venous vasoconstriction.
- Phenylephrine has demonstrated effectiveness in mitigating hypotension commonly encountered with both general and neuraxial anesthesia.
- Additionally, its rapid onset of action and short half-life render it particularly suitable for use during surgical procedures when there are transient periods of hypotension from decreases in MAP.

Phenylephrine

Doses:

IV bolus: 5–20 mcg/kg/dose every 10–15 min as needed (maximum of 500 mcg/dose)

Continuous IV infusion: usual initial dose, 0.1–0.5 mcg/kg/min; titrate to the desired response

Dopamine

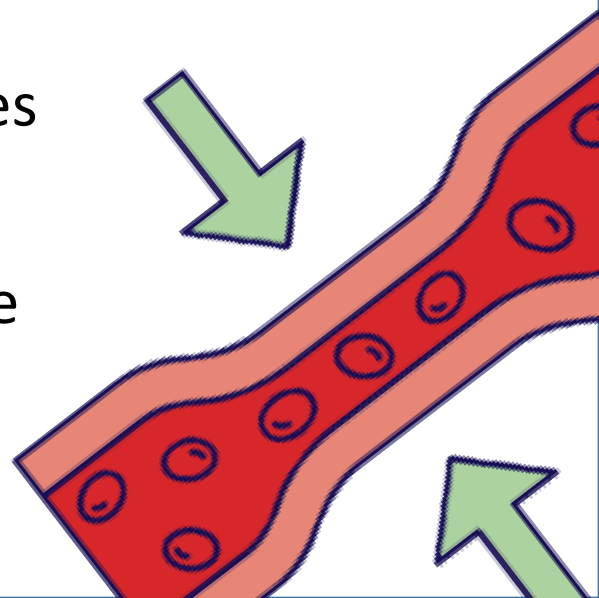
- Dopamine is likely the most ‘promiscuous’ vasopressor in terms of receptor activity and associated effects.
- At lower doses of 0–5 mcg/kg/min, dopamine mostly exerts its action via the dopamine receptors which leads primarily to inotropy and renal vasodilation as well as bloodflow.
- At moderate doses of 5–10 mcg/kg/min, dopamine becomes more similar to epinephrine, exerting its action on dopamine and primarily beta-adrenergic receptors, shifting its hemodynamic effects to inotropy.
- At doses >10 mcg/kg/min, dopamine has alpha receptor properties

leading to vasoconstriction.

- Dopamine is less favored as a vasopressor due to the results of the

SOAP II study with higher incidence of arrhythmia compared

to norepinephrine.



Vasopressin

- Stimulates the arginine vasopressin V1 receptors resulting in increased systemic vascular resistance, and V2 receptors causing increased water permeability at the renal tubules (anti-diuretic effect).
- Vasopressin receptors are not located in the pulmonary vasculature making it a suitable option for patients with right-sided heart failure, cardiopulmonary bypass, or pulmonary hypertension.
- It is recommended as an addition when there is an increase in noradrenaline requirement (usually > 0.2 mcg/kg/min).
- Adjunct therapy in the treatment of massive GI bleeding (terlipressin).
- **Doses:**

Continuous IV infusion: 0.08–10 milliunits/kg/min (0.004–0.6 units/kg/h); start with the lower range of the dose and titrate to effect.

Milrinone

- A selective phosphodiesterase III inhibitor that results in vasodilation, improved cardiac contractility (inotropy), diastolic relaxation (lusitropic effect), with little chronotropic activity.
- Decreases PVR in patients with pulmonary hypertension secondary to severe heart failure, and improve lung compliance.
- A first-line agent for children post cardiac surgery for treatment of low cardiac output syndrome (LCOS).
- An option for children with pulmonary hypertension and vasoconstrictive septic shock.
- IV/IO: Loading dose (optional) 50 mcg/kg over 10–60 min, followed by a continuous IV or intraos_x0002_seous infusion 0.25–0.75 mcg/kg/min; titrate dose to effect.

Levosimendan

- A calcium-sensitizing agent increases the sensitivity of the myocardium to calcium, resulting in potent positive inotropic effects and systemic vasodilation.
- Has a highly active metabolite with a long elimination half-life of 75–80 h; therefore, its cardiac effects last for up to 7–9 days after discontinuation of a 24-h infusion.
- Correct electrolytes before starting

levosimendan infusion.

- Electrolytes, renal function, blood gases must

be monitored.

- Continuous cardiac monitoring is needed.

Levosimendan

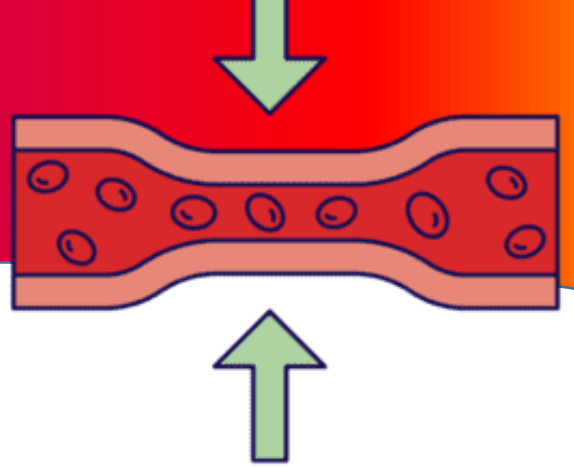
Doses:

- Loading dose 6–12 mcg/kg over 10–30 min, followed
- by an IV infusion of 0.05–0.1 mcg/kg/min; double the
- dose as tolerated every 2–3 h to a target dose of 0.2
- mcg/kg/h; continue infusion for a total of 24–48 h

Do not give a bolus dose to the hypotensive patient

- Use lower loading dose of 6 mcg/kg in case of con_x0002_comitant vasodilators or inotrope infusion

Angiotensin II



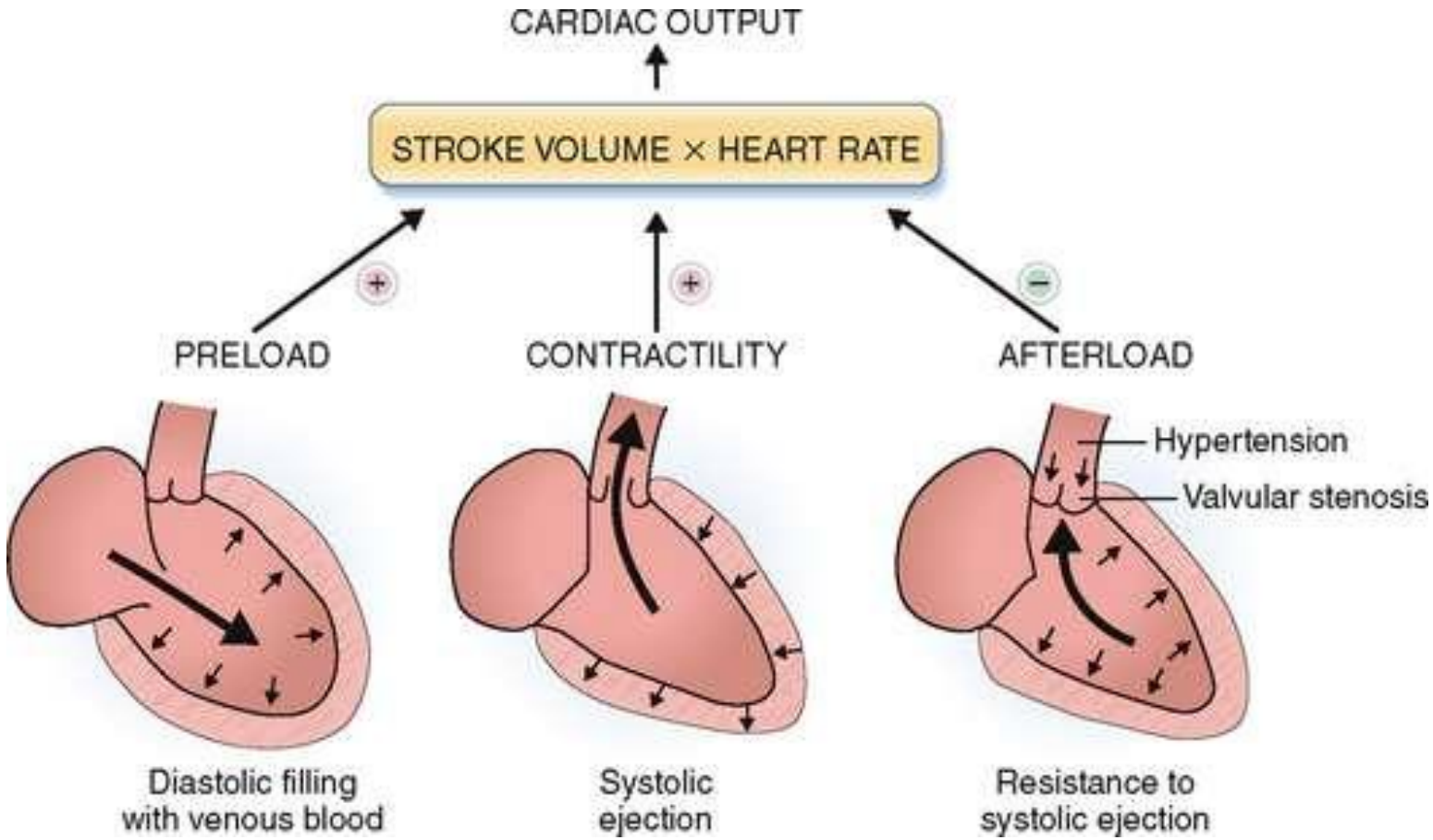
- A potent vasoconstrictor that acts directly on the smooth muscles of blood vessels causing vasoconstriction.
- It also stimulates the release of aldosterone leading to sodium and water retention.
- Approved in the USA (December 2017) and in the European Union (August 2019) for use as a second-line vasopressor for the treatment of catecholamine-refractory distributive shock.

Other vasoactive drugs

- Methylene blue:
- Metaraminol:
- Corticosteroids:

The principles of vasoactive therapy

- Consider the indication for therapy.
- Define the therapeutic targets e.g. MAP>65mmHg; Lactate<2
- Titrate drugs to the lowest dose to achieve the therapeutic targets.
- Use drugs with complementary mode of action e.g. dopamine/dobutamine/epinephrine (predominant beta-1 receptor agonists), and noradrenaline/vasopressin (predominant alpha-1 receptor agonists).
- Ensure adequate fluid rescucitation/filling to optimise preload. Fluid administration complements vasoactive drug therapy especially in fluid responsive patients. Caution must be taken in circulatory shock.
- Route of administration should be via a central line whenever possible to facilitate systemic distribution and prevent peripheral extravasation.


CARDIAC OUTPUT
STROKE VOLUME × HEART RATE
+
+
−
PRELOAD
CONTRACTILITY
AFTERLOAD
Hypertension
Valvular stenosis
Diastolic filling
with venous blood
Systolic
ejection
Resistance to
systolic ejection

Facts to consider about vasoactive therapy

- One drug activates many receptors leading to different effects; e.g., dobutamine activates β1 receptors that increase CO, and β2 receptors that induce vasodilation and hypotension.
- Dose-dependent action; e.g., smaller doses of dopamine stimulate β1 receptors whereas higher doses stimulate alpha receptors.
- Direct versus reflex actions of some agents; e.g., acti_x0002_vation of β1 receptors by norepinephrine increases HR. In addition, it activates alpha receptors inducing vasoconstriction and MAP elevation. The latter action causes a reflex decrease in the HR leading to offsetting the tachycardic effect.
- Tachyphylaxis may occur over time leading to loss of effect, which necessitates constant titration of the dose.
- Subcutaneous delivery of medications such as heparin and insulin may be decreased by cutaneous vasoconstriction caused by vasopressors.
- Neonates may have less inotropic response compared with older children due to immaturity of the autonomic nervous system.

Monitoring patients on vasoactive therapy.

- Continuous monitoring of **cardiovascular** parameters for improvement and side-effects.
- Fluid status, electrolytes, glucose, lactate levels, and acid-base status.
- **Arterial blood pressure** via catheter allows for immediate recognition of changes and precise titration.
- Pulmonary artery catheters may be considered to assess cardiac function.

Thank you for listening.

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