INOTROPES

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PEDIATRIC INTENSIVIST

IUMS

- Catecholamines modify cellular physiology through their interaction with specific adrenergic receptors.
- The classic paradigm of α and β classes of adrenergic receptors remains unchanged, although new subtypes and sub-subtypes continue to be identified.
- Currently, three subtypes of α 1 -receptors (A, B, and D), three subtypes of α 2 -receptors (A, B, and C) and three subtypes of β-receptors (β 1 , β 2 , and β 3) are recognized.

- Agents that stimulate β 1 -adrenergic receptors also tend to increase heart rate modestly unless other properties of the drug prevent this increase.
- Some inotropic agents also activate β 2 -receptors, promoting peripheral vasodilation and reflex tachycardia.
- The improvement in cardiac output produced by these agents may also permit a reflex relaxation of vascular tone and systemic vascular resistance (SVR).

- Typically, vasopressors engage α 1 -adrenergic receptors, causing contraction of vascular smooth muscle.
- In principle, the physician will use a vasopressor agent to treat peripheral vasoplegia and an inotropic agent when the major problem is impaired cardiac contractility
- Most available agents display a blend of inotropic, chronotropic, and vasopressor activity that is often dose dependent

- Data suggest that α 1 -receptors may display cardioprotective effects, including :
- activation of adaptive hypertrophy, increased contractility, and prevention of myocyte death.

- In vascular smooth muscle, medium light chain kinase is activated and phosphorylates myosin light chain 2, leading to smooth muscle contraction. A similar mechanism underlies the inotropic effect of the α 1 -receptor in the myocardium.

- Vascular smooth muscle contraction is mediated via α 1 - adrenergic receptors, of which there are three subtypes
- α 1A - and α 1B -receptors are thought to be involved in both the heart and vasculature
- While α-receptors may have less inotropic effect than β-adrenergic receptors, they do have significant effects in the myocardium. Interestingly, in patients with heart failure, downregulation of β-receptors has been noted while α-receptors are preserved

- Some agents increase the sensitivity of the myocardial contractile apparatus to calcium, causing an increase in myofilament tension development and myocardial contractility (eg, pimobendan, levosimendan).

- These agents have additional pharmacologic properties, such as phosphodiesterase inhibition, which may increase inotropy and vasodilation and contribute significantly to their clinical profile,

- patient’s response to a given dose depends on underlying condition, hemodynamics, and adrenergic receptor status, and highlights the importance of titration to individual response when using catecholamines in critically ill patients.

Dopamine

- Low infusion rates of dopamine augment renal sodium excretion;
- intermediate rates (5–10 μg/kg per minute) produce chronotropic and inotropic effects,
- and still higher infusion rates increase vascular resistance.
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- Renal blood flow, glomerular filtration rate, and sodium excretion are maintained or even increase during dopamine infusion in patients with poor cardiac output.

- The augmentation in urine output seen in patients with poor cardiac output who are started on low-dose, “renal” dopamine results from improved renal blood flow rather than a direct, receptor-mediated diuretic effect on the kidney.

- Dopamine has been shown to be an effective inotropic and vasopressor agent in neonates and infants with a variety of conditions associated with circulatory failure. Fewer data evaluating the efficacy of dopamine in older children are available.

- Until recently, dopamine was used as a first-line treatment in children with fluid refractory septic shock or distributive shock, but updated guidelines for the management of septic shock now recommend norepinephrine or epinephrine as the agent of choice.

- Dopamine may be appropriate for children with mild impairment of myocardial function

- Dopamine depresses the ventilatory response to hypoxemia and hypercarbia by as much as 60%.

- β-Agonists, including dopamine, decrease partial pressure of arterial oxygen by interfering with hypoxic vasoconstriction.

- Severe impairment of vascular tone or cardiac contractility are indications for other agents, and children with primary myocardial disease not complicated by hypotension will benefit from a more selective inotropic agent such as milrinone or dobutamine.

- Infusion rates of dopamine necessary to improve signs of severe myocardial dysfunction may be associated with tachycardia, dysrhythmia, and increased myocardial oxygen consumption—these adverse effects often outweigh any potential benefit.

- In the absence of hypotension, acute severe cardiac failure is best treated with dobutamine or milrinone.

- When septic or cardiogenic shock is complicated by severe hypotension, epinephrine or norepinephrine is preferred, depending on hemodynamics and myocardial function

Epinephrine

Its alpha-agonist effects include increased peripheral vascular resistance, reversed peripheral vasodilatation, systemic hypotension, and vascular permeability.

Its beta2-agonist effects include bronchodilation, chronotropic cardiac activity, and positive inotropic effects.

- Evidence indicates that changes in myocardial oxygen consumption are disproportionate to the increase in force of contraction, thereby decreasing myocardial efficiency.
- High concentrations of epinephrine or exposure to the compound when the myocardium is sensitized by infarction, operation, or myocarditis may produce serious atrial and ventricular dysrhythmias

- At low plasma concentrations, stimulation of peripheral β 2 -receptors promotes relaxation of resistance arterioles; SVR decreases and diastolic blood pressure falls.
- The decrease in SVR enhances the direct chronotropic effect of epinephrine.

- Epinephrine is used to treat shock and low cardiac output states associated with myocardial dysfunction. Thus, it is appropriate for treatment of cardiogenic shock or for inotropic support following cardiac surgery
- Epinephrine is most likely to be useful in patients with sepsis and “cold shock,” that is, in the setting of poor perfusion and low cardiac index that does not respond to fluid resuscitation.

- Epinephrine is first-line treatment for severe anaphylaxis in both the prehospital and hospital settings, and the case fatality rate from food-related anaphylaxis has declined since the introduction of the epinephrine autoinjector
- Epinephrine is the most frequently used medication during pediatric cardiopulmonary resuscitation
- This was attributed to improved coronary (and therefore myocardial) perfusion from an increase in aortic diastolic pressure.

- Epinephrine produces CNS excitation manifested as anxiety, dread, nausea, and dyspnea.
- Enhanced automaticity and increased oxygen consumption are the main cardiac toxicities.
- Extreme tachycardia carries a substantial oxygen penalty, as does hypertension.
- A severe imbalance of myocardial oxygen delivery and oxygen consumption produces characteristic electrocardiogram changes of ischemia.

Isoproterenol

- Isoproterenol is the synthetic N-isopropyl derivative of norepinephrine

- The bulky N-terminal substituent confers β 1 - and β 2 -receptor specificity; the compound does not affect the α-adrenergic receptor. Thus, the principal cardiovascular activities of isoproterenol relate to its inotropic, chronotropic, and peripheral vasodilator effects

- Isoproterenol enhances cardiac contractility and heart rate. Peripheral vasodilation produces a fall in SVR, augmenting the direct chronotropic action of the drug. Significant tachycardia ensues. Systolic blood pressure increases while mean and diastolic pressures fall
- Isoproterenol increases myocardial demand for oxygen and decreases supply by reducing diastolic coronary filling. Hypotension may complicate initiation of isoproterenol infusion in volume-depleted patients.

- Isoproterenol may be used to treat hemodynamically significant bradycardia. However, epinephrine is often preferable.
- When bradycardia results from heart block, isoproterenol may be used in the acute setting as a bridge to pacemaker placement.

Norepinephrine

- Norepinephrine is used for protracted hypotension following adequate fluid-volume replacement. This agent stimulates beta1- and alpha-adrenergic receptors, thereby increasing cardiac muscle contractility and heart rate, as well as vasoconstriction.

- norepinephrine has little β 2 activity and is considerably less potent at that receptor than epinephrine.

- Reflex vagal activity reduces the rate of sinus node discharge, blunting the expected β 1 -chronotropic effect. In normal subjects renal, splanchnic, and hepatic blood flows decrease.
- The increase in afterload may augment coronary blood flow. This effect may be enhanced by α-adrenergic receptors located in the coronary arteries, although in coronary arteries from explanted human hearts, the vasodilation in response to norepinephrine was mediated via β 2 -receptors

- Norepinephrine does have inotropic effects on the heart, mediated via α 1 - and β 1 -receptors. The degree of inotropic response related to α 1 stimulation may be affected by the pressure load on the right ventricle.
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- In healthy volunteers, norepinephrine produces a decrease in creatinine clearance because of the effect on renal blood flow. However, in patients with hypotension, the improvement in global perfusion produces an increase in urine output.

- Norepinephrine improves perfusion in children with distributive or septic shock who are hypotensive but in whom cardiac output is preserved or elevated
- norepinephrine is now recommended for warm shock refractory to fluid loading in children.
- high-dose norepinephrine is superior to high-dose dopamine for treating hypotension associated with hyperdynamic septic shock.

- Norepinephrine is most valuable in the context of tachycardia because, unlike dopamine, at doses required to induce a vasopressor effect, norepinephrine does not elevate and may even lower heart rate through reflex mechanisms

- The increase in afterload that norepinephrine produces can potentially increase myocardial oxygen consumption, but norepinephrine may reflexively decrease heart rate, reducing oxygen consumption and improving diastolic coronary perfusion.
- Norepinephrine may lead to compromised organ blood flow in the setting of hypovolemia and may elevate blood pressure without improving perfusion.

- Summary
- Norepinephrine is the agent of choice in patients with hypotension with low SVR and a normal or high cardiac output after fluid resuscitation.
- Recent septic shock guidelines recommend norepinephrine as the first-choice vasopressor in patients with warm (vasodilatory) shock.
- It is frequently useful in other conditions associated with distributive shock.

Dobutamine

- In healthy children, dobutamine increased left ventricular systolic function and relaxation.

- Dobutamine is a relatively selective inotrope with little effect on heart rate at usual infusion rates.
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- However, in all studies, dobutamine improved cardiac contractility without substantially altering heart rate unless high infusion rates were employed.

- dobutamine has been shown to increase cerebral blood flow velocity but not cerebral oxygen consumption in patients with septic shock.

- Dobutamine is not first-line therapy for septic shock unless the primary disturbance is complicated by myocardial dysfunction.
- Although impaired myocardial performance can be demonstrated early in patients with septic shock, the main problem relates to regulation of vascular tone, and agents that increase SVR are preferred.
- When ventricular dysfunction complicates clinical management, dobutamine may be a useful adjunct.

- dobutamine alone or in combination with dopamine has produced an increase in cardiac output, left ventricular stroke work, and blood pressure.
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- dobutamine can be combined with norepinephrine in treating the patient with myocardial dysfunction associated with hyperdynamic shock (i.e., a child with septic shock who has received cardiotoxic chemotherapy).

- Specific indications for dobutamine in the pediatric age group include low-output CHF and a normal to moderately decreased blood pressure

- Adverse cardiovascular effects include hypertension, tachycardia, and ectopic heart beats. Headache, nausea, vomiting, paresthesia, and dyspnea may also occur.
- Dobutamine also may decrease serum potassium concentrations
- Dobutamine usually increases myocardial oxygen demand.
- In subjects with myocardial dysfunction, coronary blood flow and oxygen supply improve with the increase in demand.

- Although dobutamine is less likely than other catecholamines to induce serious atrial and ventricular dysrhythmias, these may occur, particularly in the context of myocarditis, electrolyte imbalance, or high infusion rates.
- Dobutamine and other inotropes should be administered cautiously to patients with dynamic left ventricular outflow obstruction, as in hypertrophic obstructive cardiomyopathy.
- Prolonged infusion of dobutamine may inhibit platelet aggregation

VASOPRESSIN

- Its main function is to preserve fluid balance in the organism.
- In humans, it is released in response to two main stimuli: increases in plasma osmolality and decreases in effective circulating volume or blood pressure
- Although vasopressin has long been used for the treatment of diabetes insipidus, its name derives from its vasopressor effect. Vasopressin also acts as a neurotransmitter in the CNS, has a role regulating adrenocorticotropin hormone release, and is involved in thermoregulation, platelet aggregation, and smooth muscle contraction in the uterus and gastrointestinal tract.

- In the peripheral vasculature, intracellular calcium is increased, enhancing contraction and restoring systemic vascular tone. Vasopressin also inhibits potassium channels, further increasing intracellular calcium.
- Baroreceptors in the left atrium, left ventricle, and pulmonary veins sense changes in volume
- baroreceptors in the carotid sinus and aorta sense changes in arterial pressure.
- Decreased pressure leads to a reduced rate of firing and release of the tonic inhibition of vasopressin release

- Vasopressin is a potent vasoconstrictor when present in the plasma at high concentrations.
- At the lower concentrations associated with the vasopressin response to hyperosmolality, it actually induces vasodilation in the pulmonary, renal, and cerebral circulation via the V 2 -receptor or oxytocin-mediated nitric oxide release.

- It does not elevate blood pressure because an associated decrease in heart rate offsets the increase in SVR.
- For this reason, vasopressin was not originally considered to be a clinically useful agent to treat hypotension.

- Surprisingly, plasma levels of vasopressin were not elevated in patients with septic shock as compared with those with cardiogenic shock, whose plasma levels were nearly 10 times greater.
- Plasma vasopressin levels are inappropriately low in patients with vasodilatory septic shock, possibly due to impaired baroreflex-mediated secretion.
- The authors hypothesized that this phenomenon contributes to the hypotension of vasodilatory septic shock.

- In a prospective, randomized study, the combination of vasopressin at a dose of 0.06 U/min and norepinephrine was compared with norepinephrine alone in patients with catecholamine-resistant vasodilatory shock.
- The patients in the vasopressin-norepinephrine arm had a lower heart rate and higher blood pressure, SVR, and cardiac index.
- They also had reduced requirements for norepinephrine and a lower rate of new-onset dysrhythmias. Gastric perfusion also was better preserved in the vasopressin group.

- In summary, in studies of patients with vasodilatory shock, vasopressin has been shown to improve blood pressure, increase SVR, lessen the need for catecholamines, improve markers of myocardial ischemia, and improve urine output

- Standard dosing for vasopressin in vasodilatory shock has not been determined, but the dose used in a recent pediatric study ranged from 0.0005 to 0.002 U/kg per minute

- Prior to the 2015 guidelines, vasopressin was added to the Advanced Cardiac Life Support protocol for ventricular fibrillation in adults.
- However, there is insufficient evidence to make a recommendation either for or against its use in children who sustain a cardiac arrest

- Its major advantage is in the lack of dependence on adrenergic receptors, which are known to be downregulated in septic shock
- Studies to date in adults and children have not shown a benefit in reducing mortality or in decreasing intensive care mortality or ICU length of stay.
- Vasopressin should not be used in settings in which impaired myocardial function is the principal problem.
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Milrinone

- In both adults and children, milrinone acts as an inotrope and vasodilator, producing a direct reduction in preload and afterload.
- Administration to subjects with CHF results in increased cardiac index and reduced SVR, central venous pressure, and pulmonary capillary occlusion pressure, while heart rate is not affected.

- Patients experience a greater reduction in left and right heart filling pressures and SVR with milrinone than with dobutamine, even at equivalent contractility dosing.
- Improvement in global hemodynamic function is associated with a more favorable ratio of myocardial oxygen delivery to consumption.
- Blood pressure is usually maintained, even in the face of reduced SVR, because of the associated improvement in contractility and stroke volume.

- Increasing doses of milrinone have been shown to correlate with increasing mixed venous oxygen saturation.

- Milrinone may improve contractility in patients who fail to respond to catecholamines and may further augment cardiac index in patients being treated with dobutamine.

- Caution is advised when administering milrinone to patients who are intravascularly volume depleted or in whom improvement in cardiac output does not occur, as hypotension may result

- Milrinone's properties as a pulmonary vasodilator have made it a useful adjunct in the treatment of pulmonary hypertension.

- Milrinone is not physically compatible with furosemide but is compatible with many drugs used in the PICU, including dopamine, epinephrine, fentanyl, and vecuronium.

- Milrinone may be administered safely through a peripheral intravenous catheter.

- milrinone may cause hypotension in patients with intravascular volume depletion and in patients with renal dysfunction in whom drug clearance is reduced.

- Milrinone has been cited as a risk factor for early postoperative tachyarrhythmias in patients following congenital cardiac surgery.

- Milrinone is the primary phosphodiesterase (PDE) inhibitor used in pediatrics, and it works via a different mechanism than that of the catecholamines.
- Milrinone inhibits PDE III, producing an increase in intracellular cyclic adenosine monophosphate (cAMP), which raises intracellular calcium levels and thereby improving cardiac inotropy and peripheral vasodilation.

- Milrinone may be used together with catecholamines to further increase myocardial contractility while reducing systemic vascular resistance (SVR) and afterload. It can be useful in improving perfusion in patients who remain in compensated shock with poor peripheral perfusion but a normal central blood pressure and adequate intravascular volume.
- Milrinone is also often a useful adjunct in patients who have low cardiac output syndrome following congenital heart corrective surgeries.
- Adverse effects of milrinone may include arrhythmias and thrombocytopenia

Conclusion

- Significant advances have been made in our understanding of the mechanisms underlying adrenergic receptor signaling, the control of vascular tone, and the influence of genetic polymorphisms on the pathways involved in these processes.
- Despite this broader fund of knowledge, the therapeutic options for supporting the patient with impaired end-organ perfusion remain essentially unchanged.
- The catecholamines comprise the mainstay of therapy for patients in need of inotropic or vasopressor support.

- Although dopamine is still used, epinephrine and norepinephrine are now preferred for patients with poor cardiac performance or decreased systemic vascular tone, respectively.

- Milrinone or dobutamine can be used to increase myocardial contractility in the absence of hypotension.
- Milrinone is particularly useful after cardiac surgery.
- Vasopressin has emerged as an option for vasodilatory shock that is resistant to catecholamine therapy. Often, the clinical picture is mixed, and the patient may require both inotropic and vasopressor support.
- Careful attention to hemodynamics and end-organ perfusion and a thorough understanding of cardiovascular pharmacology are necessary in order to select the agent(s) that will provide the optimal results in critically ill patients.