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Low Cardiac Output Syndrome After Cardiac Surgery: A Life-Threatening Condition from the Perspective of Pediatric Intensivists

Kardiyak Cerrahi Sonrası Düşük Kardiyak Debi Sendromu: Çocuk Yoğun Bakım Uzmanlarının Perspektifinden Hayatı Tehdit Eden Bir Durum

REVIEW
DERLEME

ABSTRACT

Low cardiac output syndrome is a clinical picture insourcing from insufficient oxygen supply to tissues so as to meet the metabolic demand, myocardial dysfunction, and cardiovascular insufficiency. Low cardiac output syndrome is seen in nearly 25% of pediatric patients who underwent corrective or palliative surgery due to congenital heart defects. It is a clinical condition occurring typically 6-18 hours after surgery in pediatric patients undergoing cardiac surgery and causes organ failure, prolonged hospital and intensive care hospitalization time, increased resource utilization, and mortality. The identification and correct management of this serious complication in the early period is very important. However, there is no clear consensus or consensus report on the follow-up of this patient group and the definition of low cardiac output syndrome. Clinicians generally produced low cardiac output syndrome definitions according to their own approach. In this review, we aim to draw attention to low cardiac output syndrome and hope to summarize the pathophysiology, etiology, clinical definition, and treatment options of low cardiac output syndrome as a life-threatening condition in pediatric intensive care unit.

Keywords: Cardiac surgery, congenital heart diseases, left ventricular dysfunction, low cardiac output syndrome, pediatric

ÖZET

Düşük kardiyak debi sendromu, metabolik ihtiyacı karşılamak için dokulara yetersiz oksijen sunumu, miyokart disfonksiyonu ve kardiyovasküler yetmezlikten kaynaklanan bir klinik tablodur. Doğuştan kalp hastalıkları nedeniyle düzeltici veya palyatif cerrahi uygulanan pediatrik hastaların yaklaşık %25'inde düşük kardiyak debi sendromu görülür. Kalp cerrahisi geçiren pediatrik hastalarda ameliyattan tipik olarak 6-18 saat sonra ortaya çıkan ve organ yetmezliğine, hastanede ve yoğun bakımda yatış süresinin uzamasına, kaynak kullanımının artmasına ve mortaliteye neden olan bir klinik durumdur. Bu ciddi komplikasyonun erken dönemde saptanması ve doğru yönetimi çok önemlidir. Ancak bu hasta grubunun takibi ve düşük kardiyak debi sendromu tanımı konusunda net bir fikir birliği veya konsensus raporu bulunmamaktadır. Klinisyenler genellikle kendi yaklaşımlarına göre düşük kardiyak debi sendromu tanımlarını üretmişlerdir. Bu derlemede, düşük kardiyak debi sendromuna dikkat çekmeyi ve çocuk yoğun bakım ünitesinde hayatı tehdit eden düşük kardiyak debi sendromunun patofizyolojisi, etiyolojisi, klinik tanımı ve tedavi seçeneklerini özetlemeyi amaçladık.

Anahtar Kelimeler: Kardiyak cerrahi, konjenital kalp hastalıkları, sol ventrikül disfonksiyonu, düşük kardiyak debi sendromu, çocuk

Low cardiac output syndrome (LCOS) is observed in about one-fourth of pediatric patients undergoing corrective or palliative cardiac operation for a congenital heart defect or inadequate oxygen supply to tissues, leading to organ dysfunction.[1,2] The condition was first reported by Parr et al[1] after they detected a cardiac index below 2.0 L/min/m^2 in one-fourth of pediatric patients after cardiac surgery. Twenty years later, Wernovsky et al[3] showed a parallel incidence after arterial switch surgery, again with cardiac index below 2.0 L/min/m^2 postoperatively.

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Low cardiac output syndrome typically occurs 6-18 hours after surgery and causes organ failure, prolonged hospital and intensive care stay, higher use of resources, and mortality. Low cardiac output syndrome is called as "midnight nightmare" by intensive care specialists. As a severe complication, it should be identified early and correctly managed, otherwise resulting in serious morbidity and mortality.[2]

Given the major advances in cardiac surgery and cardiopulmonary bypass (CPB), the prevention and management of LCOS have integrated extensive strategies, both pharmacologic and non-pharmacologic, to restore the oxygen balance. Pharmacologic strategies have often included catecholaminergic inotropes, inodilators, and systemic vasodilators. On the other hand, mechanical circulatory support has been an option for medically refractory LCOS.

There has yet to be a clear guideline for the definition of LCOS and its follow-up, which leads to a variety of clinical approaches between centers and even between clinicians in the same center. The existing definitions of LCOS have often been suggested in accordance with clinicians' own approaches.[4]

In this review, we aim to draw attention to LCOS as a life-threatening condition in pediatric intensive care unit (ICU). We hope to summarize the pathophysiology, etiology, clinical definition, and treatment options of LCOS.

Low Cardiac Output Syndrome Pathophysiology

Low cardiac output syndrome is caused by multiple pathophysiologic processes that make cardiac surgery requiring CPB more complicated. The imbalances in systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac output, oxygen supply, and alterations in metabolism among patients are affected by multiple factors (Figure 1). These include the individual characteristics of the patient, their preoperative status, intraoperative management, residual anatomic lesions, rhythm abnormalities, and the inflammatory nature of CPB. During CPB, blood is exposed to foreign antigens, which may, along with hypothermia, myocardial ischemia, and reperfusion injury, lead to profound systemic inflammation. Elevations in proinflammatory cytokines and activation of complements are all related to LCOS, increased ventilator times, and negative neurological outcomes. Besides, the changes in PVR after CPB and systemic hypertension may reduce cardiac output.[5] Moreover, CPB stimulates vasopressin release, increasing SVR, causing potential harm to dysfunctional systemic ventricles, and resulting in LCOS.

Myocardial dysfunction due to ischemia/reperfusion injury, the degree of myocardial protection, systemic inflammatory responses, together with left ventricular systolic dysfunction, left ventricular diastolic dysfunction and right ventricular dysfunction and their effects, constitute the main mechanisms of LCOS pathophysiology.[6] Factors for improving LCOS are schematized in Figure 2.

Low Cardiac Output Syndrome Etiology

The etiological factors of LCOS may include certain preoperative elements, myocardial dysfunction associated with CPB, ischemia–reperfusion injury, arrhythmia, and residual heart lesions. Other factors like reduced preload, SVR, PVR, and increased metabolic demand also contribute to the development of LCOS, further complicating management.[7] The presence of concomitant organ failure or additional diseases, surgery performed under emergency conditions, long CPB duration, prolonged cross-clamp time, and incomplete revascularization play a significant role in the etiology of LCOS.

Low Cardiac Output Syndrome Incidence and Associated Mortality Rate

Low cardiac output syndrome has an incidence of 25%-30% in infants.[8] One study focused on the correlation between complications after cardiac surgery and maximum vasoactive inotropic score (VIS) and LCOS in newborns, reporting an LCOS incidence of 42%. This rate was associated with the immature myocardial nature of neonatal patients and with the complex cardiac operations performed in most of these newborns who had single ventricular physiology.[9] Aslan et al[10] reported LCOS incidence to be 24.07%, similar to the available data in the literature. One Indonesian study on 257 pediatric patients reported a mortality rate of 13%, highlighting correlations between major complications and prolonged total CPB time, increased lactate levels, cyanotic congenital heart disease, and high inotropic support.[11]

Hemodynamic Monitoring Methods in Low Cardiac Output Syndrome

Hemodynamic monitoring is very important in the diagnosis and treatment of low cardiac output. Invasive and non-invasive methods are used for the measurement of cardiac output.[8] Some conventional monitoring parameters that are often checked to identify the presence of LCOS are heart rate, blood pressure, central venous pressure, central venous oxygen saturation ($ScvO_2$), transthoracic echocardiography (TTE), near-infrared spectroscopy (NIRS), urine output, and serum lactate level.[12] Among the invasive hemodynamic monitoring methods, Fick method, dilution methods (pulmonary and transpulmonary thermodilution), radioisotope analysis method, contrast and radionuclide angiography method can be counted.[13] However, in recent years, these invasive methods, which are not easily applicable especially in pediatric patients, have been avoided in clinical practice.

Transthoracic echocardiography as a non-invasive and repeatable at bedside method is one of the key methods for preoperative and

ABBREVIATIONS

AKI	Acute kidney injury
CPB	Cardiopulmonary bypass
cTn-I	Cardiac troponin I
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
iNO	Inhaled nitric oxide
LCOS	Low cardiac output syndrome
MR-proADM	Mid-regional proadrenomedullin
NIRS	Near-infrared spectroscopy
PCICS	Pediatric Cardiac Intensive Care Society
PH	Pulmonary hypertension
PICU	Pediatric intensive care unit
PVR	Pulmonary vascular resistance
RRTs	Renal replacement treatments
$ScvO_2$	Central venous oxygen saturation
SVR	Systemic vascular resistance
T3	Triiodothyronine
TTE	Transthoracic echocardiography
VIS	Vasoactive inotropic score

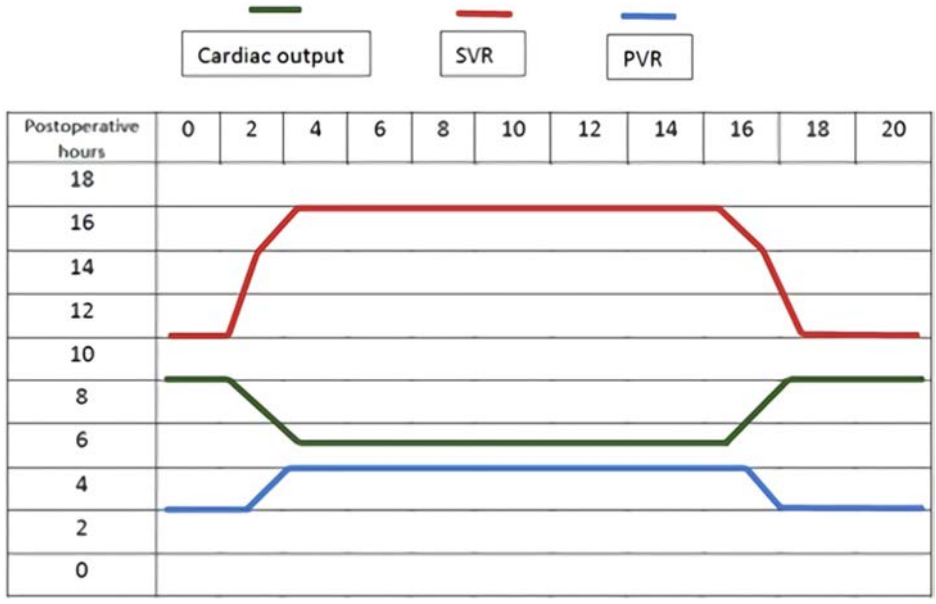

Figure 1. The changes in SVR, PVR, and cardiac output which cause LCOS during postoperative period.
SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LCOS, low cardiac output syndrome.

postoperative evaluation of cardiac functions. Echocardiography can be used to reveal the type of LCOS and assess ejection fraction, heart volumes, systolic and diastolic function, cardiac output measurements, residual defect, valve pathology, pulmonary circulation, pericardial effusion, and fluid responsiveness.[14]

An adequate oxygen supply to tissues is key point for good outcomes after congenital heart surgery.[15] Near-infrared spectroscopy, which is one of the non-invasive tool for monitoring regional oxygenation that is becoming increasingly popular, has been shown to be effective both in the determination of LCOS and in the evaluation of the response to fluid therapy in terms of demonstrating tissue perfusion.[16] Some experts recommend the introduction of NIRS as part of standard care after CPB. In a pediatric prospective observational study, the authors evaluated 15 neonates undergoing CPB to assess the usefulness of NIRS for estimating $ScvO_2$. They measured both cerebral and renal NIRS and performed serial cardiac index and cardiac output measurements by transpulmonary thermodilution method over the first 24 hours after surgery. They also obtained blood samples from the central venous catheter for measuring $ScvO_2$. In all patients studied, $ScvO_2$ was correlated with cerebral and renal NIRS levels. In addition, they reported a correlation between cardiac output and combined cerebral and renal NIRS levels.[15]

Low cardiac output syndrome presents with tachycardia, increased SVR, and oliguria due to insufficient tissue perfusion, increased lactate levels, and metabolic acidosis. According to clinical table of LCOS, Ulate et al[4] developed an LCOS scoring system, aiming to present an empirical clinical evaluation tool to determine the presence and severity of LCOS and correlations with clinical outcomes in infants undergoing surgical repair or alleviation of congenital heart defects. The LCOS score is calculated as one point each for tachycardia, oliguria, toe temperature below 30°C, volume administration requirement above 30 mL/kg/day, decreased NIRS, hyperlactatemia, and vasoactive/inotrope requirement above milrinone 0.5 μg/kg/min. They found that LCOS scores were significantly correlated with severity and duration of LCOS, morbidity rate, and intensive care and hospital stay. Aslan et al[10] evaluated 54 pediatric patients after cardiac surgery using a similar scoring tool, replacing only toe temperature, because of their pediatric ICU (PICU) resources, with prolonged capillary refilling time. Both studies have highlighted the significance of early detection and correct management, suggesting scoring systems with easily measurable bedside parameters. Gaies et al[17] developed the VIS score for predicting morbidity and mortality in infants after CPB, reporting a significant effect as an independent predictor of outcome.

Cardiac Biomarkers

Cardiac biomarkers could provide additional information to help with therapeutic decisions and minimize hemodynamic instability following CPB. In adult patients with heart failure, monitoring cardiac biochemical markers following cardiothoracic surgery is helpful.[18] However, there are few pediatric research on the efficacy and use of biomarkers after corrective surgery under CPB. Pérez-Navero et al[19] investigated 117 children who used CPB following corrective surgery for congenital heart disease in a pediatric prospective observational study. At 2, 12, 24, and 48 hours after CPB, they examined atrial natriuretic peptide, B-type natriuretic peptide, copeptin, mid-regional pro-adrenomedullin (MR-proADM), and cardiac troponin I (cTn-I) as early markers for predicting LCOS in children. The findings revealed that cTn-I at 2 hours after CPB is an obvious independent early predictor of LCOS. This prediction ability is further enhanced when cTn-I levels are paired with MR-proADM levels 24 hours after CPB. According to the findings of this large sample size investigation, a cutoff value of > 14 ng/mL for cTn-I at 2 hours post-CPB enhanced the prediction of LCOS. These 2 cardiac biomarkers, cTn-I and MR-proADM, were discovered by the authors to aid in therapeutic decision-making in clinical

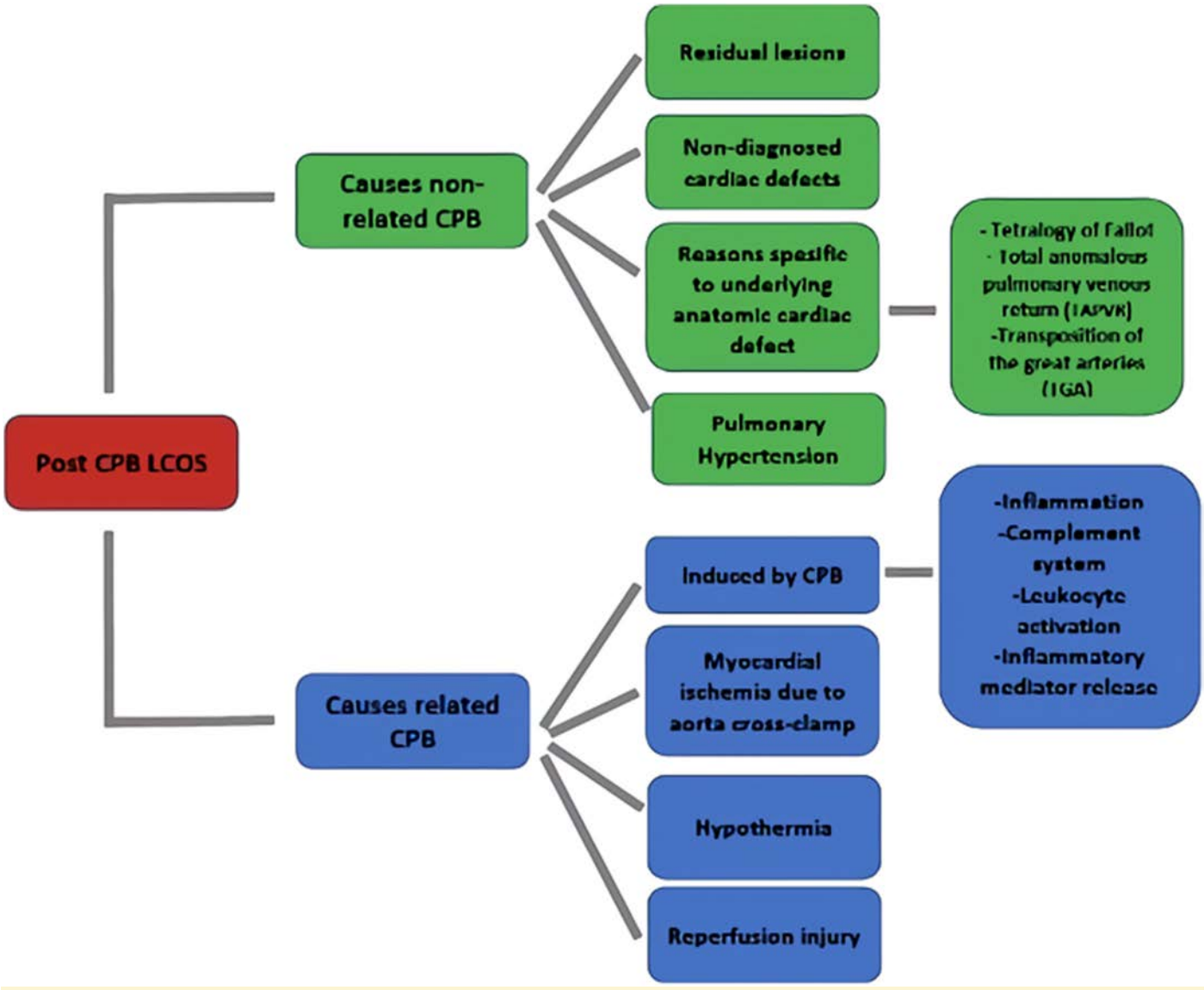

Figure 2. Etiological factors to improving LCOS.
CPB, Cardiopulmonary bypass; LCOS, low cardiac output syndrome.

practice and to allow doctors to change the type of support utilized in PICUs.

Lactate concentrations in the blood have long been utilized as a marker of altered tissue perfusion in critically ill patients as a reflection of cellular perfusion. The degree of increase in lactate concentrations has been demonstrated to be directly associated with the severity of the shock state and mortality rates.[20] Because LCOS is a type of cardiogenic shock, lactate levels can help the clinician for LCOS diagnosis. Lactate levels can also be used to monitor LCOS. The development of LCOS is monitored with lactate levels, according to 99% of participants in a survey study based on pediatric intensivists' clinical approaches to postoperative cardiac surgery patients.[21] Another study assessed at lactate levels to see if they may predict LCOS in newborns following cardiac surgery found a link between greater lactate levels and higher mortality and the need for extracorporeal membrane oxygenation (ECMO) support.[22] Because LCOS assessment is very important, Ulate et al[4] and Aslan et al[10] incorporated lactate level as a score criterion in their LCOS scoring techniques.

Despite the lack of a defined definition for LCOS and established criteria for its follow-up, different therapeutic techniques are used by different centers.[23]

Treatment Options for Low Cardiac Output Syndrome

The management of LCOS primarily involves maintaining an acceptable balance of oxygen supply and consumption. The main objectives include optimizing preload, increasing heart rate, improving stroke volume, improving cardiac output, and providing cardiac relaxation. This also includes, besides cardiac strategies, pulmonary (reducing PVR and optimizing mechanical ventilation), vascular (reducing SVR and increasing vascular tonus), and neurohormonal (reducing inflammation, providing enough sedation, and ensuring thyroid and adrenal gland

balance) factors. Therapeutic agents are often used to increase heart rate, improve contractility, and reduce afterload. Finally, normothermia, efficient mechanical ventilation strategies, and proper sedation-analgesia are beneficial for minimizing patient efforts and controlling oxygen consumption (Figure 3).

Inotropic Agents

Cardiac ICUs have for a long time used catecholaminergic inotropes like epinephrine, dopamine, and dobutamine to improve cardiac output and manage LCOS. These agents are widely available, predominantly activating β1, β2, α1, and dopaminergic receptors and increasing contractility and stroke volume. Before applying catecholaminergic inotrope therapy, clinicians need to assess intravascular volume status, serum calcium level, and cardiac rhythm carefully. Although catecholamines have extensive negative effects, including tachycardia, increased ventricular end-diastolic pressures, and increased myocardial oxygen consumption, these agents may lead to elevated SVR and PVR or provoke tachyarrhythmias, erroneously causing or intensifying LCOS. A recent survey of cardiac intensivists revealed prophylactic dopamine usage rate of 38% for preventing LCOS.[24] Despite the lack of randomized controlled studies with epinephrine in pediatric cardiac surgery, 45% and 40% of responders in this survey utilize it for LCOS prophylaxis and treatment, respectively.[24] In this survey, epinephrine and dopamine are reported to be the most common catecholaminergic inotropic agents for preventing or treating LCOS and they are most often started while on or after CPB.[24] Side effects of dopamine are increased myocardial oxygen consumption, arrhythmias, hypothyroidism, and impaired T-lymphocyte proliferation.[25] The recent literature showed an association between dopamine usage and increased mortality rate, arrhythmias, and infection in patients with septic shock.[26] In addition, the last version of surviving sepsis guideline suggests using epinephrine and norepinephrine rather than dopamine, in children with septic shock.[27] Patients with septic and cardiogenic shock who received dopamine had higher mortality, according to meta-analyses.[28] So, recently published literature do not offer routine use of high doses of dopamine. Low-to-intermediate dopamine doses may have beneficial inotropic and chronotropic effects for selected patients.[25]

Inodilator Agents

Milrinone, dobutamine, and levosimendan are commonly used after CPB to prevent LCOS. These medications have vasodilatory effects on the systemic, pulmonary, and coronary vasculature and inotropic and lusitropic effects on the myocardium.

There is extensive research on milrinone in pediatric patients after surgery requiring CPB. It inhibits phosphodiesterase type 3 and increases the concentration of intracellular cAMP, leading to increased myocardial contractility. Milrinone is also known to have a lusitropic effect by accelerating the removal of calcium from the cytosol, providing longer myocardial relaxation. It provides smooth muscle vasodilation by affecting cGMP in the peripheral and coronary smooth muscle cells, improving myocardial performance without resulting in higher myocardial oxygen consumption. When combined, these effects make milrinone very advantageous. Evidence also remarks positive hemodynamic effects of milrinone in the pediatric population following cardiac surgery. A multicentered, double-blinded, and placebo-controlled research, the PRIMACORP study, included 240 post-pediatric patients undergoing cardiac surgery, aiming to assess the use of prophylactic milrinone after CPB. Hoffman et al[8] showed a significant reduction in LCOS incidence and no increase in negative effects using high dose milrinone, which made milrinone a widely used pharmacologic agent for the prevention and treatment of LCOS in children. According to a recent Pediatric Cardiac Intensive Care Society (PCICS) survey, 97% of the surveyed centers use milrinone in routine practice to prevent or treat LCOS

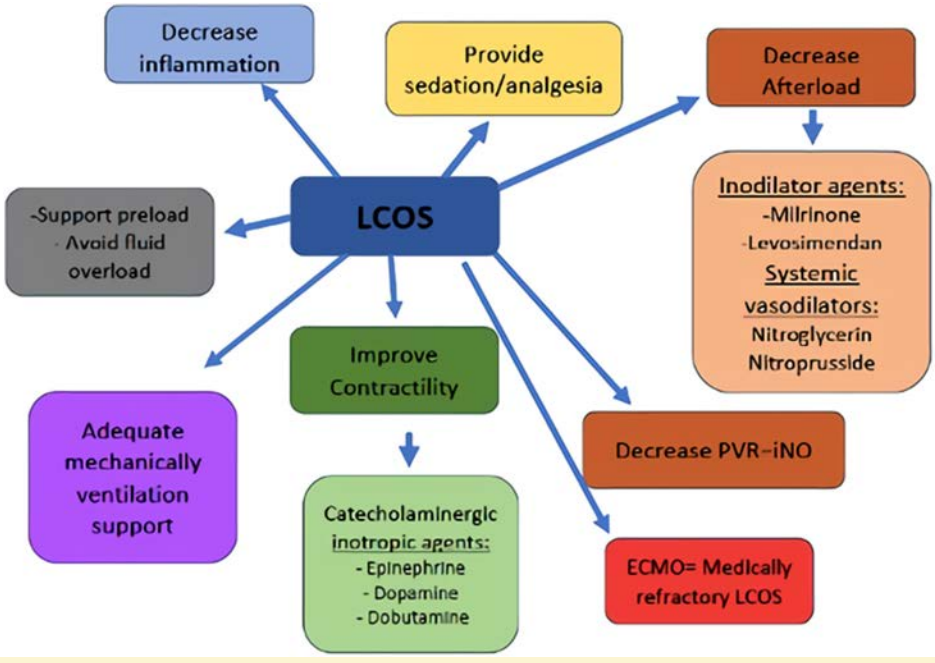

Figure 3. Common treatment strategies in patients with LCOS.
LCOS, low cardiac output syndrome.

after CPB. On the other hand, a 2015 Cochrane review argued that there was little evidence to suggest the efficacy of prophylactic milrinone in preventing mortality or LCOS after surgery for congenital heart disease.[29]

A retrospective comparative study which includes adult patients with cardiogenic shock who received initial inotrope therapy with either milrinone (n=50) or dobutamine (n=50) showed that there is no difference between milrinone and dobutamine group in the time to resolution of cardiogenic shock. In addition, they reported that milrinone was not associated with more hypotension or an increased need for vasopressors in study population in contrast to previously published reports. According to overall study results, the authors suggested that milrinone can be safely preferred as an alternative initial inotrope for patients in cardiogenic shock even in those with decreased blood pressure.[30] Clinicians need to be cautious of side effects of milrinone including hypotension and atrial and ventricular arrhythmias.[31] Dobutamine is preferred to milrinone in patients with renal impairment.

Levosimendan has been reported to be safe and efficient in adults, although with little evidence on the pediatric population. Lechner et al[32] investigated 40 infants who underwent surgery with CPB and were managed with either levosimendan or milrinone. The authors showed improvements in terms of cardiac output and cardiac index in the levosimendan group, while inotropic score, lactate levels, and ICU stay were similar in both groups. Momeni et al[33] conducted a similar research on 41 children undergoing cardiac surgery and used postoperative lactate as a substitute marker for cardiac output. They reported equal efficiency for both milrinone and levosimendan in their sample. Still, levosimendan is a costly agent and has yet to be approved by the FDA, thus currently not widely used for managing LCOS in the United States.[21]

Systemic Vasodilators

Systemic vasodilators are useful for the management of LCOS by increasing stroke volume, cardiac output, and oxygen delivery to tissues and by reducing myocardial oxygen demand. Researchers have worked with number of similar medications for treating LCOS, including systemic nitric oxide donors, natriuretic peptides, and α-antagonists. Appelbaum et al[34] first used nitroprusside following cardiac surgery, reporting cardiac index to be increased by 17%. A nitrovasodilator, nitroglycerin, activates cGMP and results in the vasodilation of systemic arterioles and venuoles. Although, as it primarily affects venodilatory properties, nitroglycerin is not as effective as nitroprusside in vasodilation. Nicardipine, a selective calcium channel blocker, has been proven safe and efficient for the treatment of postoperative systemic hypertension, even in children aged below 6 months.[35] A recombinant form of brain natriuretic peptide, nesiritide, induces smooth muscle relaxation, alleviates the effect of vasopression, results in vasodilation, and promotes diuresis.[36] At first, nesiritide was shown to be correlated with good outcomes after cardiac surgery in adults. Despite the early findings, metanalyses on randomized control trials have demonstrated otherwise. Besides, one international survey stated that pure systemic vasodilators are not indicated as first-line therapy for LCOS. One exception here is patients with single ventricle circulation, in which case nitroprusside remains the most common agent.[21]

Pulmonary Vasodilators

One of the pathophysiologic mechanisms that are thought to contribute to LCOS is increased PVR after CPB. Children with preoperative left-sided obstructive lesions or left to right shunts have a higher risk of increased PVR after bypass. Cardiopulmonary bypass leads to inflammation, inhibiting the production of nitric oxide and increasing that of endothelin-1. A selective pulmonary vasodilator inhaled nitric oxide (iNO) has a mild effect on systemic vasculature. Research has examined the use of iNO and its precursors in treating or preventing LCOS. In their prospective double-blinded study on 124 infants at risk for pulmonary hypertension (PH), Miller et al[37] reported iNO to decrease indexed PVR, the number of PH crises, and mechanical ventilation rate at 7 days. Recently, prophylactic iNO has been shown to decrease LCOS incidence and ECMO requirement, particularly in patients aged below 2 years and after very complex surgeries. Although, in their review of the PHIS database, Wong et al[38] reported that only 11.6% of 1678 surgeries used iNO on patients with known PH. The use of iNO was correlated with higher costs and longer hospital stay, albeit without improved mortality rates.[39] Thus, there is currently not enough data to support the routine use of iNO. Common treatment approaches in patients with LCOS are summarized in Figure 3.

Corticosteroids

Cardiopulmonary bypass leads to an inflammatory cascade that contributes to LCOS and postoperative morbidity, hence motivating extensive research into anti-inflammatory therapy with corticosteroids in these patients. Some researchers have examined the cellular mechanisms in which corticosteroid supplementation might be useful.[49] Recently, Li et al[40] conducted a metanalysis of 17 randomized controlled trials on a total of 848 pediatric patients. The authors found no decrease in all-cause mortality compared to controls in children receiving corticosteroids. On the other hand, a survey of 188 PCICS members from 85 centers has revealed that 94% of respondents sometimes or always used corticosteroids in moderate or severe cases of LCOS, and hydrocortisone was the most common agent.[41]

Morbidity associated with inflammation and LCOS complicates CPB often. Some patients with refractory shock have been reported to benefit from hydrocortisone "stress dosage." The development of CPB-induced adrenal insufficiency may provide additional justification for hydrocortisone treatment postoperatively. Prophylactic postoperative hydrocortisone administration reduced LCOS and proinflammatory cytokines, improved fluid balance and urine output, and provided longer inotrope/vasopressor-free days in a study of 40 newborns undergoing heart surgery with CPB.[42]

Thyroid Hormone Replacement

Triiodothyronine (T3) levels are reduced after CPB in children and infants. One research correlated continuous T3 infusions with a significant decrease in time to negative fluid balance and no major increase in cardiac index. The OTICC study on 208 patients aged below 3 years reported that LCOS incidence was lower in the oral T3 group than placebo controls.[43] The metanalysis of Flores et al[44] demonstrated significantly decreased mean inotropic scores for T3 use, albeit no difference in ventilator time, ICU and hospital stay, mortality rate, or any other outcomes.

Vasopressin and Norepinephrine

The stimulant of the V1 receptor, vasopressin, decreases fluid resuscitation and inotropic support requirement in LCOS and vasoplegia cases. Compared with catecholamines, vasopressin is associated with a lower risk of arrhythmias.[45] A national database results which includes 53 tertiary care pediatric hospital from United States revealed that vasoactive agents have decreased in frequency of use in postoperative pediatric cardiac admissions, except for vasopressin.[24]

Norepinephrine is the vasopressor of choice in patients with cardiogenic shock based on fewer arrhythmic complications and reduced mortality when compared to dopamine. Observational data suggest that the addition of an inodilator to norepinephrine may improve survival. The use of norepinephrine is less common than that of epinephrine and vasopressin for LCOS and low SVR cases. Norepinephrine can increase cardiac output by increasing venous return if the heart is preload responsive or else can decrease cardiac output by increasing afterload.[46] Catecholaminergic inotropes and vasopressors have been used less over the last decade, although the use of vasopressin has since increased following cardiac surgery in pediatric patients.[15]

Fluid Management

For the pediatric cardiac patient, there are no specific guidelines for the content and rate of intravenous fluid administration. Fluid balance management in critically ill children is difficult because fluid overload in the PICU is thought to be a cause of multiple organ failure. There are various postoperative risk factors for derangements in fluid management in pediatric patients with congenital heart disease. Patients with acute kidney injury (AKI) who are the smallest are at the greatest risk of developing severe interstitial edema, capillary leak syndrome, and fluid overload. Several studies have found that adolescents with severe renal failure who require renal replacement treatments (RRTs) have a considerably greater percentage of fluid overload, which is closely linked to poor outcomes. As a result, in children, the correction of fluid overload and the maintenance of proper fluid balance are currently given top attention. To improve hemodynamics and reduce excess circulating volume, conventional diuretics can be used. However, clinicians must be cautious about diuretic-induced metabolic disturbances because electrolyte imbalances are common in critically ill cardiac patients who are receiving diuretics. Alternative diuretic/nephroprotective medicines are now being considered in the pediatric cardiac surgery setting, in addition to standard diuretics. When fluid overload is not responded to diuretics and AKI occurs, RRTs can help.[47]

Renal Replacement Therapies

Acute kidney injury occurs often after pediatric heart surgery and is associated with considerable morbidity and mortality. In the first 72 hours after pediatric heart surgery, there was a 26% incidence of AKI, according to the findings of a retrospective study. The development of postoperative AKI is influenced by a number of pathophysiologic processes. Acute kidney injury is associated with LCOS and secondary renal vasoconstriction, both of which are well-known risk factors. Fluid overload and increased filling pressures, which cause renal congestion and, as a result, lower kidney perfusion pressure, are essential pathophysiologic mechanisms. Clinical outcomes should be improved by preventing and diagnosing postoperative AKI early. Acute kidney injury is frequently treated with RRTs. Early RRT initiation, including peritoneal dialysis in neonates and continuous RRT in pediatric patients, may reduce AKI-related morbidity and mortality.[48]

Blood Transfusion

The decision to transfuse should be based on an evaluation of the individual patient based on a combination of symptoms, clinical and physiologic signals, and laboratory measures, rather than a single Hb level. In pediatric cardiac patients, there is currently no reliable data on goal-directed transfusion techniques. Physiologic criteria such as blood lactate, mixed venous oxygen saturation or its surrogate central venous oxygen saturation, oxygen extraction ratio, or cerebral oxygen saturation determined by NIRS at the regional level could all be evaluated.

The postoperative hemoglobin threshold for transfusion in stable acyanotic cardiac children is Hb 7 mg/L, or 8 mg/L in the presence of clinical signs suggestive of symptomatic anemia, according to the Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis guideline (grade 1B recommendation). The guideline recommends a postoperative hemoglobin threshold of 9 mg/L (grade 2C recommendation) for transfusion in stable cyanotic cardiac infants with clinical symptoms suggestive of symptomatic anemia.[49]

Sedation–Analgesia

Sedation is recommended after high-risk cardiac surgery not only to decrease anxiety and distress but also to avoid LCOS by blunting the stress response and lowering energy expenditure and myocardial oxygen demand. After heart surgery, discomfort must be avoided by using appropriate sedation–analgesia with minimal side effects. In addition, early extubation after congenital heart surgery is becoming more common. Early extubation can be facilitated by carefully modifying sedation and analgesic practices.[50]

Furthermore, benzodiazepines, which are commonly used for sedation following cardiac surgery, can have negative hemodynamic and respiratory consequences, and neurotoxicity concerns are growing. Dexmedetomidine, a new sedative linked to decreased respiratory depression, has been demonstrated to reduce opioid and benzodiazepine use during and after pediatric cardiac surgery, resulting in faster extubation times. Dexmedetomidine, a selective alpha-2 adrenoceptor agonist, is becoming more popular in the perioperative phase because it can offer sedation with minimal respiratory depression and improve hemodynamics by reducing postoperative neuroendocrine stress response. In a prospective randomized double-blind study comparing fentanyl and dexmedetomidine for sedation during mechanical ventilation after pediatric congenital heart surgery, dexmedetomidine was found to offer appropriate sedation for mechanical ventilation as well as early extubation.[51] In a retrospective study comparing dexmedetomidine/fentanyl to midazolam/fentanyl for postoperative sedation in pediatric patients with congenital heart disease, it was discovered that the dexmedetomidine group required fewer additional sedative/analgesic drugs and had a lower incidence of delirium than the midazolam group.[51]

Dexmedetomidine is used off-label in children, although it has become increasingly popular in recent years. Hypotension, bradycardia, and transient hypertension are the most common adverse effects of dexmedetomidine. Dexmedetomidine use has been linked to a lower incidence of perioperative tachyarrhythmias, such as supraventricular or junctional tachyarrhythmias in a few studies.[51]

Extracorporeal Life Support

Failure to manage prolonged or severe LCOS should at the very least be recognized early to prevent cardiac arrest. Widely available, ECMO is the most common mechanical circulatory support in prolonged and medically refractory LCOS patients.[31] According to data from the Society of Thoracic Surgeons, 2.4% of patients undergoing surgery are administered postoperative mechanical circulatory support, where ECMO is used 95% of the time.[52]

In conclusion, LCOS is a life-threatening complication after cardiac surgery in pediatric patients. There is still no consensus on the criteria for LCOS, although early identification, correct management, and timely mechanical support, if needed, are crucial for preventing morbidity and mortality associated with CPB.

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References

1. Parr GV, Blackstone EH, Kirklin JW. Cardiac performance and mortality early after intracardiac surgery in infants and young children. *Circulation*. 1975;51(5):867-874. [CrossRef]
2. Wessel DL. Managing low cardiac output syndrome after congenital heart surgery. *Crit Care Med*. 2001;29(10):S220-S230. [CrossRef]
3. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*. 1995;92(8):2226-2235. [CrossRef]
4. Ulate KP, Yanay O, Jeffries H, Baden H, Di Gennaro JL, Zimmerman J. An elevated low cardiac output syndrome score is associated with morbidity in infants after congenital heart surgery. *Pediatr Crit Care Med*. 2017;18(1):26-33. [CrossRef]
5. Sahulee R, McKinstry J. Pharmacologic therapies for the low cardiac output syndrome in children after cardiac surgery: evidence of their efficacy and trends in their use. *Vessel Plus*. 2022;6:5. [CrossRef]
6. Lomivorotov VV, Efremov SM, Kirov MY, Fominskiy EV, Karaskov AM. Low-cardiac-output syndrome after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2017;31(1):291-308. [CrossRef]
7. Ravishankar C, Tabbutt S, Wernovsky G. Critical care in cardiovascular medicine. *Curr Opin Pediatr*. 2003;15(5):443-453. [CrossRef]
8. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation*. 2003;107(7):996-1002. [CrossRef]
9. Butts RJ, Scheurer MA, Atz AM, et al. Comparison of maximum vasoactive inotropic score and low cardiac output syndrome as markers of early postoperative outcomes after neonatal cardiac surgery. *Pediatr Cardiol*. 2012;33(4):633-638. [CrossRef]
10. Aslan N, Yıldızdaş D, Göçen U, et al. Low cardiac output syndrome score to evaluate postoperative cardiac surgery patients in a pediatric intensive care unit. *Turk Kardiyol Dern Ars*. 2020;48(5):504-513. [CrossRef]
11. Murni IK, Djer MM, Yanuarso PB, et al. Outcome of pediatric cardiac surgery and predictors of major complication in a developing country. *Ann Pediatr Cardiol*. 2019;12(1):38-44. [CrossRef]
12. Jones B, Hayden M, Fraser JF, Janes E. Low cardiac output syndrome in children. *Curr Anaesth Crit Care*. 2005;16(6):347-358. [CrossRef]
13. Bozdoğan ÖN. Açık Kalp Cerrahisi Sonrası Gelişen Düşük Kalp Debisi. *JARSS*. 2020;28(1):1-11.
14. Jozwiak M, Monnet X, Teboul JL. Monitoring: from cardiac output monitoring to echocardiography. *Curr Opin Crit Care*. 2015;21(5):395-401. [CrossRef]
15. Gil-Anton J, Redondo S, Garcia Urabayen D, Nieto Faza M, Sanz I, Pilar J. Combined cerebral and renal near-infrared spectroscopy after congenital heart surgery. *Pediatr Cardiol*. 2015;36(6):1173-1178. [CrossRef]
16. Protsyk V, Rasmussen BS, Guarracino F, Erb J, Turton E, Ender J. Fluid management in cardiac surgery: results of a survey in European cardiac anesthesia depart- ments. *J Cardiothorac Vasc Anesth*. 2017;31(5):1624-1629. [CrossRef]
17. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11(2):234-238. [CrossRef]
18. Yuerek M, Rossano JW, Mascio CE, Shaddy RE. Postoperative management of heart failure in pediatric patients. *Expert Rev Cardiovasc Ther*. 2016;14(2):201-215. [CrossRef]
19. Pérez-Navero JL, de la Torre-Aguilar MJ, Ibarra de la Rosa I, et al. Cardiac biomarkers of low cardiac output syndrome in the postoperative period after congenital heart disease surgery in children. *Rev Esp Cardiol (Engl Ed)*. 2017;70(4):267-274. [CrossRef]
20. Vincent JL, Quintairos E Silva A, Couto L, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care*. 2016;20(1):257. [CrossRef]
21. Roeleveld PP, de Klerk JCA. The perspective of the intensivist on inotropes and postoperative care following pediatric heart surgery: an international survey and systematic review of the literature. *World J Pediatr Congenit Heart Surg*. 2018;9(1):10-21. [CrossRef]
22. Charpie JR, Dekeon MK, Goldberg CS, Mosca RS, Bove EL, Kulik TJ. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*. 2000;120(1):73-80. [CrossRef]
23. Shi S, Zhao Z, Liu X, et al. Perioperative risk factors for prolonged mechanical ventilation fol- lowing cardiac surgery in neonates and young infants. *Chest*. 2008;134(4):768-774. [CrossRef]
24. Loomba RS, Flores S. Use of vasoactive agents in postoperative pediatric cardiac patients: insights from a national database. *Congenit Heart Dis*. 2019;14(6):1176-1184. [CrossRef]
25. Jentzer JC, Hollenberg SM. Vasopressor and inotrope therapy in cardiac critical care. *J Intensive Care Med*. 2021;36(8):843-856. [CrossRef]
26. Marik PE. Dopamine increases mortality in pediatric septic shock. *J Pediatr*. 2016;168:253-256. [CrossRef]
27. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med*. 2020;21(2):e52-e106. [CrossRef]
28. Rui Q, Jiang Y, Chen M, Zhang N, Yang H, Zhou Y. Dopamine versus norepinephrine in the treatment of cardiogenic shock: a PRISMA-compliant meta-analysis. *Med (Baltim)*. 2017;96(43):e8402. [CrossRef]
29. Burkhardt BE, Rücker G, Stiller B. Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. *Cochrane Database Syst Rev*. 2015;3(3):CD009515. [CrossRef]
30. Lewis TC, Aberle C, Altshuler D, Piper GL, Papadopoulos J. Comparative effectiveness and safety between milrinone or dobutamine as

initial inotrope therapy in cardiogenic shock. *J Cardiovasc Pharmacol Ther*. 2019;24(2):130-138. [CrossRef]
31. Smith AH, Owen J, Borgman KY, Fish FA, Kannankeril PJ. Relation of milrinone after surgery for congenital heart disease to significant postoperative tachyarrhythmias. *Am J Cardiol*. 2011;108(11):1620-1624. [CrossRef]
32. Lechner E, Hofer A, Leitner-Peneder G, et al. Levosimendan versus milrinone in neonates and infants after corrective open-heart surgery: a pilot study. *Pediatr Crit Care Med*. 2012;13(5):542-548. [CrossRef]
33. Momeni M, Rubay J, Matta A, et al. Levosimendan in congenital cardiac surgery: a randomized, double-blind clinical trial. *J Cardiothorac Vasc Anesth*. 2011;25(3):419-424. [CrossRef]
34. Appelbaum A, Blackstone EH, Kouchoukos NT, Kirklin JW. Afterload reduction and cardiac ouptut in infants early after intracardiac surgery. *Am J Cardiol*. 1977;39(3):445-451. [CrossRef]
35. Stone ML, Kelly J, Mistry M, Buck M, Gangemi J, Vergales J. Use of nicardipine after cardiac operations is safe in children regardless of age. *Ann Thorac Surg*. 2018;105(1):181-185. [CrossRef]
36. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA*. 2005;293(15):1900-1905. [CrossRef]
37. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet*. 2000;356(9240):1464-1469. [CrossRef]
38. Wong J, Loomba RS, Evey L, Bronicki RA, Flores S. Postoperative inhaled nitric oxide does not decrease length of stay in pediatric cardiac surgery admissions. *Pediatr Cardiol*. 2019;40(8):1559-1568. [CrossRef]
39. Graham EM, Atz AM, Butts RJ, et al. Standardized preoperative corticosteroid treatment in neonates undergoing cardiac surgery: results from a randomized trial. *J Thorac Cardiovasc Surg*. 2011;142(6):1523-1529. [CrossRef]
40. Li Y, Luo Q, Wu X, Jia Y, Yan F. Perioperative corticosteroid therapy in children undergoing cardiac surgery: a systematic review and meta-analysis. *Front Pediatr*. 2020;8:350. [CrossRef]
41. Flores S, FitzGerald MR, Iliopoulos I, et al. An international survey of corticosteroid use for the management of low cardiac output syndrome. *Pediatr Crit Care Med*. 2017;18(7):630-637. [CrossRef]
42. Robert SM, Borasino S, Dabal RJ, Cleveland DC, Hock KM, Alten JA. Postoperative hydrocortisone infusion reduces the prevalence of low cardiac output syndrome after neonatal cardiopulmonary bypass. *Pediatr Crit Care Med*. 2015;16(7):629-636. [CrossRef]
43. Marwali EM, Caesa P, Darmaputri S , et al. Oral triiodothyronine supplementation decreases low cardiac output syndrome after pediatric cardiac surgery. *Pediatr Cardiol*. 2019;40(6):1238-1246. [CrossRef]
44. Flores S, Loomba RS, Checchia PA, Graham EM, Bronicki RA. Thyroid hormone (triiodothyronine) therapy in children after congenital heart surgery: a meta-analysis. *Semin Thorac Cardiovasc Surg*. 2020;32(1):87-95. [CrossRef]
45. McIntyre WF, Um KJ, Alhazzani W, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. *JAMA*. 2018;319(18):1889-1900. [CrossRef]
46. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med*. 2013;41(1):143-150. [CrossRef]
47. McCammond AN, Axelrod DM, Bailly DK, Ramsey EZ, Costello JM. Pediatric cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care fluid management. *Pediatr Crit Care Med*. 2016;17(3):S35-S48. [CrossRef]
48. Sanchez-de-Toledo J, Perez-Ortiz A, Gil L, et al. Early initiation of renal replacement therapy in pediatric heart surgery is associated with lower mortality. *Pediatr Cardiol*. 2016;37(4):623-628. [CrossRef]
49. Faraoni D, Meier J, New HV, Van der Linden PJ, Hunt BJ. Patient blood management for neonates and children undergoing cardiac surgery: 2019 NATA Guidelines. *J Cardiothorac Vasc Anesth*. 2019;33(12):3249-3263. [CrossRef]
50. Brown LM, Kratz A, Verba S, et al. Pain and opioid use After thoracic surgery: where we are and where we need to go. *Ann Thorac Surg*. 2020;109(6):1638-1645. [CrossRef]
51. Jiang L, Ding S, Yan H, et al. A retrospective comparison of dexmedetomidine versus midazolam for pediatric patients with congenital heart disease requiring postoperative sedation. *Pediatr Cardiol*. 2015;36(5):993-999. [CrossRef]
52. Mascio CE, Austin EH, Jacobs JP, et al. Perioperative mechanical circulatory support in children: an analysis of the society of Thoracic Surgeons Congenital Heart Surgery Database. *J Thorac Cardiovasc Surg*. 2014;147(2):658-664. [CrossRef]