Pediatric Cardiac Intensive Care

Vasoactive and Inotropic therapy in PICU

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Introduction
Pharmacological support for the circulatory system is an integral part of intensive care. These vasoactive drugs aim to improve perfusion pressure by increasing cardiac output and modulating the vascular tone. Cardiac output (CO) can be increased by optimising preload (with adequate fluid resuscitation), and by augmenting myocardial contractility (Inotropy), enhancing diastolic relaxation (Lusitropy — thereby improving coronary circulation), and sometimes by increasing heart rate (Chronotropy) while some of the medications as well as mechanical ventilation itself help with reducing the afterload. Various agents have traditionally been used in different clinical scenarios. We review the current available evidences and recommendations on use of various vasoactive and inotropic medications in the Pediatric intensive care settings.

Physiological considerations
Before we embark on the clinical applications — it is worthwhile to recap the physiology and pharmacology of the different agents. We will only briefly consider those aspects which are clinically important for an Intensivist. For a detailed discussion on these — the reader may consult any standard pharmacology textbook.

Receptor subtypes
The classical Inotropes act via different receptors. They are as follows -

Adrenergic receptors

Alpha 1
They are present on vascular smooth muscles, sphincters of gastrointestinal(GIT) and urinary tract and muscles of the iris. Their activation leads to vasoconstriction leading to increased systemic vascular resistance(SVR) and therefore increased blood pressure(BP) and reduced blood flow to the organs. They also lead to contraction of the sphincters and dilated pupil.

Alpha 2
They are present in central nervous system(CNS) as well as in blood vessels, GIT and other areas. Their predominant function is to decrease release of nor-epinephrine(NE) from pre-synaptic membrane by negative feedback. They are not clinically important as far as Inotropes are concerned although they have clinical use as anti-hypertensives and sedatives.

Beta 1
They are present in the heart and kidney. Their stimulation leads to increased rate of phase 4 depolarisation in sino-atrial (SA) node and increased velocity of conduction through atrio-ventricular (AV) node. This leads to increased heart rate (+ve chronotropy). It also leads to increased contractility of the myocardium (+ve inotropy) thereby increasing stroke volume. Both effects augment CO. Beta 1 stimulation also leads to increased renin release from the kidneys.

Beta 2
They are present in smooth muscles of airway, blood vessels, uterus, detrusor muscle of urinary bladder, liver .. They are also present in the myocardium - although much less predominant than Beta 1. Their stimulation leads to bronchodilation, vasodilatation - mostly in muscles and increased blood sugar due to glycogenolysis and neo-glucogenesis in liver among other effects. It also has some +ve chronotropic and +ve inotropic effect.
**Dopaminergic receptors**

There are five types of them which are divided into two sub-types - D1 like (D1 and D5) and D2 like (D2, D3 and D4). As far as cardiovascular system (CVS) is concerned - D1 and D4 receptor stimulation cause increased contractility of the myocardium but the effect is less pronounced than beta receptor effects. In the vasculature - D1 activation cause vasodilatation - mostly of renal and mesenteric vessels; activation of D2 receptor cause either constriction or dilatation depending on the location of the vascular bed. Overall effect remains coronary vasodilatation.

**Pharmacology of individual agents**

**Epinephrine (Adrenaline)**: It stimulates all adrenergic receptors leading to increased contractility, heart rate and SVR. Increased contractility causes increased stroke volume. Increased stroke volume combined with increased heart rate leads to increased CO. Increased CO combined with increased SVR leads to increased systemic and pulmonary BP. At low dose - Beta affects predominate and Alpha effect i.e., vasoconstriction become more pronounced at higher doses. As heart rate and SVR rise – cardiac oxygen demand also increase. However, coronary vasodilatation due to local effects leads to increased coronary flow. Beta effects cause hyperglycemia. Epinephrine also increases lactate production and therefore contributes to metabolic acidosis. However, there is no evidence to suggest that this increase in lactate is associated with any adverse outcome.

Dose range - .05 - 1 mcg/kg/min

**Norepinephrine (Noradrenaline)**: This is mostly a pressor agent causing intense vaso-constriction and increased SVR – thereby increasing both systolic BP(SBP) and diastolic BP(DBP). It also has

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor type</th>
<th>Effect on CVS</th>
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<tr>
<td></td>
<td>α 1</td>
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<tr>
<td>Dopamine</td>
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<td>Dobutamine</td>
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<td>Norepinephrine</td>
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<td>Epinephrine</td>
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<td>Phenylephrine</td>
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<td>Isoprenaline</td>
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that of vasodilatation leading to a fall in SVR.

**Vasopressin receptors**

V1 receptors are widely present in vascular smooth muscle causing intense vasoconstriction. They are also present in the myocardium and most likely have mild +ve inotropic effect. V2 receptors are present in renal collecting ducts making them permeable to water. They are also present in vascular endothelium causing release of coagulation factors. V3 receptors are mostly central and lead to ACTH release. Vasopressin also acts via oxytocin receptors causing nitric oxide (NO) mediated vasodilatation. It also acts via some purinergic receptors in myocardium causing increased contractility and selective vasodilatation.
some +ve inotropic effect. It has minimal +ve chronotropy due to reflex bradycardia which is often advantageous in patients with intrinsic tachycardia. At high dose it can compromise perfusion of mesenteric, renal and cutaneous vasculature which has always been a concern although no clinical study has as yet proved this. It relatively spares both cerebral and coronary circulation.

Dose range - .05 - 1 mcg/kg/min

**Dopamine** :- Dopamine binds to both dopaminergic and adrenergic receptors making its action somewhat complex. At dose range of up to 5mcg/kg/min it predominantly activates dopaminergic receptors leading to increased contractility and vasodilatation mostly in the renal and mesenteric bed. This is the basis of the 'renal dose' of dopamine which has never been substantiated and is now not practiced with the possible exception of post-operative kidney transplant. At 5 - 15 mcg/kg/min – Beta1 effects predominate leading to increased contractility and heart rate – both augmenting CO and SBP with minimal effect on DBP. At >15 mcg/kg/min - Alpha affects predominately causing disproportionate vasoconstriction. This may lead to increased BP at the expense of often reduced CO and markedly increased cardiac oxygen consumption. Dopamine centrally modulates secretion of prolactin, growth hormone, thyroid hormone and possibly glucocorticoids in a complicated manner which might have important neuro-endocrine and immunological effects in critical illness much of which is still unknown.

Dose range - 5 - 20 mcg/kg/min

**Phenylephrine** :- It is effectively a pure Alpha agonist with almost no Beta activity. Consequently, it cause marked vasoconstriction and increase BP which may be associated with reflex bradycardia. Cardiac output may actually fall. It is mostly used as a bolus to correct sudden severe hypotension but may also be used as a vasopressor infusion in refractory cases. Bolus doses are also used to treat hypotension associated with left ventricular outflow tract obstruction like aortic stenosis, hypertrophic cardiomyopathy as it maintains coronary perfusion.

Dose range - 2-10 mcg/kg stat, then 1-5 mcg/kg/min

**Isoproterenol/Isoprenaline** :- This synthetic compound is almost pure non-selective Beta agonist with no Alpha action. So, it increase contractility and cause systemic and pulmonary vasodilatation. Therefore it can even cause hypotension especially if the patient is hypovolaemic. Coronary perfusion may actually fall. It also causes bronchodilation.

Dose range - 0.05 - 1 mcg/kg/min

**Some important common features of all classical adrenergic Inotropes**

These features are common for all agents although individual variations do exist.

A. Half life of epinephrine and nor-epinephrine is 2-2.5 minutes and that of dopamine and dobutamine is 22-25 minutes. So, they are short acting and needs continuous infusions for persistent effect.

B. All needs to be given intravenous(IV) for inotropic effect. Agents with significant pressor effects i.e. norepinephrine, epinephrine, vasopressin and higher concentration of dopamine should be given centrally, as infusion through peripheral veins can cause intense local vaso-constriction and extra-vasation can lead to tissue necrosis and sloughing. However, it is also recognised that getting a central access in small children can be difficult and time consuming. In view of this, in the Pediatric update of 'Surviving Sepsis' guideline, peripheral infusion of epinephrine up to 0.3 mcg/kg/min is recommended. In life saving situations, this might be relaxed while a central access is being obtained but prolonged...
peripheral infusions are definitely not recommended. All inotropes are compatible with each-other and are usually given through a dedicated lumen of the central line which should never be flushed or used for bolus injections.

C. Myocardial oxygen demand is increased by all agents. As heart rate and SVR increase myocardial oxygen demand increase. As heart rate increase, time for diastole i.e. time for coronary perfusion decrease. This can critically affect oxygen delivery to heart at very high heart rates, further compounding the problem.

D. All are arrhythmogenic, especially in higher doses and in presence of electrolyte abnormalities and hypoxia. Dopamine is probably the worst.

E. Correctable factors such as acidosis, either metabolic or respiratory, significantly reduce effectiveness. Various mechanisms have been suggested like reduced sensitivity to calcium, reduced number of receptors, reduced cAMP level .. In animal models – effect of acidosis could often be overcome by using a higher dose to produce the same effect on contractility. Hypoxia also has the same effect on all agents. It seems that effect of hypoxia is more pronounced and could not be overcome by simply increasing the dose. Reduced serum calcium, primarily the free ionic portion – is another correctable and common factor that can reduce effectiveness.

F. Non-correctable factors causing reduced effectiveness: There is a group of patients who do not respond well to inotropes and it is this group who fare badly. Prolonged use often leads to reduced effectiveness in varied clinical scenarios. A number of mechanisms have been suggested like desensitisation and down regulation of receptors, reduced generation of new receptors, down-regulation of adenylate cyclase, G-protein mediated methods. During sepsis endotoxins, nitric oxide(NO), interleukins and relative adrenal insufficiency – all may have roles. Steroid replacement in inotrope resistant shock is often practiced. But as of now, there is no established clinical intervention to address the other non-correctable factors. However, this is an area of active research and future development.

Phospho Diesterase III Inhibitors(PDI)

All classical adrenergic inotropes act via adrenergic receptors. Activated Beta receptors in myocardium and vascular smooth muscles combine with stimulatory G proteins. This stimulates adenylyl cyclase which converts adenosine-tri-phosphate (ATP) to cyclic adenosine-mono-phosphate (cAMP). Phospho diesterases(PD) are a group of 11 iso-enzymes that breakdown cAMP to AMP. PD-III is predominant in myocardium and vascular smooth muscles. PDIs specifically inhibit PD-III and therefore increase cAMP concentration in the myocardium and vascular smooth muscles. PDIs stimulate cAMP associated protein kinases, which leads to increased intracellular calcium concentration in myocardium leading to increased contractility and chronotropy. It also leads to increased calcium concentration in sarcoplasmic reticulum in vascular smooth muscles leading to vasodilatation and reduced afterload in both systemic and pulmonary circulation. They also reduce diastolic dysfunction and make the ventricles more relaxed and receptive during diastole thereby reducing pre-load which is called lusitropy. Therefore, PDIs increase contractility, and reduce both after load and pre-load and are often referred to as inodilators. The overall effect is an increase in CO and therefore perfusion with no or minimal increase in myocardial oxygen consumption. This effect is receptor independent and therefore remains effective in presence of receptor down-regulation. However, the reduced SVR can lead to hypotension specially in hypovolaemic subjects and in situations where the intrinsic SVR is not high and BP is borderline. So, PDIs are useful in situations with a low CO where BP is not low and SVR is high, often with peripheral vasoconstriction. Effect on pulmonary circuit also makes it useful in pulmonary hypertension and acute right ventricular failure. They are commonly used in post-operative cardiac patients and in selected patients with sepsis. There are two main agents namely Milrinone and Inamrinone (previously known as Amrinone).
Hypotension is the main concern. Unlike adrenergic agents, half-life of both milrinone and inamrinone is in hours (Milrinone - 2.3 hours, Inamrinone - 5.8 hours). So, effects are long-standing which makes the potential for hypotension even more concerning. Both agents are known to cause supraventricular, junctional as well as ventricular tachy-arrythmias which is more likely in presence of hypokalemia.

Milrinone is the most widely used PDI. It is mostly excreted in urine making dose adjustment necessary in renal impairment. Inamrinone has an additional disadvantage of inducing thrombocytopenia in 2.4% of patients. So, platelets should be monitored and Inamrinone stopped if platelet count goes below 50,000/cmm.

Milrinone is recommended to start as a bolus of 50 - 75 mcg/kg over 1 hour and then run as an infusion at 0.5-0.75 mcg/kg/min. Inamrinone is started as a bolus of 1 - 3 mg/kg over 1 hour and then run as an infusion at 5 - 15 mcg/kg/min. If there is particular concern about hypotension then the bolus may be reduced or even avoided. Both are incompatible with furosemide.

**Vasopressin (VP)**

Vasopressin is a natural hormone secreted from posterior pituitary and is also known as anti diuretic hormone. It acts via its receptor systems as described before. In normal physiologic states, it has minimal role in maintaining BP and it is primarily involved in maintaining plasma volume or water balance with serum osmolarity being the main regulator. It is now recognised that VP has many other diverse functions like maintaining sleep cycles, hemostasis, temperature regulation. Normal serum level is 4 - 20 pg/ml depending upon serum osmolarity and other factors. However, in shock the level massively increase up to even 1800 pg/ml and it seems VP is another hormone normally produced by body as part of stress response. It is at this level that VP exerts significant control over vascular tone and thereby influences BP. In adult studies, a relative deficiency of VP was found in up to one-third of patients with sepsis. It also seems that normally there is a biphasic response of VP and its level actually drops as the shock state continues. This relative or absolute deficiency constitutes one of the main physiological basis of use of VP in shock. However, pediatric studies have been inconsistent with some studies showing a deficiency while others shown high levels continuing as long as 96 hours after shock. It is well evidenced that unlike adults who almost universally present with a high CO, low SVR, vasoplegic state - pediatric patients present in a variety of states and some may present in a high SVR, low CO state - the so called 'cold shock'. Whether the inconsistency in the level of VP in pediatric studies is a reflection of this and there is a sub-group of pediatric patients who would benefit from VP is not yet clear. VP has a short half-life of 10-20 minutes so needs to be given as an IV infusion. It is mostly metabolised by vasopressinase from kidney and liver. As a pressor agent – it has a number of advantages over classical adrenergic agents. It has no chronotropy which can be very useful as base line heart rate can often be 180-190/min. in pediatric patients. It remains effective even in presence of acidosis. As it has its own receptor system so it remains effective in presence of adrenergic receptor down-regulation. Actually, it seems to potentiante nor-epinephrine by as yet unknown mechanisms. As intrinsic VP level is frequently low in shock states – subjects are often actually found to be highly sensitive to it, so that, even a small dose, which would have no effect in a normotensive, healthy subject can significantly increase BP in a patient with shock. Besides its use as a pressor agent it has other important clinical uses in diabetes insipidus, variceal bleeding .. which will not be covered in this review.

Dose range - It has been extrapolated from adult studies. As a pressor agent the range is 0.0003 - 0.0009 unit/kg/min.

**Choice of inotropes in different Clinical Situations**

**Resuscitation**

Pediatric cardio-pulmonary resuscitation (CPR) has always been an area where finding evidence is very hard. Most of the evidences are extrapolated from either animal or adult studies. Both have serious flaws - especially considering the fact that most
adult arrests are primarily cardiac in origin whereas pediatric arrests are mostly respiratory in origin. Epinephrine has been used for CPR for ages. Although the beginning of this practice was not following any study – it is apparent that it works. It is thought that the vasoconstrictor effect of epinephrine is as important as the inotropic effect to increase the coronary circulation during CPR. Epinephrine is also thought to make the myocardium more likely to respond to defibrillation attempts although no definite evidence is there to support this. The standard IV dose is 0.1 ml/kg of 1:10000 solution i.e. 0.01 mg/kg followed with a flush every 3-5 minutes along with chest compression and positive pressure ventilation. Intra-tracheal dose is taken to be 10 times that of IV dose although IV administration is by far the preferred route. Of course, it can be given intra-osseosus in CPR situations and the dose is same as IV as per standard pediatric life support guidelines. The standard IV dose in adults is 1 mg. These doses are essentially empirical without much evidence and have been questioned. Proportionately the pediatric dose is actually less than the adult dose. There have been adult studies of higher doses of epinephrine of up to even 5 mg compared with standard dose. Although, return of spontaneous circulation (ROSC) was often found to be higher with larger doses – they have mostly failed to translate to higher survival to hospital discharge or neurologically intact survival. As a result, the current recommendation remains to use the standard dose.

It was found that subjects who were successfully resuscitated had higher vasopressin levels compared to non-survivors. This has led to the use of vasopressin in CPR scenarios. In a large adult study of more than 1000 out of hospital arrests, people with asystole receiving 40 units of VP were more likely to get admitted to hospital than those receiving standard dose of epinephrine. Indeed, the ability of VP to increase BP by increasing SVR and at the same time increasing flow in the coronary, pulmonary and cerebral circulation seems to be ideally suited for the CPR situation. Both the current (2010) American Heart Association and the European Resuscitation Council adult guidelines have mentioned 40 units of vasopressin as an alternative to epinephrine. There are some pediatric retrospective case series of use of vasopressin 0.4 unit/kg/dose during prolonged CPR with variable outcomes. The largest such series has shown that it is still used only in 5% of arrests, used only after prolonged arrests and is actually associated with worse ROSC but no difference in discharge survival. At present there is no definite recommendation for vasopressin use in CPR.

**Septic Shock**

Sepsis is definitely one of the commonest if not the commonest indications for inotropes. Much of pediatric practice is extrapolated from adult evidence, but this is an area where significant differences do exist. In adult practice, the current situation is rather settled. It is now well evidenced that almost all adult sepsis patients present in a state of profound vasoplagia with high CI and low SVR and primarily needs a vasopressor – Dopamine and Nor-Epinephrine being the two obvious contenders. The Sepsis Occurrence in Acutely Ill Patients (SOAP) study, which involved 1058 patients who were in shock, showed that the administration of dopamine was an independent risk factor for death in the intensive care unit. Dopamine has been found to be associated with higher heart rate and more arrhythmic events than nor-epinephrine. This increase in arrhythmia is also found in the latest Cochrane review. This has tilted the balance against dopamine so that there is now a general consensus on nor-epinephrine being the first choice agent in sepsis and is reflected in the latest Surviving Sepsis 2012 guidelines.

However, the situation is much different in pediatrics. It is well known that pediatric sepsis patients present in a variety of haemodynamics. For example – in a pediatric case series of fifty children with fluid-refractory septic shock, as many as 58% presented with low CO and responded to just inotropes with or without vasodilators, 22% presented with both cardiac contractility and SVR issues and needed both inotropes and vasopressors and only 20% presented with high CO and low SVR and responded to vasopressors alone. The same study also clearly showed that a single child may...
change from one state to another as the illness evolves. This makes the choice of inotropes/vasopressors/dilators in pediatric septic shock patients interesting and complex. This difference has been recognised in different guidelines including the 2012 Surviving Sepsis guidelines.

As far as evidence goes – there is not much out there. The latest Cochrane review on vasopressors for hypotensive shock included 3212 patients in 23 studies and compared six vasopressors – namely norepinephrine, dopamine, vasopressin, epinephrine, terlipressin and phenylephrine along with dobutamine in different combinations and found no evidence of superiority of any agent or combination of agents over the other. It concluded – ‘Probably the choice of vasopressors in patients with shock does not influence the outcome’ and ‘The choice of a specific vasopressor may therefore be individualized and left to the discretion of the treating physicians’.

Vasopressin has reduced the need of other vasopressors and significantly increased BP in many studies but has not shown mortality benefit. Vasopressin is often used as a last resort vasopressor in severe shock. VAAST 10 – by far the largest multi-centre adult randomised controlled trial (RCT) (N=778) involving VP also did not find any difference in 28 day or 90 day mortality between VP and nor-epinephrine. However, contrary to the research hypothesis, mortality was significantly reduced in the vasopressin group in patients with shock does not influence the outcome and ‘The choice of a specific vasopressor may therefore be individualized and left to the discretion of the treating physicians’.

The clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine 1 is possibly the most well-known and followed guidelines for pediatric sepsis. It recommends to optimise preload first by fluid boluses and start dopamine peripherally. Once central access is obtained – dopamine should be increased and if that does not work – catecholamines should be started or further increased. Shock not responding to these measures are termed catecholamines resistant shock and they are further classified into 3 categories - 1) Cold Shock with Normal BP – Low CI/High SVR; 2) Cold Shock with Low BP – Low CI/Low SVR; and 3) Warm Shock with Low BP – High CI/Low SVR.

For Cold Shock with Normal BP – Low CI/High SVR, who has not responded to fluid and epinephrine, it recommends nitrosovasodilators like nitroprusside or nitroglycerine as the first line vasodilators and in the event of toxic side effects or continued low CO state, it recommends milrinone or inamrinone as the next line. Levosimendan and enoximone has also been suggested. However, the 2012 guideline does not mention the primary vasodilators as first line. It rather mentions PDIs first and that probably reflects practice of most pediatric intensivists.

For Cold Shock with Low BP – Low CI/High SVR, who has not responded to fluid and epinephrine, the update recommends adding norepinephrine to increase DBP and SVR. Once an adequate BP is achieved, PDIs or levsimendan can be added to improve CI and ScVO2.

For Warm Shock with Low BP – High CI/Low SVR, who have not responded to fluid and nor-epinephrine, next line includes low dose VP, angiotensin and terlipressin, but as these potent vasoconstrictors can reduce CO, it is recommended that these are used with CO/ScVO2 monitoring, and if these are low, additional inotropes like low dose epinephrine or dobutamine may be needed or vasopressors may need to be reduced.

In order to assess CI and SVR – some sort of CO monitoring (invasive or non-invasive) needs to be used along with invasive BP monitoring. However, CO monitoring is still not widely used – especially in resource-poor settings. In such a situation – we have to depend on clinical assessments like pulse
volume, capillary refill time (CRT) and pulse pressure. DBP is expected to be around half of SBP. DBP significantly higher than this is taken as a marker of vasoconstriction and high SVR and conversely, DBP significantly less than half of SBP is considered a marker of vasodilatation and low SVR.

The clinical end-point or the goal of such therapy is also fairly standardised. As per the Surviving sepsis guidelines, they are – CRT ≤ 2 seconds, normal pulses with no differential between the quality of peripheral and central pulses, warm extremities, urine output >1 mL/kg/h, targeted perfusion pressure as per Table 1, normal mental status and subsequently – mixed venous saturation (ScvO₂) > 70% and cardiac index (CI) of 3.3-6 l/min/m². Among them – the last two require central neck lines and some form of CO monitoring – and are often not available. Besides the BP and the urine output – other measures are somewhat subjective.

One important consideration is the target BP for inotrope therapy in a patient with septic shock. Not much evidence could be found. However, the guideline states the perfusion pressure target quite clearly (please note, this is MAP – CVP and not just the MAP) based mostly on 1987 second task force report on BP¹². It is noteworthy that the target perfusion pressure is 60 mm Hg for any postneonatal infant and from one year onwards – the perfusion pressure target is 65 mm Hg for the entire pediatric age group, which is also the target for the adult population. Having a universal target MAP is very user-friendly and handy to remember. However, it is well-established that normal BP increase with age in the pediatric population. As for example – as per the normative BP data of the latest update (1996) of the second task force report¹³ – which has been referenced in the surviving sepsis guideline – between 1 year and 16 year of age – the SBP increase on an average by 32 mm Hg and the DBP by 28 mm Hg. In view of this – having the same target MAP for a 2 year old as that for an adult i.e. 65 mm Hg is probably non-physiological. Often, it might be quite difficult to achieve, especially in small children and necessitates a very high dose of inotropes. In such a situation – if the child is consistently showing other signs of good perfusion i.e. good urine output, CRT < 2 sec, improving base deficit on blood gas and reducing serum lactate – then it would be the discretion of the intensivist whether to increase the inotropes further to achieve the target perfusion pressure or to settle for a lower perfusion pressure while keeping a close eye on both the BP and the other markers of perfusion. It is well evidenced that higher inotrope use is associated with worse outcome – but the cause and effect relationship is indeed difficult to tease out. This same principle is also applicable to the next section i.e. Myocarditis/Cardiogenic shock – where there is a general consensus that inotropes use should be kept to the minimum that is adequate to perfuse the organs just adequately.

Myocarditis / Heart failure

Inotropic support is required only in acute heart failure that is complicated by hypotension and peripheral hypoperfusion. An ideal inotrope in this setting would be one that (1) improves systolic and diastolic myocardial function, (2) while decreasing systemic and pulmonary vascular resistance, (3) without increasing myocardial oxygen consumption. Unfortunately none of the available

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<tr>
<th>Age</th>
<th>Heart Rate (bpm)</th>
<th>Perfusion Pressure (MAP - CVP)</th>
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<tr>
<td>Term Newborn</td>
<td>120 - 180</td>
<td>55</td>
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<td>Up to 1 yr</td>
<td>120 - 180</td>
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agents completely fulfil all these 3 criteria. Adult studies show that the use of inotropes can actually adversely impact survival. Indeed, in chronic heart failure setting there is very good adult and pediatric evidence suggesting beta-blockers improve morbidity as well as mortality. So, inotropes should be used only if necessary and as less as possible. Pediatric data is scanty and practices relating to use of inotropes in children with heart failure are mostly extrapolated from adult studies. The most commonly recommended initial inotropic therapies for refractory heart failure HF are dobutamine, dopamine and milrinone that are used to improve cardiac output and enhance diuresis by improving renal blood flow and decreasing systemic vascular resistance without exacerbating systemic hypotension. Among them, dopamine has been shown to increase mortality in cardiogenic shock (not specifically myocarditis) when compared to norepinephrine. In desperate situations epinephrine at low dose may also be used and this should prompt consideration for ventricular mechanical support device if available. Positive pressure ventilation – either invasive or non-invasive depending on the severity is of course helpful by both decreasing the work of breathing and reducing the left ventricular afterload.

Catecholamines are limited by several acute and chronic factors including (1) down-regulation of adrenergic receptors, (2) increased myocardial oxygen consumption, and (3) excessive chronotropy. PDIs, on the other hand, exhibit positive inotropy and enhanced lusitropy, and reduce systemic and pulmonary vascular resistance while having the advantage of not increasing myocardial oxygen consumption. However; milrinone can sometime cause severe systemic hypotension, necessitating the co-administration of additional pressor therapies. These medications are thus often used in combination thus offsetting the limitations of each other. Randomized comparisons of milrinone and dobutamine have demonstrated similar clinical outcomes. Levosimendan, a calcium sensitizing agent – has recently generated a lot of interest in this clinical situation. We have discussed levosimendan in a separate section.

**Post-Cardiac Surgery**

Low Cardiac Output Syndrome (LCOS), arbitrarily defined as a decline in cardiac index to < 2.0 L/min per m², is very common, typically occurring between 6 and 18 hours after a cardiopulmonary bypass surgery and contributes significantly to postoperative morbidity and mortality following cardiac surgeries. This fall in cardiac index may also be associated with an elevated SVR and a rise in pulmonary vascular resistance. Causes of LCOS are multifactorial and include myocardial ischemia during aortic cross-clamping, effects of cardioplegia, activation of inflammatory and complement cascades and alterations in systemic and pulmonary vascular activity as well as any residual cardiac lesions that may also adversely impact the postoperative course. Prevention of this hemodynamic deterioration may have significant implications for clinical outcome. Preload adjustments do not always suffice to provide adequate cardiac output and pharmacological support is often necessary. The primary aim is to support myocardial contractility without increasing the workload and oxygen consumption of the heart. Traditionally, inotropic agents and vasodilators have been used to enhance tissue perfusion and facilitate postoperative recovery. Many prefer to use dopamine first in doses of 3-10 mcg/kg/min; but doses above 15 mcg/kg/min are rarely used as dopamine is known to cause vasoconstriction and tachycardia at very high doses. Alternatives to dopamine include dobutamine and low-dose epinephrine. The use of catecholamines has several drawbacks, including increased myocardial oxygen consumption, tachycardia, increased end-diastolic pressure and afterload and risk of arrhythmias. The less compliant neonatal myocardium, may raise its end-diastolic pressure during higher-dose infusions of catecholamines, further impairing ventricular compliance and further reducing ventricular filling. PDI milrinone has emerged as an important vasoactive agent for use in post-cardiac surgery children. A large multicenter, randomized, double-blind, placebo-controlled PRIMACORP (PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics) trial evaluated the efficacy and safety of the prophylactic use of milrinone in...
pediatric patients at high risk of developing LCOS after cardiac surgery. The trial concluded that the prophylactic use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS, and since the publication of this trial in 2003, many units have begun to prefer milrinone for maintaining cardiac output in postoperative patients.

Norepinephrine and vasopressin are used infrequently in a select group of patients with states of refractory vasodilation as may sometimes occur after cardio-pulmonary bypass in children. Vasopressin is particularly useful when patients have tachyarrhythmias or sinus rates that prohibitively limit the length of diastole.

Levosemandan is a relatively new agent that has generated a lot of interest – especially in post-operative LCOS states. (Please note section under ‘Newer inotropes’.)

**Post-cardiac Arrest Syndrome**

Post–cardiac arrest syndrome is a unique and complex combination of pathophysiological processes, which include (1) post–cardiac arrest brain injury, (2) post–cardiac arrest myocardial dysfunction, and (3) systemic ischemia/reperfusion response, often complicated by a fourth component: the unresolved pathological process that caused the cardiac arrest.

Hemodynamic instability is common after cardiac arrest. Resumption of spontaneous circulation (ROSC) after prolonged, complete, whole-body ischemia is an unnatural pathophysiological state created by successful CPR. Vasodilation may occur from loss of sympathetic tone and from metabolic acidosis. Persistence of reversible vasopressor dependency has been reported for up to 72 hours after out-of-hospital cardiac arrest despite preload optimization and reversal of global myocardial dysfunction.

In terms of treatment, a critical knowledge gap exists for post-arrest interventions in children. Therefore, management strategies are based primarily on general principles of intensive care or extrapolation of evidence obtained from adults, newborns, and animal studies.

The optimal hemodynamic targets in the post-resuscitative period remain unclear. The optimal MAP for post–cardiac arrest patients has not been defined by prospective clinical trials. Post-cardiac arrest anoxic brain injury is a major cause of morbidity and mortality, and is responsible for approximately two thirds of the deaths in the post-cardiac arrest period. The loss of cerebrovascular pressure auto-regulation makes cerebral perfusion dependent on cerebral perfusion pressure (CPP=MAP–ICP) and hence predominantly on MAP. In general – it is assumed that hypotension must be avoided and BP should be kept at somewhat high levels. Good outcomes have been achieved in published studies in which the MAP target was as low as 65 to 75 mm Hg or as high as 90 to 100 mm Hg for patients admitted after out-of-hospital cardiac arrest.

The simultaneous need to perfuse the post-ischemic brain adequately without putting unnecessary strain on the post-ischemic heart is unique to the post–cardiac arrest syndrome. This makes selection of inotropes difficult. There is a paucity of data about which vasoactive drug to select first but dopamine, dobutamine, epinephrine are all used to treat post-arrest myocardial dysfunction. Vasopressin infusion has recently been used and shown to have higher short term survival. Although inotropes improve hemodynamic status of the patient and ensures blood flow to the heart and the brain, this improvement in organ perfusion does not necessarily translate into an improvement in outcome which still remains low.

**Brain Dead Child**

Normally brain-stem death constitutes a case for withholding or withdrawing life sustaining medical treatment. But life sustaining interventions may be needed to be continued on a brain dead child under some special circumstances when family requests continuation of life support for some time for family members to visit or other reasons and also for organ harvesting for a heart-beating donor organ transplant. The maintenance of blood pressure becomes crucial in these patients in order to maintain perfusion not only to the other organs but...
also to the heart itself. After some time – brain dead patients often develop marked hemodynamic instability – presumably due to loss of brain-stem reflexes. The first priority when managing a brain dead patient with hypotension is to maintain an adequate effective intravascular volume. 80% of brain-stem dead patients develop diabetes insipidus and it is common for them to be hypovolemic.

Catecholamines are liberally used by transplant retrieval services. Dopamine has traditionally been used for the first-line cardiovascular support. Low dose vasopressin infusion, which is routinely used for treating diabetes insipidus during brain death evaluation and organ recovery, has also been shown to restore vasomotor tone, improve blood pressure and reduce exogenous catecholamine requirements and is increasingly being used as first line pressor support. Low-dose vasopressin may allow reduction or complete elimination of catecholamine use in such circumstances. Terlipressin has also been used for similar purposes.

Canadian guidelines recommend vasopressin as the first-choice vasopressor for donor resuscitation, the second-line agents for hemodynamic support being norepinephrine, epinephrine and phenylephrine.

**How to prepare Infusions of Vasoactive Medications**

The universal Rule of Six for Infusion Calculations applies to the preparation of infusions of vasoactive medications as well.

\[ 6 \times \text{Body Weight (kg)} = \text{Amount (in mg)} \text{ to mix in } 100\text{ml of Solvent to give } 1\text{ml/hr} = 1 \text{ microgram /kg/min}. \]

In the PICU, infusions are usually prepared in 50ml syringes, and the calculations can be derived from this “Rule of Six” adjusted to the volume status of the child and the concentration of the infusion that can be allowed via a central or a peripheral venous line. A standard chart is presented in Table 2.

**Changing Inotrope Infusions – Double-pumping vs Quick Change**

Inotrope infusion syringes need to be changed under many circumstances which include infusion running out, changing the strength of the infusion (for fluid restriction), changing the diluent of the infusion (in hypo- or hyper-glycemic states), changing the site of infusion (eg. between femoral and neck veins). Serious adverse incidents can take place if due care is not exercised when changing syringes of inotrope infusion, particularly in patients with very labile blood pressure and high inotrope requirement. Preparing the next syringe should never be left until the last minute. Inotrope infusions should never be allowed to run out. Some patients are very dependent on their inotropes and will not tolerate them being turned off for even a short period of time. On the other hand, inotropes should never be purged

**Table 2. Infusions of Vasoactive Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dilution to Volume</th>
<th>Infusion Rate</th>
<th>Equivalent Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.3 mg/kg</td>
<td>50 ml D5 or NS</td>
<td>0.5 – 2 ml/hr</td>
<td>0.01 – 1 mcg/kg/min</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>30 mg/kg</td>
<td>50 ml D5 or D10 or NS</td>
<td>5 – 20 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>- Periph</td>
<td>3 mg/kg</td>
<td>50 ml D5 or D10 or NS</td>
<td>5 – 20 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>30 mg/kg</td>
<td>50 ml D5 or D10 or NS</td>
<td>0.5 – 2 ml/hr</td>
<td>5 – 20 mcg/kg/min</td>
</tr>
<tr>
<td>- Periph</td>
<td>3 mg/kg</td>
<td>50 ml D5 or D10 or NS</td>
<td>5 – 20 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>1.5 mg/kg</td>
<td>50 ml D5 or NS</td>
<td>0.6 – 1.5 ml/hr</td>
<td>0.3 – 0.75 mcg/kg/min</td>
</tr>
<tr>
<td>NorEpinephrine</td>
<td>0.3 mg/kg</td>
<td>50 ml D5 or NS</td>
<td>0.1 – 10 ml/hr</td>
<td>0.01 – 1 mcg/kg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1.5 IU/kg</td>
<td>50 ml D5 or NS</td>
<td>0.2 – 0.5 ml/hr</td>
<td>0.0001 – 0.00025 IU/kg/min</td>
</tr>
</tbody>
</table>

D5 = 5% Dextrose; D10 = 10% Dextrose; NS = Normal Saline
either – because this results in uneven doses of inotropes being delivered leading to sudden huge changes in hemodynamics and also runs the risk of causing life-threatening arrhythmias, particularly with drugs like epinephrine.

Two different techniques for changing inotrope syringes are commonly used in most units to overcome this problem viz. Double-Pumping (also known as piggy back) and Quick Change (also called Switching Technique).

When starting an inotrope infusion, it is a good practice to include a three-way tap to facilitate syringe changes. Double-pumping involves starting the second infusion through a three way tap while the first is still running. When the blood pressure starts to rise, the first infusion is stopped immediately. The switching technique involves running the new infusion at the same rate as the old and connecting it to the patient (preferably via a three-way tap) while turning the old infusion off.

Randomized-controlled trials comparing the two methods did not find any statistically significant difference in respect with the variation in mean arterial pressure but found the quick change technique to be the quickest and more cost-effective method. The quick change technique is now used more frequently than it was in the past. Old infusion devices were not as reliable as modern ones, so it was considered safer to titrate a new infusion alongside one ready for change (Double Pumping) in case the infusion device failed. This is no longer necessary, as the newer devices are able to deliver at their set rate immediately.

Newer Inotropes

Levosimendan (LM)

Levosimendan is a calcium sensitizing agent that has generated a lot of interest in recent years. It binds to cardiac troponin C in a calcium-dependent process thereby changing the configuration of tropomyosin which leads to increased contractility. It also opens up potassium channels in sarcolemmal membranes causing muscle relaxation in vasculature leading to reduced SVR and coronary vasodilatation. As they do not increase intracellular calcium concentration – so diastolic relaxation is not compromised. It does not increase myocardial oxygen demand either. Overall, stroke volume, CO and heart rate increase while mean arterial BP and Pulmonary arterial pressure decrease. Atrial fibrillation is more common with LM compared with either placebo or even dobutamine. Ventricular arrhythmias are more common than placebo but not more than dobutamine. No other significant adverse effects are noted so far except mild hypokalemia. The elimination half-life is 1.5 – 2 hours. However, it has an active metabolite OR-1896 – with an elimination half-life of 70-80 hours which is measurable in serum even 14 days after stopping the infusion. It is believed that the hemodynamic effects of LM persists for days after stopping because of this. This might be concerning if LM cause hypotension. However, in most pediatric studies – both hypotension and tachycardia was found to be transient after initiation of the infusion. It is excreted both in the urine and faeces.

Pediatric dose varied but the most commonly used is as follows –

IV Loading dose of 12 mcg/kg over 10 minutes followed by continuous infusion of 0.1 – 0.2 mcg/kg/min. A convenient way is to dissolve 0.3 mg/kg of LM in 5% dextrose and run at 12 ml/hr for 10 minutes and then reduce the infusion to 1 – 2 ml/hr. The range of loading doses have been 6 – 24 mcg/kg and the range of infusion has been from 0.05 – 0.6 mcg/kg/min.

Adult studies like the LIDO trial, the CASINO trial and the SURVIVE trial have compared LM with dobutamine whereas the REVIVE and the RUSSLAN trials evaluated LM in a placebo-controlled fashion. The study population essentially had low-output heart failure of different etiologies. While all these studies have demonstrated hemodynamic benefits with greater increase in cardiac output in the LM group, the REVIVE and the SURVIVE trials could not demonstrate survival benefits. A meta-analysis of 45 adult studies with 5480 patients, which includes all previously mentioned big studies have shown a significant mortality benefit with 6% absolute risk reduction giving a number needed to treat of 17. A multicentre
UK trial is underway to study the effect of LM in sepsis (LeoPARDS study). Pediatric studies have been retrospective case series and till now, four randomized controlled trials have been conducted. Overwhelming majority of them have been in post-operative LCOS situations and LM has often been compared with milrinone. They showed a trend toward an improvement in hemodynamics, a reduction in lactate, a reduction in the need for conventional inotrope use and an ability to wean catecholamines. So far, mortality benefit has not been proven. Clearly, more data is needed to further establish the role of this promising agent.

Istaroxime

This is another new molecule with ino-lusitropy. However, unlike milrinone or LM – it has a short half-life which may be useful – given the potential for hypotension. It also seems to reduce heart rate. However, besides some animal experiments – only one dose escalation adult study has been reported so far. As of now, there is no reported pediatric experience and it is still considered as an experimental molecule.

Conclusion

Inotropes remain one of the most commonly used group of drugs in intensive care setting. They are used to support the circulation in different situations. However, there is not much evidence base; either pediatric or even adult – especially regarding the classical adrenergic agents. This is somewhat surprising – more so considering the fact that they have been in use for a long time. There remains a significant void and there is a need of more robust clinical studies to generate more evidence. On the other hand, recently there have been important new entrants; like milrinone, in the group with properties that are significantly different from the traditional agents and they have found their well earned place in modern therapeutics. There are some newer agents; like levosimendan – which has been used for some time and their role in Pediatric practice is being established. There are yet other molecules – which are in the process of development. So, this is an area where we would expect exciting new advances in future. So, keep watching!

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References:


