Management of Challenging Cardiopulmonary Bypass Separation

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1053/j.jvca.2020.02.038

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SEPARATION from cardiopulmonary bypass (CPB) after cardiac surgery is a progressive transition from full mechanical circulatory and respiratory support to spontaneous mechanical activity of the lungs and heart. During the separation phase, measurements of cardiac performance with transesophageal echocardiography (TEE) provide the rationale behind the diagnostic and therapeutic decision-making process. In many cases, it is possible to predict a complex separation from CPB, such as when there is known preoperative left or right ventricular dysfunction, bleeding, hypovolemia, vasoplegia, pulmonary hypertension, or owing to technical complications related to the surgery. Prompt diagnosis and therapeutic decisions regarding mechanical or pharmacologic support have to be made within a few minutes. In fact, a complex separation from CPB if not adequately treated leads to a poor outcome in the vast majority of cases. Unfortunately, no specific criteria defining complex separation from CPB and no management guidelines for these patients currently exist. Taking into account the above considerations, the aim of the present review is to describe the most common scenarios associated with a complex CPB separation and to suggest strategies, pharmacologic agents, and para-corporeal mechanical devices that can be adopted to manage patients with complex separation from CPB. The routine management strategies of complex CPB separation of 17 large cardiac centers from 14 countries in 5 continents will also be described.

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**Key Words:** anesthesia; intensive care; cardiopulmonary bypass; inotropes; ventricular dysfunction; weaning; separation; discontinuation

CARDIOPULMONARY BYPASS (CPB) has multiple adverse effects on the cardiovascular system including transcapillary plasma loss secondary to an increase in vascular permeability, vasoconstriction, and destruction of platelets and red blood cells.1,2 Separation from CPB is the gradual transition from extracorporeal circulation to the native cardiac activity with the aim of providing satisfactory oxygen through the pulmonary and systemic circulations. This process is completed after the administration of protamine and the removal of the venous and arterial cannulae.3 While pharmacologic and temporary mechanical circulatory support (MCS) of the cardiac function can be instituted before surgery when complex CPB separation is anticipated, a prompt diagnosis has to be made in case of unexpected failed discontinuation from the extracorporeal circulation.

No single definition of challenging separation from CPB exists. However, a difficult CPB separation can be defined as the need of at least 2 inotropes or vasopressors to successfully accomplish the separation from CPB. A very difficult wean-off CPB occurs when the first weaning process fails or the patient requires a mechanical device to be separated from CPB.3 Complex CPB separation is a life-threatening complication associated with high perioperative mortality, especially when acute right heart failure also occurs.3

At the San Raffaele Scientific Institute and University in Milan, Italy, the Vasoactive and Inotropic Score (VIS) is currently used for decision making in patients with complex CPB separation. Table 1 shows how to calculate VIS.5 The authors constructed the following 3 categories of CPB separation according to VIS values: <10 is “easy”; 10 to 30 is “difficult”, >30 is “complex”, and in the latter case an MCS such as an intra-aortic balloon pump (IABP) is usually added to the inotropic support. The association between the need for high dose vasoactive drugs and poor outcome is widely addressed in literature.3,4,5

Because there are no guidelines on the management of complex separation from CPB, the aim of the present review is to describe the most common scenarios associated with complex CPB separation, and to suggest management strategies adopting pharmacologic agents and paracorporeal mechanical devices. In addition, the management of patients with difficult CPB discontinuation is summarized from information coming from 17 hospitals distributed in 5 continents.

### Predictors of Complex CPB Separation

Complex CPB separation is a life-threatening condition that increases perioperative morbidity and mortality.1–4 The identification of factors associated with complex CPB separation is a valuable and often underestimated field of research. The scores commonly used in cardiac surgery to stratify the perioperative risk of the patient (ie, ACEF [age, creatine, ejection fraction],7 Society of Thoracic Surgery Risk Score, logistic EuroSCORE8) consider only preoperative variables and fail to account for intraoperative events such as complex CPB separation. Thus, in daily practice they fail to “fully” predict the outcome. Unfortunately, there are no scores in the literature able to fill this gap predicting a rough intraoperative course. In a sub-analysis of the BART trial, Denault et al.2 observed that age, previous myocardial infarction, depressed ejection fraction, mitral surgery, previous cardiac surgery, partial thromboplastin time, and CPB duration were independent predictors of complex CPB separation. Notably, not all cardiac surgeries carried the same risk of complex CPB separation. For example, isolated aortic valve replacement for aortic stenosis was associated with “easy” CPB separation in a higher percentage of cases than mitral surgery. In another case series, when aortic valve replacement was performed together with coronary artery bypass graft (CABG) surgery, the inotropic support was required in 52% of patients to allow CPB separation.9 Long CPB and aortic cross-clamp time expose the myocardium to ischemic insult for long periods of time and are probably the

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<thead>
<tr>
<th>Table 1 How to Calculate Vasoactive and Inotropic Scores</th>
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<td>Vasoactive and Inotropic Score (VIS)=</td>
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<tr>
<td>dopamine dose (µg/kg/min) +</td>
</tr>
<tr>
<td>dobutamine dose (µg/kg/min) +</td>
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<tr>
<td>enoximone dose (µg/kg/min) +</td>
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<tr>
<td>100 × epinephrine dose (µg/kg/min) +</td>
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<tr>
<td>100 × norepinephrine dose (µg/kg/min) +</td>
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<tr>
<td>10 × milrinone dose (µg/kg/min) +</td>
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<tr>
<td>10,000 × vasopressin dose (U/kg/min)</td>
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main determinants of severe hemodynamic instability during CPB separation.10 Biomarkers of tissue hypoperfusion may anticipate complex CPB separation. Rao et al.11 found that increased myocardial lactate during reperfusion predicted the occurrence of low cardiac output (CO) syndrome.

In the modern era, TEE is a powerful tool in the management of patients undergoing cardiac surgery. Before the beginning of surgery, TEE can easily detect a preexisting left ventricle (LV) and RV failure, which are both strong risk factors for high inotropic requirements and mortality.12 At the beginning of CPB, TEE can detect LV distention during cardioplegia administration or mispositioning of the cardioplegia cannula, both of which are leading causes of suboptimal myocardial protection. After CPB, TEE can identify prosthetic valve dysfunction, paravalvular leaks, or interventricular defects that along with coronary embolization (air or debris) may represent the leading causes of complex CPB separation.

Patients with anticipated complex CPB separation can receive a pre-emptive non-pharmacologic and pharmacologic treatment. The use of prophylactic IABP is still a matter of debate. Ranucci et al.13 and Rocha Ferreira et al.14 did not observe a reduction in the rate of major postoperative morbidity in high-risk patients undergoing non-emergent CABG which were treated with prophylactic IABP. On the contrary, meta-analytic15 and retrospective data16 suggested a beneficial effect of prophylactic IABP. The authors report that at San Raffaele Hospital, they do not routinely start IABP preoperatively in high-risk patients, preferring a “wait-and-see” approach. They do, however, position the IABP introducer before CPB often. With regard to the administration of vasoactive agents, they might use preemptive administration of levosimendan or phosphodiesterase 3 inhibitors but they choose catecholamines based on TEE findings and hemodynamic parameters after the initiation of CPB separation.

### Separation from CPB

At the end of CPB, the heart recovers its mechanical activity and begins to deliver oxygenated blood to the whole body. Heart rate, rhythm, atrioventricular conduction, and ST analysis are assessed by electrocardiogram. In the authors’ institution, before starting to reduce CPB support, temporary wires are routinely sutured to the right atrium and right ventricular free wall and are then connected to a standard external dual-chamber pacemaker in order to promptly treat alteration of cardiac rhythm. In particular, sinus bradycardia is managed with atrial pacing in the absence of atrioventricular conduction block. A right atrioventricular pacing is primarily used with atrioventricular block because this modality is associated with dysynchrony and a reduction in CO when compared with atrial pacing.

Supraventricular tachycardia and AF, if not chronic cases, require treatment with electrical cardioversion. Amiodarone, esmolol, and calcium channel blockers may be used in the event of persistence or early relapse of a supraventricular tachyarrhythmia,17 with bradycardia, hypotension, and heart failure considered as possible side effects.18 Digoxin can be considered for rate control as second-line therapy.19 In a double-blind, placebo-controlled trial on 389 patients undergoing cardiac surgery, Kliger et al.20 found that 50 mg/kg of magnesium administered after the induction of anesthesia followed by an infusion of 100 mg/kg for 3 hours did not reduce the occurrence of postoperative AF.

Ventricular fibrillation occurs between 10% and 80% of patients after aortic clamp release, owing to ischemic and ischemia-reperfusion injury,21 and can be associated with subendocardial damage. Recently, Mitai et al.22 found that the prophylactic use of amiodarone is more effective than lidocaine in preventing ventricular fibrillation in patients with left hypertrophic ventricle undergoing aortic valve replacement.

A transitory ST segment elevation in the inferior leads, along with regional wall motion abnormalities of the inferior-posterior wall, is commonly observed immediately after aortic cross clamp release and is often attributed to air embolism of the right coronary artery. An increase of blood pressure may resolve the problem of “spilling out” the air from the coronaries (increasing the aorto-coronary gradient). Sustained ventricular arrhythmia in absence of electrolyte abnormalities should raise suspicion for ischemia. Electrocardiography and TEE are useful at this stage. In fact, a persistent ST segment elevation and detection of new regional wall motion abnormalities are both suggestive of coronary occlusion. In this circumstance, it is important to promptly exclude ischemia determinants which may depend on graft pathology in CABG (stenosis, kinking, anastomotic narrowing, incomplete revascularization, or poor distal run-off), suture of the circumflex coronary artery in mitral valve surgery, or coronary occlusion in surgery involving the aortic root. Surgical re-exploration and/or a new aortic coronary graft may be required to solve this condition.

The diagnosis of hypovolemia and the determination of the right amount of blood products and fluids to be infused should be done in conjunction with TEE and hemodynamic data (ie, central venous pressure [CVP] and wedge pressure).4,17 During CPB separation, it is crucial to avoid overdistension of the RV and careful fluid expansion is required. However, complex separation from CPB still occurs in about 10% to 45% of patients even after preload optimization.10 TEE is the cornerstone of diagnosis for complex CPB separation causes after fluid status has been corrected. Figure 1 summarizes the etiologies of a complex separation from CPB in normovolemic conditions and in absence of structural or dynamic abnormalities. As a practical rule, if the LV shows a low CO output with low filling pressures, fluid administration is recommended and the residual blood present in the venous reservoir can be used.17 Contrarily, low CO with elevated CVP and wedge pressure usually occurs in the event of heart failure and requires inotropes. The hemodynamic data are usually integrated with those of the TEE along with the direct inspection of the RV.

### Vasoplegic Syndrome

Vasoplegic syndrome is defined by the following criteria: hypotension (mean arterial pressure <50 mmHg or systolic blood pressure <85 mmHg), low systemic vascular resistance (<600-800 dynes s cm⁻⁵), or systemic vascular resistances
indices <1800 dyne s cm⁻¹ m²), normal or high systemic flows (cardiac index >2.5 L min m⁻²), normal or reduced central filling pressures (CVP < 10 mmHg and pulmonary wedge pressure <10 mmHg), and by an increased need for vasopressors (0.2-0.5 µg/kg/min of norepinephrine with normal intravascular volume). In this case, TEE examination usually reveals good contractility with hyperkinetic LV.

As reported by Liu et al., the incidence of vasoplegic syndrome in cardiac surgery with CPB is around 9%. Vasoplegic syndrome mortality typically ranges from 5% to 15% but may be as high as 29% when lasting >48 hours.

Under the pathophysiologic point of view, vasoplegia hypotension is secondary to a deficit of vascular smooth muscle cell contraction. In fact, the hyperpolarization of the plasmatic membrane uncouples the activated voltage-dependent channel from the influx of calcium in the cytoplasm, preventing the vasoconstriction even with high doses of catecholamines. In addition to nitric oxide, natriuretic peptide, and adenosine, activating the adenosine triphosphate sensitive potassium channel antagonizes smooth muscle cells contraction which further worsens the hypotension.

In cardiac surgery, CPB triggers a massive inflammatory response with nitric oxide production and vasopressin deficiency plays a pivotal role in the development of vasoplegia (Fig. 2).

Systemic vasodilation and reduced mean arterial pressure are common after CPB owing to the re-establishment of normothermia and to hemodilution. Under most circumstances, this problem is easily treated using a vasoactive drug (eg, norepinephrine, phenylephrine, or vasopressin). However, when vasoplegia is refractory to these medications, treatment consists of transfusing with a target Hb level of at least 9 g/dL and administering epinephrine, steroids, and diphenhydramine. This relatively high transfusion trigger, although controversial, is supported by the observation that anemia and hemodilution are trigger factors for vasoplegia. A next step may include the administration of methylene blue. However, its usage depends on the presence or absence of risk factors for the development of serotonergic syndrome (pre-operative use of serotonin norepinephrine re-uptake inhibitors, selective serotonin re-uptake inhibitors, clomipramine) or glucose 6-phosphate dehydrogenase deficiency. If the risk of serotonin syndrome is high, 5 to 10 g intravenous of hydroxocobalamin is indicated and 10 to 40 ng/Kg/min of angiotensin II is a valid alternative (if the risk of thrombosis or reactive airway disease is low). When the risk for the development of serotonergic syndrome is low, a slow bolus of 2 mg/kg of methylene blue followed by a continuous infusion of 0.25 mg/kg/h for...
6 hours may treat vasoplegia. A rescue therapy consists in the administration of Vitamin C (1.5 g every 6 hours) and thiamine (especially in thiamine depleted patients). In fact, Vitamin C is involved in the synthesis of catecholamines and as shown by Wierszewski et al., it may spare vasopressors. Because terlipressin has a longer half-life (5-6 hours) when compared with vasopressin (6 minutes) it could play a role in the management of refractory vasopleugia if administered either as continuous perfusion (1.5 \( \mu \)g/kg/min) or bolus (1 mg). However, the persistent CO decrease owing to prolonged increase of the systemic vascular resistances and the reduction of platelet count limit its used in this setting.32

**Figure 3**

### Right Ventricular Failure

Severe RV failure post-CPB is associated with high mortality rates up to 86%. The contractility of the RV may be affected by poor myocardial inotropism (secondary to pre-operative coronary artery disease, post-CPB myocardial stunning, poor myocardial protection, and arrhythmias) or by myocardial hypoperfusion (secondary to air embolism or thromboembolism in the right coronary artery, kinking of the venous graft after CAGB surgery, low aorta-coronary pressure gradient secondary to left ventricular dysfunction).36

After CPB separation, acute RV dysfunction is usually associated with high CVP in the context of an enlarged RV with depressed contractility. A tricuspid annular plane systolic excursion below 16 mm and/or an S’ wave at the Tissue Doppler index below 10 cm/sec are TEE characteristics of right ventricular failure. A right mid-cavity diameter greater than 42 mm and a longitudinal diameter greater than 92 mm are signs of right ventricular enlargement. Right fractional area change assessed in midesophageal 4 chambers view is a time effective and easy method to evaluate the RV during CPB separation. A right fractional area change below 30% or a decrease of 20% compared with the baseline is suggestive of RV dysfunction. However, the right ventricular geometry is complex and therefore the assessment of the RV function in clinical practice often remains qualitative.37 Usually, a TEE with a D-shaped LV on trans-gastric short axis view is also suggestive of RV volume overload and failure. The need for reducing RV volume by sequestering volume into the reservoir while the venous cannula is in place, avoidance of further or overzealous transfusion from the reservoir through aortic cannula are reasonable strategies in the face of a dilated, poorly functioning RV. The use of diuretics may improve a failing, dilated RV post-decannulation or in perioperative period.

Therapeutic interventions in RV dysfunction aim to optimize the preload, reduce the afterload, and improve the contractility.38 The RV is particularly sensible to increments in pulmonary vascular resistance. As reported in the supplement (Supplemental Table 1), when CPB separation is challenging because of RV failure, there is a general agreement regarding what should be the first line of therapy and simple measures such as gas exchange and preload optimization should be applied before moving toward more aggressive treatments. With respect to the next steps, the strategies are largely heterogeneous owing to the lack of convincing data and systematic trials on the effect of inotropes and vasopressors and MCS on clinically relevant outcomes in the setting of acute right heart failure. Generally speaking, the treatment of RV dysfunction is functionally linked to the occurrence of pulmonary hypertension. In the absence of pulmonary hypertension, the vast majority of centers use dobutamine or epinephrine (with or without norepinephrine according to blood pressure values). In few hospitals, nitroglycerine, dopamine, and vasopressin are considered as second-line options. If RV failure is associated with pulmonary hypertension, inodilators and/or inhaled nitric oxide are widely applied on top of catecholamines.

For moderate RV dysfunction, defined as an RV area change between 17% and 30%, dobutamine is likely the drug of choice. Epinephrine, however, is the first line therapy in case of severe RV failure, with hypotension and/or associated left ventricular failure.39 If there is high pulmonary vascular resistance, a selective phosphodiesterase III inhibitor such as milrinone or enoximone may be considered. Notably, in a recent retrospective experience, Nielsen et al. reported a higher risk of death at 30-days and 1 year when intraoperative milrinone was used compared with dobutamine.40 There are only 2 randomized controlled trials (RCTs) comparing dobutamine and milrinone as single inotropes for the management of low CO syndrome after CPB separation. Feneck et al. reported that milrinone and dobutamine were equally effective in the treatment of low CO syndrome and pulmonary hypertension when started within 2 hours from CPB separation. In particular, dobutamine was associated with atrial fibrillation (AF) and hypotension, whereas milrinone was associated with bradycardia. Similarly, a substantial equivalence between dobutamine and milrinone in terms of hemodynamic parameters was reported by Carmona et al. and recently confirmed by a network metanalysis.

Unfortunately, despite a large use of these agents during CPB separation, the scientific evidence on which drug is more effective is substantially lacking. In fact, to the best of the authors’ knowledge there are no randomized trials focusing on clinically relevant endpoints. Thus, it is not unexpected, as reported by Nielsen et al., that the perioperative choice of inotropic support remains strongly related to the cardiac anesthesiologists’ attitude and to hospitals’ internal protocols. In addition, Belletti et al. found that inotropes and vasopressors in cardiac surgery are not detrimental per se, although an accurate evaluation of risks and benefits is always required.

Enoximone is not available in North America. However, enoximone and milrinone share a similar mechanism of action (phosphodiesterase III inhibitors) and act on the cardiovascular system in a similar fashion. Enoximone has a half-life 10 times longer than milrinone, with an active metabolite which further prolongs the hemodynamic effects. Both were studied in patients with heart failure and cardiac surgery. Catecholamines show a greater increase in heart rate and mean arterial pressure, whereas phosphodiesterase III inhibitors are more efficient in reducing wedge pressure and increasing CO. The major drawback to the use of phosphodiesterase III inhibitors
Fig. 3. Pathophysiology of vasoplegic shock related to cardiac surgery.

Abbreviations: A2A ADP, A2A adenosine receptor; AVP, vasopressin; BP, blood pressure; Ca+2, ionized calcium; cG NE, norepinephrine; CO, cardiac output; GTP, guanosine triphosphate; Ip3, inositol 1,4,5-trisphosphate; KATP, potassium adenosine triphosphate channels; LV, left ventricle; MP, cyclic guanosine monophosphate; NO, nitric oxide; PHE, phenylephrine; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; V1, V1 receptor for vasopressor.
is their vasodilator effects which may lead to hypotension, particularly in hypovolemic patients and/or those with high systemic resistances. This side effect is important because hypotension owing to low diastolic and coronary perfusion pressure, rather than low CO, is associated with 30-day mortality in multivariate analysis \( (p = 0.005) \).\(^{45}\)

In a randomized multi-center double-blind placebo-controlled phase III study, Denault et al.\(^{46}\) demonstrated that in high-risk cardiac surgery patients with pulmonary hypertension, the prophylactic use of inhaled milrinone (5 mg) was associated with a better hemodynamic profile but had no effect on the rate of complex separation from CPB, RV failure, and mortality. Gebhard et al.\(^{47}\) reported that milrinone administered in the tracheal tube during challenging CPB separation secondary to severe RV dysfunction improves RV function, decreases RV size, and increases end expiratory carbon dioxide. Notably, the same authors but in a retrospective analysis observed that the intratracheal administration of 5 mg of milrinone treated hemodynamic instability in 62\% of patients, reducing CVP and improving the RV performance assessed by TEE and direct inspection.\(^{48}\) Nebulized and intratracheal milrinone were not associated with hypotension (which is common with the intravenous administration) and were equally effective in improving the RV performance. In addition, intratracheal milrinone administration was much faster, cheaper, and simpler than the inhaled route, making it particularly attractive in the setting of a challenging CPB separation. In fact, nebulized milrinone requires specific equipment and has an onset time of 20 minutes.\(^{46}\) The role of levosimendan in the context of RV dysfunction is poorly investigated. However, in light of the recent evidences which questioned its efficacy in the perioperative setting,\(^{49-51}\) the authors suggest to reserve the administration of levosimendan to patients several hours before surgery for optimal results.

**Moderate Pulmonary Hypertension and Normal RV Function**

If there is moderate pulmonary hypertension (eg, systolic pulmonary pressure between 35 and 60 mmHg)\(^{39}\) in the context of normal right ventricular function and low preload (defined as a CVP <10 mmHg and/or an inferior vena cava diameter on TEE of less than 20 mm), a gradual filling of the heart using the venous reservoir while constantly monitoring RV shape and function, as well as hemodynamic parameters, should be performed to assess if CO increases.

If the heart is already working on the plateau of the Frank-Starling curve, the administration of fluids is detrimental (eg, in patients who are not fluid-responsive) and may increase the end diastolic pressure without further improvement in stroke volume. In this context, further increments in end diastolic pressure can lead to myocardial ischemia, a shift of the interventricular septum toward the LV (ventricular interdependence) and, eventually, to biventricular failure.\(^{52}\)

CVP represents the relationship between venous return and cardiac performance rather than preload.\(^{38}\) In spite of being set aside by many authors in the last few years, CVP remains a useful parameter in the daily clinical practice especially when integrated with data on CO, contractility, and preload assessed by the TEE. In fact, CVP values may depend on cardiac function, volemia, or venous resistance. With this approach, CVP is crucial in making the diagnosis of heart failure. For example, low CO with high CVP is suggestive of poor contractility, low heart rate, or afterload augmentation. Low CO with low CVP may be related to a decrease in blood volume or venous dilation. A low CVP with high CO is a good marker of improvement of the cardiac function. High CVP and high CO may be secondary to increased venous return.

It is well known that CVP is a poor predictor of fluid responsiveness. Nevertheless, when associated with the assessment of the CO by TEE or Swan Ganz catheter, CVP is helpful in the interpretation of fluid responsiveness. Administration of fluids, increasing the bulk of blood volume, leads to an increased venous return, right heart preload and CO if the patient is on the ascending part of the Frank-Starling curve (fluid responder). On the contrary, if the CO does not change (non-responders), the direction of CVP variation is useful in order to know whether the fluid administered was insufficient or if the heart is failing. In fact, when the CVP does not change after fluid administration it may mean that an insufficient volume of fluids has been administered. By contrast, when the CVP rises, the patient is on the flat part of the Frank-Starling curve. Generally, extreme CVP values may guide the administration of fluids better than intermediate values.\(^{54}\) In a recent meta-analysis, Eskesen et al.\(^{55}\) observed that a CVP less than 8 mmHg was associated to a fluid responsiveness in two thirds of the patients whereas a CVP above 12 mmHg in one third of cases. Biasis et al.\(^{56}\) reported that the increase in stroke volume after a fluid challenge was unlikely when the CVP was above 15 mmHg and was frequent when the CVP value was below 6 mmHg. Given the above considerations, CVP is not reliable as a standalone parameter. However, extreme values when integrated with measures of flow such as the ones made by TEE assessment can be useful in guiding therapy.

High CVP (above 15 mmHg) should be treated with an aggressive diuretic therapy\(^{35}\) if there is clinical or TEE evidence of volume overload with RV or LV failure.

**Severe Pulmonary Hypertension**

Generally speaking, the RV tolerates chronic pulmonary hypertension better than acute changes in afterload.\(^{39}\) The impact of chronic PAH on outcome is related to the involvement of the RV. In fact, a longstanding pulmonary hypertension may lead to RV dilatation and dysfunction, which in turn decreases LV CO and coronary perfusion when the interventricular septum shifts toward the LV.\(^{57}\) In addition, because the RV coronary supply occurs during the entire cardiac cycle, chronic pulmonary hypertension leading to high end systolic and diastolic RV pressure puts the RV at high risk of ischemia during CPB separation. Patients with chronic pulmonary hypertension and RV failure show a high sympathetic tone and concomitant downregulation of the catecholaminergic receptors, deep anesthesia, by blunting the sympathetic tone, may
therefore further contribute to hypotension worsening even more the RV function.\textsuperscript{35} An acute increase in pulmonary vascular resistance (eg, causing an increase of mean pulmonary pressure above 40 mmHg) cannot be tolerated by the RV for a long period of time and may lead to RV failure with a proportional reduction in CO. In case of severe pulmonary hypertension with preserved right ventricular function, a pharmacologic approach should lead to a reduction in pulmonary vascular resistance without affecting the systemic vascular resistance.

The first agents used to treat this condition are the inhalational agents such as nitric oxide and iloprost (synthetic prostaglandin inhibitor 2 analog) even though a beneficial effect on clinically relevant outcomes has not been demonstrated yet.\textsuperscript{52} Nitric oxide is a rapidly-acting selective pulmonary vasodilator that, after diffusion into the smooth muscle cells, stimulates cyclic guanosine monophosphate release. The side effects of nitric oxide include the following: inhibition of platelet aggregation, methemoglobinemia, and rebound pulmonary vasoconstriction after abrupt discontinuation.

Recently, in a meta-analysis of 18 RCTs conducted in cardiac surgery by Sardo et al.,\textsuperscript{57} it was demonstrated that inhaled nitric oxide has a clinically negligible effect on the length of mechanical ventilation and intensive care unit stay when compared with any other vasodilator therapy. Even in patients with acute respiratory distress, Gebistorf et al.\textsuperscript{58} reported that inhaled nitric oxide was associated with a transient improvement in oxygenation with no effect on survival. Only in infants did inhaled nitric oxide lead to a better composite outcome reducing the incidence of death and the need for ECMO.\textsuperscript{55} However, it is important to recognize that the vast majority of the studies on inhaled nitric oxide are small and single-centered, putting them at high risk of bias.\textsuperscript{17} Moreover, clinical outcomes, such as mortality or duration of hospitalization in cardiac surgery patients, depend on several factors including comorbidities, quality of surgical repair, length of CPB, and intraoperative and postoperative supportive care. As a matter of fact, inhaled nitric oxide is largely used in daily clinical practice in postcardiotomy RV dysfunction with increased pulmonary vascular resistance refractory to standard inotropic support.\textsuperscript{50} Owing to the risk of rebound pulmonary vasoconstriction during the weaning from inhaled nitric oxide, sildenafil (a phosphodiesterase 5 inhibitor) therapy should be initiated.\textsuperscript{60}

Iloprost is a stable analogue of prostacyclin. It stimulates the production of cyclic adenosine monophosphate in the vascular smooth muscle cells, and this leads to potent muscular relaxation. This muscular relaxation reduces the pulmonary vascular resistance, improves the RV performance, and increases the CO. Iloprost might have antiplatelet and antiproliferative effects and its pulmonary vasodilatory effect is synergistic to inhaled nitric oxide. The use of intravenous prostaglandin E1 and prostacyclin is limited by systemic hypotension and subsequent ischemia that can worsen the RV performance.\textsuperscript{61} To overcome these drawbacks, the pulmonary route is usually preferred. This drug is particularly attractive because it is cheaper, easier to administer, and has no toxic metabolites when compared with inhaled nitric oxide. As inhaled nitric oxide, prostaglandin E1 is a potent vasodilator with selectivity toward pulmonary circulation and with a short half-life that is degraded spontaneously at neutral pH. As opposed to inhaled nitric oxide, it acts through the cyclic adenosine monophosphate instead of the cyclic guanosine monophosphate pathway. Hanchè et al.\textsuperscript{62} found that epoprostenol was safe and more effective than a placebo in decreasing pulmonary pressure in 60 patients with pulmonary hypertension that were undergoing cardiac surgery. In comparison with intravenous vasodilators, Fattouch et al.\textsuperscript{63} reported a cardiac population with pulmonary hypertension in which prostaglandin E1 and inhaled nitric oxide equally improved the RV function by decreasing the pulmonary artery resistance. However, both studies were single-center and underpowered to draw clinically relevant conclusions. As a matter of fact, in a meta-analysis of RCTs, Elmi-Sarabi et al.\textsuperscript{64} observed that the prescription of aerosolized pulmonary vasodilators (milrinone, iloprost, nitric oxide and prostaglandin E1) ameliorated the performance of the RV more than placebo or intravenous vasodilators (nitroglycerine or nitroprusside). No significant differences on hemodynamic parameters were observed.

**Left Ventricular Failure**

After CPB and ischemic cardioplegic arrest, the systolic performance of the left heart may be reduced owing to suboptimal cardiac protection and prolonged aortic clamping time.\textsuperscript{65} Ventricular function is a major determinant of CO. Global or regional dysfunction may also develop after CPB separation.\textsuperscript{17} Although several studies with limited sample size postulated that halogenated anesthetics might provide additional myocardial protection through an ischemic preconditioning mechanism,\textsuperscript{66} Landoni et al.\textsuperscript{51} reported that in the largest RCT comparing volatile agents versus total intravenous anesthesia in patients undergoing on-pump CABG, there was no difference in 1-year overall mortality.

LV hemodynamic decompensation after CPB separation has to be rapidly ruled out. Again, TEE allows determining whether the hypotension is secondary to a depressed myocardial contractility, to a decreased preload, or to an increased afterload.\textsuperscript{67}

**Preload**

The qualitative estimation of the left ventricular end-diastolic area in the transgastric midpapillary short axis view can distinguish whether hypotension depends on cavity obliteration (“kissing” of the papillary muscles) or marked ventricular dilatation (usually end-diastolic diameter for male \(\geq 6.9\) cm indexed \(\geq 3.7\) cm/m\(^2\), female \(\geq 6.2\) cm indexed 3.8 cm/m\(^2\)).\textsuperscript{68}

Because the dynamic indices (pulse pressure variation, stroke volume variation, and systolic pressure variation) are reliable predictors of fluid responsiveness under strict conditions including closed thorax, absence of arrhythmias, and a tidal volume of 7 to 8 mL/kg, these parameters have a marginal role in the management of patients with challenging CPB separation.\textsuperscript{69}

A low preload may lead to systolic anterior motion (SAM) of the anterior leaflet of the mitral valve. This is a unique condition of hemodynamic instability that may mimic left ventricular dysfunction when TEE is not available. SAM occurs in
4% to 8% of all patients after mitral valve repair. SAM may be responsible for complex CPB separation and should be treated with: intravascular volume expansion; decrease of the heart rate to 60 to 70 beats per minute (eg, reducing the rate of the pacemaker if the heart is stimulated); stopping epinephrine and/or switching to Beta-blockers; increase the afterload with α1 agonists. In a few selected cases, mitral valve replacement may be necessary.70 In the authors’ experience, 92% of SAM after mitral valve repair can be solved with 2-step conservative management which consists in intravascular volume expansion and discontinuation of inotropic drugs (first step) and afterload augmentation through manual compression of the ascending aorta while administering esmolol (1 mg/kg) (second step). With this approach, fewer than 10% of patients require surgical revision for persistent SAM after mitral valve repair. Similarly, Loulmet et al.70 who analyzed more than 1,900 patients undergoing mitral valve repair, observed that the mainstay of SAM treatment is pharmacologic and based on 4 pillars: volume expansion, suspension of the inotropic support, any vasopressors, and β-blockers. Interestingly, this strategy allowed successful conservative management of all patients in whom SAM occurred after mitral valve repair.71

Contractility

After pre-load optimization of the LV, the next step is the assessment of the contractility and of the wall motion of the LV (eg, to rule out a depressed contractility and new regional wall motion abnormalities). Regional dysfunction may be present preoperatively, develop intraoperatively, or immediately after CPB separation.

As part of the San Raffaele protocol in patients with preoperative left ventricular dysfunction (ejection fraction <30%), the authors started levosimendan preoperatively to enhance the likelihood of a successful CPB separation at the first attempt,72 and they positioned an IABP introducer to promptly start MCS without the risks of a femoral puncture under full anticoagulation.

In absence of evidence-based guidelines on the management of patients with challenging CPB separation, and as previously reported,43,71 the administration of inotropes varies substantially from one hospital to another. The survey of 17 centers in 5 continents (Supplemental Table 2) that the authors performed also corroborates the above information.

Myocardial contractility is the most important determinant of successful CPB separation. Mean arterial pressure, filling pressure, and CO are the key parameters to consider at this stage. Epinephrine is preferred when CO is low and the filling pressure is high or normal. By contrast, if CO is insufficient and systemic vascular resistance is elevated, inodilators can increase myocardial contractation.72 If systemic resistance and mean arterial pressure are decreased, norepinephrine can be added. It is important to highlight that the use of inotropes is independently associated with hospital mortality.73 This calls for a shift in practice, from the CPB separation being accomplished with high doses of inotropes and vasopressors to an approach in which earlier institution of MCS support is preferred as a bridge to recovery.74 For example, patients with post-cardiotomy cardiogenic shock refractory to inotropic and IABP support Khorsandi et al.75 and showed that a prompt VA-ECMO institution provides a survival benefit and a good intermediate and long-term outcome.

Factors like interventricular dyssynchrony, paradoxical septal motion, and bundle-branch block are often observed during CPB separation and may impair LV contractility and CO optimization.76 In patients with severe LV dyssynchrony, the use of biventricular pacing in the early postoperative period seems to decrease the amount of inotropes and vasopressors required after CPB separation while optimizing cardiac contractility and biventricular synchronization.77 Gielegens et al.78 showed that in patients with an left ventricular ejection fraction lower than 35% and signs of dyssynchrony with or without prolonged QRS duration undergoing CABG, a biventricular pacing is associated with significant higher dP/dtmax values and mean arterial pressure when compared with right ventricular pacing. As the use of biventricular pacing is easy and cost-effective, it may have a role in hemodynamic optimization during a complex separation from CPB. However, future studies have to assess the impact of this effect on arrhythmogenesis, morbidity, and mortality.

Evidence of myocardial ischemia at CPB separation defined by ST segment changes and new wall motion abnormalities has to be taken into account. When hemodynamic instability persists, going back on CPB may be necessary. It is not unusual to observe ST segments being significantly altered with low mean perfusion pressure and to return to isoelectricity with adequate mean arterial pressure. However, an ST segment elevation (eg, transmural ischemia) with corresponding regional wall motion abnormalities justifies myocardial revascularization. A low dose of nitroglycerine may be helpful if the ST segment is depressed (eg, subendocardial ischemia) and the mean arterial pressure is above 70 mmHg. In both scenarios the insertion of IABP must be considered.79

At the authors’ institution, strong indications for IABP implantation include the following: pulmonary artery occlusion pressure above 18 mmHg, cardiac index below 2 L/min/m2, and persistent systolic arterial pressure below 90 mmHg despite VIS above 30.30,81 Because the amount of inotropic support rather than the kind of drug administered is crucial, it is useful to have a tool to compare the degree of pharmacologic support among patients. The first version of the inotropic score included dopamine, epinephrine, and dobutamine. It was later expanded to include norepinephrine, vasopressin, and milrinone.82,83 More recently, the VIS calculation was completed by the inclusion of levosimendan and phosphodiesterase III inhibitors.84,85 The VIS, if integrated in a decision-making algorithm, is a reliable and validated tool in selecting patients with complex CPB separation who deserve a more aggressive pharmacologic treatment and MCSs.

Out of the 17 hospitals surveyed, 13 use the IABP as second line therapy in approaching the LV dysfunction refractory to inotropic support (Supplemental Table 2). Interestingly, all but one of the 17 hospitals used left ventricular assist device (LVAD) or a VA-ECMO in the event of persistent cardiogenic
shock. Low CO, low systemic blood pressure, tachycardia, and signs of poor peripheral perfusion are the main determinants of stepwise interventions. Generally speaking, in patients with cardiogenic shock after CPB separation, a MCS should be initiated as soon as possible if fluid resuscitation and pharmacologic support fail to show any benefit. In fact, a prompt institution of MCS support may mitigate the detrimental effects of systemic hypoperfusion, ischemia, and low CO syndrome.86

In patients suffering from low CO syndrome despite IABP support, LVAD or ECMO are needed to achieve circulatory recovery. The proper timing as to when to initiate MCS is the key in improving the patients’ outcome. There should be a balance between giving the patients the opportunity to respond to the ongoing extensive medical therapy and to the IABP support (to avoid the use of a more invasive device) and waiting so long that the detrimental effects of high dose pharmacologic therapy result in multigorgan failure.87

The choice of initiating the MCS depends on the presence of right, left, or biventricular failure, the potential for myocardial recovery, the lung-tissue gas exchange capability, and the presence of peripheral vascular disease.83,86 After the insertion of MCS, the goal is to achieve a mean arterial pressure >70 mmHg, a urinary output >1 mL/kg/h, and a SvO2 equal or greater than 65%. After MCS insertion, it is critical to continue to support RV function with inotropes and to optimize the preload and the heart rate of the patient. Although an Impella is seldom used for MCS support in patients failing the separation from CPB, in the near future it may be considered for the treatment of cardiogenic shock in cardiac surgery. In fact, it provides a greater hemodynamic support when compared with IABP because it guarantees a stable CO in case of arrhythmias and unloads the LV. By having a continuous flow generated by an axial pump, it increases the mean arterial pressure and the CO, and it reduces the myocardial oxygen consumption and the LV end diastolic pressure.89 However, in patients with myocardial infarction complicated by cardiogenic shock, the Impella was not superior to the IABP in terms of in-hospital and 2-year mortality despite providing a better CO.90 Interestingly, in a retrospective propensity score matched study by Schrage et al.,91 no difference in all-causes 30-day mortality between the IABP and the Impella in patients with acute myocardial infarction complicated by cardiogenic shock undergoing early revascularization were observed. That being said, bleeding and vascular complications were more common in the Impella group. These findings deserve further considerations. Of note, Schrage et al.91 conducted their work in the setting of acute myocardial infarction. However, postcardiotomy cardiogenic shock has a different pathophysiology than cardiogenic shock secondary to acute myocardial infarction. Also in their study, one third of the patients received an Impella 2.5 rather than an Impella CP, while the latter could be more useful in the setting of cardiac surgery to provide almost full support during complex separation from CPB. The study was largely underpowered to get any conclusive results on mortality. Finally, the 2 groups of patients were also unbalanced in terms of three-vessel coronary disease, thrombolysis in the previous 24 hours, glomerular filtration rate, and blood pressure levels.

Prosthetic aortic valve, RV failure, and peripheral vascular disease are absolute contraindications to Impella implantation after CPB. Compared with ECMO, it needs a much lesser degree of anticoagulation and does not unload the RV. Until now, strong indications for Impella include bridging to LVAD and heart transplantation or bridging to recovery in patients with advanced heart failure or cardiogenic shock.92 Its ease of implantation and removal and its effectiveness in supporting the LV render this option very attractive.86

In case of cardiogenic shock with or without respiratory failure, ECMO is considered the therapy of choice particularly in patients with RV or biventricular failure.93 Postcardiotomy cardiogenic shock potentially requiring VA-ECMO has an incidence ranging between 0.5% and 1.5%.90 Notably, in a meta-analysis of 24 retrospective cohort studies by Khorsandi et al.,75 patients with VA-ECMO and postcardiotomy cardiogenic shock refractory to inotropic support and IABP showed a pooled survival-to-hospital discharge of 30.8%.94 Owing to high morbidity and mortality, the decision to use VA-ECMO should consider each individual risk profile. Although the risk factors influencing early- or long-term outcome after VA-ECMO are not fully understood, Rastan et al.95 found that age (>70 years), diabetes, renal failure, obesity, and a logist EuroSCORE >20% are risk factors of in-hospital mortality. VA-ECMO allows an acceptable intermediate- and long-term outcome in an otherwise fatal clinical state at the expense of prolonged length of stay and considerable resource expenses. Central ECMO is preferred when a profound cardiogenic shock occurs. Otherwise, ECMO with percutaneous cannulation of the femoral vessels provides a satisfactory heart support. Table 2 shows the advantages, disadvantages, and other characteristics of the most commonly used MCS.

Afterload

Increased afterload has detrimental effects during the decannulation of the ascending aorta and on bleeding and suture dehiscence. TEE detection of left ventricular systolic heart failure is characterized by a reduction in systolic function and an increase in diastolic dimension. An increase in afterload may lead to low CO syndrome owing to a sympathoadrenergic reaction or to the release of various vasoactive mediators from the nonphysiologic perfusion that occurs during CPB.24 Therefore, the aim of the pharmacologic therapy should be to support the heart and to help in reducing the physiological load encountered after a cardiac arrest.96 The management of patients with high systemic vascular resistance includes short-acting vasodilatory drugs (eg, nitroglycerine or nitroprussiate). In fact, a reduction in afterload may improve the systemic blood flow. Clevidipine is a dihydropyridine calcium channel blocker with a short half-life and a quick onset and offset that reduces the blood pressure through a direct arterial vasodilation.97 In the Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE trials), Aronson et al.98 observed that there was no difference in the rate of stroke, myocardial infarction, and renal failure when clevidipine was compared with nicardipine, sodium nitroprussiate, and nitroglycerine. In particular, clevidipine was superior to sodium nitroprussiate in the achievement
and maintenance of the target blood pressure with less overshoot. On the contrary, nicardipine owing to a longer half-life and maintenance of the target blood pressure with less overshoot compared to civepdine is not routinely used in the setting of cardiac surgery.22,100

Long-acting vasodilatory drugs (eg, clonidine or angiotensin-converting enzyme [ACE]-inhibitors) during challenging CPB separation scenarios are not used owing to the possibility of sudden hemodynamic changes.

**Left Ventricular Diastolic Dysfunction**

Separation from CPB may be challenged by diastolic dysfunction. The hallmark of diastolic dysfunction is the inability of the ventricle to accept an adequate volume of blood, despite a normal preload.101 As a result, myocardial contractility is reduced but maintains a normal or almost normal systolic function. Diastolic dysfunction may occur with or without a concomitant systolic dysfunction. Although commonly observed in cardiac surgery, diastolic dysfunction alone rarely leads to failure of CPB separation. Nevertheless, in combination with factors such as supraventricular tachyarrhythmia or reduced coronary perfusion or hypertension, diastolic dysfunction may contribute to the development or to the worsening of postcardiomyopathy cardiogenic shock. In light of this, diastolic dysfunction can be considered a marker of pending myocardial ischemia.50 In the operating room, TEE allows both monitoring the diastolic function and assessing the degree of diastolic dysfunction.102 Despite recent guidelines recommending several parameters to assess the LV diastolic dysfunction, not all of them are easy to acquire in the dynamic setting of the operating room.103 Thus, in Table 3, the authors summarized the most meaningful criteria of diastolic dysfunction that can be assessed during a challenging separation from CPB that has been adopted at the San Raffaele Scientific Institute.

Diastolic filling abnormalities may become evident after volume overload, tachycardia, ischemia, acute systemic hypertension, AF, conduction abnormalities, or electrolyte abnormalities, all of which reflect a reduced cardiac reserve.104 The diastolic dysfunction is a heterogeneous disease that requires tailored management. Patients with impaired relaxation need a longer diastolic time (eg, relaxation time) and filling time so much that the heart rate must be controlled.105 The avoidance of disynchrony and the optimization of the atrioventricular interval with dual chamber pacing can be useful.106 Tachycardia should be managed with preload optimization, and in the event of normal systolic function, β-blockers and calcium antagonists can be used.107 AF requires a prompt cardioversion and/or amiodarone infusion. Digoxin contributes to a better ventricular filling, decreasing the heart rate when AF is chronic. Phosphodiesterase III inhibitors and levosimendan are effective in the treatment of diastolic dysfunction by increasing CO and decreasing wedge pressure.108 The management of diastolic dysfunction in patients with hypertrophic cardiomyopathy (idiopathic or secondary to aortic stenosis) is particularly challenging.

### Table 2

Principal characteristics, pros and cons of most used mechanical support devices.

<table>
<thead>
<tr>
<th>Pump mechanism</th>
<th>Augmentation of cardiac output</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsatile</td>
<td>0.3-0.6 L/min</td>
<td>PAD, AAA, moderate-severe AI, severe aortic disease, aortic dissection</td>
</tr>
<tr>
<td>Continuous axial flow</td>
<td>2.5-5 L/min</td>
<td>LV thrombus, severe aortic stenosis, prosthetic aortic valve, ventricular septal defect, severe RV failure, PAD, aortic dissection</td>
</tr>
<tr>
<td>Continuous centrifugal flow</td>
<td>4-10 L/min</td>
<td>PAD, severe AI, futility, inability to tolerate anticoagulation, aortic dissection</td>
</tr>
</tbody>
</table>

### Table 3


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Impaired Relaxation</th>
<th>Pseudonormal</th>
<th>Restrictive Filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>E'</td>
<td>&lt;10 cm/s</td>
<td>&lt;10 cm/s</td>
<td>&lt;10 cm/s</td>
</tr>
<tr>
<td>E/A</td>
<td>0.8</td>
<td>0.8-1.5</td>
<td>≥2</td>
</tr>
<tr>
<td>DT</td>
<td>&gt;200 ms</td>
<td>160-200 ms</td>
<td>&lt;160 ms</td>
</tr>
<tr>
<td>E/E'</td>
<td>&lt;8</td>
<td>9-12</td>
<td>≥13</td>
</tr>
<tr>
<td>Ar-A</td>
<td>&lt;0 ms</td>
<td>≥30 ms</td>
<td>≥30 ms</td>
</tr>
<tr>
<td>Vals ΔE/A</td>
<td>&lt;0.5</td>
<td>≥0.5</td>
<td>≥0.5</td>
</tr>
</tbody>
</table>

Abbreviations: A, transmitral late filling peak velocity; Ar-A, duration of the pulmonary flow atrial reversal flow minus duration of the transmitral A wave; DT, deceleration time; E', peak tissue Doppler velocity in the early diastole; E, pulmonary flow atrial reversal flow; Vals, Valsalva maneuver

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patients, even small preload increase can result in high wedge pressure, so the need of fluid expansion to maintain a sufficient stroke volume should be balanced with the intrinsic risk of pulmonary edema. To avoid pulmonary edema, fluid administration should be guided by the monitoring of the wedge pressure. Finally, IABP may play a role in the treatment of perioperative diastolic dysfunction by increasing coronary blood flow.

Conclusions

The development of CPB is one of the most important advances in medicine in the 20th century. CPB separation is a progressive transition from full MCS to spontaneous heart activity. The time taken for this process is “compressed” within the first few minutes, and necessary interventions have to be performed quickly to prevent myocardial damage. Despite the evolution of CPB techniques and the successes to minimize complications, it is essential that physicians respect the particularities of each patient’s physiological and preoperative heart function. In this context, the assessment by echocardiography plays a central role in diagnosing and managing the patients.

A standardized approach for CPB separation that focuses on simple hemodynamic targets under TEE assessment along with a therapy involving vasopressors, inotropes, vasodilators, and eventually MCS devices can potentially improve outcomes. Large trials are urgently needed to validate suitable algorithms for CPB separation and to identify the best cardio-protective strategies in cardiac surgery.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.02.038.

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