Low Cardiac Output State and Pharmacological Support of the Cardiovascular System

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Low Cardiac Output State

Definition and Presentation

Low cardiac output state (LCOS) is characterized by decreased systemic perfusion, resulting in an imbalance between oxygen delivery and oxygen consumption.

Clinically, this manifests as poor perfusion (prolonged capillary refill, cool extremities, mottled skin, decreased pulse volume, pallor), decreased conscious level, oliguria, tachycardia and hypotension, while biochemically, there may be evidence of decreased mixed venous oxygen saturation (SvO_2), metabolic acidosis and elevated lactate.

Causes of Low Cardiac Output State

The diagram below displays the various factors that impact on oxygen delivery (DO_2), cardiac output (CO) and oxygen consumption (VO_2).

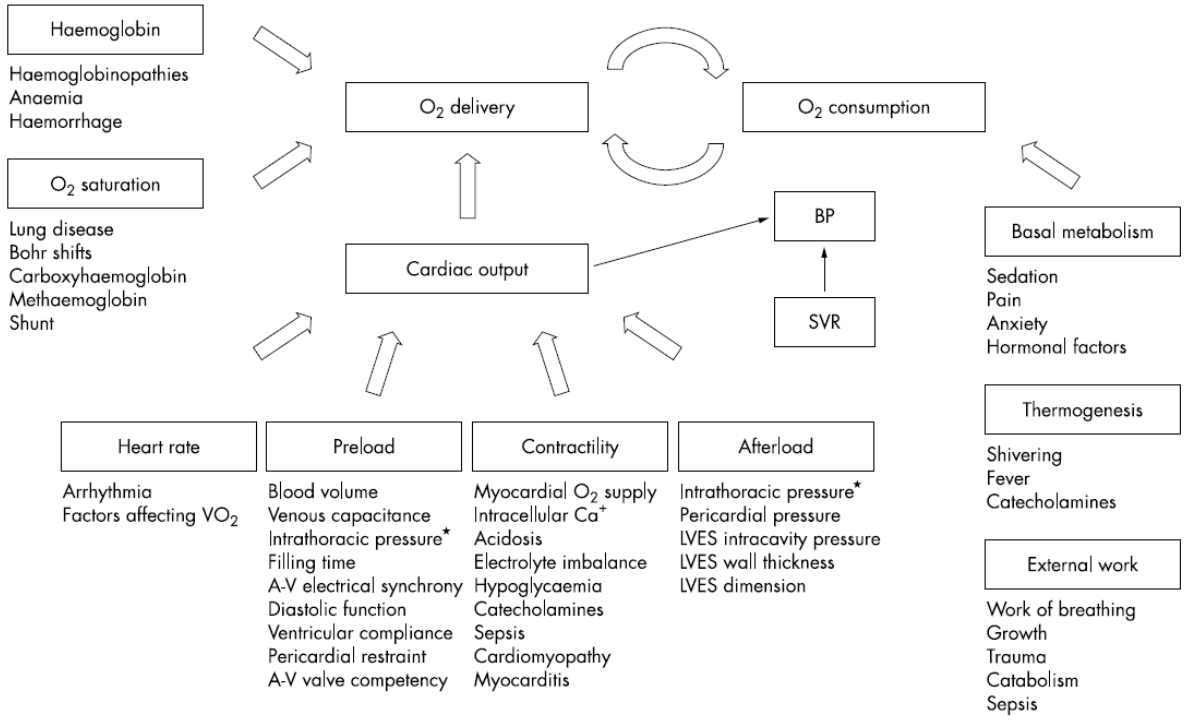

Figure 1 Factors affecting oxygen delivery and consumption. BP, systemic blood pressure; SVR, systemic vascular resistance; VO_2, oxygen consumption; A-V, atrioventricular; LVES, left ventricular end systolic. *Common intensive care scenarios augmenting intrathoracic pressure include mechanical ventilation, pneumothorax, pleural/pericardial fluid collections.

From the diagram, one can appreciate that DO_2 is affected by oxygen carrying capacity, oxygen saturation and CO, while CO is the net product of four inter-related variables: heart rate, preload, contractility and afterload. On the other hand, VO_2 is affected by basal metabolism, body temperature and additional work from body functions and catabolic processes. Thus, interventions for LCOS should be geared towards increasing DO_2, cardiac output and decreasing VO_2.

Useful Formulae and Concepts
The following formulae may also assist with understanding of concepts, guiding clinical assessments and decisions about interventions:

Blood Pressure = Cardiac Output x Systemic Vascular Resistance (SVR)

Thus, a low blood pressure may be secondary to a low CO, low SVR, or both. Conversely, a normal blood pressure can exist despite low CO if SVR is high. This highlights the limitation of using blood pressure alone to assess a patient's haemodynamic status, and emphasizes the importance of assessing other parameters of tissue perfusion.

Arterial Oxygen Content = (1.34 x Haemoglobin x SaO_2) + (0.003 x PaO_2),
where SaO_2 refers to arterial oxygen saturation (Not SpO_2)

Each gram of haemoglobin can carry 1.34ml of oxygen. The implication of this formula is that the majority of oxygen delivered to tissues is carried by haemoglobin, whereas dissolved oxygen, reflected by PaO_2, contributes a negligible portion. This does not mean that PaO_2 is unimportant, as maintaining optimal PaO_2 targets is still important and is ultimately reflective of adequate gas exchange. Thus, apart from improving cardiac output, improving oxygen delivery involves optimizing oxygen carrying capacity and oxygen saturations.

Oxygen Extraction Ratio = (SaO_2 – SvO_2) / SaO_2

A normal oxygen extraction ratio is about 0.20-0.30 (or 20-30%). In the setting of decreased DO_2, oxygen extraction increases to meet VO_2. If the increase in oxygen extraction is insufficient, CO also increases to improve DO_2. However, if the oxygen extraction ratio exceeds 0.60 (or 60%), this is indicative of global tissue hypoxia and is followed by elevated lactate. In other words, a decreasing SvO_2 may be an earlier sign of tissue hypoxia than elevated lactate.

Haemodynamic Monitoring - Assessment of Cardiac Output and its components

Assessments of CO at the bedside are challenging due to limitations in our ability to accurately quantify individual components of cardiac function and their interdependence on one another. One must also consider that multiple abnormalities may co-exist and that these evolve during illness. Hence, an appropriate therapy at one point may become inappropriate as the patient's clinical state changes. Thus, the initial assessment and intervention must be followed by serial re-assessments to judge response to therapy and evaluate changes in haemodynamic status.

A) Assessment of Preload and Fluid responsiveness

Preload refers to the amount of myocardial stretch at end-diastole (a measure of volume). There are numerous methods for estimating volume status, such as body weight trends, input/output charting, orthostatic changes and clinical examination. However, these have limited value in estimating preload or predicting fluid responsiveness.

Central venous pressure (CVP) (Normal range: 2-6 mmHg) is a static variable that has been used to estimate preload and guide fluid therapy. However, many studies and several meta-analyses show that there is no data to support this. There are several inherent limitations in using CVP:

- While intended to estimate right ventricular end-diastolic volume, it reflects right atrial pressure. However, pressure ≠ volume and these two parameters are not linearly related.
- While we may be more interested in left heart preload, CVP reflects right atrial pressure and does not directly reflect left atrial pressure
- Many factors can impact on CVP values (Table 1). Other mechanical factors that impact on CVP values include the catheter tip/transducer position, catheter occlusion and running of infusions in the catheter.

Table 1. Factors that impact CVP

	Increased CVP	Decreased CVP
Volume Status	• Hypervolemia	• Hypovolemia
Vascular Tone	• Veno-constriction	• Veno-dilatation (E.g. in sepsis)
Cardiac	• Diastolic dysfunction • Cardiomyopathy • Tricuspid regurgitation/stenosis • Intra-cardiac shunts • Pulmonary hypertension • Pericardial effusion/tamponade	
Intra-thoracic	• Increased intra-thoracic pressure • Positive pressure ventilation	
Intra-abdominal	• Increased intra-abdominal pressure	

Thus, while derangements in CVP may not be specific, trending CVP still provides a sensitive indicator of changes in haemodynamic status. For example, increasing CVP in a patient with post-operative Fallot's tetralogy may indicate worsening right ventricular diastolic dysfunction. Or, up-titrations in ventilatory settings with an increase in mean airway pressure may increase CVP. In summary, any change in CVP should trigger an evaluation for its etiology.

The abdominojugular reflux sign (also called abdominal compression), when performed with arterial blood pressure monitoring, is a useful method for predicting fluid responsiveness. Compression of the liver for 5-10 seconds should be followed by an increment in blood pressure. Unfortunately, there is no uniform definition for what constitutes an adequate compression pressure or what is considered a significant increment in blood pressure. This may be likened to the passive leg raise which is performed to predict fluid responsiveness in adults. However, the passive leg raise may be less useful in children given the relatively smaller size of the lower limbs and smaller blood volume within.

Attempts to identify other methods of predicting fluid responsiveness have described numerous static (e.g. CVP, pulmonary artery occlusion pressure, left ventricular end-diastolic area) and dynamic (e.g. systolic/pulse pressure variation, stroke volume variation, inferior vena cava variation) variables. A detailed discussion of these variables is beyond the scope of this chapter. In summary, static variables have not been found to predict fluid responsiveness. Whereas, amongst dynamic variables, only respiratory variation in aortic blood flow peak velocity was consistently predictive of fluid responsiveness in children. This is measured using doppler echocardiography and requires a skilled operator.

Finally, the risks of fluid overload must be emphasized. Fluid overload can contribute to pulmonary edema, prolonged mechanical ventilation and increased mortality in patients with sepsis, acute respiratory distress syndrome, acute kidney injury and intra-abdominal hypertension. Hence, methods of predicting fluid responsiveness should also be used to facilitate decision making about withholding further volume resuscitation.

B) Measures of Contractility

Fractional shortening (FS) (Normal range: 28-46%) and ejection fraction (EF) (Normal range: 56-78%) are the two most commonly used parameters to assess left ventricular systolic function. FS is a measure of cardiac contractility in a single plane, while EF is a volumetric parameter. Both parameters rely on an assumption that the left ventricle is cylindrical in shape. Hence, a change in shape or an underfilled left ventricle would alter the values of EF and FS.

C) Measures of Cardiac Output

Our unit does not currently routinely measure CO invasively. The gold standard for assessment of CO is the use of transcardiac thermodilution via a pulmonary artery catheter. However, it is invasive, challenging to insert in a small child and is difficult to interpret in the presence of intra-cardiac shunts. Complications include infection, thromboembolism, injury to the pulmonary artery and arrhythmias.

Several other methods for assessing CO exist, including transpulmonary thermodilution, pulse contour analysis, doppler echocardiography or transthoracic electrical bioimpedance. However, each technique requires a degree of skill and resources to use, and each have their own limitations that hinder accuracy and interpretation. In general, there is no consensus on the best method for assessing CO and unfortunately, there is a lack of evidence that monitoring CO leads to improved clinical outcomes.

Ultimately, assessing CO or any of its component parameters in isolation, even if a normal value is obtained, is not sufficient to indicate whether DO_2 is optimal. CO and its component parameters must always be interpreted together and in the context of the global clinical picture to guide interventions to achieve optimal DO_2, tissue perfusion and to decrease VO_2. Several important questions to consider are: Is this CO adequate to meet the patients demands now? If not, which parameter requires optimization? How can optimization be achieved?

Assessment of the Adequacy of Cardiac Output and Oxygen Delivery

A) Global Indicators

i. Lactate: Elevated lactate (>2mmol/L) is thought to represent anaerobic metabolism, which occurs when DO_2 is inadequate or if oxygen utilization at the tissues is impaired. However, this is an oversimplification, as lactate may also be raised due to increased glycolysis, thiamine deficiency and reduced lactate clearance. Regardless, any increase in lactate must be evaluated and addressed appropriately.

ii. SvO_2: A true mixed venous blood sample is drawn from the pulmonary artery or right ventricle, with normal values of 65-70% in the setting of normal systemic saturations. In our unit, we often obtain central venous blood samples from the superior or inferior vena cavae from jugular or femoral venous catheters, respectively. Thus, central venous oxygen saturation ($ScvO_2$) only estimates true SvO_2. As mentioned earlier, reductions in SvO_2 may precede elevations in lactate. However, there may also be situations with elevated lactate even though SvO_2 is normal.

B) Regional Indicators

i. Clinical: Capillary refill time and toe-core temperature gap are simple bedside clinical parameters, but they lack specificity and may not always be able to predict deterioration in haemodynamic status. Normal mentation and urine output are valuable and important clinical parameters and should always serve as therapeutic targets.

ii. Near Infrared Spectroscopy (NIRS): NIRS is a non-invasive tool used for continuous monitoring of regional oxygen saturations (rSO_2) at depths of 1-4 cm beneath the skin. It differs from pulse oximetry by assessing haemoglobin saturations in non-pulsatile blood, hence it primarily assesses capillary and venous oxygen saturations. Thus, rSO_2 is related, but not equal to $ScvO_2$.

NIRS probes are typically applied to the forehead and flanks to monitor cerebral and somatic (renal) rSO_2, respectively. The main drawback for using NIRS in the ICU is the inability to obtain a baseline pre-illness value. There is also no consensus on what constitutes a significant reduction in rSO_2, although some suggest that a 20-30% reduction is significant. Evidence for its use in paediatrics is still evolving. Nonetheless, NIRS is a useful tool for continuous monitoring and trending of rSO_2.

The various indicators of adequate tissue perfusion should always be considered together. While there is no strong evidence that any particular indicator is superior to another, we often rely on lactate and SvO_2 to screen for tissue hypoxia and act as therapeutic targets.

Management of Low Cardiac Output State

Table 2. Management of LCOS

Principles	Intervention
Increase O2 carrying capacity	• Transfuse packed red blood cells if required • Optimize oxygen saturations
Optimize preload	• Consider fluid bolus • Address coagulopathy / any source of haemorrhage
Augment contractility	• Inotropic support with adrenaline or dopamine • Maintain adequate ionized calcium
Reduce afterload / SVR	• Consider milrinone, sodium nitroprusside or phentolamine • Optimize cardiopulmonary interactions

Optimizing cardiopulmonary interactions	• Positive pressure ventilation:
	  ○ Optimal lung recruitment minimizes pulmonary vascular resistance
	  ○ Reduces left ventricular afterload and may be helpful with left ventricle/systemic ventricle systolic dysfunction
	• Spontaneous ventilation:
	  ○ Reduces right ventricular afterload and is helpful with right ventricle systolic dysfunction
	  ○ Improves systemic venous return and may be helpful with right ventricle diastolic dysfunction
	  ○ Improves pulmonary venous return in patients with passive pulmonary blood flow

Reducing O2 consumption	• Optimize patient comfort / work of breathing • Maintain normothermia • Optimize sedation • Consider neuromuscular blockade
Addressing vasodilatory shock	• Consider low dose noradrenaline or vasopressin if systemic ventricular function is good. Vasopressors are contra-indicated in the setting of poor ventricular function.
Addressing diastolic dysfunction	• Minimize tachycardia to increase diastolic filling time and decrease myocardial oxygen demand • Optimize preload • Consider spontaneous ventilation or decrease mean airway pressure while maintaining lung recruitment
Treat arrhythmias	• Optimize electrolytes • Consider anti-arrhythmic agents / pacing to restore atrio-ventricular synchrony
Others	• Consider hydrocortisone in catecholamine-resistant shock • Correct acid-base imbalance • Maintain adequate serum potassium and magnesium
Surgical interventions	• In post-cardiotomy patients, consider re-opening the chest if cardiac tamponade is suspected • Selected patients may benefit from a right to left shunt at the atrial level to maintain adequate left heart preload (Post-op Tetralogy of Fallot / Post-Fontan repair) • Consider extra-corporeal membrane oxygenation (ECMO)* for reversible shock states refractory to conventional therapy

*A discussion of the indications for ECMO in various settings (e.g. cardiogenic shock, septic shock, etc) is beyond the scope of this chapter. In the absence of robust evidence, our unit practice is for early consideration of ECMO if end-organ perfusion remains compromised despite high doses of multiple vaso-active drugs (e.g. adrenaline/noradrenaline infusions of 0.2 – 0.3 mcg/kg/min or vasopressin 0.04 – 0.06 u/kg/hr)

Pharmacological Support of the Cardiovascular System

Vasoactive agents can be differentiated based on their mechanism of action. In practice, most vasoactive agents display a range of different effects which can be dose-dependent.

The choice of agent can vary from centre to centre or even between physicians. Regardless, the endpoint of pharmacological cardiovascular support should still be the restoration of adequate tissue perfusion to end organs, as indicated by normalisation of heart rate, blood pressure, perfusion, urine output, conscious level, SvO_2 and serum lactate levels.

In view of possible extravasation injury, most vasoactive drugs are best administered via a central venous access. In cases of emergency, these can be administered peripherally while preparation of central line insertion is underway (Refer to Annex A for information on dilution and maximum peripheral concentration).

Inotropes

These are drugs that increase cardiac contractility and thereby increase CO.

Adrenaline

Adrenaline is an inotrope with dose-dependent alpha and beta effects. Adrenaline is the drug of choice in our unit for septic shock (cold shock with myocardial dysfunction and raised SVR), anaphylactic shock, cardiogenic shock, cardiac arrest and many post-arrest situations.

Dosage range IV 0.05 – 1 mcg/kg/min (continuous infusion):

- At low doses (< 0.1 mcg/kg/min), beta-effects predominate leading to chronotropy, inotropy and modest decrease in SVR
- At high doses (> 0.1 mcg/kg/min), alpha effects predominate leading to increased SVR, chronotropy and inotropy.
- It can also be administered via endo-tracheal tube or nebulised for its bronchodilator and mucosal vasoconstrictor properties.

Side effects include risk of tachyarrhythmias, hyperglycaemia, hypokalaemia, elevated lactate and an increase in myocardial work and oxygen consumption.

Adrenaline-induced hyperlactaemia is mediated by beta-adrenergic stimulation and occurs via increased aerobic glycolysis. Hence, it does not necessarily indicate cellular hypoxia. Adrenaline-induced hyperlactaemia has not been associated with poor outcomes and has been reported to be transient, with levels returning to baseline in 12 – 24 hours. As this may pose a challenge in relying on lactate levels to assess tissue perfusion, other surrogate markers of perfusion should be considered.

Dopamine

Dopamine is a naturally occurring catecholamine and is commonly used in many paediatric ICUs.

Dosage range IV 5 - 20 mcg/kg/min (continuous infusion). It has multiple dose-dependent actions:

- < 5 mcg/kg/min: acts on dopaminergic receptors causing vasodilation
- 5 - 10 mcg/kg/min: stimulates $beta_1$ receptors and increases cardiac contractility
- > 10mcg/kg/min: Beta receptor stimulation persists but there is an additional alpha receptor action which is dose dependent. The alpha effects result in systemic vasoconstriction, increase in myocardial workload and oxygen consumption.

Side effects include tachycardia, systemic and pulmonary vasoconstriction.

There has been no evidence that low dose “renal dopamine” improves renal function or mortality outcomes in the ICU; however, doses of 5 – 10 mcg/kg/min have been demonstrated to improve cardiac output and blood pressure.

Inodilators

These drugs produce a dual effect of increased cardiac contractility as well as vasodilatation, promoting ventriculo-arterial coupling, thereby decreasing cardiac afterload.

Milrinone

A phosphodiesterase inhibitor (PDEI) that is useful in the management of low cardiac output following cardiopulmonary bypass. Properties of PDEI include inotropy, vasodilatation resulting in decrease in systemic and pulmonary vascular resistance, and lusitropy (diastolic relaxation of cardiac muscles).

Dosage range IV 0.25 – 0.7 mcg/kg/min (continuous infusion) (Maximum 1.0 mcg/kg/min). A loading dose of 75 mcg/kg over 1 hour can be given to reach effective plasma levels quickly, although our unit does not routinely practice this. Half-life about 2.5 hours (relatively long half life). Milrinone is cleared by the kidneys and may require dose adjustment for renal dysfunction.

Side effects include hypotension (exacerbated in the presence of intravascular volume-depletion), thrombocytopenia and arrhythmias.

Dobutamine

A synthetic catecholamine with predominantly beta agonist ($\beta_1 > \beta_2$) effects. Selective beta effects result in an increase in cardiac contractility, peripheral vasodilatation and increase in heart rate. It can be administered peripherally as it does not cause vasoconstriction. This is useful in cases where central access is unavailable.

Dosage range IV 5 - 20 mcg/kg/min (continuous infusion). Doses up to 10 mcg/kg/min have been shown to increase cardiac output and blood pressure.

Side effects include risk of tachyarrhythmias and hypotension (especially if intravascularly volume-depleted). Tachyphylaxis is seen with prolonged use.

Levosimendan

A calcium sensitizer and PDEI that has been used in acute decompensation of severe chronic heart failure. Levosimendan augments myocardial contraction by increased calcium sensitivity rather than increasing intracellular calcium, hence it does not increase myocardial oxygen demand. It also acts on ATP-sensitive potassium channels in vascular smooth muscle, resulting in arterial, venous and coronary vasodilation, decreasing afterload and preload (ensure preload optimization prior to administration), increasing coronary blood flow and decreasing pulmonary vascular resistance. Levosimendan also demonstrates a positive lusitropic effect.

Dosage range IV 0.1 - 0.2 mcg/kg/min (continuous infusion) given over 24 - 48 hours. It has a half-life of 1 hour, but its cardiovascular effects persist for approximately 7 - 9 days after a 24-hour infusion.

Note: Levosimendan is not stocked within our formulary and has to be specially ordered for select situations.

Levosimendan dosing protocol (Adapted from Leeds Teaching Hospital)

Levosimendan continuous infusion can be administered via a central or peripheral line. Start the infusion at 0.1 mcg/kg/min. If tolerated for 6 hours, increase the infusion to 0.2 mcg/kg/min. If the patient becomes tachycardic or hypotensive, reduce the dose to 0.05 mcg/kg/min. The continuous infusion is typically discontinued after 24 hours.

Refer to Annex A for guideline on dilution and administration.

Side effects include headache, tachycardia, hypokalaemia, atrial fibrillation, ventricular tachycardia and hypotension. QTc prolongation may occur at doses higher than 0.4 mcg/kg/min.

Vasoconstrictors

Noradrenaline

A potent vasoconstrictor with predominant alpha$_1$ effects. It increases SVR, mean arterial blood pressure and myocardial oxygen consumption without significant changes in inotropy or chronotropy. Noradrenaline is our first-line agent for “warm” septic shock when SVR is low. It is often used in combination with adrenaline or dobutamine in septic shock. Avoid using vasopressors if cardiac contractility is poor.

Dosage range IV 0.05 – 1 mcg/kg/min (continuous infusion).

Side effects include bradycardia and decrease in tissue perfusion from potent vasoconstriction.

Vasopressin

Vasopressin is also known as anti-diuretic hormone (ADH) and is endogenously released in response to haemodynamic, osmotic and non-osmotic stimuli such as pain, stress, hypercarbia and hypoxia. A decrease in effective circulating volume is a potent haemodynamic stimulus for appropriate release of ADH. It acts on V1 receptors and the phospholipase C system, resulting in profound pulmonary and systemic vasoconstriction.

Concentrations of ADH needed to regulate water reabsorption are usually very low. Conversely, higher levels are needed to produce vasoconstriction. Despite very high levels of ADH during states of decreased circulating volume, osmoregulation via V2 receptors remains intact.

Vasopressin is useful in treating hypotension associated with brain death or in patients with sepsis and/or refractory vasodilatory shock.

Dosage range IV 0.02 - 0.06 Units/kg/hr or 0.0003 - 0.001 Units/kg/min (continuous infusion)

Side effects include severe vasoconstriction. Theoretical concerns regarding splanchnic and peripheral ischaemia due to vasoconstriction.

Phenylephrine

A pure alpha agonist. Used occasionally in tetralogy of Fallot hypercyanotic spells and in the operating room when a rapid increase in SVR is needed.

Dosage range IV 2 - 10 mcg/kg stat then 0.5 - 5 mcg/kg/min (continuous infusion)

Side effects include severe vasoconstriction.

Vasodilators

Sodium nitroprusside

A potent short-acting venous and arterial vasodilator which acts by increasing endogenous nitric oxide, resulting in vasodilatation. Good choice for afterload reduction in the setting of acute myocardial dysfunction e.g. dilated cardiomyopathy and post-operative cardiac surgical patients.

Dosage range 0.5 - 4 mcg/kg/min, maximal total dose 70 mg/kg.
Onset of action: 30 seconds, duration of action: 2 - 10 minutes and half-life: 3 minutes.

Important side effects include cyanide toxicity and methaemoglobinaemia. It can also cause reflex tachycardia. Use with caution in patients with raised intracranial pressure as it may cause cerebral vasodilatation and decrease cerebral perfusion pressure. May also cause progressive hypoxia in patients with pulmonary disease as it increases intra-pulmonary shunting from uncoupling hypoxic pulmonary vasoconstriction. This drug requires protection from light.

Signs of cyanide toxicity include increased heart rate, normal SpO_2, decreased arterio-venous oxygen difference of < 10% (SaO_2 – SvO_2), metabolic acidosis and increased lactate. Rapidly progressive tolerance or reduced response to the drug may be an early indication of cyanide toxicity.
Signs of thiocyanate toxicity (increased risk in renal failure and prolonged infusions > 72 hours) include fatigue, tinnitus, weakness, altered mental status, pupillary constriction, seizures and rash.

Signs of methaemoglobinaemia include cyanosis, decreased SpO_2 to 85-90% yet normal PaO2, and other evidence of reduced end-organ oxygen delivery (e.g. metabolic acidosis, increased lactate). Methaemoglobinaemia can be assessed via co-oximetry, which is part of arterial blood gas analysis.

Phentolamine
A non-selective alpha antagonist that acts by reversibly binding to both $alpha_1$ and $alpha_2$ receptors, temporarily inhibiting binding of catecholamines. This results in vascular smooth muscle relaxation, reducing SVR. Classically used for hypertension in the pre-operative management of phaeochromocytoma and is also an option to reduce SVR post-Norwood surgery for hypoplastic left heart syndrome, when pharmacologic manipulation of SVR may be necessary to balance the pulmonary and systemic circulations (Qp: Qs).

Dosage range 0.5 – 10 mcg/kg/min.
Onset of action: 1 – 2 minutes, duration of action: 10 - 30 minutes and half-life: 19 minutes.

Side effects include flushing, increased gastric secretions, tachycardia and hypotension, possible tachyphylaxis with ongoing use.

Nitroglycerin (GTN)
A less potent short-acting vasodilator with similar mechanism of action to nitroprusside. GTN has a greater effect on the venous rather than arterial circulation (primarily reduces preload and has limited afterload reduction). Also acts on the coronary circulation.

Dosage range IV 0.5 – 10 mcg/kg/min.
Onset of action 1 – 2 minutes, duration of action: 2 – 5 minutes and half-life: 1 – 3 minutes.

Side effects include hypotension and tachycardia, possible tachyphylaxis with ongoing use.

Hydralazine
A direct acting arterial vasodilator predominantly used in the management of systemic hypertension.

Dosage range IV 0.1 – 0.2 mg/kg/dose Q 4 – 6H (intermittent dosing, up to 3.5 mg/kg/day total daily dose) or IV 4 – 6 mcg/kg/min continuous infusion. Oral 0.4 mg/kg/dose 12H, slowly increasing to 1.5 mg (max 50 mg) 6 – 8H.
Onset of action: IV: 10 – 60 minutes, duration of action: IV: up to 12 hours and half-life: 3 – 7 hours.

Side effects include tachycardia, hypotension and drug-induced lupus-like syndrome. Combination use with beta-blockers may be helpful for afterload reduction in heart failure

Nifedipine
A calcium channel blocker that prevents influx of calcium through the cell membrane blocking smooth muscle contraction, resulting in vasodilatation and subsequent drop in blood pressure. Limited use in hypertensive emergencies.

Dosage range Oral 0.25 – 0.5 mg/kg/dose 6 – 8 hourly (max 3 mg/kg/day total daily dose)
Onset of action (immediate release): ~20 minutes, half-life: 2 – 6 hours.

Side effects include hypotension, syncope and dizziness, hyperglycaemia and hyperuricaemia

Chronotropes

These are drugs that work primarily by increasing or decreasing the heart rate.

Isoprenaline

Isoprenaline is used in very selective situations for its positive chronotropic effects eg. in patients with complete heart block while awaiting permanent pace maker insertion.

Dosage range IV 0.05 – 0.5 mcg/kg/min continuous infusion (can increase up to 2 mcg/kg/min in some patients)
Onset of action: 30 – 60 seconds, duration of action: 10 – 15 minutes and half-life: 2 – 5 minutes

Side effects include vasodilatation, possible tachyarrhythmias and increase in myocardial oxygen consumption.

Other Anti-hypertensive agents with rate controlling effects

Esmolol

A short-acting, intravenous, cardio-selective $beta_1$-adrenergic antagonist (Class II anti-arrhythmic agent) used for atrial or supraventricular tachycardia, as well as hypertension. It has negative chronotropic and inotropic effects, causing decreased cardiac conduction, heart rate, contractility and myocardial oxygen consumption. Esmolol is typically used short-term, with a maintenance infusion not exceeding 48 hours. If there is a need to transition to long-term agents, esmolol should be weaned gradually after starting the alternative agent.

Dosage range IV 25 – 300 mcg/kg/min continuous infusion.
Loading dose IV 500 mcg/kg over 1 minute as a bolus, followed by continuous infusion 25 – 100 mcg/kg/min
Onset of action: 60 seconds, reaches steady state within 5 minutes, duration of action: 10 – 30 minutes and half-life: 2 – 9 minutes.

Side effects include hypotension and thrombophlebitis.
If extravasation occurs, stop the infusion immediately and disconnect, leaving the cannula in place. Gently aspirate the extravasated solution via the cannula and remove the cannula (avoid flushing the line).
Esmolol is rapidly metabolised by red blood cell esterase and the kidneys and does not require dose adjustment for renal or hepatic dysfunction.

Labetalol

A mixed adrenergic blocker used for treatment of hypertension. Primarily causes $beta_1$ blockade and to a lesser extent $alpha_1$ blockade causing a reduction in SVR. Has a rapid onset of action with prolonged duration of action (about 8 hours). Does not appear to cause an increase in intracranial pressures. Should not be used as first-line agent for phaeochromocytoma as predominant beta blockade results in shunting of circulating catecholamines to alpha receptors, increasing SVR.

Dosage range IV 0.25 – 3 mg/kg/hour (continuous infusion)
Onset of action: IV: within 5 minutes, peak effect in 5 – 15 minutes, duration of action: IV: 16 – 18 hours and half-life: 5 – 6 hours.

Use with caution in patients with heart block, congestive heart failure, asthma and hepatic dysfunction.

Selected clinical scenarios in the ICU

Note that a 'generous' blood pressure may not necessarily be appropriate if it is at the expense of high infusions of vaso-active drugs (eg. catecholamines) which increase myocardial oxygen demand and strain at a time when the heart is already under stress. End points of vaso-active infusions should not just target an ideal blood pressure but other endpoints of adequate perfusion such as urine output, oxygenation, SvO_2 and serum lactates.

Septic shock
Many units use a combination of vaso-active drugs in the management of septic shock, depending on the predominant physiology.

The clinical picture can be divided into 'warm shock' (typically with low SVR) or 'cold shock' (typically with high SVR). Some patients may present with initial features of warm shock followed by cold shock later in the disease process; others may present with features of both.

In fluid-resistant warm shock, the first-line vaso-active drug of choice in our unit is noradrenaline (start at 0.1 mcg/kg/min and titrate upwards), followed by vasopressin if necessary. In fluid-resistant cold shock with hypotension, the first-line vasoactive drug is adrenaline (start at 0.1 mcg/kg/min and titrate according to endpoints) or dopamine (start at 5 – 10 mcg/kg/min and titrate).

In cold shock with adequate blood pressure but signs of high SVR, an inodilator such as dobutamine (start at 5 – 10 mcg/kg/min) or milrinone (start at 0.3 – 0.7 mcg/kg/min) can be used.

In catecholamine-resistant shock, consider the addition of hydrocortisone (1 – 2 mg/kg/dose Q6H, but to avoid exceeding 100 mg/m^2/day).

Low cardiac output state post-cardiac surgery
This usually manifests between 6 – 18 hours after cardiac surgery as decreased perfusion (increasing toe-core temperature gap) with haemodynamic instability, high or increasing inotropic requirement, rising serum lactates with/without evidence of metabolic acidosis and evidence of end-organ hypoperfusion (eg. oliguria, hypoxia, low SvO_2).

LCOS can be due to inadequate preload, impaired cardiac contractility, poor ventricular relaxation, high afterload (SVR or PVR), cardiac arrhythmias, cardiac tamponade, residual lesions or inadequate surgical repair.

A 2D echocardiogram should be performed to determine adequate cardiac filling, contractility, to assess for cardiac tamponade and to assess for residual lesions as a cause for the LCOS state.

For further details on the management of LCOS post-cardiac surgery, please refer to our separate CICU handbook chapter on cardiac surgery and post-operative management.

Cardiogenic shock (cause not yet determined)
This group of patients present predominantly with signs of inadequate cardiac output and cardiomegaly accompanied by high SVR. Initial management includes cautiously optimising preload. First-line agents would be either adrenaline or milrinone, titrated to achieve adequate blood pressure, tissue perfusion and urine output. Milrinone is also considered for its afterload reducing effect.

Echocardiography is useful in this setting to determine adequate cardiac filling, contractility and to assess for cardiac tamponade.

Post-cardiopulmonary resuscitation
Adrenaline infusion is used as the first line vasoactive agent in patients with hypotension post-cardiopulmonary arrest. This should be started at 0.1mcg/kg/min and titrated upwards (to 0.5 – 1 mcg/k/gmin) targeting adequate blood pressures and urine output.

Early consideration for ECMO

As mentioned earlier, a detailed discussion on the indications for ECMO is beyond the scope of this chapter. Our unit preference is for early consideration of ECMO if end-organ perfusion remains compromised despite high doses of multiple vaso-active drugs (e.g. adrenaline/noradrenaline infusions of 0.2 – 0.3 mcg/kg/min or vasopressin 0.04 – 0.06 u/kg/hr). Extra-corporeal cardiopulmonary resuscitation (ECPR) should be reserved for cardiac arrest secondary to cardiogenic shock. Patients who arrest from septic shock or respiratory failure are poor candidates for ECPR and should be identified early and placed on ECMO prior to further deterioration.

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Annex A

Drug Dilution Table

Drug Name	Central Venous Administration	Maximum Peripheral Line Concentration
Dopamine	(30 x Weight) mg in 50ml: 1ml/hr → 10mcg/kg/min	3200 mcg/ml
Dobutamine	(30 x Weight) mg in 50ml: 1ml/hr → 10mcg/kg/min	5000 mcg/ml
Milrinone	(3 x Weight) mg in 50ml: 1ml/hr → 1mcg/kg/min	200 mcg/ml
Adrenaline	(0.3 x Weight) mg in 50ml: 1ml/hr → 0.1mcg/kg/min	30 mcg/ml
Noradrenaline	(0.3 x Weight) mg in 50ml: 1ml/hr → 0.1mcg/kg/min	30 mcg/ml
Isoprenaline	(0.3 x Weight) mg in 50ml: 1ml/hr → 0.1mcg/kg/min	
Vasopressin	(1 x Weight) unit in 50ml: 1ml/hr → 0.02unit/kg/hr	
Sodium Nitroprusside	(3 x Weight) mg in 50ml: 1ml/hr → 1mcg/kg/min	200 mcg/ml
GTN	(3 x Weight) mg in 50ml: 1ml/hr → 1mcg/kg/min	400 mcg/ml
Phentolamine	(3 x Weight) mg in 50ml: 1ml/hr → 1mcg/kg/min	

Levosimendan Dilution and Administration Guide

Patient Weight < 15 kg	Patient Weight ≥ 15 kg
1. Syringe out 1 ml (2.5mg or 2500mcg) of solution from the vial 2. Dilute to 50 ml of Dextrose 5% (Final concentration 50mcg/ml) 3. Start infusion at 0.1 mcg/kg/min (Infusion rate in ml/hr = 0.12ml/kg/hr x Patient's weight (in kg)	1. Syringe out 5ml (12.5mg or 12500mcg) of solution from the vial 2. Dilute to 250ml of Dextrose 5% (Final concentration 50mcg/ml) 3. Start infusion at 0.1 mcg/kg/min (Infusion rate in ml/hr = 0.12ml/kg/hr x Patient's weight (in kg)