Low-Cardiac-Output Syndrome After Cardiac Surgery

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Review Article

Over the past decade, there has been a significant decline in cardiac surgery–associated mortality, despite an increase in procedural complexity. Although the average perioperative mortality currently is 1% to 2%, the rate of major cardiovascular complications remains high.1,3 Low-cardiac-output syndrome (LCOS) is the most common and the most serious complication and is associated with increased morbidity, short- and long-term mortality, and healthcare resource utilization.1,3 This syndrome is characterized by decreased heart pump function, leading to reduced oxygen delivery (DO2) and subsequent tissue hypoxia.5 The most common definition of LCOS also includes decreases in the cardiac index (CI) to <2.0 L/min/m² and a systolic blood pressure of <90 mmHg, in conjunction with signs of tissue hypoperfusion (cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolemia. The use of inotropic agents or mechanical circulatory support always is required to improve patient hemodynamics.7,8

Acute renal failure, neurologic and pulmonary complications, and atrial fibrillation are the most common consequences of LCOS.9,10,11 Furthermore, mortality among patients who develop LCOS after cardiac surgery can exceed 20%.11 Numerous demographic and intraoperative and postoperative factors might be responsible for the development of LCOS.12,15,16 High-risk cardiac patients, especially those with preoperative left ventricular (LV) systolic dysfunction (left ventricular ejection fraction [LVEF] <35%), develop LCOS more frequently than do patients with a normal LVEF12 and must receive special attention during the perioperative period. Thus, prompt identification of LCOS is necessary to enable goal-directed therapy to maximize DO2 and restore tissue metabolism and organ function, thus improving the clinical outcome.14

This review article aims to summarize the current data regarding the pathophysiology, diagnosis, prevention, and treatment of LCOS after cardiac surgery.

Risk Factors and Predictors

To date, several risk factors and predictors have been recognized (Table 1). Furthermore, a number of outcome prediction models have been developed, including the commonly used EuroSCORE, which predicts perioperative cardiovascular alterations.15 Independent significant risk factors for LCOS, including advanced age (>65 years), impaired LV function (<50%), on-pump coronary artery bypass grafting (CABG), emergency surgery or cardiopulmonary bypass (CPB), and incomplete revascularization, have been described.16-17 Diabetes mellitus and preoperative renal dysfunction are not separate predictors, but in combination they increase the risk of LCOS by 50%.18,19 Importantly, there have been changes in the recognized risk factors over time. Thus, during the last 20 years, common risk factors such as hypertension, being female, triple-vessel disease, and left main vessel disease are no longer statistically significant, whereas the risk associated with low preoperative ejection fraction has doubled.7 Another risk factor is malnutrition, which is associated with a 2-fold increase in the probability of postoperative inotropic support and independently predicts adverse clinical outcomes.20

Considering that cardiovascular disease, per se, and cardiac surgery with CPB cause profound alterations in systemic metabolism and endocrine function, many trials have been conducted to determine the biochemical predictors of various complications, including LCOS. The predictive impact of low hemoglobin levels was shown in one prospective cohort study.13 Furthermore, a preoperative total lymphocyte count of <2,000 cells/μL was associated with a high incidence of postoperative inotropic support.22 Preoperative levels of brain natriuretic peptide and the N-terminal of the prohormone brain natriuretic peptide in adult patients undergoing cardiac surgery have been shown to be predictors of prolonged inotropic support, hospitalization, and 30-day mortality.23,24 Furthermore, another study demonstrated that a brain natriuretic peptide level of >82 pg/mL at admission to the intensive care unit (ICU) in patients who underwent aortic valve surgery was an independent predictor of postoperative heart failure.25

Muehlschlegel et al prospectively studied a cohort of 1,298 patients undergoing primary CABG with CPB to assess the predictive value of heart fatty acid binding protein levels as early markers of perioperative myocardial injury, ventricular...
operative ventricular dysfunction. Weaning was found to be an independent predictor of postoperative heart fatty acid binding protein level (immediately after CPB).

The principal pathophysiologic mechanisms of RV dysfunction include increased RV preload, increased RV afterload, impaired right coronary artery perfusion, and decreased contractility. The specific features of RV perfusion and their alterations during increased pulmonary artery pressure are important to understand. Physiologically, perfusion of the right coronary artery, in contrast to the left coronary artery, occurs during both diastole and systole. Under conditions of stunning or may be refractory to reversal with conditions such as infection; tachycardia; cardiac valvular disease; metabolic abnormality (acidosis, hypoglycemia, hypocalcemia); exposure to cardiac toxins; idiopathic dilated cardiomyopathy; and genetic disorders (familial dilated cardiomyopathy, hypertrophic cardiomyopathy, muscular dystrophies). The impairment of cardiac response to preload leads to dramatic decreases in cardiac output (CO) and oxygen delivery to other organs, increased left atrial pressure and capillary wedge pressure, and cardiogenic pulmonary edema. Although the LV usually works against relatively high systemic arterial pressure, the significant afterload increase also may induce LV systolic dysfunction.

LV Systolic Dysfunction

LV function is derivative of preload, afterload, and contractility; LV systolic dysfunction occurs due to loss of functional myocytes or a decrease in their function. In most cases, the loss of functional myocytes develops as a result of necrosis due to impaired coronary circulation and ischemia/reperfusion injury or the less-understood phenomenon of apoptosis. A loss of function of vital myocytes commonly is transient during postoperative factors

Table 1. Predictors and Risk Factors of Postoperative LCOS

Preoperative factors

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Factor</th>
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<tbody>
<tr>
<td>Age</td>
<td>&gt;65 years&lt;sup&gt;16,17&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVEF</td>
<td>&lt;50%&lt;sup&gt;6,17&lt;/sup&gt;</td>
</tr>
<tr>
<td>On-pump CABG</td>
<td>&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>DM and CKD</td>
<td>&lt;sup&gt;16,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>&lt;sup&gt;20&lt;/sup&gt;</td>
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Intraoperative factors

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB duration</td>
<td>&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incomplete revascularization</td>
<td>&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
</tbody>
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Laboratory predictors

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>TLC</td>
<td>&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt;sup&gt;24,25&lt;/sup&gt;</td>
</tr>
<tr>
<td>hFABP</td>
<td>&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CPB, coronary artery bypass; DM, diabetes mellitus; hFABP, heart fatty acid binding protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; TLC, total lymphocyte count.

dysfunction, and all-cause mortality.<sup>26</sup> In-hospital ventricular dysfunction was defined as a new requirement for the use of 2 or more inotropes or the new placement of an intra-aortic balloon pump (IABP) or ventricular assist device during either the intraoperative period, after the patient was weaned from CPB, or postoperatively in the ICU. After adjusting for clinical predictors of ventricular dysfunction, the peak postoperative heart fatty acid binding protein level (immediately after CPB weaning) was found to be an independent predictor of postoperative ventricular dysfunction.

PATHOPHYSIOLOGY

Most interventions that include CPB with cardioplegic arrest lead to myocardial dysfunction, which typically results from ischemic/reperfusion injury of the heart. The persistence of such dysfunctions may vary from temporary (up to 24 hours), for stunning, to persistent, in cases of profound ischemia and myocardial infarction. The contributing factors include preoperative myocardial dysfunction, degree of myocardial protection, systemic inflammatory responses, and alterations in signal transduction systems.<sup>27</sup>

The following pathophysiologic mechanisms of LCOS should be highlighted: (1) LV systolic dysfunction, (2) right ventricular (RV) systolic dysfunction, and (3) diastolic dysfunction, also called heart failure with preserved ejection fraction (Fig 1). The aforementioned mechanisms may occur in isolation or in combination. Conditions such as valvular heart disease, pulmonary hypertension, mechanical valve dysfunction, and respiratory failure, also contribute to LCOS development.

LV Diastolic Dysfunction

LCOS sometimes is associated with preserved LV systolic function (ejection fraction). In such cases, the contractile function of the myocardium is diminished, despite preserved global systolic performance. These conditions result from the inability of the ventricular chamber to accept an adequate volume of blood, despite normal preload, and present as diastolic dysfunction.<sup>28</sup> However, diastolic dysfunction may be accompanied by either impaired or preserved ejection fraction. From a pathophysiologic perspective, diastolic dysfunction is characterized by abnormal relaxation and filling of the LV during the diastolic phase of the cardiac cycle that may be caused by the following mechanisms: (1) severe tachycardia (upon atrial fibrillation), (2) decreased myocardial compliance, and (3) impaired ventricular relaxation. The processes intimately involved in the development of diastolic dysfunction, at the cardiomyocyte level, relate to calcium removal from the cytosol and calcium homeostasis, the adequacy of cross-bridge detachment, and intrinsic functional cytoskeletal element disorders.<sup>30</sup>

Diastolic dysfunction is a widespread phenomenon, occurring in up to 70% of cardiac patients postoperatively.<sup>31,32</sup> Despite its high prevalence, diastolic dysfunction alone often is insufficient to induce the development of acute heart failure; however, in combination with other predisposing factors, such as atrial fibrillation, impaired coronary perfusion, and arterial hypertension, it may lead to decompensation. Diastolic dysfunction therefore is believed to be an early sign of myocardial ischemia.<sup>31</sup>

The close relationship between the systolic and diastolic functions of the LV should be acknowledged. Thus, inotropic catecholamine stimulation affects both systole and diastole and may enhance diastolic dysfunction, whereas reduced LVEF leads to increased end-systolic volume and prolongs the diastolic phase of the cardiac cycle.<sup>33</sup>

Right Ventricular Dysfunction

The principal pathophysiologic mechanisms of RV dysfunction include increased RV preload, increased RV afterload, impaired right coronary artery perfusion, and decreased contractility.<sup>34-36</sup> The specific features of RV perfusion and their alterations during increased pulmonary artery pressure are important to understand. Physiologically, perfusion of the right coronary artery, in contrast to the left coronary artery, occurs during both diastole and systole. Under conditions of
pulmonary hypertension, the RV pressure increases and leads to decreased right coronary artery perfusion, explaining why diastolic arterial pressure maintenance is highly important for providing optimal left and right coronary blood flow.37 In postoperative settings, RV dysfunction often develops due to a combination of mechanisms. Thus, cardiac patients encounter many conditions associated with RV failure. Perioperative RV ischemia and infarction are major causes of contractility impairment. Tricuspid or pulmonic regurgitation leads to excessive volume preload, whereas left-sided valvular disease or cardiomyopathy, pulmonary hypertension or embolism, acute respiratory distress syndrome, and high positive-pressure ventilation are common causes of pressure overload. Taking into account that the RV normally provides low-pressure perfusion of the pulmonary vasculature, it is highly sensitive to even moderate pulmonary artery pressure increases. RV failure may develop due to pulmonary hypertension or contractile impairment associated with a rapid progression of RV dilation, resulting in a rise in end-diastolic RV pressure.38 These alterations lead to an interventricular septum shift toward the already underfilled LV chamber,39 reducing LV preload and decreasing CO.

Fig 1. A schematic presentation of the pathophysiology of postoperative LCOS. The most common causes and typical signs are presented. The specific clinical scenario usually is associated with particular pathophysiologic type of LCOS. However, in clinical practice, a combination of different pathophysiologic pathways often leads to the development of postoperative LCOS. ARDS, acute respiratory distress syndrome; CI, cardiac index; E, early flow velocity at the level of the mitral valve; E0, early velocity of the mitral annulus (myocardial Doppler imaging); EF, ejection fraction; HR, heart rate; LVDD, left ventricular diastolic dysfunction; LV, left ventricle; LVSD, left ventricular systolic dysfunction; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; RAP, right atrial pressure; RV, right ventricle; RVSD, right ventricular systolic dysfunction; SVR, systemic vascular resistance; SvO2, mixed venous oxygen saturation.

HEMODYNAMIC MONITORING AND GOAL-DIRECTED THERAPY

The goal of perioperative hemodynamic management in cardiac surgery should be optimization of the balance between DO2 and oxygen consumption (VO2); this is especially important in patients with low CO. The individualized choice of perioperative monitoring technique depends on the type of surgery and the patient-related risk. Over time, a number of new hemodynamic monitoring methods have appeared, including real-time measurements and less-invasive approaches.40

Ultrasound Techniques

During cardiac anesthesia and in the ICU, echocardiography allows for the diagnosis of hemodynamic disorders and assessment of the static or dynamic parameters on which clinicians rely when making decisions regarding surgical procedures and perioperative management.41 As an important diagnostic tool in cardiac surgery, echocardiography can be used to reveal the type of LCOS and assess ejection fraction, heart volumes, systolic and diastolic function, valve pathology, pulmonary circulation, ventricular filling pressures, pericardial effusion, and fluid responsiveness.40
Although transthoracic echocardiography (TTE) remains the key method for preoperative and postoperative patient evaluation and in emergency ICU situations, many cardiac anesthesiologists prefer transesophageal echocardiography (TEE) for checking the adequacy of mitral valve repair and other procedures. In a recent survey investigating the use of cardiac surgery monitoring tools, TEE was used by 95% of respondents. Guidelines published by the American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists recommend the use of TEE for patients with persistent hypotension or hypoxia when timely diagnostic information cannot be obtained using TTE or other modalities. The use of echocardiography also is encouraged during the initial phase of shock to help identify the main mechanisms involved in LCOS and to aid in the selection of appropriate therapy. However, echocardiography is an operator-dependent method that is expensive and cannot provide continuous hemodynamic measurements.

Both TEE and TTE can be of enormous value in the diagnostic setting, helping to determine the pathophysiologic mechanisms of hemodynamic disorders. In several studies, echocardiography was found to be more reliable than the use of a pulmonary artery catheter for determining the cause of hypotension. TEE has a better diagnostic value than standard 2-dimensional Doppler TTE supplies sufficient information.

Direct cardiac visualization using hemodynamic TEE (hTEE; InaCor, Garden City, NY) also is possible through the use of a miniaturized disposable probe with a piezoelectric design that provides high-quality imaging of the heart (InaCor). In a pilot study, hTEE was used without major complications and provided an opportunity to determine the causes of hemodynamic instability and optimize cardiac performance after cardiac surgery. However, the hTEE probe only allows monoplane images, is expensive, and is intended for 1-time use for up to 72 hours.

Ultrasonic cardiac output monitoring (USCOM, Sydney, Australia) is another technique that applies ultrasound to suprasternal and intercostal sites, facilitating a cross-sectional view of the aortic and pulmonary outflow tracts. USCOM has been evaluated after coronary artery bypass procedures not involving valvular lesions. However, the technique has questionable accuracy compared with thermodilution.

Another possible use of ultrasound for hemodynamic monitoring is the esophageal Doppler technique, which continuously calculates blood flow in the descending aorta using the aortic blood velocity (Doppler probe), the aortic diameter, and the heart rate (HR). Esophageal Doppler devices estimate CO based on the hypothesis that blood flow in the descending thoracic aorta represents 70% of the systemic blood flow. This technique can be used to assess for changes in preload and fluid responsiveness in mechanically ventilated patients but has limited accuracy and is more suitable for the operating room than for the ICU because the probe can be displaced during movement and causes discomfort in an awake patient.

**Pulmonary Artery Catheter**

Thermomapping using a pulmonary artery catheter (PAC) remains the clinical standard for measuring CO, pulmonary artery pressure, and pulmonary artery occlusion pressure; it also serves as the reference method in most CO studies. The PAC provides intermittent measurements of CO after the injection of a saline bolus through the catheter’s proximal port into the right atrium. A modified PAC, equipped with a proximal thermal filament, provides semi-continuous CO measurements but is unable to track abrupt CO changes in real time.

As shown in a recent survey study, despite the appearance of less-invasive techniques, the majority of cardiac anesthesiologists still prefer using PACs. Subgroup analyses of the data revealed that geographic location, type of practice, and surgeon support played significant roles in the decision to use a PAC. However, the clinical use of the PAC gradually is declining because of its questionable ability to provide appropriate hemodynamic targets for goal-directed therapy and the inherent risks of mechanical, thrombotic, and infectious complications. As recently shown, PAC usage in low- and high-risk cardiac surgeries, including in patients with congestive heart failure, did not appear to be associated with reduced surgical mortality or morbidity—both of which appeared to be related to increases in the duration of ventilation and the length of ICU stay.

However, PACs should be considered for use in cardiogenic shock (CS) patients who do not respond to initial treatment. In addition, PACs can be of particular benefit in patients with RV failure to determine pulmonary artery pressures, right atrial pressures, stroke volumes, mixed venous oxygen saturation, and the effects of therapies.

**Transpulmonary Thermodilution**

The transpulmonary thermodilution technique is used in the PiCCO/PulsioFlex (Pulsion Medical Systems, Munich, Germany) and VolumeView/EV1000 (Edwards LifeSciences, Irvine, CA) systems and involves the injection of a cold saline bolus into the jugular or subclavian vein followed by measurement of the resulting temperature changes in a femoral artery using a thermistor-tipped arterial catheter. The mathematic analysis of the thermodilution curve allows for the calculation of CO, global end-diastolic volume (GEDV), global ejection fraction, cardiac function index, extravascular lung water (EVLW), and pulmonary vascular permeability index. These parameters provide additional information about the patient’s hemodynamic status and can serve as therapeutic targets.

The measurement of CO using transpulmonary thermodilution has been validated in cardiac surgery and demonstrated to be both accurate and precise, including in patients with CS, IABPs, therapeutic hypothermia, and mitral or tricuspid regurgitation. Moreover, the measured preload parameters seem to be more accurate in low CO patients than are PAC pressure parameters. Transpulmonary thermodilution also serves to calibrate the femoral artery pulse contour analysis, which provides real-time CO, stroke-volume variations (SVV), and pulse-pressure variations. Because of potential drift over time, frequent recalibration is mandatory in patients receiving vasopressors. The transpulmonary thermodilution technique is relatively expensive compared with the use of PACs and is contraindicated in patients with occlusive femoral artery disease. However, as shown in a multicenter study, the use of...
uncalibrated pulse contour
Lithium dilution
Transpulmonary thermodilution
Bioreactance

Estimated continuous cardiac output

Bioreactance

Table 2. Advantages and Disadvantages of Different Hemodynamic Monitoring Devices in Cardiac Surgery

<table>
<thead>
<tr>
<th>Method</th>
<th>Invasiveness</th>
<th>Reliability in Cardiac Surgery Patients</th>
<th>Ease of Use</th>
<th>Ability to Monitor CO in Real Time</th>
<th>Ability to Measure Variables Other Than CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound techniques†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++†</td>
<td>+++</td>
</tr>
<tr>
<td>Transpulmonary thermodilution</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++†</td>
<td>+++††</td>
</tr>
<tr>
<td>Lithium dilution</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++†</td>
<td>+++††</td>
</tr>
<tr>
<td>Uncalibrated pulse contour analysis</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++†</td>
<td>+</td>
</tr>
<tr>
<td>Applanation tonometry</td>
<td>0</td>
<td>+</td>
<td>+++†</td>
<td>++†</td>
<td>+</td>
</tr>
<tr>
<td>Estimated continuous cardiac output</td>
<td>0</td>
<td>+/−</td>
<td>+++</td>
<td>++†</td>
<td>+</td>
</tr>
<tr>
<td>Bioreactance†</td>
<td>0</td>
<td>+/−</td>
<td>++</td>
<td>+++†</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviation: CO, cardiac output.
†Including esophageal Doppler.
‡For pulmonary artery catheter with thermal filament.

Lithium Dilution

The lithium dilution (LiDCOplus monitor; LiDCO Group, London, UK) technique provides intermittent CO measurements after the injection of a small amount of lithium into a central vein and the subsequent detection of lithium concentration changes in a radial artery using a catheter with a lithium-selective sensor. This technique, validated against the PAC technique, also is used to calibrate a pulse-power algorithm of the arterial waveform that provides a continuous estimate of CO. However, in cardiac surgery patients, the pulse-power CO demonstrated a high percentage error compared with dilution methods. In addition, LiDCOplus requires a special indicator and cannot provide thermodilution-derived variables, such as GEDV or EVLW.

Uncalibrated Pulse-Contour Analysis

Real-time CO measurements from the arterial blood pressure waveform can be obtained using FloTrac/Vigileo (Edwards LifeSciences), ProAQT/PulsioFlex (Pulsion Medical Systems), and LiDCORapid (LiDCO Group) monitors. These systems are based on different algorithms that analyze the characteristics of waveforms from the radial or femoral arteries along with patient-specific anthropometric and demographic data. The main advantage of these systems is that they provide continuous CO, SVV, and pulse-pressure variation measurements without additional calibration. However, their accuracy and trending ability for reliably detecting CO changes during cardiac surgery are less than for the thermodilution methods. Moreover, these devices do not provide important variables, such as filling pressures or volumes (eg, GEDV, EVLW), representing a disadvantage compared with the PAC or transpulmonary thermodilution methods. Improvements in CO determination algorithms and software are needed for these systems.

The MostCare monitor (Vygon Health, Ecouen, France) uses a pressure-recording analytical method, based on perturbation theory, to provide real-time CO monitoring from analyses of arterial blood pressure waveforms. This device does not require external calibration and can be used with either a radial or femoral artery catheter. Although the pressure-recording analytical method has shown good agreement with thermodilution-determined CO, including in hemodynamically unstable patients receiving high doses of inotropes and/or IABPs, the accuracy of this method is reduced in patients with atrial fibrillation and in children.

Noninvasive CO Monitors

For obvious reasons, noninvasive techniques, including volume-clamp devices, applanation tonometry, estimated continuous CO, and bioreactance, provide the opportunity to avoid complications related to arterial catheter placement, handling, and removal. However, in parallel with decreasing the invasiveness, these new systems need to provide optimal accuracy and precision because these directly affect patient safety and quality of treatment. Because patients with low CO need an arterial catheter for routine management, this limits the use of all noninvasive hemodynamic monitoring methods. Furthermore, the results of hemodynamic monitoring techniques should be interpreted in conjunction with clinical, instrumental, and laboratory data assessments of the adequacy of tissue perfusion. Regardless, the advantages and disadvantages of different hemodynamic monitoring techniques are summarized in Table 2.

Goal-Directed Hemodynamic Therapy in Cardiac Surgery

Potential therapeutic interventions for the optimization of hemodynamics and oxygen transport are shown in Figure 2. In cardiac surgery, hypoperfusion, CO reduction, and decreased DO₂ may result from surgical manipulations on the heart, arrhythmias, impaired preload and vascular tone, myocardial depression, and valve dysfunction. Perioperative goal-directed therapy (GDT), guided by invasive hemodynamic monitoring and ultrasound methods, aims to counteract these pathophysiological changes and to prevent LCOS.

Although PAC use still is recommended for guiding therapy in high-risk cardiac surgeries (eg, CS, decreased ejection fraction, unstable patients receiving high doses of inotropes and/or IABPs), the accuracy of this method is reduced in patients with atrial fibrillation and in children.
fraction, IABP use, redo surgery, pulmonary hypertension), in low-risk coronary and vascular patients, the maintenance of a “supranormal” stroke volume index (SVI), CI, and DO2 using either the PAC or lithium dilution techniques did not improve clinical outcomes. Esophageal Doppler has been used to evaluate the concept of postoperative, nurse-directed circulatory status optimization to maintain an SVI >35 mL/m2 and to shorten the duration of post–cardiac surgery hospitalization. Using a combination of PAC-derived (CI and SVI) and metabolic (mixed venous oxygen saturation and lactate) targets, Pölönen et al have shown that GDT after cardiac surgery was accompanied by more frequent administration of fluids and inotropes and resulted in shorter hospitalizations and decreased morbidity.

Several other recent cardiac surgery studies have demonstrated the advantages of early hemodynamic optimization when GDT starts immediately after anesthesia induction. In one study, patients with a EuroSCORE >3 underwent on-pump CABG; the GDT group was managed with pulse-contour-based technology (FloTrac, Edwards Lifesciences) and central venous oximetry to maintain target CI, SVI, systemic vascular resistance, DO2, ScvO2, and SVV values. Compared with the control group, the GDT group received more fluids and more adjustments to their inotropic agents. Importantly, this group of patients demonstrated shorter periods of mechanical ventilation, shorter inotrope therapy duration, and reduced ICU and hospital stays.

In another study, Goepfert et al developed an algorithm for intraoperative and postoperative hemodynamic management in on-pump CABG, based on the measurements of mean arterial pressure (MAP), HR, CI, GEDV, and EVLW using the PiCCO technique. This therapy decreased the need for vasopressors and shortened the duration of mechanical ventilation and ICU stay. Hemodynamic optimization also was studied in off-pump CABG surgeries that were guided using either conventional (MAP, HR, and central venous pressure) or advanced monitoring. In the latter group, in addition to maintaining normal MAP and HR values, therapy was aimed at maintaining an intrathoracic blood volume index of 850 to 1,000 mL/m2, a continuous ScvO2 >60%, and a CI >2 L/min/m2. The advanced monitoring algorithm decreased the requirements for vasopressors, whereas colloids and dobutamine were given more frequently. These results were accompanied by increments in ScvO2, CI, and DO2. The therapy-guided using advanced monitoring decreased the time to achieve a status of “fit for ICU discharge” and shortened the postoperative hospital stay. The results of these studies were summarized and analyzed in 2 recent meta-analyses and confirmed the ability of GDT to reduce the number of postoperative cardiac surgery complications.

The outcome benefit of hemodynamic GDT might be even more evident in high-risk patients when it aims to both prevent and treat low CO. This has been confirmed in several recent studies. In a randomized study by Goepfert et al, patients undergoing CABG and/or aortic valve replacement who received early GDT, including maintenance of a CI >2 L/min/m2, SVV <10%, and optimized GEDV, had fewer complications and decreased lengths of postsurgical ICU stays. In complex elective valve surgery, GDT based on transpulmonary thermodilution and oxygen transport parameters led to increased volumes of fluid therapy, improved hemodynamics and DO2, and required shorter periods of respiratory support compared with patients treated using a PAC-guided algorithm. Summarizing the results of other authors and the authors of this study, the GDT strategy may include different therapeutic interventions, such as fluids, catecholamines,
levosimendan, diuretics, vasodilators, and other agents, and is useful for both prophylaxis and treatment of LCOS throughout the perioperative period. The algorithm of GDT in cardiac surgery are shown in Figure 3.

The results of a recent meta-analysis have shown that GDT using fluids, inotropes, and blood transfusions reduced the LCOS rate and the number of 30-day major complications, especially in high-risk cardiac surgery. Thus, goal-directed algorithms, based on adequate monitoring, facilitate early detection of low CO and hypoperfusion, and allow for the early correction of pathophysiologic changes, influencing the strategy for perioperative hemodynamic therapy that can improve the clinical outcomes.

**LCOS PREVENTION**

LCOS represents a major cardiac surgery challenge because it is associated with increased morbidity and mortality. The efforts of the surgical team aim to reduce the LCOS burden, especially in high-risk patients. Hence, the early use of numerous drugs and techniques is intended to reduce the incidence and severity of this complication.

**Cardioplegia Types**

Since its introduction into clinical practice, cardioplegia has become a gold standard in the management of patients undergoing CPB during cardiac surgery. To date, the majority of studies have compared the effects of cold crystalloid cardioplegia and cold blood cardioplegia on morbidity and mortality. A recent meta-analysis by Zeng et al examined 2,866 patients from 12 randomized controlled studies to compare the effects of these cardioplegia techniques. Although cold blood cardioplegia was observed to reduce the incidence of perioperative myocardial infarction compared with cold crystalloid cardioplegia, no differences in the overall incidences of spontaneous sinus rhythm, 30-day mortality, atrial fibrillation, or stroke were observed.

The data regarding the clinical efficacy and safety of warm versus cold blood cardioplegia are controversial. Mallidi et al, in a large retrospective study of 6,064 patients undergoing isolated CABG, demonstrated that warm or tepid blood cardioplegia may be associated with better early and late event-free survivals than cold cardioplegia. Conversely, the earliest study by Martin et al demonstrated that warm blood cardioplegia was associated with increased rates of neurologic events (warm, 4.5%; cold, 1.4%; p < 0.005) and perioperative stroke (warm, 3.1%; cold, 1.0%; p < 0.02) compared with crystalloid cardioplegia. However, the rate of postoperative mortality, Q-wave infarction, and IABP did not differ between the 2 groups.

Standard diluted blood cardioplegia can be modified to undiluted blood cardioplegia (microplegia) to retain many of the advantages, without the potential disadvantages, of hemodilution and leads to reduced rates of postoperative LCOS. The beneficial effects of microplegia might be explained by the reduced myocardial edema associated with the smaller volume of cardioplegia required.

Additional high-quality evidence is required to recommend specific types of cardioplegia for specific patient populations.
Volatile Anesthetics

Volatile halogenated anesthetics are used widely worldwide for anesthetic management of cardiac procedures. According to the CABG guidelines from the American College of Cardiology Foundation and the American Heart Association, volatile anesthesia can be useful in reducing the risk of perioperative myocardial ischemia and infarction (class of recommendations: IIa; Level of Evidence: A).92,93 A meta-analysis of 22 studies involving 1,922 patients showed that a halogenated anesthetic regimen was associated with improved outcomes after cardiac surgery.93 Specifically, volatile anesthetics were associated with significant reductions in the incidence of myocardial infarctions and mortality. Moreover, the need for inotropes support also was reduced significantly in the volatile anesthetic group.

Intra-aortic Balloon Pump

There still is debate regarding whether prophylactic IABP use can improve cardiac surgery outcomes. One single-center, prospective, randomized controlled trial in patients with poor (<35%) LVEF and no hemodynamic instability assessed the influence of preincision IABP use on clinical outcomes.94 There were no differences in the major morbidity rate (40% in the IABP group and 31% in the control group; odds ratio, 1.49 [95% confidence interval, 0.68-3.33]) or in the observed preoperative and postoperative Cls. Fewer patients in the IABP group (24%) than in the control group (44%) required dopamine infusion (p = 0.043).

Preoperative IABP use also appeared to shift high-risk patients undergoing CABG to a lower-risk category. Furthermore, the patients in 1 study demonstrated comparable perioperative troponin leakage and had short- and long-term outcomes similar to low-risk patients not receiving IABPs.95 Postponing IABP use also may be deleterious to patients with drug-refractory heart failure.96 A recent meta-analysis, performed by Pilarczyk et al, demonstrated that preoperative IABP use was associated with significant reductions in hospital mortality, LCOS, and ICU stay in high-risk patients undergoing on-pump cardiac surgery.97 Because of the study’s small sample size, additional adequately powered, prospective, randomized controlled trials are needed to show a clear benefit of prophylactic IABP use in high-risk patients. Thus, defining the patient population that may benefit from prophylactic IABP use merits further investigation.

Triiodothyronine

In the cardiovascular system, triiodothyronine is responsible for regulating CO and blood pressure.98 Cardiac surgery, with or without CPB, induces a marked and persistent depression in circulating thyroid hormone levels during the postoperative period in both adults and children.99,100 Furthermore, a low baseline triiodothyronine level is a strong predictor of LCOS and death in CABG patients.101 As a result, numerous trials have been conducted to assess the influence of perioperative triiodothyronine supplementation on cardiac surgery outcomes, with conflicting results. In a double-blind, randomized, placebo-controlled study of 170 patients undergoing CABG surgery, Mullis-Jansson et al compared the effects of prophylactic intravenous triiodothyronine, administered after removal of the aortic cross-clamp, versus placebo on patient hemodynamic profiles and inotrope requirements.102 Patients who received triiodothyronine had higher CI and lower inotrope requirements after surgery. Moreover, 7 patients in the placebo group required postoperative mechanical assistance compared with none in the triiodothyronine group (p = 0.01). On the other hand, 2 studies by Choi et al were conducted in patients who underwent either off-pump CABG or valvular cardiac surgery; a clear benefit of triiodothyronine supplementation was not reported.103,104 Thus, future trials are needed before the routine use of triiodothyronine can be recommended in cardiac patients undergoing various types of surgery.

TREATMENT

Treatment of LCOS is complex and is intended to increase tissue DO₂ and prevent worsening organ dysfunction and failure by providing adequate hemodynamic support4 (Fig 4). If identified, the cause (eg, graft dysfunction, valvular incompetence, pericardial tamponade, residual defects) must be corrected rapidly. The first line of LCOS therapy, to be initiated as soon as the volume status is optimized, is the use of inotropes and vasodilators to improve contractility, preload, and afterload. Nevertheless, inotropic agents, which are used primarily in patients with LCOS, also can improve CO, but they achieve this goal at the expense of increased myocardial consumption and an increased mortality risk.105 Maintenance of acid-base balance and normothermia, correction of electrolyte abnormalities, and ventilation management ameliorate the results of LCOS treatment and improve responsiveness to catecholamines. The properties of commonly used inotropes and vasopressors are summarized in Table 3.

Catecholamines

Dopamine

Dopamine demonstrates dose-dependent pharmacodynamics. Inappropriate dosing of dopamine is relatively common due to the significant interindividual variability of dopamine-receptor sensitivity, metabolism, and distribution.106,107 Sinus tachycardia and arrhythmia are the most common side effects of dopamine treatment. These chronotropic effects may be deleterious for patients with ischemic heart disease and may aggravate injured and hibernating myocardium, despite causing an initial CO improvement.106,108 Another unwanted effect of dopamine is the inhibition of the peripheral chemoreceptors of carotid bodies.109 Peripheral chemoreceptors are essential for abrupt ventilatory and arterial pressure responses to hypoxia, hypercapnia, and acid-base disturbances.110 Dopamine has been shown to depress ventilation, reduce oxygen saturation, prolong apnea, and provoke ventilation/perfusion mismatching.111,112 Thus, despite a theoretical background of favorable low-dose dopamine effects on renal function (presynaptic type 1 and postsynaptic type 2 dopaminergic-receptor agonism), clear evidence exists against its routine use for this purpose.113,114 Furthermore, dopamine worsened renal injury in cardiac patients, despite an increase in blood flow.115
Dobutamine

The principal action of dobutamine is on $\beta_1$-adrenergic receptors, with lesser stimulation of $\beta_2$- and $\alpha$-adrenergic receptors. This drug predominantly enhances ventricular contraction and slightly affects vascular tone. It also increases contractility, stroke volume, and CO. Dobutamine also decreases pulmonary and systemic vascular resistance without significantly increasing HR or the risk of other adverse
drug effects.

**Fig 4.** LCOS treatment algorithm based on measures of preload (PAOP) and/or heart volumes (GEDVI). CI, cardiac index; venoarterial ECMO, extracorporeal membrane oxygenation; GEDVI, global end-diastolic volume index; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; VAD, ventricular assist device.

### Dobutamine

- LCOS treatment
- Dose: 1-20 μg/kg/min
- Receptors and Effects: $\beta$-adrenergic, ↑inotropy
- Side Effects: Arrhythmia (less than dopamine), Worsens renal injury in states of LCOS

### Dopamine

- LCOS treatment
- Dose: 0.5-2 μg/kg/min
- Receptors and Effects: DA, vasodilation
- Dose: 2-5 μg/kg/min
- Receptors and Effects: $\beta$-adrenergic, ↑inotropy
- Dose: 5-20 μg/kg/min
- Receptors and Effects: $\alpha$- and $\beta$-adrenergic, vasoconstriction, ↑inotropy

### Epinephrine

- LCOS treatment, anaphylaxis
- Dose: 0.01-0.03 μg/kg/min
- Receptors and Effects: $\beta$-adrenergic, ↑inotropy
- Dose: 0.03-0.1 μg/kg/min
- Receptors and Effects: $\alpha$- and $\beta$-adrenergic, vasoconstriction, ↑inotropy

### Norepinephrine

- Decreased SVR, vasoplegic syndrome, septic shock
- Dose: 0.01-0.1 μg/kg/min
- Receptors and Effects: $\alpha$- and $\beta$-adrenergic, vasoconstriction, ↑inotropy (less pronounced)

### Vasopressin

- Decreased SVR, vasoplegic syndrome
- Dose: 0.01-0.1 IU/min
- Receptors and Effects: V1 stimulation, vasoconstriction

### Milrinone

- LCOS treatment
- Dose: 0.5-1 μg/kg/min
- Receptors and Effects: Phosphodiesterase inhibitor, vasodilation

### Levosimendan

- LCOS treatment and prophylaxis
- Dose: 10 μg/kg loading dose, 0.1 μg/kg/min infusion
- Receptors and Effects: Increasing myofilament sensitivity to calcium

**Table 3. Drugs Used for the Treatment of LCOS**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indications</th>
<th>Doses</th>
<th>Receptors and Effects</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>LCOS treatment</td>
<td>1-20 μg/kg/min</td>
<td>$\beta$-adrenergic, ↑inotropy</td>
<td>Arrhythmia (less than dopamine)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>LCOS treatment</td>
<td>0.5-2 μg/kg/min</td>
<td>DA, vasodilation</td>
<td>Worsens renal injury in states of LCOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-5 μg/kg/min</td>
<td>$\beta$-adrenergic, ↑inotropy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-20 μg/kg/min</td>
<td>$\alpha$- and $\beta$-adrenergic, vasoconstriction, ↑inotropy</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>LCOS treatment, anaphylaxis</td>
<td>0.01-0.03 μg/kg/min</td>
<td>$\beta$-adrenergic, ↑inotropy</td>
<td>Lactic acidosis, hyperglycemia, mesenteric ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.03-0.1 μg/kg/min</td>
<td>$\alpha$- and $\beta$-adrenergic, vasoconstriction, ↑inotropy</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Decreased SVR, vasoplegic syndrome, septic shock</td>
<td>0.01-0.1 μg/kg/min</td>
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<td>Arrhythmia, tachycardia</td>
</tr>
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<td>Vasopressin</td>
<td>Decreased SVR, vasoplegic syndrome</td>
<td>0.01-0.1 IU/min</td>
<td>V1 stimulation, vasoconstriction</td>
<td>Myocardial ischemia, ventricular arrhythmia</td>
</tr>
<tr>
<td>Milrinone</td>
<td>LCOS treatment</td>
<td>0.5-1 μg/kg/min</td>
<td>Phosphodiesterase inhibitor, vasodilation</td>
<td>Thrombocytopenia, arrhythmia, tachycardia</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>LCOS treatment and prophylaxis</td>
<td>10 μg/kg loading dose, 0.1 μg/kg/min infusion</td>
<td>Increasing myofilament sensitivity to calcium</td>
<td>Arrhythmia, hypotension</td>
</tr>
</tbody>
</table>

**Abbreviations:** DA, dopaminergic receptor; LCOS, low-cardiac-output syndrome; SVR, systemic vascular resistance; V1, vasopressin-1 receptor.
effects when administered to patients with proper hemodynamic status (avoid hypovolemia) and at a correct initial rate of infusion (avoid boluses).\textsuperscript{118,119} Properly administered dobutamine improves myocardial metabolism, despite increasing myocardial VO$_2$. This favorable effect is associated with increased DO$_2$ and coronary blood flow due to an improved coronary perfusion pressure, perfusion time, and direct vasodilation of the coronary arteries.\textsuperscript{120,121} These properties make dobutamine attractive for use in patients with LCOS associated with postoperative myocardial stunning or hibernation.\textsuperscript{122} In addition, dobutamine greatly enhances contractility, increases CO, and induces vasodilation compared with dopamine. However, conventional practice allows the use of dobutamine in combination with dopamine or another catecholamine with more pronounced vasopressor effects.\textsuperscript{123}

**Norepinephrine**

Norepinephrine is predominantly an $\alpha$-adrenergic agonist with modest effects on $\beta$-adrenergic receptors. It has a wide therapeutic range, which presumably is a result of the down-regulation of $\alpha$-adrenergic receptors during critical illness. Thus, successful treatment with doses ranging from 0.01-to-5 $\mu$g/kg/min have been reported for patients experiencing sepsis.\textsuperscript{124} As for any catecholamine, volume repletion is the principal condition for safe administration. Norepinephrine treatment of hypotensive, normovolemic patients experiencing shock resulted in better hemodynamic and oxygenation profiles than that achieved with dopamine\textsuperscript{125} and increased both urine output and creatinine clearance.\textsuperscript{126,127} For chronically volume-depleted individuals, such as those undergoing prolonged diuretic treatment for congestive heart failure, norepinephrine should be administered with caution due to the risk of renal dysfunction and nonocclusive mesenteric ischemia.

**Epinephrine**

Epinephrine is a nonselective adrenergic agonist with high affinity for $\beta_1$-, $\beta_2$-, and $\alpha$-adrenoceptors. Due to its unpredictable inotropic and vasoconstrictive properties, detrimental effects on splanchnic blood flow,\textsuperscript{128} and ability to induce lactic acidosis,\textsuperscript{129} epinephrine is not a first-line drug for LCOS treatment, by some clinicians, but is used occasionally in the most severe cases of LCOS that are resistant to conventional inotropic therapy. Epinephrine, a potent vasoconstrictor ($\alpha_1$-agonism) agent with remarkable inotropic and chronotropic effects ($\beta_1$-agonism) and the capacity to decrease the release of inflammatory mediators from mast cells and basophils ($\beta_2$-agonism), is the drug of choice after cardiac arrest and anaphylaxis.\textsuperscript{130,131}

**Phenylephrine**

As an $\alpha_1$-adrenergic agonist, phenylephrine increases systemic vascular resistance, without affecting CO, with doses of 0.5-to-10 $\mu$g/kg/min. Compared with norepinephrine, prolonged infusion of phenylephrine was associated with decreased DO$_2$ and splanchnic blood flow.\textsuperscript{132} This drug commonly is used for the effective management of transient arterial hypotension induced by general anesthesia but cannot be recommended for LCOS management.

Vasopressin and methylene blue are other drugs that can be used for restoring MAP in conditions associated with low systemic vascular resistance after CPB (vasoplegic syndrome).\textsuperscript{133,134}

**Phosphodiesterase Inhibitors**

Milrinone, amrinone, and enoximone increase intracellular cyclic adenosine monophosphate by inhibiting phosphodiesterase type III (PDE III) and producing inotropic, systemic, and pulmonary vasodilatory effects.\textsuperscript{135} Milrinone does not increase myocardial VO$_2$ or HR, unlike catecholamines.\textsuperscript{136} Despite their favorable hemodynamic effects, there is abundant evidence that PDE III inhibitors worsen long-term clinical outcomes in patients with acute and chronic heart failure.\textsuperscript{137-140} Concerns about the trend toward increased mortality associated with milrinone use in cardiac surgery patients were published in 2 recent meta-analyses.\textsuperscript{141,142} Such results may be explained, at least in part, by the increased incidence of new-onset postoperative atrial fibrillation after cardiac surgery, associated with intravenous milrinone.\textsuperscript{143} Milrinone most commonly is used as a second-line agent when hemodynamic improvement cannot be achieved with dobutamine and is especially effective in patients with RV systolic dysfunction due to its vasodilatory effects on pulmonary vessels, leading to a decreased RV afterload. Administration of inhaled (aerosolized) milrinone also effectively decreased pulmonary hypertension and avoided adverse systemic hemodynamic effects.\textsuperscript{144,145} Gaseous nitric oxide and aerosolized prostacyclin (epoprostenol) are other pulmonary vasodilators used in the treatment of pulmonary hypertension.\textsuperscript{146,147}

**Levosimendan**

Levosimendan is a relatively new drug that was approved initially for the management of decompensated heart failure.\textsuperscript{148} Its mechanism of action is based on increasing myofilament sensitivity to calcium (a calcium sensitizer), which leads to increased myocardial contractility without a significant increase in VO$_2$.\textsuperscript{149,150} The decreased afterload during levosimendan infusion also has been associated with higher CO.\textsuperscript{151} Some investigators have reported that the preconditioning effects of levosimendan also were associated with activation of adenosine triphosphate-dependent potassium channels.\textsuperscript{152,153}

In the largest meta-analysis of levosimendan use, including 5,480 patients from 45 randomized clinical trials, the drug reduced mortality among adult patients in cardiac surgery and cardiology settings.\textsuperscript{154} Among critically ill patients, levosimendan also was shown to reduce the incidences of acute renal failure and mortality.\textsuperscript{155,156} Current evidence indicates that levosimendan can be used effectively to treat LCOS after cardiac surgery. In the early pilot study of Labriola et al, 11 patients who developed LCOS after cardiac surgery were given levosimendan at a loading dose of 12 $\mu$g/kg over 10 minutes, followed by a continuous infusion of 0.1 $\mu$g/kg/min for 12 hours. Of 11 patients, 8 (73%) showed evidence of combined hemodynamic improvement (>30% increase in CI, and pulmonary artery occlusion pressure corrected to <18 mmHg) within 3 hours after the start of levosimendan infusion.\textsuperscript{157}
The study by Levin et al included 137 patients with LCOS after surgery who were randomly assigned to receive either levosimendan (loading dose, 10 μg/kg, followed by 0.1 μg/kg/min for 24 hours) or dobutamine (starting dose, 5 μg/kg/min) infusion. 158 Although both agents improved hemodynamic parameters, the effect of levosimendan was greater and occurred earlier than that of dobutamine. In addition, levosimendan use resulted in significantly lower postoperative mortality, less need for IABP, and reduced length of ICU stay. Taking into account the vasodilatory properties of the drug, the combination of levosimendan with norepinephrine or vasopressin might be required to maintain MAP. 159

Considering the lack of large well-designed trials of levosimendan treatment in patients with postoperative LCOS, a large, multicenter, randomized, double-blind, placebo-controlled trial (CHEETAH trial) was designed to test the hypothesis whether levosimendan could improve survival in patients with postoperative LCOS. 160 This trial is expected to enroll 1,000 patients and will provide important insights into the management of critically ill patients undergoing cardiac surgery.

Numerous studies have addressed the efficacy and safety of prophylactic levosimendan use in cardiac patients, including those with severe LV dysfunction. Starting levosimendan infusion preoperatively, or just before initiation of CPB, significantly reduced intubation time, length of ICU stay, incidence of LCOS, and need for IABPs. 162-165 Moreover, its use may serve as an alternative to prophylactic IABP use in high-risk cardiac patients. 159,164

Glucose-Insulin-Potassium Infusion

According to the available data, glucose-insulin-potassium (GIK) infusions can be used as adjunctive therapy to treat postsurgical LCOS without serious adverse events. Szabó et al reported the results from a retrospective, observational study involving 89 patients treated with high-dose GIK after cardiac surgery. 165 In the majority of patients (69.7%), GIK was used to treat postoperative cardiac failure. The authors concluded that the high-dose GIK regimen allowed for substantial amounts of glucose to be infused into both diabetic and critically ill patients while maintaining acceptable blood glucose control. Furthermore, a case series examined metabolic support using glutamate and high-dose GIK in 16 patients for whom IABP placement was considered after unsuccessful weaning from CPB. 166 Rapid improvement in hemodynamic performance was seen within the first hour, with almost full recovery within 6 hours in the surviving patients.

A meta-analysis including 33 randomized controlled trials and a total of 2,113 patients showed that the use of GIK in cardiac surgery was associated with a significant reduction in the number of myocardial infarctions, reduced requirements for inotropic support, and significant hemodynamic improvements. 167 Concerning the risk of hyperkalemia, GIK administration in cardiac patients led to mild hyperkalemia in 4.2% to 7.9% of cases, usually after the cessation of insulin infusion, and was not associated with adverse outcomes. 165,168 In addition, differences in renal failure rates were not observed.

These results suggested that metabolic support of the failing heart seemed to be a promising strategy in cardiac surgery and that this technique, with careful monitoring, can be used safely in clinical practice. However, future trials are needed to further examine this methodology.

Short-Term Mechanical Circulatory Support

Intra-aortic Balloon Pump

The timing of IABP placement in patients who develop LCOS after cardiac surgery plays a pivotal role in survival. 166 Compared with postoperative IABP insertion, intraoperative insertion resulted in a mortality reduction from 64.4% to 41.5% (p < 0.001) in a case series involving 1,051 patients. Aside from having beneficial effects on coronary perfusion, IABP therapy also improved global and regional splanchnic oxygenation in patients with LCOS after cardiac surgery. 169 The mortality rate also was higher for patients undergoing postoperative IABP placement than for patients undergoing preoperative IABP insertions. This might have been because the main preoperative indication for IABP placement included unstable angina with multiple-vessel disease, whereas postoperatively IABPs were inserted to treat LCOS. 170,171 LCOS caused predominantly by RV failure (including in heart transplant patients) may be an additional indication for IABP use. 172,173 However, the mechanisms by which IABPs mediate beneficial effects in nonischemic RV failure remain unclear. Although some experimental models of acute pressure-overload RV failure have shown the beneficial hemodynamic effects of IABP use, other studies have not confirmed these results. 174,175 Despite the widespread use of IABPs, cardiac patients still are at risk of IABP-associated complications. 176 According to data obtained from the Benchmark Registry, the frequency of IABP-associated complications was small, varying from 0.9% to 2.7%. 177

The numerous randomized controlled studies conducted in patients with and without CS undergoing percutaneous coronary intervention have shown inconsistent results. 178-180 Thiele et al reported the results of the largest prospective, randomized, multicenter trial examining the effectiveness of IABPs in patients with myocardial infarction and CS 182: 5% underwent CABG. The results showed that the use of intra-aortic balloon counterpulsation did not significantly reduce 30-day or 12-month mortality in patients with CS for whom an early revascularization strategy was planned. 181 In light of published data, the use of IABPs for this indication was not recommended routinely (class of recommendations: III; Level of Evidence: A), but remains an adjunct treatment for patients with mechanical complications as a bridge to surgery, according to the 2014 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularization. 182

Venoarterial Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is one of the earliest and most widely used mechanical circulatory support systems for the nonpharmacologic treatment of CS. 183 The cardiac indications for ECMO include failure to wean from CPB, life-threatening heart failure secondary to
myocardial infarction or fulminant myocarditis, and the need for an adjuvant to conventional cardiopulmonary resuscitation.\textsuperscript{184} To date, randomized controlled trials investigating ECMO in the context of cardiac failure have not been published.\textsuperscript{185} Rastan et al presented their experience with 517 adult patients treated with ECMO for refractory postcardiotomy CS (PCCS).\textsuperscript{186} Successful weaning from the system was possible for 63.3\% of the patients; nevertheless, hospital survival was limited to 25\%, which was comparable with the results from a smaller patient series examining ECMO treatment of PCCS.\textsuperscript{187-189} The results of a recent meta-analysis (1,195 patients from 22 observational studies) showed that venoarterial ECMO for the treatment of CS and cardiac arrest can improve short-term survival.\textsuperscript{190} According to the Extracorporeal Life Organization Registry Report, the survival rate for patients with ECMO-treated CS remains low (42\% survive to discharge).\textsuperscript{191} As for any invasive technique, ECMO carries a significant risk of neurologic and infectious complications; bleeding also must be considered.\textsuperscript{186,192-194} Thus, ECMO is an acceptable option for patients with PCCS who otherwise would die and is justified by good long-term outcomes of hospital survivors.\textsuperscript{186,195}

**Ventricular Assist Devices**

Several ventricular assist devices that provide short-term hemodynamic support are available, including the 3 described below.\textsuperscript{200} Each of these devices is capable of reducing LV load and improving tissue perfusion.

**Impella Assist Device**

The Impella 5.0 device (Abiomed Europe GmbH, Aachen, Germany) is a catheter-based axial flow device that provides continuous blood flow of up to 5 L/min and is used to support patients with CS due to isolated LV failure for up to 10 days.\textsuperscript{196} The RECOVER I study was a prospective, single-arm, clinical trial designed under US Food and Drug Administration guidance to investigate the safety and feasibility of the Impella 5.0/LD in patients experiencing PCCS or LCOS after cardiac surgery.\textsuperscript{197} Sixteen patients were enrolled in the study, and the results demonstrated that the device enabled immediate restoration of hemodynamics, with a gradual reduction in the need for inotropic support. The primary efficacy endpoint, recovery of native heart function, was achieved in 93\% of the patients discharged. The 30-day, 3-month, and 1-year survival rates were 94\%, 81\%, and 75\%, respectively.

Another group reported their experience with the Impella 5.0 device in 40 patients with refractory CS of various etiologies,\textsuperscript{198} including acute myocardial infarction (17 patients, 43\%); dilated cardiomyopathy (12 patients, 30\%); and postcardiotomy cardiac failure (7 patients, 18\%). In 15 patients, the Impella 5.0 was used in conjunction with ECMO to unload the LV. In this series, rapid decreases in inotrope scores were observed within 6 hours after starting Impella treatment, and the inotropes were withdrawn within 24 hours for most patients. The 28-day mortality rate was 35\%, which was better than predicted.

As with any mechanical circulatory support system, the Impella 5.0 is an invasive technique that requires a surgical approach to the major arteries; therefore, there are several attendant risks. The risk of complications varied between 48\% and 75\%, with the most commonly reported complications including infection, limb ischemia, vascular injury, and bleeding necessitating blood transfusions.\textsuperscript{199,200} Based on current evidence, therefore, the use of the Impella 5.0 device appeared to be safe and feasible in patients with PCCS. The device can be inserted rapidly, enables early support, and yields favorable outcomes compared with other more invasive techniques.

The Impella RP (Abiomed, Danvers, MA) is a catheter-mounted axial flow pump used to manage RV failure. The RECOVER RIGHT study evaluated the safety and efficacy of the Impella RP in a prospective, multicenter trial. The study population included 2 cohorts: 18 patients with RV failure (RVF) after left ventricular assist device (LVAD) implantation and 12 patients with RVF after cardiomyopathy or myocardial infarction. Hemodynamics improved immediately after initiation of Impella RP support, with an increase in CI from 1.8 ± 0.2 to 3.3 ± 0.23 L/min/m\(^2\) (p < 0.001) and a decrease in central venous pressure from 19.2 ± 4 to 12.6 ± 1 mmHg (p < 0.001). The overall survival at 30 days was 73.3\%, and all discharged patients remained alive at 180 days.\textsuperscript{202} There were no thromboembolic complications or pulmonary emboli and minimal cardiac structure or vascular perforation or damage. Bleeding was the most prevalent adverse event that occurred in this study.

**CentriMag**

CentriMag (Thoratec, Pleasanton, CA) is an extracorporeal system with a surgically implanted component that functions as an LV assist system. The system involves a magnetically levitated centrifugal flow pump that can provide flow of up to 10 L/min and has a very low level of hemolysis and thrombogenicity.\textsuperscript{183} Evidence from 53 observational studies suggested that the CentriMag is a versatile device for providing temporary mechanical circulatory support for all types of acute heart failure (RV, LV, and biventricular) or as a part of an ECMO circuit.\textsuperscript{202}

The CentriMag system has been shown to provide effective temporary mechanical circulatory support for acute RV failure in a variety of clinical settings, with higher rates of RV recovery and survival. In a retrospective study of 29 patients, Bhama et al demonstrated that early mortality (<30 days or before discharge) occurred in 14 patients (48\%) and late death occurred in 2 of 15 patients (13\%) who survived to discharge.\textsuperscript{203} There were no device failures. The advantages of the CentriMag system over other devices are related primarily to its magnetically levitated rotor and lack of bearings or seals.

**TandemHeart**

The TandemHeart device (TandemLife, Pittsburg, PA) is a low-speed, continuous-flow, centrifugal pump that is inserted via a transseptal puncture of the femoral vein. Blood is channeled into the pump, and a 15- to 17-F femoral artery cannula returns the blood to the systemic arterial circulation.\textsuperscript{204} The efficacy of the TandemHeart device depends on adequate
RV function. Therefore, the presence of RV failure is a relative contraindication for the classic use of this device, which was designed for LV support.184 In a randomized trial, the effects of the TandemHeart device were compared with IABP use in 42 patients with CS.205 Compared with IABPs, the TandemHeart achieved significantly greater CI and mean arterial blood pressure increases. Overall, the 30-day survivals and severe adverse events were not significantly different between the 2 groups.

The TandemHeart percutaneous RV support device was introduced to provide mechanical RV support in the setting of RVF.206 This device provides centrifugal flow from the right atrium to the main pulmonary artery, thereby bypassing a poorly functioning RV. Preliminary data suggested that the use of a percutaneous RV support device in medically refractory RVF was feasible and associated with improved hemodynamics.207 TandemHeart is not approved by the Food and Drug Administration for use as an RV assist device.

These brief descriptions provide an indication of the recent technical advances in the field of mechanical circulatory support that have led to significant improvements in the management of patients with CS after cardiac surgery. In patients with isolated LV failure, LV assist devices are preferable to IABPs, which may provide adequate support only for patients with moderate CS. In cases of biventricular failure and lung dysfunction presenting after cardiac surgery with CPB, preference should be given to the use of ventricular assistance combined with ECMO.

CONCLUSION

LCOS is a leading cause of morbidity and mortality after cardiac surgery, especially in high-risk patients. Inadequate myocardial protection, coupled with the patient’s status and numerous perioperative factors, including prolonged aortic cross-clamp time and myocardial ischemia, might contribute to the development of this complication. Treatment of LCOS is necessarily complex and is aimed at increasing tissue DO₂ by providing adequate hemodynamic support to prevent worsening organ dysfunction and failure. Goal-directed algorithms based on adequate monitoring facilitate early detection and appropriate treatment of LCOS, leading to improved clinical outcomes. The choice of proper inotropic agents to treat LCOS should be based on their mechanism of action and clinical circumstances. Future trials evaluating the clinical efficacy of interventions to prevent and to treat LCOS are required.

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