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Review

Deciphering Low Cardiac Output Syndrome: Insights and Management in Post-Cardiac Surgery

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Abstract

Low cardiac output syndrome (LCOS) is a dysfunctional state of the heart that often results in decreased cardiac output that is insufficient to meet current metabolic demands. LCOS is typically seen after post-cardiac surgery and is often associated with worsened outcomes and rising hospital costs. As cardiovascular disease becomes more common in an aging population, the prevalence of LCOS will inevitably increase. Understanding the underlying pathophysiology and management is essential to patient outcomes. This is a comprehensive review of the epidemiology, pathophysiology, treatment options, and outcomes of those who develop LCOS after cardiac surgery.

Keywords

low cardiac output syndrome; cardiogenic shock; cardiopulmonary bypass; post-cardiotomy shock

Background

Low cardiac output syndrome (LCOS) is a dysfunctional state of the heart that results in decreased cardiac output that is insufficient to meet adequate metabolic demands. Typically seen after post-cardiac surgery, the literature has varied descriptions, with no clear consensus regarding its definition [1,2]. Literature has often been limited to single-institution experiences, with wide-ranging variability regarding incidence and outcomes [3]. When present, LCOS is often associated with significantly increased mortality and hospital costs [4]. This review aims to evaluate LCOS's incidence, risk factors, underlying pathophysiology, outcomes, and management.

Methodology

A comprehensive literature search was conducted with the assistance of a certified medical librarian. The search strategy aimed to identify relevant published up-to-date studies regarding Low Cardiac Output Syndrome. The search was primarily performed utilizing the PubMed database. The search terms included variations of "Low Cardiac Output Syndrome", and "post-cardiotomy shock".

Definition

Numerous studies have been conducted to investigate the incidence and management of LCOS. Although there is a general agreement that the cardiac output (CO) and cardiac index (CI) are typically impaired in LCOS, many studies to date have had different criteria for defining low cardiac output. A systematic review by Schoonen *et al.* [3] in 2022 found 171 different definitions of LCOS in the literature. They also noted that 34% of the criteria used to define LCOS were not reproducible [3]. The most common definitions were reported to be: CI $<$2.0 L/min/m^2, Ionotropic agents used for $>$30 minutes to achieve SBP $>$90 mm Hg or CI $<$2.2 L/min/m^2, use of 1 or more Inotrope and Lactate $>$2.0 mmol/L, and use of Intra-aortic balloon pump (IABP) or mechanical support [3].

Epidemiology

Incidence

Due to heterogeneous definitions and diagnostic criteria, the reported incidence of low cardiac output syndrome has been significantly varied throughout the literature, complicating efforts to understand its prevalence in postoperative cardiac patients fully. In the past, the incidence was reported to be 3.9–7% [4–7], but a more recent 2022 systematic review found that the incidence of LCOS in adults can range from 1.5% to 91% [3]. A large retrospective observational study conducted by Duncan *et al.* [4] showed a 10% incidence among those who underwent surgery at specialized centers throughout North America (N = 59,810). However, the reported incidence was higher (13.5–14.7%) for those who had surgery outside of North America [8,9].

Predictors and Risk Factors

There are several traits that are linked to the development of LCOS post-cardiac surgery. Major independent predictors were noted to be female sex, coronary artery bypass grafting (CABG), reoperation, reduced left ventricular ejection fraction (LVEF) <20%, cardiogenic shock, emergent surgery, and peripheral vascular disease [5,6,10]. The presence of preoperative cardiogenic shock has been identified as one of the most significant risk factors in multiple studies, showing an up to eight-fold increase in risk [4,5]. Patients who underwent CABG with valve replacement had a higher risk than those who received only CABG or valve procedures [4,10]. Among those who received CABG, combined with mitral and/or tricuspid/aortic valve interventions, were at the highest risk [4].

Currently, there is no standardized method to determine the likelihood of developing LCOS. However, scoring systems have been proposed over recent years to help identify those at high risk. Mendes and associates retrospectively assessed their single institution's experience analyzing 3040 patients and developed and validated a scoring model that was 68% sensitive and 72% specific, with a positive and negative predictive value of 33% and 94%, respectively (Table 1) [11]. Ulate *et al.* [12] proposed a scoring system that looks at post-operative factors for the first 24 hours where a higher score was associated with increased morbidity. With the progressive development of artificial intelligence and machine models, risk identification and early detection have become more attainable [13]. However, their clinical applications remain in question.

Pathophysiology

Low cardiac output syndrome is not simply the result of a singular issue but is likely due to several contributing mechanisms that result in a hypoperfused, oxygen-depleted state [14]. Cardiopulmonary bypass (CPB), cardioplegia, duration of CPB, underlying heart function, hemodynamic states, and neuro-hormonal regulation are important factors.

Molecular and Cellular Mechanics

Myocardial dysfunction is heavily influenced by molecular and cellular processes. Several mechanisms thought to contribute to LCOS have been described. Of those, calcium dysregulation through ischemia-reperfusion injury has been consistently reported to play a major role in myocardial dysfunction.

Decreased contractility has been linked with an imbalance of calcium homeostasis. This occurs by (1) decreased sarcoplasm reticulum Ca^{2+} uptake via the SERCA2a receptors; (2) increased Ca^{2+} leak from Type 2 Ryanodine receptors (RYR2) [15]. This imbalance results in Ca^{2+} cycling through influx channels along with Mitochondrial co-transporters, increasing energy expenditure in an already depleted state. Reliance on the $2Na^{+}/Ca^{2+}$ exchanger and Na^{+}/K^{+} ATPase leads to increased intracellular Na and K levels, resulting in a higher susceptibility to arrhythmias.

Mitochondrial damage ensues because of an imbalance in ion homeostasis through multiple mechanisms: (1) increased activity of the mitochondrial permeability transition pore (mPTP); (2) Increased activity of $2Na^{+}/Ca^{2+}$ exchanger; (3) activation of pro-inflammatory mediators [16]. Both mechanisms result in the collapse of the mitochondrial membrane potential, resulting in cellular apoptosis and cellular necrosis. Significant amounts of ATP are needed to return the mitochondrial membrane back to homeostasis. This increased energy expenditure further results in diminished myocardial activity, potentially contributing to the development of LCOS [16].

Inadequate perfusion results in a transition to anaerobic metabolism, which depletes ATP production, leading

Table 1. Risk assessment scoring system.

Mendes Multivariate Model and Risk Score	
GFR <60 mL/min or preoperative dialysis	2
Mitral Valve Replacement or repair for mitral regurgitation	4
Non-elective Surgery	2
Extracardiac Arteriopathy	1
Preoperative Hemoglobin <13 g/dL	1
NYHA Class III/IV	2
LVEF	
31–50%	3
20–30%	9
<20%	11
Combined Surgery	2

A scoring system designed by Mendes *et al.* [11] to help assess the risk of developing LCOS. Scores ≤5 correspond to a very low risk of developing LCOS. LCOS, Low cardiac output syndrome; GFR, Glomerular Filtration Rate; LVEF, left ventricular ejection fraction.

to a production-demand mismatch. This energy deficit may negatively affect cardiac function, as energy production and myocardial metabolic regulation are strongly tied together.

Pre, Intra, and Post-operative Factors

Certain conditions may predispose patients to poor myocardial function postoperatively. Multiple pre-operative conditions, such as existing myocardial dysfunction, myocardial ischemia, chronic hypoxemia, and ventricular hypertrophy, all contribute to cardiac dysfunction [17,18]. However, three major underlying mechanisms are thought to influence the development of LCOS strongly: left ventricular systolic dysfunction (LVSD), right ventricular systolic dysfunction (RVSD), and left ventricular diastolic dysfunction (LVDD) [19,20]. Those with systolic dysfunction experience a decrease in myocardial contractility due to reduced ejection fraction. This can result in structural deformation impairing filling and ejection, typically seen in RV overload [18]. Those with diastolic dysfunction are left with stiff hearts, unable to fill and eject, ultimately impeding cardiac output [18]. In cases where cardiogenic shock is an indication for surgery, preoperative acidosis has been associated with increased risk and mortality [21].

The use of CPB has long been known to elicit a systemic inflammatory response and endothelial dysfunction through activation of the complement cascade, which may result in myocardial depression [22,23]. The natural inflammatory process is typically self-limiting, but excess inflammation may be associated with increased organ dysfunction [24,25]. Direct physical and Ischemic injury may also occur from physical manipulation or alterations in blood flow (Decreased pressures, systemic hypoxemia, and long cross-clamp times), respectively [17]. Insufficient protection of the heart during surgery can also damage the myocardium through increased myocardial oxygen requirements and metabolic demand [26–28]. It's worth noting that not all cardioplegia is the same. In fact, there seems to be a correlation between the type of myocardial protection used and the extent of the inflammatory response typically seen after CPB [25]. Guru *et al*. [29], in a meta-analysis comparing blood cardioplegia *vs.* crystalloid, demonstrated a reduction in LCOS when blood cardioplegia was used.

Cardiac Loading

Numerous physiological changes can occur after cardiac surgery, profoundly affecting a patient's hemodynamic state and overall myocardial function. Both preload and afterload influence the function of the ventricles. Patients with reduced ventricular compliance may rely on preload to maintain optimal cardiac output [30]. Changes in preload can occur due to various factors, including vasodilatory states, hypovolemia, and/or tamponade. Vasodilation typically occurs during re-warming and with afterload reduction. Hypovolemia can be the result of excess ultrafiltration, under-resuscitation, or bleeding. When combined with the development of tamponade, altered preload may lead to compromised venous return and ventricular filling [31].

Another crucial aspect of cardiac loading to consider is afterload, which should be considered for both the right and left sides of the heart. Increased right ventricular (RV) afterload is typically seen with pre-existing pathologies such as pulmonary hypertension (HTN), mitral stenosis, aortic stenosis, or pulmonary vein/arterial occlusions. Increased afterload is typically accompanied by elevations in pulmonary artery pressures (PAP), which are affected by the level of pulmonary vascular resistance (PVR) [32,33]. Chronic elevations often result in remodeling (hypertrophy) with an increase in noncompliance; this often impairs diastolic geometry and has the potential to limit LV filling and ejection [34]. The pathological changes to PAP, when combined with physiological changes associated with CPB and open heart surgery, can result in some degree of RV dysfunction and/or failure, especially in those with pre-existing heart failure [18].

Just as the remodeling occurs in the right heart from chronically increased afterload, left ventricular afterload is often associated with similar changes. Ventricular remodeling causes structural changes that impair filling and diastolic function due to poor compliance [35,36]. Increased afterload post-CPB is often due to the stimulation of catecholamines, ADH, and vasopressin release, all of which increase systemic vascular resistance (SVR) and fluid retention [37–39]. In patients undergoing CPB, increased afterload (post-operative hypertension) is not uncommon and can potentially stress an already dysfunctional heart, resulting in decreased cardiac output. Kaw *et al*. [40] conducted a systematic review to evaluate the impact of diastolic dysfunction (DD) on post-cardiovascular surgery outcomes. The study found a higher rate of mortality and major cardiac effects in patients with DD, greatest in those with grade III DD (OR: 21.22; 95% CI, 3.84–120.33; $p = 0.0006$) [40].

Management

The management of LCOS focuses on various interventions that aim to reduce the condition's impact on perfusion. This is achieved by optimizing cardiac output to restore perfusion and stabilize oxygen supply to prevent multi-organ dysfunction. These interventions are often carried out in a coordinated manner using volume replacement, diuretics, inotropes, vasopressors, and vasodilators. However, inotropic agents remain the primary pillar of support. In a Cochrane review evaluating cardiogenic shock and LCOS, Uhlig *et al*. [41] found no clinically relevant differences in hemodynamic effects (CI, PCWP, and MAP) between epinephrine *vs.* norepinephrine-dobutamine, mil-

rinone *vs.* dobutamine, dopamine-milrinone *vs.* dopamine-dobutamine, enoximone *vs.* dobutamine, piroximone, or epinephrine-nitroglycerine [41–44]. No significant differences were found between the groups, apart from milrinone *vs.* dobutamine, due to a lack of data regarding short-term mortality [41]. Their analysis also identified that norepinephrine-dobutamine *vs.* epinephrine and norepinephrine *vs.* epinephrine had a slightly improved safety profile [41,42,45].

Calcium Channel Sensitizer

Levosimendan, introduced in 2000, was the first calcium channel sensitizer used for managing decompensated severe chronic right heart failure [46]. Over the past twenty years, extensive research has been conducted to assess its usefulness and explore its potential. Though available worldwide, its use remains idle in the United States. It has demonstrated some beneficial hemodynamic effects as compared with dobutamine [47–50]. However, similar to other inotropic agents, levosimendan's nonselective effect on vasodilation can result in hypotension [48]. However, the majority of data supports its utility in reducing short-term mortality, indicating its benefit [49,51–53], although some data reported is inconsistent [54,55]. Similarly, in the three main RCTs (LICORN, CHEETAH, LEVOS-CTS) that assessed the use of Levosimendan in post-cardiac surgery patients, the results also varied regarding outcomes, duration of inotropes, or use of left ventricular assist devices (VAD) [53,56–58]. Currently, its use in cardiac surgery patients is not recommended [57]. Further investigations are necessary to assess its utility.

Corticosteroids

Given the pro-inflammatory effects of cardiac surgery and the use of CPB, corticosteroids have often been utilized for their global anti-inflammatory effects. Several studies have been performed since the 1980s evaluating their clinical and biochemical effects in relation to cardiac surgery, but the overall clinical effects remain controversial. In an international survey by Flores *et al.* [59], 94% of 188 pediatric cardiac intensive care society members from 85 centers throughout the world reported sometimes or always administering steroids to patients requiring 2 or more vasopressors with persistent hypotension. Previous studies focused on the preventive prophylactic use of corticosteroids. The STRESS trial, conducted by Hill *et al.* [60], demonstrated that using methylprednisolone did not significantly reduce adverse outcomes for infants undergoing CPB. In a 2020 systematic review, Li *et al.* [61] concluded that there was no significant difference in the incidence of all causes of mortality among children receiving corticosteroids or the occurrence of LCOS, mirrored with similar conclusions in Cheema *et al.* [62] systematic review and meta-analysis. Though there is favoritism in the use of corticosteroids in LCOS, there remains a paucity of literature on needed guidelines regarding their use.

Mechanical Circulatory Support

Once medical therapy has been maximized, with the persistence of low cardiac output, mechanical circulatory support (MCS) devices should be considered. MCS devices have been used to stabilize hemodynamics as a bridge to cardiac recovery or definitive therapy (VAD, Transplant). The timing and criteria for initiating MCS remain controversial, with current recommendations relying on a multidisciplinary approach [63,64]. Previously, MCS was utilized in 46% of patients with LCOS, with the Intra-Aortic Balloon Pump (IABP) as the most commonly used device, followed by VA-ECMO and a ventricular assist device [10].

Currently, there is a lack of consensus on the timing for initiation or the preferred form of mechanical support. Traditionally, IABP was the main type of MCS, but with technological advancements, options have expanded. Numerous multicentered randomized control trials have examined its effect in the setting of cardiogenic shock without being able to demonstrate statistical significance in 30-day mortality or 6-year mortality [65,66].

Axial (Impella) and Centrifugal (ECMO) pumps currently provide those in shock with near-to-complete cardiac support. However, no direct comparisons between the two modalities have been made. Griffith and colleagues [67] demonstrated a 93% recovery rate when using Impella for patients who developed low cardiac output syndrome and shock after failing separation from CPB. However, with the increasing use of Impella, multiple studies have examined their use as a form of prophylactic support for those undergoing high-risk cardiac surgery [68–71]. In these studies, an Impella 5.0 was selected, which is capable of producing >5 L/min (Impella 5.0). Between the 3 studies, 77–92.9% of patients were successfully weaned from mechanical support, with all patients without a low output state at 24–48 hours postoperatively [68–71]. However, these studies were significantly limited by their small sample size, though they raise the question of whether patients at risk should be prophylactically managed with mechanical support.

Extracorporeal support has also been widely used in patients with medically refractory LCOS. Park *et al.* [72] conducted a review of 93 patients who suffered from postoperative LCOS. They found that 41.9% were successfully liberated, but the overall mortality rate was 75.7%, slightly higher than the previous rate of 65% [72,73]. High lactate levels were observed to be an independent predictor of mortality after initiation of ECLS, indicating a potential need for earlier ECLS activation [72].

Outcomes

Operative Mortality

LCOS has been associated with significantly poor- in-hospital mortality and cardiovascular outcomes [5–7,53]. In a 20-year observational study by Algarni *et al*. [5], a 29-times increase in mortality was observed, with rates of 12.8–24% for those with LCOS compared to 0.6–0.9% for those without. In a more recent review by Duncan and associates [4], they demonstrated similarly a high rate of in-hospital mortality in those with LCOS (OR 12.0; 95% CI, 10.6–13.5). In those who survived, there was a significant increase in postoperative complications such as myocardial infarction, bleeding requiring reoperation, acute kidney injury, need for dialysis, and acute respiratory failure, as well as the length of stay in the intensive care unit [4].

Future Directions

Future research should focus on optimizing calcium regulation for cardiac function. Clinical trials are needed to assess medications for enhancing calcium homeostasis. Early identification of at-risk patients may improve outcomes. Comparative studies are also needed to establish best practices for cardioplegia solutions and delivery methods. Strategies for addressing myocardial edema and preventing mitochondrial damage will be crucial for improving post-ischemic cardiac function. Additionally, further studies are required to determine the optimal selection and timing of mechanical support.

Conclusion

LCOS continues to pose significant challenges for those who undergo cardiac surgery. Though new innovations in medical therapy and MCS have become available since the turn of the decade, it has been and continues to be associated with high rates of morbidity and mortality. With the increasing prevalence of cardiovascular disease in an aging population, it is likely that there will be a continued rise in the prevalence of LCOS. Therefore, understanding patient selection, underlying physiology, and updated therapies remains essential.

Author Contributions

ALC: methodology, data curation, formal analysis, writing – original draft, BAK: writing – review and editing, visualization, conceptulization, validation, and supervision, JPR: writing – review and editing, acquisition, analysis, and interpretation of data, TAS: writing – review and editing, project administration and conceptualization, JMA: writing – review and editing, investigation and validation of the work, AV: writing – review and editing, project administration and conceptualization. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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