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CONGENITAL HEART DISEASE

Perioperative manipulation of the circulation in children with congenital heart disease

Lara Shekerdemian

A low cardiac output state with reduced systemic oxygen delivery can complicate the early postoperative recovery early after surgery for congenital heart disease (CHD). All patients undergoing surgery on cardiopulmonary bypass (CPB) are at risk for a low cardiac output state, but the risk is greatest for younger patients undergoing more complex surgery. Although the clinical manifestations of a reduced cardiac output are generally transient and reversible, this can result in increased intensive care stay, and contributes to the long term morbidity and mortality associated with surgery for CHD.

The circulatory management of children with CHD should routinely be aimed at optimising systemic oxygen delivery according to the underlying diagnosis and physiology. This article will begin with a review of the pathophysiology of circulatory insufficiency, focusing on the period early after surgery for CHD. This background will provide a template for the ensuing discussions of a range of strategies for manipulating the circulation and optimising systemic oxygen delivery of infants and children with CHD, focusing mainly on postoperative management.

RECOGNISING IMPAIRED SYSTEMIC OXYGEN DELIVERY EARLY AFTER SURGERY

An evolving or established low cardiac output state should always be suspected in infants and children who are not progressing as would be expected early after cardiac surgery. The low cardiac output state may have one or more of the following manifestations: increased heart rate, worsening acidosis, organ dysfunction, elevated atrial pressures, elevated central temperature, systemic hypertension or hypotension, or cardiac arrest. In a landmark study of infants early after the arterial switch operation, Wernovsky identified a typical time course for the low cardiac output state when related to cardiopulmonary bypass itself, with the nadir of cardiac output predictably occurring between 9–12 h after surgery, with a return to “normal” by 24 h. Concomitant with this fall was an increase in calculated systemic and pulmonary resistances.¹

Clinicians caring for patients early after cardiac surgery will indeed be familiar with the notion that clinical deterioration tends to prevail during the first postoperative night. In current practice, direct measurement of cardiac output or index is rare, and our ability to estimate this accurately is poor.² In the absence of cardiac output measurement, we therefore rely more on trends in haemodynamic parameters, including heart rate, atrial pressures, systemic arterial pressure, and upon surrogate markers for adequacy of oxygen delivery. Commonly used markers of impaired oxygen delivery include a fall in mixed venous oxygen saturation, increased metabolic acidosis, and elevated blood lactate concentrations.² A fall in central venous oxygen saturation to <55% has been associated with increased early morbidity and mortality in infants after the Norwood operation.³ An increased blood lactate or base deficit during the first 8 h after surgery have also been shown independently to predict adverse outcomes in children after surgery for CHD.²

Any intervention aimed at improving systemic oxygen delivery should be followed by careful monitoring of available haemodynamic and laboratory parameters, in order to determine whether or not this has improved the situation. The lack of a desired response within a reasonable time frame, or a later onset of these features (suggesting it may not be a predictable post-bypass phenomenon) should always prompt further investigation, and may necessitate additional intervention.

PATHOPHYSIOLOGY OF REDUCED SYSTEMIC OXYGEN DELIVERY AFTER SURGERY FOR CHD

There are a number of common causes of reduced oxygen delivery early after cardiac surgery. In general the clinical manifestations of these are similar, but their treatment may be very different. Good intensive care of cardiac patients requires a pre-emptive approach which is tailored for the individual patient according to the nature of the underlying lesion and surgery. Patients who are not progressing as would be expected require early re-investigation with echocardiography, or other imaging techniques in order to distinguish between possible causes, and to guide subsequent treatment.

Abnormal ventricular–vascular interaction after bypass

CPB results in a systemic inflammatory response. This results from the interaction between host
factors with exogenous factors, including exposure of the blood to foreign surfaces, ischaemia–reperfusion injury, and temperature change. The inflammatory response after surgery for CHD is commonly associated with abnormal ventricular–vascular interaction, with systemic vasodilatation and elevated afterload, as well as myocardial injury with impaired systolic and diastolic function. In a proportion of patients, these haemodynamic manifestations produce more profound clinical effects and a low cardiac output state may ensue.

**The functionally univentricular circulation**

In infants with a functionally univentricular heart with duct dependent perfusion, or early after palliative surgery with a systemic-to-pulmonary artery shunt, the total cardiac output is distributed from a single ventricular stroke volume to the systemic and pulmonary circuits. The relative distribution of flow to each circuit is largely dictated by their respective vascular resistances. The risk of reduced systemic oxygen delivery is exacerbated by the elevated afterload which is typical early after CPB. At this time, seemingly trivial elevations in systemic resistance can result in acute pulmonary overcirculation and systemic hypoperfusion. Thus, the perioperative care of infants undergoing modified Blalock–Taussig shunts, or Norwood-type operations, must include strategies to optimise the systemic and pulmonary vascular resistances.

**Abnormalities of diastolic function after surgery to the right heart**

Children after right heart surgery and Fontan-like operations often have abnormalities of diastolic cardiac function. The clinical manifestations of the low output state in children with diastolic dysfunction are similar to patients with systolic impairment, but their haemodynamic management is very different. Echocardiography should therefore be used to guide treatment in these patients.

**Residual anatomic lesions**

In a minority of children, a low cardiac output can be directly attributable to residual anatomic lesions, which may mimic any of the causes already discussed. Residual surgical problems do not in general respond favourably to medical measures and most often require specific invasive intervention. This review will not consider the spectrum of anatomic causes of a reduced cardiac output, other than to emphasise the importance of careful assessment of any patient that is not doing well, or does not progress as expected early after surgery for CHD.

**Pathophysiology of cardiovascular dysfunction early after CPB: summary**

Most infants and older children have a degree of cardiovascular dysfunction early after surgery for CHD. In many, this is directly attributable to CPB, but can be exacerbated by factors pertaining to the associated circulatory physiology and to the surgery itself. Postoperative haemodynamic management should proactively be tailored to the individual patient’s diagnosis, in order to prevent the onset of a low output state. If these measures are unsuccessful, then early re-assessment is essential in order to confirm (or refute) the presumptive pathophysiology, and to guide ongoing treatment.

**PRINCIPLES OF CIRCULATORY MANAGEMENT OF CHILDREN AFTER SURGERY FOR CHD**

The optimisation of systemic oxygen delivery in children with CHD generally involves the manipulation of one or more of the following: systolic myocardial function, diastolic function, preload, the systemic and pulmonary vasculatures, and heart–lung interactions. Commonly used tools for the postoperative circulatory manipulation in children with CHD are: pharmacological agents which target cardiac function and vascular tone; respiratory manipulation through heart–lung interactions; mechanical support with extracorporeal techniques; and the manipulation of rate and rhythm.

The remainder of this review will provide an overview of some of these therapies and their application after surgery for CHD. The intention of this review is to provide the reader with a good understanding of how individual patients may benefit from a range of therapeutic interventions, according to their diagnosis and clinical condition. It will become clear that the ideal therapeutic approach for one type of circulatory physiology may be very detrimental in another. Moreover, for some patients, the best intensive care may require a so-called “hands-off” approach, with minimal intervention on a background of careful observation.

**CARDIOVASCULAR DRUGS**

In recent years, our understanding of the pathophysiology of circulatory insufficiency has improved. Intravenous cardiovascular drugs remain a mainstay in the early management of children after cardiac surgery. However, as our understanding of cardiovascular dysfunction after surgery for CHD has improved, so the focus of treatment has shifted from the manipulation of systolic function, to afterload and minimising myocardial work.

**Special considerations in CHD**

When considering cardiovascular drug treatment in children with CHD, it is important first to consider some factors which are unique to this patient group, and may influence the choice of agent.

**Abnormalities of sympathetic innervation**

**Maturational abnormalities**

The neonatal myocardium has less sympathetic innervation than the more mature heart, which
may impact upon the efficacy and safety, and dosing of catecholamines. This can reduce their inotropic effects and can result in less postsynaptic uptake, which may potentiate the risk of cardiotoxicity.

Abnormalities related to severity of defect
Sympathetic dysregulation is common in infants and children with CHD. Severe CHD, with or without cyanosis, is associated with reduced density of β-adrenoceptors, increased concentrations of endogenous norepinephrine (noradrenaline), and partial uncoupling of the receptor to adenylate cyclase. This can lower the responsiveness of the myocardium to exogenous catecholamines.

The pulmonary vasculature
Pulmonary hypertension after surgery for CHD is a risk factor for prolonged intensive care stay, and death. Lability of pulmonary vascular tone is common in neonates and infants after surgery for CHD. This can be most problematic after biventricular repairs in patients who had preoperative unrestricted pulmonary flow (large septal defects, common arterial trunk) or pulmonary venous hypertension (obstructed anomalous pulmonary venous drainage). Instability of the pulmonary vascular resistance is also common after palliative surgery in patients with a functionally univentricular circulation, including Norwood-type operations, a systemic-to-pulmonary artery shunt, or a pulmonary artery band.

While many therapeutic interventions optimise systemic oxygen delivery through their direct influences on the myocardium and systemic vasculature, manipulation of the pulmonary vascular tone can play an important role in optimising the circulation of children undergoing surgery for heart disease.

Complex circulations
The careful manipulation of systemic vascular tone is of particular importance in patients with a functionally univentricular heart. In these patients, it is usually necessary to maintain a well dilated systemic vasculature, while controlling the pulmonary vascular resistance. An elevated systemic vascular resistance has been implicated as a contributor to adverse outcome after palliation of hypoplastic left heart syndrome.

There are occasions where reductions in vascular resistance may be detrimental after surgery for CHD. This is particularly the case in patients with significant obstruction to systemic or pulmonary outflow. Examples include: persistent obstruction to systemic outflow after relief of aortic stenosis; residual right ventricular outflow obstruction after tetralogy of Fallot repair; or subaortic obstruction after repair of double outlet right ventricle. Many of these patients may require reoperation in order to relieve this fully and restore good haemodynamics. However, until this is achieved, a reduction of preload or afterload with vasodilators is generally not desirable as this may result in an acute fall in cardiac output with adverse consequences.

Classification of cardiovascular drugs
Cardiovascular drugs are generally classified according to their pharmacological actions, and also by their physiological effects. The main pharmacological classes of drugs are the catecholamines, the phosphodiesterase inhibitors, and the newer cardiovascular drugs which include calcium sensitisers and natriuretic peptides. Physiological effects are broadly categorised as predominantly inotropic, predominantly vasodilator, or a combination of the two—inodilator.

In this review, which offers a practical approach, we will classify vasoactive drugs according to their physiological effects. These are summarised in table 1. The dose range for catecholamines in particular is affected by a number of factors, including age and maturity, indications, timing with respect to surgery, and the duration of the infusion. It is important to note that there are no clinical trials which have produced concrete recommendations regarding dosing. Thus, the suggested dose ranges for these agents should be considered as “guides”.

Inotropes
Children early after surgery for CHD often have impaired cardiac function. Although this in itself is not an indication for inotropic support, inotropes are often administered early after surgery: during weaning from CPB, or later on the intensive care unit in the child who is developing signs of reduced oxygen delivery. A number of cardiovascular drugs have inotropic properties, but the majority which are currently used in cardiac intensive care have equally (if not more) beneficial vasodilator effects. Epinephrine (adrenaline) is the cardiovascular agent which is most commonly administered for its inotropic effects.

Epinephrine
Epinephrine is a short acting catecholamine with a half life of only a few minutes. It is most often used as a positive inotrope in patients with reduced systemic oxygen delivery and impaired systolic ventricular function after cardiac surgery. The newborn heart may be particularly sensitive to the inotropic properties of very low doses of epinephrine, and this may be very useful after biventricular repair in the early neonatal period.

Although low dose epinephrine theoretically produces systemic vasodilation through its β-adrenergic effects, in practice this is often offset by significant concomitant α-1 mediated vasoconstriction. This results in increased afterload and myocardial work which are undesirable early after CPB, and may be detrimental in infants with a functionally univentricular circulation. Systemic vasoconstriction may be avoided with the simultaneous infusion of a systemic vasodilator such as sodium nitroprusside.
Low dose epinephrine (0.01–0.05 μg/kg/min) would be recommended for infants with severe systolic dysfunction early after surgery. Higher doses are more likely to cause systemic vasodilation and increased afterload.

**Inodilators**

Inodilators combine gentle inotropic stimulation with peripheral and coronary vasodilation.

**Dobutamine**

Dobutamine is a β-adrenergic agonist with combined inotropic and vasodilator properties. Although it also has chronotropic effects, any increase in myocardial oxygen consumption which could result from an increased heart rate is offset by concomitant coronary vasodilatation and improved myocardial blood flow. The appeal of dobutamine as a single agent arises from the combination of its inotropic and dilatory effects which co-exist at a single dose. This contrasts with dopamine which often produces unwanted vasoconstriction.\(^9\) Despite its appealing properties and improved myocardial contractility, dobutamine is generally administered at doses up to 10 μg/kg/min. Higher doses would tend to result in excessive tachycardia without added benefit.

**Milrinone**

Milrinone is a phosphodiesterase 3 (PDE-3) inhibitor, which prevents the intracellular hydrolysis of 3’5’ cyclic adenosine monophosphate (cyclic AMP). PDE-3 is plentiful in the myocardium and vascular smooth muscle cells. An increase in intracellular cyclic AMP results in peripheral and coronary vasodilation, increased myocardial contractility, and improved myocardial relaxation. Milrinone has a much longer half-life than the catecholamines, and its clinical effects generally last for between 6–24 h after discontinuing an infusion.

The Primacorp study demonstrated that milrinone prevented the onset of a low cardiac output state in a heterogeneous population of infants and children who were already receiving catecholamine infusions early after biventricular repair of CHD.\(^6\) Milrinone also has pulmonary vasodilator effects which are useful for children at risk of postoperative pulmonary hypertension—for example, early after closure of a large intracardiac shunt or neonatal repairs.\(^6\) As for all systemic vasodilators, milrinone should not be used in patients with significant obstruction to systemic or pulmonary outflow.

The Primacorp study concluded that a bolus dose of 75 μg/kg be given over 1 h, and that this should be followed by an infusion at 0.75 μg/kg/min (the so-called high dose regimen). Lower doses were not found to be associated with a significant benefit. More recent investigations have focused on the dosing regimen for high risk neonates in whom the pharmacokinetics might be affected by maturational differences as well as impairment of renal function early after surgery.\(^7\)\(^,\!)\) The recommended starting infusion rate for milrinone in this population following the bolus dose is 0.2 μg/kg/min, increasing to 0.5 μg/kg/min according to clinical effect (mixed venous saturation, acid–base balance, or end organ perfusion) and intrinsic renal function.

**Levosimendan**

Levosimendan is a calcium sensitising drug. It augments myocardial contractility by increasing the sensitivity of the contractile apparatus to intracellular calcium.\(^8\)\(^,\!)\) It also opens the ATP sensitive potassium channels of vascular smooth muscle to produce coronary and peripheral vasodilation.\(^8\)\(^,\!)\) Levosimendan has relatively unique pharmacokinetics, with a single 24 h infusion producing clinical effects for several days.\(^6\) This is achieved through the continuing haemodynamic effects of its two active metabolites.

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**Table 1** Pharmacological options for postoperative circulatory manipulation in congenital heart disease

<table>
<thead>
<tr>
<th>Haemodynamic targets</th>
<th>Desired effect</th>
<th>Current recommendations</th>
<th>Other options and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biventricular circulation early after CPB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Afterload</td>
<td>• None</td>
<td>• None</td>
<td></td>
</tr>
<tr>
<td>• ± Contractility</td>
<td>• Vasodilation or inodilation</td>
<td>• Milrinone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Gentle inotropic stimulation</td>
<td>• Low dose epinephrine or dobutamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levosimendan</td>
</tr>
<tr>
<td>Severe systolic dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Contractility</td>
<td>• Inotropic stimulation</td>
<td>• Low dose epinephrine or dobutamine</td>
<td></td>
</tr>
<tr>
<td>• Afterload</td>
<td>• Inodilation</td>
<td>• Milrinone</td>
<td></td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Preload</td>
<td>• Vasoconstriction</td>
<td>• Nitroprusside, phenoxybenzamine</td>
<td></td>
</tr>
<tr>
<td>• Control systemic vascular tone</td>
<td></td>
<td></td>
<td>Levosimendan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milrinone</td>
<td></td>
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<tr>
<td>Norwood-type operations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Afterload reduction</td>
<td>• Vasodilation</td>
<td>• Dobutamine or low dose epinephrine</td>
<td></td>
</tr>
<tr>
<td>• Good contractility</td>
<td>• Gentle inotropic stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic to pulmonary artery shunt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Maintenance of diastolic perfusion pressure</td>
<td>• Minimal vasoconstriction (for diastolic pressure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Enhancement of systemic perfusion</td>
<td>• Inodilation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Norepinephrine, Dobutamine</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; ECLS, extracorporeal life support.
Levosimendan has been widely investigated in adults, and there is growing evidence to support its perioperative use in cardiac surgical patients. A recent study demonstrated improved reduced intensive care stay and better survival in high risk adults given prophylactic levosimendan during surgery. In a comparison with milrinone in adults with poor cardiac function, levosimendan resulted in superior postoperative haemodynamics, a reduced need for norepinephrine, and a shorter duration of ventilation.

There is little published evidence for levosimendan in paediatrics. We have recently reported improved ejection fraction and reduced catecholamine requirements in a cohort of children with a severe low cardiac output early after cardiac surgery (fig 1). In a laboratory comparison of levosimendan and milrinone after infant CPB, both agents similarly improved afterload and ventricular–vascular coupling, but levosimendan had superior effects on contractility. Levosimendan has potential appeal in children with CHD. It may prove to have an important role in the prevention or early treatment of the low output state in high risk patients after cardiac surgery, but this application warrants more detailed investigation.

A recent pharmacokinetic study concluded that an intravenous bolus of 12 μg/kg levosimendan over 10 min was appropriate in children with heart disease. This bolus should be immediately followed by a continuous infusion at 0.2 μg/kg/min for 24 h. Subsequent doses can safely be given at 1–2 week intervals.

Vasoconstrictors
Uncontrolled increases in afterload may jeopardise cardiac performance, and are generally not desirable early after cardiac surgery. For this reason systemic vasoconstrictors should only be used after careful assessment of the patient.

Norepinephrine
Norepinephrine produces α-1 mediated vasoconstriction, without any substantial direct myocardial effects. Although more commonly encountered in adult intensive care, a vasodilatory inflammatory response to CPB is also present in some children early after surgery, and this is often very responsive to norepinephrine. Norepinephrine may also enhance coronary flow in patients with diastolic run-off after a systemic-to-pulmonary shunt, and may improve pulmonary perfusion and systemic cardiac output in patients after Fontan operations. Norepinephrine may prove preferable to colloid administration as a means for maintaining haemodynamic stability early after surgery.

The dose of norepinephrine is generally titrated to specific haemodynamic targets such as mean arterial pressure or diastolic blood pressure. Very low doses (0.01–0.05 μg/kg/min) would normally be recommended to stabilise patients after surgery for CHD. Higher doses should be given with caution as they may result in excessive increases in afterload.

Figure 1 Early experience with intravenous levosimendan in 10 children with severe myocardial dysfunction. Five patients were given levosimendan as treatment for acute ventricular dysfunction. 9

Systemic vasodilators
Careful systemic vasodilation is often beneficial early after cardiac surgery, as this affords reduced afterload, improved myocardial performance, and promotes systemic oxygen delivery. In patients after palliation for hypoplastic left heart syndrome, systemic vasodilation affords protection from acute increases in systemic resistance and afterload which are known adversely to influence their outcome.

An important consideration when choosing a vasodilator is the patient’s likelihood of tolerating this sort of agent, and this may dictate whether a short or long acting agent is selected in the first instance. The tolerance of vasodilators is affected by the intravascular status, or by any actual or potential outflow tract obstruction. Hypovolaemia can be mitigated or pre-emptively treated with the administration of colloid; but systemic vasodilation in the present significant outflow tract obstruction may have disastrous consequences. If there is any doubt, careful imaging should be used to exclude this prior to administering a vasodilator, and a very low dose of a short acting agent such as sodium nitroprusside should first be given.

Phenoxybenzamine
In recent years the long acting α-adrenoceptor antagonist phenoxybenzamine has gained popularity for infants after surgical palliation of hypoplastic left heart syndrome or related defects. Phenoxybenzamine improves systemic oxygen delivery, though the irreversible α-blockade and prolonged effect, without any pharmacological "antidote", has limited its popularity in some
centres. In centres where it is a favoured vasodilator, phenoxybenzamine is commonly given during weaning from CPB, and then continued postoperatively on the intensive care unit.

“Full” α-blockade is generally achieved with a total of 1–2 mg/kg phenoxybenzamine. If this is given on the intensive care unit, it should be infused over several hours to avoid systemic hypotension. This can be followed by further doses of 1–2 mg/kg per day in divided doses.

Nesiritide

Nesiritide, which is recombinant B type natriuretic peptide (BNP), is a systemic vasodilator without any direct myocardial effects. It binds with the A and B type natriuretic peptide receptors of the vascular endothelium and smooth muscle, which leads to increased cyclic GMP production and vasodilation, while avoiding any reflex tachycardia through inhibition of cardiac sympathetic activity. Nesiritide also increases the glomerular filtration rate, and inhibits sodium reabsorption, leading to diuresis and natriuresis.

Nesiritide has been widely investigated in adults with acute decompensated heart failure. A recent pooled analysis of randomised trials of nesiritide in adults not receiving additional inotropic agents showed, contrary to earlier reports, that it might be associated with a worse outcome. It was suggested that adverse outcomes may be related to a worsening of renal function in the absence of any additional cardiovascular agents which might assist in maintaining an adequate renal perfusion pressure.

There is growing experience of nesiritide in children, and its safety has been demonstrated in children with acute-on-chronic cardiac failure, or a low cardiac output state early after cardiac surgery. In these patients, nesiritide was associated with improved urine output, and reduction in neurohumoral markers of cardiac failure. As for levosimendan, further research, and in particular comparative trials, will be necessary before establishing whether or not nesiritide has a role in the primary treatment of children with cardiac disease.

The recommended dose range for intravenous nesiritide infusion in infants and children with heart disease is 0.01–0.03 μg/kg/min.

Pulmonary vasodilators

Acute postoperative pulmonary hypertension and “pulmonary hypertensive crises” are relatively uncommon in the current era. This has resulted from the pre-emptive management of high risk patients with measures including earlier surgery, the use of modified ultrafiltration, careful postoperative ventilation, and the use of vasoactive drugs such as milrinone which produce pulmonary as well as systemic vasodilation. The use of inhaled nitric oxide may also have contributed to this trend (see Mechanical ventilation).

A number of systemic pulmonary vasodilators exist, though their non-selective effects may limit their usefulness in the acute postoperative setting.

Sildenafil, a phosphodiesterase 5 inhibitor, is now commonly used as a medium and long term treatment for pulmonary hypertension in patients with CHD. However, it produces systemic as well as pulmonary vasodilation, and is not selective for ventilated lung regions, thus producing increased ventilation–perfusion mismatch. This latter property can be particularly pronounced in the presence of inflammatory lung injury early after bypass, resulting in an increase in the alveolar-to-arterial gradient. As a result, the use of sildenafil as a primary pulmonary vasodilator would not be recommended in the immediate postoperative period, but should instead be considered as medium or long term treatment in patients who are at risk for, or already have more established, pulmonary hypertension. A single dose of sildenafil (0.4 mg/kg) prevents rebound pulmonary hypertension during weaning from inhaled nitric oxide, and should be routinely considered in this setting.

MECHANICAL VENTILATION

Ventilation is an important haemodynamic tool in children with CHD. As with cardiovascular drugs, appropriate ventilation for one child may be unsuitable for another depending on the underlying physiology and circulatory status. In this section, the interactions between ventilation and the cardiovascular system (heart–lung interactions) will be discussed, with respect to specific postoperative physiological problems, and circulatory patterns. These are summarised in table 2.

Systolic dysfunction

Positive pressure ventilation is beneficial to infants and children with systolic dysfunction early after cardiac surgery. Through the direct effects of increased intrathoracic pressure on the circulation, and indirectly through the associated reduction in work of breathing and the avoidance of excessive negative inspiratory swings during inspiration, positive pressure ventilation reduces left ventricular afterload and right heart preload.

Subgroups of patients who may particularly benefit from the haemodynamic effects of positive pressure ventilation include infants after a late arterial switch operation for transposition with an intact ventricular septum, and those after repair of anomalous left coronary artery from the pulmonary artery. Elective continuous positive airway pressure (CPAP) ventilation should be considered routinely in these patients after tracheal extubation.

Diastolic dysfunction

Infants and children with diastolic impairment have haemodynamic responses to positive pressure ventilation that are very different from those with systolic dysfunction. Systolic dysfunction is rare early after tetralogy of Fallot repair or after Fontan operations, whereas complex abnormalities of diastolic function are common, and may contribute to a low cardiac output state.
Education

Heart–lung interactions during spontaneous and mechanical ventilation in congenital heart disease

Table 2  Heart–lung interactions during spontaneous and mechanical ventilation in congenital heart disease

<table>
<thead>
<tr>
<th>Typical haemodynamic considerations</th>
<th>Spontaneous respiration</th>
<th>Positive pressure ventilation</th>
<th>Guide for routine ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic dysfunction (early after CPB)</strong></td>
<td>Increased LV afterload and myocardial dysfunction</td>
<td>Normal or exaggerated negative intrapleural pressure increases LV afterload</td>
<td>Reduced work of breathing; obliterates negative swings in pleural pressure</td>
</tr>
<tr>
<td><strong>Tetralogy of Fallot with restrictive RV</strong></td>
<td>Good systolic function</td>
<td>Negative pressure increases RV preload and augments diastolic pulmonary artery flow</td>
<td>Reduced RV preload</td>
</tr>
<tr>
<td><strong>Post-op Fontan</strong></td>
<td>Good systolic function</td>
<td>Negative pressure reduces pressures and improves pulmonary blood flow</td>
<td>Reduced preload; reduced pulmonary blood flow</td>
</tr>
<tr>
<td><strong>Post-op BCPS</strong></td>
<td>Good systolic function</td>
<td>Improved pulmonary blood flow and systemic oxygen delivery</td>
<td>Reduced pulmonary flow</td>
</tr>
<tr>
<td><strong>Shunt (or duct) dependent systemic flow</strong></td>
<td>Systolic function usually good</td>
<td>Preoperative tachypnoea may result in respiratory alkalosis and oversaturation. This may limit control of PVR</td>
<td>Enables pre- and postoperative control of pulmonary flow, pH, and pulmonary resistance</td>
</tr>
<tr>
<td></td>
<td>Stable PVR essential</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory alkalosis leads to excessive pulmonary flow and systemic hypoperfusion</td>
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</tr>
</tbody>
</table>

BCPS, bidirectional cavopulmonary shunt; CPAP, continuous positive airway pressure ventilation; CPB, cardiopulmonary bypass; LV, left ventricle; PA, pulmonary artery; PVR, peripheral vascular resistance; RV, right ventricle.

In his original description of the operation, Fontan observed the clinical improvement that accompanied extubation, and recommended that spontaneous respiration be established early after surgery. Pulmonary blood flow in the Fontan circulation is predominantly passive, and depends on adequate venous return to a low resistance, unobstructed pulmonary circulation. The pulmonary blood flow of Fontan patients is very dependent on a low intrathoracic pressure. It is augmented by a negative intrathoracic pressure (for example, during spontaneous inspiration) but is compromised by the increase in intrathoracic pressure during positive pressure ventilation. In patients who have restrictive right ventricular physiology early after repair of tetralogy of Fallot, diastolic pulmonary arterial flow is an important source of cardiac output. Similar to Fontan patients, this flow is obliterated by increases in intrathoracic pressure, and augmented by a negative intrathoracic pressure.

In patients after right heart surgery, therefore, positive pressure ventilation can contribute to haemodynamic instability by impeding pulmonary blood flow. Ventilation should be used routinely to manipulate the circulation, and postoperative care should include the use of conservative airway pressures aiming for early extubation. Some cardiac units have adopted a fast track approach to the care of Fontan patients, which includes extubation before return to the intensive care unit. This practice, conducted safely, requires significant commitment from personnel outside of the intensive care unit and may not be practically possible. However, the avoidance of muscle relaxants, excessive sedation, and the early use of ventilatory modes that allow spontaneous patient initiated breathing, all contribute to improved early postoperative haemodynamics and enable early tracheal extubation. This approach, which is common to many cardiac centres including our own, enables early extubation for the majority of Fontan patients (fig 2).

Bidirectional cavopulmonary shunt

There are similarities between the circulations of patients after a bidirectional cavopulmonary shunt (BCPS), and after Fontan operations, in that the pulmonary flow is preload dependent, and relies upon a low resistance pulmonary circuit. However, the pulmonary blood flow of patients after a BCPS is entirely derived from upper body venous return. Elevations of superior vena cava (pulmonary artery) pressure, related to systemic venous or pulmonary arterial obstruction, pulmonary hypertension or high airway pressures, result in systemic desaturation, and may jeopardise systemic oxygen delivery. Recent studies have demonstrated that modest elevation of arterial carbon dioxide tension improves cerebral oxygen delivery and systemic oxygenation, and reduces oxygen consumption early after BCPS. It would therefore appear that hypercapnic cerebral vasodilation predominates over any pulmonary vasoconstriction, and affords an overall improvement in haemodynamics.

On returning from the operating room, patients after a BCPS should routinely be cared for with elevation of the upper body, to assist systemic venous drainage. They should be ventilated with conservative airway pressures, with an arterial carbon dioxide tension of 5.5–6.5 kPa, aiming for early extubation. Similar to Fontan patients, early extubation of infants and children after BCPS is generally associated with haemodynamic improvement, increased systemic cardiac output, and reduced pulmonary artery pressure.
The functionally univentricular circulation
Ventilation is an important haemodynamic tool in newborns with a functionally univentricular circulation. Similar principles apply to infants with hypoplastic left heart syndrome before or after surgery, or after a systemic-to-pulmonary artery (modified Blalock–Taussig) shunt. The optimisation and control of systemic oxygen delivery in these high risk infants requires the maintenance of a stable pulmonary vascular resistance. In these infants, excessive oxygen or significant alkalosis can lead to pulmonary overcirculation and reduced systemic oxygen delivery.

In a previous era, ventilation was used to induce pulmonary vasoconstriction with acidosis or deliberate hypoxia, with the intention of augmenting systemic perfusion. Similarly, additional inspired oxygen was generally avoided in these patients, for fear of its impact on systemic oxygen balance. However, it is now recognised that these manoeuvres, and particularly deliberate hypoxia, are generally of little benefit and may in fact impair systemic oxygen delivery. It is also accepted that in the presence of systemic vasodilation, modest additional inspired oxygen, a normal arterial carbon dioxide tension, and a normal acid–base balance, results in improved systemic oxygen delivery. Indeed, the maintenance of high pulmonary venous oxygen saturation levels should be a mainstay of intensive care.

Pulmonary hypertension
Acute pulmonary hypertensive events are relatively uncommon in the current era, but early postoperative pulmonary hypertension may complicate the recovery of infants after repair of obstructed pulmonary venous drainage, or after closure of large left-to-right shunts. In these high risk patients, postoperative ventilation plays a key role in the maintenance of a stable pulmonary vascular resistance. Ventilatory targets in the early post-operative period would include a low-normal carbon dioxide tension (4.6–5.5 kPa), the absolute avoidance of hypoxia (target arterial oxygen tension >11 kPa), and the maintenance of good lung function. In addition, the avoidance of agitation or stress is important early after surgery, and, to this end, an intravenous bolus of fentanyl should routinely be considered before endotracheal suction in high risk patients.

Inhaled nitric oxide
Inhaled nitric oxide is a selective pulmonary vasodilator which has the advantage of targeting only ventilated lung regions, and thus does not exacerbate intrapulmonary shunt. Nitric oxide is used in many cardiac units to treat moderate or severe pulmonary hypertension, or to pre-emptively manage patients at high risk for this. Its recent approval by the US Food and Drug Administration has resulted in substantial increases in the cost of nitric oxide worldwide, and has prompted careful review of the indications for its use. A recent systematic review of the role of nitric oxide in patients with CHD highlighted the paucity of well designed, controlled trials. The review concluded that nitric oxide was indeed a very effective pulmonary vasodilator, but with the limited available material, it could not show any beneficial effects on outcome.
Nitric oxide is not a substitute for good, basic intensive care, and other causes of instability (abnormal gas exchange, or parenchymal lung problems) in high risk patients should always be sought. We would recommend that nitric oxide be reserved for unstable patients with moderate or severe pulmonary hypertension, or for those with escalating pulmonary pressures early after cardiac surgery. Once nitric oxide therapy is commenced, the lowest possible dose that produces the desired response should be used, and the need for its continued administration should be regularly reviewed. If there is no response to nitric oxide, then it should be discontinued. Nitric oxide is rarely indicated for more than 48 h after surgery. It should be gradually weaned, with meticulous attention to avoiding any other factors which can exacerbate rebound pulmonary hypertension. Rebound may be prevented with a single dose of enteral sildenafil.

**EXTRACORPOREAL LIFE SUPPORT**

Temporary extracorporeal life support (ECLS), using extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD), provides circulatory assistance when the intrinsic cardiovascular function cannot adequately support the circulation, and provides partial or complete myocardial rest. In most paediatric centres with an ECLS programme, the use of mechanical support after cardiac surgery is generally considered at a stage where further escalation of pharmacological support is unlikely to prevent further decline or will only do so at the expense of excessive myocardial work. The overall survival to hospital discharge for children after ECLS for cardiac disease is currently between 55–50%.

**Indications for ECLS**

ECLS has an established role as short term support for infants and children with a critical low cardiac output state secondary to severe ventricular dysfunction early after surgery, or for those who cannot be weaned from CPB. It is also occasionally used to manage acute postoperative pulmonary hypertension in children who are unresponsive to conventional medical treatments, and more recently has become established in the resuscitation of infants and children during cardiac arrest early after cardiac surgery. The spectrum of patients for whom ECLS is now offered has grown over the years, and the readiness to provide ECLS is to an extent dictated by institutional experience, expertise and resources, such that strict “criteria” no longer exist. However, mechanical support should only be considered for patients who are expected to recover to a reasonable level of function with or without additional intervention. In some cases, where the underlying reason for cardiovascular instability is uncertain, mechanical support can offer a period of stability and therefore provide an opportunity for further cardiological investigation.

**ECMO or VAD?**

ECMO provides biventricular and pulmonary support, whereas VAD assists one or both ventricles. The VAD circuit does not include an oxygenator and therefore requires less anticoagulation than ECMO, but it relies on adequate function of the unassisted ventricle, and the lungs.

ECMO can offer complete cardiopulmonary rest. It is generally used to support children with biventricular dysfunction early after CPB, those with postoperative pulmonary hypertension, and patients with isolated ventricular dysfunction and significant lung disease. ECMO, and not VAD, should be used during resuscitation from a cardiac arrest. Although this is difficult to substantiate with evidence from the literature, VAD is most likely to be successful if initiated early, in the patient in whom there is a significant likelihood of ongoing deterioration with conventional management. However, if initiated near or at the point of cardiac arrest, it is unlikely to be successful. Specific indications for VAD support include infants after reimplantation of anomalous left coronary artery arising from the pulmonary artery. VAD would also be the modality of choice for supporting patients with a functionally univentricular circulation and low cardiac output state. The decision making process for determining the type of mechanical support in the postoperative setting is summarised in table 3.

**ECLS in complex circulations**

**Systemic-to-pulmonary artery shunt**

Infants with a functionally univentricular circulation and a systemic-to-pulmonary artery shunt were previously considered to be poor candidates for mechanical support. This was in part due to delayed decision making and higher complication rates, as well as shunt management. In the past, complete shunt occlusion was performed during cannulation for ECMO, in order to prevent systemic hypoperfusion resulting from uncontrolled pulmonary flow. Although shunt occlusion was theoretically reasonable, it was proposed that the dismal outcome for ECMO in infants with a shunt may have been related to a total absence of pulmonary perfusion. More recently, leaving the shunt either completely patent or only minimally restricted, has been associated with improved survival. The overall survival outcome for infants with a functionally univentricular heart receiving ECLS is now similar to that for patients with biventricular physiology.

**Cavopulmonary connection**

Complex CHD with a bidirectional cavopulmonary shunt, or the Fontan circulation, was also historically associated with poor outcomes. Indeed, in a previous era, the cavopulmonary circulation was considered by many to be a contraindication for ECLS. However, outcomes for these patients has improved since the early 1990s, and while accepting that they still carry the highest
Risk operation, as significant uncorrected residual lesions may preclude successful weaning from support. Assessment of patients on ECLS generally begins with detailed echocardiography, and if there is any index of suspicion of an anatomic cause that is not evident on ultrasound, then additional diagnostic imaging may be necessary (cardiac catheterisation or computed tomography angiography).

Temporary ECLS for failure to wean from CPB, or for a postoperative low output state and ventricular dysfunction, should be continued until sufficient myocardial recovery has occurred to support the circulation. Myocardial recovery generally begins within 48 h of separation from CPB, and the absence of any recovery of ventricular function after 72 h of support is associated with a poor outcome.

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Competing interests: In compliance with EBAC/EACCME guidelines, all authors participating in Education in Heart have disclosed potential conflicts of interest that might cause a bias in the article. The author has no competing interests.

Table 3 Mode of extracorporeal support in children with circulatory failure

<table>
<thead>
<tr>
<th>Indication</th>
<th>ECMO/VAD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>ECMO</td>
<td>Default mode of support for children receiving CPR</td>
</tr>
<tr>
<td>Failure to wean from bypass or Early postoperative low cardiac output state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated severe ventricular dysfunction</td>
<td>Single VAD</td>
<td>Unsupported ventricle may require pharmacological support</td>
</tr>
<tr>
<td>Isolated ventricular dysfunction with pulmonary dysfunction</td>
<td>ECMO</td>
<td></td>
</tr>
<tr>
<td>Biventricular dysfunction</td>
<td>BIVAD/ECMO</td>
<td>Institutional preference may be for ECMO, especially in smaller infants</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>ECMO</td>
<td>Nitric oxide not required during ECMO</td>
</tr>
<tr>
<td>Functionally univentricular physiology with a systemic-to-pulmonary artery shunt</td>
<td>ECMO/VAD</td>
<td>Identical cannulation but no oxygenator for VAD. Shunt restriction can be considered</td>
</tr>
</tbody>
</table>

BIVAD, biventricular assist device; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

The past two decades have seen important advances in our understanding of the circulatory physiology of infants and children with CHD, and in available treatments for these complex patients. When approaching the intensive care of patients with heart disease, it is essential to approach the cardiopulmonary system in its entirety, rather than consider the heart, lungs or peripheral circulation as isolated elements. In this review we have discussed some important therapeutic tools and their role in achieving a common goal of optimising systemic oxygen delivery. The material covered is by no means exhaustive, and in the interests of space some therapies, including control or manipulation of rhythm, and the role of interventional procedures, have not been included. We have emphasised the importance of anticipatory intensive care which is tailored for the individual, and the need for early, targeted investigation and intervention when patients are not progressing as expected.

Postoperative manipulation of the circulation: summary

Temporary ECLS after cardiac surgery should be offered to patients with a known underlying pathophysiology and who would otherwise have a reasonable chance of a good outcome, or for those who require further cardiovascular assessment and/or intervention. In the latter group, this is most likely to be due to residual anatomical abnormalities. It is essential to search routinely for a remediable cause in all children who are placed on postoperative support, rather than simply assume that this is due to a long or high mortality for ECLS, most centres now occasionally support patients with these circulations.

Their less encouraging outcomes are most likely to be related to the fact that the low output state after BCPS or Fontan operations is seldom secondary to reversible ventricular dysfunction.

Expected course on ECLS

Temporary ECLS for failure to wean from CPB, or for a postoperative low output state and ventricular dysfunction, should be continued until sufficient myocardial recovery has occurred to support the circulation. Myocardial recovery generally begins within 48 h of separation from CPB, and the absence of any recovery of ventricular function after 72 h of support is associated with a poor outcome.

It is generally accepted that significant improvement in cardiac function is unlikely to occur after 7–10 days of support. Some specific indications would be expected to require shorter periods of support. For example, temporary VAD after anomalous coronary artery reimplantation is generally required for 2–5 days, and a similar period of support would be expected in children with severe, reversible pulmonary hypertension after biventricular repair.

It would certainly be recommended that a wean from ECLS be attempted on day 3 or 4 of support, with the use of modest cardiovascular pharmacological support and careful ventilation. An unsuccessful attempt at this stage should prompt further evaluation.

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Landmark paper demonstrating that cardiac output reaches a nadir at 9–12 h after surgery. This laboratory study demonstrated the importance of nesiritide in paediatrics. This well designed prospective, randomised, placebo controlled trial, a single dose of sildenafil (0.4 mg/kg) given 1 h before discontinuing nitric oxide completely prevented rebound, and this was also associated with a significantly shorter duration of mechanical ventilation and intensive care unit stay.

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9. A unique feature of levosimendan, when compared to most intravenous vasodilators, is that its effects are prolonged secondary to the continuing beneficial effects of its metabolites, primarily OR-1896, with an elimination half-life of 70–80 h. This prospective study in adults showed that while levosimendan concentrations fell rapidly in the first few hours after discontinuing the drug, metabolites continued to increase for a further 24–48 h, with haemodynamic effects lasting at least as long.


13. Phenoxybenzamine has been associated with improved survival early after stage 1 palliation. This article provides an excellent overview of the pharmacology of phenoxybenzamine, and considers its administration in the postoperative setting.


16. There is growing interest in nesiritide in paediatrics. This analysis of three randomised controlled trials, involving 485 nesiritide and 377 control patients, demonstrated increased mortality with nesiritide (hazard ratio 1.80, 95% confidence interval 0.98 to 3.31; p = 0.057). The authors emphasise that this pooled analysis should not be interpreted as an adequately powered prospective trial, but should be considered hypothesis generating rather than a conclusive negative study.


20. Rebound pulmonary hypertension can complicate the weaning of inhaled nitric oxide. In this randomised, placebo controlled trial, a single dose of sildenafil (0.4 mg/kg) given 1 h before discontinuing nitric oxide completely prevented rebound, and this was also associated with a significantly shorter duration of mechanical ventilation and intensive care unit stay.


26. Postoperative management of infants after stage 1 palliation has shifted away from the maintenance of pulmonary vasocostriction, towards the optimisation of systemic oxygen delivery and mixed venous oxygen saturation. This prospective study demonstrated that neither inspired oxygen nor hyperventilation were detrimental early after stage 1 palliation, and higher levels of inspired oxygen were associated with improved systemic oxygen delivery.


29. This important systematic review highlighted the paucity of well designed studies and longer term outcome data in the existing literature. The four studies that fitted the criteria for this analysis showed no short term benefit for children receiving inhaled nitric oxide compared to controls, in terms of the incidence of pulmonary hypoxic crises, haemodynamics, oxygenation, or mortality.


34. In this excellent retrospective review from a single institution, 60 cardiac catheterisations were carried out in children on ECMO. Catheterisation was performed safely, and resulted in 50 transcatheter, surgical, or combined interventions.