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REVIEW

Low cardiac output syndrome after adult cardiac surgery

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Abstract

Low cardiac output syndrome (LCOS) occurs frequently after cardiac surgery, and is associated with complications. Causes of LCOS include ventricular dysfunction, hemorrhage, cardiac tamponade, or arrhythmias. Management remains supportive, as etiology is identified in a minority of cases. Management includes inotropes and vasopressors, and optimization of intravascular volume and heart rhythm. A temporary epicardial pacemaker for bradyarrhythmias may be helpful. In profound cardiogenic shock, mechanical circulatory support (MCS) is required. However, ideal inotrope/vasopressors combinations, hemodynamic targets and timing of MCS initiation are not described in the literature. In this narrative review, we summarize current definition, occurrence rate, and treatment of LCOS following adult cardiac surgery.

Keywords

Cardiac surgery; Hemodynamic management; Low cardiac output syndrome; Cardiogenic shock; Mechanical circulatory support; Catecholamines

1. Introduction

Every year, more than one million patients undergo cardiac surgery in United States and Europe [1].

Despite improvement in anesthetic and surgical techniques, cardiac surgery carries a high risk of morbidity and mortality, with an overall mortality for elective procedure of 2%–3% [2–4] and a complication rate of 30%–60% [5–12].

A common and potentially severe complication following cardiac surgery is low cardiac output syndrome (LCOS) [13, 14]. LCOS is hazardous due to interplay of tissue hypoperfusion, metabolic demands, and side effects of treatments. LCOS after cardiac surgery increases risk of end-organ failure, prolonged intensive care unit (ICU) and hospital length of stay, and death [13, 15–18].

Reviews of LCOS have been published [13]. However, in recent years, several studies significantly improved our understanding of LCOS epidemiology, physiology, and management. These include large, randomized controlled trials (RCTs) on inotropes, vasopressors and mechanical circulatory support (MCS) [19–24], RCTs on organ-protection strategies [3, 25, 26], multicenter epidemiologic studies and systematic reviews [18, 27, 28], reassessment of available perfusion markers [29–32], development of novel concepts of "protective" hemodynamic management and more conservative resuscitation targets [33–36], discovery of potential novel perfusion markers [37–40], and advances towards individualization of hemodynamic support [41, 42].

In this updated review, we will summarize current evidence on definition, incidence, outcome, and treatment of perioperative LCOS following adult cardiac surgery.

2. Definition

Unfortunately, the literature does not universally utilize one definition of LCOS after cardiac surgery [27]. This complication is described with various terms, such as perioperative acute myocardial dysfunction, perioperative cardiogenic shock, postcardiotomy shock, or acute perioperative heart failure [15]. Notably, a systematic review identified 262 different definitions of LCOS used in published studies [27].

There is overall agreement that LCOS is characterized by decreased cardiac output (CO), that ultimately leads to reduced oxygen delivery (DO_2) and subsequent tissue hypoxia and organ dysfunction [13]. Indeed, available definitions generally include a combination of clinical features, hemodynamic parameters, and need for hemodynamic support [27].

Clinical features of LCOS include signs of hypoperfusion (altered mental state, skin mottling, reduced urine output), associated with hemodynamic alterations (compensatory tachycardia and hypotension), biochemical signs of hypoperfusion (metabolic acidosis and increased serum lactates) and organ failure (respiratory failure, acute kidney, and liver injury). Evidence of systemic and pulmonary congestion may also be present. The most commonly reported hemodynamic features include reduced cardiac index (CI) ($<$2.2–2.5 L/min/m^2), need for inotropes/vasopressors to maintain adequate mean arterial pressure (MAP) and/or CO, need for MCS, and elevated blood lactate [27]. Of note, some authors agree that measurement of CI is not required to diagnose LCOS, and diagnosis could

be based on clinical criteria [17, 18]. Interestingly, the most recent and largest studies include the need for MCS or need for inotropic support to maintain adequate CI and/or MAP as key features [19, 21, 28, 43] (Table 1, Ref. [15, 18, 27, 28, 44–54]). However, to further complicate the picture, there is disagreement among authors in terms of dose and duration of inotropic support required to define true LCOS [43, 55, 56].

Finally, some authors distinguish between different degrees of LCOS severity, *e.g.*, from postoperative myocardial stunning (characterized by mild-to-moderate reduction in CI, minimal or no hypotension, and mild or no organ dysfunction) to overt cardiogenic shock (characterized by severe reduction in CI, hypotension, and multiple organ failure) [17].

As of today, the only professional society to provide a definition of postoperative LCOS is the Spanish Society for Intensive Care Medicine (Sociedad Española de Medicina Intensiva, Critica y Unidades Coronarias—SEMICYUC). The SEMICYUC applies the following definitions, and sub-classify LCOS into three different conditions [17, 18]:

1. Postoperative LCOS: Measured CI <2.2 L/min/m^2, without associated relative hypovolemia. It may be due to left and/or right ventricle failure and can be accompanied or not by pulmonary congestion. Blood pressure may be normal or low.

2. Clinical condition consistent with LCOS: Patients in which cardiac output (CO) is not monitored, and is not known, but in whom the clinical manifestations are consistent with low CO: oliguria (diuresis <0.5 mL/kg/h), central venous oxygen saturation $<60\%$ (with normal arterial saturation) and/or lactate >3 mmol/L, without relative hypovolemia. This group also include patients coming from the operating room with inotropic support and/or an intra-aortic balloon pump (IABP), and in which these measures must be maintained to secure adequate hemodynamic conditions.

3. Cardiogenic shock: Defined as CI <2.0 L/min/m^2, with systolic blood pressure (SBP) <90 mmHg, without relative hypovolemia, and with oliguria.

Notably, the definition used by SEMICYUC implies that LCOS is always characterized by left or right ventricular failure and excludes hypovolemia. Furthermore, it clearly separates LCOS from cardiogenic shock by introducing specific

TABLE 1. Definition of LCOS used in selected studies.

Author	Definition of LCOS
Algarni *et al.* [48]	Any of the following: • Need for IABP in OR or ICU • Need for dopamine, dobutamine, milrinone or epinephrine to maintain SBP >90 mmHg and CI >2.2 L/min/m^2 for $\geq$30 min in ICU after optimizing preload, afterload, electrolyte, and BG abnormalities. Patients who required a renal dose of dopamine (<4 µg/kg) or those who received vasoconstrictors to increase SVR in the presence of normal or high CI (≥ 2.5 L/min/m^2) were not considered to have LCOS.
Ding *et al.* [51]	Presence of both of the following: (1) Need for inotropic support with vasoactive drugs (dopamine ≥ 4 µg/kg/min for a minimum of 12 h and/or dobutamine and/or milrinone and/or epinephrine and/or noradrenaline) or MCS with a IABP to maintain SBP >90 mmHg after correction of all electrolytes and blood gas abnormalities while adjusting preload volume to its optimal values. (2) Signs of impairment of body perfusion (cold extremities, hypotension, oliguria or anuria, lowered level of consciousness, or a combination of these signs) after correction of all electrolytes and blood gas abnormalities while adjusting preload volume to its optimal values.
Duncan *et al.* [28]	Any of the following: • Need for MCS with IABP, LVAD, or ECMO during surgery or within 5 postoperative days. • Hemodynamic instability requiring continued pharmacologic support with ≥ 2 inotropic medications (epinephrine, milrinone, dobutamine, dopamine) on postoperative day 1.
Ellenberger *et al.* [52]	Need for inotropic support for more than 120 min (dobutamine >5 µg/kg/min, epinephrine >0.05 µg/kg/min, milrinone >0.3 µg/kg/min, and norepinephrine >0.04 µg/kg/min) in the presence of impaired ventricular function and a low MAP (<60 mmHg) despite adequate circulatory filling.
Kochar *et al.* [46]	Any of the following: • Use of MCS. • Two consecutive measurements of a CI <2.0 L/min/m^2. • At least one measurement of low CI with the use of $\geq$two inotropes more than 24 h after surgery. • Use of $\geq$two inotropes more than 24 h after surgery with the indicated reason for inotrope use being low CO.
Hong *et al.* [53]	One or more of the following criteria: • Cardiac index reduced to <2.2 L/min/m^2. • SBP <90 mmHg with signs of tissue hypoperfusion, including oliguria (urine output <1 mL/kg/h), and/or elevated lactate level >3.0 mmol/L. • Need for MCS or inotropic agents (dopamine or dobutamine ≥ 4 µg/kg/min for ≥ 12 h, and/or epinephrine ≥ 0.02 µg/kg/min, and/or milrinone ≥ 0.2 µg/kg/min, and/or levosimendan ≥ 0.05 µg/kg/min) to maintain hemodynamics after optimizing preload. Patients receiving vasopressors to increase SVR at normal CI were not considered to have LCOS.

TABLE 1. Continued.

Author	Definition of LCOS
Hong *et al.* [54]	One or more of the following criteria: • Cardiac index reduced to <2.2 L/min/m^2. • SBP <90 mmHg with signs of tissue hypoperfusion, including oliguria (urine output <1 mL/kg/h), and/or elevated lactate level >3.0 mmol/L. • Need for MCS or inotropic agents (dopamine or dobutamine ≥4 µg/kg/min for ≥12 h, and/or epinephrine ≥0.02 µg/kg/min, and/or milrinone ≥0.2 µg/kg/min, and/or levosimendan ≥0.05 µg/kg/min) to maintain hemodynamics after optimizing preload. Patients receiving vasopressors to increase SVR at normal CI were not considered to have LCOS.
Maganti *et al.* [49]	Any of the following: • Need for IABP in OR or ICU. • Need for dopamine, dobutamine, milrinone or epinephrine to maintain SBP >90 mmHg and CI >2.2 L/min/m^2 for ≥30 min in ICU after optimizing preload, afterload, electrolyte, and BG abnormalities. Patients who required a renal dose of dopamine (<4 µg/kg) or those who received vasoconstrictors to increase SVR in the presence of normal or high CI (≥2.5 L/min/m^2) were not considered to have LCOS.
Maganti *et al.* [50]	Any of the following: • Need for IABP in OR or ICU. • Need for dopamine, dobutamine, milrinone or epinephrine to maintain SBP >90 mmHg and CI >2.2 L/min/m^2 for ≥30 min in ICU after optimizing preload, afterload, electrolyte, and BG abnormalities. Patients who required a renal dose of dopamine (<4 µg/kg) or those who received vasoconstrictors to increase SVR in the presence of normal or high CI (≥2.5 L/min/m^2) were not considered to have LCOS.
Mendes *et al.* [47]	Need for inotropes and/or MCS for at least 24 h postoperatively during the first five days. Patients who only received norepinephrine were not considered to have LCOS.
Pérez Vela *et al.* [18]	• Postoperative LCOS: Measured CI <2.2 L/min/m^2, without associated relative hypovolemia. It may be due to left and/or right ventricle failure and can be accompanied or not by pulmonary congestion. Blood pressure may be normal or low. • Clinical condition consistent with LCOS: Patients in which CO is not monitored, and is not known, but in whom the clinical manifestations are consistent with low CO: oliguria (diuresis <0.5 mL/kg/h), central venous oxygen saturation <60% (with normal arterial saturation) and/or lactate >3 mmol/L, without relative hypovolemia. This group also include patients coming from the operating room with inotropic support and/or an IABP, and in which these measures must be maintained to secure adequate hemodynamic conditions. • Cardiogenic shock: Defined as CI <2.0 L/min/m^2, with SBP <90 mmHg, without relative hypovolemia, and with oliguria.
Rao *et al.* [44]	• Need for IABP in OR or ICU. • Need for dopamine, dobutamine, milrinone or epinephrine to maintain SBP >90 mmHg and CI >2.2 L/min/m^2 for ≥30 min in ICU after optimizing preload, afterload, electrolyte, and BG abnormalities. Patients who required a renal dose of dopamine (<4 µg/kg) or those who received vasoconstrictors to increase SVR in the presence of normal or high CI (≥2.5 L/min/m^2) were not considered to have LCOS.
Rudiger *et al.* [15]	• Cardiogenic shock: low CI (<2.2 L/min/m^2) with or without low BP after correction of preload, with evidence of tissue hypoperfusion or organ dysfunction. • Post-operative cardiac stunning: Transient and reversible impairment of contractility after cardiac surgery, resulting in low CI after correction of preload, with need for inotropic support in order to prevent tissue hypoperfusion and organ dysfunction.
Sá *et al.* [45]	Presence of both of the following: (1) Need for inotropic support with vasoactive drugs (dopamine 4 µg/kg/min at least for a minimum of 12 h and/or dobutamine) to maintain SBP >90 mmHg or need for MCS with an IABP to maintain SBP >90 mmHg. (2) Signs of impairment of body perfusion—cold extremities, hypotension, oliguria/anuria, lowered level of consciousness or a combination of these signs.
Schoonen *et al.* [27]	N/A

CI: cardiac index; CO: cardiac output; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; LCOS: low cardiac output syndrome; MAP: mean arterial pressure; MCS: mechanical circulatory support; OR: operating room; SBP: systolic blood pressure; SVR: systemic vascular resistances; LVAD: left ventricle assist device; BG: blood gas; BP: blood pressure; N/A: not applicable.

hemodynamic thresholds. Nevertheless, clear distinction between LCOS and cardiogenic shock may be challenging in everyday practice.

In our view, the following clear distinction should be considered:

• LCOS is the general clinical manifestation of low CO, regardless of the cause, and that does not necessarily imply ventricular failure. For example, patients with hemorrhagic shock have clinical signs of low CO but may have a normal cardiac function. The same may apply to cardiac tamponade, or tension pneumothorax.

• Cardiogenic shock is a specific form of LCOS caused primarily by heart dysfunction (including ventricular failure, valvular abnormalities, arrhythmias). Cardiogenic shock is characterized by hypotension, clinical signs of insufficient cardiac output, and may include multiple organ dysfunction [57, 58].

3. Incidence and outcome

Reported incidence of LCOS is variable, depending on setting investigated and definition used. Indeed, available data indicate an incidence that ranges from as low as 1.5% to as high as 91% of cardiac surgical patients [15, 18, 27, 44–54].

The risk of LCOS development is different between different types of cardiac surgical operations. The risk appears to be lowest for aortic valve surgery [50], and highest for mitral valve surgery [49], with coronary artery bypass graft surgery (CABG) lying in the middle. Intuitively, combined procedures (*e.g.*, CABG + mitral valve surgery) carry a higher risk than isolated procedures (Table 2, Ref. [15, 18, 27, 28, 44–54]).

Mortality associated with LCOS is also dependent on the population investigated, disease severity, and length of follow-up. Most studies report short-term mortality data (*i.e.*, in-hospital or 30-day mortality), with limited data for long-term follow-up [59, 60]. Reported mortality rates range from about 2% for patients with transient postoperative myocardial stunning [4] to almost 40% for patients with cardiogenic shock [15, 18]. In the most recent and largest studies, mortality ranged from 13 to 20% (Table 2) [18, 28, 46, 47].

In addition, patients who develop LCOS are also at increased risk of other complications, including postoperative myocardial infarction, kidney failure, stroke, and respiratory complications. For example, the risk of developing severe kidney failure (Kidney Disease. Improving Global Outcome class 3 [61]) may be as high as 60%, with a 35% risk of requiring renal-replacement therapy (RRT—Kidney Replacement Therapy according to recently suggested nomenclature) [52, 62, 63]. Myocardial infarction occurs in up to 30% of patients, and pneumonia in 20%, with more than 60% of patients requiring mechanical ventilation for more than 24 hours [52].

TABLE 2. Incidence and outcome of LCOS after adult cardiac surgery.

Author	Procedure	Sample size	Incidence	Mortality	Follow-up
Algarni *et al.* [48]	CABG	25,176	5.7%	17.5%	Operative mortality
Ding *et al.* [51]	CABG	1746	13.5%	25.4%	Operative mortality
Duncan *et al.* [28]	Any procedure with CPB	59,810	10.1%	14.6%	Hospital mortality
Ellenberger *et al.* [52]	High-risk CABG and/or AVR*	222	28.4%	12.7%	Hospital mortality
Kochar *et al.* [46]	Any procedure with CPB in patients with preoperative LVEF <35%	849	28.1%	16.1%	90-days
Hong *et al.* [53]	Any procedure	1585	13.4%	N/A	N/A
Hong *et al.* [54]	Valve surgery	2218	18.0%	N/A	N/A
Maganti *et al.* [49]	MV surgery	3039	7.0%	30.0%	Operative mortality
Maganti *et al.* [50]	AV surgery	2255	3.9%	38.0%	Operative mortality
Mendes *et al.* [47]	Elective or urgent procedure with CPB	2806	12.7%	13.4%	Hospital mortality
Pérez Vela *et al.* [18]	Any procedure	2070	7.5%	19.7%	Hospital mortality
Rao *et al.* [44]	CABG	4558	9.1%	16.9%	Operative mortality
Rudiger *et al.* [15]	Any procedure	183	61.0%	10.0%	180-days
Sá *et al.* [45]	Any procedure	605	14.7%	52.8%	Hospital mortality
Schoonen *et al.* [27]	Any procedure	5934	1.5% to 91.0% depending on definition	N/A	30-days

AV: aortic valve; AVR: aortic valve replacement; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; LCOS: low cardiac output syndrome; LVEF: left ventricular ejection fraction; MV: mitral valve; N/A: not applicable.
**defined as Parsonnet score >7.*

4. Pathophysiology and risk factors

Mechanism involved in development of LCOS and myocardial stunning/dysfunction are not entirely understood [13]. In some cases, the cause can be identified (*e.g.*, coronary graft failure/occlusion, paravalvular leak, prosthetic valve malfunctioning, cardiac tamponade, massive hemorrhage, arrhythmia). In most cases, however, patients develop myocardial dysfunction, yet a definitive cause cannot be established. Mechanisms involved in perioperative myocardial injury include ischemia-reperfusion injury, coronary microembolization (including air embolism), genetic predisposition, systemic inflammatory response to cardiopulmonary bypass (CPB) [64], and suboptimal cardioprotection during cross-clamping and cardioplegic arrest [13, 65–68]. The resulting myocardial injury can lead to temporary loss-of-function of cardiac myocytes, resulting in postoperative stunning, or irreversible cardiac damage leading to permanent myocardial dysfunction. Of note, some degree of myocardial dysfunction occurs in almost every patient undergoing cardiac surgery with CPB and cardioplegic arrest. Even in patients with normal preoperative left ventricle (LV) ejection fraction (LVEF), there is a decrease in LV function that reaches its nadir at about 2 h after surgery and gradually recovers over the next 24 h (Fig. 1, Ref. [69]) [70]. However, this may not always lead to development of clinical sign of low CO. Therefore, it is important to consider that LCOS may occur with normal systolic function, and that decrease in LV performance may not always translate in development of LCOS.

As a consequence of myocardial injury, the following three mechanisms can occur in isolation or in combination, leading to a decrease in CO: LV systolic dysfunction, LV diastolic dysfunction, and right ventricular (RV) dysfunction (Fig. 2, Ref. [13]).

Left ventricular systolic dysfunction is the most frequently present hallmark of perioperative LCOS, and the easiest to diagnose. Systolic dysfunction of LV is usually directly related to temporary or permanent loss of contractile strength of cardiac myocytes. Intuitively, LV systolic dysfunction causes a reduction in CO, an increase in left atrial and pulmonary capillary wedge pressures, and cardiogenic pulmonary edema. In addition to systolic LV dysfunction, diastolic LV dysfunction can also occur [71]. Diastolic dysfunction is characterized by inability of the ventricular chamber to accept an adequate volume of blood, despite normal preload, and is generally caused by the following mechanisms: (1) severe tachycardia; (2) decreased myocardial compliance, and (3) impaired ventricular relaxation [71, 72]. Diastolic dysfunction may occur in up to 70% of patients after cardiac surgery and can be an under-recognized cause of postoperative LCOS [71]. However, it should be acknowledged that isolated diastolic dysfunction is usually insufficient to cause acute heart failure, although it may cause decompensation when associated with other predisposing factors such as atrial fibrillation, impaired coronary perfusion, or arterial hypertension [72]. Of note, diastolic dysfunction is considered an early sign of myocardial

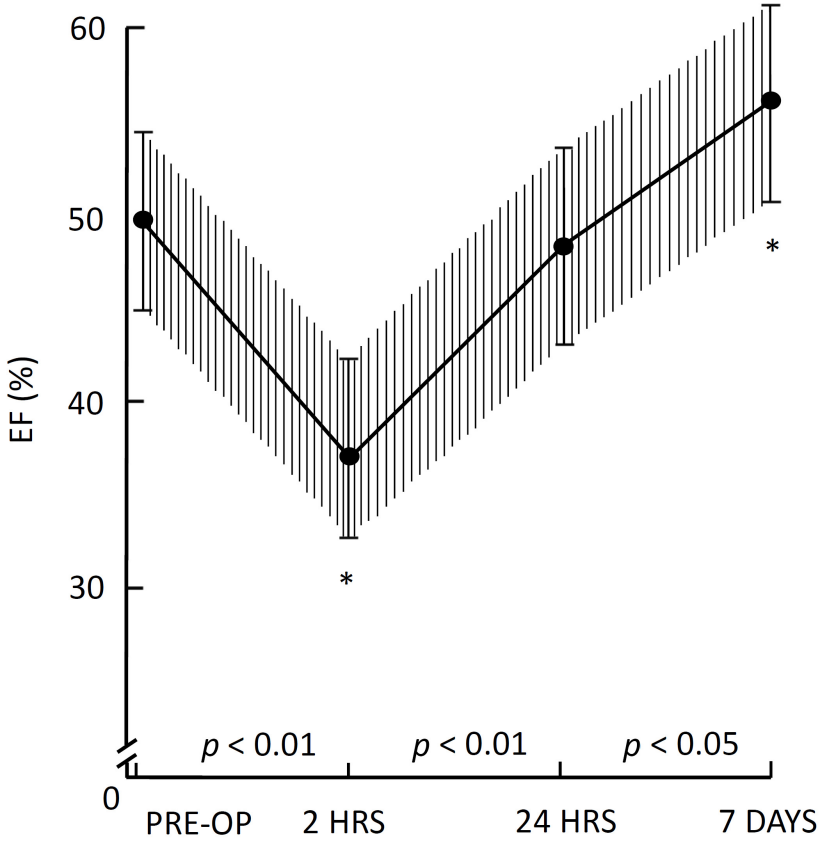

FIGURE 1. Postoperative changes in LVEF (means and standard deviations) in patients with preoperative LVEF >50% undergoing cardiac surgery. Adapted from Roberts *et al.* [69] Asterisks indicate a statistically significant difference as compared with baseline. PRE-OP: preoperatively; EF: Ejection Fraction; HRS: hours. *: statistically significant.

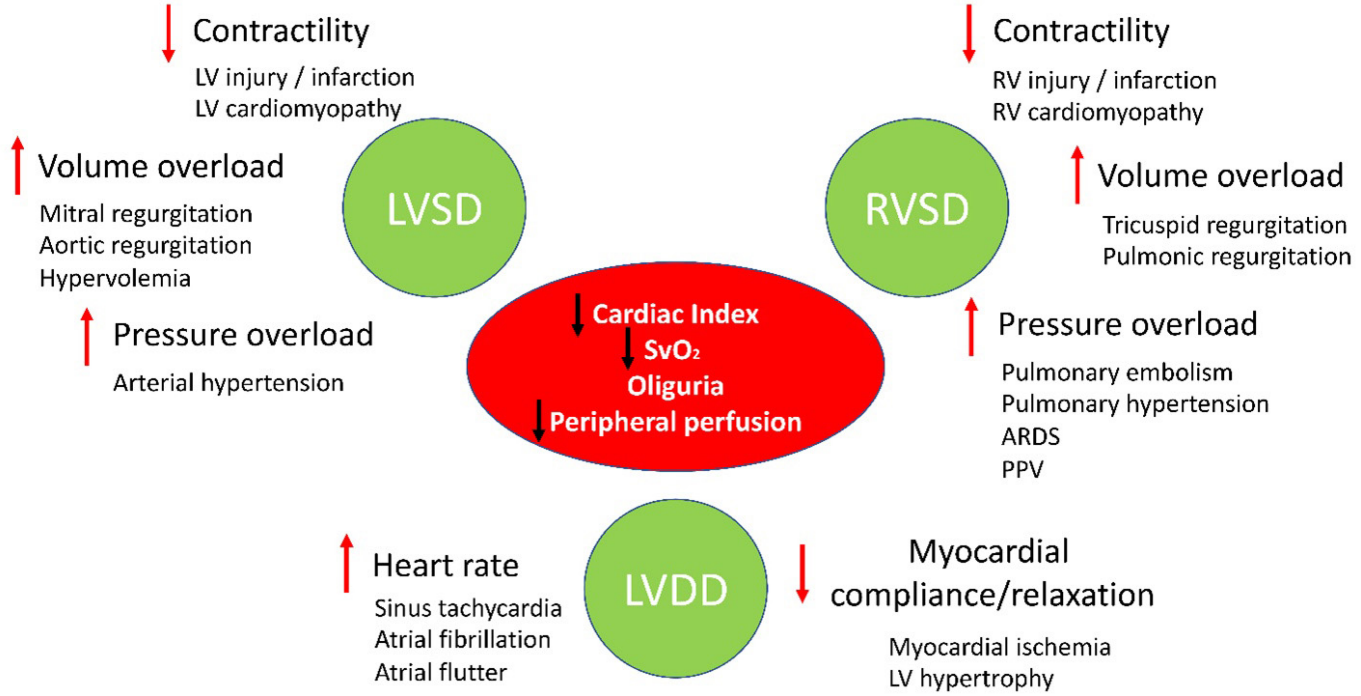

FIGURE 2. Leading triggers and pathophysiology of LCOS. Adapted from Lomivorotov *et al.* [13]. LVSD: left ventricular systolic dysfunction; RVSD: right ventricular systolic dysfunction; LVDD: left ventricular diastolic dysfunction; LV: left ventricle; RV: right ventricle; ARDS: acute respiratory distress syndrome; PPV: positive pressure ventilation; SvO_2: mixed venous oxygen saturation.

ischemia. Finally, RV dysfunction can also be associated with development of LCOS. While frequently overlooked in the past, the RV has a critical role in cardiovascular function by ensuring that all of the venous return is delivered to the LV without increase in right atrial pressure. Right ventricular dysfunction can be caused by direct injury to RV (*e.g.*, ischemia) or by abnormal increase in RV afterload (*i.e.*, increase in pulmonary vascular resistances) [73, 74]. Dysfunction of the RV will result in insufficient delivery of blood to the LV, increased right atrial pressure with venous congestion, and organ dysfunction. Furthermore, RV dilation will occur and, by ventricular interdependence, will result in decreased LV diastolic compliance, decreased LV preload, and further reduction in CO [75].

Several risk factors for LCOS have been identified. Although procedure-specific risk factors may differ, LV ejection fraction (LVEF) <40%, emergency operation, prolonged CPB time, and preoperative shock or heart failure symptoms have been consistently reported as the most frequently present. Interestingly, some studies also identified female gender as a risk factor [52–56, 76, 77], while the role of advanced age remains controversial [76].

Procedure-specific risk factors include incomplete revascularization for CABG, ischemic mitral valve pathology for mitral valve surgery, and reduced aortic valve size for aortic valve surgery.

To the best of our knowledge, there is only a single score currently available to predict development of LCOS in adult patients [51], developed by Mendes *et al.* [51] The score (details in Table 3, Ref. [51]) includes eight variables (each assigned different points) and can range from 0 to 26. The model had an area under the receiver operating characteristics curve of 0.8 (95% confidence interval of 0.77 to 0.84). With a threshold value of 5, the score had a sensitivity of 68%, a specificity of 79%, a positive-predictive value of 33%, and a negative-predictive value of 94%.

TABLE 3. Low cardiac output syndrome risk score developed by Mendes *et al.* [51].

Risk factor	No. of points
GFR <60 mL/min (calculated using Cockcroft-Gault formula) 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	3

GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

5. Diagnosis and treatment

Diagnosis of LCOS is largely clinical, with definitive diagnosis confirmed by echocardiography and invasive hemodynamic monitoring. Clinical signs of LCOS have been previously described and include the classical clinical signs of circulatory shock, *i.e.*, reduced urine output, altered mentation, and signs of peripheral vasoconstriction (*i.e.*, prolonged capillary refill time, skin mottling). Other signs, such as tachycardia and tachypnea may be masked in postoperative patients due to confounding factors such as sedation and mechanical ventilation, drugs (*e.g.*, beta-blockers) or bradyarrhythmias induced by surgical manipulation (*e.g.*, atrioventricular block). Hypotension is generally present, although some patients may have low CO with normal blood pressure or even with arterial hypertension. Serum lactates are generally elevated (>2 mmol/L), although trend in lactates is generally more informative than absolute values [78, 79]. Furthermore, in some conditions lactate levels may increase in absence of low CO (*e.g.*, epinephrine administration or liver failure). Use of other biomarkers and parameters for adequate perfusion (*e.g.*, plasma renin, pancreatic stone protein, tissue perfusion pressure) are currently under investigation [37–40]. Definitive diagnosis requires measurement of CO and/or assessment of cardiac function with echocardiography [80]. Echocardiography is fundamental to aid diagnosis, as it can detect not only left or right ventricular dysfunction, but also cardiac tamponade, regional wall motion abnormalities, valve abnormalities, or major aortic issues.

In addition to echocardiography, novel monitoring techniques could be of help in diagnosis causes of hemodynamic instability in cardiac surgical patients. These include continuous CO monitoring, near-infrared spectroscopy to assess cerebral, renal, and peripheral perfusion, and use of novel perfusion biomarkers [37, 81–83].

Unfortunately, the treatment of LCOS remains largely supportive [13]. In the selected cases where a clear factor can be identified (*e.g.*, coronary graft occlusion, cardiac tamponade…), immediate procedural intervention is required to treat and correct the underlying cause. In most cases, however, treatment consists only in providing hemodynamic and organ support until myocardial recovery occurs, and spontaneous CO is sufficient to provide adequate oxygen delivery and end-organ perfusion.

Pharmacological cardiovascular support with vasoactive drugs remains a cornerstone first-line of LCOS management [13, 17, 84]. Though they introduce some intrinsic limits and toxicity, inotropes are pivotal and are almost always administered to increase and maintain adequate CO, while vasopressors are frequently required to maintain a MAP of at least 65 mmHg. More rarely, LCOS may be associated with high systemic vascular resistances and normal or even increased systemic blood pressure. In these cases, inodilators or combinations of inotropes and vasodilators are used. When RV dysfunction or pulmonary hypertension is present, administration of pulmonary vasodilators is also undertaken to decrease RV afterload. Hemodynamic management also includes management of cardiac rhythm; optimization of circulating volume with fluid replacement and diuretics administration, as well as transfusion of blood products; optimization of mechanical ventilation and pH; and correction of electrolyte imbalances.

When pharmacologic support is insufficient to ensure hemodynamic stability, or high inotropic load is needed to maintain sufficient hemodynamic, MCS is generally considered.

Traditionally, recommended target for adequate hemodynamic resuscitation included a CI of >2.2 L/min/m^2 and a MAP >65 mmHg. While these recommendations remain valid, there is now increasing evidence that "protective" targets (*e.g.*, accept lower MAP thresholds, target capillary refill time rather than lactate, focus on optimization of unloading and cardiovascular mechanics rather than macrohemodynamic parameters) may actually improve outcome in perioperative and critically ill patients [29, 33–36].

5.1 Inotropic support in cardiac surgery

Inotropes are frequently administered in cardiac surgery to provide hemodynamic support in case of insufficient cardiac output [85]. The number of patients receiving perioperative inotropic support is highly variable and depends largely on clinician- and center-preference, with reported rate ranging from 35% to 100% of patients undergoing cardiac surgery [86–88].

Indeed, while some practitioners administer inotropes only when clinically required, others prefer to start inotropic support prophylactically to all patients in order to prevent LCOS and subsequent organ dysfunction [87, 89, 90].

Interestingly, perioperative use of inotropes has been associated with adverse outcome in cardiac surgery. Several observational trials suggested that inotrope administration is associated with increased risk of death and complications, including myocardial injury, acute kidney injury, and need for RRT, after adjustments for baseline characteristics [91–95]. A possible explanation to justify these findings is that adrenergic agents (*i.e.*, catecholamines and phosphodiesterase-3 (PDE-3) inhibitors, the most frequently used inotropes) have several potential side effects, including increased myocardial oxygen consumption, direct toxicity on cardiomyocytes, and arrhythmias [96, 97]. Indeed, the adverse effects of excessive adrenergic stress have been widely investigated and described in critical care literature [96]. Nevertheless, data from published placebo-controlled randomized controlled trials (RCTs) did not show an increase in mortality associated with inotropes use in acute care setting [98]. Therefore, association between inotropes use and increased mortality may simply reflect greater disease severity at baseline that cannot be captured by observational trials despite statistical adjustments.

Several inotropic/vasopressor agents are currently available and commonly used in clinical practice. Depending on the mechanism of actions, inotropes can be divided into catecholamines, PDE-3 inhibitors, cardiac glycosides, calcium sensitizers, vasopressin and its analogues, angiotensin II, and methylene blue [84, 85, 99–103]. Vasoactives can also be classified according to their main hemodynamic effect into inodilators, inoconstrictors, and vasoconstrictors [100]. Details on mechanism of actions, dose and relevant side effects of commonly administered inotropes is presented in Table 4 (Ref. [22, 101, 104–114]). A detailed description of mechanisms of

TABLE 4. Details on main receptors, usual dose, and side effects of commonly administered inotropes and vasopressors.

Drug	Main receptors	Usual dose range	Common side effects
Catecholamines			
Epinephrine (Adrenaline)	β- and α-adrenergic receptors	0.01–0.3 µg/kg/min infusion	Increase in lactate; increase in blood glucose; tachyarrhythmias; increased myocardial oxygen consumption; peripheral and mesenteric ischemia [104–107]
Norepinephrine (Noradrenaline)	α- and β-adrenergic receptors	0.01–0.5 µg/kg/min infusion	Increased myocardial oxygen consumption; peripheral and mesenteric ischemia
Dobutamine	β-adrenergic receptors	2–20 µg/kg/min infusion	Hypotension; tachyarrhythmias; increased myocardial oxygen consumption
Dopamine	• Dopamine receptors (low dose) • β-adrenergic receptors (medium dose) • α-adrenergic receptors (high-dose)	1–20 µg/kg/min infusion	Tachyarrhythmias; increased myocardial oxygen consumption
Phenylephrine	α-adrenergic receptors	50–100 µg bolus; 0.5–10 µg/kg/min infusion	Reduction in CO due excessive afterload increase [108]; peripheral and mesenteric ischemia
PDE-3 Inhibitors			
Milrinone	Phosphodiesterase-3 inhibitor (indirect adrenergic effect)	12.5–50 µg/kg bolus (optional); 0.125–0.75 µg/kg/min infusion	Hypotension; increased myocardial oxygen consumption; tachyarrhythmias; thrombocytopenia (rare)
Enoximone	Phosphodiesterase-3 inhibitor (indirect adrenergic effect)	0.5–1 mg/kg bolus (optional); 5–20 µg/kg/min infusion	Hypotension; increased myocardial oxygen consumption; tachyarrhythmias; thrombocytopenia (rare)
Amrinone/ Inamrinone	Phosphodiesterase-3 inhibitor (indirect adrenergic effect)	0.75 mg/kg bolus (optional); 5–10 µg/kg/min infusion	Hypotension; increased myocardial oxygen consumption; tachyarrhythmias; thrombocytopenia (more common than other PDE-3 inhibitors)
Calcium-sensitizers			
Levosimendan	• Enhance binding of calcium to cardiac troponin C [109] • Open ATP-sensitive K^+ channels of vascular smooth muscle cells [109] • Phosphodiesterase-3 inhibitor [110]	6–24 µg/kg bolus (optional); 0.025–0.2 µg/kg/min infusion	Hypotension; increased myocardial oxygen consumption (minimal); tachyarrhythmias
Vasopressin agonists			
Vasopressin	Vasopressin receptors 1A, 1B and 2	0.01–0.06 IU/min infusion 1–6 IU/h infusion	Reduction in CO due excessive afterload increase [108]; peripheral and mesenteric ischemia
Terlipressin	Vasopressin receptors 1A and 1B	1.3 µg/kg/h or 20–160 µg/h infusion (refractory shock) 0.85–1 mg bolus four times daily (hepatorenal syndrome)	Reduction in CO due excessive afterload increase [108]; peripheral and mesenteric ischemia

TABLE 4. Continued.

Drug	Main receptors	Usual dose range	Common side effects
Others			
Angiotensin II	Angiotensin receptors 1 and 2, possibly angiotensin receptors 3 and 4 via metabolites	20–200 ng/kg/min infusion [22]	Reduction in CO due excessive afterload increase [108]; peripheral and mesenteric ischemia, bronchospasm; increase in thrombotic events (controversial) [111–113]
Methylene blue	Not yet fully understood; includes inhibition of nitric oxide synthase and guanylate cyclase)	1.5–2 mg/kg bolus 0.25–2 mg/kg/h infusion [101]	Coma in patients receiving SSRI [114] Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency

ATP: adenosine triphosphate; CO: cardiac output; IU: international units; K^+: potassium; PDE-3: phosphodiesterase-3; SSRI: selective serotonin reuptake inhibitors.

actions and side effects of available inotropes is presented in the **Supplementary material**.

Despite being widely used in clinical practice, few high-quality multicenter RCTs on inotropes has been published and are available to guide clinical practice [85, 98]. Meta-analyses and systematic reviews showed that levosimendan is the most investigated inotrope of the last 20 years [98] and is the only one that has been systematically investigated in mRCTs in multiple clinical settings including acute heart failure [115, 116], cardiac surgery [19–21] and sepsis [117]. Meta-analyses repetitively suggested that levosimendan may be associated with reduction in mortality, perioperative acute kidney injury (AKI), perioperative myocardial injury, and need for inotropic support in cardiac surgery, as compared with placebo or other inodilatory agents [90, 118, 119].

However, when the effect of levosimendan on mortality in acute medical and cardiac surgical heart failure patients has been investigated in mRCTs, it showed no effect on major clinical endpoints, despite no increase in adverse events, reduction in in need for catecholamines, and potential reduction in rate of LCOS [19–21, 115, 116]. Subgroup analyses of the mRCTs suggested that levosimendan might be beneficial in specific cardiac surgery subpopulations [120, 121], however these findings remain hypothesis-generating.

High-quality evidence investigating the effect of other inotropic drugs including epinephrine, milrinone, dobutamine, and norepinephrine on major clinical outcomes in cardiac surgery is currently lacking [122–126]. Key conclusions derived from major RCTs in other settings could be summarized as follows:

- Dopamine is associated with higher rate of arrhythmias as compared with norepinephrine [127].
- Norepinephrine may improve survival as compared with dopamine [128], especially in cardiogenic shock [127].
- Epinephrine increases lactate more than norepinephrine or norepinephrine/dobutamine combination [104–106].
- High-dose epinephrine increases cardiac index more than high-dose norepinephrine in cardiogenic shock (driven by a greater increase in heart rate with similar effect on stroke volume) [104].
- Dobutamine and milrinone have similar effects on hemodynamics and outcomes in cardiogenic shock [123, 129–131]. However, safety and efficacy in patients with ventricular dysfunction and LCOS remains to be determined.

Single-center RCTs showed that vasopressin effectively reduce need for other vasoconstrictors and may reduce rate of AKI and need for RRT in patients with post-cardiotomy vasoplegic syndrome [132]. However, safety and efficacy in patients with ventricular dysfunction and LCOS remains to be determined.

Calcium salts are frequently administered as short-term inotropic agent during CPB weaning in order to directly increase cytosolic calcium and enhance inotropy [133, 134]. Safety and efficacy of this strategy is currently under investigation in a mRCT [135].

5.2 Mechanical circulatory support in cardiac surgery

Perioperative MCS due to LCOS is performed in a minority of patients undergoing cardiac surgery. An increase in its use is probably due to improved technology, growing familiarity with its capability, and treatment of more complex patients with cardiac surgery in recent years [136–138]. Due to costs, risks of complications, and expertise required, MCS remains a demanding therapy, with indications that should be evaluated with caution in every patient. However, there are some evidences that suggest early MCS might confer some advantages over high-dose pharmacologic support [139], although further studies are required to define optimal timing of MCS start in post-cardiac surgery patients [136, 140]. Furthermore, in the lack of guidelines in cardiac surgery, it should be remembered that inotropes administration in acute heart failure and cardiogenic shock has only a class IIb recommendation (level of evidence C) in the last ESC Heart Failure Guidelines [141]. On the contrary, perioperative MCS has a class of recommendation ranging from I to IIb (level of evidence B to C), according to the specific clinical scenarios and devices [136].

Temporary MCS (tMCS) in the perioperative cardiac surgery period has proven to address very different scenario, namely as preoperative stabilization tool in patients in cardiogenic shock before cardiac surgery or at high risk for development intraoperative cardiac surgery, for post-

cardiotomy cardiogenic shock, for periprocedural support in complex patients undergoing percutaneous valvular procedures and in bridging refractory cardiogenic shock patients to heart replacement therapies [142]. In most cases, MCS is used as rescue treatment for perioperative cardiogenic shock, where a recovery is generally expected [138]. In a minority of patients, cardiac function may not recover, and these patients may be translated to long-term MCS (as destination therapy or bridge-to-transplantation) or directly referred for heart transplantation. Very few studies predict recovery following post-cardiotomy shock requiring MCS, therefore there are no recommendations for specific selection criteria. Common considerations regarding MCS are generally applied [136].

Several devices, to be used alone or in combination, and multiple configurations may make the best solution for each patient. Cardiac (for example the presence of single or biventricular failure, expected duration of support) and extracardiac factors (presence and degree of respiratory failure, need of patient mobilization in case of prolonged support) both play a crucial role in the specific MCS strategy implementation. An overview of currently available devices of tMCS is presented in Table 5.

Intra-aortic balloon pump (IABP) is frequently used as a first-line MCS device due to easy of implantation and management [143], wide availability, and low costs, with escalation of support as needed up to full cardiopulmonary support with veno-arterial extracorporeal membrane oxygenation (ECMO) [13, 144]. In the last decade, microaxial flow pumps also gained wide use in this setting due to the high forward flow, coupled with powerful unloading, provided by latest generations devices [23]. The Impella® (AbioMed, Danvers, MA, USA) is an example of such a device that drains the LV and returns flow to the aorta, serving as a ventricular assist device with flows of 2 to 4 LPM common.

Intra-aortic balloon pump is currently used in about 2–6% of patients undergoing cardiac surgery [3, 145, 146]. Compared with other devices, IABP alone provides only minimal improvement in CO [143, 147]. However, IABP improves both LV unloading and coronary perfusion pressure, and may minimally improve ventriculo-arterial coupling and mechanical efficiency of cardiovascular system [147–149]. The effect of perioperative IABP on outcome remains controversial, with some studies and meta-analyses suggesting potential benefit on major clinical outcomes [150, 151], not confirmed by others [152]. Furthermore, the large multicenter RCTs in medical cardiogenic shock failed to show benefit on outcomes [153–155]. Therefore, utility of isolated IABP for perioperative LCOS remains a controversial topic that might deserve a dedicated mRCT [146, 147, 156].

Veno-arterial ECMO is generally required for less than 2% of patients undergoing cardiac surgery, even in high-risk cases [19]. Mortality of cardiac surgery patients requiring support with ECMO remains high, greater than 60% in most series [140, 157–159]. Major challenges in perioperative ECMO include the choice of cannulation strategy (central *vs.* peripheral), management of risk of bleeding, management of LV unloading, and timing of implantation [138]. Several studies suggest that outcome is similar between central and peripheral cannulation, with the latter strategy potentially associated with a lower risk of bleeding [160, 161]. Preliminary data from observational study showed that intraoperative implantation may be associated with improved survival as compared with ECMO implantation in the ICU [140]. Finally, adequate LV

TABLE 5. Currently available and most used devices for perioperative mechanical circulatory support.

	IABP	Central VA ECMO	Peripheral VA ECMO	Protekduo® RVAD	Impella CP, 5.0, 5.5®	Impella RP®
Cardiac flow	0.3–0.5 L/min	2–7 L/min	2–7 L/min	2–6 L/min	1.5–5.5 L/min	1.5–3.5 L/min
Drainage site → infusion site	N/A	Right atrium → aorta	Femoral vein → femoral artery	Right atrium → pulmonary artery	Left ventricle → aorta	Right atrium → pulmonary artery
Percutaneous *vs.* surgical implant	Both	Surgical	Both	Surgical	Percutaneous only for CP, surgical for all	Percutaneous
Possibility to insert oxygenator	No	Yes	Yes	Yes	No	No
Synchronization on cardiac rhythm	Yes	No	No	No	No	No
Afterload	−	−−	+++	−−	−−−	−−
Mean arterial pressure	+	++	++	+/−	+++	+/−
Cardiac flow	+	++	++	+/−	+++	+/−
Coronary perfusion	+	+/−	+/−	+/−	+	+/−
Myocardial oxygen demand	−	−	+/−	+/−	−−−	+/−

IABP: intra-aortic balloon pump; VA ECMO: veno-arterial extracorporeal membrane oxygenation; RVAD: right ventricular assist device; CP: Cardiac Power; RP: Right Percutaneous; +: increase; −: decrease.

unloading during ECMO support remains a critical issue. Inadequate unloading is associated with LV dilation, development of intra-cardiac thrombosis, increased myocardial mechanical stress and oxygen consumption, and potentially worse outcome [80, 149, 162–165]. Defining the optimal unloading strategy remains controversial [138]. For most cases, inotropes and/or IABP are sufficient. However, in some patient mechanical unloading with percutaneous left ventricle assist device (pVAD) such as micro-axial flow pumps is necessary. As of today, experience on use of combined ECMO and pVAD in cardiac surgery remains limited [138], although data from non-surgical cardiogenic shock are promising [166].

Perioperative use of micro-axial flow pumps in cardiac surgery has increased in recent years, although experience and available data remain more limited as compared with other MCS devices [142]. Compared with IABP and ECMO, micro-axial flow pumps can generally provide both effective unloading as well as a relevant increase in CO [148, 149]. Indeed, micro-axial flow pump is the only device that has been demonstrated to improve survival in RCTs [23, 24, 153]. Research is ongoing for both perioperative prophylactic support in high-risk patients, as well as use of pVAD as bridge to surgery in patients presenting with cardiogenic shock [167, 168]. Preliminary data are promising and suggests that early use of micro-axial flow pumps may improve outcome also in the perioperative setting [142].

6. Conclusions

LCOS occurs frequently following cardiac surgery and is associated with complications. Treatment is largely supportive, and based on vasoactives, optimization of intravascular volume and rhythm, while few patients with severe LCOS require MCS. Future areas of investigation include optimal hemodynamic and perfusion targets, and patient selection and timing for MCS.

AVAILABILITY OF DATA AND MATERIALS

Not applicable. No original data used for this article.

AUTHOR CONTRIBUTIONS

AB, MP—performed the research. VVL, AZ—formal analysis. AB, VVL—investigation. AB, AZ—data curation. AB, VVL, AZ, MP—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Alessandro Belletti, Vladimir Lomivorotov and Marina Pieri are serving as the Editorial Board members of this journal. We declare that Alessandro Belletti, Vladimir Lomivorotov and Marina Pieri had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to KLS.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://....

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