Management of the postoperative pediatric cardiac surgical patient

Ronald A. Bronicki, MD; Anthony C. Chang, MD, MBA

Objective: **To review the salient aspects and latest advances in the management of the postoperative pediatric cardiac patient.**

Data Source: **A Medline-based literature source.**

Conclusion: **The practice of pediatric cardiac intensive care has evolved considerably over the last several years. These efforts are the result of a collaborative effort from all subspecialties involved in the care of pediatric patients with congenital heart disease. Discoveries and innovations that are representative of this effort include the extension of cerebral oximetry from the operating room into the critical care setting; mechanical circulatory devices designed for pediatric patients; and surgery in very low birth weight neonates. Advances such as these impact postoperative management and make the field of pediatric cardiac intensive care an exciting, demanding, and evolving discipline, necessitating the ongoing commitment of various disciplines to pursue a greater understanding of disease processes and how to best go about treating them. (Crit Care Med 2011; 39:1974–1984)**

Key Words: pediatric cardiac surgery; postoperative management; cardiopulmonary bypass; hemodynamic monitoring; ventricular dysfunction; cardiopulmonary interaction; vasoactive support

The field of pediatric cardiac intensive care continues to evolve, which is in large part the result of collaborative efforts from anesthesia, surgery, cardiology, critical care, and other subspecialties, including neonatology, neurology, and endocrinology. Examples include an increasing number of surgeries in very low birth weight infants; the extension of technology such as cerebral oximetry from the operating room into the intensive care setting; and innovations in mechanical circulatory devices. Industry-sponsored studies and initiatives from the National Institutes of Health such as the Pediatric Heart Network have contributed to the evolution of pediatric cardiac intensive care. These collective efforts are demonstrated in the Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study and more recently the single ventricle reconstruction trial and thyroid supplementation study (to be discussed).

The increase in complexity of disease, innovations in technology, and evolving therapeutic strategies as well as national quality initiatives, individually and collectively, place a tremendous demand on the team, necessitating a focused, concerted effort by all members to challenge current practices while practicing state-of-the-art care. In this review, we discuss the salient aspects and latest advances in the primary challenge after surgery, which is to maintain adequate cardiopulmonary function and to ensure adequate tissue oxygenation.

The Inflammatory Response to Cardiopulmonary Bypass

Exposure of the blood components to the nonendothelialized circuit, pulmonary and myocardial reperfusion injury, and the formation of heparin–protamine complexes stimulate the release of systemic and local proinflammatory mediators and activate the coagulation/fibrinolytic pathways (1). Virtually every inflammatory pathway and parenchymal cell contributes to the inflammatory cascade. The magnitude of the inflammatory response to cardiopulmonary bypass (CPB) has been associated with preoperative conditions such as shock and heart failure (2); intraoperative factors such as the duration of bypass and cardioplegic arrest (3); and genetic variances have been identified that affect the inflammatory response to several stimuli, including CPB (4, 5).

Several studies have found a relationship between the inflammatory response to bypass and the development of multiorgan dysfunction and postoperative morbidity (3, 6). Prospective, randomized studies in children found the administration of glucocorticoids before bypass significantly reduced the proinflammatory and augmented the compensatory anti-inflammatory responses to bypass, reduced the extent of myocardial injury, and improved the postoperative course (7–10). Two prospective studies failed to demonstrate benefit from the use of glucocorticoids however they limited enrollment to older children (11, 12). A majority of pediatric cardiac centers use glucocorticoids to ameliorate the inflammatory response to bypass (13).

Assessment of Hemodynamics and Tissue Oxygenation

An accurate and timely determination of cardiac output (CO), systemic O_2 delivery (DO_2), and tissue oxygenation is essential to optimizing outcomes. Studies have demonstrated that it is not uncommon for there to be discordance between measurements of these parameters and estimations based on the physical examination and interpretation of conventional hemodynamic parameters such as heart rate, blood pressure, and right atrial pressure (14, 15). Compensatory increases in systemic vascular resistance maintain arterial blood pressure as CO falls and central venous/right atrial pressures may not correlate well with right

From the Children's Hospital of Orange County (RAB, ACC), Orange, CA; and the David Geffen School of Medicine at the University of California Los Angeles (RAB), Los Angeles, CA.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: rbronicki@choc.org

DOI: 10.1097/CCM.0b013e31821b82a6

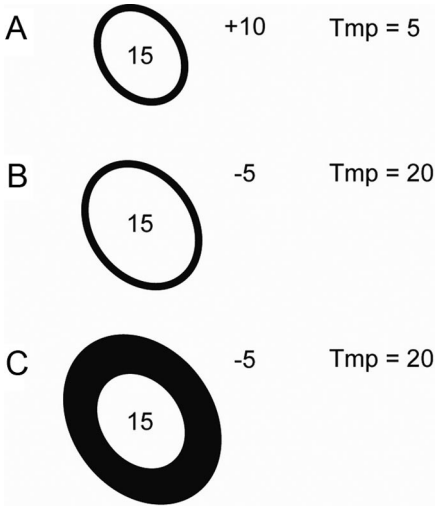

Figure 1. The relationship of ventricular filling pressure (*EDP*), ventricular compliance, and intrathoracic pressure (*ITP*) to ventricular filling. The EDP is 15 for each variable. *A*, The ITP is +10 (positive pressure ventilation). *B*, The ITP is −5 (spontaneous breathing). *C*, Ventricular compliance is reduced. Ventricle A vs. B, Ventricular compliance is the same; however, because ventricle B has a greater Tmp, it fills to a greater extent. Ventricle B vs. *C*, The Tmp is the same; however, because ventricle B is more compliant, it fills to a greater extent. *Tmp*, ventricular transmural pressure; *Tmp*, intracavitary − extracavitary pressure.

Table 1. Oxygen transport balance

Fick equation:
$VO_2 = CO \times CaO_2 - CvO_2$
By ignoring the amount of O_2 dissolved in blood, the Fick equation may be simplified to:
$SaO_2 - SmvO_2 = VO_2/DO_2 = O_2$ transport balance

VO_2, O_2 consumption (mL/min); CO, cardiac output (L/min); $Ca - CmvO_2$, arterial − mixed venous O_2 content difference (mL/dL); SaO_2, arterial O_2 saturation; $SmvO_2$, mixed venous O_2 saturation; DO_2, oxygen delivery ($CO_2 \times CaO_2$; mL/min).

ventricular filling or left atrial pressures (16, 17). The primary determinants of ventricular filling are the ventricular diastolic transmural pressure (ventricular diastolic pressure – surrounding pressure) and ventricular compliance (Fig. 1). With pericardial disease, increases in intrathoracic pressure, and impaired diastolic function, the optimal filling pressure increases.

Echocardiography provides an assessment of ventricular filling and function and quantification of valvular regurgitation. Doppler measurements assess obstructions and pulmonary arterial pressures. Trending serial lactate levels has prognostic value (18, 19). A low serum HCO_3^- level and base deficit are reflective of tissue hypoxia to the extent that serum lactate levels are elevated, producing an anion gap; otherwise, these abnormalities are consistent with a hyperchloremic metabolic acidosis (20–23).

Table 2. Oxygen extraction ratio (O_2ER)

$O_2ER = SaO_2 - SmvO_2/SaO_2$	
SaO_2, arterial O_2 saturation; $SmvO_2$, mixed venous O_2 saturation;	
Oxygen extraction ratios based on mixed venous oximetry	
25%	Normal
30% to 40%	Increased
40 to 50%	Impending shock
>50% to 60%	Shock, elevated lactate levels
Normal O_2 extraction ratios for central venous oximetry	
Right atrium 25%	
Jugular vein 35%	
Superior vena cava 30%	
Inferior vena cava 20%	

Table 3. Factors responsible for increased metabolic requirements

Catecholamines, endogenous and exogenous
Systemic inflammatory response
Fever
Consciousness, pain and anxiety
Spontaneous breathing
Enteral nutrition

The routine placement of central venous catheters readily enables the clinician to use venous oximetry to assess oxygen transport balance (Table 1). The critical O2 extraction ratio is defined by the onset of shock and ranges from 50% to 60% (Table 2) (24). The critical DO_2 changes in parallel with changes in oxygen consumption (VO_2); however, the critical O_2 extraction ratio remains constant, which is an important consideration in the postoperative period when oxygen demand changes over time and with therapy (25). When mixed venous oxygen saturations are unavailable, alternative sampling sites include the right atrium, superior vena cava, jugular vein, and inferior vena cava–right atrial junction (Table 2) (26–28). As CO falls, blood flow is redistributed to maintain vital organ perfusion. As a result, inferior vena cava saturations fall first, which is accompanied by a less severe drop in mixed venous oxygen saturations. As CO falls further, superior vena cava and jugular saturations begin to decrease (28, 29). Venous oximetry has been shown to improve outcomes in pediatric patients at risk for developing shock, including severe sepsis and the hypoplastic left heart syndrome (30, 31).

Cerebral near-infrared spectroscopy noninvasively assesses cerebral oxygenation. Cerebral oximetry relies on the relative transparency of biological tissue to near-infrared spectroscopy light where oxy- and deoxy hemoglobin have distinct absorption spectra (32). The oximeter monitors the nonpulsatile signal reflecting the microcirculation where 75–85% of the blood volume is venous. Thus, the O_2 saturation is used as an indicator of O_2 extraction for the area of the brain immediately beneath the probe (frontal cortex). Because of technical constraints, the technology is limited to relative quantitation and is thus useful for tracking changes for a given patient. Studies have demonstrated a good correlation between cerebral O_2 saturations and jugular bulb and superior vena cava saturations (33, 34). A study by Li and colleagues (35) evaluated the relationship between cerebral oxygenation and hemodynamic and oximetric parameters in neonates following the Norwood procedure. They found that cerebral oxygen saturations closely and negatively correlated with the O_2 extraction ratio. Cerebral oximetry is also used as a surrogate for central and mixed venous oxygen saturations; however, the correlation between these readings is marginal (36, 37). The reasons for this include the technical constraints described; the fact that in a low CO state, blood flow is redistributed to maintain perfusion of vital organs; and cerebral blood flow is sensitive to changes in arterial P_{CO_2}.

Maintenance of Tissue Oxygenation

The primary goal after surgery is to maintain adequate tissue oxygenation, which is accomplished by optimizing oxygen transport balance (i.e., minimizing oxygen demand and consumption and maintaining adequate oxygen delivery (Table 3) (38). Underlying respiratory and circulatory dysfunction, the inflamma-

tory response to CPB, myocardial and pulmonary reperfusion injury, and surgery all place the patient at risk for developing shock (39, 40).

Table 4. Factors responsible for diminished infant respiratory reserve

Decreased functional residual capacity
Decreased subglottic cross-sectional area
Decreased ventilatory reserve
Highly compliant chest wall
Less diaphragmatic contractile reserve
Increased respiratory demand
Higher O_2 consumption and minute ventilation

Table 5. Impaired respiratory mechanics

Upper airway dysfunction
Postextubation croup/subglottic edema
Neurologic dysfunction
Injury to the recurrent laryngeal nerve
Central nervous system injury
Excessive sedation /analgesia
Lower airway dysfunction
Bronchiolar compression due to interstitial edema from left–right cardiac shunting, cardiopulmonary bypass and pulmonary venous hypertension
Parenchymal lung disease
Atelectasis
Edema (hydrostatic and permeability)
Pneumonia
Chest wall edema
Pleural effusion
Abdominal load increased (visceromegaly, ascites)

Table 6. Ventilatory failure

Neuromuscular competence
Central nervous system depression
Diaphragmatic paralysis
Disuse atrophy (compounded by muscle relaxants and glucocorticoids)
Malnutrition
Respiratory load
Compliance of lung/chest wall
Resistive load
Respiratory muscle energetics
Muscle oxygen consumption α respiratory load
Respiratory muscle perfusion
Cardiac output state

Table 7. Infant cardiovascular reserve

Decrease contractile reserve
Cardiomyocyte contains fewer and poorly organized contractile proteins
Immature sarcoplasmic reticulum
Decrease myocardial compliance
Increase circulatory demands due to greater oxygen consumption

Respiratory Dysfunction

Infants in particular are at risk for developing respiratory insufficiency after cardiac surgery as a result of diminished respiratory reserve (Table 4) (41). Respiratory mechanics are impaired to varying degrees (Table 5). The inflammatory response to CPB increases vascular permeability and extravascular lung water, leading to interstitial and alveolar edema and impaired surfactant function (42). As a result, lung compliance decreases and if an adequate end-expiratory lung volume is not maintained, pulmonary venous admixture and arterial hypoxemia result. Ventilatory failure after cardiac surgery may result from a number of causes (Table 6), some unique to patients undergoing repair of structural heart disease. Ventilatory failure results from a combination of increase respiratory load, decreased neuromuscular competency, and impaired respiratory muscle energetics (i.e., VO_2/DO_2 relationship) (Table 6) and is manifested by hypercapnia with a normal arterial to end tidal CO_2 gradient (43, 44). An additional cause of impaired gas exchange is low CO and abnormally distributed pulmonary blood flow, which produce an increase in ventilation-to-perfusion ratios, wasted ventilation, and hypercapnia with an elevated arterial to end-tidal CO_2 gradient (45–48).

Cardiovascular Dysfunction

There is invariably some degree of postoperative myocardial diastolic and systolic dysfunction, in part the result of the inflammatory response and ischemia–reperfusion injury (49, 50). Improving CO involves optimizing ventricular loading conditions, myocardial conduction, and ventricular performance. These challenges are even greater in neonates as a result of their diminished cardiovascular reserve (Table 7) (51, 52).

Diastolic Dysfunction

Vasoactive Support. Diastolic dysfunction is characterized by reduced ventricular compliance and operating volumes despite an elevated filling pressure. Inotropic and afterload-reducing agents are of little benefit (53–56). Nitroglycerin, nitroprusside, natriuretic peptides, and milrinone have been shown to provide lusitropic support (54). However, because these agents also cause venodilation and an increase in venous capacitance, venous return and ventricular filling may decrease (58–62). Volume administration may increase stroke volume; however, this will come at the expense of an increase in systemic and pulmonary venous pressures.

Cardiopulmonary Interaction. Positive pressure ventilation (PPV) may decrease ventricular filling and in the presence of diastolic dysfunction further compromise CO. PPV decreases the pressure gradient for venous return (mean circulatory filling pressure – right atrial pressure) by increasing the right atrial pressure. As intrathoracic pressure increases, the right atrial transmural pressure (right atrial pressure – intrathoracic pressure) decreases. As a result, right atrial size decreases and its pressure increases. Circulatory reflexes (adrenergic-mediated decreases in venous capacitance and renin–angiotensin–aldosterone system-induced volume expansion) increase the mean circulatory filling pressure and attempt to maintain the pressure gradient for venous return. PPV also reduces the ventricular diastolic transmural pressure (Fig. 1), which also limits ventricular filling by reducing its effective compliance (63).

Systolic Dysfunction

Nitric Oxide Donors. The primary strategy for treating systolic dysfunction is to optimize ventricular loading conditions. Nitroglycerin in low to moderate doses (<3 μg/kg/min) increases venous capacitance without much effect on the arterial resistance vessels (64). As a result, ventricular filling pressures fall, whereas stroke volume is unaffected. High-dose nitroglycerin and nitroprusside increase venous capacitance and reduce systemic vascular resistance and thus filling pressures fall and stroke volume and CO rise significantly (65).

Natriuretic Peptides. The natriuretic peptides act primarily as counterregulatory hormones to the renin–angiotensin–aldosterone system. Atrial and B-type natriuretic peptides are produced primarily by myocardium in response to chamber wall stress (66). Stimulation of natriuretic peptide receptors causes vasodilation of venous capacitance and arterial resistance vessels, a dose-dependent natriuresis/diuresis, and improved ventricular relaxation. Nesiritide (Natrecor, Scios, Inc., Fremont, CA) is the human recombinant form of B-type natriuretic peptide. In contrast to nitroglycerin and

nitroprusside, tachyphylaxis does develop to the hemodynamic effects of nesiritide (67) and its use is not associated with reflex stimulation of systemic and cardiac adrenergic activity (68).

Studies in adults have demonstrated its efficacy in treating congestive heart failure, whereas studies in children have been limited (69). A study by Jefferies et al (70) evaluated the safety and efficacy of nesiritide in pediatric decompensated heart failure by prospectively monitoring 55 separate infusions in 32 patients. They found results similar to those found in adults: a significant increase in diuresis; reduction in ventricular filling pressures and increase in CO; and a marked improvement in the mean New York Heart Association functional class. No hypotension or arrhythmias were noted during 478 cumulative days of therapy and serum creatinine levels trended downward after therapy.

Catecholamines. The use of catecholamines is limited because they are chronotropic, arrhythmogenic, and increase global and myocardial VO_2 (68). Dopamine and dobutamine provide modest inotropic support. In contrast to dobutamine, dopamine decreases venous capacitance and as a result ventricular filling pressures do not decrease (72, 73). At higher doses (>10 μg/kg/min), systemic vascular resistance begins to increase as a result of β-agonist activity. Dobutamine decreases systemic vascular resistance, which is thought to be the result of β_2 agonist activity. Epinephrine provides unparalleled inotropic support and in low doses (<0.05–0.10 μg/kg/min) reduces systemic vascular resistance (74, 75).

Phosphodiesterase Inhibitors. Milrinone, and its predecessor amrinone, act through selective inhibition of phosphodiesterase III. The advantages of milrinone over catecholamines are that it is not chronotropic and arrhythmogenic, it does not increase myocardial VO_2, and it is unaffected by adrenergic receptor desensitization. Milrinone provides modest inotropic support, vasodilates pulmonary and systemic vessels, and exerts a lusitropic effect (76). As a result, ventricular filling pressures decrease while stroke volume and CO increase (77). A study by Hoffman and colleagues (78) evaluated the efficacy and safety of prophylactic milrinone in pediatric patients undergoing cardiac surgery. Patients (n = 238) were randomized to low-dose (25 μg/kg/min) or high-dose (75 μg/kg/min) milrinone or placebo. High-dose milrinone significantly reduced the risk of developing low CO syndrome compared with placebo, a 64% relative risk reduction, and there was no significant difference in the incidence of hypotension or arrhythmia compared with placebo.

Levosimendan. Levosimendan represents the first of a new class of agents, the calcium sensitizers, which are in use in Europe (79). These agents provide modest inotropic support by enhancing the sensitivity of the myofilaments to the prevailing cytosolic calcium concentration. Because less energy is consumed in the cycling of calcium, myocardial VO_2 remains unchanged. By stimulating adenosine 5-triphosphate-dependent K+ channels in vascular smooth muscle cells, levosimendan decreases systemic and pulmonary vascular resistance. In contrast to other vasoactive agents, levosimendan has a long duration of action as a result of the generation of active metabolites with an elimination half-life of 3–4 days.

Namachivayam and colleagues evaluated levosimendan in 15 children with severe ventricular dysfunction who were catecholamine-dependent (80). A combination of a loading dose and continuous infusions (24–48 hrs) allowed for a substantial reduction in catecholamine infusions with discontinuation in a majority of patients. A prospective randomized trial was performed by Momeni and colleagues (81) of children (n = 36) undergoing cardiac surgery in which patients received either milrinone or levosimendan with initiation of CPB for up to 48 hrs. There was no difference between groups in terms of serum lactate levels (primary aim) or oxygen extraction; however, the rate pressure index was significantly greater in those receiving milrinone.

Cardiopulmonary Interaction. In systolic heart failure, PPV improves CO. As discussed, PPV may compromise ventricular filling (82). However, so long as the dilated ventricle resides on the flat portion of its pressure volume curve, a decrease in venous return will not affect stroke volume. PPV reduces systemic ventricular afterload and by unloading the respiratory pump respiratory muscle VO_2 decreases, allowing for a redistribution of a limited CO (83, 84).

Other Strategies for Improving Circulatory Function

Arginine Vasopressin. Arginine vasopressin (AVP) plays a vital role in the defense of arterial blood pressure, because physiological levels are required for normal vascular tone of venous capacitance and arterial resistance vessels. The rationale behind the use of exogenous AVP in critical illness is that neurohypophyseal stores of AVP may become exhausted, leading to vasodilatory shock (85). Prospective, randomized studies in adults have yielded equivocal results (86, 87). There have been a few reports on the use of AVP in children (88, 89). A retrospective analysis was performed by Rosenzweig et al of their experience with AVP in 11 children after cardiac surgery. All had refractory hypotension and all but two had normal or mildly depressed left ventricular function. During the first hour of AVP, there was a significant improvement in blood pressure and the inotrope score.

Glucocorticoids. A similar rationale exists for the use of glucocorticoids (90). Cortisol is essential for maintaining vascular tone and may affect myocardial function (91). Particularly in premature and stressed term neonates, a relative adrenal insufficiency may develop as a result of the effects of inflammation on an immature hypothalamus–pituitary axis (92). Although the definition of a relative adrenal insufficiency remains unclear, most would agree that a normal or near-normal cortisol level in a critically ill patient is indicative of an inadequate hypothalamus–pituitary axis response (93). Prospective randomized studies of critically ill premature infants with refractory hypotension demonstrated improved hemodynamics in those treated with glucocorticoids (94, 95). Studies in children with refractory hypotension after cardiac surgery have been limited to several retrospective studies and one small prospective randomized study. All studies demonstrated a significant improvement in arterial blood pressure over the first several hours after the initiation of therapy that coincided with a weaning of vasoactive support (96–99).

Thyroid Hormone. After CPB, serum thyroid hormone levels are depressed (100). Because of the known effects of thyroid hormone on ventricular function, several studies have evaluated the role of thyroid replacement therapy in children after cardiac surgery (101–104). A rela-

tively large prospective randomized study (n = 193) was performed by Portman and colleagues of T3 supplementation in children undergoing cardiac surgery. Analysis using age stratification found those patients <5 months of age who received T3 experienced a significantly shortened time to extubation (primary end point), improved cardiac function, and required less vasoactive support.

A study by Mackie and colleagues randomized 42 infants undergoing the Norwood procedure or repair of interrupted aortic arch to T3 supplementation or placebo. There was no difference in the primary end points of clinical outcome score and CO between groups; however, those receiving therapy did have a significantly higher systolic blood pressure. A study by Chowdhury and colleagues demonstrated an improved postoperative course including reduced need for vasoactive support in children (n = 28) randomized to T3 as did the study by Bettendorf and colleagues that demonstrated an improved postoperative course and systolic function in those children (n = 40) randomized to treatment.

Postoperative Management: Lesion-Specific

Single Ventricle Physiology. Patients with single ventricle physiology are at risk for developing shock, the result of systolic dysfunction compounded by the inefficiencies of a parallel circulation. The aortic–pulmonary artery shunt allows for continuous flow throughout the cardiac cycle, leading to excessive pulmonary perfusion (Qp), which occurs at the expense of systemic perfusion (Qs), diastolic hypotension, and potentially inadequate coronary perfusion. The distribution of total CO (Qp + Qs) is determined by the systemic to pulmonary vascular resistance ratio, which is much greater than one. Pulmonary overcirculation increases as this ratio increases; as Qs wanes, neurohormonal systems are activated, which further increases the systemic to pulmonary vascular resistance ratio, and a vicious cycle ensues culminating in shock.

Management begins with an accurate assessment of Qs. Studies have demonstrated the limitations of inferring Qs and systemic DO_2 from arterial oxygen saturations and studies have found improved outcomes using venous oximetry from the superior vena cava (31, 105). The focus on postoperative management is to not increase pulmonary vascular resistance but rather to lower systemic vascular resistance, which improves stroke volume, Qs, and Qp, producing a marked increase in systemic DO_2 (106–108). Milrinone is an ideal agent for this strategy. Low-dose epinephrine (<0.05– 0.10 μg/kg/min) provides greater inotropic support while reducing systemic vascular resistance (109). Dopamine provides modest inotropic support but does not reduce systemic vascular resistance and has been shown to worsen oxygen transport balance by increasing VO2 without an appreciable effect on systemic DO_2 (110, 111).

An alternative strategy for the initial palliation of the hypoplastic left heart syndrome is the use of a right ventricle to pulmonary artery conduit. Because shunting occurs only during systole, the Qp/Qs ratio tends to be lower and the diastolic blood pressure higher compared with the standard approach (112, 113). The single ventricle reconstruction trial prospectively randomized (n = 549) infants with the hypoplastic left heart syndrome or a related single, morphologic right ventricular anomaly and a planned Norwood procedure to one of these two strategies (114). The rate of transplantation-free survival at 12 months was significantly better in those infants receiving the right ventricular to pulmonary artery conduit (74 vs. 64%, $p = .01$); however, after 12 months, there was no difference in transplantation-free survival between groups ($p = .06$). The rate of composite "serious adverse events" (death, acute shunt failure, cardiac arrest, extracorporeal membrane oxygenation, or necrotizing enterocolitis) during the Norwood hospitalization was significantly lower in the right ventricle to pulmonary artery conduit group (36 vs. 48%, $p = .02$).

Bidirectional Glenn. The primary challenge after the bidirectional Glenn is hypoxemia. This may be the result of pulmonary venous admixture, systemic venous collaterals, pulmonary arteriovenous malformations, or inadequate Qp (115–116). One strategy to improve Qp and oxygenation is permissive hypercapnia, which uncouples cerebral blood flow from cerebral metabolism allowing for an increase in superior vena cava flow and Qp (118). A study by Hoskote et al (119) demonstrated that progressive increases in $Paco_2$ led to increases in Qp and oxygenation without increasing pulmonary vascular resistance. These changes were accompanied by a decrease in systemic vascular resistance and increase in Qs and a marked increase in DO_2. In the absence of systemic hypotension, manipulation of systemic blood pressure will not affect cerebral blood flow and oxygenation because cerebral pressure autoregulation is intact (120).

Fontan Procedure. The primary challenge after the Fontan procedure is a low CO state, which results from inadequate ventricular volume. Diastolic dysfunction is present to varying degrees. In contrast to the bidirectional Glenn, all systemic venous return must overcome the resistance of the pulmonary circulation without a subpulmonic pumping chamber, which further compromises ventricular filling (60, 61, 121). Inotropic support provides marginal support as a result of limited venous return and ventricular filling (54). Negative pressure ventilation improves ventricular filling and CO by increasing venous return and the ventricular diastolic transmural pressure and is in part the rationale for an early extubation after surgery (Fig. 1) (122, 123). Volume administration increases the upstream driving pressure for venous return, whereas venodilators increase venous capacitance compromising venous return (59). Even modest increases in pulmonary vascular resistance may not be tolerated and normalizing the functional residual capacity, pH, and alveolar PO2 may improve Qp (124); some patients may respond to inhaled nitric oxide (125).

Hypoxemia may also complicate the postoperative course and may be the result of systemic venous collaterals (126). Transudative and chylous pleural and pericardial effusions are not uncommon after the Fontan procedure and may result from traumatic injury to a lymphatic tributary or elevated systemic or pulmonary venous pressure impeding lymphatic drainage (127, 128). Pleural fluid accumulation may also be the result of systemic–pulmonary artery collaterals (129). Any space-occupying thoracic lesion will increase intrathoracic pressure and compromise the gradient for venous return; a pericardial effusion will further reduce the ventricular diastolic transmural pressure; either lesion will further compromise an already under filled ventricle.

Tetralogy of Fallot. After repair of tetralogy of Fallot, a low CO state may develop as a result of right ventricular diastolic failure (130); this most likely

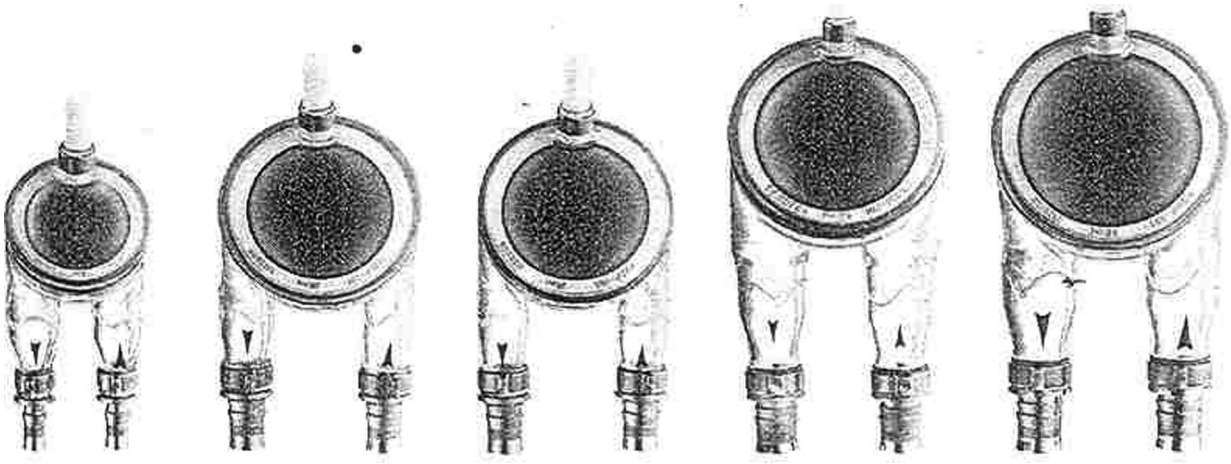

Figure 2. Berlin Heart pumps of different sizes (range 10–60 mL).

results from exposure of the hypertrophied right ventricle to CPB and reperfusion injury. Because systolic function is intact, inotropic agents are of little benefit (55, 56). Low CO output results from inadequate right ventricular filling, which is compounded by a reduction in the effective compliance of the left ventricle. During diastole, the hypertensive right ventricle alters the normal transeptal pressure gradient, causing the ventricular septum to bow into the left ventricle (130, 131). As discussed, a fall in intrathoracic pressure as occurs with the use of a cuirass or after extubation has been shown to improve hemodynamics and tissue oxygenation (132, 133). Invariably some degree of right bundle branch block is present after surgery and cardiac resynchronization therapy has been shown to improve hemodynamics in some patients (134–136).

Mechanical Circulatory Support. Mechanical circulatory support devices may be used as a bridge to recovery, like in fulminant myocarditis and the postcardiotomy syndrome, or as a bridge to transplantation. The mainstay of short-term pediatric mechanical circulatory support has been and remains extracorporeal membrane oxygenation and the centrifugal ventricular assist device (VAD). By and large, long-term mechanical circulatory support in pediatrics has relied on extracorporeal membrane oxygenation with a 47% to 57% success rate as a bridge to transplantation (134, 135). Over the last several years, several long-term VADs have been designed for or applied to the pediatric patient, leading to improved outcomes. A study of the Pediatric Heart Transplant Study database found a survival to transplantation rate of 77% using VADs from 1993–2003 with an even higher success rate from 2000–2003 of 86% (139). Despite improved overall outcomes, the success rate is significantly lower in patients with congenital heart disease and in the smaller, younger patients.

The Berlin Heart Excor (Berlin GmbH, Berlin, Germany) is the first commercially available VAD designed for the pediatric population (Fig. 2). It has specialized cannulae and a miniaturized pneumatically driven pump that produces pulsatile flow. The device is suitable for patients with a body weight of >2.5 kg and may be implanted as a bilateral VAD, left VAD, or right VAD. The Berlin Excor has been in use in Europe since 1992 and recently was approved by the Food and Drug Administration under a limited investigational device exemption. A prospective multicentered trial is underway in the United States as part of an effort to obtain Food and Drug Administration approval. The MEDOS HIA VAD (MEDOS Medizintechnik GmbH, Stollberg, Germany) is a paracorporeal pneumatically driven pump that that is in use in Europe and been used in children as small as 3 kg.

Other paracorporeal VADs designed for adults have been used in children with a body surface area of >0.7 m^2. The HeartMate II by Thoratec (Thoratec Corp., Pleasanton, CA) is a relatively new intracorporeal device that relies on rotary pump technology to provide continuous flow and has been used in patients down to a body surface area of 1.3 m^2 (140). The MicroMed Debakey VAD Child (MicroMed Technology, Houston, TX) is an implantable device with an actuated axial flow pump that provides nonpulsatile flow for patients with a body surface area of 0.7–1.5 m^2. The pediatric experience has been limited.

Pulmonary Hypertension. Patients with cardiac disease are prone to developing pulmonary hypertension, which may be exacerbated by the adverse effects of CPB and reperfusion injury on pulmonary vascular, respiratory, and right ventricular function (141, 142). Initial therapies include normalization of blood pH; correction of alveolar hypoxia with titration of end-expiratory pressure to achieve a normal functional residual capacity; and right ventricular inotropy. Pharmacologic strategies to reduce pulmonary vascular resistance are included in Figure 3. Nonselective vasodilators may precipitate systemic hypotension if systemic vascular resistance falls to a much greater extent than pulmonary vascular resistance and may impair oxygenation by releasing hypoxic pulmonary vasoconstriction.

Inhaled nitric oxide (iNO) is highly effective at reducing pulmonary vascular resistance and its effects are limited to the pulmonary circulation (144). Too rapid a discontinuation of iNO may lead to downregulation of endogenous iNO and rebound pulmonary hypertension, which may be ameliorated with the use of oral sildenafil (145, 146). The use of iNO in left-sided obstructive lesions such as mitral stenosis and "obstructed" total anomalous pulmonary venous return leads to an increase in pulmonary venous pressure and may precipitate pulmonary edema without improving CO (147, 148). In patients with pulmonary hypertension secondary to left ventricular systolic heart failure, the reduction of right ventricular afterload with iNO exacerbates

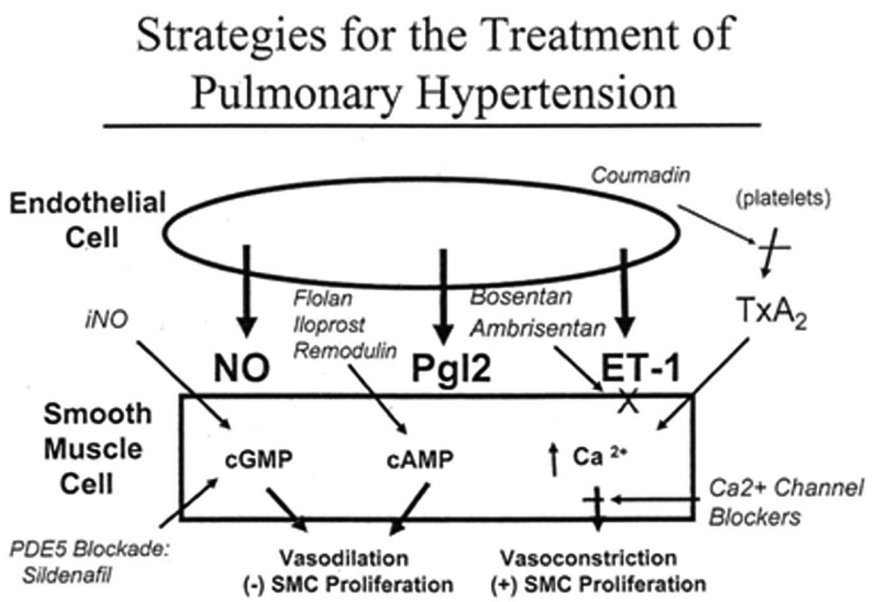

Figure 3. Physiologic approach to the treatment of pulmonary hypertension. Ca^{2+}, calcium; *cAMP*, cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *ET-1*, endothelin-1; *iNO*, inhaled nitric oxide; *NO*, nitric oxide; *PDE5*, type V cGMP-specific phosphodiesterase; *PGI2*, prostacyclin; *SMC*, smooth muscle cell; *TxA2*, thromboxane A_2. Reprinted with permission from Abman SH (143).

left ventricular congestive heart failure if the left ventricle is not unloaded (149). A study by Argenziano and colleagues (150) demonstrated the utility of iNO in adult patients with severe left ventricular failure whose left ventricle was unloaded with a left VAD but whose flow rate was limited by elevated pulmonary vascular resistance. The use of iNO in this setting allowed for a significant increase in left VAD flow.

Arrhythmia. After cardiac surgery, temporary epicardial pacing wires are frequently attached to the right atria and right ventricle or single ventricle enabling atrial, atrioventricular sequential, and ventricular pacing. Cardiac resynchronization therapy after surgery is a relatively new strategy to improve cardiac function. Cardiac resynchronization therapy involves nonconventional pacing strategies targeting prolonged atrioventricular and intraventricular conduction, which may improve ventricular filling and lessen the degree of discoordinate ventricular contraction (151, 152).

Several studies have evaluated cardiac resynchronization therapy after pediatric cardiac surgery. A study by Zimmerman and colleagues (153) demonstrated significant improvements in hemodynamics and CO by using multisite ventricular pacing after pediatric cardiac surgery in 29 patients with single and biventricular anatomy and prolonged QRS duration. In a follow-up study from the same center, 26 single ventricle patients regardless of electrocardiographic criteria demonstrated improved hemodynamics and CO with multisite ventricular pacing (154). A study by Janousek and colleagues (135, 136) demonstrated improved blood pressure using atrial synchronous right ventricle and biventricular pacing for primarily atrioventricular and intraventricular conduction delay after pediatric cardiac surgery. A study by Jeewa et al (155) evaluated cardiac resynchronization therapy in children undergoing biventricular repair of congenital heart disease. Patients were atrioventricular paced using right ventricle or biventricular pacing. There was no hemodynamic improvement using either strategy. A similar study conducted by Pham et al (156) demonstrated improved CO during biventricular pacing but not during conventional atrioventricular pacing. The QRS duration for each study was not prolonged. Although there are variations between these studies, including the underlying cardiac lesion, baseline conduction, and pacing strategies, the longer the baseline QRS duration, the more likely cardiac resynchronization therapy will be hemodynamically beneficial and a normal QRS duration does predict lack of benefit.

Summary

The practice of pediatric cardiac intensive care has evolved considerably over the last several years. Exciting advances are being made in other areas of perioperative care, which directly or indirectly impact postoperative management and outcomes. Industry-sponsored studies and the advent of the Pediatric Heart Network of the National Institutes of Health will contribute to the growth of the field by conducting randomized controlled studies. Discoveries and innovations in imaging, genomics, and mechanical circulatory devices are occurring; refinements in CPB are taking place, which target myocardial reperfusion injury, the inflammatory response to bypass, and neurologic sequelae. Some centers are bridging the catheterization laboratory and the operating room by exploring hybrid techniques. Fetal interventions and surgery in very low birth weight neonates are providing additional strategies for dealing with the most challenging lesions, whereas an ever-increasing population of adults with congenital heart disease is emerging, necessitating the development of a new subspecialty. The field of pediatric cardiac intensive care is an exciting, demanding, and evolving discipline, necessitating the ongoing commitment of various disciplines to pursue a greater understanding of disease processes and how to best go about treating them.

REFERENCES

1. Seghaye M-C: The clinical implications of the systemic inflammatory reaction related

to cardiac operations in children. *Cardiol Young* 2003; 13:228–239
2. Mou SS, Havdek SB, Lequier L, et al: Myocardial inflammatory activation in children with congenital heart disease. *Crit Care Med* 2002; 30:827–832
3. Kirklin JK, Westaby S, Blackstone EH, et al: Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983; 86:845–857
4. van Deventer SJH: Cytokine and cytokine receptor polymorphisms in infectious disease. *Intensive Care Med* 2000; 26: S98–S102
5. Gaudino M, Di Castelnuovo A, Zamparelli R, et al: Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary artery surgery. *J Thorac Cardiovasc Surg* 2003; 126:1107–1112
6. Seghaye MC, Duchateau J, Grabitz RG, et al: Complement activation during cardiopulmonary bypass in infants and children. Relation to postoperative multiple system organ failure. *J Thorac Cardiovasc Surg* 1993; 106:978–987
7. Bronicki RA, Backer CL, Baden HP, et al: Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg* 2000; 69:1490–1495
8. Schroeder VA, Pearly JM, Schwartz, et al: Combined steroid treatment for congenital heart surgery improves oxygen delivery and reduces postbypass inflammatory mediator expression. *Circulation* 2003; 107: 2823–2828
9. Checchia PA, Backer CL, Bronicki RA, et al: Dexamethasone reduces postoperative troponin levels in children undergoing cardiopulmonary bypass. *Crit Care Med* 2003; 31: 1742
10. Malagon I, Hogenbirk K, van Pelt J, et al: Effect of dexamethasone on postoperative cardiac troponin T production in pediatric cardiac surgery. *Intensive Care Med* 2005; 31:1420–1426
11. Lindberg L, Forsell C, Jogi P, et al: Effects of dexamethasone on clinical course, C-reactive protein, S100B protein and von Willebrand factor antigen after paediatric cardiac surgery. *Br J Anaesthesia* 2003; 90:728–732
12. Varan B, Tokel K, Mercan S, et al: Systemic inflammatory response related to cardiopulmonary bypass and its modification by methylprednisolone: High dose versus low dose. *Pediatr Cardiol* 2002; 23:437–441
13. Checchia PA, Bronicki RA, Costello JM, et al: Steroid use before pediatric cardiac operations using cardiopulmonary bypass: An international survey of 36 centers. *Pediatr Crit Care Med* 2005; 6:441–444
14. Connors AF Jr, McCaffree DR, Gray BA: Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med* 1983; 308: 263–267
15. Tibby SM, Hatherill M, Marsh MJ, et al: Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child* 1997; 77:516–518
16. Reuse C, Vincent J-L, Pinsky MR: Measurements of right ventricular volumes during fluid challenge. *Chest* 1990; 98:1450–1454
17. Toussaint GPM, Burgess JH, Hampson LG: Central venous pressure and pulmonary wedge pressure in critical surgical illness. *Arch Surg* 1974; 109:265–269
18. Hatherill M, Sajjanhar T, Tibby SM, et al: Serum lactate as a predictor of morality after paediatric cardiac surgery. *Arch Dis Child* 1997; 77:235–238
19. Munoz R, Laussen PC, Palacio G, et al: Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: An early indicator of morbidity and mortality. *J Thorac Cardiovasc Surg* 2000; 119:155–162
20. Fencl V, Leith DE: Stewart's quantitative acid-base chemistry: Applications in biology and medicine. *Respir Physiol* 1993; 91:1–16
21. Ring T, Frische S, Nielsen S: Clinical review: Renal tubular acidosis—A physicochemical approach. *Crit Care* 2005; 9:573–580
22. Kellum J: Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: Improved short-term survival and acid-base balance with hextend compared with saline. *Crit Care Med* 2002; 30:300–305
23. Hatherill M, Salie S, Waggie Z, et al: Hyperchloraemic metabolic acidosis following open cardiac surgery. *Arch Dis Child* 2005; 90:1288–1292
24. Vincent JL: Determination of oxygen delivery and consumption versus cardiac index and oxygen extraction ratio. *Crit Care Clin* 1996; 12:995–1006
25. Li J, Zhang G, McCrindle BW, et al: Profiles of hemodynamics and oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure. *J Thorac Cardiovasc Surg* 2007; 133: 441–448
26. Perez AC, Eulmesekian PG, Minces PG, et al: Adequate agreement between venous oxygen saturation in right atrium and pulmonary artery in critically ill children. *Pediatr Crit Care Med* 2009; 10:76–79
27. Scheinman MM, Brown MA, Rapaport E: Critical assessment of use of central venous oxygen saturation as mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 1969; XL:165–172
28. Lee J, Wright F, Barber R, et al: Central venous oxygen saturation in shock: A study in man. *Anesthesiology* 1972; 36:472–478
29. Scheinman MM, Brown MA, Rapaport E: Critical assessment of use of central venous oxygen saturation as mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 1969; XL:165–172
30. de Oliveira CF, de Oliveira DSF, Gottschald AFC, et al: ACCM/PALS haemodynamic support guideline for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008; 34: 1065–1075
31. Tweddell JS, Hoffman GM, Mussatto KA, et al: Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: Lessons learned from 115 consecutive patients. *Circulation* 2002; 106(Suppl I):I-82–I-89
32. Watzman HM, Kurth CD, Montenegro LM, et al: Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology* 2000; 93:947–953
33. Kirshbom PM, Forbess JM, Kogon BE, et al: Cerebral near infrared spectroscopy is a reliable marker of systemic perfusion in awake single ventricle children. *Pediatr Cardiol* 2007; 28:42–45
34. Nagdyman N, Fleck T, Schubert S, et al: Comparison between cerebral tissue oxygenation index measured by near-infrared spectroscopy and venous jugular bulb saturation in children. *Intensive Care Med* 2005; 31:846–850
35. Li J, Zhang G, Holtby H, et al: The influence of systemic hemodynamics and oxygen transport on cerebral oxygen saturation in neonates after the Norwood procedure. *J Thor Cardiovasc Surg* 2008; 135:83–90
36. McQuillen PS, Nishimoto MS, Bottrell CL, et al: Regional and central venous oxygen saturation monitoring following pediatric cardiac surgery: Concordance and association with clinical variables. *Pediatr Crit Care Med* 2007; 8:154–160
37. Bhutta AT, Ford JW, Parker JG, et al: Noninvasive cerebral oximeter as a surrogate for mixed venous saturation in children. *Pediatr Cardiol* 2007; 28:34–41
38. Bronicki RA: Shock states. *In*: Pediatric Hospital Medicine. Perkin R, Anas N, Swift J (Eds). Philadelphia, Lippincott Williams & Wilkins, 2007, pp. 192–207
39. Graham TP Jr: Ventricular performance in congenital heart disease. *Circulation* 1991; 84:2259–2274
40. Shernan SK: Perioperative myocardial ischemia reperfusion injury. *Anesth Clin N Am* 2003; 21:465–485
41. Nichols DG: Respiratory muscle performance in infants and children. *J Pediatrics* 1991; 118:493–502
42. McGowan FX Jr, Ikegami M, del Nido PJ, et al: Cardiopulmonary bypass significantly reduces surfactant activity in children. *J Thorac Cardiovasc Surg* 1993; 106:968–977
43. Supinski G, Ketai DL, Altose M: Reversibility of diaphragm fatigue by mechanical hyperfusion. *Am Rev Respir Dis* 1988; 138: 604–609
44. Supinski G, DiMarco A, Dibner-Dunlap M: Alterations in diaphragm strength and fatigability in congestive heart failure. *J Appl Physiol* 1994; 76:2707–2713
45. Burrows FA: Physiologic dead space, venous admixture, and the arterial to end-tidal carbon dioxide difference in infants and children undergoing cardiac surgery. *Anesthesiology* 1989; 70:219–225

46. Fletcher R: Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease. *Br J Anaesth* 1989; 62:168–176
47. Tamir A, Melloul M, Berant M, et al: Lung perfusion scans in patients with congenital heart defects. *J Am Coll Cardiol* 1992; 19: 383–388
48. Matsushita T, Matsuda H, Ogawa M, et al: Assessment of the intrapulmonary ventilation–perfusion distribution after the Fontan procedure for complex cardiac anomalies: Relation to pulmonary hemodynamics. *J Am Coll Cardiol* 1990; 15: 842–848
49. Blatchford DW, Barragry TP, Lillehei TJ, et al: Effects of cardioplegic arrest on left ventricular systolic and diastolic function of the intact neonatal heart. *J Thorac Cardiovasc Surg* 1994; 107:527–535
50. Chaturvedi RR, Herron T, Simmons R, et al: Passive stiffness of myocardium from con genital heart disease and implications for diastole. *Circulation* 2010; 121:979–988
51. Legato MJ: Cellular mechanisms of normal growth in the mammalian heart: I. Qualitative and quantitative features of ventricular architecture in the dog from birth to five months of age. *Circ Res* 1979; 44:250–262
52. Marijianowski MH, Van Der Loos CM, Mohrschladt M, et al: The neonatal heart has a relatively high content of total collagen and type I collagen, a condition that may explain the less compliant state. *J Am Coll Cardiol* 1994; 23:1204
53. Zile MR, Brutsaert DL: New concepts in diastolic dysfunction, diastolic heart failure: Part II. Causal mechanisms and treatment. *Circulation* 2002; 105:1503–1508
54. Senzaki H, Masutani S, Kobayashi J, et al: Ventricular afterload and ventricular work in Fontan circulation. Comparison with normal two-ventricle circulation and single-ventricle circulation with Blalock-Taussig shunts. *Circulation* 2002; 105: 2885–2892
55. Jaccard C, Berner M, Rouge JC, et al: Hemodynamic effect of isoprenaline and dobutamine immediately after correction of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 1984; 87:862–869
56. Berner M, Rouge JC, Friedli B: The hemodynamic effect of phentolamine and dobutamine after open-heart operations in children: Influence of the underlying heart defect. *Ann Thorac Surg* 1983; 35:643–650
57. Matter CM, Mandinov L, Kaufmann PA, et al: Effect of NO donors on LV diastolic function in patients with sever pressure-overload hypertrophy. *Circulation* 1999; 99: 2396–2401
58. Thomson HL, Morris-Thurgood J, Atherton J, et al: Reflex responses of venous capacitance vessels in patients with hypertrophic cardiomyopathy. *Clin Sci* 1998; 94:339–346
59. Krishnan US, Taneja I, Gewitz M, et al: Peripheral vascular adaptation and orthostatic tolerance in Fontan physiology. *Circulation* 2009; 120:775–1783
60. Mace L, Dervanian P, Bourriez A, et al: Changes in venous return parameters associated with univentricular Fontan circulation. *Am J Physiol Heart Circ Physiol* 2000; 279:H2335–H2343
61. Myers CD, Ballman K, Riegle LE, et al: Mechanisms of systemic adaptation to univentricular Fontan conversion. *J Thorac Cardiovasc Surg* 2010; 140:850–856
62. Braunwald E, Oldham HN, Ross J Jr, et al: The circulatory response of patients with idiopathic hypertrophic subaortic stenosis to nitroglycerin and to the Valsalva maneuver. *Circulation* 1964; XXIX:422–431
63. Bronicki RA, Anas NG: Cardiopulmonary interaction. *Pediatr Crit Care Med* 2009; 10: 313–322
64. Hill NS, Antman EM, Green LH, et al: Intravenous nitroglycerin. A review of pharmacology, indications, therapeutic effects and complications. *Chest* 1981; 79:69–76
65. Ilbawi MN, Idriss FS, DeLeon SY, et al: Hemodynamic effects of intravenous nitroglycerin in pediatric patients after heart surgery. *Circulation* 1985; 72(Suppl II): II-101–II-107
66. Levin ER, Gardner DG, Samson WK: Natriuretic peptides. *N Engl J Med* 1998; 339: 321–328
67. Gori T, Parker JD: Nitrate tolerance. *Circulation* 2002; 106:2510–2513
68. Brunner-La Rocca HP, Kaye D, Woods R, et al: Effect of intravenous brain natriuretic peptide on regional sympathetic activity in patient with chronic heart failure as compared with healthy control subjects. *J Am Coll Cardiol* 2001; 37:1221–1227
69. Colucci WS, Elkayam U, Horton D, et al: Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med* 2000; 343:246–253
70. Jefferies JL, Denfield SW, Price JF, et al: A prospective evaluation of nesiritide in the treatment of pediatric heart failure. *Ped Cardiol* 2006; 27:402–407
71. Atgie C, D'Allaire F, Bukowiecki LJ, et al: Role of B1- and B3-adrenoceptors in the regulation of lipolysis and thermogenesis in rat brown adipocytes. *Am J Physiol* 1997; 273:C1136–C1142
72. Loeb HS, Bredakis J, Gunnar RM: Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation* 1977; 55:375–381
73. Pang C: Autonomic control of the venous system in health and disease. Effects of drugs. *Pharmacol Ther* 2001; 90:179–230
74. Allwood MJ, Cobbold AF, Ginsburg J: Peripheral vascular effects of noradrenaline, isopropyl noradrenaline and dopamine. *Br Med Bull* 1963; 19:132–136
75. Greenway CV: Mechanisms and quantitative assessment of drug effects on cardiac output with a new model of the circulation. *Pharm Rev* 1982; 33:213–251
76. Yano M, Kohno M, Ohkusa T, et al: Effect of milrinone on left ventricular relaxation and Ca^{2+} uptake function of cardiac sarcoplasmic reticulum. *Am J Physiol Heart Circ Physiol* 2000; 279:H1898–H1905
77. Chang AC, Atz AM, Wernovsky G, et al: Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med* 1995; 23:1907–1914
78. Hoffman TM, Wernovsky G, Atz AM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107:996–1002
79. Nieminen MS, Akkila J, Hasenfuss G, et al: Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *J Am Coll Cardiol* 2000; 36:1903–1912
80. Namachivayam P, Crossland DS, Butt WW, et al: Early experience with levosimendan in children with ventricular dysfunction. *Pediatr Crit Care Med* 2006; 7:445–448
81. Momeni M, Rubay J, Matta A, et al: Levosimendan in congenital cardiac surgery: A randomized, double-blind clinical trial. *J Cardiothorac Vasc Anesth* 2010 Sep 7 [Epub ahead of print]
82. Bark H, LeRoith D, Myska M, et al: Elevations in plasma ADH levels during PEEP ventilation in the dog: Mechanisms involved. *Am J Physiol* 1980; 239:E474–E480
83. Peters J, Kindred MK, Robotham JL: Transient analysis of cardiopulmonary interactions. II. Systolic events. *J Appl Physiol* 1988; 64:1518–1526
84. Viires N, Aubier SM, Rassidakis A, et al: Regional blood flow distribution in dog during induced hypotension and low cardiac output. *J Clin Invest* 1983; 72:935–947
85. Landry DW, Oliver JA: The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345: 588–595
86. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
87. Dunser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock. A prospective, randomized, controlled study. *Circulation* 2003; 107: 2313–2319
88. Rosenzweig EB, Stare TJ, Chen JM, et al: Intravenous arginine–vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999; 100(Suppl II):II-182–II-186
89. Choong K, Kissoon N: Vasopressin in pediatric shock and cardiac arrest. *Pediatr Crit Care Med* 2008; 9:372–379
90. Lamberts SWJ, Bruining HA, De Jong FH: Corticosteroid therapy in severe illness. *N Engl J Med* 1997; 337:1285–1292
91. Wehling M: Specific, nongenomic actions of

steroid hormones. *Annu Rev Physiol* 1997; 59:365–393
92. Sasidharan P: Role of corticosteroids in neonatal blood pressure homeostasis. *Clin Perinatol* 1998; 25:723–740
93. Bronicki RA: Is cardiac surgery sufficient to create insufficiency? *Pediatr Crit Care Med* 2010; 11:150–151
94. Ng PC, Lee CH, Bnur FL, et al: A double-blind, randomized, controlled study of a 'stress dose' of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. *Pediatrics* 2006; 117:367–375
95. Kopelman AE, Moise AA, Holbert D, et al: A single very early dexamethasone dose improves respiratory and cardiovascular adaptation in preterm infants. *J Pediatr* 1999; 135:345–350
96. Ando M, Park I-S, Wada N, et al: Steroid supplementation: A legitimate pharmacotherapy after neonatal open heart surgery. *Ann Thorac Surg* 2005; 80:1672–1678
97. Shore S, Nelson DP, Pearl JM, et al: Usefulness of corticosteroid therapy in decreasing epinephrine requirements in critically ill infants with congenital heart disease. *Am J Cardiol* 2001; 88:591–594
98. Millar KJ, Thiagarajan RR, Laussen PC: Glucocorticoid therapy for hypotension in the cardiac intensive care unit. *Pediatr Cardiol* 2007; 28:176–182
99. Suominen PK, Dickerson HA, Moffett BS, et al: Hemodynamic effects of rescue protocol hydrocortisone in neonates with low cardiac output syndrome after cardiac surgery. *Pediatr Crit Care Med* 2005; 6:655–659
100. Mainwaring RD, Healy RM, Meier FA, et al: Reduction in levels of triiodothyronine following the first stage of the Norwood reconstruction for hypoplastic left heart syndrome *Cardiol Young* 2001; 11:295–300
101. Bettendorf M, Schmidt KG, Grulich-Henn J, et al: Tri-iodothyronine treatment in children after cardiac surgery: A double-blind, randomised, placebo-controlled study. *Lancet* 2000; 356:P529–P534
102. Chowdhury D, Ojamaa K, Parnell VA, et al: A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease. *J Thorac Cardiovasc Surg* 2001; 122:1023–1025
103. Mackie AS, Booth KL, Newburger JW, et al: A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. *J Thorac Cardiovasc Surg* 2005; 130:810–816
104. Portman MA, Slee A, Olson AK, et al: Triiodothyronine supplementation in infants and children undergoing cardiopulmonary bypass (TRICC). A multicenter placebo-controlled randomized trial: Age analysis. *Circulation* 2010; 122(Suppl 1):S224–S233
105. Taeed R, Schwartz SM, Pearl JM, et al: Unrecognized pulmonary venous desaturation early after Norwood palliation confounds Qp:Qs assessment and compromises oxygen delivery. *Circulation* 2001; 103:2699–2704
106. Hoffman GM, Tweddell JS, Ghanayem NS, et al: Alteration of the critical arteriovenous oxygen saturation relationship by sustained afterload reduction after the Norwood procedure. *J Thorac Cardiovasc Surgery* 2004; 127:738–745
107. De Oliveira NC, Ashburn DA, Khalid F, et al: Prevention of early sudden circulatory collapse after the Norwood operation. *Circulation* 2004; 110(Suppl II):II-133–II-138
108. Stieh J, Fischer G, Scheewe J, et al: Impact of preoperative treatment strategies on the early perioperative outcome in neonates with hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg* 2006; 131:1122–1129
109. Reddy VM, Liddicoat JR, McElhinney DB, et al: Hemodynamic effects of epinephrine, bicarbonate and calcium in the early postnatal period in a lamb model of singleventricle physiology created in utero. *J Am Coll Cardiol* 1996; 28:1877–1883
110. Li J, Zhang G, Holtby H, et al: Adverse effects of dopamine on systemic hemodynamic status and oxygen transport in neonates after the Norwood procedure. *J Am Coll Cardiol* 2006; 48:1859–1864
111. Riordan CJ, Randsbaek F, Storey JH, et al: Inotropes in the hypoplastic left heart syndrome: Effects in an animal model. *Ann Thorac Surg* 1996; 62:83–90
112. Maher KO, Pizarro C, Gidding SS, et al: Hemodynamic profile after the Norwood procedure with right ventricle to pulmonary artery conduit. *Circulation* 2003; 108: 782–784
113. Mair R, Tulzer G, Sames E, et al: Right ventricular to pulmonary artery conduit instead of modified Blalock-Taussig shunt improves postoperative hemodynamics in newborns after the Norwood operation. *J Thorac Cardiovasc Surg* 2003; 126: 1378–1384
114. Ohye RG, Sleeper LA, Mahony L, et al: Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med* 2010; 362:1980–1992
115. McElhinney DB, Reddy VM, Hanley FL, et al: Systemic venous collateral channels causing desaturation after bidirectional cavopulmonary anastomosis: Evaluation and management. *J Am Coll Cardiol* 1997; 30:817–824
116. Gatzoulis MA, Shinebourne EA, Redington AN, et al: Increasing cyanosis early after cavopulmonary connection caused by abnormal systemic venous channels. *Br Heart J* 1995; 73:182–186
117. Chang R-KR, Alejos JC, Atkinson D, et al: Bubble contrast echocardiography in detecting pulmonary arteriovenous shunting in children with univentricular heart after cavopulmonary anastomosis. *J Am Coll Cardiol* 1999; 33:2052–2058
118. Bradley SM, Simsic JM, Mulvihill DM: Hypoventilation improves oxygenation after bidirectional superior cavopulmonary connection. *J Thorac Cardiovasc Surg* 2003; 126:1033–1039
119. Hoskote A, Li J, Hickey C, et al: The effects of carbon dioxide on oxygenation and systemic, cerebral, and pulmonary vascular hemodynamics after the bidirectional superior cavopulmonary anastomosis. *J Am Coll Cardiol* 2004; 44:1501–1509
120. Simsic JM, Bradley SM, Mulvihill DM: Sodium nitroprusside infusion after bidirectional superior cavopulmonary connection: Preserved cerebral blood flow velocity and systemic oxygenation. *J Thorac Cardiovasc Surg* 2003; 126:186–190
121. Garofalo CA, Cabreriza SE, Quinn A, et al: Ventricular diastolic stiffness predicts perioperative morbidity and duration of pleural effusions after the Fontan operation. *Circulation* 2006; 114(Suppl I):I-56–I-61
122. Shekerdemian LS, Bush A, Shore DF, et al: Cardiopulmonary interactions after Fontan operations. Augmentation of cardiac output using negative pressure ventilation *Circulation* 1997; 96:3934–3942
123. Cooper DS, Costello JM, Bronicki RA, et al: Current challenges in cardiac intensive care: Optimal strategies for mechanical ventilation and timing of extubation. *Cardiol Young* 18 suppl 2:226–233, 2008
124. Williams DB, Kiernan PD, Metke MP, et al: Hemodynamic response to positive end-expiratory pressure following right atrium-pulmonary artery bypass (Fontan procedure). *J Thorac Cardiovasc Surg* 1984; 87: 856–861
125. Goldman AP, Delius RE, Deanfield JE, et al: Pharmacological control of pulmonary blood flow with inhaled nitric oxide after the fenestrated Fontan operation. *Circulation* 1996; 94(Suppl II):II-44–II-48
126. Buheitel G, Hofbeck M, Tenbrink U, et al: Possible sources of right-to-left shunting in patients following a total cavopulmonary connection. *Cardiol Young* 1998; 8:358–363
127. Mellins RB, Levine R, Fishman AP: Effect of systemic and pulmonary venous hypertension on pleural and pericardial fluid accumulation. *J Appl Physiol* 1970; 29:564–569
128. Szabo G, Magyar Z: Effect of increased systemic venous pressure on lymph pressure and flow. *Am J Physiol* 1967; 212: 1469–1474
129. Kantner KR, Vincent RN, Raviele AA: Importance of acquired systemic-to-pulmonary collaterals in the Fontan operation. *Ann Thorac Surg* 1999; 68:969–675
130. Cullen S, Shore D, Redington A: Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot. *Circulation* 1995; 91:1782–1789
131. Bronicki RA, Baden HP: Pathophysiology of right ventricular failure in pulmonary hypertension. *Pediatr Crit Care Med* 2010; 11: S15–S22
132. Shekerdemian L, Bush A, Shore DF, et al: Cardiorespiratory responses to negative pressure ventilation after tetralogy of Fallot repair: A hemodynamic tool for patients with a low-output state. *J Am Coll Cardiol* 1999; 33:549–555

133. Bronicki RA, Herrera M, Mink R, et al: Hemodynamics and cerebral oxygenation following repair of tetralogy of Fallot: The effects of converting form positive pressure ventilation to spontaneous breathing. *Cong Heart Dis* 2010; 5:416–421
134. Mikesell CE, Bronicki RA, Domico M, et al: Right ventricular synchronization therapy following repair of tetralogy of Fallot. *Pediatr Crit Care Med* 2010; 11(Suppl):S102
135. Janousek J, Vojtovic P, Hucin B, et al: Resynchronization pacing is a useful adjunct to the management of acute heart failure after surgery for congenital heart defects. *Am J Cardiol* 2001; 88:145–152
136. Janousek J, Vojtovic P, Chaloupecky V, et al: Hemodynamically optimized temporary cardiac pacing after surgery for congenital heart defects. *PACE* 2000; 23:1250–1259
137. Del Nido PJ, Armitage JM, Ficker FJ, et al: Extracorporeal membrane oxygenation support as a bridge to pediatric heart transplantation. *Circulation* 1994; 90:II-66–II-69
138. Gajarski RJ, Mosca RS, Ohye RG, et al: Use of extracorporeal life support as a bridge to pediatric cardiac transplantation. *J Heart Lung Transplant* 2003; 22:28–34
139. Blume ED, Naftel DC, Bastardi HJ, et al: Outcomes of children bridged to heart transplantation with ventricular assist devices. A multi-institutional study. *Circulation* 2006; 113:2313–2319
140. Owens WR, Bryant R III, Dreyer WJ, et al: Initial clinical experience with the HeartMate II ventricular assist system in a pediatric institution. *Artif Organs* 2010; 34: 600–614
141. Eppinger MJ, Ward PA, Bolling SF, et al: Regulatory effects of interleukin-10 on lung ischemia–reperfusion injury. *J Thorac Cardiovasc Surg* 1996; 112:1301–1306
142. Serraf A, Sellak H, Herve P, et al: Vascular endothelium viability and function after total cardiopulmonary bypass in neonatal piglets. *Am J Respir Crit Care Med* 1999; 159: 544–551
143. Abman SH: Pulmonary hypertension in children: A historical overview. *Pediatr Crit Care Med* 2010; 11(Suppl 1):S4–S9
144. Wessel Dl, Adatia I, Giglia TM, et al: Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993; 88:2128–2138
145. Atz A, Adatia I, Wessel DL: Rebound pulmonary hypertension after inhalation of nitric oxide. *Ann Thorac Surg* 1996; 62:1759–1764
146. Atz AM, Wessel DL: Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. *Anesthesiology* 1999; 91:307–310
147. Phoon CKL, Silverman NH: Conditions with right ventricular pressure and volume overload, and a small left ventricle: 'Hypoplastic' left ventricle or simply a squashed ventricle? *J Am Coll Cardiol* 1997; 30: 1547–1553
148. Atz AM, Adatia I, Jonas RA, et al: Inhaled nitric oxide in children with pulmonary hypertension and congenital mitral stenosis. *Am J Cardiol* 1996; 77:316–319
149. Seminigran MJ, Cockrill AB, Kacmarek R, et al: Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol* 1994; 24:982–988
150. Argenziano M, Choudhri AF, Moazami N, et al: Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg* 1998; 65:340–345
151. Leclercq C, Kass DA: Retiming the failing heart: Principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002; 39:194–201
152. Nishimura RA, Hayes DL, Holmes DR, et al: Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: An acute Doppler and catheterization hemodynamic study. *J Am Coll Cardiol* 1995; 25:281–288
153. Zimmerman FJ, Starr JP, Koenig PR, et al: Acute hemodynamic benefit of multisite ventricular pacing after congenital heart surgery. *Ann Thorac Surg* 2003; 75: 1775–1780
154. Bacha EA, Zimmerman FJ, Mor-Avi F, et al: Ventricular resynchronization by multisite pacing improves myocardial performance in the postoperative single-ventricle patient. *Ann Thorac Surg* 2004; 78:1678–1683
155. Jeewa A, Pitfield AF, Potts JE, et al: Does biventricular pacing improve hemodynamics in children undergoing routine congenital heart surgery? *Pediatr Cardiol* 2010; 31:181–187
156. Pham PP, Balaji S, Shen I, et al: Impact of conventional versus biventricular pacing on hemodynamics and tissue Doppler imaging indexes of resynchronization postoperatively in children with congenital heart disease. *J Am Coll Cardiol* 2005; 46:2284–2289