

# Is there light at the end of the tunnel? – new perspectives in ECMO survival

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**Abstract:** Cardiogenic shock (CS) is a state of systemic hypoperfusion, secondary to a deficit in cardiac contractile activity. Acute myocardial infarction (AMI) accounts for the majority of cases of CS, with a high mortality rate, despite the great improvements in revascularisation therapy. Nowadays, mechanical circulatory support (MCS) in CS often represents the only therapeutic approach able to restore systemic perfusion, determining a survival benefit. Recently, many efforts have been made to identify factors associated with mortality in patients receiving MCS devices. New insights into the pathophysiology of CS prompted the concept that the use of MCS should be considered early in the course of the disease, before the progression to multiorgan dysfunction. However, many questions remain unsolved and randomised trials in this field are hard to perform. Looking at the future, the timely implantation of temporary MCS, the correct selection of patient, the concomitant use of different temporary devices, the improvement in weaning strategies and the increasing use of durable devices as a destination or bridge therapy appear to be the most promising areas of development.

**Keywords:** Extracorporeal membrane oxygenation; shock, cardiogenic; myocardial infarction

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Cardiogenic shock (CS) is a state of critical end organ hypoperfusion secondary to a deficit in cardiac contractile activity, leading to low cardiac output condition (1).

Despite advances in medical therapy, mortality rate is still high, ranging from 40% to 50% (1,2).

Clinical and haemodynamic criteria for the diagnosis include the presence of persistent hypotension despite pharmacological therapy together with signs of impaired organ perfusion, severe reduction of cardiac index (<1.8 L/min/m<sup>2</sup> without support or <2.0 to 2.2 L/min/m<sup>2</sup> with support) with adequate or elevated filling pressure (1,3,4).

Acute myocardial infarction (AMI) accounts for 80% of CS, with an overall incidence of 7.9% of CS in patients hospitalized with AMI (5).

The current therapeutic panel in CS secondary to AMI includes early revascularisation, antithrombotic drugs,

pharmacologic interventions aimed to increase cardiac contractility and restore systemic perfusion and the use of mechanical circulatory support (MCS) devices.

In this scenario, two questions are of paramount importance: the identification of the “optimal” candidate to MCS and of the correct timeframe in which MCS should be considered. Indeed, the cornerstone of current pharmacological therapy, represented by catecholamines, has only a limited role in counteracting the low cardiac output state in the more advanced stages of disease and may per se cause a myocardiotoxic effects, by the increase of myocardial oxygen demand.

Driven by the great technological improvement and the growing clinicians’ confidence, recent studies reported a significant increase of percutaneous MCS devices implantation (2,6).

However, in the face of an increasing use, definitive

evidence on MCS in CS is lacking and several questions are still unsolved.

A recent study added another piece to this complex puzzle. Muller *et al.* conducted a retrospective study in 138 patients suffering from CS secondary to AMI underwent Venous-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO), to identify factors associated with ICU death and assess long term survivors quality of life (HRQOL), anxiety, depression and post traumatic disorder (PTSD) frequencies (7).

Patients were enrolled in two high-volume Frech ICU.

Indication for VA-ECMO was acute refractory CS, defined as evidence of tissue hypoxia, decreased left ventricle ejection fraction (<25%), low cardiac index (<2.2 L/min/m<sup>2</sup>) and sustained hypotension despite very high dose of catecholamines.

The characteristics of this cohort of patients indicate a very high degree of disease severity, as median values of pre-ECMO lactates, creatinine and bilirubin were elevated and the inotropic score was very high. Notwithstanding, the authors reported a 30-day mortality of 53%, lower than previously reported mortality of VA-ECMO patients.

Multivariable logistic regression identified seven pre-ECMO risk factors and, on the basis of that, the Authors constructed a seven-items score for prediction of mortality.

The ENCOURAGE (prEdictionN of CS OUtcome foR AMI patients salvaGed by VA-ECMO) score include: age >60 years, female sex, BMI >25, GCS <6, creatinine >160 micromol/L, elevated lactates and prothrombin activity <50%.

ENCOURAGE is the first mortality risk score regarding a cohort of CS patients treated with VA-ECMO sharing the same aetiology.

Previously, on the basis of the Extracorporeal Life Support Organisation (ELSO) registry, Schmidt *et al.* identified pre-ECMO factors predicting survival from refractory CS, creating the Survival after Venous-arterial ECMO (SAVE) score (8). In this study, data of 3,846 CS patients were analysed as derivation cohort and then the performance of the score was tested on a validation cohort of 180 patients in a single tertiary care centre. The aetiology of CS in both the cohort was heterogeneous, encompassing medical and surgical causes. The SAVE score consider 11 items: age, diagnosis, weight and a series of pre-ECMO parameters: organ failure (kidney, liver and central nervous system), duration of mechanical ventilation, peak inspiratory pressure, cardiac arrest, serum bicarbonates, diastolic blood pressure, pulse pressure. According to the

score, patients were divided in five classes, where “zero” equates a mortality risk of 50%.

The comparison of the discriminatory power of the ENCOURAGE score with the SAVE score showed a significantly better performance of the former, as well as towards other scoring systems for mortality prediction in AMI patients (7).

The design of the study of Muller *et al.* does not allow for inference about the effect of ECMO on mortality, and the explanations for the lower than expected mortality could be found only theoretically in the timely implementation of mechanical support and in the extensive experience in management of MCS of the two centres (9).

Furthermore, analyzing the study flow chart for survivors, it is noteworthy that a significant percentage of patients (40% of ICU survival) was treated with heart transplantation (HTx) or a LVAD implantation after VA-ECMO.

Therefore, the lower-than-expected mortality in this cohort has to be interpreted considering the possibility to bridge the not-recovering patients from a temporary MCS to definitive therapy.

In light of these considerations, should MCS be provided only by centres able to offer the complete panel of short- and long-term MCS together with HTx? This issue has been recently addressed in a debate about the founding for LVAD programs in non-heart transplant centres in United Kingdom, where five designated centres perform 100–120 transplants per year with funding for a small number of LVADs, preventing the possibility to triage all the CS patients, who often are too sick to be centralized to hub centers (10,11).

Moreover, the number of HTx is low in the face of an increasing demand.

However, LVAD offers a concrete alternative to HTx, with 2-years survival and quality of life now comparable (12,13). The restriction of MCS deployment to heart transplant centres amounts to an unacceptable restriction to a life-saving technology, causing many avoidable death (10). On these premises, emerges the concept of “comprehensive MCS”, that can be defined as the presence of medical expertise and technology to fully address the issues arising from CS patients needing MCS, even in the absence of facility for HTx.

Some components of the ENCOURAGE score deserve a careful evaluation.

The prognostic value of lactates levels, renal failure and central nervous system dysfunction is not a new finding

and highlights the concept of the correct timeframe in the course of the disease in which MCS should be considered. If the multiorgan dysfunction syndrome (MODS) takes place, the possibility to revert the negative clinical course is very low even if a full circulatory support is established (4).

This concept is reflected in small seminal studies on postcardiotomy CS, where the implementation of therapy early in the course of the disease with a MCS was able to induce a survival benefit (14,15).

The authors identified in prothrombin time <50% an independent predictor of ICU-death. In patients on MCS, recent studies shed light on the role of hepatic dysfunction in determining the outcome in CS. Traditionally, the hepatic failure during ECLS was considered more a witness than an active element in determining a worse prognosis (16). Recently, Roth *et al.* demonstrated that, in patients undergoing VA-ECMO following cardiovascular surgery, liver function tests (pre-ECMO alkaline phosphatase and total bilirubin) were strong predictors of short- and long-term mortality (17).

These findings are consistent with the SAVE score, where liver failure was a strong negative prognostic determinant.

Mazzeffi *et al.* recently analysed the incidence of acute liver failure and its impact on outcome in 132 patients underwent ECLS for cardio-respiratory failure (18). They found an incidence of 8%, with a median of 5 days on ECLS for developing ALF and a net negative impact on mortality.

However, reduced prothrombin time may be considered a marker of hepatic dysfunction as well as a laboratory finding indicating a derangement of coagulation system.

Recently, Okada and co-workers analysed a cohort of patients suffering from acute decompensation of chronic heart failure, demonstrating that increased INR is an independent predictor of all-cause mortality (19). They interpreted this finding as a result of concomitant hepatic dysfunction and coagulation abnormalities, sustained by systemic inflammation state, neuro-hormonal activation and venous congestion.

It is noteworthy that coagulation alteration is a well-known phenomenon in patients suffering from acute cardiac disease, especially in out-of-hospital cardiac arrest (20-22).

As a significant percentage of patient in the ENCOURAGE study experienced cardiac arrest before ECMO implantation, one might speculate that the prognostic role of decreased prothrombin activity derives from initial hepatic dysfunction and/or concomitant but

independent whole coagulation derangement.

This is of particular value in patients candidate to MCS, because bleeding heavily affect prognosis and every effort should be made to carefully address the coagulation management. Interestingly, 16 patients in the study were switched from peripheral to central ECMO, with 12 deaths. The number of patients in the study and the design itself does not allow for a comparison between the two techniques, but it is important to underscore the higher risk of bleeding in central versus peripheral configuration, without any proven benefit (23).

Muller *et al.* did not find any survival benefit arising from successful percutaneous coronary intervention (PCI), in contrast to previous report (24). Very recently, Wayangankar *et al.* reported a secondary analysis of data from the Cath-PCI Registry, showing that in 2011–2013, compared to 2005–2006, the in-hospital mortality increased for CS patients treated with an early invasive strategy (25). Many factors may account for this finding (26), but it is noteworthy that, even in the presence of a class I European Society of Cardiology (ESC) recommendation for PCI in CS (27), no RCTs sustain this recommendation (28), and, in the setting of CS, many points are unclear in the PCI strategy itself (multivessel versus culprit lesion) (29).

Analysing the long-term outcomes, Muller *et al.* found that a global evaluation of quality of life through a structured questionnaire revealed poorer score in survivors than age- and sex-matched controls. Moreover, significant frequencies of anxiety, depression and risk for post-traumatic stress disorder were also reported. Critical illness and ICU-stay often determine physical, cognitive and psychological sequelae in survivors (30). Neurocognitive and psychiatric morbidity in ARDS survivors are well described (31,32). Several pathological events may intervene during the course of a devastating disease as CS or during VA-ECMO causing multiple neurocognitive sequelae (33), with a long term impact on quality of life. However, the complex interplay between critical illness, organ dysfunction and extracorporeal circulation makes difficult the meaning of the single determinants of the final result.

Looking at future perspective on MCS in CS, several questions should be addressed.

Many points of the pathophysiology of CS are still unclear and the negative results of IABP SHOCK trial II (34,35) taught that haemodynamic improvement does not necessarily translate into survival benefit.

CS is sustained not only by a depression of left and/or right ventricular function, but always accompanied by a

whole derangement of the cardiovascular system.

Indeed, whatever the initial cause, the unique physiology of the failing heart, which benefits from afterload reduction and, at the same time, suffers from reduction of coronary perfusion pressure, make each hemodynamic change a double-edged sword (3).

As a consequence of reduced cardiac output, peripheral hypoperfusion leads to catecholamine release, enhancing peripheral vasoconstriction in order to increase tissues perfusion, but, simultaneously, increasing the myocardial oxygen consumption and exerting proarrhythmic and myocardiotoxic effects (3).

In the last decade, new insights have emerged, suggesting a key role of microcirculatory dysfunction (36,37). Interestingly, macro- and microhaemodynamics may differ, as it is demonstrated that the global haemodynamic improvement observed with IABP support does not necessarily translate into microcirculatory improvement (37,38).

These microcirculatory disturbances have a prognostic role, even in patients with CS secondary to myocardial infarction (39). Moreover, little is known about many factors driving the transition from hypoperfusion phase to multiorgan dysfunction, nowadays scarcely susceptible of therapeutic measures.

Obtaining sound evidence in this field is a hard task. Available trials enrolled small numbers of patients, and are affected by high risk of bias due to heterogeneity of clinical conditions sustaining CS and differences in criteria of inclusion.

Today, only for the intra-aortic balloon pump (IABP) a randomised controlled trial has been conducted (34,35). However, the study is affected by some important limitations (40), and the cohort of patients enrolled is far from depicting the complexity of CS patients encountered in the daily clinical practice.

Organising RCTs in CS remains a challenge, owing to high cost, to the need of homogeneity in aetiologies and to difficulties in enrolling an adequate number of patients to attain the sufficient statistical power in a field where the mortality reduction is expected low. Notwithstanding, the high number of deaths attributable to CS should prompt studies to achieve a break-through in CS treatment (41).

Currently available MCS differs for mechanical properties and haemodynamic performances. Recent expert consensus (42) recommends the use, in CS, of MCS devices able to provide a full circulatory support. VA-ECMO combines the possibility of full cardiac and respiratory

function restoration with a relatively ease and quickness of implantation even at bedside.

However, VA-ECMO, despite the great technical improvement in the last decade, remains associated with a considerable burden in terms of complication, especially ischaemic and haemorrhagic (43).

The drawback of VA ECMO is that, although restores perfusion of the end organ, increases cardiac afterload, thus increasing left ventricle wall tension and unfavourably affecting an eventual cardiac recovery.

In the ENCOURAGE study, 12% of patients had overt pulmonary oedema during ECMO treatment. To address this issue, of particular interest is the possibility of concomitant use of different MCS devices, taking advantage from mutual haemodynamic performances. In the study of Muller *et al.*, a significant percentage of patients received concomitant IABP and ECMO. This is a possible strategy to reduce afterload and the left ventricle wall stress when the cardiac function is completely abolished. In this field, the evidence is limited (44) and a recent metanalysis concluded that there is not survival benefit in CS patients underwent concomitant IABP and VA ECMO support (45). Another interesting option is the association between ECMO and Impella, a transaortic axial pump able to generate a flow up to 5 liters per minute, where the latter is used to unload the left ventricle (46-49). This approach appears to be promising and deserves further investigation.

In the ENCOURAGE study, the majority of deaths happened before ECMO weaning. However, other studies have reported different outcomes, as weaning from VA-ECMO does not necessarily result in survival: a recent large Japanese database involving more than 5,000 patients treated with VA ECMO showed an in-hospital mortality of 37.9% in patients weaned from VA-ECMO (50). No randomised evidence exists in this field and there is a remarkable variability in protocols among centres, making complex the path (51,52). Moreover, the concept of weaning from ECMO should be considered in the broader framework of possibility to bridge the patients to durable devices or HTx when the recovery of native heart function is not attained.

Regarding the timing to transition from temporary to durable MCS devices as LVAD or HTx, several factors must be taken into account, including the potential of recovery from underlying disease, the eligibility to HTx, the potential of recovery from end organ dysfunction and the adequacy of the evaluation of the neurological function, often uncertain in CS patients (53).

Patients on temporary mechanical support represent a very high-risk cohort of LVAD candidates, as pre-implantation organ dysfunction and INTERMACS 1 class are recognized as factors adversely affecting outcome in continuous flow LVAD (54). The temporary support should guarantee the resuscitation and resolution of organ dysfunction before LVAD implant, as well as performance of an adequate transplant evaluation (55).

The worse category of SAVE score reports a hospital survival of 18% (8). Therefore, even if the development of scores may be useful in identifying, in a cohort of high-risk patients, those with the highest risk, no decision about futility can be made on the basis of pre-ECMO parameters. This decision should be based, rather, on individual basis, keeping in mind that VA-ECMO is a lifesaving technique in patients who surely will die in the absence of MCS. To date, no one predictor of mortality has a sufficient predictive power to drive decisions about the withholding of a MCS in CS patients. Finally, in the last decade we observed a great improvement in the knowledge of the pathogenesis of CS and an extraordinary technical progress in MCS, but the high morbidity and mortality that CS still carries should prompt toward an extensive investigation of potential therapeutic resources.

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### Footnote

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