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From escalation to weaning strategies: how to integrate the ECMELLA concept

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The additional implantation of a micro-axial flow pump (mAFP) in patients receiving extracorporeal life support by a veno-arterial extracorporeal membrane oxygenation (V-A ECMO) for cardiogenic shock (CS) has gained interest in recent years. Thus far, retrospective propensity score-matched studies, case series, and meta-analyses have consistently shown an improved survival in patients treated with the so-called ECMELLA concept. The pathophysiological context is based on the modification of V-A ECMO-related side effects and the additive benefit of myocardial unloading. From this point of view, knowledge and detection of these pathophysiological mechanisms are of utmost importance to successfully manage mechanical circulatory support in CS. In this article, we describe best practices for the indication of the two devices as well as escalation and de-escalation approaches including implantation and explantation strategies that are key for success.

Introduction

Extracorporeal life support (ECLS) using veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has been increasingly used to treat patients with severe cardiogenic shock (CS) including acute myocardial infarction-associated CS (AMI-CS).[1] Until recently, there was no strong evidence for this approach. However, the ECLS-SHOCK trial showed that routine use of V-A ECMO in AMI-CS not only does not improve 30-day survival but also exposes patients to the risk of bleeding complications and leg ischaemia.[2] The ECLS-SHOCK enrolled both patients with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Despite including a high-risk population (median lactate 6.8 mmol/L), no subgroups appeared to benefit from V-A ECMO. This is supported by an individual patient data meta-analysis that included all four available randomized controlled trials applying V-A ECMO in AMI-CS; only the subgroup of patients with a lactate of $\geq$5.0 mmol/L demonstrated a borderline treatment effect (*P*-value of interaction = 0.079).[3]

One reason for the neutral results of ECLS-SHOCK might be that V-A ECMO is most frequently implanted via peripheral vessels in the emergency setting of CS. This device provides an un-physiologic retrograde perfusion of the aorta and therefore increases left ventricular (LV) afterload.[4,5] Aside from hampering myocardial recovery, this might also have detrimental short-term effects, such as LV thrombus formation due to blood stasis or severe pulmonary congestion. To counteract the increased LV afterload of V-A ECMO, the addition of a micro-axial flow pump (mAFP) like Impella for active LV unloading has been suggested as an approach. This aims to not only prevent complications during V-A ECMO but also facilitate V-A ECMO weaning. A recent

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retrospective, propensity-score matched analysis suggested that this approach might be associated with a better outcome in patients with severe CS; this is under further evaluation in an ongoing, randomized controlled trial (UNLOAD-ECMO; NCT05577195).[6] However, data on this topic also indicate a higher risk of bleeding and ischaemic complications, highlighting the need to implement best practice approaches for patient selection and device management. Here, the aim is to summarize the current expertise on the combined use of Impella and V-A ECMO, otherwise referred to as the ECMELLA approach, with a particular focus on indications for escalation to and de-escalation from this two-device strategy, as well as on bridging strategies for patients who require long-term support.

Escalation to ECMELLA for treatment of cardiogenic shock

The ECMELLA approach is flexible and can be adjusted to the clinical situation and the patient's needs. Escalation to ECMELLA should be considered in several clinical scenarios (*Figure 1*). The first common scenario includes patients with deteriorating CS (e.g. SCAI D or E) despite treatment with a mAFP. In these cases, the mAFP does not provide enough cardiac output augmentation on its own, and V-A ECMO is implanted to provide sufficient tissue perfusion and oxygenation. Once V-A ECMO is added, the mAFP is used to unload, and thereby protect the LV. Specific clinical signs that indicate escalation from solo mAFP to ECMELLA might be persistent or deteriorating hypoperfusion (e.g. cold and clammy skin, increasing or stable lactate, decrease in urinary output, and progressive end-organ damage) or hypotension (e.g. increasing need for inotropes/vasopressors to stabilize the patient).[7] While fixed cut-offs are difficult to implement and the final indication for escalation to ECMELLA should always be based on specific patient factors determined by the interdisciplinary shock team, initial high lactate (>6 mmol/L) and absent lactate clearance within the first few hours after mAFP initiation are strong indicators for ECMELLA use.[8] Other indications for the addition of a V-A ECMO are severe respiratory failure unmanaged by non-invasive or invasive mechanical ventilation and right heart failure if the use of Impella RP is unable to be applied due to the absence of respiratory support.

A second common scenario includes crash and burn patients in SCAI shock stages D and E who require immediate ECLS using V-A ECMO. In these patients, V-A ECMO is implanted to provide tissue perfusion/oxygenation, while the mAFP is used to unload the LV and to facilitate myocardial recovery. Recent retrospective analysis indicates a lower mortality risk for patients with severe CS who are treated with the ECMELLA approach.[6] However, this approach has a high risk of complications, particularly bleeding and ischaemic events, which might prompt one to use this as a bail out approach in patients who show signs of LV overload (such as LV distension and/or pulmonary oedema) on V-A ECMO support. A subsequent analysis from the same data source illustrates that the mortality risk might be even lower when the mAFP is implanted earlier, preferably before or at the time of V-A ECMO implantation.[9] The single arterial access for implantation of a mAFP and V-A ECMO may reduce access-related complications.[10] Together, these findings support an up-front use of the ECMELLA approach in patients presenting with severe CS. However, this recommendation must be considered with caution, as the existing evidence is based on retrospective data, and therefore prone to bias and overestimation of the beneficial effect. The ongoing UNLOAD-ECMO trial (NCT05577195) is currently testing this approach in a randomized fashion and will hopefully provide a clearer estimate on its efficacy and safety.

Protected weaning in ECMELLA

To date, the strategy and timing to wean any temporary mechanical circulatory support (tMCS) in general, or ECMELLA in particular, have not been well studied. However, it appears to be reasonable to start weaning upon initiation of cardiac dysfunction resolution, or evidence of at least partial myocardial recovery, improvement in end-organ hypoperfusion, intravascular euvolaemia, minimal intravenous inotropic support, or improved contractility on echocardiography. Criteria of readiness to wean include clinical indications, haemodynamic stability, laboratory measurements, and imaging (*Figure 2*).

In ECMELLA, the concept of protected weaning has been suggested.[11] As such, this might be the default strategy in LV or biventricular CS patients and in those having any accompanying moderate–severe mitral regurgitation. The weaning process begins by first removing inotropes, at which point low vasopressor doses might be administered. Upon patient stability, V-A ECMO reduction can be initiated at a rate of 0.5 L/min every 2–4 h, to a minimal support of 1.5–2 L/min. At that point, the focus should be on right ventricular (RV) function, as this is the major limitation for de-escalating from biventricular to univentricular support. Moreover, a decrease in urine production and a rise in lactate levels are sensitive to detect low cardiac output translating into weaning failure. If biventricular failure is predominant, despite successful haemodynamic optimization, evaluation for advanced heart failure treatment such as heart transplantation or biventricular support might become necessary in selected patients. If only LV support is required, de-escalation to a mAFP alone can be performed based on the clinical situation. Specifically, the availability of an axillary approach using Impella 5.5 for prolonged support and unloading of the LV and enabling mobilization of patients should be considered for this approach. In stabilized patients on LV support, weaning of the mAFP is done by reducing the level of support, monitoring the before-mentioned parameters for success or failure.[12] It is practical to use low-dose inotropic or vasopressor support to facilitate the weaning of tMCS. An inotropic agent, such as intravenous dobutamine or milrinone, may be used to enhance cardiac contractility and to reduce ventricular afterload. In other cases, a vasoactive medication with inotropic and vasopressor properties may be more ideal.[11] However, the persisting dependency on mechanical or

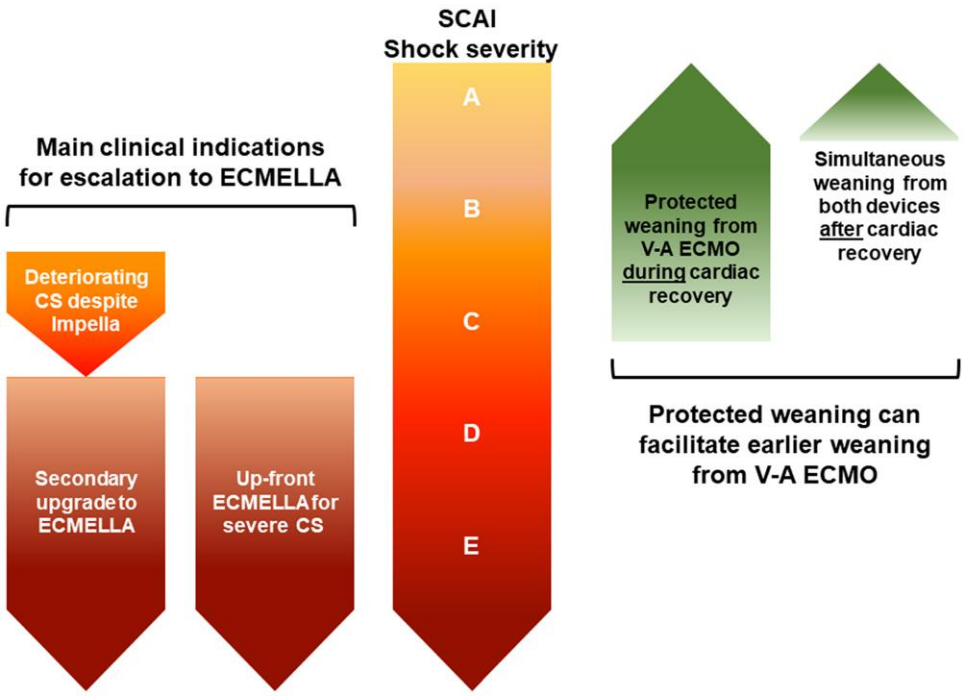

Figure 1 Clinical indications for escalation to ECMELLA. The ECMELLA approach is used in patients with cardiogenic shock who deteriorate despite treatment with a micro-axial flow pump so that additional perfusion by a veno-arterial extracorporeal membrane oxygenation is provided or as an up-front treatment strategy in patients with severe cardiogenic shock and at risk of left ventricular distension/overload. Over time, in cases of clinical stabilization and myocardial recovery, these devices can either be weaned subsequently or concomitantly. CS, cardiogenic shock; ECMELLA, combination of ECMO and Impella; LV, left ventricle; SCAI, Society for Cardiovascular Angiography & Interventions; V-A ECMO, venous-arterial extracorporeal membrane oxygenation.

pharmacological support should trigger further evaluation for a durable percutaneous ventricular assist device (pVAD) or heart transplantation.

If RV failure remains and LV function improves to near-normal values, it is advisable to wean and explant the mAFP first. One might also consider afterwards to switch V-A ECMO to a right-side tMCS. This might be the case when RV parameters such as central venous pressure, central venous pressure to pulmonary capillary wedge pressure ratio, pulmonary artery pulsatility index (PAPi), imaging parameters of RV dysfunction (e.g. tricuspid annular plane systolic excursion and fractional area change), and clinical signs of right heart failure remain pathologic. However, those parameters are difficult or even impossible to interpret while on V-A ECMO, and evaluation requires a meticulous clinical and haemodynamic assessment.

In scenarios in which pulmonary disease is prominent, the use of V-A ECMO or even a veno-arterio-venous (V-A-V) ECMO should be switched to veno-venous (V-V) ECMO after successful weaning of cardiac support. Afterwards, the mAFP may be weaned while V-V ECMO remains for further oxygenation and decarboxylation to support weaning from mechanical ventilation.

The decannulation of pVADs can be done surgically or by applying dedicated vascular closure devices such as the suture-based Perclose ProGlide™ (Abbott Vascular) or the plug-based MANTA® vascular closure device (Teleflex). While there is no randomized comparison between those two strategies, observational data suggest the feasibility and safety of the percutaneous approach.[13,14]

Surgical transition for the ECMELLA approach

In cases of insufficient unloading of the LV with ECMELLA or insufficient isolated support with percutaneously implanted mAFP (e.g. Impella CP), the switch to surgically implanted mAFP (e.g. Impella 5.5) is indicated. This transition will increase support of the LV and facilitate weaning of V-A ECMO and support future de-escalation from ECMELLA to isolated mAFP support.

Typically, two arterial access sites are required for V-A ECMO and mAFP, thereby increasing the risk of access-related complications such as bleeding, vessel damage, and infections.[6,15,16] The novel single-arterial access technique (ECMELLA 2.0) aims to both achieve patient mobilization and reduce the risk associated with the cannulation technique.[10] With this technique, a Y-shaped prosthesis anastomosed to the axillary artery is used for the placement of both mAFP and arterial cannula of the V-A ECMO.[10]

The cannulation strategy for ECMELLA therapy should be carefully scheduled to avoid complications and provide fast and adequate circulatory support. In a setting that allows for the surgical approach, the implementation of ECMELLA employing single arterial access is an optimal solution in specialized centres. In a haemodynamically critical situation in which a patient requires ongoing cardiopulmonary resuscitation, INTERMACS 1, or SCAI E, rapid initiation of circulatory support is crucial. In this scenario, peripheral percutaneous V-A ECMO implantation is the therapy of choice. After stabilization of all cardio-pulmonary situations, LV unloading should be

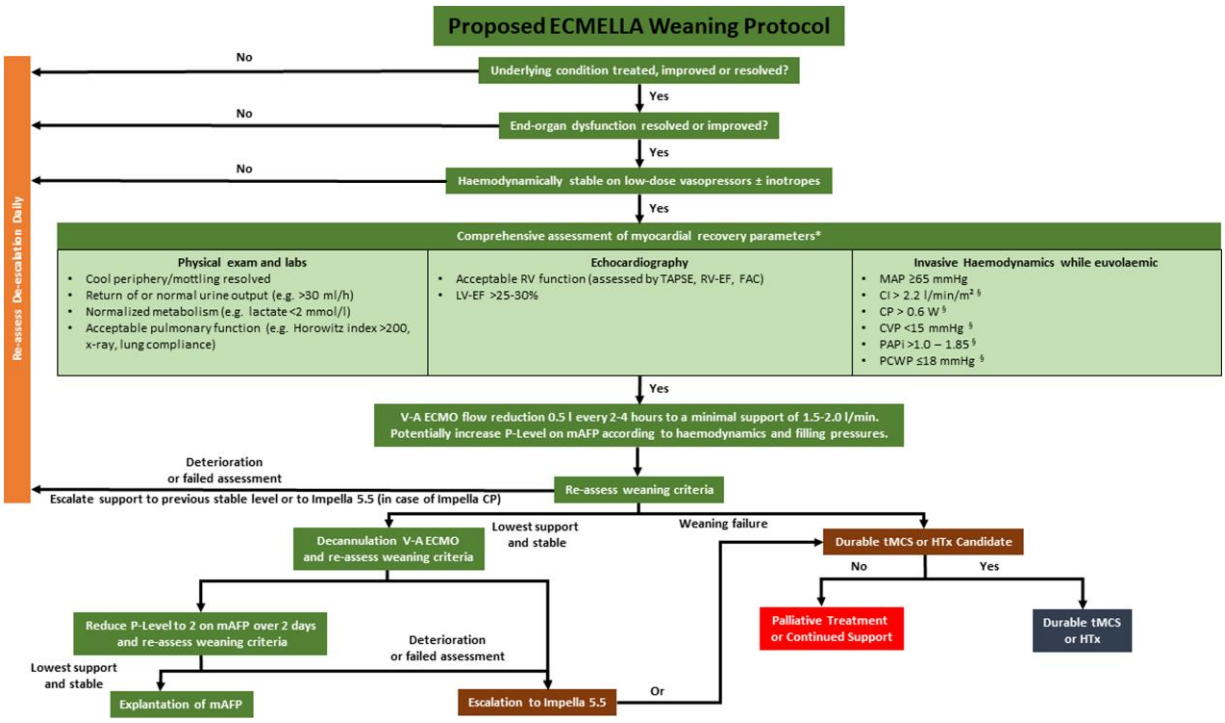

Figure 2 Proposal for an ECMELLA weaning protocol. Flow diagram adapted from Geller *et al.*[11] CI, cardiac index; CP, cardiac power (mean arterial pressure × cardiac output/451); CVP, central venous pressure; FAC, fractional area change; HTx, heart transplantation; LV-EF, left ventricular ejection fraction; mAFP, micro-axial flow pump; MAP, mean arterial pressure; tMCS, temporary mechanical circulatory support; PAPi, pulmonary artery pulsatility index (systolic PA pressure-diastolic PA pressure/central venous pressure); PCWP, pulmonary capillary wedge pressure; RV, right ventricle; RV-EF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; V-A ECMO, veno-arterial extracorporeal membrane oxygenation. *Combination of metrics used to assess weaning eligibility. §Not evaluated and/or not reliably measured in the setting of ECMELLA, but potentially helpful for weaning of the mAFP.

immediately initiated by employing single or double arterial access. The size of the mAFP appears to be less crucial than the timely unloading of the LV.[9]

Clinical outlook

Currently, the clinical application of ECMELLA typically includes one of the two scenarios outlined above. Generally, patients on mAFP are escalated to an additional V-A ECMO due to the progression of shock severity that often occurs due to concomitant right heart failure, rhythm disturbances, and/or pulmonary failure, or an additional mAFP is implanted in patients experiencing complications of the V-A ECMO therapy, typically to treat or prevent LV distension. While there are shortcomings with the concept of ECMELLA including increased risk for bleeding complications, haemolysis, and ischaemic concerns,[6,15] the use of V-A ECMO for organ/tissue perfusion and the mAFP for unloading of the LV aiming to uncouple the oxygen demand of the body from the oxygen consumption of the myocardium has the potential to improve patient outcome in CS.[6,9,15] To reduce vascular access-related complications and improve patient's mobility, the ECMELLA 2.0 single arterial access approach can be taken into consideration.[10] The currently ongoing UNLOAD-ECMO trial (NCT05577195) is designed to test the ECMELLA approach in a randomized fashion and, ultimately, provide a clear estimation of ECMELLA efficacy and safety.

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Data availability

No new data were generated or analysed in support of this research.

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