Managing low cardiac output syndrome after congenital heart surgery

David L. Wessel, MD

Patients with congenital or acquired heart disease comprise a major diagnostic category for admissions in large pediatric intensive care units (ICUs) across the country, compromising 30% to 40% or more of admissions in many centers. Obviously, assessment and treatment of low cardiac output states among patients with heart disease can be life saving. Although some causes of low cardiac output after cardiopulmonary bypass (CPB) are attributable to residual or undiagnosed structural lesions, progressive low cardiac output states do occur (1). A number of factors have been implicated in the development of myocardial dysfunction after CPB, including the following: 1) the inflammatory response associated with CPB; 2) the effects of myocardial ischemia from aortic cross-clamping; 3) hypothermia; 4) reperfusion injury; 5) inadequate myocardial protection; and 6) ventriculotomy (when performed). The expression and prevention of reperfusion injury after aortic cross-clamping on CPB is currently the subject of intense investigation. Figure 1 shows the typical decrease in cardiac index in newborns after an arterial switch operation. In this group of 122 newborns, the median maximal decrease in cardiac index was 32% (2). A quarter of all these newborns reached a nadir of cardiac index that was <2 L/min/m² on the first postoperative night. Low cardiac output states do occur in the postoperative patient, but appropriate anticipation and intervention can do much to avert morbidity or the need for mechanical support (Table 1).

**Volume Adjustments**

After CPB, the factors that influence cardiac output, preload, afterload, myocardial contractility, heart rate, and rhythm must be assessed and manipulated. Volume therapy (increased preload) is commonly necessary, followed by appropriate use of inotropic and afterload-reducing agents (3). Atrial pressure and the ventricular response to changes in atrial pressure must be evaluated. Ventricular response is judged by observing systemic arterial pressure and waveform, heart rate, skin color and peripheral extremity temperature, peripheral pulse magnitude, urine flow, core body temperature, and acid-base balance.

**Preserving and Creating Right-to-Left Shunts**

Selected children with low cardiac output may benefit from strategies that allow right-to-left shunting at the atrial level in the face of postoperative right ventricular dysfunction. A typical example is early repair of tetralogy of Fallot, when the moderately hypertrophied, noncompliant right ventricle has undergone a ventriculotomy and may be further compromised by an increased volume load from pulmonary regurgitation secondary to a transannular patch on the right ventricular outflow tract. In these children it is very useful to leave the foramen ovale patent to permit right-to-left shunting of blood, thus preserving cardiac output and oxygen delivery, despite the attendant transient cyanosis. If the foramen is not patent or is surgically closed, right ventricular dysfunction can lead to reduced left ventricular filling, low cardiac output, and ultimately, left ventricular dysfunction. In infants and neonates with repaired truncus arteriosus, the same concerns apply and may even be exaggerated if right ventricular afterload is elevated because of pulmonary artery hypertension (4). This concept has been extended to older patients with single-ventricle physiology who are at high risk for Fontan operations. The Fontan circulation relies on passive flow of blood through the pulmonary circulation, without benefit of a pulmonary ventricle. If an atrial septal communication or fenestration is left at the time of the Fontan procedure, the resulting right-to-left shunt helps to preserve cardiac output. These children have fewer postoperative complications (5). It is better to shunt blood right to left, accept some decrement in oxygen saturation, but maintain ventricular filling and cardiac output than to have high oxygen saturation but low blood pressure and cardiac output.

**Other Strategies**

Newer strategies to support low cardiac output associated with cardiac surgery in children include the use of atrio-biventricular pacing for patients with complete heart block or prolonged interventricular conduction delays and asynchrony contraction. Appreciation of the hemodynamic effects of positive and negative pressure ventilation may facilitate cardiac output. Avoidance of hypothermia and even induced hypothermia may provide end organ protection during periods of low cardiac output. Finally, anti-inflammatory agents including monoclonal antibodies, competitive receptor blockers, inhibitors of compliment activation, and preoperative preparation with steroids are being actively investi-
gated in an effort to prevent and protect major organs from ischemic injury imposed by CPB and the reperfusion injury associated with the recovery period.

**Pharmacologic Support**

*Catecholamines*. Failure to improve cardiac output after volume adjustments requires the additional use of an inotropic drug (3, 6–9). Table 2 lists commonly used vasoactive drugs and their actions. Many prefer to use dopamine first in doses of 3–10 μg/kg/min. One rarely uses >15 μg/kg/min because of the known vasoconstrictor and chronotropic properties of dopamine at very high doses. However, extreme biologic variability in pharmacokinetics and pharmacodynamics defies placing narrow limits on recommended dosages. Dobutamine’s chronotropic and vasodilatory advantages recognized in adults with coronary artery disease have not always proved equally efficacious in clinical studies in children. In fact, dobutamine has fewer, or no, dopaminergic advantages for the kidney. This may be an especially important limitation in infants with excess total body water and interstitial edema. The significant chronotropic effect and increased oxygen consumption induced by isoproterenol have also increasingly limited its use in neonates and infants. Epinephrine is occasionally useful for short-term therapy when high systemic pressures are sought, provided the temporary increase in peripheral vascular resistance can be tolerated. High doses of epinephrine are occasionally necessary to increase pulmonary blood flow across significantly narrowed systemic-to-pulmonary artery shunts when oxygen saturations are low and falling. Arginine vasopressin has been advocated for states of refractory vasodilation associated with low circulating vasopressin levels as may rarely occur after CPB in children (10).

**Table 1. Managing low cardiac output syndrome after congenital heart surgery**

<table>
<thead>
<tr>
<th>I. Extent of the problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. One quarter of newborns will decrease their cardiac index to &lt;2.0 L/min/m² after CPB</td>
</tr>
<tr>
<td>II. Exclude residual disease</td>
</tr>
<tr>
<td>A. Transesophageal echocardiography and intracardiac catheters provide important anatomic and physiologic data for planning the need for reintervention</td>
</tr>
<tr>
<td>III. Optimize preload</td>
</tr>
<tr>
<td>A. Monitor filling pressure and interpret values in light of underlying cardiac disease</td>
</tr>
<tr>
<td>B. Afterload reduction</td>
</tr>
<tr>
<td>A. Milrinone, a phosphodiesterase inhibitor, increases cardiac output and lowers filling pressures; nitrates are commonly employed as vasodilators</td>
</tr>
<tr>
<td>2. Phenoxybenzamine is a potent α-blocker and has been advocated as part of the postoperative management of patients with hypoplastic left heart syndrome but has a long duration of action</td>
</tr>
<tr>
<td>3. Nitric oxide is a selective pulmonary vasodilator that will reduce afterload on the right heart</td>
</tr>
</tbody>
</table>

**V. Pharmacologic support**

A. Catecholamines

1. Dopamine (5–15 μg/kg/min) supports cardiac output and preserves aortic perfusion pressure during weaning from CPB; dobutamine may reduce afterload

2. Prolonged high-dose epinephrine after CPB in neonates is associated with myocardial necrosis and marked diastolic dysfunction and is increasingly avoided

**C. Preserving a R-L shunt in patients with known elevation in pulmonary vascular resistance may preserve cardiac output during postoperative pulmonary hypertensive crises or during CPR**

**Table 2. Catecholamines**

<table>
<thead>
<tr>
<th><strong>Catecholamine</strong></th>
<th><strong>Dosage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>5–15 μg/kg/min</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2–5 μg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>10 μg/kg/min</td>
</tr>
<tr>
<td>Milrinone</td>
<td>1–2 μg/kg/min</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0.5 mg/kg/min</td>
</tr>
</tbody>
</table>

**VI. Rhythm**

A. A-V sequential pacing is important for arrhythmias, such as JET or complete heart block

B. Atrio-biventricular pacing may improve hemodynamics substantially in patients with complete right or left bundle branch block

**VII. Ventilation/cardiorespiratory interactions**

A. Positive pressure ventilation reduces left ventricular afterload but decreases preload and may raise pulmonary vascular resistance and RV afterload

B. Negative pressure ventilation (Hayek oscillator) may augment R heart function

**VIII. Hypothermia**

A. There is renewed interest in lowering core body temperature to 34–35°C for patients in low cardiac output states in an effort to reduce oxygen consumption and to optimize oxygen delivery

**IX. Ischemia reperfusion injury**

A. Anti-inflammatory agents including monoclonal antibodies, competitive receptor blockers, inhibitors of complement activation, and preoperative preparation with steroids are being actively investigated in an effort to prevent and protect major organs from ischemic injury imposed by cardiopulmonary bypass and the reperfusion injury associated with the recovery period

**X. Mechanical support**

A. Extracorporeal membrane oxygenation

B. Ventricular assist device

CPB, cardiopulmonary bypass; R, right; L, left; TOF, tetralogy of Fallot; CPR, cardiopulmonary resuscitation; A-V, atrioventricular; JET, junctional ectopic tachycardia; RV, right ventricular.

In the past, the side effects of inotropic support of the heart with catecholamines seemed a lesser concern in children than in adults with an ischemic, noncompliant heart. Tachycardia, an increased end-diastolic pressure and afterload, or increased myocardial oxygen consumption, despite their undesirable side effects, was tolerated by most children in need of inotropic support after CPB. However, with increasing perioperative experience in neonates and young infants, the adverse effects of vasoactive drugs have become more evident. The less compliant neonatal myocardium, like the ischemic adult heart, may raise its end-diastolic pressure during higher doses of dopamine infusion or may develop even more extreme noncompliance. Actual myocardial necrosis caused by high doses of epinephrine infusions has been identified in neonatal animal models after CPB (11, 12). Although these agents do increase the cardiac output, the concomitant increase in ventricular filling pressure is less well tolerated by the immature myocardium than it is in older chil-
Table 2. Summary of selected vasoactive agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Doses (IV)</th>
<th>Peripheral Vascular Effect</th>
<th>Cardiac Effect</th>
<th>Conduction System Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noncatecholamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin (total digitalizing dose)</td>
<td>20 μg/kg premature</td>
<td>Increases peripheral vascular resistance 1–2+; acts directly on vascular smooth muscle</td>
<td>Inotropic effect 3–4+; acts directly on myocardium</td>
<td>Slows sinus node slightly; decreases A-V conduction</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>10–20 mg/kg/dose (slowly)</td>
<td>Variable; age dependent; vasoconstrictor</td>
<td>Indirectly increases cardiac output by decreasing afterload</td>
<td>Slos sinus node; decreases A-V conduction</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>50–100 mg/kg/dose (slowly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.5–5 μg/kg/min</td>
<td>Donates nitric oxide group to relax smooth muscle and dilate pulmonary and systemic vessels</td>
<td>Indirectly increases cardiac output by decreasing afterload</td>
<td>Reflex tachycardia</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0.5–10 μg/kg/min</td>
<td>Primarily venodilator; as a nitric oxide donor may cause pulmonary vasodilation and enhance coronary vasoreactivity after aortic cross-clamping</td>
<td>Decreases preload, may decrease afterload; reduces myocardial work related to change in wall stress</td>
<td>Minimal</td>
</tr>
<tr>
<td>Amrinone</td>
<td>1–3 mg/kg loading dose 5–20 μg/kg/min maintenance</td>
<td>Systemic and pulmonary vasodilator; thrombocytopenia</td>
<td>Diastolic relaxation (lusitropy)</td>
<td>Minimal tachycardia</td>
</tr>
<tr>
<td>Milrinone</td>
<td>50 μg/kg loading dose 0.25–1.0 μg/kg/min maintenance</td>
<td>As above; shorter half-life</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.003–0.002 U/kg/min</td>
<td>Potent vasoconstrictor</td>
<td>No direct effect</td>
<td>None known</td>
</tr>
</tbody>
</table>

**Doses (IV)**: Doses are given intravenously.

**Peripheral Vascular Effect**: The effect on peripheral vascular resistance.

**Cardiac Effect**: The effect on cardiac output.

**Conduction System Effect**: The effect on cardiac conduction.

**Comment**: Additional information about the agents, such as the effect on oxygen consumption or other clinical effects.

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**Catecholamines**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Range</th>
<th>Alpha</th>
<th>Beta₂</th>
<th>Delta</th>
<th>Beta₁</th>
<th>Beta₂</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>0.1–0.5 μg/kg/min</td>
<td>4+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Increases systemic resistance, no inotropy; may cause renal ischemia; useful for treatment of TOF spells</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0.05–0.5 μg/kg/min</td>
<td>0</td>
<td>4+</td>
<td>0</td>
<td>4+</td>
<td>4+</td>
<td>Strong inotropic and chronotropic agent; peripheral vasodilator; reduces preload; pulmonary vasodilator; limited by tachycardia and oxygen consumption</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1–0.5 μg/kg/min</td>
<td>4+</td>
<td>0</td>
<td>0</td>
<td>2+</td>
<td>0</td>
<td>Increases systemic resistance; moderately inotropic; may cause renal ischemia</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.03–0.1 μg/kg/min</td>
<td>2+</td>
<td>1–2+</td>
<td>0</td>
<td>2–3+</td>
<td>2+</td>
<td>Beta₂ effect with lower doses; best for blood pressure in anaphylaxis and drug toxicity</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2–4 μg/kg/min</td>
<td>4+</td>
<td>0</td>
<td>4+</td>
<td>0</td>
<td>0</td>
<td>Splanchnic and renal vasodilator; may be used with isoproterenol; increasing doses produce increasing α-effect</td>
</tr>
<tr>
<td>&gt;10 μg/kg/min</td>
<td>4–8 μg/kg/min</td>
<td>2+</td>
<td>2+</td>
<td>1–2+</td>
<td>1+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debutamine</td>
<td>2–10 μg/kg/min</td>
<td>2–4+</td>
<td>0</td>
<td>1–2+</td>
<td>2+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Beta₂ effect with lower doses; best for blood pressure in anaphylaxis and drug toxicity |

**Comment**: Increases systemic resistance, no inotropy; may cause renal ischemia; useful for treatment of TOF spells. Strong inotropic and chronotropic agent; peripheral vasodilator; reduces preload; pulmonary vasodilator; limited by tachycardia and oxygen consumption. Increases systemic resistance; moderately inotropic; may cause renal ischemia. Beta₂ effect with lower doses; best for blood pressure in anaphylaxis and drug toxicity. Splanchnic and renal vasodilator; may be used with isoproterenol; increasing doses produce increasing α-effect. Less chronotropy and arrhythmias at lower doses; effects vary with dose similar to dopamine; chronotropic advantage compared with dopamine may not be apparent in neonates.

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**A-V**: atrioventricular; **TOF**: tetralogy of Fallot.

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**dren. Many of the complex corrective procedures performed in neonates and small infants are accompanied by transient postoperative arrhythmias that are either induced or exacerbated by catecholamines, which can have a profound adverse effect on the patient's recovery after surgery. Diastolic function is crucial in older patients with single ventricles and can be adversely affected by catecholamines. Nevertheless, the predictable and often significant decrease in cardiac output documented by many investigators after CPB in infants and older children continues to justify the practice of judiciously using inotropic agents to support the heart and circulation while weaning them from CPB and during the immediate postoperative period (6).**

**Phosphodiesterase III Inhibitors.** Amrinone and milrinone have emerged as important inotropic agents for use in children after open heart surgery. They are nonglycosidic, noncatecholamine inotropic agent with additional vasodilatory and lusitropic properties. They have been used extensively in adults for the treatment of chronic congestive heart failure and, more recently, introduced to pediatric practice (5, 13, 14). These drugs exert their principal effects by inhibiting phosphodiesterase, the enzyme that metabolizes cyclic adenosine monophosphate (cAMP). By increasing intracellular cAMP, calcium transport into the cell is favored, and the increased intracellular calcium stores enhance the contractile state of the myocyte. In addition, the re-uptake of calcium is a cAMP-dependent process, and these agents may, therefore,
enhance diastolic relaxation of the myocardium by increasing the rate of calcium re-uptake after systole (lusitropy). The drug also appears to work synergistically with low doses of &-agonists and has fewer side effects than other catecholamine vasodilators, such as isoprotrenol. Although the use of amrinone, beginning in the operating room, has become more commonplace in many cardiovascular centers (9, 15), the half-life of 2–4 hrs rather than minutes and its potential toxicity in the face of hepatic and renal failure have discouraged some from using this drug more frequently. Milrinone has the advantage of a shorter half-life and may, therefore, be more titratable in the face of hemodynamic instability (16, 17). It also may have a lower incidence of thrombocytopenia and is preferable when longer term use of a phosphodiesterase inhibitor is indicated.

Other Afterload-Reducing Agents. When systemic blood pressure is elevated and cardiac output appears low or normal, a primary vasodilator is indicated to normalize blood pressure and to decrease the afterload on the left ventricle. This is especially true for the newborn myocardium, which is especially sensitive to changes in afterload and tolerates elevated systemic resistances poorly. Although nitroprusside has no known direct inotropic effects, this potent vasodilator has the advantage of being readily titratable and possessing a short biologic half-life. Use of nitroglycerin avoids the toxic metabolites, cyanide and thiocyanate, associated with nitroprusside use (especially in hepatic and renal insufficiency), but its potency as a vasodilator is less than that of nitroprusside. Inhibitors of angiotensin-converting enzyme have proven to be important adjuvants to chronic anticoagulative therapy in pediatric patients. Intravenous forms are available and may be useful in the treatment of systemic hypertension immediately after coarctation repair or when afterload reduction with these inhibitors would benefit patients unable to receive oral medications (18).

Pulmonary Hypertension

Anatomical Considerations. Children with many forms of congenital heart disease are prone to develop perioperative elevations in pulmonary vascular resistance (19, 20). This may complicate the postoperative course, when transient myocardial dysfunction requires optimal control of right ventricular afterload (21–24).

Although it is understandable to presume that postoperative patients with pulmonary hypertension have active and reversible pulmonary vasoconstriction as the source of their pathophysiologic abnormality, the critical care physician is obligated to explore anatomical causes of mechanical obstruction that impose a barrier to pulmonary blood flow. Elevated left atrial pressure, pulmonary venous obstruction, branch pulmonary artery stenosis, or surgically induced loss of the vascular tree all will raise right ventricular pressure and impose an unnecessary burden on the right heart. Similarly, a residual or undiagnosed left-to-right shunt will raise pulmonary artery pressure postoperatively and must be addressed surgically. Extended use of pulmonary vasodilator strategies will only augment residual or undiagnosed shunts and increase the volume load on the heart

Several factors peculiar to CPB may raise pulmonary vascular resistance: microemboli, pulmonary leukosequestration, excess thromboxane production, atelectasis, hypoxic pulmonary vasoconstriction, and adrenergic events have all been suggested to play a role in postoperative pulmonary hypertension (23, 25). Postoperative pulmonary vascular reactivity has been related not only to the presence of preoperative pulmonary hypertension and left-to-right shunts (19, 22, 26), but also to the duration of total CPB (27, 28). Treatment of postoperative pulmonary hypertensive crises has been partially addressed by surgery at earlier ages, pharmacologic intervention, and other postoperative management strategies (Table 3). However, recent developments in vascular biology offer new insights into the possible causes and correction of post-CPB pulmonary hypertension.

Pulmonary Vasodilators. Success with vasodilators for the treatment of pulmonary hypertension caused by pulmonary vasoconstriction has had mixed results because of systemic vasodilating effects that may predominate and limit effectiveness. Tolazine, prostaglandin E1, and prostacyclin have all been suggested as useful pharmacologic treatments for this condition (Table 4) (29–32). Nitric oxide (NO) is a selective pulmonary vasodilator that can be breathed as a gas and distributed across the alveoli to the pulmonary vascular smooth muscle. Nitric oxide is formed by the endothelium from l-arginine and molecular oxygen in a reaction catalyzed by NO synthase. It then diffuses to the adjacent vascular smooth muscle cells where it induces vasodilation through a cyclic guanosine monophosphate-dependent pathway (33–37). Because NO exists as a gas it can be delivered by inhalation to the alveoli and then to the blood vessels that lie in close proximity to the ventilated lung. Because of its rapid inactivation by hemoglobin, inhaled NO may achieve selective pulmonary vasodilation when pulmonary vasoconstriction exists. It has advantages over intravenously administered vasodilators that cause systemic hypotension and increase intrapulmonary shunting. Inhaled NO lowers pulmonary artery pressure in a number of situations without the unwanted effect of systemic hypotension. This is especially dramatic in children with cardiovascular disorders and postoperative patients with pulmonary hypertensive crises.

Pulmonary vascular endothelial dysfunction may be a contributing factor in post-CPB pulmonary hypertension. Structural damage to the pulmonary endothelium is demonstrable after CPB,
Table 4: Pharmacologic agents available as pulmonary vasodilators during acute illness

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>Easily titratable, rapid onset and offset</td>
<td>Nonspecific, tachycardia, tachyphylaxis, cyanide toxicity</td>
</tr>
<tr>
<td>α-Antagonists</td>
<td>Powerful, dense blockade</td>
<td>Nonspecific, very long duration of action, serious systemic hypotension</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Orally active, facilitates myocardial remodeling</td>
<td>Little effect on pulmonary circulation</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Orally active, best defined role in primary pulmonary hypertension</td>
<td>Myocardial depression, raises end-diastolic pressure, bradycardia, sudden death, hypotension in infants</td>
</tr>
<tr>
<td>Prostaglandins (e.g., prostacyclin)</td>
<td>Good afterload reduction, increases cardiac output, some pulmonary selectivity, titratable, long-term benefit for remodeling, antiplatelet, and cytoprotective effect</td>
<td>Systemic hypotension, increases intrapulmonary shunt, value in acute illness unproven, long-term administration, requires central vascular access, expensive Clinical experience is preliminary, range of applicable disease states may be limited</td>
</tr>
<tr>
<td>Endothelin receptor blockers</td>
<td>Effective for disease states with high endothelin levels; may be tailored to have some pulmonary specificity</td>
<td>Nonspecific, tachycardia, increases myocardial oxygen demand, maldistribution of cardiac output, arrhythmogenic</td>
</tr>
<tr>
<td>β-Agonists</td>
<td>Increases cardiac output, titratable</td>
<td>Nonspecific, tachycardia, increases myocardial oxygen demand, maldistribution of cardiac output, arrhythmogenic</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors type III</td>
<td>Increases contractile function, reduces afterload, lowers filling pressures, acts synergistically with catecholamines, not arrhythmogenic</td>
<td>Nonspecific, hypotension at high doses for refractory pulmonary hypertension, slightly long duration of action (1–3 hrs) Clinical experience is preliminary, may be nonspecific vasodilator, longer acting oral or intravenous forms under development, concomitant nitrate therapy contraindicated (hypotension)</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors type V</td>
<td>Orally active, acts synergistically with inhaled nitric oxide to raise cGMP, attenuates withdrawal response to nitric oxide, may have utility as single-agent pulmonary vasodilator</td>
<td>Methemoglobin, nitrogen dioxide, complex delivery, rebound effects, short acting, expensive</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>Selective potential pulmonary vasodilator, rapid onset, improves intrapulmonary shunt, no myocardial depression, may have benefit from selected long-term applications</td>
<td>cGMP, cyclic guanine monophosphate.</td>
</tr>
</tbody>
</table>

and the degree of pulmonary hypertension is correlated with the extent of endothelial damage after CPB (27, 28). The decreased pulmonary blood flow on CPB may result in postoperative impairment of endothelial function and the inability to release nitric oxide. Transient pulmonary vascular endothelial cell dysfunction has been demonstrated in neonates and older children by documenting the transient loss of endothelium-dependent vasodilation immediately after CPB (38). NO production measured by exhaled NO is reduced postoperatively (39). This and other evidence provides a theoretical basis for administering NO after surgery.

Therapeutic uses of inhaled NO in children with congenital heart disease abound. For example, newborns with total anomalous pulmonary venous connection (TAPVC) frequently have obstruction of the pulmonary venous pathway as it connects anomalously to the systemic venous circulation. When pulmonary venous return is obstructed preoperatively, pulmonary hypertension is severe and demands urgent surgical relief. Increased neonatal pulmonary vasoreactivity, endothelial injury induced by CPB, and intravascular anatomical changes in the pulmonary vascular bed in this disease (40) contribute to postoperative pulmonary hypertension. In one study, 20 infants presenting with isolated TAPVC were monitored for pulmonary hypertension. A mean percentage decrease of 42% in pulmonary vascular resistance and 32% in mean pulmonary artery pressure was demonstrated with 80 ppm of NO. There was no significant change in heart rate, systemic blood pressure, or vascular resistance (41).

Inhaled NO can also be used diagnostically in neonates with right ventricular hypertension after cardiac surgery to discern those with reversible vasoconstriction. Failure of the postoperative newborn with pulmonary hypertension to respond to NO successfully discriminated anatomical obstruction to pulmonary blood flow from pulmonary vasoconstriction (42). Failure of the postoperative newborn to respond to NO should be regarded as strong evidence of anatomical and possibly surgically remediable obstruction.

Patients with TAPVC, congenital mitral stenosis, and other pulmonary veins hypertensive disorders associated with low cardiac output appear to be among the most responsive to NO. These infants are born with significantly increased amounts of smooth muscle in their pulmonary veins. Histologic evidence of muscularized pulmonary veins as well as pulmonary arteries suggest the presence of vascular tone and capacity for change in resistance at both the arterial and venous sites. The increased responsiveness seen in younger patients with pulmonary venous hypertension to NO may result from pulmonary vasorelaxation at a combination of pre- and post-capillary vessels.

Successful use of inhaled NO in a variety of congenital heart defects after cardiac surgery has been reported by several groups (43–46). It may be especially helpful when administered during a pulmonary hypertensive crisis. Descriptions of use after Fontan procedures (47) and after ventricular septal defect repair have been reported, along with a variety of other anatomical lesions. Very young in-
fants who are excessively cyanotic after a bidirectional Glenn anastomosis do not generally improve oxygen saturation in response to inhaled NO.

At the relatively low levels of NO used therapeutically (1–80 ppm), the metabolic fate of inhaled NO is an accumulation of nitrate and nitrite in plasma, a small increase in methemoglobin but little detectable nitrosylhemoglobin (48). Possible toxicities of inhaled NO include methemoglobinemia because of the intravascular binding to hemoglobin (49), cytotoxic effects in the lung resulting from free radical formation, development of excess nitrogen dioxide, peroxynitrite production, or injury to the pulmonary surfactant system (50). Carcinogenic and teratogenic potential of inhaled NO exist, as well as effects on glutathione metabolism, unknown effects on the immature or immunocompromised lung, potential interaction with other heme containing proteins, and effects on platelet function and hemostasis.

Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension. In adults with ischemic cardiomyopathy, sudden pulmonary vasodilatation may occasionally unload the right ventricle sufficiently to increase pulmonary blood flow and harmfully augment preload in a compromised left ventricle (51, 52). The attendant rise in left atrial pressure may produce pulmonary edema (53). This is not likely to arise from any negative inotropic effect of NO (54) and may be ameliorated with vasodilators or diuretics. Clinicians should be cognizant of this potential adverse effect during acute testing of unstable patients during cardiac catheterization, even though it has not been reported to occur in children with congenital heart disease. Abrupt withdrawal effects of NO or even rebound pulmonary hypertension are important issues. Appreciation of the transient characteristics of withdrawal of NO may facilitate weaning from NO and has important implications for patients with persistent pulmonary hypertensive disorders when interruption of NO is necessary (41, 55). If the underlying pulmonary hypertensive process has not resolved, then the tendency for an abrupt increase in pulmonary artery pressure may be hazardous when NO therapy is withdrawn or interrupted (56, 57). If withdrawal of NO is necessary before resolution of the pathologic process, hemodynamic instability may be expected. If a lable patient with pulmonary hypertension is stabilized with NO before transfer to a specialized center for further management, NO should be available during patient transport. Recent work suggests that the withdrawal response to inhaled NO can be attenuated by pretreatment with the type V phosphodiesterase inhibitor, sildenafil (Viagra) (58).

**Diastolic Dysfunction**

Occasionally, there is an alteration of ventricular relaxation, an active energy-dependent process, which reduces ventricular compliance. This is particularly problematic in patients with a hypertrophied ventricle undergoing surgical repair, e.g., tetralogy of Fallot, and after CPB in some neonates when myocardial edema may significantly restrict diastolic function (i.e., “restrictive physiology”). The ventricular cavity size is small, and the stroke volume is decreased. β-Adrenergic antagonists and calcium channel blockers add little to the treatment of this condition. In fact, hypotension or myocardial depression produced by these agents frequently outweighs any gain from slowing the heart rate. Calcium channel blockers are relatively contraindicated in neonates and small infants because of their dependence on transsarcolemmal flux of calcium both to initiate and sustain contraction.

A gradual increase in intravascular volume to augment ventricular capacity, in addition to the use of low doses of inotropic agents, has proven to provide a modest benefit in patients with diastolic dysfunction. Tachycardia must be avoided to optimize diastolic filling time and to decrease myocardial oxygen demands. If low cardiac output continues despite the above-outlined treatment, therapy with vasodilators can be attempted to alter systolic wall tension (afterload) and, thus, decrease the impedance to ventricular ejection. Although, intuitively, one may hesitate to use vasodilators in the presence of marginal systemic arterial blood pressure because blood pressure is the product of cardiac output and systemic vascular resistance, a decrease in systemic vascular resistance could increase flow with no undesirable changes in pressure (3). Because the capacity of the vascular bed increases after vasodilation, simultaneous volume replacement is indicated. Amrinone, milrinone, or enoximone are useful under these circumstances because these agents are non-catecholamine so-called inodilators with vasodilating and lusitropic (improved diastolic state) properties, in contrast to other inotropic agents (59–64).

**Mechanical Support**

For more refractory but potentially reversible ventricular dysfunction, ventricular assist devices may be useful when gas exchange appears satisfactory (65). Although this technique offers potential advantages for selected patients over extracorporeal membrane oxygenation (ECMO), ECMO is indicated when pulmonary function is also significantly impaired (66, 67). It is also more reliable therapy for biventricular dysfunction. In our experience, which is similar to many other centers, mechanical support is necessary in <2% of all patients who undergo CPB (68).

The availability of extracorporeal cardiorespiratory support for children with congenital heart disease has had a dramatic impact on a broad range of issues in the ICU (66, 69–78). Prolonging intraoperative CPB for cardiac surgical patients returning to the ICU was an early and obvious extension of CPB technology. The effect on hospital mortality is unequivocal and even more obvious when used as rescue therapy during cardiopulmonary resuscitation (CPR) (79, 80). However, the impact is felt across many disciplines, including medicine, surgery, nursing, pharmacy, and respiratory therapy, and involves cardiovascular surgeons, cardiologists, intensivists, anesthesiologists, neonatologists, and ECMO specialists. Extracorporeal cardiorespiratory support has expanded our options for supporting reversible heart failure and utilizing organ transplantation (81, 82). It has enabled us to perform difficult catheter interventions in unstable patients and allowed treatment of life-threatening arrhythmias with catheter ablation techniques. It has altered the way intensive care physicians select patients for intervention and conduct CPR, and it has made clinicians confront practical issues of informed consent for starting and stopping potentially life-saving treatment. This in turn has challenged the medical ethicists to opine on study designs involving ECMO and the important issues of parental input and consent. The technology has confused the clergy by introducing ambiguities about the temporal domains of life and death in the ICU. It has put extraordinary demands on
administrators and ECMO specialists to provide more time and personnel during an era of cost reduction. The care of these patients provides intellectual challenges in understanding unique pathophysiology and requires expertise that physicians and other healthcare professionals seek to obtain. The intensity and experience associated with using the ultimate resuscitative tool to achieve sudden shifts from near certain death to dramatic recovery is highly motivating and enormously gratifying. Tables 5 and 6 show the cumulative activity through 1999 in the Extracorporeal Life Support Organization registry with survival by diagnostic category. With the advent of high-frequency oscillatory ventilation, use of surfactant, inhaled NO, and other advances in critical care of the newborn, the need for ECMO for hypoxic respiratory failure has declined since its peak in 1992. Cardiac ECMO (including adults) seems to have declined more recently as adult use of ventricular assist devices (including implantable) has gained acceptance. In contrast, the proportion of children who received ECMO support for congenital or acquired heart disease at Children’s Hospital (Boston, MA) has steadily increased; this is typical of the pediatric experience in many large cardiac centers. More than half of all ECMO runs in our institution are now for cardiovascular support rather than respiratory support. Survival for patients on ECMO after cardiac surgery has also steadily improved but has not reached the survival rates of neonates on ECMO for respiratory failure (Table 6). Substantial institutional variability in patient selection for ECMO makes comparison with published experience difficult. Even within institutions, practice has substantially evolved, and this confounds the interpretation of trends over time. Overall, one can propose that the use of ECMO for cardiovascular support is increasing, and results are improving; however, there is room for further progress (83). Refinement of ECMO personnel and organization to include an in-hospital team for rapid resuscitation may improve outcome (80). During the past year at Children’s Hospital, Boston, >20 patients have been cannulated for cardiovascular support during resuscitation for cardiac arrest; hospital survival exceeds 60%. Survivors among neonates has dramatically improved to 70%, including those patients with hypoplastic left heart syndrome who have undergone a Norwood operation.

**Indications for ECMO.** General indications for the use of mechanical support in patients with heart disease include inadequate oxygen delivery or a requirement for temporary support during cardiac catheterization interventions. Inadequate oxygen delivery is caused most commonly by low cardiac output, profound cyanosis with intracardiac shunting and cardiovascular collapse, or profound hypoxemia from-associated lung disease (Table 7).

The most common cause of inadequate oxygen delivery in a pediatric cardiac ICU stems from low cardiac output, which is usually a result of myocardial dysfunction. Ventricular dysfunction may occur as a component of chronic cardiomyopathy or from other causes of congestive heart failure. It may occur more dramatically with acute decompensation, typified by acute fulminating viral myocarditis.

Patients who fail to wean from CPB may be converted to an ECMO circuit in the operating room and brought to the ICU in hopes of recovering myocardial function (84). These children typically have poorer survival rates for multifactorial reasons, including severity and complexity of disease, as well as increased bleeding. Other children have progressive myocardial failure after successful weaning from CPB. This typically occurs during the first 24 hrs after cardiac surgery, and subsequent survival may be better in this group of patients after a period of myocardial rest and decompression.

Pulmonary hypertensive crises after CPB may be refractory to therapy and necessitate mechanical support of the right heart. These patients are notoriously difficult to resuscitate after cardiac arrest if they have advanced pulmonary vascular obstructive disease. Resuscitation is facilitated if a small right-to-left communication is created or left in place at the time of surgical intervention.

Refractory arrhythmias are occasionally controlled only after the heart has been decompressed on ECMO and sufficient time has been gained to achieve adequate pharmacologic control of the arrhythmia.

Cardiac arrest may occur suddenly in the postoperative period, without substantial warning. It may also occur as the culmination of progressive postoperative myocardial dysfunction, resistant to therapy. Although anticipation of this event with timely preparation for ECMO is preferable, cannulation during CPR is not uncommon (83).

### Table 5. Cumulative Extracorporeal Life Support Organization (ELSO) registry data through 1999

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total Patients</th>
<th>Survived ECMO, %</th>
<th>Survived to Discharge, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Respiratory</td>
<td>14,543</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1,085</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>Pediatric Respiratory</td>
<td>1,711</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1,642</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>Adult Respiratory</td>
<td>483</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>Cardiac</td>
<td>244</td>
<td>36</td>
<td>32</td>
</tr>
</tbody>
</table>

ECMO, extracorporeal membrane oxygenation.

### Table 6. Cumulative Extracorporeal Life Support Organization registry data through 1999 for neonatal respiratory failure by diagnostic category

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total Runs</th>
<th>Average Run Time</th>
<th>Percent Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS</td>
<td>5177</td>
<td>127</td>
<td>94</td>
</tr>
<tr>
<td>CD hernia</td>
<td>3132</td>
<td>216</td>
<td>55</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2088</td>
<td>138</td>
<td>76</td>
</tr>
<tr>
<td>PPHN/PFC</td>
<td>2065</td>
<td>137</td>
<td>80</td>
</tr>
<tr>
<td>RDS</td>
<td>1268</td>
<td>132</td>
<td>80</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>151</td>
<td>216</td>
<td>55</td>
</tr>
<tr>
<td>Other</td>
<td>740</td>
<td>164</td>
<td>68</td>
</tr>
</tbody>
</table>

MAS, meconium aspiration syndrome; CD, congenital diaphragmatic; PPHN/PFC, persistent pulmonary hypertension of newborn/persistent fetal circulation; RDS, respiratory distress syndrome.
Relative Contraindications to ECMO. Although there may be few structural heart defects that preclude the use of ECMO, there are some potentially important contraindications that should be considered (Table 7). Obviously, if the underlying disease is felt to be irreversible or inoperable, common sense may dictate that mechanical support of the circulation merely prolongs a terminal illness that is destined to have a fatal outcome in the near future. However, perspective on the term “inoperable” may vary among healthcare professionals and is closely tied to the parents’ perception of the likelihood of survival and the quality of life during survival.

Significant central nervous system disease or injury may also preclude the use of ECMO. Chromosomal abnormalities associated with central nervous system impairment may complicate the assessment of patients and affect predictions about the quality of life. Generally speaking, the presence of Trisomy 21 has not been considered recently to be a contraindication to ECMO after cardiac surgery. However, most families and practitioners believe that the severe limitation in cognitive function and predicted life span associated with Trisomy 13 or 18 would not be consistent with the guideline that the underlying disease or diseases must be reversible to merit consideration for ECMO.

Active bleeding from relatively inaccessible locations such as the brain or abdominal structures before initiation of ECMO may also present a relative contraindication, because heparinization would in all likelihood aggravate previously existing disease. Extremes of size and weight may pose limitations on ECMO technology, but those limits expand each year.

Unattainable vascular access may deter ECMO cannulation during CPR. Occasionally, a child with congenital heart disease will have had surgery many weeks or months before an in-hospital cardiopulmonary arrest that would otherwise prompt consideration for ECMO as part of the resuscitative maneuvers. However, if the jugular veins or superior vena cava are known to be obstructed from previous interventions and there are anatomical limitations (size or previous procedures) to cannulating through the groin, then the notion of continuing CPR through a prolonged procedure to reopen the sternum through extensive scar tissue may be inadvisable.

Finally, if progressive myocardial dysfunction characterizes the postoperative course of a patient who is identified as having significant residual anatomical disease, then the temptation to support the child with ECMO must be balanced against the more prudent need to return to the operating room and to address directly the residual anatomical lesion.

Identifying Residual Disease. The importance of identifying residual or previously undiagnosed anatomical disease in the postoperative patient with progressive myocardial dysfunction and low cardiac output cannot be underestimated. This is one of the prime responsibilities of those who participate in postoperative management (85, 86). Intracardiac catheters to measure pressure and to sample blood for oxygen saturation will help assess the adequacy of diagnosis and repair. Transthoracic and transesophageal echocardiography are valuable in the postoperative evaluation of the child with low cardiac output. When acoustic windows are limited with echocardiography, the patient may benefit from cardiac catheterization, including physiologic assessment and angiographic imaging. Aggressive diagnostic intervention is a critical component in the assessment of low cardiac output in the postoperative patient. This is especially appealing if suspected residual lesions can be addressed with interventional catheterization techniques.

Optimizing Cardiac Output Before and After Mechanical Support. Physicians in the ICU bare the responsibility of anticipating changes in cardiac output after cardiac surgery, excluding residual disease as a causative factor and optimizing physiologic conditions that will achieve optimal cardiac output. The need
Initiation of ECMO requires the perfusion can be guaranteed (Table 1). The patient from mechanical support as fore invoking ECMO, they must again be support oxygen delivery short of ECMO can often be averted by an experienced for mechanical support of the circulation whenever possible. The precise moment and necessary components when resuscitation complete in 15 mins and cannulation during cardiopulmonary arrest is rarely the result of prolonged circuit preparation time. A parallel consideration involves the decision process for determining suitability for ECMO. This must occur before cardiac arrest whenever possible. Institutions may adopt general philosophies about rapid resuscitation ECMO for broad categories of patients in the ICU. For example, infants with two ventricles and uncomplicated repair of congenital heart disease who have no other underlying disease may all be candidates for ECMO should they have a sudden, unexpected cardiac arrest in the early postoperative period. In contrast, it may be generally inadvisable to impose ECMO on an older patient with end-stage heart disease or severe neurologic disease who declines or is not otherwise a candidate for transplantation but has an acute decompen- sation and cardiac arrest. In between these extremes is an area that requires discussion and individualization of care plans that must be accomplished before any anticipated or unanticipated decompen- sation. Thus, daily patient rounds in the ICU must now incorporate a dialogue among physicians, nurses, family, and support staff that addresses the patient’s suitability for ECMO. The moment after cardiac arrest is not the time to initiate discussions about the appropriateness of invasive, potentially life-prolonging technology. Addressing these issues during rounds and fully discussing the appropri- ate limitation of technology is an impor- tant new responsibility.

SUMMARY

Aggressive identification and treatment of low cardiac output conditions after cardiac surgery are central to the critical care of children with congenital heart disease. Successful application of these strategies has undoubtedly contributed to the remarkable decline in mortality associated with congenital heart surgery in the past two decades.

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