Review Article

Clinical Review: Management of weaning from cardiopulmonary bypass after cardiac surgery

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ABSTRACT

A sizable number of cardiac surgical patients are difficult to wean off cardiopulmonary bypass (CPB) as a result of structural or functional cardiac abnormalities, vasoplegic syndrome, or ventricular dysfunction. In these cases, therapeutic decisions have to be taken quickly for successful separation from CPB. Various crisis management scenarios can be anticipated which emphasizes the importance of basic knowledge in applied cardiovascular physiology, knowledge of pathophysiology of the surgical lesions as well as leadership, and communication between multiple team members in a high-stakes environment. Since the mid—90s, transoesophageal echocardiography has provided an opportunity to assess the completeness of surgery, to identify abnormal circulatory conditions, and to guide specific medical and surgical interventions. However, because of the lack of evidence-based guidelines, there is a large variability regarding the use of cardiovascular drugs and mechanical circulatory support at the time of weaning from the CPB. This review presents key features for risk stratification and risk modulation as well as a standardized physiological approach to achieve successful weaning from CPB.

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INTRODUCTION

Although off-pump surgery has emerged as an innovative technique, cardiopulmonary bypass (CPB) is performed in the majority of cardiac surgeries including coronary artery bypass grafting (CABG), valvular repair/replacement, congenital heart defects repair, and correction of abnormalities of great vessel.[1]

Weaning from CPB entails the progressive transition of the patient from full mechanical circulatory support to spontaneous heart activity of the patient with an aim to provide sufficient blood flow and pressure through the pulmonary and systemic circulation. The time taken for surgical verifications and hemodynamic optimization is "compressed" within the first few minutes and important information needs to be shared between surgeons, anesthesiologists, and perfusionists. Therapeutic decisions regarding pharmacological support, ventricular assistance, and additional surgical interventions have to be taken quickly to prevent myocardial damage. A scientific and individualized approach takes into account the patient's preoperative disease status and the specificities of the surgical intervention. In this context, hemodynamic monitoring and transoesophageal echocardiography (TEE) provide a snapshot of the circulatory system by assessing cardiac performances, the adequacy of surgical repair, the interdependence of both ventricles, and the coupling between the heart and the circulatory arteriovenous compartment.

Although the importance of body temperature,

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acid–base control, arterial inflow/venous outflow and blood pressure management during CPB have been thoroughly investigated,[2-4] the weaning procedure itself has been poorly described and most algorithms rely on empirical data and expert opinions.[5-6] In two large surveys performed in France and North America, the use of inotropes varied between 12% and 100% and guidelines or specific algorithms were applied in less than 10% of surgical centers.[7,8] In some institutions, inotropes were used routinely while in others inotropes were administered to reverse postischemic myocardial stunning or to normalize blood pressure values, even in the absence of clear documentation of ventricular insufficiency.

Currently, there are no specific criteria defining the "difficult-to-wean" situation.[9] Many patients come easily off CPB without requiring supportive treatments, except for minor interventions such as electrical defibrillation, temporary electrophysiological stimulation, and/or small doses of cardiovascular drugs. The purpose of this review is to provide anesthesiologists, cardiac surgeons, perfusionists, and intensive care physicians with updated guidelines regarding perioperative management and the weaning process, particularly in the high risk cases.

ORGANIZATIONAL ASPECTS AND HUMAN FACTORS

Large cohort studies have shown that better outcomes are achieved when cardiac procedures are performed by well-trained and qualified professionals in high-volume hospitals where safety practice and standardized clinical pathways have been established.[10] An extensive literature exists about ways to optimize safety and work performance in complex organizational settings such as aerospace, nuclear power, and chemical engineering.[11] With the increasing burden of patients' comorbidities, and the complexity of the surgical operations, the achievement and maintenance of clinical excellence has become increasingly challenging. Although medical errors were traditionally attributed to lack of skills, inaccurate judgement and inappropriate actions, recent work has revealed that errors may also result from poor communication and the absence of written guidelines.[12] This might also be true at the time of CPB weaning when the information flow and communication between the team members must be optimized, amid uncertainty and time pressure. In an observational study involving 102 pediatric cardiac surgical cases, an average of 16 adverse events were reported per patient, 30% occurring shortly after coming off CPB and most of them being related to communication and coordination failure.[13] Cognitive adjustment was the compensatory intervention in most of these near-misses emphasizing the importance of qualification, training, and expertise. Another study from the Mayo clinic highlighted a strong correlation between the occurrence of technical error and teamwork disruption resulting from insufficient procedural information and poor communication/coordination between the surgeon, the anesthesiologist, and the perfusionist.[14] Although many of these "sentinel events" appear inconsequential, they predispose patients to serious complications if not addressed with effective compensatory interventions. It should be noted that the operative death was highly associated with serious adverse events (1.2 per patient).

Cardiac surgical care may benefit from restructuring the team with better cohesiveness and familiarity (teamwork education), by adopting standardized communication pattern and embracing the briefing–debriefing technique as an adjunct to continuous improvement through reflective learning, deliberate practice, and immediate feedback.[15] Simulation-based training has also been shown to enhance physician's performances during weaning from CPB. Immersive training focusing on nontechnical skills are believed to be superior to passive discussion in traditional interactive teaching seminars.[16] By providing a surrounding mimicking both the standardized process and dynamic crisis, high-fidelity simulation improves active memorization and enhances appropriate behaviors in real-life while sparing patients from potential harm.[17]

HEMODYNAMIC MONITORING AND ECHOCARDIOGRAPHIC ASSESSMENT

The use of the pulmonary artery catheter (PAC) is no longer routinely indicated in cardiac surgery.[18] Although cardiac output (CO), pulmonary artery pressure (PAP), and mixed venous oxygen saturation offer valuable information, errors (unreliable data, false interpretation) and iatrogenic complications (arrhythmias, pulmonary embolism or hemorrhage) may negate any potential benefit.[19-21]. In a propensity-matched observational study involving 5,065 CABG patients from 70 centers, the use of a PAC during CABG surgery was associated with increased mortality and a higher risk of severe end-organ complications.[22] Failure to demonstrate improved clinical outcome with PAC

may result from the lack of evidence-based treatments guided by PAC information.[23]

New hemodynamic monitors have recently emerged (e.g., Esophageal Doppler and Pulse contour analysis), providing the ability to monitor CO noninvasively and to assess patient's responsiveness to fluid loading.[24] Simple and reproducible measurements of cardiac preload, intrathoracic volume (by PiCCO®, LiDCO® systems), and tissue oxygenation (by near-infrared-spectroscopy) might be helpful to optimize the circulatory condition while getting more insight into the adequacy of tissue O_2 supply/demand.[25,26]

Before TEE became routinely available, problems such as hypovolemia, and anatomical, or functional defects were largely overlooked, and some hypotensive conditions were erroneously attributed to myocardial stunning or heart failure which led to inappropriate use of inotropes. Although transthoracic echocardiography (TTE) is generally regarded as superior for assessing the aortic valve, some diagnosis are missed and TEE almost always gives clearer images. Before starting CPB, new diagnosis (e.g. patent foramen ovale, undiagnosed valvular dysfunction, severe atheromatosis of the ascending aorta) might be revealed by TEE that justify a modification of the surgical plan in 5-15% cases.[27-31] Likewise after coming off bypass or under partial CPB, TEE allows a quick assessment of the completeness of surgery, ruling out any valvular or prosthetic dysfunction, paravalvular leaks, and wall motion abnormalities. During the weaning process, TEE provides a rational basis for diagnostic and therapeutic decision making, most importantly the need for inotropes and vasopressors, intra-aortic balloon pump, and volume replacement. Although TEE measurements of cardiac performance are well validated, some measurements are tedious and impractical to be performed intraoperatively.[32-34] For cardiac preload assessment, end-diastolic areas or diameter of the LV are more reliable than filling pressures derived from PAC and/or central venous catheter. Other simple measurements such as the fractional area changes of the LV and Doppler flow measurements in addition to a "trained eye vision" are valid methods to guide fluid loading and cardiovascular drug administration.[35] Till recently, category 1 indications for intra-operative use of TEE were restricted to repair of valve(s), congenital cardiac defects, hypertrophic obstructive cardiomyopathy, valvular endocarditis, and aortic dissection.[36] Whereas coronary artery surgery for patients with poor ventricular function was a category 2b indication. Since 2010, both European and American Task Forces have recommended that TEE should be used in all elective and emergency cardiac operations unless contraindicated and the use of TEE in CABG has been upgraded as a category 2a indication.[37,38] The risk of major complications of TEE probe insertion, notably perforation of the oesophagus, is between 1:1000 and 1:10000. No death has been reported to date. Minor complications, e.g. sore throat and odynophagia, are common but could be minimized by cautious placement of the probe with a laryngoscope.[39]

THE "DIFFICULT TO WEAN" SITUATIONS

Definitions

At the time of separation from bypass, underfilling of the heart is a frequent cause of hypotension that can easily be detected by TEE and by direct inspection of the right ventricle (RV) and right atrium. Optimization of cardiac preload by first reinfusing blood from the cardiotomy reservoir and then by titrating IV fluids is a simple and effective way to normalize CO and mean arterial pressure (MAP) in the majority of patients with preserved ventricular function.

In normovolemic conditions, difficulties in weaning from CPB are encountered in about 10 to 45% of patients[40] and TEE is helpful to diagnose the underlying mechanisms that can be ascribed to one of four contextual scenarios:

1. Structural abnormalities such as intracardiac shunt, valvular regurgitation, para-prosthetic leaks, or an occluded bypass graft.
2. Dynamic abnormalities such as left (or right) ventricular outflow tract obstruction.
3. Ventricular systolic dysfunction characterized by depressed contractility, impairment in ventricular diastolic relaxation and restrictive filling pattern.
4. Vasoplegic syndrome characterized by normal-to-elevated CO with preserved ventricular function and low systemic vascular resistance.

Key diagnostic features and therapeutic approaches to these pathological conditions are briefly described in Table 1.

Mechanisms and Risk Factors of Ventricular Dysfunction and Vasoplegic Syndrome

To predict perioperative mortality, the Euroscore, the Society of Thoracic Surgeons (STS), and the Parsonnet scores have been validated in cardiac surgical

patients.[41] Most items included in these scoring systems are also considered independent risk factors for vasoplegic syndrome and ventricular dysfunction.

Vasoplegic syndrome has been linked to deficient release/activity of vasopressin and angiotensin II, overexpression of inflammatory mediators, and endothelial dysfunction resulting from the activation of vascular smooth muscle ATP-sensitive potassium channels, and/or overexpression of the inducible NO synthase.[42-44] The systemic inflammatory response to CPB and surgical trauma may contribute to worsen cardiocirculatory disturbances.[45] Long-term use of certain drugs (e.g., angiotensin-converting enzyme inhibitors, calcium-channel antagonists, and heparin), patients co-morbidities (e.g., heart failure, diabetes mellitus) and procedure-related factors (e.g., prolonged CPB, residual hypothermia) have been identified as predictors of norepinephrine-resistant vasoplegia that has been associated with mortality rates as high as 25% when vasoplegia persisted for more than 36 h [Table 2].[43-48]

Ventricular function has been reported to be impaired in as much as 96% of patients following CPB with a

Table 1: Characteristics and treatment modalities of weaning difficulties

	Surgical or technical failure	Ventricular dysfunction	Vasoplegic syndrome	Left ventricular outflow tract obstruction
Diagnostic criteria	TEE • Valvular regurgitation or stenosis • Patient-Prothesis-mismatch • Para-prosthetic leakage • Intracardiac shunt • Occluded vasculargraft	1. TEE • ↙Contractility of LV / RV • Dilated LV / RV • ↙Relaxation 2. Hemodynamics • ↙CO and ↙ MAP	1. TEE • Preserved Ventricular Contractility 2. Hemodynamics • ↗or normal CO and ↙ MAP	TEE • Systolic anterior motion of the anterior mitral leaflet • LV septal hypertrophy • Pressure gradient in the LV outflow tract
Incidence	2–6%	15–40%	4–20%	5–10% after mitral valve surgery
Risk Factors	• Team and operator's experience, qualification • Low surgical volume • Extended disease, difficult anatomy	• Age (>65 years), female gender • CHF, low LV ejection fraction • LV diastolic dysfunction • Previous MI, COPD • eGFR< 60 ml/min • Extensive CAD, left main CAD • Re-operation, emergency, combined procedure • Prolonged CPB	• Preop therapy with ACEI or AII antagonist, β-blockers, heparin • High EuroScore • Prolonged CPB • Low LVEF (<35%)	• Myxomatous mitral valve • Hyperdynamic LV • Short distance between the MV coaptation point and LV septum
Specific Treatment	RE-OPERATION • Secondary repair or valve replacement • Shunt closure • Additional coronary bypass graft	1. DRUGS • Adrenergic agonists (Dobutamine, Adrenaline, Dopamine) • Phosphodiesterase inhibitors (Milrinone) • Calcium sensitizer (Levosimedan) • Systemic vasodilators (NTG, NPS) • Pulmonary vasodilator (NO, PGI2) 2. ELECTRO-MECHANICAL SUPPORT • Bi-Ventricular pacing • Intra-Aortic Balloon Pump • Extra-Corporeal Membrane Oxygenation • Ventricular Assist Device	VASOPRESSORS • Phenylephrine • Norepinephrine • Terlipressin • Methylene Blue (1.5 mg/kg)	MEDICAL • Volume expansion • Inotrope discontinuation • β-blockers SURGICAL • Septal bulge resection • Mitral valve re-repair/ replacement

ACEI - Angiotensin-converting enzyme inhibitor, BPCO - Broncho-pulmonary chronic obstructive disease, CAD - Coronary artery disease, CHF - Congestive heart failure, CO and MAP - Cardiac output and mean arterial pressure, EF - Ejection fraction, LV/RV - Left/right ventricule, MI - Myocardial infarction, MV - mitral valve, NO - Nitric oxide, NPS - Nitroprussiate, NTG - Nitroglycerine, PGI_2 - Prostacyclin, TEE - Transoesophageal echocardiography

nadir occurring between 2 and 16 h following surgery with, complete recovery being achieved 24 to 48 h after surgery.[49] In the operating room, low cardiac output syndrome (LCOS) has been defined as the inability to wean off CPB despite maximal support with a low cardiac index (<2.0–2.5 l/min/m^2) and evidence of end-organ dysfunction (e.g., urine output < 0.5 ml/kg/h). The prevalence of LCOS in cardiac surgical patients range from 0.2% to 6% and it is associated with increased postoperative morbidity and mortality, increasing hospital length of stay, resource utilization, and overall costs.[7,8] The reasons for poor clinical outcome are likely related to the severity of the underlying disease and to the delay or failure to institute mechanical support.

The causes of ventricular dysfunction are multifactorial, including surgical tissue trauma, myocardial ischemia-reperfusion injuries, down-regulation of beta-adrenergic receptors, coronary embolization (e.g., air, atheroma particule), activation of inflammatory and coagulation cascades, as well as uncorrected pre-existing cardiac disease. Myocardial stunning owing to cytosolic and mitochondrial calcium overload is usually a transient phenomenon. Perioperative myocardial infarction occurs in 7% to 15% of cardiac surgical patients and has also been incriminated in causing LCOS.[49,50] Knowledge of specific risk factors of post-CPB ventricular dysfunction is important for planning prophylactic cardioprotective interventions as well as early supportive therapy with cardiovascular drugs and eventually with mechanical circulatory devices [Table 3]. Patient-related risk factors include advanced age, decreased LV systolic function, altered LV diastolic function, chronic beta-blocker treatment, recent myocardial infarction, and other end-organ dysfunction comorbidities [renal failure, arterial disease, and pulmonary hypertension (PH)]. Among procedure-related risk factors, prolonged aortic cross-clamping and the complexity of surgery (combined procedure) have been associated with ischemic myocardial injuries.[45-60] More recently, genetic variation within defined regions of the NPPA/NPPB and NPR3 natriuretic peptide system genes has been shown to be associated with post-CPB ventricular dysfunction.[61] However, in a genome-wide study of over 100 single-nucleotide polymorphisms (SNPs), no SNP was consistently associated with

Table 2: Studies reporting the risk factors of vasoplegic syndrome after cardiac surgery

Authors	*N*	Type of Surgery	Protocol for weaning from CPB	Criteria for vasoplegic syndrome	Incidence	Risk factors of LV dysfunction
Levin MA *et al.*[43]	2,823	CABGS, valvular, or combined	PAC	Need for vasopressors > 12h, • Dopamine ≥ 10 µcg/kg/min or • Epinephrine/Norepinephrine > 0.15 µg/kg/min • Vasopressin > 4U/h	20.4	• High Euroscore • Preop β-blocker or ACEI treatment • Valvular surgery • Prolonged CPB • Intraop use of aprotinine
Mekontso-Dessap A *et al.*[47]	108	CABGS	Not reported	• Low SVR: <1400 dynes-s/cm^5/m^2, with CI > 2.5 L/min/ m^2 • Need for dopamine > 10µg/kg/min or Norepinephrine > 0.15 µg/kg/min	N/A	• Preop ACEI treatment • Preop Heparin treatment
Argenziano M *et al.*[48]	145	Cardiacsurgery	Not reported	• MAP <70 mmHg with CI > 2.5 L/min/ m^2 • Need for Norepinephrine > 3 hours	8	• LVEF<35% • preoperative ACEI treatment
Carrel T *et al.*[46]	800	Cardiacsurgery	TEE and PAC	• MAP<70 mmHg with CI > 2.5 L/min/ m^2 • Need for norepinephrine > 3 hours	14.4	• Preoperative ACEI therapy • Low LVEF • Prolonged CPB • Hypothermic CPB
Sun X *et al.*[44]	334	CABGS	Not reported	• MAP < 70 mmHg with CI > 2.5 L/min/ m^2 • Need for norepinephrine > 3 hours	6.9	• LVEF < 35% • Increased BMI • Emergency surgery

ACEI - Angiotensin-converting enzyme inhibitor, BMI - Body mass index, CABGS - Coronary artery bypass graft surgery, CI - Cardiac index, CPB - Cardiopulmonary bypass, IABP - Intra-aortic balloon pump, LVEF - Left ventricular ejection fraction, MAP - Mean arterial pressure, PAC - Pulmonary artery catheter, TEE - Transesophageal echocardiography

Table 3: Studies reporting the risk factors of ventricular dysfunction after cardiac surgery

Authors	*N*	Type of surgery	Protocol for weaning from CPB	Criteria for LV dysfunction	% pts with inotropes	Risk factors of LV dysfunction
Butterworth *et al.*[58]	149	Mitral and AVR	Visual observation and CI > 2.2L/min/m2	• Dopamine ≥ 5 μg/kg/min • Any dose of dobutamine, epinephrine or amrinone	52	• Age • CHF or low LVEF • Anesthesiologist
Royster *et al.*[60]	128	CABGS	Visual observation and SAP	• Need for IABP • Dopamine ≥ 3 μg/kg/min • Any dose of dobutamine, or epinephrine > 12 h	55	• Age, female • Wall motion abnormalities • Low LVEF • High LVEDP
Breisblatt *et al.*[49]	24	CABG	Visual observation and SAP	• Any dose of inotropes	63	• Low LV ejection fraction • Preoperative β-blockers,
McKinlay *et al.*[55]	1,009	CABGS, valvular, or combined	TEE	• Need for IABP • Dopamine ≥ 5 μg/kg/min • Any dose of dobutamine, epinephrine or milrinone	39	• Wall motion abnormalities • Low LVEF (<35%) • Re-operation, combined surgery • Mitral regurgitation • Prolonged CPB
Maganti *et al.*[59]	3,039	Isolated Mitral Valve Surgery	SAP < 90 mmHg and CI < 2.2 L/min/m2	• Dopamine ≥ 4 μg/kg/min • Any dose of dobutamine, epinephrine or milrinone	7	• Urgency • NYHA class IV, LVEF < 40% • BSA < 1.7 m^2 • Ischemic mitral valve pathology • Prolonged CPB
Muller *et al.*[56]	1,471	CABGS, valvular, or combined	TEE and CI > 2L/min/m2	• Need for epinephrine, dobutamine or enoximone at any dosage; single or combined	32	• Previous myocardial infarct, • CHF, COPD • Age >65 • Aortic cross-clamping >90min, • CABGS
Ahmed *et al.*[54]	97	CABGS + AVR	Not reported	• Need for IABP • Dopamine > 5μg/kg/min • Any dose of epinephrine, norepinephrine, dobutamine, or milrinone	52	• Chronic kidney disease • LVEF ≤ 40% • LVEDP > 20 mmHg • Low pre-bypass CI (< 2.5L/min/m^2)
Licker *et al.*[53]	94	AVR	TEE	• Need for IABP • Dobutamine > 5μg/kg/min • Any dose of epinephrine, norepinephrine, or milrinone	40	• Age • LV diastolic dysfunction • Aortic cross-clamping time
Muehlschlegel *et al.*[57]	1298	CABGS	TEE	• Need for > 2 or more inotropes, and/or intraaortic balloon pump or ventricular assist device.	12	• Male • Preop ACEI or diuretics • Low LVEF • Anemia • Prolonged CPB

AVR - Aortic valve replacement, CABGS - Coronary artery bypass graft surgery, CHF - Congestive heart failure, CI - Cardiac index, COPD - Chronic obstructive pulmonary disease, IABP - Intra aortic balloon pump, LVEDP - Left ventricular end-diastolic pressure, SAP - Systolic arterial pressure, TEE - Transesophageal echocardiography

a strong risk [odds ratio (OR) > 2.1] of developing postoperative ventricular dysfunction.[62]

Prognostic Implications of PH and/or Right Ventricular Dysfunction

PH is defined by a mean PAP ≥ 25 mmHg at rest (or ≥ 30 mmHg with exercise) in the presence of a pulmonary capillary wedge pressure ≤15 mmHg.[63] Although the prevalence of idiopathic PH is low (1 per 15 million), secondary forms of PH are frequently encountered in patients with HIV (0.5%), portal hypertension (2% to 6%), sickle cell disease (10% to 30%), and chronic obstructive pulmonary disease (1% to 4%). The prevalence of PH is much higher in patients with an advanced stage of LV failure (NYHA class IV, LVEF < 40%), in patients undergoing mitral valve repair (40% to 50%) and in patients undergoing aortic valve replacement for aortic stenosis (10% to 50%).[63-65] Severe PH (systolic PAP > 60 mmHg) has been included in the Euroscore and Parsonnet score for

predicting 30-day operative mortality but not in the STS scoring system.[41,66] Following valve replacement for aortic stenosis, Melby et al reported a two-fold higher operative mortality and decreased long term survival (relative risk 1.7) in patients with preoperative PH versus those with normal PAP.[67,68] Among survivors, PAP decreased immediately by about 20% following surgery and persisted at lower levels over the 1-year follow up period.[68]

The criteria defining RV functional abnormalities are largely arbitrary and no strong consensus exists given the complex geometry of the RV with its extensive trabeculations.[69] Several observational studies indicate that various indices of RV function (RVEF < 20–40%, RV fractional area change <35%, RV myocardial performance index > 0.5) are associated with increased requirement of inotropic support, a higher incidence of postoperative heart failure, longer stay in ICU, and lower survival.[70]

A Protocol-Driven Approach for Weaning from CPB

Weaning off bypass and landing procedures in aviation share many similarities. Such procedures can be seen as models of how a multi-professional team comes together, utilizes continuously flowing information, interacts effectively and safely perform a complex task under time pressure.

Besides qualification and individual expertise, knowledge of emergency procedures, application of checklists and goal-directed protocols are key elements for successful management. Given the importance of hemodynamic and echocardiographic evaluation, the anesthesiologist should assume the leadership during this important period of weaning from CPB, albeit agreement with the surgeon is always sought for therapeutic decisions. For instance, consensus should be reached when a second pump run is justified in case of nonpatent vascular graft, persistent or new intracardiac shunt, valvular dysfunction, or ventricular outflow tract obstruction. A stepwise standardized approach for managing CPB weaning is summarized in Figure 1.

Checklist Before Weaning Off Bypass

Before initiating the weaning procedure, several prerequisites should be routinely met:

1. Normothermia is achieved by active rewarming by using CPB heat exchanger, by convective air circulation, and by circulating water blanket.
2. Arterial blood analysis to ensures that oxygen content of the blood (hematocrit > 25%, PaO_2 >100 mmHg), electrolytes (K^+, Ca^{++}, Mg^{++}), blood sugar, and pH are within normal limits; while full anticoagulation is maintained (activated clotting time > 400 s).
3. Lungs are manually re-inflated (FIO_2 > 0.8). Mechanical ventilation is reset, and the alarms of the cardiopulmonary monitoring are reactivated.
4. After aortic unclamping and electrical ventricular defribillation (if required), a heart rate (HR) between 70 and 100 beats/min should be targeted. Bradycardia and atrioventricular blockade are treated with atropine, beta-adrenergic receptor agonists, or cardiac pacing.

Goal-Directed Approach for Weaning Off Bypass

While the circulatory work is shifted from the pump to the patients' heart, information on hemodynamic parameters (e.g., HR, cardiac preload indices, MAP, and functional imaging of the heart) should be shared between the cardiac surgeon, the anaesthesiologists, and the perfusionnist.

Scenario 1

During stepwise reduction of both venous return and arterial pump flow, filling of the cardiac chambers is appreciated by inspection of the RV and atrium, by TEE examination (e.g., LV end-diastolic diameter 3.5–5 cm, in transgastric short-axis view), and by central filling pressure measurement (venous or pulmonary capillary wedge pressure). Cardiac preload is considered "optimal" when further filling fails to increase blood pressure and/or CO according to the preload-recruitable stroke work concept. Indeed, progressive elongation of the sarcomeres with increasing cardiac preload enhances myocardial contraction resulting in increased stroke volume and MAP (Frank–Starling mechanism).

As soon as a critical perfusion pressure is reached (MAP > 70 mmHg), patients with normal LV function may benefit from the infusion of vasodilators (e.g., nitroglycerine, clevidipine, or nitroprussiate) which improve the efficiency of ventricular contraction and avoid hypertension during removal of the aortic cannula. Patients with arterial hypertension and hypertrophic cardiomyopathy have restrictive physiology and are at risk of ventricular outflow tract obstruction and myocardial ischemia; in these patients control of the HR, and maintenance of adequate preload and afterload is important to prevent outflow tract obstruction and to ensure adequate myocardial perfusion. Abnormal systolic motion of the anterior

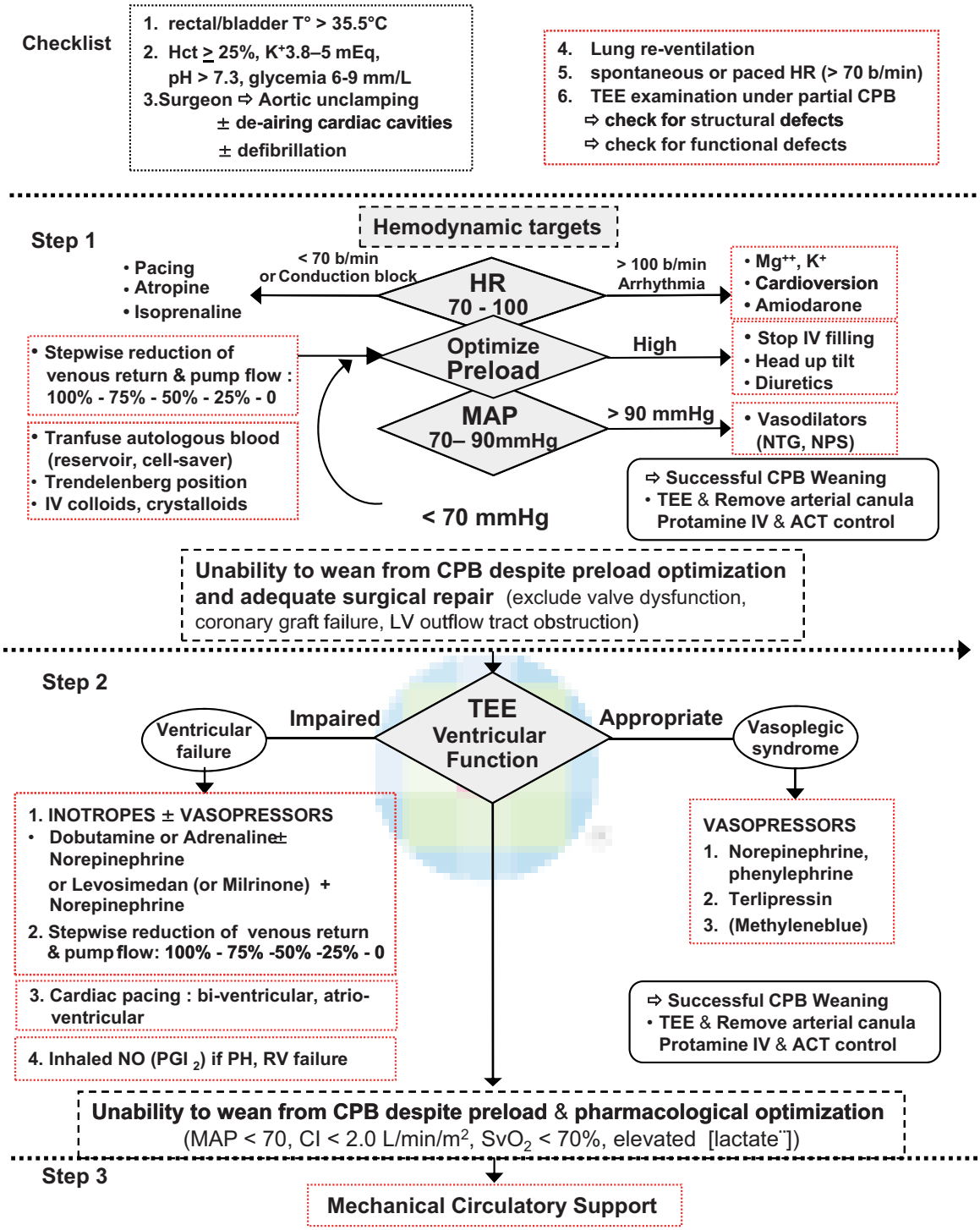

Figure 1: Algorithm for weaning from cardiopulmonary bypass

mitral leaflet and acceleration of the blood flow in the LV outflow tract can be detected in midesophageal aortic long axis view and in transgastric long axis view of the LV at 120°, respectively. Finally, after separation from CPB and removal of the venous cannula, transfusion of autologous blood from the cardiotomy reservoir, and cell-saver device may further enhance stroke volume by optimizing cardiac preload. During the infusion of protamine, ventilatory pressures, and hemodynamic parameters should be closely monitored since protamine may induce a bronchospastic response and severe PH with RV failure, particularly in patients with specific risk factors such as prior protamine exposure, history of PH, fish allergy, and vasectomy.[71] Slow infusion of protamine through the aortic cannula or preemptive administration of inhaled nitric oxide or prostacyclin

has been recommended to mitigate or to prevent these deleterious reactions. [71-74]

Scenario 2

If hypotension (MAP < 70 mmHg) persists despite adequate cardiac filling, a brief TEE examination is helpful to discriminate between a vasoplegic syndrome, LV failure, or RV failure (with or without PH).[75] In patients with vasoplegic syndrome, ventricular function is well preserved and normal levels of MAP (>70 mmHg) can be restored with incremental doses of norepinephrine or phenylephrine [Table 4]. Vasopressin receptor agonists (vasopressin 4 U/min, terlipressin 0.5-1 mg) are considered as second-line treatments. Successful management with nitric oxide inhibitors (methylene blue 1.5 mg/kg) has been reported in few cases of nonresponsive hypotension to alpha-adrenergic agonists.[76-77]

Hypotensive states resulting from ventricular dysfunction can benefit from inotropic drug support often in association with vasopressors in case of LV dysfunction and with selective pulmonary vasodilators (inhaled nitric oxide or prostacycline) in case of RV dysfunction and/or PH.[78,79] Beta-adrenergic receptor agonists represent the first option, whereas phosphodiesterase inhibitors (PDEIs) might be preferred in patients chronically treated with β-blockers. Among β-agonists, dobutamine offers the most favorable side effects profile compared with epinephrine and dopamine [Table 4].[80]

Tachy-arrhythmias might convert to sinus rhythm on delivering a low-intensity direct electric shock or on administration of lidocaine or amiodarone. Various modes of biventricular or atrial pacing can reduce ventricular dyssynchrony and might improve mechanical efficiency of cardiac contraction (about 14% increase in SV) without increasing myocardial oxygen consumption.[81]

Evidence of myocardial ischemia (e.g., ST segment abnormalities, new/worsening LV/RV wall motion abnormalities) may justify the need for further myocardial revascularization (ST segment elevation, transmural ischemia) or the infusion of nitroglycerine (ST segment depression, subendocardial ischemia). However, limitations in the interpretation of regional wall motion abnormalities should be considered since they have also been reported in case of hypovolemic states, conduction abnormalities (bundle branch block, ventricular pacing), and myocardial stunning. Anecdotally, transient LV dysfunction has also been attributed to Takotsubo cardiomyopathy which is characterized by ECG abnormalities (ST elevations or T wave inversion) in the absence of obstructive coronary artery disease and pathognomonic wall motion abnormalities (mid-ventricular akinesia and LV "apical ballooning").[82-84] Excessive catecholamine stimulation, metabolic disturbances, and dysfunction of the microcirculation are thought to be the underlying mechanisms. In such cases, administration of the inotropes should be discontinued and replaced by nitroglycerin. [85]

Acute RV dysfunction after CPB can be detected by high CVP and by TEE examination which shows poor contractility and dilated RV, tricuspid regurgitation, and low tricuspid annular plane systolic excursion.[70] Ischemic causes of RV dysfunction, often missed by standard ECG, requires medical and/or surgical treatment aimed to enhance RV perfusion. If nonischemic etiologies are suspected, therapeutic options are aimed to increase contractility and to selectively reduce the afterload of the RV by inhaled NO, prostacyclin, or milrinone.

Indications and Risks of Inotropic Drugs

Based on TEE assessment and CO measurements, inotropic support is indicated in less than 50% patients following CPB.[40] Ideally, the hemodynamic response to incremental doses of inotropic agents should be tested within a short time frame of less than 5–10 min. Any delay in restoring adequate systemic oxygen delivery may aggravate ventricular dysfunction and trigger the onset of multiple organ dysfunction. Despite the wide range of available inotropes, consensus lacks regarding the optimal therapeutic regimen.[40] Conceptually, inotropes enhance postischemic recovery and facilitate weaning from CPB. The downside is that, by promoting insulin resistance and fatty acid oxidation over glucose, catecholamines increase myocardial oxygen consumption and deplete energetic substrates within the cardiomyocytes.[86] Consequently, transient hemodynamic improvement may be outweighed by adverse events related to arrhythmias, hyperglycemia, lactic acidosis and beta-adrenergic receptor desentitization.[87,88] A mismatch between increased myocardial oxygen demand and oxygen delivery may further amplify myocardial reperfusion injuries. Increasing levels of catecholamines have also been associated with bacterial growth, increased germ virulence, and biofilm formation.[89]

Interestingly, the potential clinical impact of cardiovascular drug support in cardiac surgery has been examined in four observational studies, three of them suggest a link between the administration of

Table 4: Recommandations for perioperative administration of inotropes and vasopressors

Inotropic agents	Usual Infusion regimen	Mode of action	Hemodynamic effects (at usual dosage)	Indications Adverse effects
Dopamine	• <3 mg/kg/min renal vasodilatation • 3–5 mg/kg/min inotropic effect • >5 mg/kg/min: vasoconstriction	D-AR ++ β1-AR +++ β2-AR - α-AR +++	HR ↗ CI ↗ MAP ↗ MPAP (↘) MVO_2↗	• LV/RV dysfunction • Potential mismatch of DO_2/VO_2 in splanchnic area • Immune and endocrine disturbances
Isoprenaline	• Bolus 5-20 µg or • 0.02–0.2 mg/kg/min	D-AR - β1-AR +++ β2-AR +++ α-AR -	HR ↗↗↗ CI ↗ MAP ↘ MPAP ↘ MVO_2↗↗	• Brady-arrhythmia, heart transplantation • Risk of hypotension, tachy-arrhythmias
Adrenaline	• 0.01–3.0 µg/kg/min	D-AR - β1-AR +++ β2-AR ++ α-AR ++	HR ↗(↗) CI ↗ MAP (↗) MPAP (↘) MVO_2↗ (↗)	• LV/RV dysfunction, long CPB duration • Tachyphylaxis • Lactic acidosis • ↗glycemia
Dobutamine	• 2–20 µg/kg/min	D-AR - β1-AR +++ β2-AR + α-AR -	HR ↗↗ CI ↗ MAP (↘) MPAP ↘ MVO_2↗ (↗)	• First line inotrope • Tachyphylaxis • Hypotension
Milrinone	• Loading dose: 25-75 µg/kg • Maintenance: 0.3-0.8 µg/kg/min	Phospho-diesterase type III inhibitors	HR ↗ CI ↗ MAP ↘ (↘) MPAP ↘↘ MVO_2 (↗)	• RV dysfunction • Chronic β-blockers • Hypotension • Atrial fibrillation
Levosimedan	• Loading dose: 12-24 mg/kg • Maintenance: 0.05-0.2 µg/kg/min	Calcium sensitizer of myofilament Mitochondrial ATP-sensitive K^+ channels	HR (↗) CI ↗ MAP ↘ MPAP ↘↘ MVO_2-	• High-risk patients • Hypotension
Norepinephrine	• 0.01–3.0 µg/kg/min	β1-AR + α-AR +++	HR - CI =, ↗ or ↘ MAP ↗ MPAP - MVO_2 (↗)	• Vasoplegia • Combined with Mirinone, Dobutamine or levosimedan • Tachyphylaxis
Phenylephrine	• 100 µg bolus or infusion 0.01–3.0 µg/kg/min	β1-AR - α-AR +++	HR - CI = ↗ or ↘ MAP ↗ MPAP - MVO_2 (↗)	• Vasoplegia • Tachyphylaxis
Terlipressin	• 0.5 -2 mg bolus (repeated after 6h)	V1, V2 receptor agonist	HR ↗- CI = or ↘ MAP ↗ MPAP - MVO_2 (↗)	• Resistant vasoplegia to norepinephrine • Vasoconstriction (skin, intestine, myocardium)

catecholamines during weaning off bypass and worse clinical outcome. In a dataset of 1,471 adults undergoing elective cardiac surgical procedures, Muller *et al*, reported a higher 30-day mortality among patients receiving inotropes (60% of the whole cohort) compared with those untreated, although the preoperative risk profile did not differ between the two groups.[56] Likewise, in unselected consecutive cardiac cases (N=657), Fellahi *et al*, found that inotrope-dependent patients (13%) experienced larger release of troponin in the early postoperative period than patients nonexposed to inotropes.[90] After adjustment for confounding factors and propensity score stratification, the administration of catecholamines was highly predictive of cardiac

morbidity [OR of 3.0 and 95% confidence interval (CI) between 1.2 and 7.3]. In another large cohort study (N = 1,326 patients), inotrope exposure was independently associated with increased hospital mortality (OR 2.3, 95% CI 1.2–4.5) and with renal dysfunction (OR 2.7, 95% CI 1.5–4.6).[91] In contrast to these observations, Williams et al failed to demonstrate an association between inotrope treatment and major postoperative morbidity in a retrospective analysis of 2,390 high-risk patients undergoing CABGs.[8] Given the considerable variability in inotrope use and conflicting results gathered from observational studies, randomized prospective trials are needed to evaluate specific algorithm for cardiovascular drug support in moderate-to-high-risk patients. The authors believe that the inotropes should not routinely be administered since optimization of loading conditions, fluid filling and vasodilators, may ensure adequate organ perfusion in the majority of the low risk patients.

MANAGEMENT OF HIGH-RISK PATIENTS

Prophylactic Interventions

Cold blood cardioplegia rather than crystalloid cardioplegia has been adopted in the majority of heart centers. In a meta-analysis of 10 randomized clinical trials (N = 879 patients), the use of blood cardioplegia (compared with crystalloid hyperkaliemic solutions) was associated with a reduced incidence of LCOS (13% vs. 16.5%) and lesser release of myocardial biomarkers.[92]

Selected patients with easily accessible coronary lesions may benefit from off-pump revascularization, avoiding ischemic cardiac arrest and its consequent postreperfusion stunning. For the majority of patients undergoing on-pump CABG, preconditioning the heart by repeated short-lasting coronary occlusion has been shown to confer cardioprotection as evidenced by a significant reduction in cardiovascular drug support and fewer episodes of ventricular arrhythmias following separation from bypass.[93] Anesthetic preconditioning is much easier to apply and affords similar cardioprotective effects compared with ischemic preconditioning. In a meta-analysis of 27 trials including 2,979 patients, lesser requirements for inotropic support, lower troponin serum concentration, and higher cardiac indexes were reported in patients pretreated with volatile anesthetic agents compared with those receiving intravenous anesthetics.[94]

Glucose-insulin-potassium infusion (GIK) is one of the oldest cardioprotective interventions. Beneficial effects have been attributed to several physiological pathways including activation of phospatidylinositol 3-kinase, hyperpolarization of cardiomyocytes, predominant glucose utilization, up-regulation of the L-arginine-nitric-oxide pathway, and anti-apoptotic effects. Administration of GIK before CPB tends to improve postoperative myocardial recovery with lesser requirement for inotropes, higher cardiac index, fewer episodes of atrial fibrillation, and shorter length of stay in ICU.[95,96] However, in view of the deleterious consequences of hypo- and hyperglycemia, close monitoring of blood glucose levels is advocated whenever insulin treatment is initiated.[97]

Levosimendan is a novel noncatecholamine inotropic agent that binds to cardiac troponin C and enhances myofilament responsiveness to calcium, thereby increasing contractility and relaxation of the cardiomyocyte at minimal metabolic cost without promoting arrhythmias. It also increases coronary flow reserve and is thought to exert preconditioning effects by opening mitochondrial ATP-sensitive K^+ channels.[98] Preliminary data suggest that prophylactic administration of levosimedan in patients with severe LV dysfunction improves ventricular performance and enhances primary weaning from CPB with lesser need for additional inotropic or mechanical therapy.[99-103]

Phosphodiesterase inhibitors (PDEI) such as milrinone and enoxinone inhibit breakdown of cyclic adenosine monophosphate (cAMP) resulting in increased inotropy and decreased vascular tone.[104] In the PRIMACORP trial, the prophylactic administration of high-dose milrinone was associated with a 64% relative risk reduction in the development of LCOS following congenital cardiac operations.[105] Both PDEI and levosimendan are expected to be particularly efficacious in patients chronically treated with β-blockers and those with myocardial β_1-down-regulation owing to congestive heart failure.[106-108]

The insertion of an intra-aortic balloon pump (IABP) should be considered in patients with ongoing myocardial ischemia or unstable hemodynamic condition. Indeed, by reducing LV afterload and improving diastolic coronary blood flow particularly in subendocardial area, IABP exerts anti-ischemic myocardial effects and increases systemic oxygen delivery.[109] Dyub *et al*, performed a meta-analysis involving 2,363 high-risk patients that showed a lower mortality and shorter ICU stay in the group pretreated with IABP (4.7% vs. 8.3% in the control group).[110] Overall, one death could be prevented by treating 17

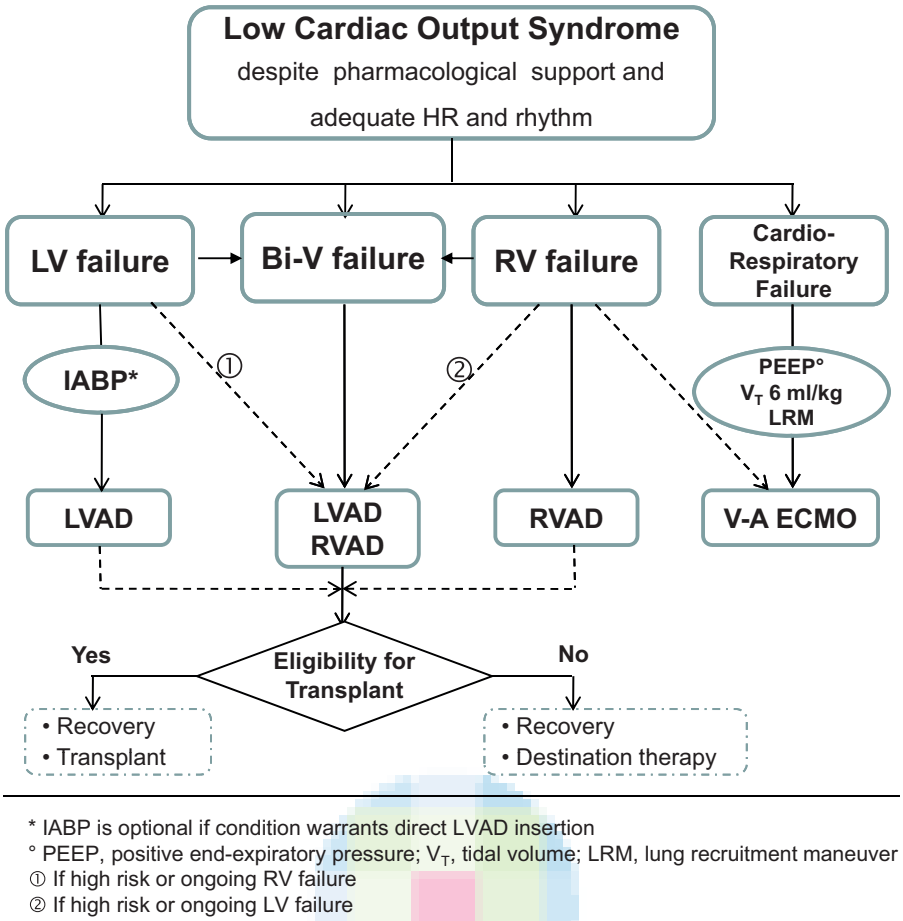

Figure 2: Mechanical circulatory support

patients with an IABP. A recent cohort study including 7,440 patients confirms that preoperative IABP is associated with a strong trend toward reduced rate of operative mortality (10%) despite a higher predicted mortality based on the Parsonnet score.[111]

Ultrafiltration during CPB has been advocated in patients with congestive heart failure to remove excessive fluid volume, it eliminates inflammatory mediators, and concentrates circulating erythrocytes.[112,113] Although this technique has been shown to reduce the need for cardiovascular drug support and blood transfusion, there are no data demonstrating an improvement in postoperative clinical outcome.

Pharmacological Treatment of Severe Ventricular Dysfunction

Patients with LCOS become (or are already) tolerant to the effects of beta-adrenergic agonists. Hence, the adjunction of non-catecholamines agents is deemed mandatory when the incremental infusion of beta-adrenergic agonists fails to enhance ventricular contractility. Both levosimendan and PDEIs (milrinone, enoximone), augment the efficiency of cardiac contraction, and increases stroke volume at a lesser metabolic cost than catecholamines, thereby facilitating the separation from CPB. Several studies including small series of patients suggest that milrinone therapy is associated with enhanced blood flow through coronary grafts, improved RV function, better LV diastolic function, attenuated release of biomarkers, and fewer myocardial infarcts.[114-117] However, in the randomized controlled OPTIME-CHF trial involving patients with acute heart failure, the use of milrinone failed to produce any clinical improvement and was associated with more frequent adverse events.[106] Likewise, in patients coming off bypass, milrinone treatment was associated with a higher incidence of hypotension and atrial fibrillation (56% vs.26% in nonusers).[118] More convincing scientific data lend support to the use of levosimedan in acute heart failure and in high-risk cardiac surgery. In a meta-analysis of 19 RCTs enrolling 3,650 patients with acute heart failure, levosimendan was associated with reduced mortality and a better hemodynamic profile compared with dobutamine.[119] Likewise, in 440 cardiac surgical patients included in 10 RCTs, favorable clinical and hemodynamic effects

were attributed to levosimendan compared with control patients receiving dobutamine or milrinone.[120] Interestingly, levosimendan was associated with significant reductions in perioperative mortality and in the rate of acute renal failure as well as with fewer episodes of myocardial infarction and atrial fibrillation. Although levosimendan is a promising agent, further randomized controlled clinical trials are warranted to confirm its cardioprotective effects and to assess its safety profile while optimizing the management of perioperative heart failure. However, at present the beta-adrenergic receptor agonists remain the first-line treatment of LV or RV dysfunction. Levosimendan is administered in selected high-risk patients (LV or RV EF < 30%) as a prophylactic treatment or as a rescue therapy in advanced stage of ventricular failure.[40]

Mechanical Circulatory Support

Mechanical assist devices to augment blood flow include the IABP, LV and RV assist devices, and extracorporeal membrane oxygenation (ECMO) devices [Table 5]. The decision to initiate IABP, or ECMO or implant ventricular assist device (VAD) should be made in a timely manner before the deleterious effects of increasing pharmacological therapy and multiorgan failure from persistent end-organ ischemia set in. Selecting the appropriate support device should take into account residual cardiac function, the presence of left/right or bi-ventricular failure, concomitant respiratory failure, underlying co-morbidities such as peripheral vascular disease as well as the potential of myocardial recovery [Figure 2].[121] Once mechanical support has been instituted, efforts should be made to keep MAP above 70 mmHg and mixed venous oxygen saturation above 70%. If VAD is implanted for isolated LV or RV failure, there is a critical need to optimize preload, to maintain HR and to support the other ventricle with inotropes. Periodically, it is imperative to set goals for weaning off mechanical support based on real-time hemodynamic monitoring, echocardiographic assessment, and end-organ function.

Intraortic Balloon Pump (IABP)

The IABP has stood the test of time and remains the first-line device therapy of postcardiotomy LCOS due to LV failure. In RV failure, its use is more controversial. The IAPB provides a marginal increase in CO (10–15%, +0.5 L/min), alleviates ventricular work and allows a reduction in inotropic infusion. The main limitation is that IABP requires a certain level of residual LV function. The IABP is usually inserted via femoral artery, although alternative sites of insertion (ascending aorta, axillary, or brachial artery) can be considered in patients with previous vascular surgery, calcifications of the ilio-femoral arteries as well as severe atheromatous disease or tortuosity of the descending aorta. In a benchmark study including 22,663 patients treated with IABP, weaning from CPB was rated as the third most frequent indication (18%) after cardiac catheterization (19%) and cardiogenic shock (20%).[122] Procedure-related complications—leg ischemia, local infection and hemorrhage—are observed in up to 5% of patients.[123] In contrast to pre-CPB insertion, post-CPB and postoperative insertion of IABP is associated with much higher operative mortality (10% vs. 16% and 47%, respectively).[124]

Ventricular Assist Device (VAD)

From the early 1970s, mechanical circulatory support devices have evolved into advanced easy-to-implant and easy-to-use devices, capable of reversing postcardiotomy LCOS in an "exit" strategy tailored specifically for each patient ("bridge" to recovery or transplantation or as "destination" therapy).[1,125] Overall, VADs can be divided into two main types: (1) the pulsatile pump that mimics the natural cardiac stroke volume and (2) the continuous flow devices that can be subdivided into centrifugal and axial flow pumps. In a meta-analysis including 125 patients with cardiogenic shock, Cheng et al found that, support with LVAD resulted in higher cardiac index and MAP compared with the IABP.[126] However, higher rates of bleeding and hemolysis were observed in the VAD group and 30-day mortality did not differ between the two groups.

Extracorporeal Membrane Oxygenation (ECMO)

Although initially proposed for treating the failing lungs, ECMO is also considered a suitable short-term therapy of cardiorespiratory insufficiency following cardiac surgery, particularly for patients with severe pulmonary edema, those with persistent ventricular arrhythmias due to extensive myocardial infarct and those with RV failure.[127] For initiation of ECMO right atrial blood is drained via a large cannula, pumped through an artificial lung and delivered for organ perfusion through the femoral artery. The vascular access is usually percutaneous, although direct cutdown access might be preferred in patients with profound cardiogenic shock. ECMOs with non-porous hollow fiber (polymethylpentene) lung membranes offer low resistance to blood flow and allow safe use of centrifugal pumps. Nonthrombogenic coatings of the whole circuit reduce the need for anticoagulation and the risk of bleeding.

Table 5: Mechanical devices used to separate from cardiopulmonary bypass

	Mechanism of assistance	Insertion route	Location	Max Flows	Remarks	Risks
Short-term assistance						
IABP	Pneumatic, pulsatile LV (RV) support	Percutaneous; femoral artery or transaortic	Extracorporeal	+ 0.5 L/min	Easy to implant and to use	Limb ischemia + Hemolysis 0 Bleeding +
ECMO	Non-pulsatile, centrifugal pump	Percutaneous or cutdown; femoral artery and vein	Extracorporeal	6 L/ min	Provide biventricular support and blood gas exchange	Limb ischemia ++ Hemolysis ++ Bleeding ++ Inflammation +
Intermediate/ Long-term assistance						
Impella 2.5 Impella 5.0 Impella LD Impella RD	Microaxial, non-pulsatile	Femoral cutdown/ percutaneous, retrograde across the aortic or pulmonary valve	Intravascular Intravascular Sternotomy	2.5 L/ min 5.0 6.0 6.0	Systemic anticoagulation is not necessary due to continuous flushing by a heparin containing purge solution; mainly used for LV support	Limb ischemia ++ Hemolysis ++++ Bleeding +
TandemHeart	Centrifugal, non-pulsatile	Femoral artery and femoral vein with transseptal puncture to the LA; pulmonary artery access via the RA	Intravascular (transthoracic)	8.0 L/ min	Can be placed percutaneously or transthoracically; Provide uni- biventricular support	Limb ischemia ++ Hemolysis ++ Bleeding +++
Abiomed BVS 5000	Pneumatic, pulsatile	Sternotomy	Extracorporeal	6 L/ min	Safe and easy to use with minimal monitoring; patient needs to be immobilized	Hemolysis 0 Bleeding + Thrombus +
Abiomed AB	Pneumatic, pulsatile	Sternotomy	Paracorporeal	6 L/ min	Patient can deambulate; potential clots pump can be visualized in the pump housing	Hemolysis 0 Bleeding + Thrombus +
Thoratec IVAD or PVAD	Pneumatic, pulsatile	Sternotomy	Intracorporeal Paracorporeal	6.5 L/ min	Can provide left, right or bi-ventricular support	Limb ischemia + Hemolysis 0 Bleeding +
Centrimag	Centrifugal, non-pulsatile	Sternotomy	Paracorporeal	9.9 L/ min	Magnetic levitation technology minimized blood stagnation, turbulence and hemolysis	Limb ischemia + Hemolysis 0 Bleeding +

CONCLUSIONS

Knowledge of patient- and procedure-related risk factors should be integrated in the medical decision process along with the implementation of perioperative protective strategies. Team education, adoption of checklists, and simulation-based training may further enhance physician'performances during the CPB weaning process. Integration of a standardized approach for weaning off bypass focusing on simple hemodynamic targets, TEE assessment, along with a goal-directed therapy involving pharmacological agents (inotropes, vasodilators, and vasopressors) and eventually mechanical support devices can potentially improve the outcome. Large trials are warranted to assess the best cardioprotective strategies and to validate algorithms suitable for the CPB weaning process in cardiac surgery.

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