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REVIEW

The ICM research agenda on extracorporeal life support

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Abstract

Purpose: This study aimed to concisely describe the current standards of care, major recent advances, common beliefs that have been contradicted by recent trials, areas of uncertainty, and clinical studies that need to be performed over the next decade and their expected outcomes with regard to extracorporeal membrane oxygenation (ECMO).

Methods: Narrative review based on a systematic analysis of the medical literature, national and international guidelines, and expert opinion.

Results: The use of venovenous ECMO (VV-ECMO) is increasing in the most severe forms of acute lung injury. In patients with cardiogenic shock, short-term veno-arterial ECMO (VA-ECMO) provides both pulmonary and circulatory support. Technological improvements and recently published studies suggest that ECMO is able to improve patients' outcomes. There are, however, many uncertainties regarding the real benefits of this technique both in hemodynamic and respiratory failure, the territorial organization to deliver ECMO, the indications and the use of concomitant treatments.

Conclusions: Although there have been considerable advances regarding the use of ECMO in critically ill patients, the risk/benefit ratio remains underinvestigated. ECMO indications, organization of ECMO delivery, and use of adjuvant therapeutics need also to be explored. Ongoing and future studies may be able to resolve these issues.

Keywords: Extracorporeal membrane oxygenation, Acute respiratory distress syndrome, Cardiogenic shock, Research agenda, Position article

Introduction

Extracorporeal membrane oxygenation (ECMO) is an old technique that has beneficiated from recent technical improvements. Interest for venovenous ECMO (VV-ECMO) for the most severe forms of severe acute lung injury, including acute respiratory distress syndrome (ARDS) has been renewed since the publication of the CESAR study [1] and its extensive use during the H1N1 pandemic [2–5]. In patients with cardiogenic shock, mortality remains high despite advances in treatment. Short-term percutaneous mechanical circulatory support (MCS) devices can be used for cardiogenic shock patients refractory to conventional therapies. Veno-arterial ECMO (VA-ECMO) provides both pulmonary and circulatory support and can be used as a bridge to myocardial recovery or to other therapies such as transplantation or the implantation of a long-term ventricular assist device (VAD). Even with the many advances in the last decade, a lot of uncertainties remain concerning the use of ECMO

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during respiratory and/or cardiogenic failure. This review summarizes recent developments and identifies the main areas for future research.

What is the current standard for delivering the best possible critical care to patients on extracorporeal life support?

VV-ECMO for acute respiratory failure

Positive results of the CESAR trial [1] and the successful rescue of the most severe ARDS cases associated with the Influenza A(H1N1) pandemic [2–7] have led to an exponential use of VV-ECMO for acute respiratory failure in the last decade. High blood flow through ECMO circuits to provide full blood oxygenation and CO_2 elimination is now considered as a reasonable option to support patients with severe acute lung injury or status asthmaticus refractory to conventional measures. Alternatively, VV-ECMO may be applied in less severe patients in whom it might allow "lung rest" by lowering airway pressures and tidal volume rather than improving oxygenation per se [8]. Cannulation strategies for VV-ECMO can either include two single-lumen cannulas or one double-lumen cannula, the latter currently can only be implanted via the right internal jugular vein [8]. Most commonly, the right femoral vein for outflow and the right internal jugular vein for return flow are used, although the best cannulation configuration has not been tested in randomized trials. Less blood recirculation within the ECMO circuit occurs with double-lumen cannulas [9]. They might, however, be reserved for selected indications (mobilization, groin cannulation impossible), as they are more expensive, flow-restricted and potentially more hazardous to implant.

Support of the cardiogenic shock patient (Fig. 1)

Although there is no strong scientific evidence to support routine MCS therapy in cardiogenic shock patients to date [10, 11], its use is increasing since that it can provide emergency circulatory support while a definite solution is sought.

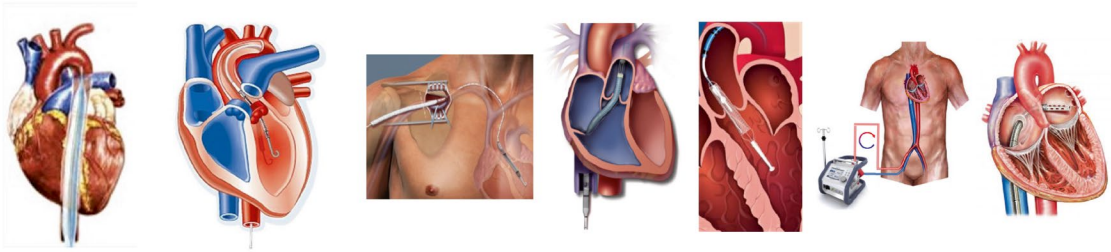
Most of these highly instable patients receive a device as salvage therapy after having already developed signs of multiple organ failure. In these situations, mechanical assistance is frequently used as a bridge to decision, in which cardiogenic shock patients are rescued and optimized until cardiac recovery allowing weaning from MCS or implantation of a surgical solution such as durable VAD or heart transplantation. In the last decade, VA-ECMO has become the first-line therapy in this setting since it provides both respiratory and cardiac support, is easy to insert, even at the bedside, provides stable flow rates, and is associated with less organ failure after implantation compared to large biventricular assist devices that require open-heart surgery [12, 13]. Other short-term MCS devices are the Impella© (ABIOMED, Danvers, MA, USA) which is a catheter-based axial pump positioned retrogradely across the aortic valve into the left ventricle [14, 15] and the TandemHeart© (TandemLife, Pittsburgh, PA, USA) which is an extracorporeal centrifugal pump that drains blood from the left atrium via a cannula introduced trans-septally through the femoral vein and pumps back blood into the femoral artery [16]. Compared to VA-ECMO, these systems are currently more expensive and are not adapted to patients with severe biventricular failure. The traditional configuration for peripheral VA-ECMO involves femoral venous drainage and femoral arterial reinfusion. ECMO cannulation can also be performed by direct transthoracic access of cardiac cavities following cardiac operations.

Accepted medical indications for MCS may be classified into the following categories [12, 13]: acute myocardial infarction complicated by cardiogenic shock [13, 17, 18], acute decompensated heart failure with refractory cardiogenic shock [12], fulminant myocarditis [19], cardiotoxic drug intoxication [20], stress-induced cardiomyopathy [13], post-cardiac arrest resuscitation syndrome [21], decompensated pulmonary vascular disease [28–33], or massive pulmonary embolism [34, 35]), the highest rate of survival being reported in these case-series for acute myocardial infarction and fulminant myocarditis [17, 19, 22]. In a single-center, retrospective study, cardiogenic shock post-MI patients treated with PCI and adjunctive ECMO had a higher 30-day survival than historical controls without ECMO (60 vs. 35%) [18].

MCS therapy can also be initiated in cases of low cardiac output syndrome after heart surgery [23]. A retrospective single-center study of 517 post-heart surgery VA-ECMO patients reported a rate of 1.28% with hospital survival of only 25% [24]. Successful VA-ECMO therapy in primary graft failure following heart transplantation is encouraging [25]. Earlier initiation of MCS in cardiac surgery, preoperatively or postoperatively, might improve the outcomes of these patients [26].

ECMO for cardiac arrest resuscitation (ECPR)

Extracorporeal cardiopulmonary resuscitation with ECMO (ECPR) can give a chance for better neurologic outcome than conventional CPR for in-hospital (IHCA) and out-of-hospital (OHCA) cardiac arrest patients [27–29] and contribute to organ donation in those who die [28]. A landmark study of 46 IHCA patients demonstrated that ECPR provided significantly higher 1-year survival than conventional CPR [30]. Similar results were reported by Shin et al. in 85 IHCA ECPR patients [31]. Results of ECPR for OHCA patients are more contrasted.



Device features	IABP	Impella 2.5	Impella CP	Impella 5	Impella RP	HeartMate PHP	VA ECMO	TandemHeart
Pump mechanism	Pneumatic	Axial flow	Axial flow	Axial flow	Axial flow	Axial flow	Centrifugal	Centrifugal
Cannula	8 Fr	13 Fr	14 Fr	23 Fr	9 Fr	13 Fr at insertion 24 Fr when opened across aortic valve	18-21 Fr inflow 15–22 Fr outflow	21 Fr inflow 15–17 Fr outflow
Insertion	Percutaneous; descending aorta via femoral artery	Percutaneous; femoral artery retrograde across aortic valve	Percutaneous ; femoral artery retrograde across aortic valve	Surgical cutdown: subclavian artery retrograde across aortic valve	Percutaneous; femoral vein across pulmonic valve	Percutaneous; femoral artery retrograde across aortic valve	Percutaneous and surgical; inflow via femoral vein, outflow via femoral artery	Percutaneous; inflow via femoral vein into left atrium; outflow via femoral artery
Maximum implant duration	7-10 days	7-10 days	7-10 days	2-3 weeks	7-10 days	7-10 days	3-4 weeks	2-3 weeks
Delivered flow	Negligible	1.5-2 l/min	2.5–3.5 l/min	4.5-5 l/min	>2.5 l/min RV	3.5–4.5 l/min	3-6 l/min	4 l/min
Afterload	Slightly reduced	Neutral	Neutral	Neutral	Neutral	Neutral	Increased	Increased
LV end-diastolic pressure	Slightly reduced	Slightly reduced	Reduced	Markedly Reduced	Neutral or slightly increased	Markedly Reduced	Increased	Reduced
Haemodynamic support	Left ventricle only	Left ventricle only	Left ventricle only	Left ventricle only	Right ventricle only	Left ventricle only	Biventricular	Biventricular

Fig. 1 Temporary mechanical circulatory support devices for cardiogenic shock

Complications								
Limb ischaemia	+	+	++	++	+/-	++	+++	+++
Haemolysis	+	++	++	++	++	++	++	++
Hemorrhage at cannulation site	+	++	++	++	+	++	+++	+++
Evidence for survival benefit								
RCT	Negative RCT [65]	-	Negative RCT [15]	-	-	-	-	-
Propensity matched cohorts	-	-	-	-	-	-	Cardiac arrest [30, 31]	-
Case-series	-	+	+	+	-	-	+++	+

Fig. 1 continued

Single-center studies from Japan, in which transport time from scene to ECMO center was around 30 min, reported up to 30% survival with good neurological outcome. However, a French series of 51 OHCA ECPR patients for whom mean ischemic time was 120 min reported only two survivors [32]. Survival with favorable neurological recovery was low although better than in control patients (11 vs. 2%), in the largest (260 VF/VT patients) multi-center (20 hospitals) prospective observation study of ECPR in Japan [33]. Lastly, survival was not improved in ECPR OHCA patients in a large Korean nationwide OHCA database [34]. Data from all these ECPR studies stress that shorter time from collapse to ECMO and then early coronary angioplasty are the most important determinants of outcomes.

What have been the major recent advances in the field?

Technical breakthrough in ECMO equipment

The renaissance of ECMO for severe cardiac and respiratory failures was accelerated by several major technical developments. First, the old silicon membrane oxygenators were replaced by miniaturized, low-resistance poly-methyl-pentene oxygenators. These systems offer more effective gas exchange with lower resistance to flow, have smaller priming volumes, are more biocompatible with less platelet and plasma protein consumption and are coated with a thrombo-resistant coating allowing less anticoagulation [6, 35]. Second, centrifugal pumps have permitted major improvements in efficacy and security over the older roller pumps, with less blood cell trauma, no requirement for venous reservoirs, and very few failures over weeks of support [6, 35]. More recently, the continuing miniaturization of devices has permitted the integration of pump and oxygenator within one low weight device and has facilitated transport by mobile ECMO teams [36]. Lastly, sensors without direct blood contact to continuously measure pressures as well as hemoglobin and venous saturation are useful tools for enhanced circuit and patient safety.

Extracorporeal Life Support Organization and the International ECMO Network

The Extracorporeal Life Support Organization (ELSO, https://www.elso.org) has maintained a large international registry since 1989, and has collected data on over 75,000 ECMO patients. Important data regarding

patients' selection, ECMO results and center organization have been derived from the registry over the last 25 years [37–40]. This organization also provides valuable resources to clinicians, ECMO center directors and coordinators, hospital directors and health care organizations [9], and organizes regular training activities and meetings. Centers providing ECMO should be encouraged to join ELSO to benchmark their results against other national and international institutions, and participate in epidemiologic studies.

The recently formed International ECMO Network (ECMONet http://www.internationalecmonetwork.org) is a growing consortium of ECMO centers and individuals dedicated to conducting high-quality, high-impact research in the field. By ensuring that expert centers adhere to current best practices for the organization and conduct of ECMO, this group aims to foster the highest quality research.

Regional/National Organization of ECMO support

The soaring growth of centers performing ECMO in adult patients has occurred mostly in the absence of oversight or coordination [41]. However, recent data from the ELSO registry suggested an inverse linear relationship between case volume and mortality, with centers performing more than 30 adult ECMO cases per year having a significantly lower mortality than centers performing fewer than 6 cases per year [40]. Although the minimum acceptable case volume for an ECMO center remains controversial, many centers conduct few cases annually and outcomes may be suboptimal in this setting [41]. By creating networks of hospitals at the local or regional level (Fig. 2), and concentrating case volume in expert centers, using standardized protocols for case selection and management, outcomes would certainly improve. Recent attempts to build regional ECMO networks suggest that some of these goals can be met [3, 42, 43]. However, experience with directing ECMO cases to high-volume centers is limited, and has not been scientifically proven superior as a strategy. A recent study even suggested that low-volume centers have better ECMO in-hospital mortality than high-volume centers [44], questioning the existence of a positive volume–outcome relationship in this population. Another unresolved issue is the nurse-to-patient ratio for ECMO patients [45].

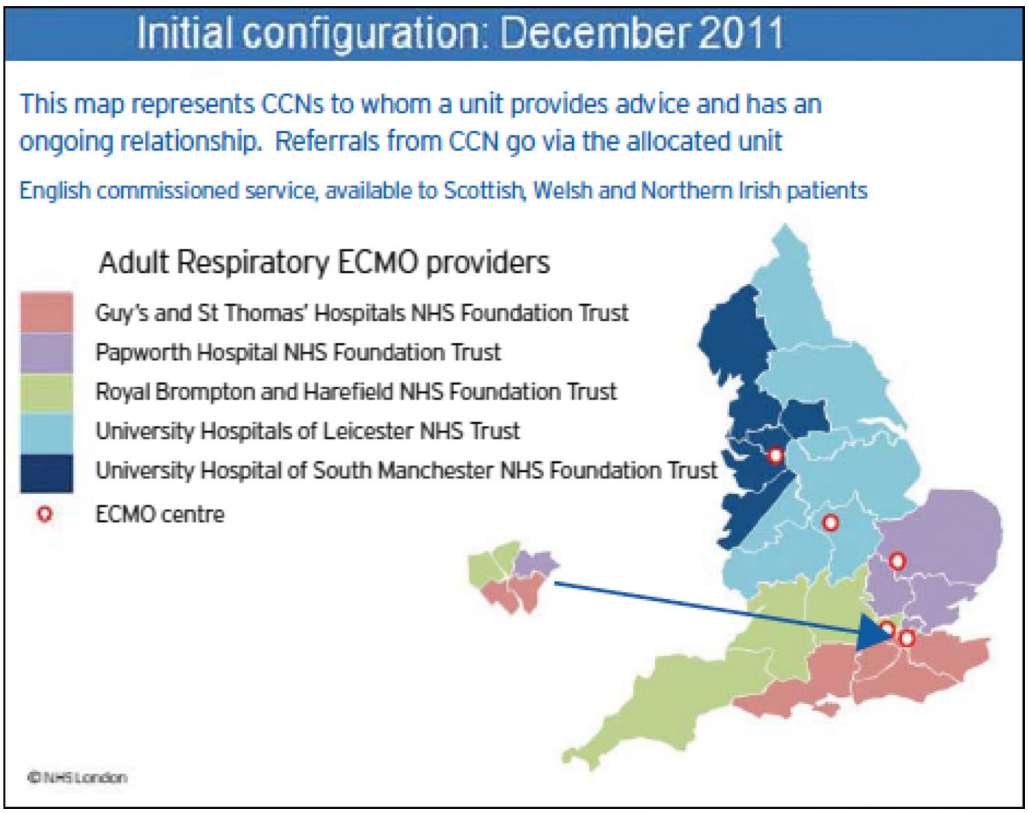


Fig. 2 The regional coverage of England by the National Severe Respiratory Failure Service

ECMO retrieval teams

Mobile ECMO retrieval teams might allow safe transportation under cardiopulmonary support to experienced tertiary centers and might ultimately improve survival of the sickest respiratory or cardiac failure patients initially treated in centers where ECMO is not possible. The mobile team ideally should be available 24 h a day, 7 days a week. and employ experienced personnel trained in the transport of critically ill patients, insertion of ECMO cannulae, and circuit and patient management [9]. Successful transportation of patients on cardiopulmonary support by ambulance, helicopter, and fixed-wing aircraft has been reported [42, 46–48]. Centers performing ECMO should develop specific guidelines and ensure adequate staff training to provide uninterrupted availability of transport on ECMO. Development of telemedicine is also important to improve patients selection for ECMO, and also to provide adequate advices regarding alternative strategies to ECMO to less experienced centers.

Scoring systems to predict the outcomes

In very recent years, several scoring systems to predict the outcomes of patients after ECMO for cardiac or respiratory indications have been proposed [17, 38, 49–52]. Respiratory scores constantly demonstrate the strong negative impact of older age, immunocompromised status, associated extra-pulmonary organ dysfunction, pre-ECMO duration of mechanical ventilation, impaired pulmonary compliance and non-influenza-induced ARDS diagnosis (Table 1). In addition, the RESP and the PRESERVE scores [17, 52] have been consistent with recent randomized controlled trials by demonstrating that pre-ECMO prone positioning and neuromuscular blockade were associated with improved survival. Interestingly, no predictive score has shown hypoxemia to be predictive of survival in this setting. The survival after veno-arterial-ECMO (SAVE)-score based on the ELSO registry data from 3846 cardiogenic shock patients showed that preexisting comorbidities, pre-ECMO organ failures and cardiac arrest, lower pulse pressure, and lower serum bicarbonate were risk factors associated with mortality [38]. The ENCOURAGE score [17], which was constructed on data from VA-ECMO-treated acute myocardial infarction patients, demonstrated the major impact of age, liver and renal failure, coma and serum lactated on patients' survival.

These scoring systems should only be considered appropriate for predicting survival in patients for whom ECMO has already been initiated. They might help offering population management information and might facilitate risk-adjusted comparison of outcomes between institutions, regions, and time periods. They have not been validated for prediction of survival in larger

Table 1 Ongoing and future research areas in ECMO

	Organization	Technological improvements	Improve patient selection	Evaluate risk–benefit ratio	Better define the place of associated treatments	Identify criteria for ECMO weaning	Indications of other supportive treatments
VV-ECMO	Regionalization Nurse-to-patient ratio	Miniaturization Less blood cells injuries Less anticoagulation requirements	Non refractory hypoxaemia	Of utmost importance including long-term outcomes	MV settings prone positioning	Yes	Nutrition, modulation of inflammation, blood cell requirements, anticoagulation
VA-ECMO		Better membrane capacities	ECPR		IABP, Impella		Inotropes, vasodilators

populations of patients where ECMO has not yet been instituted and should be used with great caution to select individual patients for cardiac or respiratory ECMO or to decide on futility. These scores have still to be prospectively validated and regularly recalibrated on large populations of patients.

What are the common beliefs that have been contradicted by recent trials? (Table 1)

Anticoagulation

Older ECMO circuits using poorly biocompatible materials required major anticoagulation and were associated with substantial bleeding. The advent of coated circuits has permitted a decrease in anticoagulation, small studies reporting that prophylactic systemic anticoagulation was possible in ECMO patients with reduced incidence of complications [6]. In the setting of severe bleeding, the avoidance of anticoagulation for as long as 20 consecutive days has even been reported [53]. However, proof beyond doubt is missing that oxygenator clotting or risk of deep vein thrombosis does not increase with less anticoagulation. Anticoagulation targets might also be higher for cardiac patients on VA-ECMO. Rigorous evaluations of anticoagulation use in ECMO patients are needed, since practices vary widely [7, 54].

Transfusion strategies

The transfusion thresholds for red blood cells and platelets in patients receiving ECMO were traditionally set to maintain values close to the normal range (120–140 G/L and >100 g/L, respectively) [1]. This notion has, however, been challenged in recent years [8] as transfusions of blood products are costly, induce alloimmunisation in transplant candidates and might cause specific lung injury [55]. Small observational trials indicated that ECMO can be successfully conducted in patients with a hemoglobin content of less than 80 g/L [56] with consecutive reduced need for red blood cell substitution. Similarly, platelet transfusion might be discouraged except when severe thrombocytopenia is accompanied by bleeding [8, 9]. More studies are, however, needed in order to evaluate the short- and long-term consequences of lower transfusion thresholds.

Early mobilization and physical therapy on ECMO

Historically, ECMO patients have been nursed with full bed rest and managed with high levels of sedation and minimal interventions because of concerns about short-term safety [1, 7, 8]. However, prolonged immobility exposes the patient to exacerbated muscle weakness and poor long-term outcomes. A recent systematic review of early rehabilitation in adults during mechanical

Fig. 3 Ambulation in an ECMO patient at the Medical ECMO program, Columbia University Medical Center/New York-Presbyterian Hospital. Courtesy of Dr. Daniel Brodie

ventilation reported that early rehabilitation may improve strength, functional recovery at hospital discharge, and days alive and at home in the 6 months after critical illness [57]. Patients receiving ECMO may benefit from less sedation and early rehabilitation, and recent studies found that rehabilitation, including mobilization (Fig. 3), during ECMO was feasible and safe [58, 59].

ECMO as a bridge to lung transplantation

Due to organ shortage, severe respiratory or circulatory failure develops in many patients on waiting lists for lung transplantation (LTx). Deterioration of waiting list patients commonly triggers the need to proceed with transplantation to avoid imminent death despite an increased risk of mortality. Therefore, VV- and VA-ECMO have been increasingly used to bridge patients with acute-on-chronic respiratory and/or circulatory failure to LTx. In an analysis using United Network for Organ Sharing (UNOS) data from 1987 to 2008, patients supported preoperatively by mechanical ventilation or ECMO had markedly worse survival after LTx compared to those transplanted unsupported [60]. More recent analyses using UNOS data from 2010 to 2015 showed that the adverse influence of ECMO was absent in high-volume lung transplant centers [61]. A systematic review including 14 retrospective studies pointed out that current data do not permit a definitive conclusion on the efficacy of ECMO as a bridge to transplantation [62]. However, these patients may have an acceptable 1-year survival [62–64]. These data contradicted the widespread belief that the outcome of ECMO patients after lung transplantation is dismal [60, 62].

Pathophysiological approach and research in cardiogenic shock

From a methodological point of view, the major advance has been the proof-of-concept that large randomized trials with mechanical support devices and clinically relevant endpoints (i.e. mortality) are feasible, as shown for the use of IABP in the IABP-SHOCK II trial [65]. Common beliefs in shock research which have been contradicted in recent trials are that: (1) devices that increase cardiac output automatically improve prognosis; (2) positive haemodynamic findings seen in healthy laboratory animals without cardiogenic shock can be uncritically translated to the patient with cardiogenic shock; (3) what seems reasonable from a pathophysiological point of view necessarily transforms into clinical benefit; and (4) cardiogenic shock is a pure hemodynamic problem. Especially, the latter view must be disregarded. Cardiogenic shock is a hemodynamic problem only at the very beginning, and soon becomes a very complex disease, with bacterial translocation, overshooting inflammation and the development of multiple organ failure [66]. Indeed, in patients with cardiogenic shock complicating myocardial infarction, the APACHE II score is a better predictor of mortality than cardiac output [67].

What are the remaining areas of uncertainties? (Table 1)

Risk–benefit evaluation of ECMO support

Although ECMO can improve survival of patients with advanced lung and heart disease, there is significant associated morbidity with performance of this intervention [68]. Specifically, the use of ECMO for severe ARDS remains controversial, with conflicting data regarding its impact on survival [69, 70]. A recent study showed a rapid increase in the use of ECMO in Germany, while mortality remained high [41]. Evidence regarding the benefits of temporary MCS in cardiogenic shock not responding to standard therapy, including inotropes, is also still limited. In a meta-analysis of three randomized clinical trials comparing a percutaneous MCS versus IABP in cardiogenic shock patients, MCS appeared safe and demonstrated better hemodynamics, but did not improve 30-day mortality and was associated with more bleeding complications [71]. Furthermore, in a recent randomized controlled trial involving 48 mechanically ventilated cardiogenic shock patients after acute myocardial infarction, the Impella CP was not associated with reduced 30-day mortality compared with IABP [15]. Based on these results, temporary MCS only received a class IIb recommendation from the European Society of Cardiology [10].

LV unloading in VA-ECMO

Peripheral VA-ECMO increases LV afterload that may delay myocardial recovery in cases of myocardial infarction or myocarditis. Excessive LV afterload and lack of LV unloading under VA-ECMO might induce serious complications such as LV stasis with thrombus formation, pulmonary edema, myocardial ischaemia caused by ventricular distension, and ultimately increased mortality [12, 68, 72, 73]. Current strategies of LV unloading in VA-ECMO patients include atrial septostomy, central percutaneous cannulation of the left atrium or ventricle, combined support with VA-ECMO and Impella, as well as concomitant utilization of an IABP [11]. Adding an IABP to VA-ECMO was shown to improve hemodynamics, to reduce LV dimensions and to decrease pulmonary artery pressures [72]. Furthermore, IABP combined with VA-ECMO was independently associated with improved mortality and successful weaning from ECMO in a Japanese national inpatient database [73]. Alternatively, association of the Impella device to VA-ECMO might provide a greater reduction in LV overload while increasing the

net forward flow [14]. Indeed, a recent study suggested better outcomes in patients with combined support with VA-ECMO and Impella [74].

Mechanical ventilation under VV-ECMO

The optimal ventilator strategy in VV-ECMO patients is not clear [75]. Tidal volume can be very low, resulting in near-absent tidal stress and strain, and minimal or absent atelectrauma. While some experts endorse a higher PEEP strategy (>10 cmH_2O) to keep the lung open and prevent atelectasis [76, 77], some endorse a strategy that includes no external PEEP (i.e., patient extubated) [78]. In a recent meta-analysis of 9 VV-ECMO studies, the driving pressure was the only parameter that was independently associated with in-hospital mortality [79]. Avoiding injurious mechanical ventilation should therefore be a principle of lung protection [5, 76, 79].

In general, any mode (e.g., volume/assist-control, APRV, NAVA) that can decrease harmful ventilation might be used. Once patients stabilize transitioning to spontaneous breathing, partial-assist modes (e.g., pressure support ventilation) should be considered.

Nutrition therapy in ECMO patients

Nutrition therapy is used in almost all critically ill patients, with no clear evidence about optimal administration. A study of 107 ECMO patients in Australia and New Zealand to determine current nutrition practice [80] showed that enteral nutrition was the most commonly used nutrition-delivery mode during ECMO, but was interrupted on 53% of study days. The authors reported that acceptable amounts of calories and proteins were delivered, although these were less than the estimated requirements. The two most commonly reported barriers to the delivery of enteral nutrition included fasting for a therapeutic or diagnostic procedure and high gastric residual volumes.

ECPR

Rescuing cardiac arrest patients with ECMO requires disproportionate human, financial and material resources. However, to date, long-term outcomes of the ECPR patients are still poor compared to other groups of ECMO patients [32–34]. Therefore, what should be patient selection criteria for ECPR? To reduce low-flow time, should on-site ECPR be preferred to rapid transport of refractory cardiac arrest patients to the closest ECMO center [81]? Would mechanical chest compression device give better results than long-term conventional CPR awaiting ECMO in this setting? Will additional therapies such as therapeutic hypothermia or other brain protection treatment to attenuate ischemic/reperfusion injuries improve neurological outcome?

What the international group of experts recommend as the top 10 studies/trials to be carried out in the next 10 years, and what are expected outcomes/results of these trials (Table 2)

Randomized controlled trial (RCT) of VV-ECMO for severe respiratory failure

Beyond rescuing ARDS patients dying of refractory hypoxemia, ECMO may improve the outcomes of less severe ARDS patients by facilitating less-damaging ventilation. The ongoing international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA, NCT01470703) trial may help to resolve the ongoing controversy in this indication. This trial tests the efficacy of early VV-ECMO in patients with severe (main entry criteria PaO_2/FiO_2 < 80 mmHg) or refractory ARDS compared to conventional mechanical ventilation with systematic prone positioning.

RCT of VA-ECMO or other MCS devices for severe cardiogenic shock

Although widely used for over three decades, the IABP-SHOCK II trial demonstrated that the IABP provided no benefit over medical treatment alone in AMI-related cardiogenic shock. A large randomized trial should now be rapidly conducted to test VA-ECMO, other catheter-based MCS devices or combination MCS support in this setting.

RCT of restrictive or very restrictive transfusion policy in ECMO patients

Compared with more liberal strategies, a trial in ECMO patients might demonstrate non-inferiority (or even superiority regarding patients centered outcomes) of transfusion thresholds as low as 70 or 20 g/L for red blood cells and platelets, respectively. Patients with ongoing serious bleeding or myocardial ischemia should, however, be excluded from such trials.

RCT of reduced anticoagulation or alternative anticoagulant drugs in ECMO patients

Reducing anticoagulation might result in fewer bleeding complications and ultimately better short- and long-terms outcomes, especially in patients on VV-ECMO. Alternative anticoagulant drugs together with better monitoring of the balance between coagulation and anticoagulation might also improve patient outcomes.

RCT testing early mobilization and physical therapy on ECMO

This study might prove that less sedation and early rehabilitation on ECMO is safe and feasible and is associated with improved strength, faster functional recovery,

Table 2 Top 10 studies/trials to be carried out in the next 10 years

Studies/trials	Expected outcome/results
1. RCT of VV-ECMO for severe respiratory failure	Lower mortality/better long-term quality of life with early VV-ECMO in patients with severe or refractory ARDS compared to conventional mechanical ventilation with systematic prone positioning
2. RCT of VA-ECMO or other MCS devices vs. medical treatment only for patients with AMI-related cardiogenic shock	Lower mortality/better long-term quality of life with early VA-ECMO or other MCS devices
3. RCT of restrictive or very restrictive transfusion policy in ECMO patients	Transfusion thresholds as low as 70 or 20 g/L for red blood cells and platelets associated with less transfusion, less cost, less complications and similar short- and long-term outcomes
4. RCT of reduced anticoagulation or alternative anticoagulant drugs in ECMO patients	Fewer bleeding complications and ultimately better short- and long-terms outcomes
5. RCT testing early mobilization and physical therapy on ECMO	Less sedation and early rehabilitation on ECMO, feasible, safe, and associated with improved strength, faster functional recovery, shorter duration of ICU stay and better long-term outcomes
6. RCT comparing pre-hospital vs. in-hospital ECMO in refractory cardiac arrest	Feasibility of pre-hospital ECMO. Cost and results compared to immediate transfer on CPR and in-hospital ECMO initiation
7. Drug pharmacokinetics, pharmacodynamics and innovative pharmacologic strategies in ECMO patients	Impact of circuit, drug and critical illness factors on drug PK during ECMO. Less toxicity or treatment failure with optimized drug dosing on ECMO
8. Physiologic studies evaluating best ventilation strategies in VV-ECMO patients	Effects of individualizing MV settings including PEEP, plateau and driving pressures, modes of MV and prone positioning on duration of ECMO and respiratory support and mortality
9. Studies of regionalization of ECMO service with ECMO retrieval teams	Coordinated, regionalized network of ECMO centers and satellite hospitals is cost-effective and improves outcomes and resource utilization
10. Large international retrospective and prospective cohorts to refine indications, to evaluate long-term outcomes and to explore ethical issues in ECMO patients	Real-life data to refine indications, improve scoring algorithms and explore ethical issues of ECMO patients, their proxies and the ICU staff

shorter duration of ICU stay and better long-term outcomes.

RCT comparing pre-hospital versus in-hospital ECMO in refractory cardiac arrest

This study is already recruiting cardiac arrest patients in France (ACPAR2, NCT02527031). Patients randomized to the experimental group will receive VA-ECMO support at the site of cardiac arrest within 20–30 min of collapse. Control patients will receive on-site resuscitation with secondary transfer to the hospital for ECMO initiation. The primary endpoint of ACPAR2 will be survival with good neurological outcome (CPC 1 or 2) 6 months following the event.

Drug pharmacokinetics, pharmacodynamics and innovative pharmacologic strategies in ECMO patients

Since most drug pharmacokinetics and pharmacodynamics are altered in ECMO patients and can lead to either toxicity or treatment failure, future research should investigate circuit, drug and critical illness factors that can affect drug PK during ECMO [82]. Alternatively, it could make sense to combine ECMO support with drugs dampening inflammation, autonomous dysfunction, cytopathic hypoxia and MODS. The inotropic and calcium sensitizer Levosimendan might also accelerate weaning from VA-ECMO in cardiogenic shock patients.

Physiologic studies evaluating best ventilation strategies in VV-ECMO patients

These studies should test the effects of MV settings including PEEP, plateau and driving pressures, modes of MV and prone positioning at the different phases of VV-ECMO support. For example, assessing lung recruitability and optimizing PEEP at the individual patient level may translate in shorter duration of ECMO and respiratory support and even lower mortality [77].

Would regionalization of ECMO with ECMO retrieval teams improve outcomes?

A carefully designed trial comparing a coordinated, regionalized network of ECMO centers and satellite hospitals, with a region hosting a similar population but lacking such coordination, will need to be undertaken. This should demonstrate a cost-effective improvement in outcomes and resource utilization with regionalized care. While ECPR would clearly benefit from concentration of expertise, satellite facilities may not be served rapidly enough by specialized centers. ECPR indications might therefore require a separate study.

Retrospective and prospective cohorts to refine indications, to evaluate long-term outcomes and to explore ethical issues in ECMO patients

Such studies including large international cohorts of patients may refine the specific indications and scoring algorithms for patients requiring ECLS support. Ethical issues regarding ECMO patients, their proxies and the ICU staff should also be the focus of future studies.

Conclusion

Although there have been considerable advances regarding the use of ECMO in critically ill patients, the risk–benefit ratio remains underinvestigated. Organization of ECMO delivery and use of adjuvant therapeutics also need to be explored. Finally, ECMO indications must be carefully identified in order to take into account the costs associated with the use of this unusual salvage therapy.

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