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Pathophysiology of Post-Operative Low Cardiac Output Syndrome

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Abstract: Low cardiac output syndrome frequently complicates the post-operative care of infants and children following cardiac surgery. The onset of low cardiac output follows a predictable course in the hours following cardiopulmonary bypass, as myocardial performance declines in the face of an elevated demand for cardiac output. When demand outstrips supply, shock ensues, and early recognition and intervention can decrease mortality. Multifactorial in etiology, this article will discuss the pathophysiology of low cardiac output syndrome, including myocardial depression following bypass, altered cardiac loading conditions, and inflammation driving a hypermetabolic state. Contributions from altered neurohormonal, thyroid, and adrenal axes will also be discussed. Sources included the clinical experiences of four cardiac intensivists, supported throughout by primary sources and relevant reviews obtained through PubMed searches and from seminal textbooks in the field. This article addresses the second of eight topics comprising the special issue entitled "Pharmacologic strategies with afterload reduction in low cardiac output syndrome after pediatric cardiac surgery".

Keywords: Cardiopulmonary bypass, low cardiac output syndrome, cardiopulmonary interactions, adrenal axis, thyroid axis.

INTRODUCTION

Low cardiac output syndrome (LCOS) is the clinical manifestation of mismatched oxygen delivery and metabolic demand driven by myocardial dysfunction and cardiovascular insufficiency. Following complex cardiac surgery requiring cardiopulmonary bypass (CPB), a predictable decline in cardiac performance occurs as pulmonary and systemic afterload increase, while relative myocardial contractility decreases [1]. The cardiac index has been shown to reach a nadir 9-12 hours postoperatively in neonates with an average decline of 30% [2]. Many factors contribute to LCOS and insufficient tissue perfusion in the perioperative period [3]. These include certain preoperative factors, myocardial dysfunction associated with CPB, ischemia-reperfusion injury, arrhythmias, and residual cardiac lesions. Altered loading conditions, increased metabolic demands, temperature instability, systemic inflammation, and derangements of the neurohormonal axis also contribute (Fig. **1**). Low cardiac output syndrome after pediatric cardiac surgery is associated with higher mortality and morbidity, including longer duration of cardiopulmonary support and CICU length of stay. Small infants with more complex lesions, as well as those requiring longer periods of bypass and aortic cross-clamp are at increased risk for the development of LCOS [4]. The incidence of LOCS following CPB is as high as 25-30% in neonates [2]. Clinically, LCOS is manifest by a compensatory response (tachycardia, elevated systemic vascular resistance) and is associated with findings and biomarkers reflecting inadequate tissue perfusion (oliguria, increased arterial-venous O_2 content difference, elevated lactate, and metabolic acidosis) [5]. In this article we review common processes contributing to the pathophysiology of post-operative LCOS in infants and children.

CARDIAC CAUSES OF LOW CARDIAC OUTPUT SYNDROME

Preoperative Considerations

The preoperative cardiac anatomy and hemodynamics may impact postoperative cardiac output. Preoperative myocardial dysfunction can be seen in the context of congestive heart failure, chronic hypoxemia, ventricular hypertrophy or myocardial ischemia [4] and is associated with a significant compromise in cardiac output in the postoperative period. Poor myocardial contractility also occurs in patients with cardiomyopathy, functional single ventricles, endocardial fibroelastosis, conduction disturbances, or previous infarctions. Myocardial infarctions can be seen in patients with anomalous coronary arteries, sub-endocardial ischemia, or previous surgical mishaps [4]. Preoperative acidosis and shock have been associated with increased postoperative risk for LCOS and negative clinical outcome [6]. Preoperative congestive heart failure also contributes to postoperative risk, as both myocardial work and tissue oxygen demands are increased [4].

Intraoperative Factors

The conduct of corrective cardiac surgery, while necessary, may contribute to myocardial ischemia and systolic

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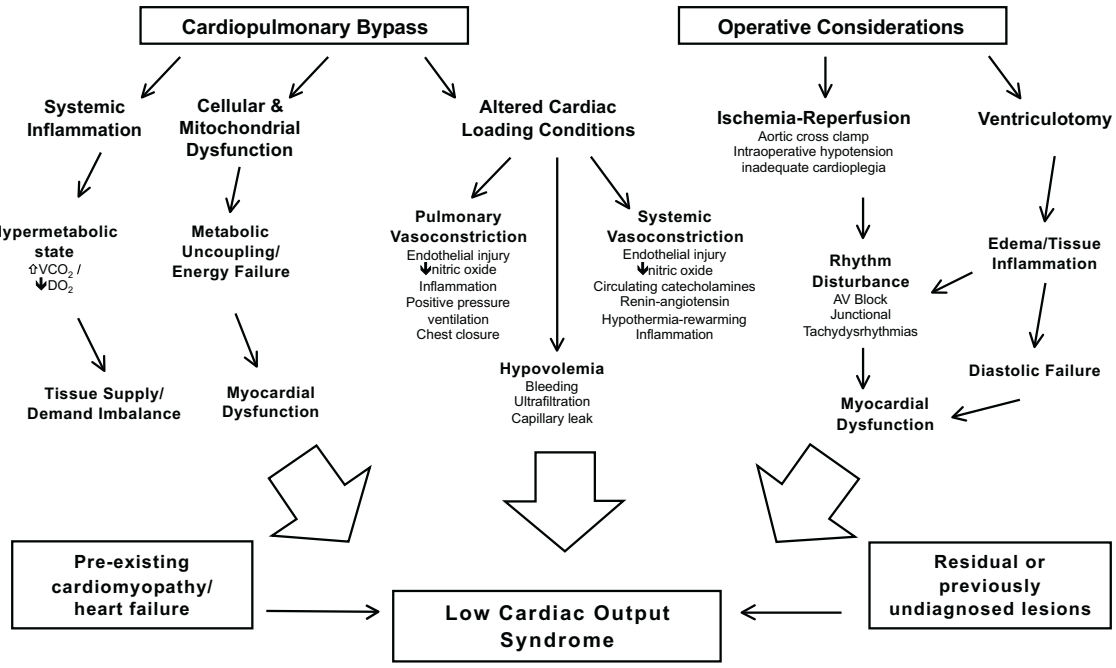

Fig. (1). Perioperative Factors Contributing to LCOS. Factors driven by exposure to CPB (*i.e.,* systemic inflammation, cellular & mitochondrial dysfunction, altered loading conditions) and those influenced by cardiac surgery (*i.e.,* ischemia, ventriculotomy) are noted schematically contributing to LCOS.

dysfunction. A number of intraoperative factors impact postoperative myocardial performance (Fig. **1**). Depressed myocardial contractility often results from the inflammatory response to CPB, myocardial ischemia from aortic cross clamp, hypothermia, reperfusion injury, inadequate myocardial protection, and, when performed, ventriculotomy [7]. Thus, depressed myocardial contractility and compliance, as a result of CPB and operative repair, contribute to the development of LCOS [4]. Direct mechanical injury can result from manipulation of the heart during surgery from handling, pressure from tools or retractors, and cannulation itself [4]. Incisions and sutures can directly interrupt synchronized conduction and impair myocardial contraction [4]. Ischemic injury may occur from intraoperative alterations in blood pressure, decreased coronary perfusion, systemic hypoxemia, and long cross-clamp times [4]. There is also a small risk of air embolus and thromboembolus, which is increased in polycythemic patients [4]. Chest closure may increase the pressure on edematous cardiac structures, increasing the transmitted forces from the ventilator that alter cardiac loading conditions.

Cardiopulmonary bypass is known to elicit an inflammatory cytokine cascade leading to myocardial depression as well as myocyte apoptosis and necrosis [8]. Insufficient or ineffective myocardial protection during cardioplegic arrest may worsen ventricular systolic and diastolic performance [9, 10]. Myocardial protection is particularly important in neonates given the immaturity of the neonatal myocardium, and their greater dependence on the right ventricle and its anterior position [11]. Thus optimal cardioplegia is a critical part of the operative strategy for myocardial protection. There continues to be controversy and ongoing research regarding the components, temperature, and mode of delivery for cardioplegia. A meta-analysis of primarily adults undergoing coronary artery bypass grafting demonstrated a reduction of LCOS with blood-enriched cardioplegia versus crystalloid [12]. However, in a randomized trial of crystalloid versus blood cardioplegia in neonates undergoing biventricular repair, those patients assigned to receive crystalloid cardioplegia had a higher cardiac index and shorter length of stay in the ICU [13]. Both bypass and myocardial ischemic times are associated with an increased dependence upon inotropic support [2].

Postoperative Factors

In addition to the decline in cardiac output expected during the first 12 hours following CPB [1, 2], other postoperative factors may contribute to myocardial dysfunction, exacerbating contributions from pre-existing disease and intraoperative events. Ongoing hypothermia may depress cardiac contractility and cardiac output, while hyperthermia and systemic inflammation drive tissue demand. Myocardial dysfunction is seen in the setting of hypoxemia leading to anaerobic myocardial metabolism [4]. Electrolyte imbalances are common and can promote rhythm disturbances and decreased contractility, as seen in hypocalcemia, hypoglycemia, and hyper- or hypokalemia [4]. Trending of biomarkers following CPB can provide early warning of a potential decline in cardiac performance. Newer approaches trending multiple biomarkers reflecting endothelial dysfunction, tissue injury, and inflammation are emerging and offer the promise to prospectively identify high-risk patients [14].

Postoperative Diastolic Dysfunction

Diastolic dysfunction often contributes to LCOS, with elevated atrial pressures characteristically noted in such patients. Diastolic dysfunction is seen in the setting of ventricu-

lar hypertrophy, typically seen in patients with preoperative outflow tract obstruction, such as those with tetralogy of Fallot (TOF) or aortic stenosis [9]. In TOF, the diastolic dysfunction associated with right ventricular (RV) hypertrophy may be exacerbated if a ventriculotomy is performed during surgical repair. The anterior position of the RV may make it more difficult to achieve myocardial protection [9]. The use of a transannular patch may result in pulmonary insufficiency and subsequent volume load to the RV, exacerbating RV dysfunction. Such *restrictive RV physiology* is thus a common postoperative finding in infants with TOF and neonates with repaired common arterial trunk (truncus arteriosus) [15]. Neonates with critical aortic stenosis and other left-sided obstructive lesions may also demonstrate diastolic dysfunction. These patients may have endocardial fibroelastosis (EFE), a thickening of the ventricular endocardium from preoperative myocardial stress, resulting in ventricular restriction impeding both systolic and diastolic function [16]. The presence of EFE contributes to poor cardiac output in those patients who undergo biventricular repair.

Arrhythmias

Arrhythmias often contribute to LOCS after cardiac surgery. The incidence of postoperative arrhythmias in children undergoing cardiac surgery is as high as 30% [17]. Factors predisposing patients to arrhythmias include pre-existing accessory pathways, intraoperative mechanical trauma, cardiac manipulation, edema or hemorrhage near the conduction system, as well as sympathetic stimulation from chronotropic medications [4]. Prolonged CPB, aortic cross clamp, and elevated postoperative serum troponin levels are also associated with the development of arrhythmias [18]. Loss of atrioventricular synchrony, seen in the context of junctional and other tachyarrhythmias, can quickly compromise ventricular filling, increase myocardial oxygen consumption, decrease coronary blood flow, and further impair cardiac output [19]. Tachyarrhythmias also impair diastolic filling, while bradyarrhythmias decrease contractions per minute, a significant problem in young infants for whom cardiac output is particularly rate-dependent [4, 19]. Arrhythmias may be exacerbated not only by chronotropic medications, but in the presence of hyperthermia, acidosis, hypoxemia, electrolyte imbalances, and hypoglycemia [7].

Residual Lesions

An assessment for residual lesions should be made intraoperatively and in the intensive care unit following cardiac surgery. Incomplete diagnoses, inadequate imaging, suboptimal surgical-decision making, and technical operative issues all contribute to the risk for residual lesions. The index of suspicion should be high for patients who deviate from the expected post-operative course, especially in those who progress to ECMO support. The postoperative care team must review the preoperative data and intraoperative course, including the transesophageal echocardiogram, pressure measurements, and oxygen saturation data. Important residual lesions can have a profound impact on cardiac output and have been associated with a substantially higher mortality, while early recognition and re-intervention may improve outcome [20]. Residual outflow tract obstruction and atrioventricular valvar regurgitation (AVVR) reduce the effective stroke volume and increase myocardial workload. Acute cardiac failure from new AVVR clinically manifests with elevated atrial pressures, pulmonary congestion, hepatomegaly, cardiomegaly, and tachycardia. Findings consistent with new atrioventricular valvar disease are suggested by echocardiography, coupled with an abnormal atrial pressure or waveform, and findings of LCOS. Atrioventricular valvar regurgitation or stenosis may been seen after valvar surgery and septal defect repairs [9]. Residual left-to-right shunts increase pulmonary blood flow, which may cause pulmonary edema, pulmonary hypertension, volume overload of the systemic ventricle, and decreased systemic blood flow. Residual outflow tract obstruction can persist after attempts to relieve outflow tract obstructions (myocardial, subvalvar, or valvar), and new obstructions can be created following atrioventricularseptal defect repairs [9]. Clinical findings of residual outflow obstructions, aside from TEE findings, include the presence of a new ejection murmur and elevated atrial pressures. Pulmonary artery stenosis is a complication that can occur after a variety of congenital heart defect repairs, and may contribute to LCOS [21]. Valvar insufficiency can often be medically managed with afterload reduction, diuresis, and inotropic support, while valvar stenosis may be treated with primarily with diuretics to reduce atrial filling pressures. Residual lesions may be evaluated by echocardiogram, computed tomography scan, or cardiac catheterization, and should prompt discussion regarding the risks versus benefits of re-intervention [9, 22, 23].

CARDIAC LOADING CONDITIONS AND CARDIOPULMONARY INTERACTIONS CONTRIBUTE TO LCOS

Preload

Alterations in ventricular loading conditions must be assessed and optimized in the post-operative period. Preload effects on ventricular stroke volume are demonstrated by the Frank-Starling mechanism, where increased venous return increases the ventricular filling (end-diastolic volume), representing the stretched state of the cardiac myocytes before contraction [24]. To a point, myocyte stretching increases sarcomere length, which causes an increase in force generation and enables the heart to eject the augmented venous return, thereby increasing stroke volume (Fig. **2**). Interestingly, this physiologic mechanism to augment cardiac output is not as effective in neonatal patients. Inadequate ventricular preload is common post-operatively as a result of hypovolemia secondary to blood loss and perioperative fluid shifts out of the intravascular space secondary to capillary leak. Changes in vascular tone may compound fluid shifts as patients tend to vasodilate with rewarming and afterload reduction [25, 26]. The use of intraoperative ultrafiltration also contributes to relative hypovolemia. Patients with poor ventricular compliance or select operations (*e.g.*, Fontan completion) may require additional preload for optimal cardiac output [25, 27]. Children with pre-operative hypertrophied ventricles (*e.g.,* TOF, critical aortic stenosis) may require higher than normal filling pressures post-operatively given the changes in geometry and worsening diastolic compliance [28]. Another condition affecting ventricular filling is cardiac tamponade, which must always be considered as an etiology of post-operative LCOS. As blood or fluids accumu-

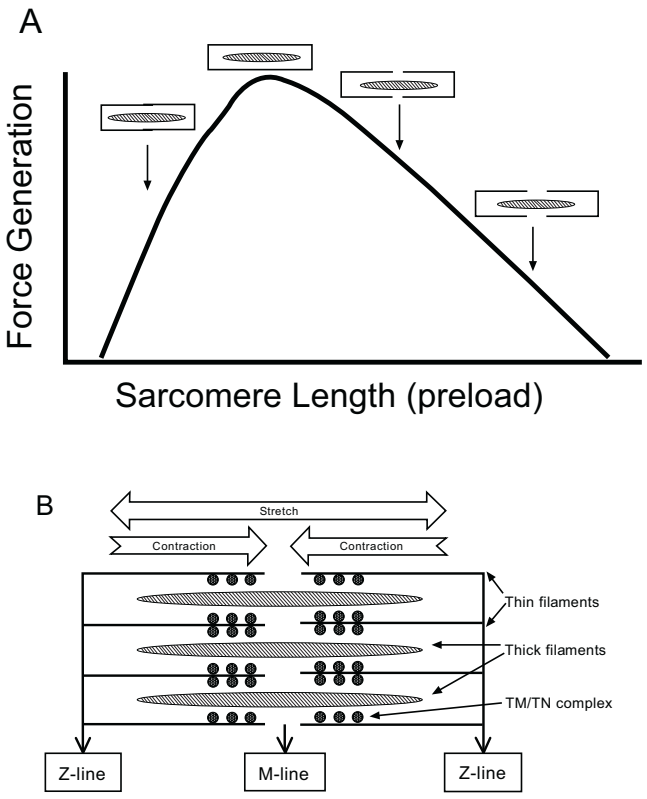

Fig. (2). Frank-Starling relationship. (**A**) As the sarcomere stretches, potential force generation increases, peaks, and then diminishes with overstretch. (**B**) Stylized sarcomeric units demonstrate progressive stretch from left-to-right with variable overlap or separation between Z-lines. Lateral movement of the sarcomere during contraction brings the Z-lines closer together in systole, while excessive stretch in diastole decreases maximal force generation. The tropomyosin (TM) and troponin (TB) protein complex support calcium-binding and filament interactions.

late and pericardial pressure rises, both venous return and ventricular filling are compromised [29]. It is important to recognize that the fluid accumulation does not need to be large or circumferential to cause tamponade; smaller fluid collections can cause substantial limitations to venous return if compressing the atria or inflow tracts. Pleural effusions, pneumothorax or elevated mean airway pressures associated with positive pressure ventilation may also compromise venous return, and thus dictate altered preload targets. Finally, both sinus tachycardia from common etiologies (*e.g.*, pain, anxiety, fever, catecholamines, or poor myocardial function), and tachyarrhythmias (*e.g.,* junctional tachycardias) can compromise ventricular filling time and thus further jeopardize ventricular preload.

Pulmonary Hypertension / Right Ventricular Afterload

Elevations in pulmonary arterial pressure (PAP) occasionally complicate the post-operative management of children following CPB [30]. A variety of pre-existing pathologies (obstructed pulmonary veins, mitral stenosis) and post-operative stimuli contribute to the acute and chronic elevation of PAP. Elevations in PVR can complicate the post-operative management of fragile patients, especially those with RV failure, severe RV hypertrophy, and those with shunted single ventricle physiology struggling to balance systemic and pulmonary blood flow. Pre-existing and residual unrestricted systemic-to-pulmonary shunts contribute substantial risk for the development of PAH secondary to pulmonary overcirculation. CPB itself triggers a series of events that promote reactivity of the pulmonary vascular bed, including systemic inflammation, endothelial dysfunction, diminished nitric oxide release, release of vasoconstrictors, and microemboli [31]. Intraoperative lung deflation and manipulation may alter the pulmonary vascular resistance and promote atelectasis. When considering the impact of PHTN on the post-operative patient, clinicians should consider not only the pulmonary artery pressure, but also the functional status of the RV. Right ventricular coronary blood flow is normally luxurious, yet in cases of severely elevated PAP, or if the RV is non-compliant and the RVEDP elevated, declining coronary blood flow can contribute to acute RV ischemia. Furthermore, the severely hypertensive RV will deform its systolic and diastolic geometry, impairing LV filling and ejection [32]. Signs of a failing RV can be subtle, and include progressive tachycardia, hepatic enlargement, elevations in CVP, progressive hypoxemia if a right-to-left shunt is present, elevation in $ETCO_2$, acute decreases in volumetric CO_2, and finally hypotension from lack of LV preload [33]. Intracardiac monitoring lines placed in the RA, LA, and/or PA are extremely useful adjuvants in the post-operative management of the high-risk patient with acute post-operative reactive PAP in the face of chronic PAH. Emerging tools such as continuous Doppler ultrasound and volumetric CO_2 monitoring may eventually increase our ability to monitor cardiopulmonary interactions in real-time [33, 34].

Pulmonary Venous Hypertension

Pulmonary venous hypertension presents a special challenge for the post-operative patient, and management must be carefully directed based on the underlying cause [44]. Venous hypertension may result from obstructed pulmonary veins (acute or chronic) or conditions associated with left atrial hypertension, including mitral stenosis, severe mitral regurgitation, and LV diastolic failure. In neonates with a restrictive atrial septum, such as occasionally seen in HLHS, or in patients with *in-utero* obstructed pulmonary veins, the pulmonary venous hypertension can be severe, generating pulmonary edema, impairing lung compliance, gas exchange, and promoting a very reactive pulmonary vascular bed with secondary PAH impacting RV function and LV filling. In addition to urgent relief of the obstruction, close attention to the reactive pulmonary hypertension is required in the post-operative setting.

In addition to early recognition, the management of PAH involves supporting RV function, minimizing pulmonary vascular resistance and reactivity, and providing right-to-left shunts capable of preserving cardiac output during acute elevations in PAP. Cautious use of catecholamines (*e.g.*, epinephrine) for RV support is generally indicated if the RV is struggling to accommodate the increased afterload. Inodilators such as milrinone impact both the pulmonary and systemic vascular beds, thus while a non-specific approach to minimizing RV afterload is effective; it tends to be limited by systemic vasodilatation. Generally patients with PAH after CPB should be well sedated to attenuate stimuli-driven

alterations in PVR, and patients should be fully compliant with the ventilator. It is especially important to blunt the elevated PVR that may occur with airway or carinal stimulation from suctioning through pre-medication with narcotics and avoidance of hypercarbia and alveolar hypoxia. Occasionally, to achieve optimal ventilation, pharmacologic neuromuscular blockade is useful, although the routine use of paralytics in all cases of PAH may be unnecessary.

Pulmonary vascular resistance is typically lowest when the patients are ventilating at normal FRC (the state of maximal dynamic lung compliance) with a minimum of atelectasis [35]. Thus positive pressure ventilation strategies should be targeted to achieve optimal PEEP, monitoring lung compliance curves for peak compliance and chest radiographs to confirm optimal lung expansion [36]. In select circumstances, where RV failure is present or imminent, or for patients with passive pulmonary blood flow (Glenn and Fontan circulations), the earliest safe transition to negative pressure ventilation should be considered [37]. Walsh and colleagues demonstrated that alternative ventilation using airway pressure release ventilation (APRV) was beneficial for patients following TOF repair or for those with cavopulmonary anastomoses [38]. Hypoventilation, with elevations in $PaCO_2$, alveolar hypoxia, and acidosis, should generally be avoided because of the negative impact upon both PVR and the myocardium. However, deliberate hypoventilation to achieve mild hypercarbia (an elevated $PaCO_2$ with a normal pH) in hypoxemic patients with Glenn physiology can improve systemic oxygenation by improving cerebral blood flow, thus driving downstream pulmonary blood flow. Inhaled vasodilators, such as oxygen (F_iO_2 >0.21), nitric oxide, and prostanoids (*e.g.,* PGI_2, iloprost), are very effective at reducing PVR and should be considered in patients with post-operative pulmonary vasoreactivity and evidence for RV dysfunction [39]. The intensivist should be aware that separation from nitric oxide can produce a life-threatening rebound PHTN regardless of pre-existing anatomy [40]. Rebound PHTN may be minimized by a single dose of sildenafil administered one hour before the discontinuation of iNO, therefore preemptive vasodilator therapy should be considered in patient with PAH who will require iNO support [41]. The preservation or creation of a right-to-left atrial level shunt has utility in select patients, such as following common arterial trunk or TOF repair, where the hypertrophic RV has experienced a myotomy and is under increased volume and pressure load, or following the Fontan operation in the form of a baffle fenestration [42]. Many centers practice delayed sternal closure for high-risk patients, minimizing the pressure on the edematous heart, and aiding in access for chest exploration or the institution of mechanical circulatory support (*e.g.*, ECMO). The presence of an open chest will attenuate cardiopulmonary interactions by minimizing the transmural pressure transmitted from the ventilator and will improve compliance of the respiratory system [43].

Systemic Hypertension / Left Ventricular Afterload

Ventricular afterload is frequently increased following congenital heart surgery requiring CPB, and systemic hypertension in the face of myocardial depression often decreases cardiac output [45]. Both the systemic and pulmonary endothelial beds are altered during CPB, leading to changes in vascular reactivity and elevated pulmonary and systemic vascular resistance. CPB has been shown to induce endotoxin release, activate leukocytes and complement, upregulate expression of vascular adhesion molecules, and promote the release of many inflammatory mediators such as cytokines, oxygen-free radicals, arachidonic acid metabolites, platelet-activating factor, and endothelin-1 [46-49]. The adrenergic system is broadly stimulated following CPB, releasing epinephrine and norepinephrine, which contribute directly to systemic vasoconstriction and tachycardia [50, 51]. Surgical stress, non-pulsatile pump flow, circulatory arrest and re-warming all drive catecholamine levels. Hypothermia may exacerbate these surges by down-regulating catecholamine receptors and slowing catecholamine metabolism [52]. Adequate anesthesia serves to blunt this response, but catecholamine elevation persists well into the post-operative period. Acidosis and hypoxemia also contribute to catecholamine release, and detrimentally affecting vascular tone and myocardial performance.

CPB elicits ADH/vasopressin release, which also contributes to increased SVR and fluid retention [53, 54]. Non-pulsatile pump flow and diminished renal perfusion activates the renal renin-angiotensin-aldosterone system, contributing further to systemic vasoconstriction and derangement of fluid and sodium homeostasis [55, 56]. In addition to promoting vasoconstriction, many of these substances contribute directly to endothelial injury, decreased nitric oxide production, and may promote coronary vasospasm or thrombosis, worsening ischemic injury [57-59]. The interactions between the inflammatory cascade and the sequelae of ischemia-reperfusion injury are inexorably linked, and synergistically increase systemic and pulmonary vascular resistances.

Finally, postoperative vasoconstriction may be a compensatory or maladaptive mechanism for decreased preload or poor cardiac output, and care should be taken to recognize and address the underlying problems. There is evidence suggesting that an increase in arterial elastance is not compensated for with an equal increase in ventricular contractility after CPB. This impaired ventriculo-vascular coupling (dynamic interaction between the systemic ventricle and arterial afterload) is one component that likely contributes to low cardiac output after cardiac surgery, a phenomenon that is well treated with inodilators such as milrinone [1] or nitroprusside. Children with chronically low cardiac output preoperatively appear to have greater risk for afterload derangements after surgery [60], and such patients may experience not only vasoconstriction but also exaggerated vasodilation post-operatively.

NEUROHORMONAL CONTRIBUTION TO LCOS

Systemic Inflammation and the Hypermetabolic State

Exposure to the foreign surfaces and membranes associated with CPB, as well as induced hypothermia, myocardial ischemia, and tissue hypoperfusion, cause profound alterations in systemic inflammation [61, 62]. Unregulated activation of the endothelium and neutrophils are considered critical events driving inflammation [63, 64]. Additional changes include acute elevations in pro-inflammatory cytokines, notably IL-1β, IL-6, IL-8, and TNFα, as well as diffuse activation of complement [65]. Elevated levels of pro-

inflammatory cytokines have been associated with increased post-operative complications, including LCOS, and prolonged need for mechanical and inotropic support (reviewed in [64]), and also may herald a negative neurologic outcomes [66]. These inflammatory changes and the hyperthermic response increase metabolic demand, and diffuse endothelial dysfunction promotes organ dysfunction [63]. It is intriguing to hypothesize that diffuse activation of endothelial innate immunity may underlie the systemic inflammation following CPB, converging on the activation of NF-κB [64, 67]. Deregulation of systemic inflammation also involves the compensatory anti-inflammatory response, manifest by elevations of IL-10 and immuno-paralyzed monocytes with decreased HLA-DR expression [68, 69]. The study of systemic inflammation following CPB remains ripe for ongoing investigation and the development of targeted therapeutic interventions. Steroids are in widespread use to non-specifically combat inflammation, although the literature supporting their use and effectiveness remains inadequate. Collectively, systemic inflammation, complement activation, endothelial dysfunction, as well as the counter-regulatory stress response (*e.g.*, high levels of circulating catecholamines) contribute substantially to myocardial dysfunction and altered cellular metabolism, thus promoting LCOS.

Cardiopulmonary bypass and cardiac surgery may promote a hypermetabolic-catabolic state in the post-operative period, driving energy utilization and oxygen tissue demands [70-72]. Derangements of mitochondrial function may underlie many cellular changes following CPB, as well as alterations in lipid/carbohydrate metabolism, representing an area of active investigation [73, 74]. LCOS is compounded by ischemic-reperfusion injury, elevated endogenous catecholamines and counter-regulatory hormones, hyperthermia, tachycardia, and increased oxygen demand outstripping cardiac output and oxygen delivery [75]. Modern anesthetic techniques and ongoing post-operative sedation/narcosis may minimize the impact of these surgical stressors. It remains controversial how cardiac surgery and CPB directly impact critical metabolic variables, such as the resting energy expenditure, respiratory quotient, VCO_2, and VO_2 of children in the perioperative period. Several studies have demonstrated near normal resting energy expenditure and metabolic variables when adjusted for patient temperature [76-78]. However, up to 27% of patients undergoing a primary Fontan operation were noted to be hypermetabolic [78], and others have found that neonates undergoing the stage I Norwood palliation had elevations in their VCO_2 and VO_2 for up to 8 hours post-operatively, and are at risk for decreased cerebral oxygen saturations post-bypass [79, 80]. There are clear associations linking fevers, systemic inflammation, and increases in VO_2 during the early post-CPB period [81]. It is reasonable to hypothesize that patients experiencing a hypermetabolic state are also at an increased risk for the development of LCOS. Clinically, post-operative patients often have high minute ventilation demands, likely secondary to pulmonary non-compliance, pulmonary edema, increase airway resistance, and elevated VCO_2 from increase tissue metabolism and in response to systemic inflammation [82]. Patients with accumulating oxygen debt and elevated lactate are manifesting LCOS following surgery, and close attention to the timely restoration of oxygen delivery is critical [83]. Patients undergoing palliative operations often remain cyanotic, thus dramatically decreasing DO_2 by lowering the oxygen content of the arterial blood, diminishing the substrate available for metabolism and contributing to the need for tachycardia to augment cardiac output. Simultaneously systemic inflammation and endothelial dysfunction promoting hyperthermia, capillary leak syndrome, pulmonary edema, pulmonary non-compliance, worsening V-Q matching, and a decline in myocardial performance create the perfect storm for LCOS.

Thyroid Axis

Infants and children undergoing CPB demonstrate substantial decreases in thyroid hormone levels that may impact postoperative hemodynamics [84]. Pro-inflammatory cytokines released during and after CPB, as well as commonly used inotropes such as dopamine, are known to inhibit the thyroid hormone axis. While it is biologically plausible that low thyroid hormone levels could contribute to LCOS after congenital heart surgery, the literature remains inconclusive. There have been several clinical trials investigating the utility of thyroid hormone supplementation in children undergoing CPB. Many of these studies are underpowered and have substantial age and diagnosis heterogeneity, making the results difficult to apply broadly. Bettendorf *et al*. performed a randomized, double-blind, placebo-controlled trial where 40 children received daily tri-iodothyronine (T3) versus placebo up to 12 days after surgery. A therapeutic intervention scoring system (TISS) was used to assess their postoperative course and need for interventions. Children receiving T3 were given a lower mean TISS than patients treated with placebo, had a greater increase in mean cardiac index, and an improvement in systolic function [85]. This improvement in systolic function was even more pronounced in patients with longer bypass times. Chowdhury *et al.* randomized 28 patients to receive T3 versus placebo if their hormone levels fell below a pre-determined cut-off after surgery. There were no differences in TISS or inotrope scores between groups. Sub-group analysis of nine neonates revealed that patients who received a T3 infusion had lower mean TISS scores and lower mean inotrope scores when compared to the placebo group [86]. Mackie *et al*. similarly showed that T3 infusion improved a composite clinical score and time to negative fluid balance in neonates after aortic arch reconstruction [87].

The largest and most recent trial to examine the effects of T3 supplementation in children (<2 years of age) undergoing CPB was the Triiodothyronine supplementation in Infants and Children undergoing Cardiopulmonary Bypass (TRICC) study, which was a multicenter, prospective, randomized, double blind, placebo-controlled trial [88]. Duration of mechanical ventilation after completion of CPB was the primary outcome measure, but this trial was also designed to determine safety of T3 supplementation. The study did not reveal a difference in the primary outcomes between groups treated with placebo or given thyroid supplementation. However, sub-group analysis did reveal that for younger patients, those less than 5 months of age, thyroid supplementation significantly decreased the time to extubation, lowered inotrope use, and improved function on echocardiography. While the study design utilized in the TRICC trial was supe-

rior to those smaller trials that preceded it, the clinical significance of improved cardiac output surrogates (improved function on echocardiograms or inotrope scores) is unclear. While there is a promising body of literature suggesting a benefit from thyroid supplementation in younger patients following CPB, further investigation will be necessary to determine if diminished thyroid hormone levels contribute to LCOS after CPB and whether T3 supplementation ameliorates or attenuates the low cardiac output state.

Adrenal Axis

Since the introduction of steroids in the perioperative period to combat systemic inflammation, the role of adrenal axis suppression has been an area of active investigation (reviewed in [89]). Despite several studies, it remains unclear if post-operative adrenal dysfunction contributes negatively to outcome or to the development of LCOS. Many studies are limited in scope, either being underpowered or retrospective. Investigators have measured bound cortisol, which correlates poorly with the physiologically active free cortisol, especially in critically ill or post-surgical patients in whom hypoproteinemia or low binding-globulin states are common. Cosyntropin (ACTH) stimulation tests are rarely performed and it is difficult to interpret the results in pediatric populations, as varied definitions of adrenal dysfunction exist. To provide insight into the adrenal axis after CPB, Gajarski *et al*. studied 58 neonates who underwent preoperative ACTH stimulation tests and had intact adrenal responses. There was no relationship between operative conditions, post-operative variables and cortisol levels [90], and the majority demonstrated an intact adrenal response postoperatively. In the subset of patients with abnormal adrenal responses, those with high adrenocorticotropic hormone/cortisol ratios, and those with elevated inotrope scores failed to demonstrate a clear correlation between adrenal responses and clinical outcomes.

Wald *et al.* examined 51 children following CPB of whom 96% had a normal cortisol increase (> 9mg/dL) postoperatively after ACTH stimulation tests [91]. Nine patients had low baseline post-operative total cortisol levels (<3μg/dL), but all had an adequate response to stimulation. Two patients who had inadequate cortisol increases after stimulation had excellent clinical outcomes and did not require supplemental corticosteroids. Corticosteroid-binding globulin levels declined significantly in all patients, further evidence that measurements of bound cortisol post-CPB are inadequate to assess adrenal function. The calculated free cortisol increased 15-fold after stimulation in the overall cohort, and children with the highest increase in free cortisol after stimulation had worse clinical outcomes, manifest by longer ventilator times, longer length of stay, and higher inotrope scores [91]. This observation suggests that a heightened stress response post CPB may be maladaptive, or alternatively, that the adaptive stressed state may be insufficient to compensate for the degree of critical illness. These findings are consistent with those recently reported by Mackie *et al*. who described a modest association between serum cortisol and decreased cardiac performance after cardiac surgery with CPB. Greater serum cortisol levels correlated with higher right atrial filling pressures, as well as with a lower cardiac index in the post-operative period [92]. Thus the relationship between baseline and stimulated adrenal function post CPB does not suggest that uniform adrenal axis suppression exists.

Only four studies have examined the effects of postoperative hydrocortisone use in children undergoing congenital heart surgery. Two retrospective studies noted improved hemodynamics and a decrease in inotrope requirements following steroid administration. Longer-term clinical outcomes attributed to the therapy, such as hospital length of stay, days of mechanical ventilation and mortality could not be analyzed due to absence of appropriate controls [93-95]. In a prospective trial, 20 neonates were randomized to receive hydrocortisone or placebo. No significant difference in hemodynamics, inotrope dependence, nor the duration of mechanical ventilation was identified between groups [96]. The neonates in the hydrocortisone group had higher measured left ventricle-shortening fractions and lower lactic acid levels, but these differences were not clinically meaningful.

In summary, corticosteroids may have beneficial hemodynamic effects in neonates and children for perioperative inflammation, and may have hemodynamic impact in the management of LCOS, independently of exposure to CPB. There is little evidence to suggest, however, that neonates or children require routine corticosteroid supplementation due to adrenal axis dysfunction or inadequate adrenal reserve, and some studies support that the risk of post-operative infections increase with cumulative steroid administration [97, 98].

CONCLUDING REMARKS

Low cardiac output syndrome is a multifactorial process frequently complicating the post-operative management of patients following complex cardiac surgery involving cardiopulmonary bypass. Pre-operative conditions, intraoperative management, residual lesions, and arrhythmias contribute meaningfully to the development of LCOS, as do derangements of preload, pulmonary and systemic afterload, the neurohormonal axis, systemic inflammation, and augmented metabolic demand. Diligence from the entire treatment team, including nurses, surgeons, anesthesiologists, and intensivists is required to recognize low cardiac output, rapidly correct the supply-demand imbalance, and address the underlying cause to reverse the syndrome prior to cardiovascular collapse.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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