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1. Fisiopatologia Respiratória e Cardiovascular

1.1. Molecular mechanisms underlying hyperoxia acute lung injury.

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Review article

Molecular mechanisms underlying hyperoxia acute lung injury

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ABSTRACT

The management of acute hypoxemic respiratory failure frequently includes the use of supra-physiological fractions of inspired oxygen (FiO_2), which can be beneficial in the short-term but not without risks in the long-term, causing acute lung injury (ALI). Over the last few years, much attention has been devoted to the intracellular signaling transduction pathways that lead to hyperoxia-induced cell damage, particularly MAP kinase cascades. Identification of involved signaling molecules and understanding of the regulation of the main signal transduction pathways might provide the basis for improving the outcome of patients under high FiO_2 exposure through more effective therapeutic interventions. This review, which includes studies published from 1987 to 2015, presents an overview on recent progresses in the hyperoxia ALI field with special emphasis on potential therapeutic targets and clinical approaches based on the molecular mechanisms underlying hyperoxia-induced inflammation. Further studies are needed to gain deeper insight into controversial molecular mechanisms underlying hyperoxia-induced cell death, which may play a critical role in future pharmacological interventions, as well as into hyperoxia-induced cell damage, that could monitor and therefore prevent hyperoxia ALI.

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Abbreviations: ALI, acute lung injury; AP-1, activator protein 1; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; CHI3L, chitinase 3-like 1; DPI, diphenyleneiodonium; DUOX, dual oxidase; Egr-1, early growth response gene-1; ENaC, epithelial sodium channel; EP, ethylpyruvate; ERK, extracellular signal-regulated kinase; HMGB-1, high mobility group box-1; HS, hydrogen-rich saline; JNK, c-Jun N-terminal kinase; LC3B, protein 1 light chain 3B; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-activated protein kinase kinase; MAPKKK, mitogen-activated kinase kinase kinase; MIP-2, macrophage inflammatory protein-2; mtALDH, mitochondrial aldehyde dehydrogenase; NF-κb, nuclear factor κb; NOX, NADPH oxidase; Nrf2, nuclear factor-like 2; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; PKCδ, protein Kinase Cδ; PMNs, polymorphonuclear leucocytes; RA, retinoic acid; SP, substance P; STAT-3, signal transducer and activator of transcription 3; TGFβ1, transforming growth-factor beta-1; TNF-α, tumor necrosis factor alpha; Trx, thioredoxin.

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1. Introduction

Acute hypoxemic respiratory failure remains a leading cause of intensive care unit admission with high rates of associated morbidity and mortality [1]. The treatment of acute hypoxemic respiratory failure frequently includes the use of mechanical ventilation, which is not without risks [2]. In fact, mechanical ventilation can worsen the injury of previously damaged lungs. This ventilator-induced lung injury can occur mainly due to ventilation with high tidal volumes and airway pressures. Accordingly, current clinical recommendations suggest mechanical ventilation with tidal volume (6 ml/kg predicted body weight) and airway pressure

(30 cmH_2O) limitation [3].

The management of acute hypoxemic respiratory failure also commonly includes the use of supraphysiological oxygen concentrations in inspired air (pO_2 (a) > 300 mmHg) to ensure adequate blood oxygenation [4,5]. Although potentially lifesaving in the short-term, prolonged hyperoxia is not without risks and has been implicated in organ toxicity processes, such as ALI [6–8]. On the one hand, O_2 plays a vital role in ATP synthesis; on the other hand, it is responsible for the production of ROS, which are capable of damaging alveolar epithelial cells, thus causing disturbances in the pulmonary system and gas exchange impairment. There is a narrow margin between therapeutic and deleterious effects of high concentrations of inspired oxygen, suggesting that the potential benefits and risks of ventilation with high FiO_2 (0.8–1.0) must be weighed, since whether the exposure to supranormal PaO_2 in critically ill patients is safe or not is yet to be clarified.

PMNs are the major inflammatory cells involved in the process of ALI, generating ROS and leading to alveolar epithelial cells' death [9–12]. ROS have been shown to participate in the pathogenesis of many human diseases; however, the biochemical mechanisms by which ROS cause cell damage and ultimately organ dysfunction are so far not completely understood [4,5,13,14]. Under hyperoxic conditions, excessive ROS act both as direct cell toxins and as secondary messengers, by inducing the activation of intracellular transduction pathways and secretion of proinflammatory cytokines by the alveolar epithelial cells [15]. This leads to the destruction of the alveolar-capillary barrier, increased pulmonary permeability, endothelial and epithelial cell death and PMN influx into alveolar spaces [15–18].

Over the last few years, much attention has been devoted to the signaling pathways and proinflammatory cytokines that lead to hyperoxia-exposed cells' death during supplemental oxygen therapy [19,20]. The comprehension of the molecular mechanisms responsible for the development of ALI is based on the identification of crucial lung injury response signaling molecules. A thorough understanding of the regulation of the main signal transduction pathways that can lead to alveolar epithelial cell injury after prolonged hyperoxia might provide the basis for improving the outcome of patients under high FiO_2 exposure through more effective therapeutic interventions.

The purpose of this review is to provide a critical evaluation of the current bibliography on hyperoxic ALI, focusing on recently described intracellular molecular pathways and exploring potential therapeutic targets and future clinical applications.

2. Methods

Eligible studies were identified by an electronic search of PubMed, involving studies published from 1987 to 2015. The sensitive search strategy combined the following keywords: *molecular mechanisms*; *hyperoxia*; and *acute lung injury*. All articles and cross-referenced studies from retrieved articles were screened for pertinent information and reviewed by the Authors.

Inclusion criteria consisted in experimental and systematic review articles, published as original studies, with available abstract. Publications not written in English were excluded.

3. Signal transduction pathways

ROS generated by NOX family enzymes play a pivotal role in hyperoxia-induced ALI [5,16]. Although the effect of ROS in ALI has not been completely defined, previous studies have shown evidence of direct pulmonary cells injury through lipid peroxidation, enzyme inactivation, DNA damage, and cellular reducing agents' decrease [21]. Distinct NOX enzymes may specifically activate a range of different signaling pathways by modulating their subcellular location, expression level and interaction with membrane proteins [21–25]. Previous studies have reported NOX1 as the main participant member of NOX family in ALI through complementary mechanisms: a direct genotoxic effect and the activation of redox-sensitive STAT3 signaling, while NOX2 and NOX4 were shown to induce cell migration and cell death, regardless of some remaining controversy under this topic [25–28].

DUOXs are major NOX homologues and a significant source of ROS in lung epithelium [5]. Previous studies have suggested that DUOX-generated ROS play a central role in the regulation of innate immune responses and modulation of cell death in airway epithelial cells exposed to prolonged hyperoxia, rather than NOX1 [5,21,29].

Generation of ROS under supraphysiological concentrations of oxygen is reported to be one of the main damaging stimuli capable of inducing or mediating phosphorylation of MAPK signal transduction pathways by altering the structure and function of signaling proteins through modification of critical amino acid residues [22,30,31]. MAPK signal transduction pathways regulate a wide range of vital cellular mechanisms, such as cell growth, proliferation, differentiation, stress responses, and ultimately survival and apoptosis through distinct intracellular and nuclear substrates' modulation [32,33]. To date, several studies described four distinct MAPK cascades: ERK 1/2, JNK, p38 and ERK 5 [32].

Hyperoxia-induced ROS, together with NOX1 activation, are responsible for the triggering of ERK 1/2 pathway, characterized by the activation of a broad range of substrates in distinct locations, particularly the nucleus (Fig. 1) [32,34]. In addition to directly interacting with ERK 1/2, ROS are also responsible for increasing mtALDH and CHI3L activity, which significantly stimulated ERK1/2 activation under normoxic and hyperoxic conditions [32,35]. As a defense mechanism against the damaging effects induced by hyperoxia, phosphorylated ERK 1/2 pathway promotes transcription of survival genes, such as Egr-1, Nrf2, and AP-1 [32]. Among these, it was demonstrated that Nrf2 decreased transcription promotes an increase in ALI and overall mortality through suppressed expression of several antioxidant enzymes and superoxide dismutase, which are involved in cellular protection against hyperoxia-induced inflammation [5,23,34]. Although most studies describe ERK 1/2 cascade as a pro-survival signal transduction pathway in hyperoxia-exposed cells, additional research has reported alveolar macrophage apoptosis under specific conditions, findings that can be ascribed to the particular cell type that was implicated [13,31]. Thus, in hyperoxic conditions, ERK 1/2 phosphorylation may have a dual role as either promoter or inhibitor of apoptosis, which appears to depend on the cell type and culture conditions involved [36].

As a key member of the MAPK family, JNK activation in hyperoxia-exposed cells is induced by ROS and NOX1 (Fig. 1) [22]. Once activated, JNK induces phosphorylation of several substrates located in the cytoplasm and nucleus, therefore promoting transcription of apoptotic genes, as well as immune and stress responses [32]. Several studies have reported AP-1 complex as a major target of phosphorylated JNK [32]. Activated through various mechanisms, including oxidant signaling, immune responses, and cell differentiation and apoptosis, AP-1 complex has been shown to play an important role in modulating both cell proliferation and death in a cell-type and stimulus-dependent manner [33,37]. However, Romashko et al. demonstrated that sustained activation of AP-1 is more closely associated with apoptosis [37]. Together with the AP-1 complex, TGFβ1 is involved in inflammation and hyperoxia-induced cell death, as well as impaired alveolarization [38]. Furthermore, despite the final effect of JNK activation supports necrosis and apoptosis, Porzionato et al. suggested that JNK

phosphorylation might stimulate pro-survival mediators such as microtubule-associated LC3B [32]. Thus, in hyperoxia-exposed cells, the effect of JNK pathway activation is distinct according to the stimuli and its strength, as well as duration of phosphorylation, and can range from apoptosis to increased cell survival [32,39]. Most studies propose JNK as a pro-apoptotic factor; however, a protective role of JNK activation in response to hyperoxia has been described [40].

Similar to other members of MAPK family, p38 activation is caused by stress stimuli and signal transmission through the recruitment of specific receptors, thus playing an important role in hyperoxia-induced lung injury (Fig. 1) [32,37]. Li et al. reported p38 as a central regulator of immunological effects, cell apoptosis, senescence, and survival, as well as cell-cycle checkpoints [39]. Apart from direct activation from ROS, p38 activity is stimulated by ROS-induced PKCδ and CH3IL [32]. To date, p38 activation role in ALI is known to be variable: while some reports have described protective effects, most studies have reported detrimental actions [41,42]. Further analysis is needed in order to identify the contributing factors to the variability of p38 activation under supraphysiological concentrations of oxygen.

Under hyperoxic conditions, ROS-mediated cell death is partially dependent on caspase-mediated signaling pathways (Fig. 1) [22,33]. Hyperoxia-induced activation of these signal transduction pathways leads either to necrosis or apoptosis [17,43,44]. Indeed, both mechanisms can co-exist, since they share identical induction agents in similar cell types [37,43]. ROS induce death receptor Fas activation, which results in initiator caspase 8 stimulation [13]. This triggers a range of events, such as Bax, Bid, Bim and Back activation, which belong to the Bcl-2 family and increase PKCδ expression [13]. As an apoptotic modulator, PKCδ stimulates cleavage of executioner caspases 3 and 9, culminating in cell death by apoptosis and/or necrosis [13]. Caspase 3 is considered the most important of the effector caspases [45]. The main role of apoptosis in epithelial damage under hyperoxic conditions remains unclear; however, several mechanisms underlying hyperoxia-induced cell death have already been proposed [46].

Pro-inflammatory cytokines have been implicated in mediating neutrophil influx into hyperoxic lungs; however, molecular processes underlying PMNs recruitment remain unclear [13,45]. Such pro-inflammatory cytokines, including TNF-α, MIP-2, PAI-1, IL-1β, IL-6 and IL-8, are crucial mediators in the early stages of inflammatory response [4]. The transcriptional factor NF-κB is often described as required for maximal expression of numerous cytokines implicated in ALI [45]. Entezari et al. determined that hyperoxia-exposed cell injury is characterized by increased extracellular HMGB-1 production [12]. As a DNA-binding protein, extracellular HMGB-1 triggers an overwhelming late inflammatory response that promotes the progression of ALI [47–50]. Indeed, extracellular HMGB-1 increases the release of cytokines such as IL-

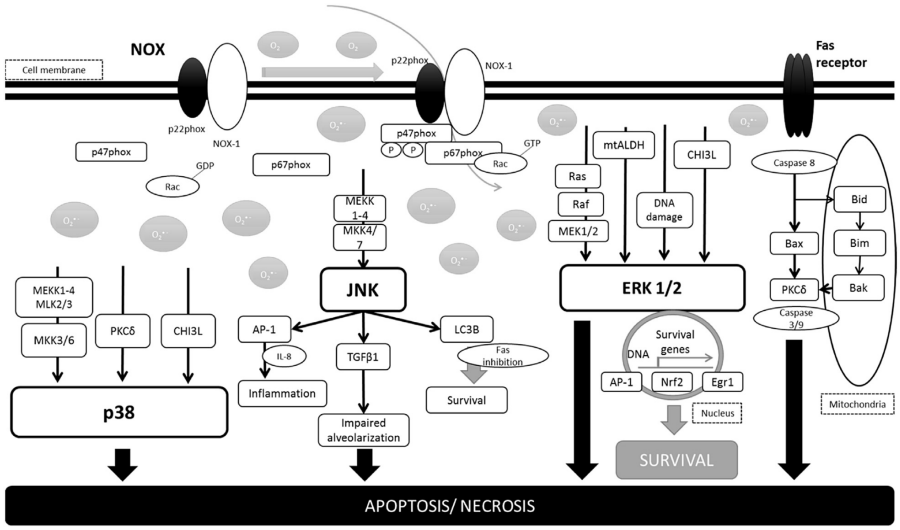

Fig. 1. Schematic diagram of activated signaling pathways in lung cells exposed to prolonged hyperoxia: supraphysiological oxygen concentrations in inspired air can lead to reactive oxygen species (ROS) production via NADPH oxidase (NOX) phosphorylation. ROS promote stimulation of mitochondrial aldehyde dehydrogenase (mtALDH) and chitinase 3-like 1 (CHI3L), and cause DNA damage. The signal is also transduced to small GTP-binding proteins (Ras), which in turn activate the core unit of the cascade, which encompasses MAPKKK (Raf), MAPKK (MEK1/2) and MAPK (Erk). Activated extracelular signal-regulated kinase (ERK) leads to transcription of survival genes, such as activator protein 1 (AP-1), early growth response gene-1 (Egr-1), nuclear factor-like 2 (Nrf2). These inhibit necrotic and apoptotic cell death. In contrast, ERK activation might induce apoptosis/necrosis of alveolar macrophages. ROS also stimulate c-Jun *N*-terminal kinase (JNK) activation through proximal membrane kinase MAPKKK, typically MEKK1–4, which phosphorylates and activates MKK4 or MKK7, the JNK kinases. Once phosphorylated, JNK promotes inflammation and impaired alveolarization through induction of activator protein 1 (AP-1) and transforming growth factor-beta 1 (TGFβ1), respectively. Thus, the final effect of JNK activation supports necrosis and apoptosis. JNK might stimulate microtubule associated protein 1 light chain 3B (LC3B) factor, which induces autophagic mechanisms to protect the cell against hyperoxia. ROS induce p38 activation through protein kinase Cδ (PKCδ), chitinase 3-like 1 (CHI3L), and also MAPKKK, typically MEKK 1 to 4 or a mixed lineage kinase (MLK) 2 or 3, that phosphorylate and activate MKK3 or 6, the p38 MAPK kinases. Once activated, p38 supports necrosis and apoptosis. Supraphysiological oxygen concentrations in inspired air can lead to Fas receptor phosphorylation and further activation of caspase 8, which induces the activation of the pro-apoptotic proteins Bax, Bid, Bim and Back, resulting in increased protein kinase Cδ (PKCδ) expression. Once activated, PKCδ stimulates caspases 3 and 9, culminating in cell death by necrosis or apoptosis.

1β, TNF-α, MIP-2 and macrophage migration inhibitory factor. Conversely, these cytokines control further release of HMGB-1 both to plasma and lung epithelial lining fluids [12].

4. Potential therapeutic targets

Understanding the molecular mechanisms underlying the course of ALI is useful for the identification of potential therapeutic targets, as well as biomarkers to be used for clinical monitoring (Table 1).

Regarding the described role of DUOX in lung injury after prolonged hyperoxia, Kim et al. reported that an acute reduction of DUOX isoform 2 (DUOX 2) expression is sufficient to inhibit ALI and consequent cell death [5]. Simultaneously, Xu et al. demonstrated that the overexpression of mtALDH attenuates hyperoxia-induced cell death by inducing ERK 1/2 phosphorylation. Furthermore, inhibition of ERK 1/2 cascade partially suppresses the positive effect of mtALDH, supporting ERK 1/2 activation through mtALDH as a defense mechanism against hyperoxia [35]. Additionally, CHI3L knock-down and increased survival genes' transcription has been shown to play a protective role from hyperoxia-induced apoptosis by increasing ERK 1/2 phosphorylation [32,51]. Meanwhile, Areshkov et al. reported that ERK 1/2 phosphorylation was induced by both CHI3L1 and CHI3L2, which can be associated with specific outcomes. In contrast to the activation of ERK1/2 phosphorylation by CHI3L1 that leads to a proliferative signal, CHI3L2 inhibits cell mitogenesis and proliferation [52]. Furthermore, Kim et al. demonstrated increased survival in CHI3L-deficient cells through p38 attenuation [51]. These findings may prove helpful in developing potential therapies based on DUOX 2 specific inhibitors for the treatment of ALI.

JNK cascade exposure to supranormal concentrations of O_2 activates morphological and biochemical markers, such as LC3B [53]. Tanaka et al. reported that LC3B overexpression stimulates cytoprotection against hyperoxia injury through autophagy promotion and caspase-3 cleavage inhibition [32,53]. Meanwhile, several studies described the selective inhibition of p38 as a plentiful mechanism to increase cell survival in hyperoxic-exposed cells [41,42].

5. Clinical implications

Over the last few years, much progress has been made in developing possible therapeutic strategies for hyperoxia-induced ALI (Table 2). Regarding the described role of NOX enzymes, Papaiahgari et al. demonstrated that NOX inhibition by DPI considerably reduces the generation of intracellular and extracellular ROS, supporting that NOX actively contributes to the conversion of oxygen into $O_2^{\cdot}$. Therefore, its inhibition may be helpful as a potential therapeutic target for ALI by reducing hyperoxia-induced oxidative stress [5,34].

Porzionato et al. have identified numerous exogenous stimulators of MAPK family members as protective modulators of hyperoxic stimuli [32]. Incubation of hyperoxia-exposed cells with ATP, inosine and laminin substrates results in an increased cell survival response through ERK 1/2 phosphorylation [32]. In addition, Ahmad et al. demonstrated that ATP release and subsequent ATP-mediated signaling events are vital for cell survival under hyperoxia [54]. Buckley et al. described the protective role of inosine administration under hyperoxic exposure [55]. These researchers also demonstrated that cell cultures on laminin substrates, with respect to other plastic supports, resulted in increased phosphorylation of ERK 1/2 [56]. Huan et al. have shown that the addition of SP to cell cultures promotes proliferation and inhibits apoptosis by suppressing JNK and p38 signaling pathways after hyperoxia exposure, which attenuates oxidative lung injury [57,58]. Other researchers reported ERK 1/2, JNK and p38 significant increase under prolonged exposure to hyperoxic conditions [59,60]. Additional studies demonstrated that RA and Trx treatment induces JNK and p38 decline, as well as ERK 1/2 activity increase [59,60].

Sureshbabu et al. have reported TGFβ1 as a critical mediator of ALI [38]. Indeed, Tamarapu et al. described TGFβ1 as a modulator of ENaC, reducing its expression and alveolar sodium transport in epithelial cells [61]. The inhibitory effect of TGFβ1 on ENaC is the main determinant of alveolar fluid clearance across the alveolar epithelium, being mediated by ERK 1/2 cascade activation [61]. The same study has identified serotonin as an endogenous inhibitor of ENaC through TGFβ1 expression stimulation [61]. Therefore, miR-16, a molecule that regulates serotonin system and upregulates ENaC, should be considered as a potential therapeutic target to modulate ENaC expression and restore alveolar fluid balance in ALI [61].

Regarding the p38 cascade, once activated by oxidative stress, PKCδ was reported as an important apoptosis modulator through increased production of caspase-induced PKCδ cleavage products [32]. Interestingly, Grinnell et al. demonstrated that PKCδ chemical inhibitor (rottlerin) significantly attenuates p38 activation, as well as apoptosis, suggesting a potential dual role for PKCδ in ROS-induced apoptosis [32,62]. Therefore, rottlerin acts as an upstream regulator of p38 activation and as a DNA damage inducer, by means of its caspase-3-dependent cleavage fragment. This may prove helpful in developing future therapies for ALI based on PKCδ chemical inhibitors [62]. Simultaneously, Otterbein et al. reported

Table 2
Overview of potential pharmacological treatments for hyperoxia-induced ALI.

Reference	Year	Potential target	Mechanism
[53]	1999	Laminin substrates	ERK 1/2 phosphorylation
[51]	2004	ATP	ERK 1/2 phosphorylation
[31]	2004	DPI	NOX inhibition
[52]	2005	Inosine	ERK 1/2 phosphorylation
[56]	2006	RA	ERK 1/2 phosphorylation JNK and p38 inhibition
[54]	2009	SP	JNK and p38 inhibition
[57]	2010	Trx	JNK and p38 inhibition
[1]	2011	Enoxaparin	PAI-1 and HMGB-1 inhibition
[59]	2012	rottlerin	PKCδ inhibition
[42]	2012	H_2 and HS	Caspase 3/9 and NfκB inhibition
[58]	2012	miR-16	TGFβ1 inhibition
[9]	2014	Anti-HMGB-1 and EP	HMGB-1 inhibition
[60]	2015	CO	p38 inhibition

Table 1
Overview of therapeutic targets in hyperoxia-induced ALI.

Reference	Year	Molecule	Mechanism	Role in ALI
[35]	2006	mtALDH	ERK 1/2 phosphorylation	Protector
[51]	2012	CHI3L	ERK 1/2 phosphorylation and p38 inhibition	Deleterious
[53]	2012	LC3B	Autophagy stimulation and caspase-3 cleavage inhibition	Protector
[5]	2014	DUOX 2	ERK 1/2 and JNK phosphorylation	Deleterious
[32]	2015	Survival genes	ERK 1/2 phosphorylation	Protector

the protective role of low CO concentration in hyperoxic lung injury, its extended survival and its potent anti-inflammatory effects with reduced inflammatory cell influx into the lungs and marked attenuation of pro-inflammatory cytokines' expression [63]. Indeed, exogenous administration of CO limits the progress of histopathological changes and attenuates cytokine expression induced by hyperoxia [32,63].

Xie et al. demonstrated a decrease in caspase 3 activity after H_2 or HS treatment, suggesting a preventing role of H_2 administration in lung cell apoptosis [45]. Additionally, the effective therapeutic role of H_2 or HS in hyperoxia-induced ALI was proven to occur by inflammation and apoptosis downregulation via suppressing NF-κB activation [45]. Most of the data suggested that endogenous NO, similarly to H_2, exerts an effective therapeutic role in many disorders, including oxygen toxicity through decreasing oxidative stress, inflammation, and apoptosis, despite some existing controversy [13,45].

Entezari et al. suggested a link between extracellular HMGB-1 and ALI pathogenesis, once low levels of extracellular HMGB-1 decreased inflammation [12]. In addition, they have shown that HMGB-1 inhibition by neutralizing both anti-HMGB-1 antibodies and the small molecule EP significantly protects lung tissue against hyperoxia-induced extracellular HMGB-1 [12]. In addition, heparin was shown to modulate infiltration of neutrophils and improve gas exchange [4]. Thus, Li et al. demonstrated that pharmacological inhibition with enoxaparin resulted in HMGB-1 and PAI-1 decreased production during prolonged hyperoxia [4].

6. Conclusion

The present review focused on recent progresses in the ALI field with special emphasis on molecular mechanisms underlying hyperoxia-induced inflammation after high FiO_2 ventilation. The wide involvement of signal transduction pathways in lung responses to hyperoxia suggests their modulation may have a significant effect in improving therapies to alleviate ALI in patients undergoing oxygen therapy, by suppressing endothelial and epithelial cell death. In summary, further analysis is needed to gain deeper insight into controversial molecular mechanisms underlying hyperoxia-induced cell death, which may play a critical role in future pharmaceutical interventions, as well as in the identification of clinical biomarkers targeted at ALI prevention, monitoring and management.

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1.2. MicroRNA-155 Amplifies Nitric Oxide/cGMP Signaling and Impairs Vascular Angiotensin II Reactivity in Septic Shock.

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MicroRNA-155 Amplifies Nitric Oxide/cGMP Signaling and Impairs Vascular Angiotensin II Reactivity in Septic Shock

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Objectives: Septic shock is a life-threatening clinical situation associated with acute myocardial and vascular dysfunction, whose pathophysiology is still poorly understood. Herein, we investigated microRNA-155–dependent mechanisms of myocardial and vascular dysfunction in septic shock.

Design: Prospective, randomized controlled experimental murine study and clinical cohort analysis.

Setting: University research laboratory and ICU at a tertiary-care center.

Patients: Septic patients, ICU controls, and healthy controls. Postmortem myocardial samples from septic and nonseptic patients. Ex vivo evaluation of arterial rings from patients undergoing coronary artery bypass grafting.

Subjects: C57Bl/6J and genetic background–matched microRNA-155 knockout mice.

Interventions: Two mouse models of septic shock were used. Genetic deletion and pharmacologic inhibition of microRNA-155 were performed. Ex vivo myographic studies were performed using mouse and human arterial rings.

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Measurements and Main Results: We identified microRNA-155 as a highly up-regulated multifunctional mediator of sepsis-associated cardiovascular dysfunction. In humans, plasma and myocardial microRNA-155 levels correlate with sepsis-related mortality and cardiac injury, respectively, whereas in murine models, microRNA-155 deletion and pharmacologic inhibition attenuate sepsis-associated cardiovascular dysfunction and mortality. MicroRNA-155 up-regulation in septic myocardium was found to be mostly supported by microvascular endothelial cells. This promoted myocardial microvascular permeability and edema, bioenergetic deterioration, contractile dysfunction, pro-inflammatory, and nitric oxide-cGMP-protein kinase G signaling overactivation. In isolate cardiac microvascular endothelial cells, microRNA-155 up-regulation significantly contributes to LPS-induced proinflammatory cytokine up-regulation, leukocyte adhesion, and nitric oxide overproduction. Furthermore, we identified direct targeting of CD47 by microRNA-155 as a novel mechanism of myocardial and vascular contractile depression in sepsis, promoting microvascular endothelial cell and vascular insensitivity to thrombospondin-1–mediated inhibition of nitric oxide production and nitric oxide–mediated vasorelaxation, respectively. Additionally, microRNA-155 directly targets angiotensin type 1 receptor, decreasing vascular angiotensin II reactivity. Deletion of microRNA-155 restored angiotensin II and thrombospondin-1 vascular reactivity in LPS-exposed arterial rings.

Conclusions: Our study demonstrates multiple new microRNA-155–mediated mechanisms of sepsis-associated cardiovascular dysfunction, supporting the translational potential of microRNA-155 inhibition in human septic shock. (*Crit Care Med* 2018; 46:e945–e954)

Key Words: angiotensin II; cardiomyopathy; endothelium; nitric oxide; septic shock; vasoplegia

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (1), accounting for up to 30% of all ICU admissions and representing a leading cause of ICU morbidity and mortality (2). Importantly, the presence of sepsis-associated cardiovascular dysfunction (SCVD) is correlated with a worse outcome (3).

SCVD is associated with profound myocardial and vascular contractile impairment, generally attributed to inflammation-mediated intrinsic muscular dysfunction and reduced responsiveness to inotropic and vasopressor mediators. Despite growing evidence for a key role of inflammatory signaling pathways in sepsis, to date, all inflammation-directed therapeutic strategies have failed to reproductively improve sepsis clinical outcomes (4). Therefore, current sepsis management still relies on immediate antibiotic treatment, infection source control, and supportive measures for organ dysfunction (5, 6).

MicroRNAs are small noncoding RNAs that posttranscriptionally inhibit gene expression of complementary targets (7). Therefore, microRNAs are frequently multifunctional, interacting with cell type–specific transcriptomes and regulating the translation of multiple gene products. This makes microRNAs attractive therapeutic targets in SCVD, which comprises a complex array of signaling pathways.

MicroRNA-155 (*miR-155*) is up-regulated by a multitude of inflammatory and infectious mediators (8), promoting cardiac inflammation and injury in viral myocarditis (9) and pressure overload (10). Higher plasma *miR-155* levels were associated with worse prognosis in human sepsis-induced acute lung injury (11). Here, supported by human and experimental data, we demonstrate multiple conserved *miR-155*–mediated mechanisms contributing to sepsis-associated myocardial injury, vasoplegia, and mortality. Importantly, *miR-155* deletion and pharmacologic inhibition improve survival and cardiovascular performance in different septic shock models, supporting the potential therapeutic benefit of *miR-155* inhibition in human sepsis.

METHODS

Animal Studies

All mouse experiments were subjected to approval by the Faculty of Medicine of University of Porto Animal Ethics Committee and performed according to local guidelines. Male wild-type (WT) and *miR-155* knockout mice were injected with lipopolysaccharide (LPS) or submitted to cecal ligation and puncture (CLP). For anti-microRNA experiments, WT mice were injected on two consecutive days with locked nucleic acid (LNA)-modified anti-*miR-155* (20 mg/kg) or scramble probes (Exiqon, Vedbæk, Denmark) followed by LPS injection or CLP procedure. Group sizes are described in the **supplemental methods** (Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

Human Septic Shock

A set of experiments was performed in order to ascertain the conservation of *miR-155* up-regulation in human sepsis.

Plasma quantification of *miR-155-5p* was performed in septic shock patients ($n = 27$) during the first 3 days following ICU admission and compared with ICU nonseptic patients (ICU-control [Ctrl]), as well as with healthy blood donors (Ctrl). The study was approved by the São João Hospital Ethics Committee, and written informed consent was obtained from each patient or next of kin.

MiR-155 quantification and cellular localization were evaluated in myocardial autopsy samples ($n = 28$) from septic shock patients and compared with myocardial autopsy samples from nonseptic patients.

Cardiac and Vascular Functional Evaluation

In vivo cardiac function was assessed in mechanically ventilated mice using transthoracic echocardiography (Siemens, Erlangen, Germany).

Vascular reactivity to angiotensin II (AngII) and thrombospondin-1 was assessed in isolated rings from mouse abdominal aorta and human left internal mammary artery collected during cardiac surgery. Myocardial vascular permeability in experimental sepsis was assessed by measuring Evans Blue dye-albumin (EBA) conjugate leakage.

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Primary Myocardial Microvascular Endothelial Cells

Primary human myocardial microvascular endothelial cells (HMVEC-Cs; Lonza, Basel, Switzerland) were cultured in EGM-2MV BulletKit (Lonza). WT and *miR-155* knockout mouse cardiac microvascular endothelial cells (MMVEC-Cs) were isolated by fluorescence-activated cell sorting. LPS-induced endothelial proinflammatory activation was analyzed by quantitative real-time polymerase chain reaction, immunoblotting, and flow cytometry.

Supplemental Information

Supplemental information includes a supplemental methods section (Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

RESULTS

Myocardial *miR-155* Up-Regulation in Human and Murine Sepsis Is Mostly Supported by Endothelial Cells and Infiltrating Leukocytes

Myocardial *miR-155* expression was significantly up-regulated in experimental and human sepsis (**Fig. 1*A***). To identify the cellular source of myocardial *miR-155* up-regulation, immunofluorescence localization and flow cytometry analysis of *bic*/*miR-155* promoter-driven *LacZ* reporter was performed. In mouse septic myocardium (**Fig. 1*B*–*D***), β-galactosidase expression mainly colocalized with macro- and microvascular endothelial cells and infiltrating leukocytes. An identical pattern was observed in human septic myocardium by in situ hybridization (Fig. 1*B*). Cardiomyocyte staining was not detected in either species. Furthermore, LPS-exposed isolated cardiomyocytes revealed a nonsignificant less than 1.5-fold increase in *miR-155* expression relative to vehicle-incubated cells. Importantly, cardiomyocyte basal and LPS-induced *miR-155* expression levels were negligible when compared with endothelial cells or macrophages (**Fig. 1*E***).

Plasma *miR-155* concentration was also increased in experimental and human sepsis (**Supplemental Fig. 1*A***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). In ICU-admitted septic shock patients, *miR-155* plasma levels were higher in nonsurvivors when compared with survivors (**Supplemental Fig. 1*B***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Additionally, circulating *miR-155* significantly declined at 48 hours postadmission, suggesting that *miR-155* up-regulation is restricted to the hyperinflammatory phase of human sepsis (**Supplemental Fig. 1*C***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

MiR-155 Inhibition Attenuates Mortality and Structural, Bioenergetic, and Functional Myocardial Changes in Sepsis

MiR-155 deletion protected mice from sepsis-associated microvascular hyperpermeability and myocardial edema, as evaluated by EBA leakage and cardiac interstitial area fraction (CIAF) (**Fig. 2**, ***A*** and ***B***; and **Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). In humans, septic shock was also associated with increased CIAF, compared with controls (**Fig. 2*C***). Histologically, sepsis was associated with enlarged pericapillary spaces (Fig. 2, *B* and *C*). In human sepsis, myocardial *miR-155* expression was positively associated with the extent of interstitial area expansion (**Fig. 2*D***).

To evaluate the impact of *miR-155* on septic myocardial bioenergetics, adenine nucleotides and creatine compounds were analyzed (**Supplemental Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Experimental sepsis was associated with profound myocardial bioenergetic deterioration, which was prevented by *miR-155* deletion.

The impact of *miR-155* genetic and pharmacologic manipulation in sepsis-associated myocardial dysfunction was evaluated by echocardiography (**Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/D657), revealing left ventricular dilatation and decreased fractional shortening, heart rate, and cardiac output in WT septic mice. *MiR-155* knockout and pharmacologic inhibition significantly attenuated cardiac dysfunction in both models. Accordingly, *miR-155* knockout mice displayed reduced mortality when compared with WT counterparts in both model of experimental sepsis (**Supplemental Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Similar results were obtained with WT mice treated with anti-*miR-155* LNA.

MiR-155 Promotes Cardiac Microvascular Endothelial Activation Increasing Leukocyte Adhesion and Infiltration Into Septic Myocardium

After identifying myocardial microvascular endothelial cells as the main contributors for *miR-155* up-regulation in the septic myocardium, we subsequently evaluated the role of *miR-155* in LPS-induced activation of primary mouse and human cells (MMVEC-C and HMVEC-C, respectively). LPS up-regulated endothelial *miR-155* in both species, as well as proinflammatory cytokines and cell adhesion molecules (CAMs) (**Supplemental Fig. 5, *A*** and ***B***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* deletion in sorted MMVEC-C and pharmacologic inhibition in HMVEC-C significantly blunted cytokine and CAM up-regulation. Flow cytometry confirmed a LPS-induced shift toward higher CAM expression levels, which was significantly attenuated in *miR-155* knockout MMVEC-C (**Supplemental Fig. 5*C***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

The impact of *miR-155* inhibition on HMVEC-C adhesive properties was confirmed in vitro by a monocyte adhesion assay (**Supplemental Fig. 5*D***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Accordingly, histologic analysis of experimental septic myocardium revealed decreased leukocyte infiltration in *miR-155* knockout hearts (**Supplemental Fig. 5*E***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Flow cytometry evaluation of myocardial leukocyte infiltrate predominantly showed proinflammatory monocytes ($CD11b^+Ly6C^+$) and granulocytes ($CD11b^+Ly6G^+$) (**Supplemental Fig. 5*F***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). In human sepsis, leukocyte infiltration was also significantly increased compared with nonseptic controls

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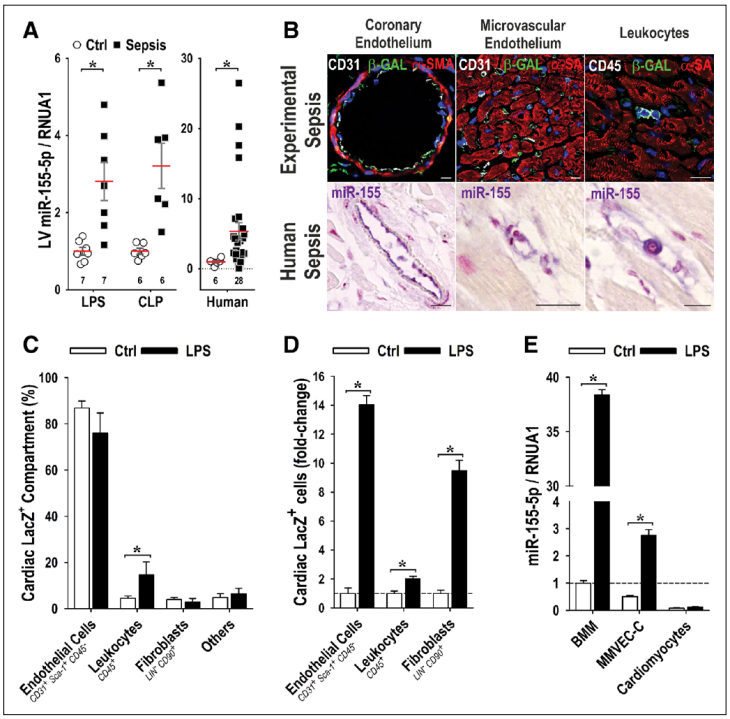

Figure 1. Myocardial microRNA-155 (*miR-155*) expression is increased in experimental and human sepsis, predominantly localizes to cardiac endothelium and infiltrating leukocytes. **A**, Left ventricular (LV) microRNA-155-5p (*miR-155-5p*) expression is increased after LPS (LPS) injection and cecum ligation and puncture (CLP) procedure, compared with respective controls (Ctrl); expression of miR-155 mature form is also increased in autopsy LV samples from septic shock patients, compared with nonseptic autopsy control samples; Mann-Whitney *U* test. **B**, *LacZ* reporter gene (β-galactosidase [β-GAL] immunolocalization and *miR-155* in situ hybridization (human myocardium), revealing strong expression in cardiac macrovascular and microvascular endothelium ($CD31^+$) and infiltrating leukocytes ($CD45^+$); α-smooth muscle actin (α-SMA), α-sarcomeric actinin (α-SA); scale bar: 20 μm. **C**, Flow cytometry analysis of cardiac *miR-155* expression in noncardiomyocyte cell fraction reveals a predominance of endothelial cells among *LacZ*-expressing population and a relative LPS-mediated increase in leukocyte percentage ($n = 4$/group); Mann-Whitney *U* test. **D**, The percentage of $LacZ^+$ cells is increased within endothelial, leukocyte, and fibroblast populations in response to LPS; Mann-Whitney *U* test. **E**, Relative-fold change in *miR-155* expression between mouse bone marrow–derived macrophages (BMMs), cardiac microvascular endothelial cells (MMVEC-Cs), and adult cardiomyocytes ($n = 4$/group); Mann-Whitney *U* test. Data are represented by mean ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. LIN = lineage, RNUA1 = U1 snRNA, Sca-1 = stem cell antigen-1.

(**Supplemental Fig. 5*G***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657) and positively associated with myocardial *miR-155* expression (**Supplemental Fig. 5*H***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

MiR-155 Up-Regulation Mediates Human and Experimental Sepsis-Associated Vasoplegia by Targeting Angiotensin Type 1 Receptor

Expression of *miR-155* was increased in LPS-incubated mouse and human arterial rings (**Fig. 3*A***).

Angiotensin type 1 (AT1) receptor has been described as a *miR-155* target (12, 13). Human and mouse vascular expression of AT1 and reactivity to AngII were significantly decreased in LPS-exposed arterial rings (**Fig. 3**, ***B*** and ***C***). AT1 isoform messenger RNA analysis confirmed an LPS-induced down-regulation of the *Agtr1b* isoform (**Supplemental Fig. 6*A***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* knockout rescued LPS-induced AT1 down-regulation and significantly improved AngII reactivity (Fig. 3*C*). Regarding angiotensin type 2 (AT2) receptor expression, no significant changes were observed between groups, resulting in a decreased AT1-to-AT2 ratio in LPS-exposed vessels (**Supplemental Fig. 6, *B*** and ***C***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

MiR-155 Up-Regulation Promotes Inducible Nitric Oxide Synthase-Derived Nitric Oxide Overproduction

Nitric oxide (NO) systemic production, evaluated by nitrite/nitrate plasma concentration, was significantly increased in septic patients, but not in aseptic inflammation (ICU-Ctrl) (**Supplemental Fig. 7*A***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* deletion significantly blunted sepsis-induced systemic and myocardial NO overproduction (**Fig. 4*A***; and **Supplemental Fig. 7*B***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). In accordance with NO-mediated activation of cGMP-protein kinase G (PKG) signaling pathway, *MiR-155* knockout mice showed reduced LPS-induced up-regulation of myocardial cGMP, vasodilator-stimulated phosphoprotein phosphorylation, and PKG activity levels (**Fig. 4*B***).

NO synthase (NOS) isoform expression analysis in experimental septic myocardium revealed marked inducible NOS (iNOS) and mild endothelial NOS (eNOS) up-regulation (**Fig. 4*C***; and **Supplemental Fig. 8*A***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* deletion attenuated sepsis-induced myocardial iNOS up-regulation,

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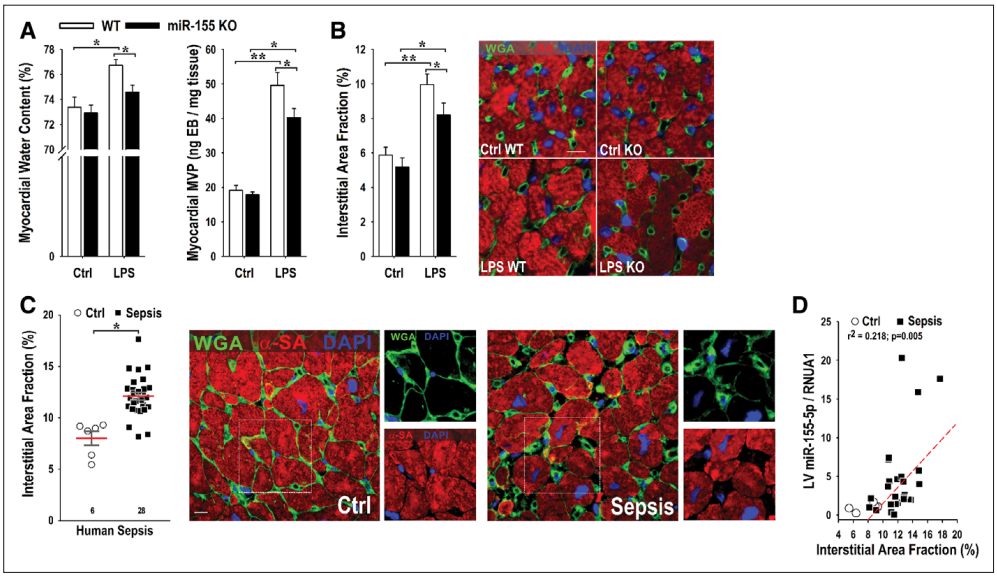

Figure 2. MicroRNA-155 (*miR-155*) knockout (KO) attenuates lipopolysaccharide (LPS)-induced myocardial interstitial edema in experimental sepsis. **A**, *MiR-155* genetic ablation attenuates LPS-induced myocardial microvascular permeability (MVP), measured by Evans blue (EB)-albumin conjugate leakage to interstitial space and myocardial water content ($n = 4$–5 per group), two-way analysis of variance (ANOVA) and Holm-Sidak test. Accordingly, myocardial interstitial area fraction is increased in experimental (**B**) ($n = 7$ per group; two-way ANOVA and Holm-Sidak test) and human (**C**) (Mann-Whitney *U* test) sepsis. Representative images of myocardial tissue immunostained for wheat germ agglutinin (WGA, *green*) and α-sarcomeric actin (*red*) are shown with enlarged pericapillary spaces; scale bar: 20 μm. **D**, In human sepsis, myocardial *miR-155* expression is positively associated with the extent of interstitial area expansion ($n = 33$; $r^2 = 0.218$; $p = 0.005$). Data are represented by mean ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Ctrl = control group, LV = left ventricular, RNUA1 = U1 snRNA, WT = wild type.

whereas eNOS expression remained unchanged. However, LPS-exposed HMVEC-C showed iNOS up-regulation and a trend toward eNOS down-regulation (Fig. 4*C*; and **Supplemental Fig. 8*B***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). This was in line with LPS-induced NO production, which was shown as mainly iNOS-dependent, whereas non-iNOS–derived NO production was decreased by LPS incubation in scramble-incubated cells (**Supplemental Fig. 8*C***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* inhibition blocked LPS-induced up-regulation of iNOS expression/activity (Fig. 4*C*; and Supplemental Fig. 8*C*, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Regarding eNOS, described as a *miR-155* target in humans (14), *miR-155* inhibition attenuated LPS-induced down-regulation, increasing eNOS expression and non-iNOS–derived NO production in LPS-stimulated conditions (**Supplemental Fig. 8, *B*** and ***C***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

In mouse and human vessels, LPS induced eNOS hypophosphorylation (Ser1777) and iNOS up-regulation (**Supplemental Fig. 8, *D*** and ***F***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Additionally, eNOS was down-regulated in human vessels (**Supplemental Fig. 8*F***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). This was associated with impaired NO-mediated relaxation in response to acetylcholine, which was not significantly affected by *miR-155* deletion (**Supplemental Fig. 8, *E*** and ***G***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

MiR-155 Amplifies NO-cGMP-PKG Signaling in Sepsis by Targeting CD47

CD47 is a ubiquitous transmembrane thrombospondin-1 receptor, mediating potent inhibitory effects at several steps of NO-cGMP-PKG signaling cascade. However, its role in SCVD has not yet been addressed. We confirmed *miR-155*–mediated CD47 knockdown using a luciferase reporter assay (**Supplemental Fig. 9*A***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* deletion and inhibition prevented CD47 down-regulation in experimental septic myocardium and LPS-exposed HMVEC-C, respectively (**Fig. 5**, ***A*** and ***B***). Thrombospondin-1 expression in experimental septic myocardium was up-regulated, independently of *miR-155* deletion (Fig. 5*A*).

In HMVEC-C, LPS-mediated CD47 down-regulation prevented response to physiologic concentrations of thrombospondin-1 (**Supplemental Fig. 9*B***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). In LPS-exposed cells, *miR-155* knockdown rescued thrombospondin-1 inhibitory effect on NO production (**Supplemental Fig. 9*C***, Supplemental Digital Content

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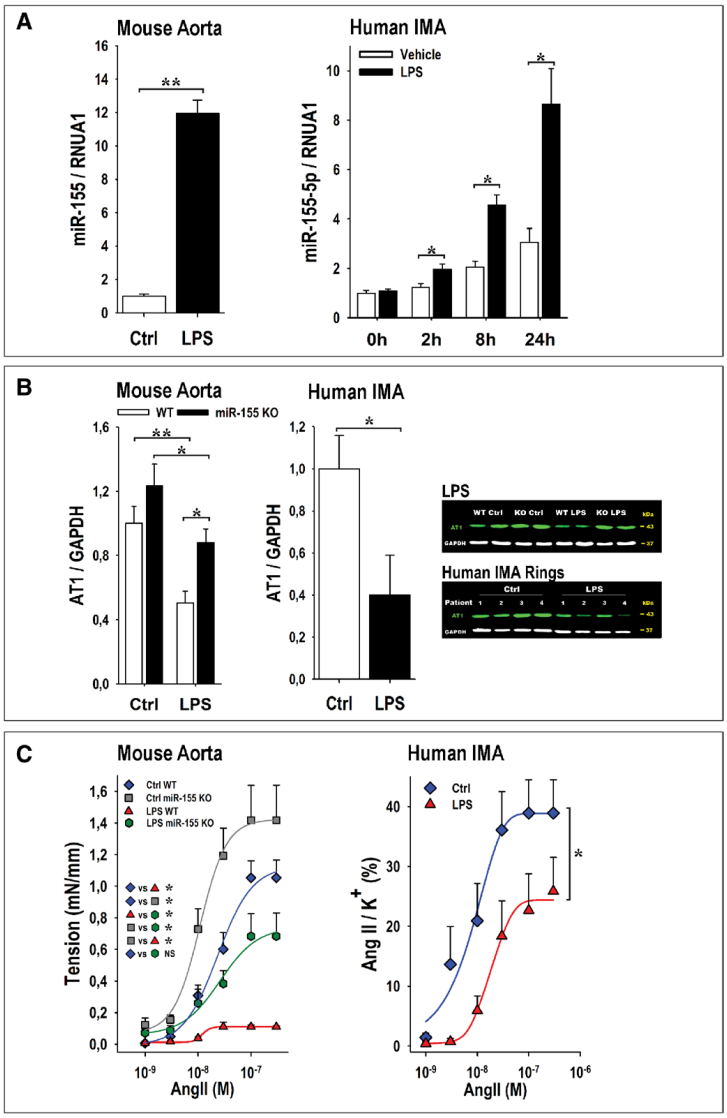

Figure 3. MicroRNA-155 (*MiR-155*) up-regulation mediates lipopolysaccharide (LPS)-induced vasoplegia by promoting angiotensin II (AngII) hyporesponsiveness in mouse and human vessels. **A**, Vascular *miR-155* expression is increased in abdominal aorta (mAo) from mice injected with LPS ($n = 7$ per group) and in human internal mammary artery (hIMA) rings incubated with LPS in vitro ($n = 4$–6 per group), Mann-Whitney *U* test. **B**, Angiotensin type 1 (AT1) expression is down-regulated in wild-type (WT) mAo (2-way analysis of variance [ANOVA] and Holm-Sidak test) and hIMA rings (Mann-Whitney *U* test) exposed to LPS. *MiR-155* knockout (KO) rescues vascular AT1 expression in experimental sepsis ($n = 4$ per group). **C**, LPS incubation decreases vascular responsiveness to AngII in WT mAo ($n = 7$–8 per group) and hIMA rings ($n = 6$ per group); 2-way repeated-measures ANOVA and Holm-Sidak test. *MiR-155* KO potentiates vascular response to AngII, rescuing vascular reactivity in LPS-injected mice. Data are represented by mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Ctrl = control group, GAPDH = glyceraldehyde 3-phosphate dehydrogenase, K+ = KCl-induced membrane deporlarization, RNUA1 = U1 snRNA.

1, http://links.lww.com/CCM/D657). To confirm that endothelial *miR-155* amplifies NO production via thrombospondin-1-CD47 axis targeting, we prevented CD47 derepression using a small interfering RNA. CD47 knockdown avoided anti-*miR-155*–mediated recovery of thrombospondin-1 effect on NO production (**Supplemental Fig. 9*D***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

Incubation of arterial rings with thrombospondin-1 greatly decreased NO-mediated vasorelaxation in Ctrl groups (**Supplemental Fig. 9, *E* and *F***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). However, LPS-induced *miR-155* up-regulation down-regulated vascular CD47 (**Fig. 5*C***) and blocked thrombospondin-1 inhibitory effect on NO-mediated vasorelaxation (Supplemental Fig. 9, *E* and *F*, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). *MiR-155* knockout successfully rescued vascular CD47 expression and thrombospondin-1 inhibitory effect on NO-mediated vasorelaxation (Fig. *5C*; and **Supplemental Fig. 9*F***, Supplemental Digital Content 1, http://links.lww.com/CCM/D657).

DISCUSSION

We identified *miR-155* as an important multifunctional mediator in SCVD (**Supplemental Fig. 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/D657). Both genetic deletion and pharmacologic inhibition of *miR-155* significantly attenuated SCVD and mortality in two experimental sepsis models. Importantly, described *miR-155*–mediated mechanisms in

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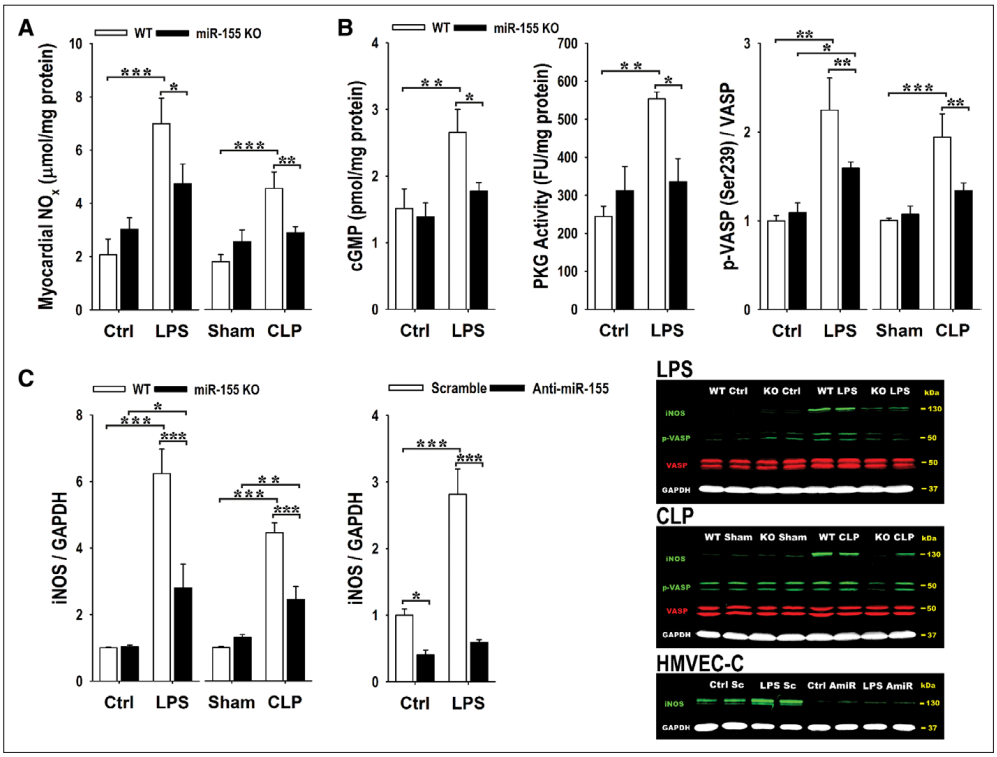

Figure 4. MicroRNA-155 (*MiR-155*) up-regulation promotes myocardial inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO) overproduction. **A**, *MiR-155* knockout (KO) mice are protected from sepsis-induced myocardial NO overproduction ($n = 4$–6 per group); two-way analysis of variance (ANOVA) and Holm-Sidak test. **B**, Lipopolysaccharide (LPS)-induced NO overproduction is associated with increased myocardial cGMP levels and PKG activity, also evaluated by vasodilator-stimulated phosphoprotein (VASP) phosphorylation (Ser239), which are attenuated by *miR-155* KO ($n = 4$–5 per group); two-way ANOVA and Holm-Sidak test. **C**, iNOS expression is increased in septic mouse myocardium ($n = 4$ per group) and LPS-exposed human myocardial microvascular endothelial cell (HMVEC-C) ($n = 6$ per group). *MiR-155* deletion and inhibition significantly attenuate experimental sepsis- and LPS-induced iNOS up-regulation, respectively ($n = 4$–6 per group); two-way ANOVA and Holm-Sidak test. Data are represented by mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. CLP = cecal ligation and puncture, cGMP = cyclic guanosine monophosphate, Ctrl = control group, FU = fluorescence units, GAPDH = glyceraldehyde 3-phosphate dehydrogenase, PKG = protein kinase G, p-VASP = phosphorylated VASP, WT = wild type.

experimental models were posteriorly found to be conserved in human samples, supporting the translational potential of *miR-155* inhibition in septic shock.

MicroRNAs are powerful gene expression regulators in cardiovascular physiology and pathology (7). However, assessing microRNA-related disease mechanisms in complex organ systems is challenging because specific microRNA expression regulation and microRNA-transcriptome interactions can significantly differ between distinct cell types (15). To address this complexity, we used a reporter gene approach to evaluate *miR-155* up-regulation pattern in experimental septic myocardium. Histologic and flow cytometry reporter analysis identified endothelial cells as the main contributor for sepsis-induced myocardial *miR-155* up-regulation. This is especially relevant because labeled anti-*miR-155* LNA probe mainly localizes to microvascular endothelial cells (MVEC) in the myocardium (9), effectively targeting the main overexpressing cell type. In accordance with previous reports (9, 10), we found cardiomyocyte expression to be negligible, challenging the relevance of putative cardiomyocyte-dependent *miR-155* effects.

Despite the recognized importance of microvascular dysfunction in sepsis (3), cardiac MVEC role in septic cardiomyopathy is still poorly understood. Endothelial exposure to bacterial and proinflammatory mediators leads to loss of barrier function, increased permeability, and edema (16, 17). Myocardial edema, decreased coronary flow, and hypoxia have all been described in experimental and human sepsis (18–20), contributing to global myocardial ischemia and functional impairment (21). Here, we demonstrate an attenuation of sepsis-induced myocardial edema, bioenergetic, and contractile dysfunction by *miR-155* genetic and pharmacologic inhibition, whereas in human septic cardiac specimens, a correlation

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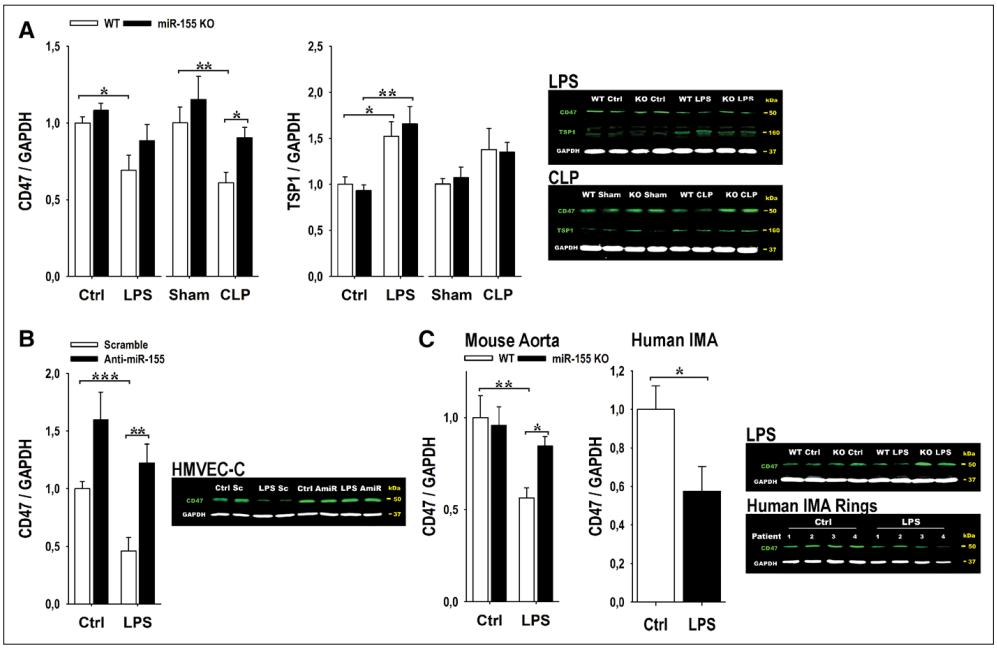

Figure 5. MicroRNA-155 (*MiR-155*) amplifies nitric oxide (NO) signaling pathway by targeting CD47. **A**, Myocardial lipopolysaccharide (LPS)-induced CD47 down-regulation is attenuated by *miR-155* knockout (KO), whereas the expression of its ligand, thrombospondin-1 (TSP-1), is increased during LPS endotoxemia ($n = 4$ per group); two-way analysis of variance (ANOVA) and Holm-Sidak test. **B**, In human myocardial microvascular endothelial cell (HMVEC-C), LPS incubation significantly decreases CD47 expression, which is restored by *miR-155* inhibition ($n = 4$ per group); two-way ANOVA and Holm-Sidak test. **C**, CD47 expression was decreased in LPS-exposed mouse (two-way ANOVA and Holm-Sidak test) and human (Mann-Whitney *U* test) vessels, and in accordance with functional data. *miR-155* KO attenuates CD47 down-regulation in LPS-exposed vessels ($n = 4$ per group). Data are represented by mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. CLP = cecal ligation and puncture, IMA = internal mammary artery, WT = wild type.

between *miR-155* expression and interstitial expansion was observed. These results suggest an important role of *miR-155* in promoting sepsis-induced myocardial edema and dysfunction.

Endothelial proinflammatory activation is a major contributor for SCVD (22). In accordance with previous reports (9, 10, 23), we demonstrate a key role for endothelial *miR-155* in LPS-induced cytokine/CAM up-regulation and leukocyte adhesion. Increased myocardial leukocyte infiltration was observed in human and experimental sepsis and these cell were characterized as expressing high levels of *miR-155*. *MiR-155* knockout hearts showed decreased leukocyte infiltration, whereas in human sepsis, *miR-155* myocardial expression correlated with $CD45^{+}$ cell infiltration, suggesting an important role of *miR-155* in myocardial leukocyte recruitment. Importantly, *MiR-155* deletion not only inhibited leukocyte infiltration but also decreased monocyte proinflammatory activation, supporting a role of *miR-155* in monocyte activation and protecting cardiomyocytes against leukocyte-derived contractile depressant factors.

Despite increased activity of plasma renin and AngII plasma concentrations in human septic shock, a reduced vasopressor effect has been described, though the underlying mechanisms remain poorly understood (24). Notwithstanding, however, AngII has been recently proposed as a useful alternative vasopressor in septic shock patients (25). While in the human genome, only one AT1 isoform exists, there are two isoforms in the mouse genome, *Agtr1a* and *Agtr1b*, with different tissue-specific expression and function (26). Human AT1 receptor and mouse *Agtr1b* were previously described as *miR-155* targets (12, 13). Here, we show that LPS promotes *miR-155*–dependent decrease in AT1 receptor expression and AT1-to-AT2 ratio in mouse and human arterial rings, impairing vasoconstrictive response to AngII. *MiR-155* knockout significantly recovered AT1 expression and restored the vasoconstrictive response to AngII in LPS-injected mice. Therefore, we propose that *miR-155*–mediated AT1 down-regulation promotes sepsis-associated vasoplegia by reducing the vasoconstrictive response to AngII.

NO is a key mediator of sepsis-induced myocardial and vascular contractile depression (3, 27–29). Notwithstanding, nonselective NOS inhibition was associated with impaired myocardial function and increased mortality in human septic shock (30, 31). NO role in sepsis is further complicated by the different cell and enzymatic sources of NO, which may have opposing effects and influence each other's activity (32). Although

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iNOS knockout and inhibition have reproductively improved hemodynamics and mortality in small and large animal models of sepsis (33, 34), respectively, contradictory results have come from eNOS and neuronal NOS knockout regarding cardiovascular performance and mortality (35–38). Interestingly, however, cardiomyocyte eNOS activity has been shown to be protective in experimental sepsis, underscoring the importance of NO source (35, 39). In this work, *miR-155* knockout mice were protected from systemic and myocardial sepsis-induced NO overproduction and myocardial PKG activity up-regulation. We identified iNOS as the main contributor for sepsis-induced NO overproduction, being up-regulated in septic myocardium and in LPS-incubated arterial rings and HMVEC-C. In accordance with decreased proinflammatory transcriptional activity, *miR-155* inhibition significantly attenuated iNOS expression and activity. Regarding eNOS expression, the effect of LPS differed between mouse and human samples, as down-regulation was only observed in human samples. *MiR-155* inhibition blocked eNOS down-regulation and increased non-iNOS NO production in LPS-incubated HMVEC-C. Interestingly, these results expose interspecies differences in the regulation of eNOS expression, as mouse eNOS 3′UTR apparently lacks the *miR-155* seed sequence, present in the human counterpart (14). Despite this difference, both species demonstrate LPS-induced eNOS hypophosphorylation (Ser1177) and impaired acetylcholine-mediated vasorelaxation. These results suggest that *miR-155* contributes to sepsis-associated NO overproduction mainly by up-regulating proinflammatory transcriptional activity and iNOS expression. Additionally, due to its expression pattern, *miR-155* inhibition could preferentially target noncardiomyocyte NO production with minimal impact on cardiomyocyte-intrinsic NOS activity.

Thrombospondin-1 is a large matricellular glycoprotein mainly stored in platelet α-granules and has been shown to be increased in inflammatory conditions (40). CD47 interaction with thrombospondin-1 at physiologic concentrations has been shown to potently and redundantly inhibit canonical NO signaling cascade. Importantly, CD47 knockout mice present resting hypotension, greater hypotensive response to systemically administered NO-donor agents and resistance to thrombospondin-1–mediated inhibition of NO-stimulated vasodilation, compared with WT mice (41, 42). Interestingly, CD47 knockout increased mortality in experimental sepsis (43), but cardiovascular dysfunction has not been addressed. CD47 has been shown to be down-regulated in inflammatory conditions (44) and in platelets from septic mice (45), but the molecular mechanisms regulating its expression remain unknown. Transcriptome analysis has identified CD47 as a *miR-155* target in human and mouse cells (44). Here, we confirmed CD47 as a conserved *miR-155* target and observed myocardial and vascular CD47 down-regulation in response to septic stimuli, which is attenuated by *miR-155* deletion and inhibition. In HMVEC-C and isolated human and mouse arterial rings, LPS exposure down-regulates CD47, blocking its response to thrombospondin-1. Inhibition of *miR-155*-CD47 interaction recovered thrombospondin-1 inhibitory effect on NO production and NO-mediated vasorelaxation. We, therefore, propose thrombospondin-1-CD47 axis down-regulation as a new mechanism of sepsis-associated myocardial dysfunction and vasoplegia, promoting overactivation of NO-cGMP-PKG signaling pathway.

MiR-155 inhibition has been recently described to attenuate sepsis-associated myocardial dysfunction by targeting *Pea15a*, decreasing LPS-induced apoptosis in cultured neonatal rat cardiomyocytes (NRCMs) (46). However, the relevance of apoptosis in the clinical setting remains controversial because no significant cardiomyocyte apoptosis has been detected in human septic myocardial autopsy samples (47). Additionally, we could not observe LPS-induced cardiomyocyte *miR-155* up-regulation or traces of cardiomyocyte *miR-155* staining in mouse or human septic myocardium. Notably, *miR-155* inhibition could not confer any protection against viral-mediated NRCM apoptosis (9). Therefore, our results align with previous data (9, 10), arguing against relevant cardiomyocyte-dependent *miR-155* effects.

Mouse models of sepsis have been recently criticized for poor transcriptomic alignment with humans (48), exposing interspecies physiologic differences that can limit the direct translation of animal research in this field. Additionally, indiscriminate targeting of up-regulated mediators or biomarkers of clinical severity in sepsis without proper understanding of the pathophysiologic mechanisms has proven many times to be the wrong approach to find new effective therapies. In this study, however, we describe new conserved *miR-155*–dependent mechanisms of human and experimental SCVD, based on the targeting CD47- and AT1-dependent signaling pathways. We have shown that *miR-155* deletion significantly attenuates sepsis-associated myocardial edema and dysfunction, vasoplegia, and mortality, by reducing proinflammatory and NO-cGMP-PKG signaling pathway overactivation and preserving AngII-mediated vasoconstriction. Importantly, results on mortality and myocardial function were reproduced by in vivo *miR-155* pharmacologic inhibition, reinforcing the translational potential of our findings and supporting *miR-155* inhibition as a novel potential therapeutic strategy in human SCVD.

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1.3. Myocardial oedema: pathophysiological basis and implications for the failing heart.

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REVIEW

Myocardial oedema: pathophysiological basis and implications for the failing heart

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Abstract

Myocardial fluid homeostasis relies on a complex interplay between microvascular filtration, interstitial hydration, cardiomyocyte water uptake and lymphatic removal. Dysregulation of one or more of these mechanisms may result in myocardial oedema. Interstitial and intracellular fluid accumulation disrupts myocardial architecture, intercellular communication, and metabolic pathways, decreasing contractility and increasing myocardial stiffness. The widespread use of cardiac magnetic resonance enabled the identification of myocardial oedema as a clinically relevant imaging finding with prognostic implications in several types of heart failure. Furthermore, growing experimental evidence has contributed to a better understanding of the physical and molecular interactions in the microvascular barrier, myocardial interstitium and lymphatics and how they might be disrupted in heart failure. In this review, we summarize current knowledge on the factors controlling myocardial water balance in the healthy and failing heart and pinpoint the new potential therapeutic avenues.

Keywords Heart failure; Myocardial oedema; Cardiac microcirculation; Cardiac pericytes; Cardiac lymphatics; Myocardial interstitium; Extracellular matrix

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Introduction

The adequate compartmentalization of water in the myocardium is essential to maintain normal cardiac function.[1] Despite several mechanisms known to regulate cardiomyocyte and interstitial volume,[2] the myocardium remains particularly susceptible to oedema formation due to its dense microvascular network and high interstitial flow rate.

Myocardial oedema (MO), defined by the accumulation of cardiac water in interstitial and/or intracellular compartments, has been shown to induce cardiomyocyte injury, dysfunction[3–6] and remodelling.[3,4]

The recent introduction of magnetic resonance imaging (MRI) techniques (e.g. myocardial T1 and T2 mapping) has enabled the non-invasive assessment of the extracellular component, namely, the myocardial water content, suggesting that MO negatively affects the prognosis across acute and chronic heart failure (HF).[7–9] Moreover, advances in the understanding of the myocardial microvascular barrier and lymphatics suggest that myocardial fluid balance disturbances are key determinants of the extent and duration of myocardial injury. These aspects may recast MO as a therapeutic target yet to explore in clinical practice.

The present review aims to summarize the current knowledge on the pathophysiological mechanisms of MO formation and their contribution to the disruption of cardiac homeostasis in the failing heart, also discussing future perspectives on therapeutic targeting of MO.

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Basic concepts

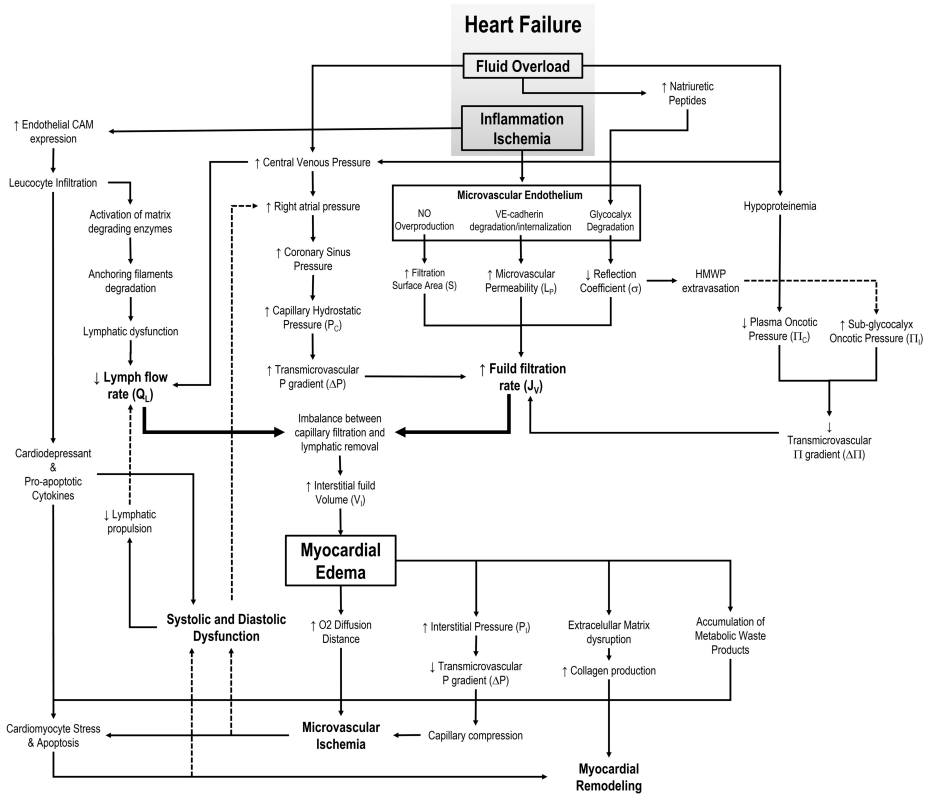
Myocardial fluid balance and myocardial oedema

To maintain fluid homeostasis, microvascular fluid filtration into the myocardium must be matched by its removal rate via myocardial lymphatic vessels. Microvascular fluid exchange is governed by the Starling principle, expertly reviewed elsewhere,[1,10] summarized by the revised Starling equation:

$$J_V = L_P S\left[(P_C - P_I) - \sigma\,(\Pi_C - \Pi_G)\right]$$

where L_P is the hydraulic conductivity, S is the filtration surface area, P_C and P_I are the intracapillary (C) and interstitial (I) hydrostatic pressures, σ is the protein reflection coefficient and Π_C and Π_G are the intracapillary and subglycocalyx (G) colloid osmotic pressures, respectively (*Figure 1*). In order to keep a stable interstitial volume (V_I) and defend against oedema formation, several physiological mechanisms counteract primary perturbations in P_C, Π_C and endothelial barrier function—oedema safety factors.[2]

Figure 1 The disruption of myocardial fluid balance in the failing heart. Multiple mechanisms can contribute for oedema formation in the failing heart and are differentially observed in several types of acute and chronic heart failure. Myocardial ischaemia, inflammation and volume overload negatively impact on microvascular barrier function by promoting the glycocalyx degradation and pericyte detachment, resulting in excessive fluid filtration. The resulting increase in interstitial volume and pressure disrupt the extracellular matrix (ECM) architecture, pulling cardiomyocytes away from capillaries and increasing oxygen diffusion distance. Moreover, ECM degradation and high central venous pressure impair lymphatic recruitment and drainage, leading to the accumulation of inflammatory cells, cytokines and metabolic waste products in the myocardial interstitium. Collectively, these mechanisms can impair myocardial contractility and bioenergetics, increase myocardial stiffness and promote cardiomyocyte apoptosis.



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Myocardial oedema develops when fluid filtration rate exceeds lymphatic fluid removal and can be generated by increased ΔP or S, decreased $\Delta\Pi$ or alterations of microvascular membrane properties (increased L_P or decreased σ) (*Figure 1*). Increased P_C can be driven by high pre-capillary pressure in the setting of acute[11] and chronic[12] arterial hypertension, or high post-capillary pressure in coronary sinus occlusion,[4,13,14] pulmonary hypertension[15] or in acute HF with increased central venous pressure.[16] Moreover, increased S, caused by increased capillary recruitment or vasodilation, promotes MO formation and is particularly relevant in inflammatory HF aetiologies (e.g. myocarditis and sepsis). Finally, as albumin is the major determinant of Π_C, states of hypoalbuminemia facilitate fluid filtration and global interstitial oedema.[6] This is particularly relevant in crystalloid coronary perfusion during cardiac surgery[17] and in shock management (e.g. septic and cardiogenic) in which, excessive fluid resuscitation worsens prognosis.[18,19]

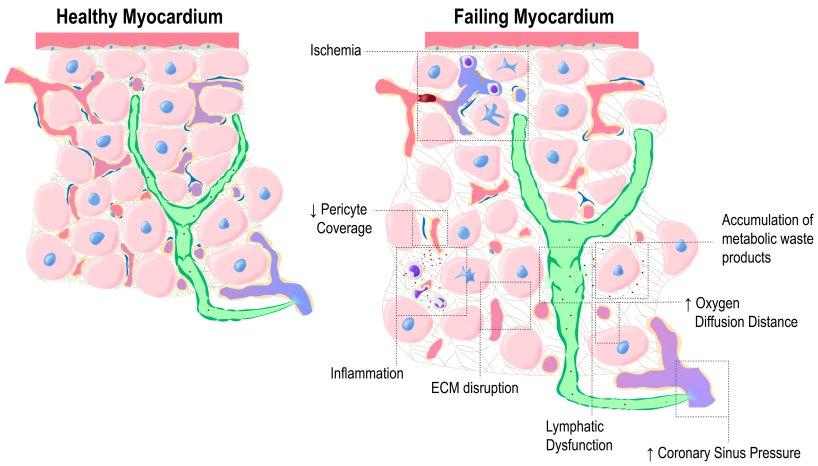
Myocardial oedema dramatically reduces energetic efficiency, impairing both contraction and relaxation.[1,20,21] However, increased V_I and P_I have been shown to primarily affect myocardial viscoelastic properties, resulting in higher diastolic stiffness.[6,22] Due to its low interstitial compliance, small interstitial volume expansions create high interstitial pressures, making the myocardium particularly sensitive to oedema formation. The experimental increase in myocardial water content by 3.5% was associated with a 40% drop in cardiac output.[3] In addition, MO directly opposes filtration, by decreasing ΔP and physically compressing the capillaries and disrupting nutrient and oxygen delivery.[23] The disruption of the extracellular matrix structure, increased oxygen diffusion distance and accumulation of metabolic waste products are additional proposed mechanisms of MO-associated functional deterioration (*Figure 2*).[1,24]

In summary, myocardial fluid balance is largely dependent on microcirculation dynamics, microvascular barrier, interstitial architecture and lymphatic drainage. Disruption of any of these components may disturb myocardial fluid homeostasis. In this review, each factor will be addressed in detail regarding its physiological role and how it may be disrupted in the failing heart.

Coronary microcirculation

The healthy myocardium is one of the most densely vascularized tissues in human body, possessing a high density capillary network (3.000–4.000/mm^2) closely disposed around cardiomyocytes[25,26] (*Figure 2*). Such proximity between cardiomyocytes and capillaries is of utmost importance to maintain a short diffusion distance not only for oxygen, but also for potentially toxic byproducts of cellular metabolism.[23] Moreover, the high metabolic rate of the myocardium, which primarily depends on oxidative phosphorylation, translates in an elevated oxygen demand that is matched by a very high oxygen extraction rate (70%–80% in resting conditions).[27–29] Consequently, in stress conditions, additional increments in oxygen demand are predominantly met by parallel increases in myocardial blood flow (MBF).[27] This metabolic contribution to MBF autoregulation is made possible by the close contact

Figure 2 Pathophysiological pathways contributing to myocardial oedema in heart failure.



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between cardiac muscle and vasculature, enabling cardiomyocyte-derived mediators (CO_2[30] and lactate[31]) and microenvironmental factors (pH[32] and extracellular K^+[33]) to modulate local vasomotor tone and haemoglobin dissociation curve. Therefore, pathological conditions limiting the close communication between cardiomyocytes and vasculature, namely, the expansion of the interstitial space due to oedema or fibrosis, as well as arteriolar and capillary rarefaction, common features in chronic HF,[34] impair diffusional transport and MBF autoregulation, contributing to oxygen supply/demand mismatch (*Figure 2*).

Another consequence of the proximity between coronary microvasculature and cardiomyocytes is their mechanical interaction. Previously considered an important modulator of contractility (i.e. Gregg phenomenon), the effect of coronary perfusion was later shown to be negligible within the autoregulatory pressure-flow range.[35,36] Extravascular forces are not uniform across the ventricular wall and a gradual increase in interstitial pressure and vascular compression is observed from the subepicardium to the subendocardium.[37,38] This is partly compensated by a higher arteriolar density at the subendocardium so that, in physiological conditions, MBF is similar in both myocardial layers.[39,40] Yet, the distinct mechanical cross-talk between different myocardial layers, makes arterio-venous pressure gradient (i.e. perfusion pressure) at the subendocardium about half of that of subepicardium.[41] Consequently, in the setting of decreased coronary pressure (e.g. coronary artery disease), the subendocardial perfusion is predominantly affected.[42–44] This intricate relation between microcirculation and perfusion may underly, at least partially, the existence of clearly distinct patterns of MO distribution associated with different kinds of myocardial injury: in acute inflammatory conditions (e.g. viral myocarditis, sepsis) oedema is generally evident in the subepicardial layers whereas in acute ischaemia, the oedema is transmural or predominantly affects the subendocardium.[7,45–47]

Coronary vasculature also influences myocardial tissue properties. Higher coronary perfusion pressure is associated with increased myocardial stiffness, shifting diastolic pressure-volume relationship left and upwards, even in the absence of oedema formation.[48–50] The underlying mechanism resides in the fact that cardiomyocyte contraction increases the cell diameter, which happens at the expense of coronary vascular diameter, contributing to the abovementioned systolic vascular compression.[36,51] Accordingly, higher intravascular volume and pressure, caused by increased coronary perfusion or venous outflow pressure, oppose intravascular fluid displacement, and therefore impair muscle contraction and relaxation. This has been shown to be especially relevant in the setting of increased coronary sinus pressure, seen in acute and chronic HF, where increased intravascular and interstitial volume act cooperatively to impair systolic function and diastolic compliance.[52–54]

Coronary microvascular barrier

Overlooked in the past, the cardiac microvascular barrier became increasingly recognized as highly active and complex structure, composed of a continuous non-fenestrated endothelial cell monolayer, which is internally coated with a negatively charged gel-like mesh (i.e. glycocalyx) and externally covered by pericytes and basement membrane (*Figure 3*).

Interendothelial junctions

Endothelial cells (EC) are tightly bonded by interendothelial junctions (IEJ), mostly comprised by tight (occludins, claudins and JAMs) and adherens junctions (VE-cadherin), which define endothelial pore size and can be dynamically regulated at the expression level and through internalization, to finely tune endothelial permeability and regulate the passage of macromolecules and cells[55–57] (*Figure 3*). Accumulating evidence suggests IEJ disruption as a potential pathophysiological mechanism in cardiac diseases. Importantly, endothelial expression of claudin-5, a critical player in size-selective barrier function, is reduced in human end-stage HF hearts.[58] This was also shown in experimental diastolic dysfunction induced by western diet, where claudin-5 and occludin down-regulation was associated with increased vascular permeability,[59] an effect attenuated by amiloride, suggesting an important role for endothelial ENaC expression and sodium overload. Regarding adherens junctions, reduced VE-cadherin/β-catenin expression in dilated cardiomyopathy was associated with endothelial cell degeneration,[60] whereas in post-ischaemic MO, Src inhibition prevented VEGF-mediated disruption of Flk/VE-cadherin/β-catenin complex and attenuated post-ischaemic MO, fibrosis and mortality.[61] In addition, key risk factors for HF development and progression have been shown experimentally to promote endothelial hyperpermeability by disrupting EIJ, namely, renin-angiotensin-aldosterone system activation,[62] inflammation,[63,64] hypoxia,[65] cardioplegic arrest,[66] hyperglycaemia,[67] oxidative stress,[68] increased circulating LDL[69,70] and free fatty acid[71] levels.

The endothelial surface layer

The endothelial glycocalyx (eGC) covers the apical side of endothelial cells and consists of a complex meshwork of varied membrane-associated macromolecules[72–74] (*Figure 3*). These include proteoglycans and glycoproteins, forming a backbone in which soluble proteins, plasma- or endothelial-derived, are incorporated. eGC proteoglycans are constituted by linear core proteins, mostly Syndecan-1, to which multiple glycosaminoglycans (GAGs) side chains can be covalently attached.

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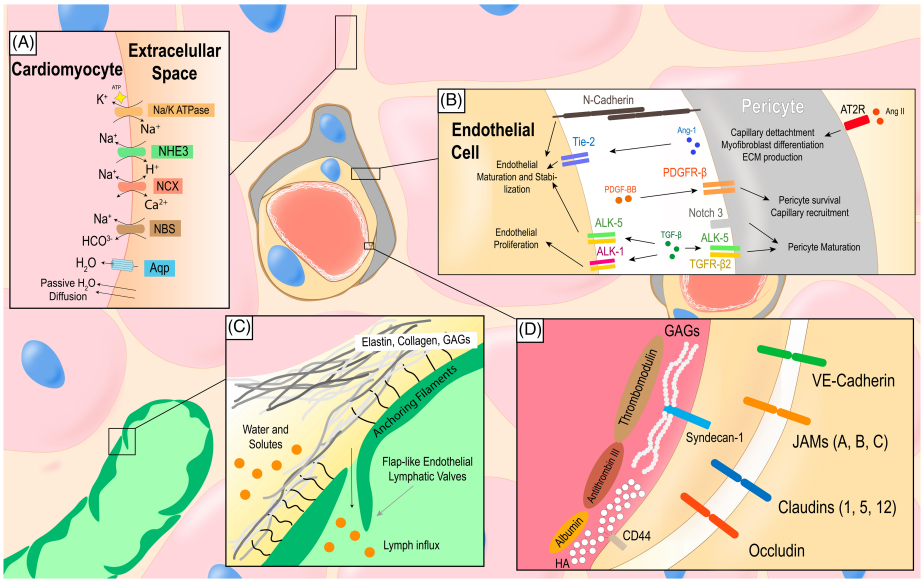
Figure 3 Molecular interactions in myocardial fluid balance. The myocardium is composed by cardiomyocytes, microvascular capillaries enclosed by pericytes and lymphatic capillaries: fluid is filtrated in microvascular capillaries, through the endothelial surface layer and interendothelial junctions. In the myocardial interstitium, fluid entry is limited by type I and type III collagen fibres and GAGs, extracellular matrix components that act as a buffer for Na^+ and water. Interstitial and intracellular water are in delicate balance, maintained by cardiomyocyte volume regulators. Interstitial fluid (IF) and solutes are collected by initial lymphatic capillaries, enabling a continuous IF renovation, which is returned ultimately to the venous circulation. (A). Cardiomyocyte ionic transporters: cardiomyocytes closely regulate intracellular water entry and extrusion. Water enters through aquaporins or passively diffuses through the cell membrane, according to osmotic gradients established by ionic and solute concentrations. (B). Endothelial cell–pericyte interaction: these cells establish close paracrine and physical (N-cadherin) interactions regulating microvascular stability. Endothelial cells secrete PDGF-BB that binds to PDGFR-β, promoting pericyte recruitment and microvascular integrity, whereas pericytes secrete angiopoietin 1 (Ang-1), which acts on Tie-2 and stabilizes endothelial cells. (C). Endothelial surface layer and interendothelial junction: the endothelial surface layer is composed by endoluminal glycocalyx, which binds plasma proteins and protects endothelial cells. Furthermore, endothelial cells establish varied connections, maintaining cohesiveness and cell survival. (D). Lymph drainage in initial lymphatic capillary: fluid enters the lymphatic vasculature via lymphatic capillaries, which are blunt-ended vessels attached to the extracellular matrix by anchoring filaments. Lymphatic endothelial cells overlap, creating valve-like structures that promote unidirectional lymph flow. These vessels converge progressively from the subendocardium to the subepicardium, forming epicardial lymphatic collectors. ALK-1 and -5, anaplastic lymphoma kinase-1 and 5; Ang-1, angiopoietin-1; AngII, angiotensin II; Aqp, aquaporins; GAG, glycosaminoglycans; HA, hyaluronic acid; JAMs, junctional adhesion molecules; NBS, Na^+/HCO_3^- Symporter; NCX, Na^+/Ca^{2+} exchanger; NHE, Na^+/H^+ exchanger; PDGF-BB, platelet-derived growth factor BB; PDGFR-β, PDGF receptor β; TGF-β, transforming growth factor β; TGFR-β2, TGF receptor β2; Tie-2, angiopoietin-1 receptor.



GAGs are highly polyanionic compounds composed of disaccharide repeating units which can be non-sulfated [hyaluronic acid (HA)] or sulfated (chondroitin sulfate, dermatan sulfate, keratan sulfate and heparan sulfate). Together, they form a negatively charged surface that will enable electrostatic interactions with plasma cations, mostly with divalent metal cations (e.g. Ca^{2+}), but also with Na^+ due to its high plasma concentration.[75,76] The resulting high cation concentration at the interface with the plasma enables negatively charged circulating proteins (albumin, antithrombin III and thrombomodulin), that would otherwise not be able to electrically interact with the glycocalyx, to approach and incorporate this layer, forming together the endothelial cell surface layer (ESL).[77,78] The ESL, measuring between 0.2 and 2.0 mm *in vivo*, is therefore a highly complex structure with critical functions in microvascular physiology by (i) physically shielding the underlying endothelium from luminal aggressions; (ii) regulating microvascular flow by transmitting shear-stress forces; (iii) constituting a barrier for plasma proteins and ions, thereby maintaining intravascular oncotic

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pressure; (iv) avoiding platelet aggregation by accumulating platelet-inhibitory factors (antithrombin III and thrombomodulin) and physically restricting its interaction with subendothelium at the endothelial gaps; (v) inhibiting endothelial proinflammatory activation (i.e. increased permeability and adhesiveness) by binding circulating cytokines; and (vi) limiting the access and adhesion of circulating immune cells to the EC surface.[79,80,81]

The ESL structure is maintained by a fragile balance between flow and enzymatically mediated shedding, and *de novo* production of its components.[82] Not surprisingly, most pathological mechanisms shown to increase microvascular barrier permeability act concomitantly on IEJ and ESL, namely, in inflammation, ischaemia–reperfusion,[83] hypoxia[84] and hyperglycaemia.[85] Importantly, the activity of glycocalyx-degrading enzymes (i.e. hyaluronidases, heparanase and MMPs) is increased in the setting of inflammation, which, in combination with endothelial CAM overexpression, facilitates leukocyte adhesion and diapedesis.[86] The importance of the permissive effect of ESL degradation on cardiac leukocyte infiltration has been shown in myocardial infarction,[87,88] viral myocarditis[89] and sepsis,[90,91] aggravating the myocardial inflammatory injury. Moreover, degradation of eGC components (hyaluronan[92] and heparan sulfate[93]) has been shown to promote MO by increasing microvascular permeability to water and proteins.

Perhaps, the more striking association between eGC and HF is the fact natriuretic peptides (NP), mostly produced by cardiomyocyte stretching in the setting of hypervolemia and ventricular overload, have been repeatedly shown to promote eGC degradation.[94–98] This effect seems to act concurrently with Na^+ overload, which also leads to the destabilization and collapse of the eGC, mainly through loss of heparan sulfate residues, an effect attenuated by the use of spironolactone.[99] This can be interpreted essentially as a compensatory mechanism, by enabling the escape of excessive intravascular fluid and sodium to the interstitium, which has a high Na^+ buffering capacity due to its GAG content,[100] and acting in conjunction with NP-mediated venodilation to reduce cardiac overload. However, eGC degradation in the setting of myocardial functional impairment might also carry some drawbacks. In addition to eGC degradation being an inherently proinflammatory stimuli for EC,[101,102,103] the impairment of glycocalyx Na^+ buffering capacity may increase the amount of Na^+ presented to the endothelium, promoting intracellular endothelial Na^+ overload and increased transport to the interstitium, resulting in endothelial dysfunction and aggravated interstitial oedema, respectively.[104,105,106] Furthermore, this combined effect of hypervolemia and Na^+ overload also has important implications in the critical care setting (e.g. cardiogenic and septic shock),[107,108] where the frequently excessive crystalloid resuscitation might disrupt microvascular barrier function and complicate haemodynamic management and prognosis. Despite its proposed pathophysiological importance, a direct observation of ESL disruption in HF is still lacking.

Cardiac pericytes

Cardiac pericytes (CPc) are a highly heterogeneous population of perivascular contractile cells that ensheath and intimately interact with underlying endothelial cells, forming a microvascular syncytium.[109,110] Despite conflicting reports, recent data suggest that CPc cover up to 99% of the length of the myocardial microvasculature.[111] CPc share the basement membrane with EC and establish numerous physical interactions, ensuring an adequate control of microvascular permeability. Moreover, an intense reciprocal communication between CPc and EC takes place through gap junctions and paracrine factors, which has been shown to be especially relevant for angiogenesis and stabilization of newly formed vessels[101] (*Figure 3*). Importantly, multiple pericyte phenotypes with distinct cell-surface marker signatures and variable expression of contractile proteins have been shown to be differentially distributed across the arteriolar, microvascular and venular sections of coronary vasculature.[99,112] Such diversity probably underlies distinct pathological roles attributed to pericytes in the context of myocardial injury and remodeling.

Extensive evidence supports a key role for CPc in the regulation of myocardial microvascular flow and permeability. Indeed, the disruption of key trophic and homeostatic pathways for CPc, namely, PDGF-BB/PDGFR-β,[113,114] Ang-1/Tie2,[115,116] Sirtuin-3[117,118] and Notch3,[119,120] has been shown to decrease CPc density and EC coverage, resulting in increased microvascular permeability in response to injury, MO and functional impairment. Importantly, common observations in genetic and drug-induced CPc dysfunction are increased microvascular tortuosity and decreased coronary reserve in response to vasodilator challenge, with cardiac up-regulation of hypoxia-related genes.[121] In knockout mouse models, the genetic ablation of Notch3[122] and Sirtuin-3[123] impairs microvascular maturation and pericyte/EC interaction, exacerbating ischaemic injury and hindering post-ischaemic functional recovery. Similar observations were made in experimental models of endotoxemia and diet-induced obesity, in which Sirtuin-3 has been shown to be down-regulated.[124,125] Accordingly, in the setting of ischaemic injury, cardiomyocyte-derived proNGF activates p75 neurotrophin receptor, causing pericyte process retraction, resulting in a lack of support of the microvascular endothelium and perivascular oedema.[126] Moreover, Hypoxia-Induced Endoplasmic Reticulum Stress Regulating (HypER) lncRNA, which promotes pericyte proliferation, viability and interactions with EC, is down-regulated in human HF,[127] supporting pericyte degeneration as a potentially important pathophysiological mechanism.

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In line with the diversity of CPc phenotypes and functional roles in the setting of myocardial ischemia, CPc have also been implicated in the no-reflow phenomenon.[128] Importantly, some pericyte subpopulations express variable amounts of myosin and actin isoforms (α-SMA and γ-actin), having the ability to contract and relax in response to multiple paracrine factors (catecholamines and adenosine).[129,130] Being circumferentially disposed around capillaries, CPc contraction can decrease microvascular flow and theoretically reduce capillary luminal diameter enough to impede the passage of leukocytes. Indeed, in an ischaemia/reperfusion injury model, post-ischaemic capillary blockage sites have been shown to be disproportionally close to pericytes, suggesting ischemic CPc contraction, probably mediated by an increase in intracellular Ca^{2+},[131] as an important mediator of impaired reoxygenation of ischemic tissue following myocardial revascularization.[132]

In inflammatory conditions, CPc detachment from EC surface was associated with differentiation into myofibroblasts and increased production of ECM, potentially contributing to pathological myocardial remodelling.[134,135] In fact, galectin-3, a well-validated biomarker and mediator of cardiac fibrosis in HF patients,[136] has been shown to stimulate pericyte proliferation and procollagen I secretion.[137] This is in accordance with observations in angiotensin II-induced myocardial hypertrophy model, in which $Gli1^+$ cells were shown to consist in a subpopulation of pericytes that, in the setting of injury, differentiate into myofibroblasts and produce ECM in perivascular and interstitial spaces.[138] Further supporting this role of CPc, in a clinically relevant rat model of HF with preserved ejection fraction (ZSF1 obese rats), decreased EC coverage was associated with subendocardial foci of CPc proliferation, which colocalized with ECM deposition and inflammatory cell infiltration.[139] Consistently with this finding, pericytes have been shown to respond to proinflammatory stimuli with overexpression of cytokines, chemokines and CAMs,[140] regulating immune cell diapedesis.[141] In the setting of experimental sepsis, inflammatory-mediated CPc loss facilitates the infiltration of immune cells in cardiac interstitium.[142] These findings highlight the fact that, beyond being key determinants in the microvascular barrier, pericytes may detach from endothelial cells and promote interstitial remodelling in inflammatory injury.

Myocardial interstitium

The myocardial interstitium is a highly organized and compact structure, comprised by fibrillar collagen, non-collagen matrix proteins, proteoglycans, GAGs and a wide array of bioactive signalling molecules[143] (*Figure 3*). Cardiomyocytes are enclosed in a basement membrane, mostly constituted by integrins, laminin and fibronectin, behaving as anchoring points for fibrillar collagen and other matrix components (proteoglycans and GAG) attachment. Collagens (type I and III) are the predominant components of cardiac ECM, and their high tensile strength is assumed to be the main contributor for ECM structural integrity.[144] Cardiac ECM architecture enables an effective force summation of individually contracting cardiomyocytes, allowing a coordinated myocardial tissue contraction, while at the same time maintaining adequate spatial relationships between cells, which prevents cardiomyocyte overstretching, preserves intercellular connections and opposes microcirculatory collapse.

Cardiac ECM composition is an important determinant of interstitial space volume and pressure. The interstitial space is densely crowded with intertwined components, which occupy the available physical space and limit the entrance of plasma proteins or cells, a phenomenon called steric interstitial exclusion.[2] Given their polyanionic nature, interstitial GAGs futher contribute to limit the entrance of plasma proteins, while also binding free ions (mostly Na^+) and annulling their osmotic force.[93] Interestingly, changes in sulfated GAG conformation are associated with decreased Na^+ buffering capacity and interstitial oedema.[93] Moreover, the high stiffness of cardiac ECM not only preserves cardiomyocyte function by generating passive tension and avoiding tissue overstretching but also confers a low interstitial compliance to the myocardium and opposes interstitial space expansion.[145] Consequently, in the setting of increased transcapillary filtration, interstitial fluid (IF) buildup stretches the ECM, causing a steep increase in interstitial pressure, which, in turn, forces IF into the lymphatic system.[22]

Alterations in ECM architecture or composition critically influence myocardial function. Increased ECM deposition, mainly in the form of collagen, has been recognized as an important mechanism of increased stiffness and diastolic dysfunction in most forms of chronic HF.[16] However, mechanical and enzymatic disruption of the ECM also significantly impairs myocardial systolic and diastolic function by compromising force transmission by displacing collagen struts from their anchoring points and breaking intercellular connections.[146,147] Moreover, inflammation-driven up-regulation of ECM-degrading enzymes promotes both ECM and basement membrane degradation, decreasing interstitial exclusion effect and facilitating the interstitial passage of fluid, proteins and immune cells.[148] ECM degradation has been shown in acute high-grade myocardial inflammation, especially in experimental myocarditis[149] and sepsis,[150] where a significant acute decrease in total myocardial collagen content and collagen degradation were observed and associated with MO, systolic and diastolic dysfunction. Further supporting this experimental observation, post-mortem evaluation of human septic myocardium found significant ECM disruption and interstitial oedema at the subepicardium, which colocalized with macrophage infiltration and cardiomyocyte apoptosis.[45] Importantly, disruption of collagen struts may also increase coronary microvasculature suscepti-

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bility to external compression, which might compromise MBF in the setting of oedema-associated increased interstitial pressure.[36,123]

Interestingly, chronic oedematous states produced by increased microvascular filtration or decreased lymphatic drainage are associated with increased myocardial collagen deposition.[3,4] The interstitial remodelling may be interpreted as a compensatory mechanism, by decreasing interstitial compliance and preventing interstitial expansion, therefore minimizing the disruption of cardiac architecture. However, increased collagen deposition also causes long-term detrimental effects on overall myocardial compliance and function.[151]

Impaired turnover of non-collagen ECM elements can also promote fibrosis and have detrimental effects on myocardial function. HA is observed in healthy cardiac ECM in its high-molecular-weight HA form and has a unique capacity to bind and retain water molecules.[152] Interestingly, while eGC HA degradation has been consistently associated with endothelial dysfunction, increased microvascular permeability and MO,[85,153] cardiac interstitial accumulation of HA, has similarly been shown to promote MO and structural remodelling.[154] Cardiac interstitial accumulation of HA is normally associated with increased interstitial water content and MO, and is observed in myocardial infarction,[155] hypertrophic cardiomyopathy,[156] myocarditis[157] and experimental cardiac transplant rejection.[158,159] Curiously, hyaluronidase treatment was able to decrease MO in rejected heterotopic transplants,[160] whereas accumulation of low-molecular-weight HA (LMWHA) in hypertrophic cardiomyopathy is not associated with increased water content,[161] raising the possibility of distinct contributions of high-molecular-weight HA and LMWHA for oedema generation. Indeed, in the setting of inflammation and myocardial injury, production of LMWHA is preponderant and has been shown to stimulate TLR inflammatory signalling pathways.[127] Collectively, these results underscore the importance of GAG structure, composition and regional distribution for IF balance.

Cardiac lymphatic system

The cardiac lymphatic system is essential in maintaining myocardial fluid balance and immunological homeostasis.[139] It represents the main route for the removal of cellular metabolites, allowing the continuous IF renewal while avoiding the buildup of interstitial volume and pressure.[2] Additionally, an immunomodulatory role has also been attributed to cardiac lymphatics due to the washout of proinflammatory mediators and immune cells from the myocardial interstitium in the setting of myocardial injury.[162,163]

Lymphatic capillaries are highly specialized blind-ended structures, composed by oak-leaf shaped lymphatic endothelial cells (LEC), which mostly lack basement membrane and are connected by permeable flap-like intercellular junctions that favour unidirectional passage of IF, solutes and immune cells[164,165] (*Figure 3*). Moreover, cardiac LEC are connected to the surrounding ECM and cardiomyocytes by structures designated as anchoring filaments, constituted by type VII collagen projections, integrins and focal adhesion kinases. Anchoring filaments maintain lymphatic patency by exerting tensile forces and opening the lumen of lymphatic capillaries, facilitating lymphatic flow.[166,167] Anatomically, the lymphatic capillary plexus progressively converges from the subendocardium to the subepicardium, suffering structural alterations along the way, namely, the appearance of a continuous basement membrane, intraluminal valves to promote unidirectional flow, tight junctions, and, in larger trunks outside the myocardium, an adventitial layer and surrounding smooth muscle cells to help pump lymph.[168,169] Subepicardial lymphatic pre-collectors converge to form epicardial lymphatic collectors that transport cardiac lymph via lymph nodes towards thoracic ducts, ultimately draining into the superior vena cava.[170]

Several factors influence cardiac lymph flow, most of which known to be unique to the heart. A distinctive feature of the intramyocardial lymphatic system is the absence of smooth muscle in intramyocardial vessels. Therefore, lymph flow is highly dependent on external forces, namely, muscle contraction and deformation along the cardiac cycle, heart rate and contractility.[1] However, factors not intrinsic the heart function also impact lymph drainage. By concentrating interstitial metabolic products and proteins, lymph oncotic pressure exceeds interstitial oncotic pressure, promoting water osmotic dragging and fluid drainage.[1] Coronary venous pressure is also an important regulator of lymph flow. Experimental coronary sinus blockade increases capillary hydrostatic pressure and promotes fluid filtration upstream, which requires compensatory lymphatic dilation and increased lymph flow to maintain fluid homeostasis.[13,14,147] On the other hand, downstream, because lymph is ultimately drained into the venous circulation, increased central venous pressure acts synergically with decreased contractility to impair lymph flow in acute HF, promoting MO.[16,93]

The frequent observation of MO in several aetiologies of HF suggests that cardiac lymphatic inability to respond to increased filtration is a rather common finding. Despite the recognized ability of the healthy heart to respond to an increased capillary filtration by increasing lymph drainage severalfold,[1] multiple disease mechanisms may render the cardiac lymphatic system incapable to cope. In this setting, lymphatic dysfunction will not only promote accumulation of a protein-rich IF, which contributes to microvascular and cardiomyocyte stress, but will also have a proinflammatory effect by decreasing the clearance of proinflammatory cytokines and immune cells.[171] Prolonged residence of cellular debris, inflammatory mediators and cells in myocardial interstitium will aggravate and prolong myocardial

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inflammation, especially in the setting of myocardial infarction and myocarditis.[172] Furthermore, the distortion of interstitial architecture mediated by oedema and the activation of collagen and GAG-degrading enzymes may have a negative impact on anchoring filaments and initial lymphatics, further compromising lymphatic patency and function. Whereas acute lymphatic obstruction leads to oedema, chronic obstruction is associated with interstitial fibrosis and ECM remodelling.[125] Moreover, given the close proximity of the lymphatic and electrical conduction system, lymphatic dysfunction has also been shown to be associated with electrical disturbances.[173]

Lymphangiogenesis, the process of producing new lymphatic vessels is known to be a dynamic process mainly regulated by VEGF-C and VEGF-D binding to lymphatic-specific receptor VEGFR3, and to be affected by inflammation and other cardiovascular factors (diabetes and obesity).[146] In acute inflammation[174] and in myocardial infarction,[175] higher fluid filtration increases the need for lymph drainage, with resulting up-regulation of lymphangiogenic factors. However, this endogenous response appears to be insufficient and to result in deficient lymphangiogenesis, with a predominance of lymphatic capillaries and lack of pre-collectors. In fact, in post-infarct mouse models, stimulating lymphangiogenesis with exogenous VEGF-C or adrenomedullin increases lymph flow, decreases MO, attenuates myocardial inflammation and fibrosis and improves cardiac function.[176–180] Still, this promising therapeutic avenue has been recently questioned by the absent impact of genetic blockade of lymphangiogenesis on cardiac function after experimental myocardial infarction.[181]

Cardiomyocyte volume regulation

The cardiomyocyte membrane is highly permeable to water, which moves passively according to osmotic gradients and directly sets cell volume.[182] Normal cell function requires a stable volume and excessive water entry may disrupt membrane and cytoskeleton integrity. To prevent abrupt cell volume alterations, intracellular osmolarity is highly controlled, either with active ionic fluxes or the synthesis/degradation of osmotically active solutes[39,183] (*Figure 3*).

In the isotonic steady-state, intracellular osmotic pressure exceeds extracellular osmotic pressure due to celullar concentration of organic phosphates and proteins, thus favouring passive water entry. To maintain the volume constant, the membrane Na^+/K^+ ATPase promotes the exit of 3 Na^+ and entry of 2 K^+ ions, a phenomenon known as the 'Pump and Leak' concept. Together with low Na^+ membrane permeability, both mechanisms contribute to maintain a low intracellular [Na^+] and a constant transmembrane gradient, on which many ionic transporters that regulate cell volume are highly dependent. In myocardial ischaemia, Na^+/K^+ ATPase dysfunction results in extracellular accumulation of K^+, intracellular accumulation of lactate, Na^+ and Cl^- and consequent cell swelling and membrane depolarization.[159,160] Furthermore, anaerobic metabolites accumulate in extracellular and intracellular spaces. Following reperfusion of the coronary vessels will re-establish water delivery and wash out extracellular, but not intracellular, metabolic products, creating an osmotic gradient that promotes cell swelling. Highlighting the pathophysiological importance of cardiomyocyte oedema in ischaemia/reperfusion injury, reperfusion with a hypertonic solution limited MO and infarct size, when compared with isotonic solution.[184,185]

Cell swelling depolymerizes actin filaments and disrupts cytoskeleton interactions with membrane proteins.[159] Of note, cardiomyocyte swelling induced by ischaemia–reperfusion injury was associated with variable degrees of mitochondrial damage, cytoskeleton abnormalities and significant increases in sarcomere length, radial distance between myofibrils and distance between mitochondria and myofibrils, repercussing on maximal tension and calcium sensitivity.[186] Accordingly, swelling of isolated cardiomyocytes induced by hypotonic medium was associated with lower contractility and activated NO/cGMP/PKG pathway.[158]

Despite most of myocardial water being confined to the intracellular compartment, few studies have addressed the pathophysiological role of cardiomyocyte swelling in HF.

Clinical perspective

In clinical research and practice, MRI stands out as the gold-standard method for non-invasive MO evaluation, based on its ability to identify the tissue 'free' water pool. 'Free' water molecules rotate very rapidly when subjected to a magnetic field and produce long T1 and T2 relaxation times, whereas 'bound' water molecules have their motion restricted due to hydrogen bonding with macromolecules, producing short T2 relaxation time values. The recent introduction of parametric mapping techniques—T1, T2 and extracellular volume, has enabled the detection of subtle changes in myocardial free water content and precise estimation of the interstitial fraction volume and composition.[187]

Making use of aforementioned MRI capabilities, evidence supporting the disruption of myocardial water balance has been shown in a broad range of cardiac and systemic diseases (*Table 1*). Overall, the increase in myocardial free water content is generally associated with depressed left ventricular function, increased NP plasma levels, disease progression and severity, and poor prognosis (*Table 1*). Nevertheless, due to the observational nature of these studies, a causal association between the presence of MO, LV dysfunction and cardiac prognosis could not yet be drawn.

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Table 1 Magnetic resonance imaging evidence of myocardial oedema in cardiac and systemic diseases

Disease	Myocardial oedema	CMR imaging	Analytical associations[a]	Clinical associations[a]	References
Acute heart failure	Global	T2 mapping	—	(+) PAWP (−) Decongestion	16,188
Myocardial infarction/ Ischaemia–reperfusion	Focal	T2-weighted imaging, T1, T2 and ECV mapping	(+) Troponin	(+) Infarct extension (+) MACE (+) LV dilatation (−) LV function	189,190
Aortic stenosis	Global	T1 and T2 mapping	—	—	191
Cardiomyopathies					
Non-ischaemic dilated cardiomyopathy	Global	T2-weighted imaging, T2 mapping	—	(−) LVEF (+) Disease progression	192,193
Hypertrophic cardiomyopathy	Focal	T2-weighted imaging, T2 mapping	(+) Troponin (+) BNP	(+) Risk of Syncope	194,195
Takotsubo cardiomyopathy	Focal	T1 and T2 mapping (USPIO enhancement)	(+) Myocardial macrophages	—	196,197
Peripartum cardiomyopathy	Global	T1 and T2 mapping	—	(−) LVEF	198
Infiltrative diseases					
Cardiac amyloidosis	Global	T2 and ECV mapping	(+) NT-proBNP	(+) Mortality (AL)	199
Cardiac sarcoidosis	Focal	T1 and T2 mapping	—	—	200,201
Fabry disease	Focal	T1 and T2 mapping	(+) Troponin	(+) ECG Changes (+) Clinical worsening	202
Infectious diseases					
Viral myocarditis	Focal, subepicardial	T2-weighted and LGE imaging, T2 mapping	(+) Troponin	(+) Arrhythmia (+) MACE (+) Death	9,203–205
COVID-19	Focal	T2-weighted and LGE imaging, T2 mapping	(+) Troponin (+) EMB macrophages	—	206–209
Sepsis	Focal	T2-weighted imaging	—	—	45,210
HIV	Global	T2-weighted and LGE imaging, T1 mapping	—	(+) Adverse cardiovascular events	211
Chagas disease	Focal	T2-weighted and LGE imaging	—	(+) Disease severity	212
Inflammatory diseases					
Rheumatoid arthritis	Focal	T1 and ECV mapping	—	(+) Disease activity (−) Circumferential Strain	213
ANCA-associated vasculitides	Diffuse	T1 and T2 mapping	—	—	214,215
Systemic sclerosis	Focal	T1 and T2 mapping	—	(+) Cold pressor test (+) Disease activity (−) Circumferential Strain	216,217
Systemic lupus erythematosus	Focal	T1 and T2 mapping	—	(+) Disease activity	218,219
Endocrine diseases					
Acromegaly	Global	T2 mapping	—	(+) Reversal of acromegalic cardiomyopathy	220
Hypothyroidism	Global	T2-weighted and LGE imaging, T1 mapping	(−) FT3	(−) Stroke volume (−) Cardiac index	221
Cardiac surgery					
Cardiac transplant	Global	T1 and T2 mapping	—	(+) Transplant rejection	222,223
Systemic diseases and others					
Pulmonary arterial hypertension	Focal	T1 and ECV mapping	—	(−) RV function (+) RV dilatation	224
Chronic kidney disease	Global	T1 and T2 mapping	(+) Troponin T	(+) Uremic Cardiomyopathy	225–228

(*Continues*)

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Table 1 (continued)

Disease	Myocardial oedema		CMR imaging	Analytical associations[a]	Clinical associations[a]	References
Breast cancer chemotherapy (Anthracyclines/Trastuzumab)	Focal	T2 mapping	—	(+) NT-proBNP —	(+) Predictor of cardiotoxicity	229

[a]Positive (+) and negative (−) associations with myocardial oedema.
AL, amyloid light-chain; ECV, extracellular volume; EMB, endomyocardial biopsy; FT3, free triiodothyroinine (T3); LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, composite of total death, myocardial infarction, coronary revascularization, stroke and hospitalization; PAWP, pulmonary arterial wedge pressure; RV, right ventricle; USPIO, ultra-small particles of iron oxide

Myocardial oedema has been particularly well-studied in the acute setting of ischemic heart disease, in which it may have a role on early injury during reperfusion and also late tissue healing.[165–171] During the initial phase of reperfusion, MO may contribute to the pathophysiological process of microcirculation compression and perfusion defects underlying the 'no-reflow' phenomenon.[171,172] MO is also detectable later, at the time of tissue healing and collagen deposition,[166] which discloses the complex interplay between myocardial fluid balance and inflammation and underscores the need for a cautious interpretation of MRI assessment of infarcted and at-risk myocardium.[171,173] Interestingly, patient comorbidities might impact on the development of MO in a disease-specific and somewhat unpredicted way, underscoring the lack of clinical knowledge on this topic. As an illustration, diabetes was shown to aggravate post-ischaemic MO,[174,175] whereas the opposite effect may be present in Takotsubo cardiomyopathy.[176]

Myocardial oedema has not been evaluated as an endpoint in HF randomized clinical trials, and the effect of most drugs on myocardial fluid balance is currently unknown. However, pre-clinical evidence supports the beneficial effect of spironolactone[92] and SGLT2 inhibitors[177] by protecting endothelial glycocalyx. Interestingly, these two drug classes were shown to provide clinical benefit across a wide ejection fraction range in HF,[178–181] supporting a possible role for myocardial fluid balance among their mechanisms of action. Other drugs have proved useful to protect microvascular barrier in distinct clinical scenarios and may oppose MO formation. Of note, aprotinin, a fibrinolysis inhibitor, preserves adherens junctions and reduces MO in experimental cardioplegic arrest,[65] whereas in sepsis, hydrocortisone[182] and sulodexide, a mixture of GAGs (heparan and dermatan sulfates),[183] may protect the glycocalyx and diminish oedema formation.

In contrast, some drugs may facilitate the development of MO by impacting on microvascular filtration and ESL preservation. NP are known disruptors of the ESL[89,91] and BNP levels correlate with myocardial water content across several clinical scenarios (*Table 1*), an association not yet known to be causal. However, it is tempting to speculate that this effect might have contributed to the somewhat disappointing results of BNP analogue nesiritide in the setting of acute HF treatment.[184] In line with this, neprilysin is a known regulator of microvascular permeability by increasing the half-life of NP and bradykinin,[185] suggesting that sacubitril may also perturb microvascular barrier function.[230] Preclinical evidence suggests that beta-blockers[186] and calcium channel blockers[187] may increase microvascular permeability, an effect not yet observed in the myocardium.

Finally, experimental data suggest that stimulators of lymphangiogenesis (e.g. VEGF-C and adrenomedullin) may accelerate oedema resolution after myocardial

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infarction,[152,231] but clinical studies are needed before considering this therapeutic pathway in HF.

Conclusion

In the failing heart, myocardial fluid balance is disrupted due to alterations in microcirculation dynamics, microvascular barrier, extracellular matrix composition and lymphatic function. Experimental data suggest that MO significantly impairs cardiac performance, affecting systolic and diastolic properties and promoting long-term adverse remodelling. In the last decade, CMR has been increasingly used for HF phenotyping and data suggest the increase in myocardial free water content as relevant pathophysiological mechanism of cardiac injury and dysfunction, also representing an important prognosticator across multiple cardiac and systemic diseases. The recent advances in the knowledge of microvascular barrier and lymphatic function open the prospect for novel therapeutics targeting myocardial fluid disturbances in HF.

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2. ECMO na Falência Respiratória Aguda

2.1. Artificial placenta: Recent advances and potential clinical applications.

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Reviews

Artificial Placenta: Recent Advances and Potential Clinical Applications

Catarina Metelo-Coimbra, MD,[1] and Roberto Roncon-Albuquerque, Jr., MD, PhD[1,2]*

Summary. Lung immaturity remains a major cause of morbidity and mortality in extremely premature infants. Positive-pressure mechanical ventilation, the method of choice for respiratory support in premature infants, frequently promotes by itself lung injury and a negative impact in the circulatory function. Extracorporeal lung support has been proposed for more than 50 years as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of extremely premature infants. Recent advances in this field included the development of miniaturized centrifugal pumps and polymethylpentene oxygenators, as well as the successful use of pump-assisted veno-venous extracorporeal gas exchange systems in experimental artificial placenta models. This review, which includes studies published from 1958 to 2015, presents an update on the artificial placenta concept and its potential clinical applications. Special focus will be devoted to the milestones achieved so far and to the limitations that must be overcome before its clinical application. Notwithstanding, the artificial placenta stands as a promising alternative to mechanical ventilation in extremely premature infants. **Pediatr Pulmonol. 2016;51:643–649.**
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Key words: Artificial placenta; bronchopulmonary dysplasia; extracorporeal membrane oxygenation; extremely premature infant; respiratory distress syndrome.

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INTRODUCTION

According to the World Health Organization, 15 million premature infants are born every year, with almost 1 million deaths directly attributed to prematurity.[1] Although all premature infants are at risk for complications, extremely premature (EPT) infants, born at or before 28 weeks of gestation, suffer the greatest morbidity and mortality.[1] Respiratory distress syndrome and bronchopulmonary dysplasia remain a major cause of morbidity and mortality in EPT infants.[2] This relates with pulmonary immaturity, given that EPT infants are born during the canalicular period of lung development, characterized by capillarization and pulmonary acini morphogenesis, with insufficient surfactant production.[3]

Positive-pressure mechanical ventilation with high oxygen concentrations remains the method of choice to provide lung support in preterm infants with severe respiratory failure.[4] However, mechanical ventilation in preterm infants promotes, by itself, lung injury that negatively impacts survival. The known direct mechanisms of ventilator-induced lung injury are barotrauma, volutrauma, and atelectrauma.[5] These mechanisms promote biotrauma with capillary endothelium, alveolar epithelium, and basal membrane damage, which results in fluid, protein and blood extravasation into the airways,

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Conflict of interest: None.

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alveoli, and pulmonary interstitium, with consequent surfactant inhibition and activation of local and systemic inflammatory responses.[6] Mechanical ventilation also adversely affects the circulatory function of preterm infants, reducing pulmonary blood flow and left ventricular output.[7,8] In fact, positive-pressure mechanical ventilation decreases the alveolar/capillary transmural pressure gradient, causing compression of the intra-alveolar capillaries, which increases pulmonary vascular resistance, therefore decreasing pulmonary blood flow.[9] Further increases in airway pressure and pulmonary vascular resistance may sustain pulmonary arterial pressures above systemic arterial pressures, potentiating continued right-to-left shunt through the ductus arteriosus. The effect of positive-pressure ventilation is not limited to the pulmonary vasculature, with direct compressive effects observed on the newborn heart, resulting in reduced cardiac performance and ventricular output.[10] This could be particularly relevant in the immature myocardium of the preterm heart that presents low contractility with an inability to cope with increasing afterload in the days after birth.[11]

In light of these limitations, extracorporeal lung support has been proposed more than 50 years ago as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of EPT infants.[12] Its main benefits reside in the fact that, by bypassing the lungs completely, the AP avoids potential barotrauma resulting from mechanical ventilation. However, by then, artificial organ technology was still in its infancy and the understanding of EPT pathophysiology was very limited. More recently, important developments in extracorporeal lung assist technology were observed, fostering a renewed interest in artificial placenta (AP) research.

In this review, an update on the AP concept and its potential applications is presented. Special focus will be devoted to the milestones achieved so far and to the major limitations that must be overcome before its clinical application.

METHODS

Eligible studies were identified by an electronic search of PubMed and Scopus, involving studies published from 1958 to 2015. The sensitive search strategy combined the following keywords: *artificial placenta*; *bronchopulmonary dysplasia*; *extracorporeal lung assist*; *extracorporeal membrane oxygenation*; *extremely premature infants*; *polymethylpentene oxygenator*; and *respiratory distress syndrome*. All articles and cross-referenced studies from retrieved articles were screened for pertinent information and reviewed by both Authors.

Inclusion criteria consisted in experimental and systematic review articles, published as original studies, with available abstract. Publications not written in English or not related to the neonatal period were excluded.

ARTIFICIAL PLACENTA: THE CONCEPT

The terminology describing extracorporeal life support (ECLS) in premature infants is divided in three categories, established according to the gestational age[13]: (i) neonatal ECMO: for infants of at least 34 weeks of gestation (moderate to late preterm newborns[1]); this technique is successfully used in clinical practice for more than 30 years; (ii) preemie ECMO: for premature infants between 29 and 33 weeks of gestation (very preterm newborns); although technically feasible, reduced survival and increased rates of intra-ventricular hemorrhage have been reported[14]; and (iii) artificial placenta: for EPT infants, born before 28 weeks; the AP currently remains under experimental research.

Therefore, the AP concept consists in extracorporeal membrane gas exchange (blood oxygenation and extracorporeal CO_2 removal) for EPT infants with immature pulmonary system and severe respiratory failure, as a bridge to the development of native lung function.[8] The AP does not include provision of other placental functions such as nutrient or metabolic product exchange.

AP models are generally defined by the following characteristics[8,13,15,16]: (i) extracorporeal lung support with preservation of fetal circulation: either the umbilical artery (pumpless arteriovenous ECLS, AV-ECLS) or a central vein (pump-assisted venovenous ECLS, VV-ECLS) are used for blood outflow from the patient to the extracorporeal circuit; the umbilical vein is always used for inflow to the patient from the extracorporeal circuit[17] (Fig. 1); (ii) low partial pressure of oxygen, given that oxygen-binding capacity of fetal hemoglobin and hematocrit are increased; (iii) absence of positive-pressure mechanical ventilation; (iv) simulated fetal breathing with fluid-filled lungs; (v) biocompatibility of the extracorporeal circuit inner surfaces in direct contact with blood; high levels of systemic anticoagulation associate with an unacceptable risk of intracranial hemorrhage in EPT infants.[18]

Pump-assisted VV-ECLS systems presents several advantages when compared to pumpless AV-ECLS[17]: (i) arterial vessel cannulation is not required; cannulation of umbilical arteries in EPT infants is technically challenging and frequently complicates with vessel spasm; (ii) an external blood reservoir is not required given that the EPT infant's own venous system is used as blood reservoir; (iii) it operates in parallel with systemic circulation, therefore not increasing afterload of the fetal heart; differently, pumpless AV-ECLS operates in series with systemic circulation, increasing the fetal heart workload that can complicate with high-output heart failure.

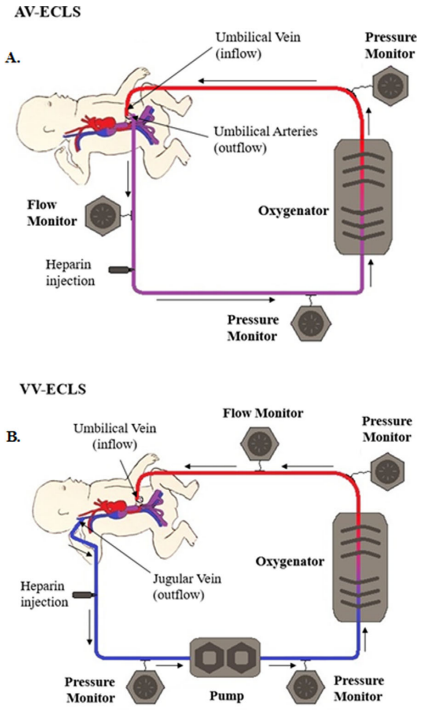

Fig. 1. Artificial placenta circuit configurations. (A) Pumpless arterio-venous extracorporeal lung support (AV-ECLS): blood inflow to the extracorporeal circuit is performed by cannulation of umbilical arteries; the oxygenated blood is then returned to EPT infant through the umbilical vein. (B) Pump-assisted veno-venous extracorporeal lung support (VV-ECLS): blood is drained from central vein(s) (e.g., internal jugular vein); the oxygenated blood is then returned to EPT infant through the umbilical vein.

Membrane lung permeability to O_2 and CO_2 is a critical factor influencing AP performance. Silicone rubber membranes were initially used, composed of a permeable non-porous polymeric material with loosely packed polymeric chains.[19] Another type of oxygenator is the hollow-fiber membrane, which has woven capillary tubes composed of microporous polypropylene.[20] Despite higher gas permeability, polypropylene membranes are less frequently used given the high plasma leakage risk with increased extracorporeal circuit blood pressures.[20] Moreover, silicone rubber membranes present higher biocompatibility when compared with polypropylene fibers for long-term ECLS.[21]

Polymethylpentene (PMP) oxygenators have been used in clinical practice for a decade.[22] PMP fibers have an asymmetric pore structure with a very thin dense outer skin that allows gas transference while suppressing the direct contact of blood and gas across micropores.[23] These features enhance durability and greatly reduce plasma leakage.[23] Moreover, PMP oxygenators present more efficient priming, reduced hemodynamic resistance and better preservation of coagulation proteins.[21]

EARLY MILESTONES

Following the development and implementation of the heart–lung machine, it was soon recognized that this concept could be similarly applied to the treatment of severe respiratory failure of the premature infant.[24] In 1958, Westin et al. prolonged the life of previable human fetuses by cannulating the umbilical vessels and circulating the fetal blood through a rotating oxygenator.[25] When injecting regular doses of glucose solution, the fetal heart continued to beat for a period up to 12 hr.[25] The fetuses were maintained in a warm artificial amniotic fluid bath.[25]

Callaghan et al. were the first to develop the AP concept in animal experiments, back in 1961. A pump-assisted VV-ECLS circuit with a rotating disc oxygenator was used in eight sheep.[26] Blood outflow from the animal to the extracorporeal circuit was performed via both femoral and jugular veins, while inflow to the animal from the extracorporeal circuit was made either through the right atrium or the right ventricle.[26] In 1962, a period of up to 2.5 hr survival of mongrel dogs using this procedure was reported.[27]

These achievements have been overcome by Lawn and McCance,[28] who conceived a pumpless AV-ECLS circuit with a dialyzer that was tested in previable pig fetuses. Blood drained from the umbilical arteries circulated through the oxygenator and then through cellophane tubing immersed in a suitable rinse. Blood returned to the umbilical vein without requiring external pump assistance.[28] A similar perfusion apparatus was constructed in 1964 by Alexander et al., but the dialyzer was excluded.[29] It was concluded from their experiments that a perfusion system with constant volume would be necessary, due to changes in venous pressure.[29]

Meanwhile, SenGupta et al. described a portable, self-contained and self-powered AP consisting of a flexible, inert silicone elastomer membrane oxygenator and a pump.[30] Their first experiment had 11 out of 16 survivors during up to 5 hr of connection to the AP.[30] Two years later, there were 16 survivors out of 20 dogs, and most perfusions took more than 2 hr. Though satisfactory oxygenation was obtained, the short period of survival was considered unsafe.[31]

Significant progress was achieved in 1969 by Zapol et al.,[32] when a premature lamb fetus was totally sustained by extracorporeal perfusion using a silicone-membrane

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blood oxygenator.[32] The animal received parenteral nutritional support and remained metabolically stable for up to 55 hr. A study with 10 lamb fetuses using angiocardiographic techniques was presented the following year.[33] Zapol et al. also described the modulation of ductus arteriosus and pulmonary blood flow by blood oxygen tension in their AP model.[34]

Efforts on the development of an AP were almost entirely abandoned by 1979, when a completely different approach to treat severe respiratory failure in premature infants was implemented: positive-pressure mechanical ventilation.[35,36] This led to a dramatic improvement of premature infants survival, although many problems remained.[37] Compared with positive-pressure mechanical ventilation, the AP was at that time too complex and unsafe for clinical use leading to a gap of research in the next decade.

In 1987, Kuwabara et al.[38] developed a novel AP system. They compared two types of circuits, with and without a blood reservoir, using goat fetuses. In the first group, the duration of incubation was increased to 165 hr, in contrast to the 8 hr achieved by the control group.[38] The oxygenator was made of silicone, and blood was drained from the umbilical arteries and returned to the umbilical vein.[38] This was the first report on animal experiments of successful long-term (up to 7 days) AP support. Several improvements were made to this novel AP system, including alterations in fetal catheterization and addition of a dialyzing system to the extracorporeal circuit, which allowed the survival of goat fetuses up to 236 hr.[39]

In 1993, continuing this work, Unno et al. tried a new protocol to study the influence of body movement on goat fetuses' survival.[40] It was demonstrated that AV-ECLS with umbilical blood access could support premature goat fetuses for up to 3 weeks.[40] The following studies focused on fetal hemodynamics, such as goat fetal ductal blood velocity through Doppler echocardiography[41] and the effect of prostaglandin E1.[42] This last experiment suggested that the administration of prostaglandin E1 prevented the constriction of ductus arteriosus, a phenomenon that was found to disturb fetal circulation to the AP.[43] This research group also compared four different methods to control blood flow in an AV-ECLS circuit, concluding that the control of extracorporeal circulation flow by altering the circuit resistance was one of the main contributing factors to the success of long-term incubation.[44]

In 1998, Sakata et al. reported the successful use of a centrifugal pump, which allowed higher extracorporeal flow rates.[45] This group used polyolefin hollow fiber membrane oxygenators, which contributed to low circuit resistance[45]. In the same year, Yasufuku et al. refined the AP concept by performing upper tracheal ligation, which maintained lung expansion and protected from meconium aspiration.[46,47]

RECENT MILESTONES

In 2012 Gray et al.,[48] from the University of Michigan ECLS Laboratory, hypothesized that a pump-assisted VV-ECLS circuit would preserve systemic fetal circulation while providing adequate extracorporeal gas exchange.[48] The right jugular vein was cannulated for outflow from the animal to the extracorporeal circuit, whereas an umbilical vein was used for blood inflow to the animal from the extracorporeal circuit.[48] Blood cavitation was reduced, since blood was passively drained from the right atrium.[48] A miniaturized polypropylene hollow fiber oxygenator was used. The experiment was successful, being the first report of a 24 hr survival of five Lamb fetuses using a pump-assisted VV-ECLS circuit. Continuing this work, seven lambs were incubated on a dry heated waterbed and maintained on VV-ECLS for up to 70 hr.[49] This AP model was able to provide hemodynamic stability and efficient extracorporeal gas exchange, with preservation of cerebral perfusion for an extended period of time.[49] No signs of gross or microscopic intra-ventricular hemorrhage were found despite systemic anticoagulation with heparin.[49]

In 2015, Bryner et al. compared a pump-assisted VV-ECLS system with positive-pressure mechanical ventilation in EPT lamb fetuses.[16] Four lambs were successfully supported for 1 week using a polypropylene oxygenator and a rotary pump.[16] Differently, lambs treated with positive-pressure mechanical ventilation survived on average less than 4 hr, despite the use of exogenous surfactant and steroids.[16] No evidence of intracranial hemorrhage was observed. The main issues faced by researchers were directly related to cannulation, with one case of pericardial tamponade and arrhythmias.[16]

Besides the improvements in extracorporeal circuit configuration, important advances were achieved in oxygenator technology. Arens et al.[50] developed a miniaturized oxygenator to be used in AP models. This research group catheterized lambs through two umbilical arteries and two umbilical veins, and the fetuses were kept in a warming bed. Their oxygenator, NeonatOx, was placed as close as possible to the lambs, allowing short tubing and low circuit resistance.[50] Furthermore, the oxygenator was miniaturized to a priming volume of only 20 ml. This reduced device surface area, decreasing thrombogenesis and inflammation.[50] NeonatOx allowed successful extracorporeal gas exchange for 6 hr in six out of seven animals.[51] One limitation related to the durability of umbilical vascular accesses, since artificial amniotic medium submersion was not performed.[51]

Meanwhile, Canadian investigators designed a microfluidic oxygenator with efficient gas exchange.[20] Four different gas permeable membranes were tested using human blood. The porous polydimethylsiloxane

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TABLE 1— Overview of Early Experiments Performed With Several AP Models

Reference	Year	Model	Circuit	Oxygenator	Pump	Submersion	Survival
25	1958	Human	AV-ECLS	Rotating film	Yes	Yes	5–12 hr
26	1961	Lamb	VV-ECLS	Rotating disc	Yes	Yes	8–19 hr
27	1962	Dog	VV-ECLS	Rotating disc	Yes	Yes	2.5 hr
28	1962	Piglet	AV-ECLS	Rotating disc film	Yes	Yes	8 hr
56	1963	Lamb	AV-ECLS	Rotating disc film	Yes	Yes	40 min
29	1964	Lamb	AV-ECLS	Rotating disc film	Yes	No	1 hr
30	1964	Dog	AV-ECLS	Membrane	Yes	—	2–5 hr
12	1965	Lamb	AV-ECLS	Rotating disc film	No	Yes	0.3–3 hr
57	1968	Human	—	Coiled membrane	Yes	—	1.5–5 hr
58	1968	Lamb	AV-ECLS	Rotating disc film	Yes	Yes	24 hr
32	1969	Lamb	AV-ECLS	Silicone coiled	Yes	Yes	4–55 hr
59	1979	Lamb	AV-ECLS	Microchannel membrane	Yes	No	—
38	1987	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 165 hr
39	1989	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 236 hr
40	1993	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 542 hr
46	1998	Goat	AV-ECLS	Polyolefin hollow fiber	Yes	Yes	Up to 237 hr

membrane had the highest gas exchange rate.[20] Recently, further improvements were performed to this oxygenator,[52] with the novel device being modifiable according to the EPT infants' body weight. This microfluidic oxygenator was tested in piglets during 4 hr.[52]

FUTURE DIRECTIONS

Although much progress has been made in the AP field and despite the different models studied so far (Tables 1 and 2), several limitations still preclude its clinical application.

Regarding the extracorporeal circuit itself, pump-assisted VV-ECLS models have shown many advantages over pumpless AV-ECLS circuits. Although its simplicity is appealing, the use of pumpless AV-ECLS in EPT infants seems technically impracticable due to the small size and tortuosity of the umbilical arteries, as well as to the need of prolonged extracorporeal lung support and hemodynamic stability.

Concerning anticoagulation, the development of novel biomaterials will presumably improve surface biocompatibility of the extracorporeal circuit, reducing (or even eliminating) the need for systemic anticoagulation, importantly decreasing intracranial hemorrhage risk.[18] In this regard, research is underway towards the development of non-thrombogenic surface extracorporeal circuit coating.[53,54]

Artificial placenta miniaturization will also be improved, decreasing extracorporeal surface area and circuit resistance.[51] The use of PMP oxygenators, which present high durability and reduced plasma leakage, is a predictable next step, given its successful use in adult ECMO.[23]

Further studies are required to show that the lung is protected and continues to mature during AP support. This implies that lung development between the stages of birth, AP support and progression to air breathing needs to be demonstrated and documented.

Concerning the brain, studies need to show that there is adequate brain perfusion and that this organ in protected without bleeding or white matter injury during AP support. This is essential given that, regarding neurological complications, the majority of sequelae appear to be related to hypoxemia and hemodynamic instability that occurs before the onset of ECLS.[55]

The impact of the AP in the cardiovascular, gastrointestinal, and renal systems also deserves further investigation. Cardiovascular stability during pump-assisted VV-ECLS in EPT infants also needs to be confirmed,

TABLE 2— Overview of Recent Experiments Performed With AP Models

Reference	Year	Model	Circuit	Oxygenator	Pump	Submersion	Survival
60	2009	Lamb	AV-ECLS	Hollow fiber	No	No	4 hr
50	2011	Lamb	AV-ECLS	Polypropylene	No	No	3 hr
61	2012	Lamb	AV-ECLS	Membrane	No	Yes	Up to 30 hr
48	2012	Lamb	VV-ECLS	Polypropylene	Yes	Yes	24 hr
49	2013	Lamb	VV-ECLS	Polypropylene	Yes	No	70 hr
52	2014	Piglet	AV-ECLS	Microfluidic	No	No	4 hr
51	2014	Lamb	AV-ECLS	Polypropylene	No	No	6 hr
16	2015	Lamb	VV-ECLS	Polypropylene	Yes	No	Up to 1 week

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before establishing this configuration as the preferred AP circuit.

The ability of EPT infants to wean from AP support without major lung sequelae is a central issue that needs further demonstration. This will impact on clinical criteria for AP use, which remain to be established.

CONCLUSION

Lung immaturity still associates with high morbidity and mortality in EPT infants. Extracorporeal lung support has been proposed for more than 50 years as a potential treatment of severe respiratory failure of EPT infants. Recent progresses in extracorporeal circuit biotechnology renewed the interest in experimental and clinical AP research. Notwithstanding the several challenges remaining, the AP remains an attractive potential alternative for EPT infants failing positive-pressure mechanical ventilation. The successful application of the AP into clinical practice would definitely be a milestone in neonatal medicine.

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2.2. Portable miniaturized ECMO systems for H1N1-related severe ARDS: A case series.

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Portable miniaturized extracorporeal membrane oxygenation systems for H1N1-related severe acute respiratory distress syndrome: A case series

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Extracorporeal membrane oxygenation;
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Oseltamivir

Abstract

Background: Technological advances improved the practice of "modern" extracorporeal membrane oxygenation (ECMO). In the present report, we describe the experience of a referral ECMO center using portable miniaturized ECMO systems for H1N1-related severe acute respiratory distress syndrome (ARDS).

Methods: An observational study of all patients with H1N1-associated ARDS treated with ECMO in Hospital S. João (Porto, Portugal) between November 2009 and April 2011 was performed. Extracorporeal membrane oxygenation support was established using either ELS or Cardiohelp systems (Maquet-Cardiopulmonary-AG, Hirrlingen, Germany).

Results: Ten adult patients with severe ARDS secondary to H1N1 infection (Pao_2/fraction of inspired oxygen, 69 mm Hg [56-84]; Murray score, 3.5 [3.5-3.8]) were included, and 60% survived to hospital discharge. Five patients were uneventfully transferred on ECMO from referring hospitals to our center by ambulance. Six patients were treated during the first postpandemic influenza season. All patients were treated with oseltamivir, and 1 received in addition zanamivir. Four patients received corticosteroids. Nosocomial infection was the most common complication (40%). Of the 4 deaths, 2 were caused by hemorrhagic shock; 1, by irreversible multiple organ failure; and 1, by refractory septic shock.

Conclusion: In our experience, ECMO support was a valuable therapeutic option for H1N1-related severe ARDS. The use of portable miniaturized systems allowed urgent rescue of patients from referring hospitals and safe interhospital and intrahospital transport during ECMO support.

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1. Introduction

Since the first outbreak of a respiratory illness caused by a novel swine-origin influenza A (H1N1) virus in Mexico during late March 2009 [1], several reports were published regarding the fact that it can sometimes lead to rapidly progressive acute respiratory distress syndrome (ARDS), with mortality rates ranging from 17% to 46% [2-4]. In some severe cases, ARDS "rescue therapies" were used in face of progressive refractory respiratory failure. Initial experience with extracorporeal membrane oxygenation (ECMO) for severe ARDS secondary to H1N1 infection during the pandemic was gathered in the 2009 southern hemisphere winter [5]. Extracorporeal membrane oxygenation was also used for respiratory support in H1N1 infection in North American and European ECMO centers during the 2009 northern hemisphere winter [6-10]. The favorable outcomes and low adverse event rates fostered the use of ECMO by other critical care centers.

Several technological advances significantly improved the practice of "modern" ECMO. Polymethylpentene oxygenators and centrifugal pumps show higher biocompatibility and durability compared with older silicon membrane oxygenators and roller pumps [11,12]. This allows lower blood product consumption as well as reduced circuit component exchange, enhancing the safety profile of modern ECMO support [13]. Moreover, these technological advances were accompanied by a simplification of the circuitry as well as by the recent development of portable miniaturized systems. These novel systems expanded the use of emergent ECMO support as well as interhospital and intrahospital transportation of patients while on ECMO [14-16].

Despite these recent advances, there is no significant experience with the use of portable miniaturized systems in the management of patients with H1N1 infection. In the present article, we describe the experience of a referral ECMO center using portable miniaturized ECMO systems for H1N1-related severe ARDS.

2. Materials and methods

An observational study of patients with H1N1-related ARDS treated with ECMO in Hospital S. João (Porto, Portugal), an 1100-bed tertiary university hospital, was performed. The Hospital S. João ECMO Center is the sole ECMO referral center for the north of Portugal, a region with approximately 4 million inhabitants. It has a case volume of 20 to 30 patients per year, being an Extracorporeal Life Support Organization (ELSO) member. Specific ECMO data were prospectively collected from a dedicated database from our ECMO Program. Clinical data were collected retrospectively from clinical records.

2.1. Study population

H1N1 infection was confirmed by means of polymerase chain reaction on either nasopharyngeal swab samples and/or lower respiratory tract secretions ordered by the attending physicians at emergency or intensive care unit (ICU) admission. Consideration of ECMO was based on the presence of severe respiratory failure (Murray score >3.0 and/or pH <7.20 under protective ventilation) with sustained clinical deterioration despite optimal conventional treatment. Patients were ventilated either in pressure-controlled ventilation or in volume-controlled ventilation modes. When pressure-controlled ventilation was selected, peak airway pressure was used as airway pressure criteria. When volume-controlled ventilation was selected, plateau pressure was used as the airway pressure criteria. Aggressive mechanical ventilation (peak or plateau airway pressure >30 cm H_2O or fraction of inspired oxygen [Fio_2] >0.8) for more than 7 days, uncontrolled active bleeding, severe comorbidity, age > 65 years, and modified Rankin score 3 or higher (moderately severe disability) [17] were used as contraindications for ECMO institution.

2.2. Technique of extracorporeal support

The miniaturized portable ECMO system consisted of 2 venous cannulae, a centrifugal pump, a membrane oxygenator, and 3/8" connecting tubes. For outflow, the right femoral vein was cannulated percutaneously using the Seldinger technique with a 38-cm-long, 21F to 23F heparin-coated cannula (BE-PVS 2138 and BE-PVS 2338, respectively; Maquet-Cardiopulmonary-AG, Hirrlingen, Germany). For reinfusion, a 15-cm-long, 15F to 17F heparin-coated cannula (BE-PAS 1515 and BE-PAS 1715, respectively; Maquet Cardiopulmonary AG) was used, implanted in the right internal jugular vein. In peripheral venoarterial (VA) ECMO, a 23-cm-long, 17F cannula in the right common femoral artery was used for reinfusion. Blood flow was generated by centrifugal pump (Rotaflow-Centrifugal Pump; Maquet-Cardiopulmonary-AG). The membrane oxygenator (PLS-Quadrox; Maquet-Cardiopulmonary-AG) is made of polymethylpentene and has a total gas exchange surface of 1.8 m^2 with a very low inherent resistance, avoiding plasma leakage. For interhospital and intrahospital transport of patients, specific handheld adaptors were used (ELS System; Maquet-Cardiopulmonary-AG). In 2 patients, an ultracompact system with 1-piece integrated pump and oxygenator (Cardiohelp; Maquet-Cardiopulmonary-AG) was used. Both systems have an integrated battery backup for intrahospital and interhospital transport. When available, an oxygenator water supply unit was used for thermoregulation (Heater Unit 35; Maquet-Cardiopulmonary-AG) at the bedside. The filling volume of the complete device is between 400 to 500 mL,

depending on tubing length. All the components of the extracorporeal system were heparin coated (BIOLINE coating; Maquet-Cardiopulmonary-AG), and systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time of 1.5 normal. Pure oxygen was used as sweep gas with a flow of 1 to 12 L/min. Blood gas analysis was performed using the RAPIDLab 1200 Systems (Siemens, Munich, Germany). The oxygen transfer rate by the ECMO system was calculated daily by multiplying the difference of oxygen content premembrane and postmembrane oxygenator with the circuit blood flow. The estimation of carbon dioxide transfer rate was performed daily by multiplying the difference of calculated carbon dioxide premembrane and postmembrane oxygenator with the circuit blood flow. Pressures on the ECMO circuit, premembrane oxygenator hemoglobin saturation, general laboratories, and complete blood coagulation study were also monitored daily by the ECMO specialist. Echocardiography was not performed routinely.

2.3. Referral and interhospital rescue to the ECMO center

For both in-house and outside patients, referral was triggered by a first telephone contact between the referring physician and the ECMO center coordinator. Based on the initial evaluation, a decision was made either for optimization of in loco treatment followed by reassessment or for ECMO rescue. When a decision for ECMO rescue was made, an ECMO rescue team was organized within a short time frame, including 2 intensive care physicians, 1 nurse, and 1 perfusionist. The ECMO rescue team composition was similar for both in-house and outside cannulation. Although the treatment strategy was discussed in advance with the attending physicians, final decision for ECMO implantation was taken at the patient's bedside. For patients from referring hospitals accepted for ECMO support, our protocol consists in patient rescue by our mobile ECMO team, with in loco ECMO implantation and stabilization before transportation to our center. After initial patient stabilization, patients were

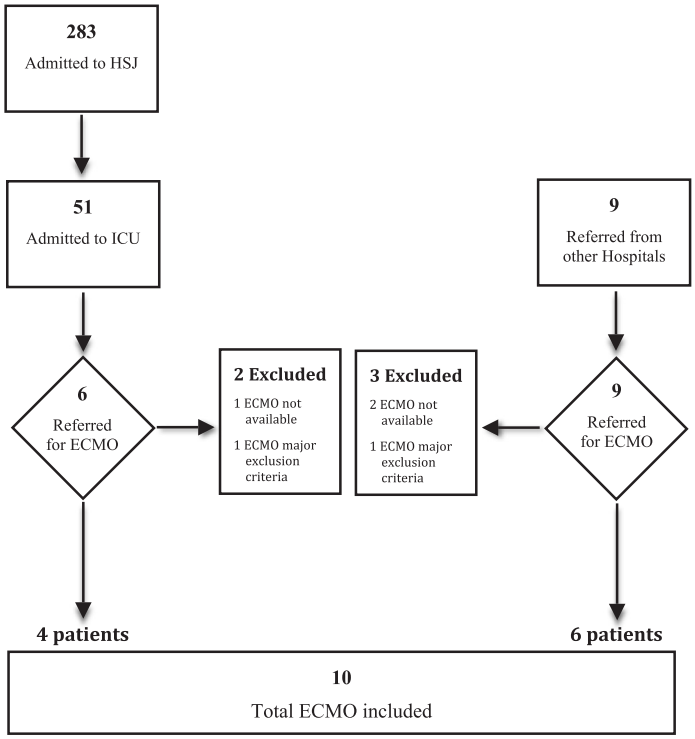

Fig. 1 Flow chart detailing all the patients admitted to ICUs for severe respiratory failure due to confirmed H1N1 infection in Hospital S. João in the study period.

transferred to our ECMO center by ambulance (distance 117 km [116-133]), fully equipped for medical emergencies (vital signs monitor, ventilator, infusion pumps, defibrillator, and oxygen tanks). Most ambulances did not provide electrical supply to our ECMO device, so we had to rely on its built-in battery (battery backup of 90 minutes) plus a manual emergency pump.

2.4. Patient management on ECMO and weaning from extracorporeal support

After cannulation, patient management was optimized to minimize further ventilator-induced lung injury, according to the standards of our ECMO center. Regarding oxygenation, ECMO blood flow was maximized to reduce Fio_2 less than 0.6 and maintain hemoglobin saturation more than 85%. Positive end-expiratory pressure (PEEP) was maintained above 8 cm H_2O to avoid lung atelectasis. If severe hypoxemia (Pao_2, <60 mm Hg) still subsisted, the threshold for red blood cell transfusion was elevated from 7.0 to 9.0 g/dL. The threshold for prophylactic platelet transfusion was 30.000/μL, whereas the targeted posttransfusion goal was 100.000/μL in the presence of active bleeding. Regarding CO_2 removal, sweep gas flow was maximized to allow a normal pH, small tidal volumes (<6 mL/kg per predicted body weight), and plateau pressures less than 30 cm H_2O. Whenever possible, paralysis was withheld, and sedation was reduced to allow spontaneous breathing.

After improvement of native lung function (Fio_2 <0.5, PEEP <10 cm H_2O, peak inspiratory pressure in pressure-controlled ventilation [PIP] <27 cm H_2O), ECMO blood flow was stepwise reduced to 2.0 L/min. Thereafter, sweep gas flow was tapered and finally shut off for 30 minutes. If blood gases remained stable, the ECMO system was removed, and decannulation with skin suture was carried out. An eco-Doppler was routinely performed after decannulation to exclude femoral vein thrombosis.

2.5. Data collection and statistical analysis

Approval for this study was gained from the Ethics Committee of the Hospital S. João. Informed consent was not required for ECMO treatment, as the devices used are approved for long-term therapy and its use was considered a rescue therapy in all patients. Nevertheless, disease severity and indication for ECMO treatment were extensively explained and discussed with the surrogate decision maker.

Variables are reported as median and interquartile ranges, if not told otherwise, after testing for normal distribution. Nonparametric test procedures were used for paired analysis (Wilcoxon signed rank test) and unpaired analysis (Mann-Whitney U test). $P < .05$ was considered statistically significant. For statistical analysis, we used SPSS 18.0 (SPSS, Inc, Chicago, Ill).

3. Results

3.1. Characteristics of patients with H1N1 requiring ECMO

During the H1N1 pandemic and the first postpandemic influenza season, 283 patients were directly admitted to Hospital S. João with confirmed H1N1 infection (Fig. 1; Tables 1 and 2). Of note, a significant number of cases were admitted to Hospital S. João independently of disease severity, within the national contingency strategy of case

Table 1 Characteristics of patients with influenza A (H1N1) requiring ECMO

Characteristic	N
No. of cases	10
Age (y)	40 (36-47)
Male	6
Comorbidities	6
Obesity	4
Hypertension	2
Diabetes mellitus	1
Asthma	1
Pregnancy	1
Bone marrow transplant	1
Duration (d)	
Symptoms to hospital admission	5 (4-8)
Hospital to ICU admission	2 (1-3)
ICU admission to ECMO	6 (2-12)
ECMO retrieval	6
SAPS II	40 (25-45)
Murray score	3.5 (3.5-3.8)
Before ECMO	
Prone position	6
Nitric oxide	1
Renal replacement therapy	0
Inotrope score	25 (4-45)
During ECMO	
Prone position	1
Nitric oxide	1
Renal replacement therapy	3
Inotrope score	13 (9-30)
Treatment of influenza A (H1N1)	
Oseltamivir	10
Zanamivir	1
Corticosteroids	5
Tracheostomy	4
Mechanical ventilation (d)	32 (21-49)
ECMO (d)	22 (14-32)
ICU LOS (d)	36 (24-50)
ICU survival	6
Hospital survival	6

Data are presented as number of cases or median (interquartile range). Inotrope score before ECMO refers to the inotrope score in the last day before ECMO implantation. Inotrope score during ECMO refers to the inotrope score on day 1 after ECMO implantation. SAPS II indicates Simplified Acute Physiology Score II; LOS, length of stay.

Table 2 Characteristics of patients with H1N1 infection supported with ECMO

	Age (y)	Sex (male/female)	Comorbidities	P-ECMO-MV (d)	MV duration (d)	ECMO duration (d)	ECMO type (VV/VA)	Hospital LOS (d)	EQ-5D	EQ-VAS (%)	Outcome (alive/death)
Patient 1	36	M	None	17	79	43	VV > VA	181	22 211	60	A
Patient 2	31	F	None	14	30	12	VV	46	11 111	100	A
Patient 3	36	F	None	10	10	NA	VV	13	NA	NA	D
Patient 4	25	M	Obesity	3	25	22	VV	26	NA	NA	D
Patient 5	46	M	BMT	2	20	14	VV	30	11 111	85	A
Patient 6	45	M	None	9	16	6	VV	22	11 122	75	A
Patient 7	54	M	Obesity	4	35	29	VV	36	NA	NA	D
Patient 8	50	M	Obesity	2	59	18	VV	117	UN	UN	A
Patient 9	47	F	Obesity and asthma	1	41	32	VV	44	12 111	80	A
Patient 10	36	F	Pregnancy	13	52	39	VV	55	NA	NA	D

EuroQol 5 dimensions and EuroQol visual analog scale were obtained at 6 months of follow-up. A indicates alive; BMT, bone marrow transplant; D, death; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analog scale; MV, mechanical ventilation; NA, not applicable; P-ECMO-MV, pre-ECMO duration of mechanical ventilation; UN, unavailable.

isolation in the beginning of the pandemic phase. Of these, 51 patients were admitted to ICU for severe respiratory failure, of which 6 were referred for ECMO. In addition, 9 patients were referred for ECMO from referring hospitals. Of the 15 patients referred for ECMO, 5 patients were not included: ECMO was not available in 3 cases and 2 patients presented a major contraindication for ECMO support (uncontrolled active bleeding in one case and 23 days of aggressive mechanical ventilation in the other case). None of these 5 patients survived to hospital discharge. Of the 10 patients treated with ECMO, 4 patients were included during the H1N1 pandemic (between November 2009 and March 2010), and 6, during the first postpandemic influenza season (between December 2010 and April 2011).

Comorbidities were present in 60% of the patients, obesity being the most frequently encountered. In 1 patient, H1N1-related ARDS was established during the third trimester of pregnancy, and ECMO support was initiated 13 days after emergent cesarean delivery. One patient was on molecular remission of Philadelphia chromosome–positive acute lymphoblastic leukemia after bone marrow allotransplantation.

The clinical course consisted of rapid in-hospital deterioration with early ICU admission for ventilatory support. The Murray score was used to evaluate respiratory failure severity before ECMO implantation. In 60% of patients, alternative rescue therapies such as prone position and inhaled nitric oxide were used before ECMO referral. All patients were treated with oseltamivir; 1 received in addition intravenous zanamivir due to persistence of H1N1 in bronchoalveolar lavage, after a 10-day course of oseltamivir; 5 patients received corticosteroids. Long ECMO runs, with prolonged mechanical ventilation and ICU length of stay, were observed.

Intensive care unit and hospital survival were 60%. Of the 4 deaths, 2 were due to hemorrhagic shock (due to superior vena cava perforation during cannulation in patient 3 and due to pulmonary hemorrhage in patient 10); 1, to irreversible multiple organ failure (patient 7); and 1, to refractory septic shock (patient 4) due to multidrug-resistant (MDR) *Acinetobacter baumannii* ventilator-associated pneumonia with accompanying secondary bacteremia (Table 2).

3.2. Transport of patients on ECMO

There were no significant complications during ECMO transport from referring hospitals to our center. Although most ambulances did not provide electrical supply to our ECMO device, battery backup was sufficient for patient transportation.

In 2 patients, otherwise unexplained respiratory deterioration was observed, and thoracic computed tomography (CT) was performed during ECMO treatment. Head CT scan was concomitantly performed in these 2 patients to exclude intracranial bleeding. In both patients, thoracic CT scan information was used in further management decisions: in one case, percutaneous drainage of thoracic collections was performed; on the second case, extensive destruction and fibrosis of lung parenchyma after prolonged ECMO support led to a withdrawal of life support decision. No significant complications were observed during intrahospital transport of these 2 patients.

3.3. Gas exchange and hemodynamic parameters before, during, and after ECMO

Extracorporeal membrane oxygenation support allowed early (ECMO day 1 and ECMO day 2) improvement of Pao_2/Fio_2 because of high flow in the ECMO circuit allowing high O_2 transfer in the ECMO membrane (Table 3), although 1 patient was converted to peripheral VA-ECMO because of concomitant refractory hypoxemia under venovenous (VV)-ECMO (Pao_2 <50 mm Hg) on day 3. In survivors,

Table 3 Gas exchange and hemodynamic parameters before, during, and after ECMO

	Pre-ECMO	Pre-ECMO survivors	Pre-ECMO nonsurvivors	ECMO day 1	ECMO day 2	End of ECMO survivors	End of ECMO nonsurvivors	Day 1 after ECMO
Pao_2/Fio_2 (mm Hg)	69 (56-84)	68 (45-93)	69 (67-73)	NA	NA	NA	NA	260 α (229-282)
$Paco_2$ (mm Hg)	64 (51-70)	64 (60-68)	59 (47-78)	47 (40-52)	55 (48-61)	45 (40-58)	47 (44-52)	48 (38-50)
pH	7.33 (7.28-7.39)	7.33 (7.28-7.38)	7.37 (7.28-7.47)	7.46 (7.43-7.50)	7.43 α (7.40-7.49)	7.40 α (7.39-7.43)	7.34 (7.28-7.36)	7.44 α (7.40-7.48)
Inotrope score	25 (4-45)	40 (13-45)	8 (3-32)	13 (9-30)	4 α β (0-10)	0 α (0-0)	186 δ (98-233)	0 α ε (0-0)
Fluid balance (L/24 h)	+1.74 (0.86-2.54)	+2.48 (1.74-2.60)	+1.24 (0.64-1.84)	+0.75 (0.70-2.50)	+0.91 (−0.01 to 1.80)	+0.56 (−0.13 to 0.98)	+1.41 (1.36-2.36)	+0.98 (0.58-1.16)
ECMO O_2 transfer (mL/min)	NA	NA	NA	156 (145-198)	197 (162-232)	108 γ (72-135)	187 δ (186-193)	NA
ECMO blood flow (L/min)	NA	NA	NA	4.2 (3.2-4.5)	4.1 (3.6-4.2)	2.5 β γ (2.1-2.9)	3.6 δ (3.5-4.2)	NA
ECMO CO_2 transfer (mL/min)	NA	NA	NA	176 (170-237)	290 (213-310)	120 γ (109-184)	275 δ (254-295)	NA
ECMO sweep flow (L/min)	NA	NA	NA	3.0 (2.5-4.0)	5.0 (3.5-5.5)	2.0 γ (2.0-2.5)	6.0 (5.0-7.0)	NA

Data are presented as median (interquartile range). $\alpha < .05$ vs pre-ECMO; $\beta < .05$ vs day 1; $\gamma < 0.05$ vs day 2; $\delta < 0.05$ vs end of ECMO survivors; $\varepsilon < 0.05$ vs end of ECMO nonsurvivors.

improvement of native lung function allowed progressive weaning of ECMO O_2 transfer, whereas in nonsurvivors, no improvement in Pao_2/Fio_2 was observed. After ECMO implantation, correction of respiratory acidosis was achieved by increasing CO_2 transfer in the ECMO membrane. In survivors, improvement of native lung function allowed progressive reduction of CO_2 transfer in the ECMO circuit. Low inotrope scores [18] were present in survivors before, during, and after ECMO support, whereas in nonsurvivors, high inotrope scores were present at the end of ECMO support.

3.4. Respiratory parameters before, during, and after ECMO

Extracorporeal membrane oxygenation support allowed the institution of lung-protective ventilation, as evaluated by low tidal volumes, PIP less than 30 cm H_2O, and lower Fio_2,

Table 4 Respiratory parameters before, during, and after ECMO

	Pre-ECMO	Pre-ECMO survivors	Pre-ECMO nonsurvivors	ECMO day 1	ECMO day 2	End of ECMO survivors	End of ECMO nonsurvivors	Day 1 after ECMO
Fio_2 (%)	100 (85-100)	90 (72-100)	100 (100-100)	60 α (60-80)	60 α (60-80)	45 α β γ (36-50)	100 δ (80-100)	48 α β ε (41-58)
Minute ventilation (L/min)	11.4 (7.8-12.0)	11.4 (7.0-11.5)	10.4 (9.5-11.4)	4.1 α (3.8-4.9)	4.1 α (3.4-4.9)	9.2 β (8.0-9.3)	4.8 (2.6-5.4)	12.1 β γ ε (10.4-13.7)
Tidal volume (mL)	470 (390-472)	400 (380-470)	550 (508-584)	250 α (200-270)	250 α (210-260)	385 (342-430)	240 δ (120-245)	480 β γ δ ε (430-614)
Tidal volume/PBW (mL/kg)	5.5 (4.6-6.2)	5.5 (4.5-6.2)	5.8 (5.2-6.4)	2.9 α (2.7-3.4)	3.1 α (2.7-3.5)	5.4 (5.2-5.6)	2.5 δ (1.2-2.6)	7.0 β γ δ ε (6.2-7.1)
PIP or PlatP (cm H_2O)	35 (32-36)	34 (30-36)	35 (34-38)	29 α (28-30)	29 α (25-30)	28 α (27-29)	31 α (28-32)	30 α δ (28-30)
PEEP (cm H_2O)	16 (13-18)	14 (8-17)	17 (16-18)	12 α (9-15)	11 α (8-15)	8 α (6-8)	16 δ (13-17)	5 α β γ ε (5-6)
Compliance (mL/cm H_2O)	22.2 (14.6-27.7)	15.7 (13.6-22.2)	24.8 (19.4-25.4)	13.1 α (10.5-16.0)	14.7 α (13.0-18.7)	17.5 (15.7-20.4)	10.4 (5.2-13.6)	19.2 β γ ε (17.7-30.7)

Data are presented as median (interquartile range). PBW indicates predicted body weight; PlatP, plateau pressure in volume-controlled ventilation. $\alpha < .05$ vs pre-ECMO; $\beta < .05$ vs day 1; $\gamma < 0.05$ vs day 2; $\delta < 0.05$ vs end of ECMO survivors; $\varepsilon < 0.05$ vs end of ECMO nonsurvivors.

on ECMO days 1 and 2 (Table 4). In survivors, lung-protective ventilation was sustained during ECMO support and on the first day after ECMO cessation. In contrast, nonsurvivors presented high Fio_2 and decreased lung compliance at the end of ECMO support.

Before ECMO support, a wide range of PEEP was observed probably reflecting distinct ventilation practices used in different ICUs. After initiation of ECMO support, the level of PEEP was chosen over 8 cm H_2O to avoid atelectasis. The level of PEEP was then gradually decreased during weaning from ECMO and afterward during weaning from mechanical ventilation.

Tracheostomy was performed in 4 patients. In 2 patients, tracheostomy was performed percutaneously during ECMO support. In the other 2 cases, tracheostomy was performed surgically after ECMO support in weaning from mechanical ventilation.

3.5. Transfusion requirements, nosocomial infection, and ECMO-related complications

During ICU stay, the period of ECMO support was the one with highest transfusion requirements, namely, of red blood cells and platelets (Table 5). No significant increase in plasma transfusion requirement was detected during ECMO support.

Regarding ECMO-related complications, hemorrhagic complications were the most frequently observed (Table 6). Blood oozing from neck cannulation site was observed in 2 patients. Diffuse bleeding secondary to consumption coagulopathy was observed in 2 patients and resolved 12 to 24 hours after oxygenator substitution. Superior vena cava perforation during right internal jugular vein cannulation was observed in 1 patient rescued in a referring hospital. This patient was submitted to emergency exploratory sternotomy but eventually deceased from hemorrhagic shock at the referring hospital. Of the remaining 5 patients rescued in referring hospitals, all were stabilized after cannulation and uneventfully transferred on ECMO to our center. Ischemic stroke was observed in 1 patient converted from VV-ECMO to VA-ECMO due to persistent hypoxia under VV-ECMO. In 2 patients, oxygenator failure (increased transmembrane pressure gradient and/or low postoxygenator Po_2) was detected requiring circuit exchange. Flow difficulties were regularly observed in 1 obese patient (patient 9 of Table 2) due to dynamic collapse of the femoral outflow cannula, which was attenuated by maintenance of muscle paralysis during ECMO support. Decannulation was uneventful in all 6 survivors, with no need for second ECMO runs.

Ventilator-associated pneumonia (VAP) was the most common nosocomial infection during ECMO support, being present in 3 patients (of which 1 survived). In 2 patients, MDR *A baumannii* was detected in quantitative cultures of bronchoalveolar lavage samples, with accompanying secondary bacteremia. In 1 patient, MDR *Pseudomonas aeruginosa* was isolated in quantitative cultures of bronchoalveolar lavage samples. In 1 patient, primary *Enterococcus faecium* bacteremia was detected.

Table 5 Transfusion requirements in the ICU

	On ECMO	Off ECMO	ICU
RBC/day	0.55 (0.33-1.09)	0.00 α (0.00-2.00)	0.37 α β (0.20-0.52)
FFP/day	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
PC/day	0.47 (0.16-0.67)	0.00 (0.00-0.00)	0.26 (0.03-0.47)

Data are presented as median (interquartile range). RBC indicates red blood cell concentrate; FFP, fresh-frozen plasma; PC, platelet concentrate. $\alpha < .05$ vs on ECMO; $\beta < .05$ vs off ECMO.

Table 6 Summary of complications during ECMO support

	n
Hemorrhagic complications	
DIC-like condition	2
Pulmonary hemorrhage	1
Vascular perforation	1
Thrombotic complications	
Femoral vein thrombosis	1
Neurologic complications	
Ischemic stroke	1
Mechanical complications	
Oxygenator failure	2
Infectious complications	
A baumannii VAP	2
P aeruginosa VAP	1
E faecium bacteremia	1

Data are presented as number of cases. DIC indicates disseminated intravascular coagulation.

4. Discussion

In our experience, ECMO support was a valuable therapeutic option for H1N1-related severe ARDS. The use of portable miniaturized systems allowed urgent rescue of patients from referring hospitals and safe interhospital and intrahospital transport during ECMO support.

Four types of respiratory presentations were described in patients with H1N1 infection requiring ICU admission: (1) viral pneumonitis, (2) secondary bacterial pneumonia, (3) exacerbations of asthma or chronic obstructive pulmonary disease, and (4) exacerbation of other underlying disease [19]. In our case series, viral pneumonia was presumably the most common cause of ARDS, given the rapidly progressive hypoxemia and bilateral alveolar infiltrates on chest radiograph observed in all cases. In 1 patient, secondary bacterial pneumonia could have complicated H1N1 infection and contributed to ARDS, given that *Streptococcus pneumoniae* was isolated from an endotracheal aspirate sample at ICU admission. In addition, 1 patient was asthmatic, so

asthma exacerbation could have contributed to the severity of respiratory failure.

The use of portable miniaturized systems significantly expanded the use of ECMO by our referral center, allowing urgent rescue of patients with H1N1-related severe ARDS from referring hospitals and safe interhospital and intrahospital transport of patients while on ECMO. Miniaturized ECMO systems have been previously shown to be efficient and safe in a large sample of adults with severe respiratory failure [20]. Moreover, we used handheld adaptors [21] and ultracompact mobile systems [16] to allow in loco ECMO implantation and interhospital transportation of patients who otherwise could not be transferred to our ECMO center. In fact, patients with H1N1 from referring centers are often too severely ill to allow safe interhospital transfer, precluding the feasibility of ECMO support. In a recently published report, Muller et al [22] described the successful use of an ultracompact mobile ECMO system in a case of severe H1N1-related ARDS. The use of portable miniaturized ECMO systems was also useful for safe intrahospital transportation at our institution for CT scan. Jepson et al [23] demonstrated that with an experienced team, CT imaging of patients on ECMO can be performed safely, providing valuable information for subsequent management of patients. Recently, several ECMO centers also reported the feasibility of interhospital transfer on ECMO for patients with H1N1 [7,24,25]. We believe that the reduced weight and compact design of the portable miniaturized ECMO systems used by our center would have further contributed to the safe transport and handling of these unstable patients.

Lower inotropic scores early after VV-ECMO initiation were observed (Table 3). Improvement of right ventricular function probably had a significant contribution to this cardiovascular stabilization. The oxygenation improvement and hypercapnia control observed after VV-ECMO initiation allowed lowering of ventilator settings. This is particularly relevant, given that limiting plateau pressure and lowering PEEP have been shown to improve right ventricular function in patients with ARDS [26].

In different case series, the mortality rates of patients with H1N1-related severe ARDS supported with ECMO varied from as low as 8% [8] to as high as 56% [9]. In our case series, 60% of survival to hospital discharge was observed, a result similar to the one reported by ELSO H1N1 Registry [27]. Several factors could contribute, in our opinion, to such a wide range of survival for ECMO-supported, H1N1-related ARDS. First, patient age, risk factors for H1N1 infection, and comorbidities significantly varied among case series. Namely, the use of ECMO in bone marrow transplant patients is a basis for exclusion at many experienced centers. However, the outcome of patients with Philadelphia chromosome–positive acute lymphoblastic leukemia submitted to bone marrow transplant improved significantly after the introduction of tyrosine kinase inhibitor imatinib [28]. Our case series includes a 46-year-old patient on molecular remission from acute lymphoblastic leukemia under imatinib treatment 1 year after allogeneic bone marrow transplant. The patient was supported with ECMO during 14 days, and no major complications were observed. Presently, the patient is still in remission from acute lymphoblastic leukemia. Moreover, prolonged (>7 days) high-pressure ventilation with high Fio_2 requirements constitutes an accepted relative contraindication for ECMO support [29]. In our study, 5 patients had more than 7 days of mechanical ventilation pre-ECMO, of which 3 survived (Table 2). The decision of our group was based on young patient age, absence of significant comorbidities, or other contraindication to initiate ECMO support. Second, given that ECMO is a high-risk procedure, it is expected that high-volume ECMO centers perform better than low-volume ECMO programs [30,31]. Finally, it is not known if patient population and/or disease severity from patients with H1N1-related severe ARDS supported with ECMO in the postpandemic period is significantly different from the pandemic period. A prospective, observational, multicenter study conducted in 148 Spanish ICUs analyzed 300 patients with severe H1N1 infection during the first influenza season after the 2009 pandemic influenza [32]. These patients presented poor rates of vaccination, higher frequency of severe comorbidities, severity of illness, incidence of primary viral pneumonia, and increased mortality (33.5%) when compared with those observed in the 2009 pandemic outbreak. In our case series, 60% of patients were treated during the postpandemic period and most (5/6) from referring hospitals. This could reflect, at least in part, increased knowledge of ECMO referral by adult critical care physicians after the first case series describing successful use of the technique during H1N1 pandemic [3,33] and the publication of the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial [34].

The mean duration of ECMO support in our study was high (22 days). However, long ECMO runs (>15 days of median duration of ECMO support) were previously reported in other H1N1 case series [6,8]. In our experience, consecutive positive fluid balance was frequently needed during VV-ECMO support, particularly with high pump flows. Given the importance of negative fluid balance in respiratory improvement in ARDS [35], this could have contributed to protracted recovery of native lung function.

In our case series, several ECMO-related complications were observed. Refractory hypoxemia was observed in 1 patient under VV-ECMO. Despite the potential risks for hypoxemia of coronaries and brain, this patient was converted to peripheral VA-ECMO. In 2 patients, a disseminated intravascular coagulation-like condition was observed in association with thrombus deposition in the oxygenator, which was corrected after oxygenator change. Oxygenator failure requiring exchange was observed in 2 additional patients. In 1 patient, femoral vein thrombosis was detected after decannulation, which implicated a 3-month course of anticoagulation. These observations could be significant given previously reported hypercoagulable states

in patients with H1N1 infection [36]. The incidence of these complications is comparable with the one reported by Muller et al [20] using a similar miniaturized ECMO system and analogous systemic anticoagulation goals. Superior vena cava perforation during cannulation was observed in 1 patient, a complication previously described in a series of patients with percutaneous VV-ECMO cannulation [37].

Nosocomial infection was a frequent complication during ECMO support, being diagnosed in 40% of patients. Bizzarro et al [38] recently published a retrospective analysis of data from the ELSO registry to quantify the infection rates associated with ECMO. The highest rates of infections were observed in the adult patients (31%), and the duration of ECMO support was associated with increased incidence of infections. These data are in line with the high infection rate in our case series because most patients needed prolonged ECMO support. In a recently published multiinstitutional survey, antibiotic prophylaxis was used by several ECMO centers [39]. That is not the case of our ECMO center, where antibiotics are only used if infection is suspected clinically and/or confirmed microbiologically. Whether these different practices between ECMO centers have impact in clinical outcome cannot, however, be ascertained.

In conclusion, portable miniaturized ECMO was successfully used to rescue patients with H1N1-related severe ARDS. The safety and flexibility of these recently developed systems represent an improvement of this advanced respiratory support technique.

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2.3. Outcome and Management of Refractory Respiratory Failure With Timely ECMO: Single-Center Experience With Legionella Pneumonia.

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Outcome and Management of Refractory Respiratory Failure With Timely Extracorporeal Membrane Oxygenation: Single-Center Experience With *Legionella* Pneumonia

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Abstract

Objective: To analyze the management and outcome of patients with refractory respiratory failure complicating severe *Legionella* pneumonia rescued with extracorporeal membrane oxygenation (ECMO) in our Center. **Design and Setting:** Observational study of patients with refractory respiratory failure treated with ECMO in Hospital S.João (Porto, Portugal), between November 2009 and September 2016. **Participants:** A total of 112 patients rescued with ECMO, of which 14 had *Legionella* pneumonia. **Results:** Patients with *Legionella* pneumonia were slightly older than patients with acute respiratory failure of other etiologies (51 [48-56] vs 45 [35-54]), but with no significant differences in acute respiratory failure severity between groups: Pao_2/Fio_2 ratio 67 (60-75) versus 69 (55-85) and Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score 4 (1-5) versus 2 (-1-4), respectively. *Legionella* pneumonia was associated with earlier ECMO initiation (days of invasive mechanical ventilation [IMV] before ECMO: 2.0 [1.0-4.0] vs 5.0 [2.0-9.5]). After IMV adjustment to "lung rest" settings, this group presented higher respiratory system (RS) static compliance (28.7 [18.8-37.4] vs 16.0 [10.0-20.8] mL/cmH_2O) but required higher ECMO support (blood flow 5.0 [4.3-5.4] vs 4.2 [3.6-4.8]). Patients with *Legionella* pneumonia had shorter IMV (16 [14-23] vs 27 [20-42] days) and lower incidence of intensive care unit nosocomial infections (35.7% vs 64.3%), with a trend to higher hospital survival (85.7% vs 62.2%; $P = .13$). **Conclusion:** In *Legionella* pneumonia complicated by refractory respiratory failure, ECMO support allowed patient stabilization under lung protective ventilation and high survival rates. Timely ECMO referral should be considered for *Legionella* pneumonia failing conventional treatment.

Keywords

acute respiratory distress syndrome, extracorporeal membrane oxygenation, *Legionella* pneumonia

Introduction

Since the first known outbreak in 1976, *Legionella pneumophila* has been recognized as a common agent of severe community-acquired pneumonia.[1] Age, immunosuppression, cigarette smoking, and chronic lung disease are well-known risk factors of disease severity and timely appropriate antibiotic treatment a major determinant of patient outcome.[2,3] The clinical spectrum of the disease may vary from a mild flu-like illness to acute severe respiratory failure with multiple organic failure.[4] In fact, a 33% mortality rate has been reported for patients with *Legionella* pneumonia requiring intensive care unit (ICU) admission.[3]

Extracorporeal membrane oxygenation (ECMO), referring to an extracorporeal circuit that directly oxygenates and removes carbon dioxide from the blood, may be considered

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in refractory respiratory failure when lung-protective positive-pressure ventilation alone is insufficient to maintain adequate gas exchange.[5,6] Recently, there has been increasing interest in ECMO as a result of advances in extracorporeal technology, along with multiple reports of improved survival with ECMO for severe acute respiratory distress syndrome (ARDS).[7-10] In the present study, we review the management and outcome of patients with refractory respiratory failure complicating severe *Legionella* pneumonia rescued with ECMO in our Center.

Methods

An observational study of adult patients with severe respiratory failure treated with ECMO in Hospital S. João (Porto, Portugal) between November 2009 and September 2016 was performed. Hospital S. João is a 1100-bed tertiary university hospital and has the sole ECMO referral center of the north of Portugal, a region with approximately 4 million inhabitants. It has a case volume of 30 to 40 patients per year, being an Extracorporeal Life Support Organization member (center 227). Specific ECMO data were prospectively collected from a dedicated ECMO Program database. Data from clinical records were collected retrospectively. Patients with *Legionella* pneumonia (*Legionella*; n = 14) were compared to patients with other causes of acute severe respiratory failure (other; n = 98; Table 1).

Study Population

Consideration of ECMO for respiratory support was based on the presence of severe but potentially reversible respiratory failure (Murray score ≥3.0 and/or uncompensated hypercapnia with a pH ≤7.20 under protective ventilation) with sustained clinical deterioration despite optimal conventional treatment. Aggressive invasive mechanical ventilation (IMV; plateau pressure ≥30 cmH_2O or fraction of inspired oxygen [Fio_2] ≥0.8) for more than 7 days, uncontrolled active bleeding or other contraindication to limited heparinization, severe comorbidity, or other contraindications to continue active treatment were used as exclusion criteria for ECMO enrollment.

Diagnosis and Treatment of Legionella Infection

Legionella infection was diagnosed by the urinary antigen test in all patients. Fluoroquinolone treatment with levofloxacin (750 mg every day, intravenously [IV] 7-10 days) was the preferred antibiotic regimen and administered in 11 of 14 diagnosed patients. Macrolide treatment with azithromycin (500 mg every day, IV 10 days) was used in 2 patients and clarithromycin (500 mg twice a day, IV 8 days) in 1 patient. One patient received levofloxacin–azithromycin combined therapy. No guidance regarding antibiotic dose adjustments was suggested by the ECMO program.

Table 1. Causes of Acute Severe Respiratory Failure Requiring ECMO Support.

	n (%)
Total	112 (100)
Viral pneumonia	30 (26.8)
Bacterial pneumonia	29 (25.9)
Lung contusion	12 (10.7)
Pneumonia without SPD	8 (7.1)
Extrapulmonary sepsis	7 (6.2)
Pulmonary tuberculosis	6 (5.4)
Interstitial lung disease	6 (5.4)
Severe malaria	4 (3.6)
Diffuse alveolar hemorrhage	4 (3.6)
Organophosphate poisoning	3 (2.7)
Invasive pulmonary aspergillosis	2 (1.8)
Macroaspiration	1 (0.9)

Abbreviations: ECMO, extracorporeal membrane oxygenation; SPD, specific pathogen detected.

Technique of Extracorporeal Support

The venovenous ECMO circuit consisted of 2 venous cannulae, a centrifugal pump, a membrane oxygenator, and 3/8' connecting tubes. For blood outflow from the patient, a femoral vein was cannulated percutaneously using the Seldinger technique with a 38- or 55-cm–long, 23F to 29F heparin-coated cannula (Maquet-Cardiopulmonary-AG, Hirrlingen, Germany). For blood inflow to the patient, a 15-cm–long, 17F to 19F heparin-coated cannula was used, implanted in the right internal jugular vein.

The membrane oxygenators used (PLS-Quadrox or HLS Set Advanced 7.0 from Maquet-Cardiopulmonary-AG or HILITE 7000 LT from Medos Medizintechnik AG, Stolberg, Rheinland, Germany) are made of polymethylpentene and have a total gas exchange surface of 1.8 to 1.9 m2. The centrifugal pumps used were either the Rotaflow, the integrated pump of the HLS Set Advanced 7.0 (both from Maquet-Cardiopulmonary-AG), or the CentriMag (from Thoratec Corporation, Pleasanton, California, US). For interhospital and intrahospital transport of patients, either special handheld adaptors (ELS System from Maquet-Cardiopulmonary-AG and the CentriMag Compact System Transporter from Thoratec Corporation) or the Cardiohelp system (Maquet-Cardiopulmonary-AG) was used. All systems have an integrated battery backup for intrahospital and interhospital transport. When available, an oxygenator water supply unit was used for thermoregulation (Heater Unit 35; Maquet-Cardiopulmonary-AG) at the bedside. The filling volume of the complete device is between 400 and 500 mL, depending on tubing length. Systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time of 1.5 normal. Sweep gas flow consisted exclusively in pure oxygen with a flow of 1 to 12 L/min. Blood gas analysis was performed using the RAPIDLab 1200 Systems (Siemens, Munich, Germany). Pressures on the ECMO circuit, arterial, premembrane and postmembrane blood gas analysis, and general laboratories and complete blood coagulation studies were monitored daily by the ECMO

specialist. Oxygen transfer rate by the ECMO system was calculated daily multiplying the difference between postmembrane and premembrane oxygen blood content by ECMO blood flow.

Patient Management and Weaning From ECMO

After cannulation, patient management was optimized to minimize further ventilator-induced lung injury, according to the standards of our ECMO Center. Pressure control ventilation mode was used with a recommendation for lung rest (tidal volume <4 mL/kg predicted body weight [PBW] and plateau pressure limitation <25 cmH_2O) by the ECMO team. For static RS compliance calculation, end-inspiratory plateau pressure was measured after a 1-second period of no airflow. Recruitment maneuvers and prone position were not routinely performed during ECMO support. Whenever possible, paralysis was withheld, and sedation was reduced to allow spontaneous breathing.

Regarding oxygenation, ECMO blood flow was maximized to reduce Fio_2 <0.6 and maintain hemoglobin saturation >85%. Positive end-expiratory pressure (PEEP) was maintained >8 cmH_2O to avoid lung atelectasis. If severe hypoxemia (Pao_2 <60 mm Hg) still subsisted, the threshold for red blood cell transfusion was elevated from 7.0 to 9.0 g/dL. The threshold for prophylactic platelet transfusion was 30.000/μL, whereas the targeted posttransfusion goal was 100.000/μL in the presence of active bleeding. Regarding CO_2 removal by the ECMO system, sweep gas flow was progressively increased to allow a normal pH and normal $Paco_2$.

As native lung function improved, ECMO blood flow and sweep gas flow were progressively reduced to 2.5 to 3.0 L/min and 1.0 L/min, respectively. Thereafter, sweep gas flow was shut off under Fio_2 <0.5, PEEP <10 cmH_2O, and peak inspiratory pressure <27 cmH_2O. If blood gases remained stable, the ECMO system was removed, and decannulation with skin suture was carried out. An eco-Doppler was routinely performed after decannulation to exclude vascular complications.

Data Collection and Statistical Analysis

The study was approved by the ethics committee of the Hospital S. João. Data from other published cases were duly quoted. Normally distributed data are reported as mean ± standard error of the mean, whereas nonnormally distributed data are reported as median and interquartile range. Comparisons between groups (*Legionella* vs other) were performed using independent-samples *t* test (normally distributed data) or Mann-Whitney *U* test (nonnormally distributed data) for continuous variables, whereas the χ^2 test was used for categorical variables. $P < .05$ was considered statistically significant. For statistical analysis, SPSS version 23.0 (SPSS, Inc, Chicago, Illinois) was used.

Results

Baseline Patient Characteristics

During the time frame of the study, 112 adult patients with acute severe respiratory failure supported with ECMO were included. Of these, 14 had *Legionella* pneumonia (*Legionella* group), whereas the remaining 98 patients had other acute severe respiratory failure causes (other group). Our cohort included mostly relatively young patients without significant comorbidities, as indicated by low Charlson indexes (Table 2).

Male gender preponderance was present in the *Legionella* (92.3%) group but not observed in patients with other causes for acute severe respiratory failure (54.1%). Regarding pre-ECMO course, patients with *Legionella* presented faster clinical deterioration with earlier ECMO support: 3.5 (1.0-6.5) versus 6.5 (3.0-12.5) days from hospital admission to ECMO initiation and 2.5 (1.0-5.0) versus 5.0 (2.0-9.5) days of IMV before ECMO initiation.

Pre-ECMO management was similar in both groups, with the majority of patients treated with neuromuscular blocking agents (100% in *Legionella* vs 95.9% in other) and prone position (92.3% in *Legionella* vs 84.5% in other). Both groups presented similar Simplified Acute Physiology Score II scores on ICU admission as well as similar Sequential Organ Failure Assessment score (SOFA) scores on the day of ECMO implantation. Regarding the severity of acute respiratory failure, no significant differences were detected between groups in Pao_2/Fio_2 (PF) ratio and Murray scores on the day of ECMO implantation nor in Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.

Invasive Mechanical Ventilation Parameters Before and During ECMO

No significant differences in IMV parameters were detected between patients with *Legionella* pneumonia and patients with other causes of acute severe respiratory failure before ECMO implantation (Table 3).

Extracorporeal membrane oxygenation implantation was accompanied by a subsequent reduction in ventilatory parameters such as Fio_2, tidal volume, and plateau pressure, in patients with *Legionella* group presenting higher tidal volumes, minute ventilation, and static RS compliance at ECMO day 1 and ECMO day 7, when compared to other group.

Gas Exchange and ECMO Parameters

There were no significant differences in gas exchange parameters between patients with *Legionella* pneumonia and patients with other causes of acute severe respiratory failure before ECMO implantation (Table 4). Full ECMO support was accompanied by a subsequent improvement in PF ratio, decrease in $Paco_2$, increase in pH, and reduction in blood lactate concentration in both groups. At ECMO day 1, patients with *Legionella* had higher ECMO support, with higher ECMO blood flow and higher sweep gas flow. No significant differences were detected in gas exchange parameters between groups at ECMO day 7.

Table 2. Baseline Patient Characteristics.[a,b]

	Legionella	Other	*P*
n	14	98	-
Age, years	51 (48-56)	45 (35-54)	.044
Male	13 (92.9%)	53 (54.1%)	.007
Charlson Index	1 (1.0-2.0)	0 (0.0-2.0)	.08
Immunocompromised	1 (7.1%)	6 (6.1%)	1.00
Pre-ECMO course			
Hospital to ECMO, days	3.0 (1.0-6.0)	6.5 (3.0-12.5)	.016
IMV to ECMO, days	2.0 (1.0-4.0)	5.0 (2.0-9.5)	.033
Pre-ECMO management			
NMB	14 (100%)	93 (95.9%)	1.00
Prone position	13 (92.9%)	82 (84.5%)	.69
ECMO retrieval	12 (85.7%)	59 (60.2%)	.08
SAPS II	50 (31-59)	46 (35-59)	.95
SOFA	9 (7-11)	9 (7-12)	.65
PF ratio	67 (60-75)	69 (55-85)	.70
Murray score	3.25 (3.00-3.50)	3.25 (3.00-3.50)	.47
RESP score	4 (1-5)	2 (-1-4)	.10

Abbreviations: ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; NMB, neuromuscular blockade; PF ratio, Pao_2/Fio_2; RESP score, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score.
[a]Data are presented as number of cases (%) or median (interquartile range).
[b]SOFA score and PF ratio were calculated in the last day before ECMO implantation. Significant difference between *Legionella* and other when $P < .05$.

Patient Outcomes

Extracorporeal membrane oxygenation-related complications were observed in 21.4% of patients with *Legionella* pneumonia and in 31.6% of patients with other causes of acute severe respiratory failure, without significant differences between groups. The only complication of patients with *Legionella* was cannula-associated thrombosis (Table 5).

Patients with *Legionella* pneumonia had lower ICU nosocomial infections when compared to patients with other causes of acute severe respiratory failure (35.7% vs 64.3%). The most frequent ICU nosocomial infection was ventilator-associated pneumonia.

Regarding patient outcome, no significant differences were detected in ECMO duration, ICU and hospital lengths of stay, and tracheostomy rate between groups. However, patients with *Legionella* pneumonia had lower IMV duration (16 [14-23] vs 27 [20-42] days). A nonstatistically significant trend toward higher hospital survival in patients with *Legionella* pneumonia was also observed (85.7% vs 62.2%; $P = .13$).

Comparative Analysis With Published Case Series

When compared to the Michigan[11] and Leicester[12] case series of patients with *Legionella* pneumonia supported with ECMO,

Table 3. Invasive Mechanical Ventilation Parameters Before and During ECMO.[a]

	Legionella	Other	*P*
Pre-ECMO			
Fio_2 (%)	100 (100-100)	100 (100-100)	.26
PEEP, cmH_2O	14 (10-15)	12 (9-15)	.55
Tidal volume, mL	535 (434-620)	420 (360-500)	.040
Tidal volume/PBW, mL/kg	7.8 (7.14-8.29)	6.8 (5.71-8.21)	.30
Minute ventilation, L/min	10.4 (4.07-11.85)	10.0 (8.16-12.10)	.66
Plateau pressure, cmH_2O	34 (27-36)	32 (29-36)	.73
Static RS compliance, mL/cmH_2O	23.7 (21.5-28.0)	20.0 (15.0-29.7)	.13
ECMO day 1			
Fio_2 (%)	38 (31-50)	50 (40-60)	.040
PEEP, cmH_2O	10 (9-10)	9.5 (8-11)	.60
Tidal volume, mL	312 (227-355)	248 (176-316)	.13
Tidal volume/PBW, mL/kg	5.4 (4.53-6.54)	3.6 (2.66-5.09)	.005
Minute ventilation, L/min	4.5 (3.72-5.90)	3.4 (2.20-5.00)	.046
Plateau pressure, cmH_2O	24 (23-25)	26 (24-28)	.036
Static RS compliance, mL/cmH_20	28.7 (18.8-37.4)	16.0 (10.0-20.8)	.001
ECMO day 7			
Fio_2 (%)	40 (35-50)	50 (40-60)	.19
PEEP, cmH_2O	8 (8-10)	9 (7-10)	.83
Tidal volume, mL	425 (343-460)	225 (150-343)	<.001
Tidal volume/PBW, mL/kg	5.6 (4.50-6.30)	4.1 (2.64-5.89)	.098
Minute ventilation, L/min	5.7 (3.80-6.60)	3.7 (2.40-5.50)	.025
Plateau pressure, cmH_2O	25 (22-27)	26 (24-28)	.14
Static RS compliance, mL/cmH_2O	24.6 (16.8-27.3)	13.7 (10.1-20.9)	.011

Abbreviations: ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RS, respiratory system.
[a]Data are presented as median (interquartile range). Significant difference between *Legionella* and other when $P < .05$.

Table 4. Gas Exchange and ECMO Parameters.[a]

	Legionella	Other	*P*
Pre-ECMO			
Pa_{O_2}/Fi_{O_2}, mm Hg	67 (60-74)	69 (55-85)	.70
Pa_{CO_2}, mm Hg	52 (43-60)	62 (50-75)	.043
pH	7.29 (7.22-7.35)	7.34 (7.25-7.40)	.19
Lactate, mM	2.0 (1.55-2.80)	1.6 (1.14-2.44)	.14
ECMO day 1			
Pa_{O_2}/Fi_{O_2}, mm Hg	194 (148-231)	149 (105-198)	.13
Pa_{CO_2}, mm Hg	40 (35-43)	47 (40-56)	.007
pH	7.39 (7.36-7.45)	7.43 (7.36-7.47)	.25
Lactate, mM	2.0 (1.4-3.0)	1.6 (1.20-2.10)	.22
ECMO blood flow, L/min	5.0 (4.34-5.40)	4.2 (3.60-4.81)	.014
ECMO sweep, L/min	6 (4.50-7.50)	4 (3.50-5.00)	.007
ECMO day 7			
Pa_{O_2}/Fi_{O_2}, mm Hg	176 (124-214)	160 (119-219)	.86
Pa_{CO_2}, mm Hg	45 (39-46)	46 (42-53)	.16
pH	7.44 (7.41-7.44)	7.43 (7.40-7.46)	.91
Lactate, mM	1.2 (1.08-1.68)	1.2 (0.87-1.55)	.41
ECMO blood flow, L/min	4.1 (4.0-5.0)	4.0 (3.27-4.60)	.16
ECMO sweep, L/min	4 (3.8-6.5)	5 (3.0-6.0)	.72

Abbreviations: ECMO, extracorporeal membrane oxygenation; Fi_{O_2}, fraction of inspired oxygen.
[a]Data are presented as median (interquartile range). Significant difference between *Legionella* and other when $P < .05$.

Table 5. Patient Outcomes of Patients Requiring ECMO.[a]

	Legionella	Other	*P*
ECMO-related complications	3 (21.4%)	31 (31.6%)	.55
Cannula-associated thrombosis	3 (21.4%)	22 (22.4%)	–
Intracerebral hemorrhage	0 (0.0%)	4 (4.1%)	–
Ischemic stroke	0 (0.0%)	3 (3.1%)	–
Major bleeding	0 (0.0%)	2 (2.0%)	–
ICU nosocomial infections	5 (35.7%)	63 (64.3%)	.041
Ventilator-associated pneumonia	3 (21.4%)	44 (44.9%)	–
Bacteremia	2 (14.3%)	9 (9.2%)	–
Other	0 (0.0%)	9 (9.2%)	–
ECMO duration, days	9 (7-19)	13 (8-23)	.37
IMV duration, days	16 (14-23)	27 (20-42)	.007
ICU LOS, days	22 (16-44)	29 (20-52)	.33
Hospital LOS, days	25 (14-32)	30 (17-61)	.09
Tracheostomy, n (%)	7 (50.0)	47 (48.0)	.48
Hospital survival, n (%)	12 (85.7)	61 (62.2)	.13

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; SEM, standard error of the mean.
[a]Data are presented as mean ± SEM. Significant difference between *Legionella* and other when $P < .05$.

our cohort presented a similar sample size and patient age. Male gender predominance observed in our case series was also present in Michigan cohort, but not in Leicester's case series (Table 6).

Regarding acute respiratory failure severity before ECMO implantation, our case series presented similar PF ratios and Murray scores to Leicester cohort. Nevertheless, in Leicester cohort, prone position was infrequently used before ECMO implantation (26.3%), whereas in our series, prone position was used in the majority of patients (92.9%) with *Legionella* pneumonia. Extracorporeal membrane oxygenation duration was similar in all case series.

Table 6. *Legionella* Pneumonia and ECMO: Comparative Analysis With Published Case Series.[a]

	Michigan[11]	Leicester[12]	Porto
n	12	19	14
Time period	1994-2006	2000-2010	2009-2016
Age, years	46 (38.5-50.5)	50 (46.5-59)	51 (48-56)
Male	10 (83.3%)	11 (57.9%)	13 (92.9%)
PF ratio	–	66 (53-69)	67 (60-75)
Murray score	–	3.5 (3.5-3.75)	3.25 (3.00-3.50)
Pre-ECMO Prone Position	–	5 (26.3%)	13 (92.9%)
IMV to ECMO, days	1 (1-2.3)	1 (1-2.5)	2 (1.0-4.0)
ECMO duration, days	9 (6-15)	8 (6-10)	9 (7-19)
ICU LOS, days	21 (19-25)	–	22 (16-44)
Tracheostomy	11 (91.7%)	13 (68.4%)	7 (50.0%)
Hospital survival	8 (66.7%)	16 (84.2%)	12 (85.7%)

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; NMB, neuromuscular blockade; PF ratio, Pa_{O_2}/Fi_{O_2}.
[a]Data are presented as number of cases (%) or median (interquartile range).

Regarding patient outcome, 66.7% patients survived hospital discharge in Michigan's series, whereas in Leicester's and our case series, this rate was 84.2% and 85.7%, respectively.

Discussion

In *Legionella* pneumonia complicated by refractory respiratory failure, ECMO support allowed patient stabilization under lung protective ventilation and high survival rates. Timely ECMO referral should be considered for *Legionella* pneumonia failing conventional treatment.

L pneumophila remains a common agent of severe community-acquired pneumonia.[1] In our cohort of patients with severe acute respiratory failure supported with ECMO, *Legionella* pneumonia represented 12% of all cases. In patients requiring ICU admission for *Legionella* pneumonia, a significant mortality is still reported.[3,13,14] In fact, in our cohort, patients with *Legionella* pneumonia presented faster clinical deterioration after hospital admission with earlier ECMO initiation, when compared to patients with other causes of acute respiratory failure and requiring ECMO support. This is in agreement with the Michigan[11] and Leicester[12] cohorts, in which very early ECMO initiation was reported. This difference could not be accounted for by variation in conventional severe acute respiratory failure treatment, given that no significant differences were detected in neuromuscular blockade and prone position use before ECMO implantation between groups. Moreover, PF ratio, Murray score, and SOFA score at the day of ECMO implantation were not different between groups, indicating that identical criteria for ECMO initiation were used.

Therefore, fast clinical deterioration should be anticipated in *Legionella* pneumonia requiring ICU admission and IMV for timely ECMO referral. In fact, early ECMO initiation has been consistently associated with better clinical outcome.[15,16]

In our study, patients with *Legionella* pneumonia presented a trend for higher hospital survival when compared with patients with refractory acute respiratory failure of other etiologies ($P = .13$). This could relate to the considerable heterogeneity of this later group, which includes patients with less reversible acute lung diseases (eg, interstitial lung diseases) requiring prolonged IMV. Accordingly, the incidence of ICU nosocomial infections was lower in *Legionella* pneumonia group, with nearly half the incidence of ventilator-associated pneumonia when compared to the group of patients with acute respiratory failure of other etiologies.

The high hospital survival (86%) in patients with *Legionella* pneumonia rescued with ECMO in our cohort (2012-2016) goes in line with the results observed in the Leicester cohort (2000-2010),[12] whereas in the Michigan cohort (1994-2006), 66.7% of patients survived to hospital discharge. These differences could partially be explained by recent improvements in ECMO technology, more specifically, the use of polymethylpentene oxygenators and centrifugal pumps with higher biocompatibility and durability when compared to older silicon membrane oxygenators and roller pumps.[17,18] This also allows lower blood product consumption as well as reduced circuit component exchange, enhancing the safety profile of modern ECMO support.[19] Moreover, these technological advances were accompanied by a simplification of the circuitry as well as by the recent development of portable miniaturized systems, highly convenient for interhospital and intrahospital transportation of patients while on ECMO.[20-22] Patient management during ECMO support has also been suggested to importantly determine clinical outcome. Particularly, mechanical ventilation during ECMO support received growing attention.[23,24] In our cohort, ECMO implantation was accompanied by a substantial reduction of IMV parameters, namely with tidal volume, plateau pressure, and driving pressure limitation, while maintaining relatively high PEEP. This ventilatory strategy has been associated to improved outcomes in recent studies using ECMO for severe ARDS.[7,24,25] Finally, the results of the present study may not be transferable to a lower volume ECMO center.[26,27]

Limitations of the Present Study

In the present study, the etiologies of acute respiratory failure in patients without *Legionella* pneumonia (other group) were highly heterogeneous, limiting the statistical accuracy of *t* test for independent data given the wide difference in sample size between groups (14 patients in "*Legionella*" group vs 98 patients in "other" group).

Declaration of Conflicting Interests

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2.4. PaO_2/FiO_2 Deterioration During Stable ECMO Associates With Protracted Recovery and Increased Mortality in Severe ARDS.

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PaO_2/FiO_2 Deterioration During Stable Extracorporeal Membrane Oxygenation Associates With Protracted Recovery and Increased Mortality in Severe Acute Respiratory Distress Syndrome

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Background. During extracorporeal membrane oxygenation (ECMO), arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF ratio reflects native and artificial lung blood oxygenation). In this study we analyzed PF ratio during ECMO support and its association with clinical outcome.

Methods. This was a single-center observational study of adult patients (n = 81) undergoing veno-venous ECMO support for severe acute respiratory distress syndrome.

Results. In 37 patients (46%) PF ratio decreased from ECMO-day 1 to ECMO-day 7 (PF ratio deterioration [PF-d]; −37 ± 6.1 mm Hg), whereas in 44 patients PF ratio improved (PF-i; 65 ± 10.8 mm Hg). PF-d group required prolonged ECMO (median 21 days [interquartile range (IQR)]:14–35 days] versus 13 days [IQR: 10–20 days]) and invasive mechanical ventilation (median 33 days [IQR: 24–52 days] versus 26 days [IQR: 22–34 days]), longer intensive care unit (median 44 days [IQR: 32–74 days] versus 30 days [IQR: 25–47 days]), and hospital (median 66 days [IQR: 39–95 days] versus 36 days [IQR: 28–54 days]) lengths of stay, with higher hospital mortality rates (48.7% versus 22.7%). ECMO oxygenation did not explain PF ratio variation that remained stable in PF-d and decreased in PF-i (198 ± 12.7 mL/min versus 171 ± 8.8 mL/min). Pre-ECMO PF ratio, neuromuscular blockade, and prone position, as well as ventilatory variables did not differ between groups. The PF-d group was older (49 ± 2.1 years versus 41 ± 1.8 years) and presented lower Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) scores (0.57 ± 0.63 versus 2.2 ± 0.52). With the use of logistic regression, PF ratio variation remained an independent predictor of hospital mortality after adjusting for age or RESP score.

Conclusions. In severe acute respiratory distress syndrome, PF ratio deterioration during stable ECMO associates with protracted recovery and increased mortality, not accounted for by patient baseline characteristics, acute respiratory distress syndrome severity, or pre-ECMO management.

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Extracorporeal membrane oxygenation (ECMO) is a resource-intensive technique [1, 2], increasingly used in refractory severe acute respiratory distress syndrome (ARDS) [3, 4]. Recently, several scores have been developed to predict mortality in severe acute respiratory failure before ECMO initiation [5–8]. Despite the usefulness of these established pre-ECMO risk scores, data are still lacking on variables that could stratify patients after ECMO initiation and therefore assist clinical decision making during ECMO support. This could be particularly relevant if we take into account that, although recent technologic advances increased the feasibility, and therefore the prevalence, of long ECMO runs [9, 10], prolonged ECMO support for adult respiratory failure still associates with high mortality [11].

Despite the widespread use of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF ratio) as a simple index of hypoxemia to diagnose and grade ARDS severity [12], its prognostic

The Appendix and Supplemental Tables can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2016.06.026] on http://www.annalsthoracicsurgery.org.

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utility in patients requiring ECMO support remains unknown. Importantly, in these patients, PF ratio reflects native lung function as well as artificial lung support. For each hemoglobin concentration, blood oxygenation by modern artificial lungs is mainly determined by ECMO circuit blood flow as well as by the fraction of oxygen in the sweep gas ventilating the artificial lung [13, 14]. The type of circuit can also influence blood oxygenation, with blood recirculation in the ECMO circuit constituting a potential limitation for blood oxygenation when a veno-venous ECMO (VV-ECMO) configuration is used [15]. In severe ARDS patients with residual native lung function undergoing VV-ECMO, cardiac output is also an important determinant of arterial blood oxygenation. In these patients, when cardiac output considerably increases during stable VV-ECMO blood flows (eg, hyperdynamic septic shock), PF ratio decreases as a result of a reduction in the ratio between the blood oxygenated by the artificial lung and the patients' venous blood [16, 17]. Notwithstanding its multifactorial nature, PF ratio variations in the same patient during stable VV-ECMO support may reflect changes in native lung oxygenation with prognostic relevance.

In the present study, we analyzed PF ratio variation during the first 7 days of VV-ECMO support for adult severe ARDS and its association with ECMO blood oxygenation, respiratory mechanics, and clinical outcome. We hypothesize that PF ratio deterioration during stable ECMO blood oxygenation would associate with protracted lung recovery and increased mortality.

Patients and Methods

An observational study of adult patients with severe respiratory failure treated with VV-ECMO for more than 7 days in Hospital S. João (Porto, Portugal) between November 2009 and September 2015 was performed.

Patients were divided in two groups in accordance with PF ratio deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support. More specifically, in the PF-d group the PF ratio at ECMO-day 7 compared with the PF ratio at ECMO-day 1 was less than 1, whereas in the PF-i group the PF ratio at ECMO-day 7 compared with PF ratio at ECMO-day 1 was greater than 1. PF ratio for each time point was obtained using the values of PaO_2 and FiO_2 obtained during the daily circuit monitoring by the ECMO specialist.

Study Population and Technique of Extracorporeal Support

A detailed description of the studied population and technique of extracorporeal support, as described previously [18], is provided in the Supplemental Methods section of the Appendix.

Data Collection and Statistical Analysis

The Ethics Committee of the Hospital S. João approved the study and waived the requirement for patient consent. Normally distributed data are reported as mean ± standard error of the mean, whereas nonnormally distributed data are reported as median and interquartile range. Comparisons between groups (PF-d versus PF-i) were performed using independent-samples t test (normal distributed data) or Mann-Whitney U test (nonnormal distributed data) for continuous variables, whereas the χ^2 test was used for categorical variables. In Tables 2 and 3 comparisons between different time points (pre-ECMO, ECMO-day 1, ECMO-day 3, and ECMO-day 7) were performed using repeated-measures analysis of variance. In Table 5 logistic regression was performed with hospital mortality as outcome and different PF ratios as potential explanatory variables. In Table 6 and Supplemental Table 6 the independence of the association between (PF-d versus PF-i) PF ratio, age, and Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score in clinical outcome was tested using bivariate linear and logistic regression. In Figure 1, the p value of the Kaplan-Meier curve was calculated by means of the log-rank test. A p value less than .05 was considered statistically significant. For statistical analysis, SPSS 23.0 (SPSS, Inc, Chicago, IL) was used.

Results

Baseline Patient Characteristics

During the time frame of the study, 81 adult patients with severe ARDS supported with VV-ECMO for 7 days or more were included (Table 1). In 44 patients (54.3%) PF ratios improved in the first 7 days of ECMO support (PF-i), whereas in 37 patients (45.7%) PF ratios deteriorated in the same period (PF-d).

Our cohort included mostly relatively young patients without significant comorbidities, as indicated by low Charlson indexes. Notwithstanding, PF-d patients were older than patients in the PF-i group. However, using univariate logistic regression, patient age did not predict hospital mortality (Supplemental Table 1), ventilator parameters (Supplemental Table 2) or gas exchange and ECMO parameters (Supplemental Table 3). No significant differences were observed between groups in ARDS cause or in the pre-ECMO use of neuromuscular blockade and prone position. Both groups presented similar Simplified Acute Physiology II and Sequential Organ Failure Assessment scores. However, the PF-d group presented lower RESP scores (0.57 ± 0.63) compared with the PF-i group (2.2 ± 0.52).

Ventilatory Variables Before and During Initial ECMO Support

No significant differences were detected in baseline ventilatory variables between groups in the last day before ECMO implantation (Table 2).

ECMO implantation was accompanied by a significant reduction in ventilatory variables. To ascertain if there was a time/era effect in the ventilatory strategy during ECMO support, a regression analysis of ECMO and ventilation variables using year of ECMO as an independent predictor was performed (Supplemental

Table 1. Baseline Characteristics of Patients Requiring ECMO for Severe ARDS

Variable	All	PF-i	PF-d	*p* Value
No. of patients	81	44 (54.3)	37 (45.7)	…
Age, years	44 ± 1.4	41 ± 1.8	49 ± 2.1	0.005
Male sex	44 (54.3)	23 (52.3)	21 (56.8)	0.69
Charlson Index	0.80 ± 0.123	0.60 ± 0.129	1.03 ± 0.216	0.09
Type of ARDS				
Pulmonary/nonpulmonary	75 (93)/6 (7)	41 (93)/3 (7)	34 (92)/3 (8)	0.82
Cause of ARDS				
Viral pneumonia	21 (25.9)	14 (31.8)	7 (18.9)	0.19
Bacterial pneumonia	21 (25.9)	11 (25.0)	10 (27.0)	0.84
Lung contusion	7 (8.6)	2 (4.5)	5 (13.5)	0.24
Pneumonia without SPD	6 (7.4)	3 (6.8)	3 (8.1)	0.83
Extrapulmonary sepsis	5 (6.2)	3 (6.8)	2 (5.4)	0.79
Other	21 (25.9)	11 (25.0)	10 (27.0)	0.84
Pre-ECMO course, days				
Hospital to ECMO	8.1 ± 1.10	7.7 ± 1.42	8.6 ± 1.77	0.69
IMV to ECMO	5.6 ± 0.61	5.3 ± 0.84	6.1 ± 0.89	0.55
Pre-ECMO management				
NMB	78 (96.3)	44 (100)	34 (91.9)	0.09
Prone position	67 (82.7)	37 (84.1)	30 (81.1)	0.72
ECMO retrieval	54 (66.7)	30 (68.2)	24 (64.9)	0.75
SAPS II	45.7 ± 1.85	43.6 ± 2.38	48.4 ± 2.88	0.20
SOFA	10.8 ± 0.47	10.7 ± 0.55	10.9 ± 0.85	0.77
PF ratio	72 ± 2.8	71 ± 4.2	72 ± 3.3	0.80
Murray's score	3.2 ± 0.06	3.2 ± 0.08	3.1 ± 0.09	0.32
RESP score	1.5 ± 0.41	2.2 ± 0.52	0.57 ± 0.63	0.04

Data are presented as number of patients (%) or mean ± SEM. SOFA score and PF ratio were calculated in the last day before ECMO implantation.

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; IMV = invasive mechanical ventilation; NMB = neuromuscular blockade; PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PF ratio = PaO_2/FiO_2; RESP = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; SAPS II = Simplified Acute Physiology Score II; SEM = standard error of the mean; SOFA = Sequential Organ Failure Assessment; SPD = specific pathogen detected.

Table 4). We could observe a time/era effect, with positive end-expiratory pressure (PEEP) increasing, whereas tidal volume/predicted body weight (PBW) as well as plateau pressure decreased during the time frame of the study.

The reduction in ventilatory variables after ECMO initiation was similar in both groups, with no significant differences between groups in ECMO-day 1 and ECMO-day 3.

However, at the end of the first week of ECMO support (ECMO-day 7) the PF-i group presented lower FiO_2, higher tidal volumes (and higher tidal volumes/PBW), and increased static RSc (respiratory system compliance), compared with the PF-d group.

Gas Exchange and ECMO Variables Before and During Initial ECMO Support

No significant differences were detected in gas exchange variables before ECMO implantation between the PF-d and PF-i groups (Table 3).

ECMO support was accompanied by a subsequent improvement in PF ratio, decrease in $PaCO_2$, and increase in pH in ECMO-day 1. Gas exchange variables, blood lactate concentration, and ECMO support settings were similar in the PF-i and PF-d groups in ECMO-day 1 and ECMO-day 3.

In the PF-d group, ECMO oxygen transfer remained stable between ECMO-day 1 and ECMO-day 7, whereas it decreased in the PF-i group.

ECMO-Related Complications and ICU Nosocomial Infections

ECMO-related complications were observed in 27.2% of patients, with no significant differences observed between the PF-i and PF-d groups (Table 4 and Supplemental Table 5). The main ECMO-related complications observed were cannula-associated thrombosis (16.0%), intracerebral hemorrhage (4.9%), ischemic stroke (3.7%), and major bleeding (2.5%). We observed a prevalence of 7.6 cannula-associated thrombosis per 1000 cannula days.

Intensive care unit (ICU) nosocomial infections were diagnosed in 60.5% of patients, with no significant differences observed between the PF-i and PF-d groups. The most frequent ICU nosocomial infections were ventilator-associated pneumonia (45.7%) and bacteremia (9.9%).

Table 2. Ventilatory Variables Before and During ECMO Support

Variable	All	PF-i	PF-d
Pre-ECMO			
FiO_2, %	95 ± 1.4	97 ± 1.7	93 ± 2.2
PEEP, cm H_2O	12.0 ± 0.48	11.6 ± 0.74	12.4 ± 0.58
Tidal volume, mL	470 ± 21	469 ± 37	471 ± 19
Tidal volume/PBW, mL/kg	7.4 ± 0.31	7.5 ± 0.52	7.3 ± 0.31
Minute ventilation, L/min	11.1 ± 0.69	11.0 ± 0.92	11.2 ± 1.06
Plateau pressure, cm H_2O	33.0 ± 0.96	34.4 ± 1.37	31.1 ± 1.2
Static RS compliance, mL/cm H_2O	26.7 ± 2.31	23.5 ± 2.28	30.5 ± 4.16
ECMO day 1			
FiO_2, %	53 ± 2.1[a]	54 ± 3.2[a]	52 ± 2.8[a]
PEEP, cm H_2O	9.5 ± 0.31[a]	9.6 ± 0.47	9.5 ± 0.41[a]
Tidal volume, mL	251 ± 13[a]	241 ± 17[a]	263 ± 19[a]
Tidal volume/PBW, mL/kg	4.2 ± 0.21[a]	4.1 ± 0.31[a]	4.3 ± 0.29[a]
Minute ventilation, L/min	4.3 ± 0.58[a]	3.6 ± 0.32[a]	5.1 ± 1.24
Plateau pressure, cm H_2O	25.5 ± 0.43[a]	25.6 ± 0.49[a]	25.5 ± 0.74[a]
Static RS compliance, mL/cm H_2O	17.7 ± 1.07[a]	17.0 ± 1.55[a]	18.4 ± 1.45
ECMO day 3			
FiO_2, %	54 ± 4.2[a]	55 ± 7.6[a]	53 ± 2.9[a]
PEEP, cm H_2O	9.4 ± 0.31[a]	9.5 ± 0.47	9.2 ± 0.39[a]
Tidal volume, mL	262 ± 14[a]	264 ± 18[a]	258 ± 20[a]
Tidal volume/PBW, mL/kg	3.7 ± 0.21[a]	3.5 ± 0.27[a]	4.0 ± 0.31[a]
Minute ventilation, L/min	3.5 ± 0.23[a]	3.3 ± 0.31[a]	3.7 ± 0.33[a]
Plateau pressure, cm H_2O	25.8 ± 0.32[a]	25.5 ± 0.46[a]	26.1 ± 0.44[a]
Static RS compliance, mL/cm H_2O	14.6 ± 0.88[a]	13.8 ± 1.16[a]	15.6 ± 1.34[a]
ECMO day 7			
FiO_2, %	50 ± 1.8[a]	45 ± 1.9[a,b,c]	56 ± 3.1[a,d]
PEEP, cm H_2O	8.7 ± 0.31[a,c]	8.8 ± 0.42[a,c]	8.8 ± 0.46[a]
Tidal volume, mL	285 ± 14[a]	312 ± 19[a]	251 ± 20[a,d]
Tidal volume/PBW, mL/kg	4.7 ± 0.24[a]	5.2 ± 0.34[a,b]	4.2 ± 0.32[a,d]
Minute ventilation, L/min	4.6 ± 0.30[a]	4.7 ± 0.36[a]	4.3 ± 0.49[a]
Plateau pressure, cm H_2O	25.9 ± 0.40[a]	25.6 ± 0.54[a]	26.2 ± 0.61[a]
Static RS compliance, mL/cm H_2O	18.3 ± 1.29[a]	20.8 ± 1.95	14.9 ± 1.27[a,d]

[a] $p < .05$ versus pre-ECMO. [b] $p < .05$ versus ECMO day 1. [c] $p < .05$ versus ECMO day 3. [d] $p < .05$ versus PF-i.

Data are presented as mean ± SEM.

ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = arterial oxygen partial pressure; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RS = respiratory system; SEM = standard error of the mean.

PF Ratio and Clinical Outcome

PF ratio before ECMO implantation, at ECMO-day 1, at ECMO-day 3 and at ECMO-day 7 did not predict hospital mortality (Table 5). However, PF ratio (PF-d versus PF-i) variation during the first week of ECMO support significantly predicted hospital mortality (Table 5; Fig 1).

Moreover, the PF-d group presented significantly longer duration of ECMO support and invasive mechanical ventilation, higher tracheostomy rate in survivors, and longer ICU and hospital length of stay compared with the PF-I group (Table 4 and Supplemental Table 5).

Bivariate regression analysis was performed to test for independence of (PF-i/PF-d) PF ratio in patient outcome. Given that age is itself a variable included in the RESP score, two different bivariate models were constructed for each clinical outcome variable: model I with (PF-i/PF-d) PF ratio and age and model II with (PF-i/PF-d) PF ratio and RESP score. With the use of both model I and model II, clinical outcome could not be accounted for by differences in age or RESP score, respectively, whereas (PF-i/PF-d) PF ratio remained an independent predictor of clinical outcome (Table 6; Supplemental Table 6).

Comment

In adult severe ARDS requiring ECMO support, PF ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery, and increased mortality.

In our study, PF ratio at different time points during ECMO support for severe ARDS did not associate with

Table 3. Gas Exchange and ECMO Variables Before and During ECMO

Variable	All	PF-i	PF-d
Pre-ECMO			
PaO_2/FiO_2, mm Hg	72 ± 2.8	71 ± 4.2	72 ± 3.3
$PaCO_2$, mm Hg	65 ± 2.7	63 ± 3.1	68 ± 4.7
pH	7.31 ± 0.016	7.32 ± 0.019	7.30 ± 0.027
Lactate, mmol/L	2.3 ± 0.27	2.1 ± 0.22	2.5 ± 0.56
ECMO day 1			
PaO_2/FiO_2, mm Hg	150 ± 6.8[a]	139 ± 9.0[a]	162 ± 10.1[a]
$PaCO_2$, mm Hg	48 ± 1.3[a]	46 ± 1.7[a]	49 ± 2.1[a]
pH	7.42 ± 0.009[a]	7.44 ± 0.012[a]	7.41 ± 0.014[a]
Lactate, mmol/L	2.3 ± 0.35	2.0 ± 0.22	2.6 ± 0.71
ECMO blood flow, L/min	4.4 ± 0.10	4.5 ± 0.15	4.2 ± 0.14
ECMO O_2 transfer, mL/min	194 ± 8.6	198 ± 12.7	190 ± 11.2
ECMO sweep, L/min	4.8 ± 0.24	5.1 ± 0.32	4.5 ± 0.35
ECMO day 3			
PaO_2/FiO_2, mm Hg	145 ± 6.0[a]	153 ± 8.7[a]	137 ± 7.9[a,b]
$PaCO_2$, mm Hg	47 ± 1.1[a]	47 ± 1.4[a]	46 ± 1.6[a]
pH	7.40 ± 0.044[a]	7.44 ± 0.008[a]	7.34 ± 0.10[a,b]
Lactate, mmol/L	1.8 ± 0.15	1.7 ± 0.21[b]	1.9 ± 0.20
ECMO blood flow, L/min	4.2 ± 0.11	4.2 ± 0.17[b]	4.2 ± 0.15
ECMO O_2 transfer, mL/min	195 ± 6.0	197 ± 8.0	193 ± 9.3
ECMO sweep, L/min	5.1 ± 0.26	5.0 ± 0.32	5.2 ± 0.41[b]
ECMO day 7			
PaO_2/FiO_2, mm Hg	168 ± 8.6[a,c]	204 ± 12.0[a,b,c]	126 ± 7.7[a,b,c,d]
$PaCO_2$, mm Hg	47 ± 0.8[a]	46 ± 1.0[a]	47 ± 1.3[a]
pH	7.42 ± 0.008[a]	7.41 ± 0.013[a]	7.44 ± 0.008[a,b]
Lactate, mmol/L	1.3 ± 0.068[a,c]	1.2 ± 0.10[a,b,c]	1.3 ± 0.085[c]
ECMO blood flow, L/min	3.9 ± 0.10	3.7 ± 0.14[b,c]	4.3 ± 0.13[d]
ECMO O_2 transfer, mL/min	178 ± 6.4[c]	171 ± 8.8[b,c]	187 ± 9.1
ECMO sweep, L/min	4.9 ± 0.25	4.5 ± 0.34	5.4 ± 0.35

[a] $p < .05$ versus pre-ECMO. [b] $p < .05$ versus ECMO day 1. [c] $p < .05$ versus ECMO day 3. [d] $p < .05$ versus PF-i.

Data are presented as mean ± SEM.

ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; SEM = standard error of the mean; Sweep = sweep gas flow.

hospital mortality. This could relate to the multifactorial nature of PF ratio in patients during ECMO support, reflecting blood oxygenation by both native and artificial lungs [13, 14]. Accordingly, the increase in PF ratio observed early after ECMO implantation (pre-ECMO versus ECMO-day 1) most probably reflects ECMO blood oxygenation, not native lung function recovery.

However, PF ratio variation during the first week of ECMO support was associated with clinical outcome. Patients in the PF-d group required prolonged ECMO support and invasive mechanical ventilation, required longer ICU and hospital lengths of stay, and presented higher hospital mortality compared with the PF-i group. PF ratio variation within the first week of ARDS diagnosis was also found to have prognostic significance in patients treated without ECMO. Bone and colleagues [19] analyzed PF ratio and its early response to conventional therapy in the placebo group of a large multicenter study. PF ratio was not different at the time of diagnosis of ARDS in survivors compared with nonsurvivors. After 1 day of conventional therapy, including PEEP, those patients who survived increased their PF ratio, whereas nonsurvivors did not improve over a 7-day course. Villar and colleagues [20] demonstrated that the use of standardized ventilator settings in the first 24 hours after ARDS onset improved PF ratio in a significant proportion of patients, with 61.3% of patients with severe ARDS to be reclassified as moderate, mild, and non-ARDS. Moreover, this ARDS reclassification improved PF ratio risk stratification.

Importantly, PF ratio variation in the PF-d and PF-i groups could not be accounted for by differences in ECMO blood oxygenation. In fact, ECMO oxygen transfer remained stable between ECMO-day 1 and ECMO-day 7 in PF-d, whereas in PF-i ECMO blood oxygenation even decreased during this period. By comparing PF ratios of the same patient in different time points that could not be accounted for by differences in ECMO blood

Table 4. Outcome of Patients Requiring ECMO for Severe ARDS

Variable	All	PF-i	PF-d	*p* Value
ECMO-related complications	22 (27.2)	10 (22.7)	12 (32.4)	0.33
Cannula-associated thrombosis	13 (16.0)	7 (15.9)	6 (16.2)	0.97
Intracerebral hemorrhage	4 (4.9)	1 (2.3)	3 (8.1)	0.33
Ischemic stroke	3 (3.7)	1 (2.3)	2 (5.4)	0.59
Major bleeding	2 (2.5)	1 (2.3)	1 (2.7)	0.90
ICU nosocomial infections	48 (59.3)	25 (56.8)	23 (62.2)	0.78
Ventilator-associated pneumonia	37 (45.7)	18 (40.9)	19 (51.4)	0.35
Bacteremia	8 (9.9)	4 (9.1)	4 (10.8)	0.80
Other	3 (3.7)	3 (6.8)	0 (0.0)	0.25
ECMO duration, days	16 (11–28)	13 (10–20)	21 (14–35)	0.003
IMV duration, days	28 (22–42)	26 (22–34)	33 (24–52)	0.043
ICU LOS, days	37 (25–56)	30 (25–47)	44 (32–74)	0.033
Hospital LOS, days	45 (32–70)	36 (28–54)	66 (39–95)	0.018
Tracheostomy in survivors, %	31 (57.4)	15 (44.1)	16 (80.0)	0.010
Hospital mortality, %	28 (34.6)	10 (22.7)	18 (48.7)	0.015

Data are presented as number of patients (%) or median (interquartile range).

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; LOS = length of stay; PF-d = deterioration of ratio of arterial oxygen partial pressure to fractional inspired oxygen in the first 7 days of ECMO support; PF-i = improvement of ratio of arterial oxygen partial pressure to fractional inspired oxygen in the first 7 days of ECMO support.

oxygenation, PF ratio variation could importantly reflect the initial impact of ECMO treatment on native lung function. In fact, VV-ECMO support allowed a substantial reduction in tidal volume, plateau pressure, and FiO_2 beyond conventional protective ventilation settings, which has been suggested to enhance lung protection in ARDS [21, 22]. Accordingly, the PF-i group presented improved respiratory system mechanics with higher tidal volumes and improved static RSc at ECMO-day 7, compared with the PF-d group. These differences in respiratory system mechanics most probably do not relate with differences in lung recruitment, given that PEEP and plateau pressure did not significantly differ between PF-i and PF-d at ECMO-day 7. Moreover, our results suggest that ventilatory strategies during initial ECMO support that avoid lung atelectasis could improve the outcome of ARDS patients. This goes in line with recent recommendations on mechanical ventilation during ECMO support, underlying the role of higher PEEP levels to avoid atelectasis and associated severe ventilation/perfusion mismatch under low tidal volume and plateau pressure limitation [23]. Finally, our results suggest PF ratio variation during initial ECMO support for severe ARDS as a surrogate end point to ascertain the potential of any novel therapeutic intervention.

In septic patients undergoing VV-ECMO support, PF ratio can decrease as a result of a substantial cardiac output increase that reduces the ratio between the blood oxygenated by the artificial lung and the patients' venous blood [16, 17]. Although in the present study cardiac output was not assessed, hyperdynamic septic shock most probably did not explain PF ratio reduction

Table 5. Univariate Logistic Regression With Hospital Mortality As Outcome and Different PF Ratios as Potential Explanatory Variables

Hospital Mortality	OR (95% CI)	*p* Value
PF ratio: pre-ECMO	0.99 (0.978–1.006)	0.26
PF ratio: ECMO day 1	1.00 (0.998–1.012)	0.18
PF ratio: ECMO day 3	1.00 (0.997–1.012)	0.23
PF ratio: ECMO day 7	1.01 (0.999–1.012)	0.10
(PF-i/PF-d) PF ratio	3.22 (1.239–8.374)	0.016

Patients were divided into two groups in accordance with PF ratio deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support.

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; PF ratio = ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table 6. Bivariate Binary Logistic Regression Models With Hospital Mortality as Outcome

Hospital Mortality	OR (95% CI)	*p* Value
Model I		
Age, years	0.98 (0.944–1.024)	0.40
(PF-i/PF-d) PF ratio	2.83 (1.032–7.771)	0.043
Model II		
RESP score	1.01 (0.881–1.160)	0.88
(PF-i/PF-d) PF ratio	2.73 (1.009–7.386)	0.048

Patients were divided in two groups in accordance with PF ratio improvement (PF-i) or deterioration (PF-d) in the first 7 days of ECMO support.

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; PF ratio = ratio of arterial oxygen partial pressure to fractional inspired oxygen; RESP Score = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.

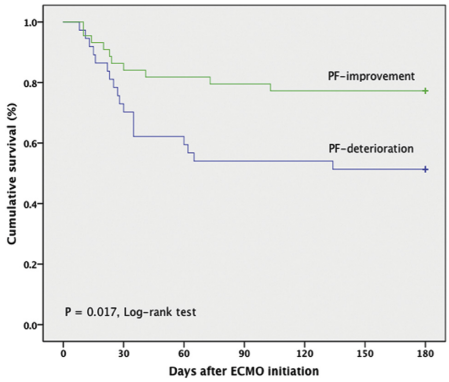

Fig 1. Kaplan-Meier cumulative probabilities of survival after extracorporeal membrane oxygenation (ECMO) initiation for severe acute respiratory distress syndrome. Patients with arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF) improvement during the first 7 days of ECMO support (PF-improvement; green line; n = 44) presented higher cumulative survival compared with patients presenting PaO_2/FiO_2 deterioration (PF-deterioration; blue line; n = 37). The p value was calculated by means of the log-rank test.

in the PF-d group, given the significant decrease in arterial blood lactate observed between ECMO-day 1 and ECMO-day 7.

In our cohort of mostly relatively young adult patients without significant comorbidities no significant differences were found between the PF-d and PF-i groups in most baseline patient characteristics, ARDS cause, ARDS and ICU severity scores, and in pre-ECMO management. However, PF-d patients were older compared with the PF-i group. Age has been consistently shown to be an independent predictor of death in ARDS [24, 25], and it has been incorporated in ECMO survival prediction scores for severe acute respiratory failure such as PRESERVE (Predicting Death for Server ARDS on VV-ECMO), RESP, and the hospital mortality score proposed by Roch and colleagues [6, 8, 26]. This could account, at least in part, to lower RESP scores observed in the PF-d group. Importantly, the PF-d group presented more than double hospital mortality compared with PF-i that could not be anticipated by the observed differences in RESP scores. In fact, when bivariate regression was performed, the RESP score could not account for differences in several clinical outcome variables, whereas PF ratio variation in the first week of ECMO support remained a predictor of clinical outcome.

We could not observe a significant difference in ECMO-related complications between the PF-d and PF-i groups. The prevalence of cannula-associated thrombosis agrees well with the one reported recently by Cooper and colleagues [27] in patients with severe respiratory failure after VV-ECMO. Regarding neurologic complications, its occurrence was comparable with that reported in recent studies [28, 29].

In conclusion, in adult patients with severe ARDS, PF ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery, and increased mortality. PF ratio monitoring could therefore represent a simple tool to stratify patients with severe ARDS during ECMO support.

The present study has a relatively small sample size, which importantly limits its internal and external validity. Moreover, the PF-i and PF-d groups are not completely balanced in the indications for ECMO support, which may be affecting survival (and PF ratio change).

A time/era effect in the mechanical ventilation strategy during ECMO support was also observed, probably reflecting progressively increased compliance to lung rest ventilatory settings during VV-ECMO support in the time frame of the study.

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INVITED COMMENTARY

Dr Roncon-Albuquerque, Jr and colleagues [1] evaluated the effect of changes in Pao_2/Fio_2 (P/F) ratios between day 1 and day 7 after the institution of venous-venous (VV) extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome. They demonstrated a marked difference in patient outcomes for patients presenting an improving P/F ratio in1 week versus a decreasing P/F, eg, mortality was significantly decreased with an improving P/F ratio (22% versus 48%). Many factors can affect systemic blood oxygenation during VV ECMO. Among the most important are ECMO flow versus cardiac output and the residual lung function contribution. Other factors include recirculation (fraction of oxygenated circuit blood drained back to the circuit by the drainage cannula), body temperature, and oxygen extraction rate. The main message of this study is that the P/F ratio during the first week of an ECMO run can have significant prognostic value. However, it is likely that this is simply a representation of patients with less severe lung injury, leading to a more rapid recovery of native lung function. However, other important patient factors, such as absence of sepsis and therefore a less hyperdynamic patient (increased ratio between the blood oxygenated by the artificial lung and the patients' venous blood), may play a role in both the P/F ratio and final patient outcomes. Although the relatively low number of patients is a weakness of this study, the single-institution, well-standardized ventilation protocols before and after ECMO and consistent ECMO techniques (dual-cannula VV) and management add significant value to the findings. Once this is confirmed in a larger number of patients, the variation of P/F ratio in the first week after the institution of VV ECMO could be used as a simple prognostic marker that could aid not only in informing the patient's family of his or her ultimate chance of recovery but also in the prediction of hospital resource use. Finally, it can also be used to stratify more equal groups for novel therapeutic trials in ECMO for acute respiratory distress syndrome.

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2.5. Bleeding and Thrombotic Complications in COVID-19-Associated ARDS Requiring ECMO.

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Bleeding and Thrombotic Complications in COVID-19–Associated ARDS Requiring ECMO

Eduardo P Tavares, José R Rebolo, Rodrigo Pimentel, and Roberto L Roncon-Albuquerque Jr

BACKGROUND: We analyzed bleeding and thrombotic complications in COVID-19–associated ARDS requiring extracorporeal membrane oxygenation (ECMO). METHODS: This was a single-center observational study of adult subjects undergoing ECMO for COVID-19 ($n = 67$) or all other cause of ARDS ($n = 60$), excluding trauma patients. RESULTS: In the COVID-19 group, duration of invasive mechanical ventilation prior to ECMO was lower (2 [0–4] d vs 3 [1–6] d) and ECMO retrieval less frequent (71% vs 87%). No significant differences were found in Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation II (APACHE II), or in the in-hospital survival predicted by the Respiratory ECMO Survival Prediction score. During the first 7 d of ECMO support, the COVID-19 group presented higher platelets and fibrinogen, lower activated partial thromboplastin time, but no differences in D-dimer. Thrombotic complications were similar between groups. Higher rates of severe bleeding, namely airway bleeding (37.3% vs 15.0%) and hemothorax (13.4% vs 3.3%), were found in COVID-19, with lower hemoglobin and higher red blood cell transfusions. COVID-19 ARDS was associated with longer ECMO duration (47 [17–80] d vs 19 [12–30] d) and absence of a statistically significant difference concerning in-hospital mortality. CONCLUSIONS: COVID-19–associated ARDS requiring ECMO presented high rates of severe bleeding complications and a protracted course. Further studies are needed to clarify the risks and benefits of ECMO in severe COVID-19–associated ARDS. *Key words: ARDS; COVID-19; bleeding; thrombosis; extracorporeal membrane oxygenation.* [Respir Care 2023;68(5):575–581. © 2023 Daedalus Enterprises]

Introduction

COVID-19 can lead to severe ARDS. Extracorporeal membrane oxygenation (ECMO) may be considered in refractory respiratory failure when positive-pressure ventilation alone is insufficient to maintain adequate gas exchange or when adherence to lung-protective ventilation strategies and prone position results in unacceptable levels of hypoxemia and respiratory acidosis.[1] From the beginning of the pandemic, ECMO has been used in refractory severe COVID-19–associated ARDS,[2,3] with a recent systematic review describing a ~7% use rate, with overall in-hospital mortality of 39%.[4]

However, ECMO is a resource-intensive and invasive technique with a procoagulant effect[5] and major bleeding and thrombotic complications. This could be particularly relevant given that severe COVID-19 is an acute inflammatory disease and hypercoagulable state, with endothelial injury[6-8] and increased circulating prothrombotic factors.[9-11] This COVID-19–associated coagulopathy is characterized by a high rate of thrombotic events.[12-15] Bleeding, despite being less frequent, still occurs in ~30% of subjects,[12,13,16] having a greater impact than thrombosis in the mortality of ECMO subjects.[12,17] This finding is in line with pre-pandemic data on subjects receiving ECMO for ARDS of other causes.[18]

In this context, to better ascertain the potential benefits and risks associated with ECMO use in severe COVID-19, the aim of the present study was to compare the incidence of thrombotic and hemorrhagic complications between subjects with COVID-19 and non–COVID-19 subjects with severe ARDS requiring ECMO. Namely, we compared baseline characteristics, pre-ECMO ventilatory and gas exchange parameters, blood and coagulation, bleeding and thrombotic complications, as well as clinical outcome, between adult non-trauma subjects with COVID-19 or all other causes of ARDS.

Methods

A retrospective cohort study of adult subjects without trauma and with severe respiratory failure treated with ECMO for > 7 d in Hospital S. João (Porto, Portugal) between January 2018–September 2021 was performed.

We excluded patients with ECMO runs shorter than 7 d. For this period, we screened 171 potentially eligible patients. Of these, 16 were excluded due to polytrauma, 7 due to ECMO runs shorter than 7 d, and 21 because important data were missing, namely regarding hemostatic parameters. Our primary outcome was the incidence of bleeding and thrombotic complications under ECMO support. São João University Hospital is a 1,100-bed tertiary hospital. With a current case volume of ~100 patients/y (~50% respiratory ECMO; neonatal and pediatric ECMO representing < 10% of the total), our ECMO reference center is an Extracorporeal Life Support Organization member (center 227). Being the sole ECMO reference center in the north of Portugal, a region with approximately 4 million inhabitants, most of our respiratory patients are transported by our ECMO team from referring hospitals, with cannulation in loco and patient transfer to our center already under ECMO support. Specific ECMO data were collected and presented from a dedicated database.

Subjects undergoing ECMO for COVID-19 (COVID-19 group, $n = 67$) or all other cause of ARDS (non-COVID, $n = 60$) were compared. In the COVID-19 group, confirmation of SARS-CoV-2 infection on hospital admission was performed via nasopharyngeal swabs and tracheal aspirate (in mechanically ventilated subjects) with polymerase chain reaction assays. Airway bleeding severity was classified as mild/moderate or severe based on bronchoscopy reports. Bleeding was considered severe whenever a high volume of active bleeding was documented, large clots obstructing the main airways were present, and/or hemostatic interventions were required.

Study Population and Technique of Extracorporeal Support

Criteria and contraindications for ECMO in refractory acute respiratory failure, the technique of extracorporeal support, subjects' management on ECMO, including anticoagulation therapy, and weaning from extracorporeal support were described previously.[19] No relevant alterations were made to this protocol since its publication. Regarding anticoagulation, unfractionated heparin was used for a target activated partial thromboplastin time (aPTT) of 1.5 times the normal.

QUICK LOOK

Current knowledge

COVID-19 is a hypercoagulable state with increased thrombotic and bleeding risk. Thrombotic complications are described as more frequent than bleeding events in patients with COVID-19 requiring extracorporeal membrane oxygenation (ECMO); however, the latter appears to have greater impact on mortality. Reported mortality in these patients varies from 18–68%.

What this paper contributes to our knowledge

Thrombotic complications were similar between groups. COVID-19 subjects presented more bleeding events, namely airway bleeding and hemothorax. These complications were associated with prolonged ECMO courses.

Data Collection and Statistical Analysis

The Ethics Committee of the Hospital S. João approved the study and waived the requirement for subject consent. Variables are reported either as number of cases and percentage or median and interquartile ranges. Comparisons between groups (COVID-19 vs other etiologies) were performed using independent samples *t* test (normal distributed data) or Mann-Whitney U test (non-normal distributed data) for continuous variables, whereas the chi-square test or Fisher exact test was used for categorical variables, as appropriate. Results were considered statistically significant if $P < .05$. For statistical analysis, SPSS 28.0 (IBM, Armonk, New York) was used.

Results

Baseline Subject Characteristics

Our study included relatively young subjects, mostly male, with no significant comorbidities (Table 1). Smoking was less frequent in the COVID-19 group (3% vs 28%). Non-pulmonary ARDS was present in 18% of subjects in the non-COVID group.

Notably, subjects with COVID-19 had a shorter duration of invasive mechanical ventilation pre-ECMO. Most subjects were retrieved from referring hospitals, although this occurred less frequently in the COVID-19 group. No

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The authors have disclosed no conflicts of interest.

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Table 1. Baseline Characteristics of Subjects Requiring Extracorporeal Membrane Oxygenation for Severe ARDS

	All ($N = 127$)	COVID-19 ($n = 67$)	Non-COVID* ($n = 60$)	P
Age, y	52 (45–59)	49 (44–58)	53 (45–62)	.14
Male	89 (70)	45 (67)	44 (73)	.45
Charlson Index	1 (0–2)	1 (0–2)	1 (0–2.5)	.15
Comorbidities				
Hypertension	57 (45)	29 (43)	28 (47)	.70
Obesity	52 (41)	30 (45)	22 (37)	.35
Diabetes mellitus	22 (17)	13 (19)	9 (15)	.51
Smoking	19 (15)	2 (3)	17 (28)	< .001
Type of ARDS				
Pulmonary/non-pulmonary	116 (91)/11 (9)	67 (100)/0	49 (82)/11 (18)	< .001
Etiology ARDS				< .001
Viral pneumonia	84 (66)	67 (100)	17 (28)	
Bacterial pneumonia	22 (17)	0	22 (37)	
Pneumonia without SPD	7 (6)	0	7 (12)	
Extra-pulmonary sepsis	5 (4)	0	5 (8)	
Other	9 (7)	0	9 (15)	
Pre-ECMO course, d				
Hospital to ECMO	4 (1–7)	4 (1–7)	4 (1–9)	.31
Invasive ventilation to ECMO	2 (1–5)	2 (0–4)	3 (1–6)	.008
ECMO retrieval	99 (79)	47 (71)	52 (87)	.035
SAPS II	44 (31–55)	44 (31–56)	42 (30–52)	.50
APACHE II	21 (14–26)	21 (14–26)	21 (14–26)	.18
RESP score	4 (2–5)	4 (3–5)	3 (1–5)	.003
Pre-ECMO cardiac arrest	6 (4.7)	3 (4.4)	3 (5)	> .99

Data are presented as *n* (%) or median (interquartile range).
*Non-COVID refers to subjects supported with extracorporeal membrane oxygenation due to severe ARDS whose etiology was not COVID-19.
SPD = specific pathogen detected
ECMO = extracorporeal membrane oxygenation
SAPS II = Simplified Acute Physiology Score II
APACHE II = Acute Physiology and Chronic Health Evaluation II
RESP = Respiratory ECMO Survival Prediction

significant differences were found in Simplified Acute Physiology Score II and Acute Physiology and Chronic Health Evaluation II (APACHE II). In-hospital survival predicted by the Respiratory ECMO Survival Prediction (RESP) score (76%) was similar in both groups. Three subjects in each group suffered cardiac arrest before ECMO cannulation. The preferred cannulation strategy was femoro-jugular in both groups (93.9% in the COVID-19 group and 75.9% in the non-COVID cohort).

Ventilatory Parameters and Gas Exchange Before ECMO

Regarding ventilatory parameters (Table 2), no significant differences were detected between groups in the level of F_{IO_2}, PEEP, tidal volume, minute ventilation, plateau pressure, or static respiratory system compliance before starting ECMO support. Likewise, similar pre-ECMO levels in gas exchange parameters such as P_{aO_2}/F_{IO_2}, P_{aCO_2}, pH, and blood lactate were observed in both groups.

Blood and Coagulation Before and During ECMO

Hemoglobin, platelets, aPTT, D-dimers, and fibrinogen values on the first (day 1), third (day 3), and seventh day (day 7) of ECMO support are presented (Table 3).

At day 1 and day 3, COVID-19 had higher platelet count, but at day 7 no significant differences were detected between groups. Inversely, aPTT raised at a similar extent in both groups during the first week of ECMO support as systemic anticoagulation ensued, except in day 3, where it was significantly lower in COVID-19 group. Except for day 1, fibrinogen was higher in COVID-19 group. No differences were observed between groups concerning hemoglobin and D-dimer levels. COVID-19 group had an inferior lowest hemoglobin and mean aPTT during the first week of ECMO support.

Regarding transfusion support, COVID-19 group had a significantly higher need for red blood cell (RBC) units when compared with non-COVID group (8 [2–16] vs 2 [1–6], $P = .001$). Other blood products, such as platelets,

Table 2. Ventilatory Parameters and Gas Exchange Before Starting Extracorporeal Membrane Oxygenation Support

	All ($N = 127$)	COVID-19 ($n = 67$)	Non-COVID ($n = 60$)	*P*
Ventilatory parameters				
F_{IO_2}	1 (0.8–1)	0.92 (0.75–1)	1 (0.8–1)	.46
PEEP, cm H_2O	12 (10–14)	12 (10–14)	10 (8–14)	.14
Tidal volume, mL	460 (410–500)	455 (420–500)	460 (400–500)	.89
Tidal volume/PBW, mL/kg	7.0 (6.5–7.7)	7.0 (6.5–7.7)	7.0 (6.5–7.7)	.45
Minute ventilation, L/min	11.7 (9.8–13.9)	12.3 (9.8–14.1)	11.0 (9.9–12.5)	.24
Plateau pressure, cm H_2O	28 (24–30)	28 (24–29)	28 (24–30)	.88
Static C_{RS}, mL/cm H_2O	32.1 (25.0–37.9)	31.9 (25.0–37.9)	32.5 (26.7–36.4)	.89
Gas exchange				
P_{aO_2}/F_{IO_2}, mm Hg	85 (68–95)	86 (71–94)	83 (65–97)	.80
P_{aCO_2}, mm Hg	52 (45–65)	52 (44–65)	54 (45–65)	.85
pH	7.34 (7.25–7.42)	7.36 (7.26–7.43)	7.29 (7.23–7.40)	.17
Lactate, mmol/L	1.3 (1.0–1.9)	1.3 (1.0–1.8)	1.3 (1.0–2.1)	.39

Data are presented as median (interquartile range).
*Non-COVID refers to subjects supported with extracorporeal membrane oxygenation due to severe ARDS whose etiology was not COVID-19.
PBW = predicted body weight
C_{RS} = respiratory system compliance

Table 3. Blood and Coagulation Before and During Extracorporeal Membrane Oxygenation

	All ($N = 127$)	COVID-19 ($n = 67$)	Non-COVID ($n = 60$)	*P*
		ECMO Day 1		
Hb, g/dL	10.2 (8.7–11.3)	10.3 (8.7–11.4)	10.0 (8.6–11.3)	.58
Platelets, 10^9/L	219 (164–284)	234 (187–296)	190 (138–278)	.008
aPTT, s	42.5 (35.0–51.1)	42.0 (35.0–50.5)	45.5 (36.0–53.8)	.34
D-dimers, ug/dL	5.04 (3.02–9.43)	4.99 (2.48–15.87)	5.04 (3.33–7.91)	.87
Fibrinogen, mg/dL	592 (448–696)	629 (509–689)	554 (403–696)	.11
		ECMO Day 3		
Hb, g/dL	9.3 (8.5–10.8)	9.6 (8.8–10.9)	9.1 (8.2–10.6)	.12
Platelets, 10^9/L	210 (154–282)	220 (167–315)	196 (101–262)	.007
aPTT, s	45.4 (40.2–51.3)	43.1 (38.5–49.8)	48.0 (42.2–53.0)	.006
D-dimers, ug/dL	6.15 (3.21–14.03)	5.10 (3.21–13.25)	6.35 (3.22–16.62)	.30
Fibrinogen, mg/dL	595 (445–706)	625 (516–741)	534 (376–654)	.01
		ECMO Day 7		
Hb, g/dL	8.4 (7.8–9.5)	8.8 (7.9–9.9)	8.3 (7.8–9.3)	.10
Platelets, 10^9/L	196 (146–271)	202 (152–265)	190 (132–279)	.38
aPTT, s	49.6 (43.3–55.3)	50.0 (43.9–55.3)	48.6 (42.1–55.5)	.57
D-dimers, ug/dL	7.80 (3.61–15.24)	7.37 (3.52–12.30)	9.69 (3.76–17.94)	.18
Fibrinogen, mg/dL	599 (464–724)	634 (507–744)	565 (421–675)	.02
		Others		
Lowest Hb(g/dL) during ECMO	6.8 (6.5–7.3)	6.7 (6.4–7.0)	7.0 (6.7–7.5)	.001
Mean aPTT during ECMO, s	49.0 (44.9–52.6)	46.6 (43.6–50.2)	51.2 (47.8–54.4)	< .001

Data are presented as median (interquartile range).
*Non-COVID refers to subjects supported with extracorporeal membrane oxygenation due to severe ARDS whose etiology was not COVID-19.
Hb = hemoglobin
aPTT = activated partial thromboplastin time
ECMO = extracorporeal membrane oxygenation

Table 4. Incidence of Post-Cannulation Complications

	All ($N = 127$)	COVID-19 ($n = 67$)	Non-COVID ($n = 60$)	P
Bleeding Complications				
Airway bleeding	34 (26.8)	25 (37.3)	9 (15.0)	.02
Hemothorax	11 (8.7)	9 (13.4)	2 (3.3)	.043
Hemorrhagic shock	8 (6.3)	8 (11.9)	0	.007
Cannulation site bleeding	52 (40.9)	26 (38.8)	26 (43.3)	.60
Cardiac tamponade	2 (1.6)	1 (1.5)	1 (1.7)	> .99
Hematuria	19 (15.0)	12 (17.9)	7 (11.7)	.32
Cerebral hemorrhage	4 (3.1)	3 (4.5)	1 (1.7)	.62
Gastrointestinal bleeding	27 (21.3)	14 (20.9)	13 (21.7)	.92
Nasopharyngeal and oropharyngeal bleeding	64 (50.4)	38 (56.7)	26 (43.3)	.13
Thrombotic Complications				
DVT	55 (43.3)	32 (47.8)	23 (38.3)	.28
Pulmonary embolism	2 (1.6)	1 (1.5)	1 (1.7)	> .99
Stroke	5 (3.9)	4 (6.0)	1 (1.7)	.37
Limb ischemia	3 (2.4)	3 (4.5)	0	.25
Clinical Outcome				
ECMO duration, d	26 (13–57)	47 (17–80)	19 (12–30)	< .001
Hospital LOS, d	35 (20–73)	54 (23–96)	31 (18–48)	.004
ICU mortality	35 (27.6)	21 (31.3)	14 (23.3)	.31

Data are presented as *n* (%).
*Non-COVID refers to subjects supported with extracorporeal membrane oxygenation due to severe ARDS whose etiology was not COVID-19.
DVT = deep vein thrombosis
ECMO = extracorporeal membrane oxygenation
LOS = length of stay

fresh frozen plasma, or fibrinogen, were rarely administered (< 25% of subjects) and did not differ between groups.

ECMO Complications and Clinical Outcome

A significantly higher rate of severe bleeding was found in COVID-19 group (Table 4). Airway bleeding was significantly higher in the COVID-19 group, both the mild/moderate bleeding (18 [26.9%] vs 8 [13.3%], $P = .03$) and the severe cases (7 [10.4%] vs 1 [1.7%)], $P = .03$). Within the 7 subjects with COVID-19 who suffered severe airway bleeding, 4 died, whereas mild/moderate airway bleeding 8 of 18 subjects did not survive. Hemorrhagic shock was mainly associated with hemothorax ($n = 4$; ~50% of cases); 2 cases were caused by lower-limb hematomas, 1 by retroperitoneal bleeding, and 1 due to nontraumatic lesion of an iliolumbar artery. Of note, 6 of the 9 subjects with COVID-19 with hemothorax died, whereas the 2 subjects with hemothorax in the non-COVID group survived. Ocular, nasal, and pharyngeal bleeding was common, whereas cardiac tamponade and intracerebral hemorrhage were rare.

Regarding thrombotic complications, no differences were detected between groups. Deep vein thrombosis, mostly related to ECMO cannulation, was common in both groups. Stroke, limb ischemia, and pulmonary embolism were rare events. Acute kidney injury was a notably frequent complication in both COVID-19 and non-COVID groups (40.3% vs 46.6%, $P = .47$). The COVID-19 group required longer ECMO support and hospital stay.

Discussion

In our single-center experience, severe COVID-19–associated ARDS requiring ECMO presented high rates of severe bleeding complications and a protracted course, with a statistically significant difference concerning in-hospital mortality.

No relevant differences were found between groups in the severity scoring systems. Of note, although the RESP score significantly differed between groups (COVID-19: 4 [3–5] vs non-COVID-19: 3 [1–5]), both scores 3 and 4 are associated with similar in-hospital survival. Accordingly, no significant differences were found in the pre-ECMO ventilatory and gas exchange parameters between group. Subjects with COVID-19 had a shorter duration of invasive mechanical ventilation pre-ECMO when compared with non-COVID group. However, in contrast to pre-pandemic evidence, pre-ECMO invasive ventilation duration in COVID-19 does not seem to have impact on survival,[20] although more studies are needed to confirm this finding.

In our study, severe COVID-19–associated ARDS supported with ECMO did not show increased thrombotic complications. ECMO support requires systemic anticoagulation, which could have contributed to decreased thrombotic complications in COVID-19 group. Pre-ECMO cardiac arrest, higher P_{aCO_2} at ECMO initiation, and obesity, all recognized risk factors for thrombosis,[18] were similar between groups and, therefore, are unlikely to have confounded the results. In our medical center, computed tomography pulmonary angiogram (CTPA) is not routinely performed in every patient in the first day of ECMO support, which could have underestimated incidence of pulmonary thromboembolism (PTE). The difference between incidentally detected PTE on CTPA and clinically suspected PTE in ICU-treated subjects with COVID-19 can be as high as 93–7%.[21]

Bleeding events occurred more frequently in COVID-19 group. Accordingly, statistically significant inferior mean lowest hemoglobin and higher need for RBC transfusion was detected in this group. This could not have been caused by higher systemic anticoagulation in this group given that the mean aPTT during ECMO support was lower. Moreover, ECMO-associated coagulopathy most likely did not account for the bleeding risk observed in COVID-19 group given the higher platelet count and fibrinogen observed in this group during the first week of ECMO support. Additionally, it's worth mentioning the absence of differences concerning D-dimer levels between cohorts, as D-dimers have popularly been attributed with prognostic significance; and although pre-cannulation D-dimer levels have been associated with an increased predicted disease severity and longer ECMO course,[22] their value under ECMO must be carefully interpreted as it may reflect thrombus within the oxygenator or hemostatic perturbance rather than hypercoagulability.[23] Furthermore, D-dimer has poor specificity, with increased levels seen in a variety of conditions, and fails to capture the dynamic interplay between platelets, endothelium, and coagulation cascade phenomena.[24] Thus, interpretation of D-dimer levels is difficult and should be careful given the complexity of these subjects.

In our COVID-19 cohort, airway bleeding was more common and more severe. In subjects with severe airway bleeding and large blood clots causing significant airway obstruction, clots were removed by cycles of saline instillation and aspiration. In 2 cases, debridement with tissue-grasping forceps was required. In one case, cryoextraction and thrombectomy with Fogarty catheter were performed. When active bleeding was observed or emerged as a complication of clot extraction, cold saline, adrenaline, and tranexamic acid instillation were used to control the hemorrhage. Bleeding relapse was common, and a bronchoscopy to review hemostasis was often required.

Similarly, hemothorax was a frequent and severe complication with difficult management and high associated mortality. In 4 of 9 subjects with hemothorax, thoracic surgery was required. Two thoracotomies and 2 video-assisted thoracoscopic surgeries were performed. Surgical re-intervention was needed in 2 occasions due to relapsing bleeding, and in one case intrathoracic gauze packing was performed in the presence of a hemorrhagic suffusion that involved all thoracic cavity without visible bleeding point. A possible underlying etiology for these events may be the development of peripheral medium and small pulmonary artery branch aneurysms in COVID-19's highly inflammatory setting.[25]

Conclusions

In our single-center experience, severe COVID-19–associated ARDS requiring ECMO presented high rates of severe bleeding complications and a protracted course. This could not have been accounted for by differences in the severity of the acute respiratory failure or in ECMO-associated coagulopathy. Further studies are needed to further clarify the risks and benefits of ECMO in severe COVID-19–associated ARDS.

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2.6. Standardized approach for extubation during ECMO in severe ARDS: a prospective observational study.

Roncon-Albuquerque R Jr, Gaião S, Vasques-Nóvoa F, Basílio C, Ferreira AR, Touceda-Bravo A, Pimentel R, Vaz A, Silva S, Castro G, Veiga T, Martins H, Dias F, Pereira C, Marto G, Coimbra I, Chico-Carballas JI, Figueiredo P, Paiva JA. *Ann Intensive Care* 2023; 13: 86. DOI: 10.1186/s13613-023-01185-y.

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Standardized approach for extubation during extracorporeal membrane oxygenation in severe acute respiratory distress syndrome: a prospective observational study

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Abstract

Background Extubation during extracorporeal oxygenation (ECMO) in severe acute respiratory distress syndrome (ARDS) has not been well studied. Despite the potential benefits of this strategy, weaning from ECMO before liberation from invasive mechanical ventilation remains the most frequent approach. Our aim was to evaluate the safety and feasibility of a standardized approach for extubation during ECMO in patients with severe ARDS.

Results We conducted a prospective observational study to assess the safety and feasibility of a standardized approach for extubation during ECMO in severe ARDS among 254 adult patients across 4 intensive care units (ICU) from 2 tertiary ECMO centers over 6 years. This consisted of a daily assessment of clinical and gas exchange criteria based on an Extracorporeal Life Support Organization guideline, with extubation during ECMO after validation by a dedicated intensive care medicine specialist. Fifty-four (21%) patients were extubated during ECMO, 167 (66%) did not reach the clinical criteria, and in 33 (13%) patients, gas exchange precluded extubation during ECMO. At ECMO initiation, there were fewer extrapulmonary organ dysfunctions (lower SOFA score [OR, 0.88; 95% CI, 0.79–0.98; $P = .02$] with similar PaO_2/FiO_2) when compared with patients not extubated during ECMO. Extubation during ECMO associated with shorter duration of invasive mechanical ventilation (7 (4–18) vs. 32 (18–54) days; $P < .01$) and of ECMO (12 (7–25) vs. 19 (10–41) days; $P = .01$). This was accompanied by a lower incidence of hemorrhagic shock (2 vs. 11%; $P = .05$), but more cannula-associated deep vein thrombosis (49 vs. 31%; $P = .02$) and failed extubation (20 vs. 6%; $P < .01$). There were no increased major adverse events. Extubation during ECMO is associated with a lower risk of all-cause death, independently of measured confounding (adjusted logistic regression OR 0.23; 95% confidence interval 0.08–0.69, $P = .008$).

Conclusions A standardized approach was safe and feasible allowing extubation during ECMO in 21% of patients with severe ARDS, selecting patients who will have a shorter duration of invasive mechanical ventilation, ECMO course, and ICU stay, as well as fewer infectious complications, and high hospital survival.

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Keywords Acute respiratory distress syndrome, Awake-ECMO, Extracorporeal membrane oxygenation, Extubation, Standardized approach, Weaning

Background

In patients with severe acute respiratory distress syndrome (ARDS) failing invasive mechanical ventilation (IMV) and rescued with extracorporeal membrane oxygenation (ECMO), the best weaning strategy remains unknown [1–3]. Prioritizing weaning from IMV may significantly reduce ventilator-induced lung injury and ventilator-associated pneumonia, as well as the complications of sedation and patient deconditioning [4]. However, deferring ECMO weaning could increase the risks of this invasive technique such as bleeding, thrombosis, hemolysis, and cannula-related infection [5–9]. Moreover, in awake patients with ECMO, specific risks such as accidental decannulation and ECMO equipment failure must also be considered [10]. In that context, the Extracorporeal Life Support Organization (ELSO) published a guideline for endotracheal extubation in patients with respiratory failure receiving ECMO, with clinical and gas exchange criteria to select patients to be safely and successfully managed without IMV [11].

Despite the potential benefits of early liberation from IMV in severe ARDS, weaning from ECMO before liberation from IMV remains the most frequent approach [1]. In a recent survey that included 253 ECMO centers worldwide, only one-third reported performing extubation during ECMO [2]. This latter strategy was considered mostly for other causes of respiratory failure such as end-stage respiratory disease awaiting lung transplantation [2], where there is evidence of the feasibility of an awake non-intubated approach during ECMO [12–15]. Differently, spontaneous breathing in severe ARDS could be more challenging due to spontaneous hyperventilation and strenuous respiratory muscle effort [4], lung derecruitment and collapse delirium, inability to handle pulmonary secretion [16], hemodynamic instability, and multiple organ failure [2].

To assess the safety and feasibility of a standardized approach for extubation during ECMO in severe ARDS, we conducted a prospective observational study among adult patients across 4 ICUs from 2 tertiary ECMO centers over 6 years. This consisted of a daily assessment of clinical and gas exchange criteria based on an Extracorporeal Life Support Organization guideline [11], with extubation during ECMO after validation by a dedicated intensive care medicine specialist.

Methods

A prospective observational study of patients with severe ARDS rescued with ECMO in 2 European tertiary ECMO centers from January 2016 to July 2022 was carried out. The institutional Ethics Committee reviewed and approved the study and waived the requirement for patient consent (Approval number: CES 205/2022). All the procedures followed in the study were by the ethical standards of the institutional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as most recently amended.

ECMO case volume, clinical criteria for ECMO consideration, and ECMO technical considerations are described in detail in the supplemental data. The initial type of ECMO support was venovenous (VV), except for one trauma patient in the CTRL group with both lung and cardiac contusion and simultaneous severe respiratory failure and cardiogenic shock, in which veno-venoarterial (VVA) ECMO was the initial type of ECMO support. The 2 centers have intensivist-led respiratory ECMO programs comprising dedicated intensive care medicine specialists that are responsible for: (i) the decision to initiate ECMO; (ii) coordination of ECMO patient retrieval from referring hospitals; (iii) performing percutaneous ECMO cannulation; (iv) daily monitoring and management of ECMO-related complications (e.g., circuit exchange for ECMO-related hemolysis); (v) the decision to wean from ECMO, and (vi) to perform ECMO decannulation. A team of ECMO Specialists on-call 24/7 is responsible for (i) ECMO circuit priming; (ii) daily circuit maintenance (e.g., transmembrane pressure monitoring); (iii) ECMO circuit component exchange (e.g., oxygenator exchange), and (iv) ECMO circuit management during patient retrieval from referring hospitals. The nurse-to-ECMO patient ratio was 1:1 and was not modified in case of extubation during ECMO support.

A standardized approach for extubation during extracorporeal membrane oxygenation

After cannulation, a standardized approach for extubation during ECMO was performed (Fig. 1). Given that ECMO consideration required sustained clinical deterioration despite optimal conventional treatment, including prone position unless contraindicated, prone positioning was not performed routinely after ECMO implantation. Following initial patient stabilization and optimization of ECMO support, weaning from neuromuscular blocking agents (NMB) and sedation was pursued to achieve

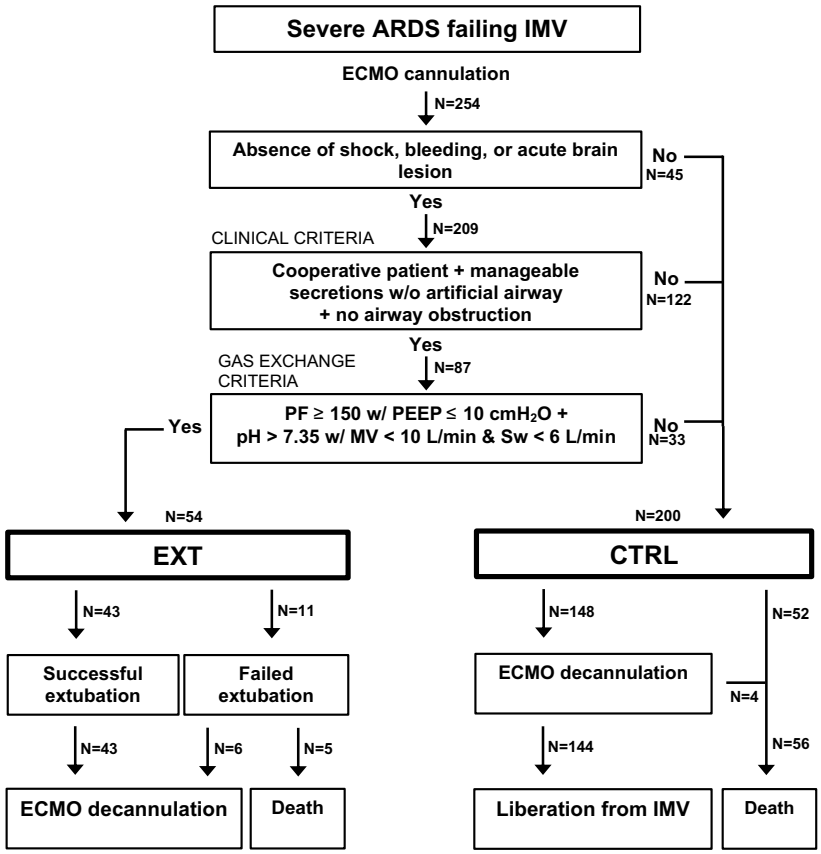

Fig. 1 Flowchart for extubation during extracorporeal membrane oxygenation (ECMO) in severe acute respiratory distress syndrome (ARDS). Following initial patient stabilization and optimization of ECMO support, conscious sedation was pursued in the absence of circulatory shock, significant bleeding, or acute brain injury. A daily assessment of clinical and gas exchange criteria based on an Extracorporeal Life Support Organization guideline [11] was then performed, with extubation during ECMO after validation by a dedicated intensive care medicine specialist. CTRL, group without extubation during ECMO; EXT, group with extubation during ECMO; IMV, invasive mechanical ventilation; MV, minute ventilation; PEEP, positive end-expiratory pressure; PF, the ratio between the partial pressure of oxygen in arterial blood (PaO_2; mmHg) and the fraction of inspired oxygen (FiO_2; %); Sw, ECMO sweep gas flow

conscious sedation (Richmond Agitation-Sedation Scale (RASS) = − 1/0) if all the following were absent: (i) circulatory shock; (ii) significant bleeding, and (iii) acute brain injury. Conversion to VVA ECMO during VV ECMO support was considered for circulatory support in the setting of cardiovascular collapse complicating persistent severe respiratory failure. There were no cases of venoarterial (VA) ECMO, namely as initial ECMO circuit configuration in the setting of respiratory failure with associated septic shock, or as conversion from VV ECMO.

Whenever conscious sedation was successfully achieved, a daily assessment of clinical and gas exchange criteria based on the Extracorporeal Life Support

Organization (ELSO) guideline for 'Endotracheal extubation in patients with respiratory failure receiving venovenous ECMO' [11] was performed. Readiness for endotracheal extubation was considered when: (i) the patient was cooperative enough not to be at significant risk for dislodgement of cannulas or other important catheters or devices; (ii) secretions were manageable without an artificial airway, and (iii) there was no airway obstruction. Regarding the gas exchange criteria, the following parameters had to be present: (i) the ratio of the PaO_2 (arterial oxygen partial pressure obtained from an arterial blood gas) to the FiO_2 (fraction of inspired oxygen expressed as a decimal) (PF ratio) ≥ 150 with positive end-expiratory pressure (PEEP) ≤ 10 cmH_2O, and (ii) pH > 7.35 with minute ventilation (MV) < 10 L/min under pressure support ventilation while receiving a sweep gas flow < 6 L/min. These criteria differed from the ELSO guideline [11] for the P/F ratio (≥ 150 vs. ≥ 200 in the ELSO guideline) and for the PEEP value (≤ 10 vs. ≤ 5 cmH_2O in the ELSO guideline). Whenever the predefined clinical and gas exchange criteria were fulfilled, validation by a dedicated intensive care medicine specialist from the ECMO Program was required before the final decision for extubation during ECMO was made.

After extubation during ECMO (EXT group) high-flow nasal cannula was initiated immediately after extubation with flow started at 40 L/min and FiO_2 set to peripheral capillary oxygen saturation (SpO_2) > 92%. Sweep gas flow was then titrated to avoid respiratory acidosis and to minimize the work of breathing, with a respiratory rate goal of 10–20 breaths per minute. Paracetamol was used for analgesia; whenever necessary, opioids (morphine or fentanyl), titrated to the lowest effective dose, were also administered. Dexmedetomidine was used for anxiolysis; whenever necessary, benzodiazepines, titrated to the lowest effective dose, were also administered. Fever control was pursued using non-steroidal anti-inflammatory drugs and/or metamizole unless contraindicated. Whenever present, the non-productive cough was suppressed with codeine and titrated to the lowest effective dose.

No specific standardized criteria were used for reintubation in the EXT group. Whenever a significant patient deterioration occurred after extubation during ECMO support, a dedicated intensive care medicine specialist from the ECMO Program was involved to exclude a lack of ECMO support optimization, being part of the decision to reintubate when indicated. In this group, tracheostomy was considered after failed extubation.

When significant improvement in native lung function was suspected (increased PF ratio with better lung aeration evaluated by chest X-ray or lung ultrasound), ECMO blood flow was stepwise reduced to 3.0 L/min. Sweep gas flow was then tapered to 1 L/min with close monitoring of respiratory rate and effort. After a 12–24 h period of clinical stability, the sweep gas flow was finally shut off for > 30 min. If blood gases remained stable (PF ratio ≥ 150, no respiratory effort, and absence of uncompensated respiratory acidosis) the ECMO system was removed.

When the clinical and gas exchange criteria for extubation during ECMO were not met at the time of consistent native lung function improvement (increased PF ratio, improved respiratory system (RS) compliance, and better lung aeration evaluated by chest X-ray or lung ultrasound), weaning from ECMO was prioritized (CTRL group). Invasive mechanical ventilation parameters were then progressively reduced to FiO_2 ≤ 0.5, PEEP ≤ 10 cmH_2O, and plateau pressure (PPlat) ≤ 25 cmH_2O. ECMO blood flow was then stepwise reduced to 3.0 L/min. Thereafter sweep gas flow was tapered and finally shut off for > 30 min. If blood gases remained stable (PF ratio ≥ 150, MV < 10 L/min with no respiratory effort, and absence of uncompensated respiratory acidosis), the ECMO system was removed. In this group, tracheostomy was considered when no significant native lung function improvement was observed during the second week of ECMO support.

Data collection and statistical analysis

Statistical analysis methods used in the study are detailed in the supplemental data.

Results

Flowchart for extubation during ECMO in severe ARDS

Of the 254 patients with severe ARDS included in the study (Fig. 1), 54 (21%) met the clinical and gas exchange criteria and were extubated during ECMO (EXT group). Of the remaining 200 patients (CTRL group) 45 (18%) patients had a circulatory shock, significant bleeding, or acute brain injury contraindicating conscious sedation, 122 (48%) patients did not reach the clinical criteria for extubation during ECMO, and 33 (13%) patients fulfilling the clinical criteria did not meet the gas exchange criteria for extubation during ECMO. Conversion to VVA ECMO was performed for circulatory support during VV ECMO in 5 patients due to: (i) acute cor pulmonale in 4 patients; (ii) cardiac tamponade complicating ECMO cannulation in one patient. All but one patient were from the CTRL group. In the patient from the EXT group, conversion to VVA ECMO was performed in the setting of acute cor pulmonale after reintubation.

Eleven patients (20%) failed extubation in the EXT group. The reasons for reintubation were: (i) excess pulmonary secretions in 4 patients; (ii) respiratory muscle fatigue in 3 patients; (iii) upper airway obstruction in 2 patients; (iv) refractory hypoxemia in 1 patient; and (v)

cardiac arrest in 1 patient. Of the 11 patients with failed extubation 5 died, while all patients successfully extubated in the EXT group survived hospital discharge. In the CTRL group, ECMO weaning and decannulation were achieved in 148 patients (74%), while 52 (26%) patients died during ECMO. Of the 148 patients with ECMO decannulation in the CTRL group, 144 (97%) were liberated from IMV and survived to hospital discharge.

Baseline patient characteristics

Patients included in the study were relatively young and mostly male. Cardiovascular risk factors were common, with hypertension more frequently present in the CTRL group (Table 1).

Most patients (90%) had a pulmonary type of ARDS, with viral pneumonia in 117 (46%) patients (82 (32%) of which had COVID-19-related pneumonia), bacterial pneumonia in 37 (15%) patients, and pneumonia without a specific pathogen detected in 36 (14%). Lung contusion was the cause of ARDS in 25 (10%) patients, 14 (6%) had extrapulmonary sepsis, while 25 (10%) patients had an ARDS of other etiology. No significant differences were detected in the ARDS type or etiology between groups.

Regarding the pre-ECMO course, no significant differences were detected between groups in the time from hospital admission to ECMO initiation or in the duration of IMV before ECMO cannulation. Regarding pre-ECMO management, the rate of NMB use and prone position was high (98 and 79%, respectively) and did not differ between groups.

Most patients (68%) were retrieved from referring hospitals, with no significant differences between groups. EXT group had lower SAPS II and lower SOFA scores, but similar Murray scores. Hospital survival predicted by the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score (RESP score) was 76%, being similar in EXT and CTRL groups.

Ventilatory parameters and gas exchange before and during initial ECMO support

Pre-ECMO ventilator parameters and respiratory mechanics differed between groups: EXT group presented lower FiO_2 and higher static RS compliance when compared with the CTRL group, with no significant differences in PEEP, tidal volume, minute ventilation, and plateau pressure (Additional file 1: Table S1). After ECMO initiation (ECMO Day 1) FiO_2 was still lower in the EXT group, but with no significant differences in the other ventilatory parameters. On the day of liberation from IMV, the EXT group presented higher PEEP, but lower tidal volume, minute ventilation, and static RS compliance, when compared with CTRL.

Table 1 Baseline characteristics

Characteristics	All ($n=254$)	CTRL ($n=200$)	EXT ($n=54$)	*P*-value
Age (years)	51 (42–59)	52 (42–60)	50 (41–58)	0.29
Male gender	179 (70)	141 (70)	38 (70)	0.98
Comorbidities				
Hypertension	95 (37)	82 (41)	13 (24)	0.02
Obesity	91 (36)	72 (36)	19 (35)	0.91
Dyslipidemia	86 (34)	70 (35)	16 (30)	0.46
Smoking	67 (26)	54 (27)	13 (24)	0.66
Diabetes mellitus	42 (16)	35 (18)	7 (13)	0.43
Alcoholism	32 (13)	29 (14)	3 (6)	0.08
Type of ARDS				
Pulmonary	227 (90)	176 (89)	51 (94)	0.23
Extrapulmonary	25 (10)	22 (11)	3 (6)	
ARDS etiology				
Viral pneumonia	117 (46)	91 (46)	26 (48)	0.78
COVID-19	82 (32)	64 (32)	18 (33)	0.85
Bacterial pneumonia	37 (15)	28 (14)	9 (17)	0.62
Pneumonia without SPD	36 (14)	28 (15)	8 (15)	0.88
Lung contusion	25 (10)	19 (10)	6 (11)	0.72
Extrapulmonary sepsis	14 (6)	12 (6)	2 (4)	0.74
Other	25 (10)	22 (11)	3 (6)	0.23
Pre-ECMO course (days)				
Hospital to ECMO	4.0 (1.0–8.0)	4.0 (1.0–8.0)	4.0 (1.0–7.0)	0.33
IMV to ECMO	2.5 (1.0–6.0)	3.0 (1.0–6.0)	2.0 (1.0–5.0)	0.07
Pre-ECMO management				
NMB	245 (98)	193 (97)	52 (98)	1.00
Prone position	198 (79)	154 (78)	44 (83)	0.41
ECMO retrieval	173 (68)	134 (67)	39 (72)	0.46
SAPS II	46 (34–57)	49 (36–60)	39 (24–54)	< 0.01
SOFA	8.0 (5.0–11)	8.0 (6.0–12)	7.0 (4.0–9.0)	< 0.01
Murray score	3.3 (3.0–3.7)	3.3 (3.0–3.7)	3.3 (3.0–3.5)	0.21
RESP score	3.0 (1.0–5.0)	3.0 (1.0–5.0)	4.0 (1.0–5.0)	0.12

Data are presented as numbers (%) or median (interquartile range)

COVID-19 COVID-19-related pneumonia, *CTRL* group without extubation during ECMO, *EXT* group with extubation during ECMO, *NMB* neuromuscular blocking agents, *RESP Score* Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score, *SAPS II* Simplified Acute Physiology Score II at ICU admission, *SOFA* Sequential Organ Failure Assessment score at ECMO cannulation, *SPD* specific pathogen detected; SOFA score was calculated in the last day before ECMO implantation

No significant differences in gas exchange parameters such as PF ratio, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and pH between EXT and CTRL groups pre-ECMO and at ECMO Day 1 (Additional file 1: Table S1). On the day of ECMO implantation, arterial blood lactate was slightly higher in the CTRL group

when compared with the EXT group. Regarding ECMO support parameters, ECMO blood flow and sweep gas flow also did not differ between groups on ECMO Day 1. ECMO blood flow also did not differ between groups on ECMO day 3 (CTRL group: 4.3 (3.9–4.6) vs. EXT group: 4.2 (3.9–4.5) L/min; $P=0.28$) and on ECMO Day 7 (CTRL group: 4.2 (3.8–4.7) vs. EXT group: 4.2 (3.8–4.7) L/min; $P=0.89$). On the day of liberation from IMV, the EXT group presented a lower PF ratio and pH, and higher $PaCO_2$ when compared with the CTRL group (Additional file 1: Table S2). In the EXT group, ECMO blood flow and sweep gas flow were lower on the day of decannulation when compared to the day of extubation. ECMO blood flow and sweep gas flow were also lower on the day of decannulation in the EXT group when compared to the CTRL group (Additional file 1: Table S2).

Given the significant differences observed between EXT and CTRL groups in some pre-ECMO characteristics, a multivariate analysis was performed. Arterial hypertension, pre-ECMO FiO_2, lactate, and SAPS II score were identified as relevant predictors of group (EXT vs. CTRL) assignment (Table 2).

Table 2 Logistic regression model including pre-ECMO variables describing independent associations with group assignment

Variables	OR (95% CI)	*P*-value
Lactate (log_2-transformed)	0.44 (0.26–0.74)	0.002
Hypertension	0.46 (0.22–0.97)	0.041
FiO_2	0.98 (0.96–0.99)	0.035
SAPS II	0.97 (0.95–0.99)	0.004

Results are presented as odds ratio (OR) with correspondent 95% confidence interval. CTRL, group without extubation during ECMO; EXT, group with extubation during ECMO; SAPS II, Simplified Acute Physiology Score II at ICU admission; FiO_2, fraction on inspired oxygen

ECMO-associated complications and major adverse events

The incidence of nosocomial infections was high (68%), and significantly more frequent in the CTRL group (Table 3). Ventilator-associated pneumonia was the most frequent nosocomial infection, followed by the bloodstream, urinary tract, abdominal, and skin and soft-tissue infections, respectively. The incidence of ventilator-associated pneumonia was higher in the CTRL group. Although this group also presented a higher incidence of bloodstream, urinary tract, abdominal and skin, and soft-tissue infections, it did not reach statistical significance. The lower incidence of nosocomial infection observed in the EXT group was accompanied by a shorter duration of antibiotic therapy in the ICU and more antibiotic-free days in the ICU (%).

Table 3 ECMO-associated complications and major adverse events

	All ($n=254$)	CTRL ($n=200$)	EXT ($n=54$)	*P*-value
Infectious complications				
Nosocomial infections	172 (68)	147 (74)	25 (46)	< 0.01
Ventilator-associated pneumonia	147 (58)	127 (64)	20 (37)	< 0.01
Bloodstream infection	59 (23)	51 (26)	8 (15)	0.10
Urinary tract infection	43 (17)	37 (18)	6 (11)	0.20
Abdominal infection	9 (4)	9 (5)	0 (0)	0.21
Skin and soft-tissue infection	8 (3)	8 (4)	0 (0)	0.21
Duration of antibiotic therapy in ICU (days)	16 (9–35)	20 (11–41)	7 (6–14)	< 0.01
Antibiotic-free days in ICU (%)	35 (10–52)	29 (9–50)	42 (25–62)	0.01
Bleeding complications				
Hemorrhagic shock	22 (8.7)	21 (10.6)	1 (1.9)	0.05
Intracerebral hemorrhage	5 (2.0)	3 (1.5)	2 (3.7)	0.29
Thrombotic complications				
Cannula-associated deep vein thrombosis	69 (36)	45 (31)	24 (49)	0.02
Limb ischemia	3 (1.2)	3 (1.5)	0 (0)	0.49
Ischemic stroke	1 (0.4)	1 (0.5)	0 (0)	1.00
Major adverse events				
Refractory hypoxemia	15 (5.9)	12 (6.0)	3 (5.6)	1.00
Cardiac arrest	8 (3.2)	5 (2.5)	3 (5.6)	0.37
Accidental decannulation	1 (0.4)	0 (0)	1 (1.9)	0.21

Data are presented as numbers of cases (percentage). CTRL, group without extubation during ECMO; ECMO, extracorporeal membrane oxygenation; EXT, group with extubation during ECMO

Hemorrhagic shock was found in 11% of the CTRL group, with one case in the EXT group due to a non-fatal accidental ECMO decannulation of a 19-Fr and 15-cm-long jugular return cannula. This adverse event occurred 5 days after a failed extubation attempt when the patient was with IMV under light sedation. This was immediately handled with ECMO circuit clamping and local compression, conversion to femoro-femoral veno-venous ECMO configuration, and blood transfusion. The incidence of intracerebral hemorrhage was low (2.0%) and did not differ between groups.

Cannula-associated deep vein thrombosis was more frequent in the EXT group. No significant differences were found in the incidence of limb ischemia and ischemic stroke between groups. Before ECMO implantation the EXT group presented higher platelet counts and shorter aPTT and PT values, with no significant differences in D-dimers and fibrinogen levels, when compared to the CTRL group (Additional file 1: Table S3). During ECMO support (ECMO Day 1, 3, and 7) higher platelet counts were also consistently observed in the EXT group, while no significant differences in aPTT, PT, D-dimers, and fibrinogen levels were detected between groups.

Regarding major adverse events, the incidence of refractory hypoxemia, cardiac arrest, and accidental decannulation was low and did not significantly differ between groups.

Clinical outcomes

EXT group presented shorter ECMO runs, IMV duration, and ICU length of stay, even after adjustment for clinically relevant covariates (Table 4; Additional file 1: Table S5). In this group, the delay between successful extubation and ECMO decannulation was 6 (4–10) days. Failed extubation rate was lower in the CTRL group, but the tracheostomy rate was higher. In this group, tracheostomy was performed mostly before ECMO weaning (78 vs. 22%), 21 (16–31) days after IMV initiation, and 17 (11–25) days after ECMO implantation. In the EXT group, a tracheostomy was performed after extubation failure, except for one case in which a second extubation attempt was made. Regarding the health-related quality of life evaluated 3–6 months after hospital discharge, the EQ-5D-5L level summary score was significantly lower in the EXT group, while no significant differences were detected in the EQ-VAS score between groups. All-cause mortality at 150-day follow-up was lower in EXT (Table 4).

The impact of EXT on key clinical outcomes was assessed using multiple approaches to control for confounding, namely standard unadjusted and adjusted logistic regression, least absolute shrinkage, and selection operator (LASSO) logistic regression and propensity-score (PS) matching followed by standard logistic regression (Fig. 2). After PS matching (54 pairs), groups were well balanced for all variables included in the PS model, as appraised by absolute standardized bias < 10% (Additional file 1: Table S4).

Table 4 Clinical outcomes

	All ($n=254$)	CTRL ($n=200$)	EXT ($n=54$)	*P*-value
ECMO duration (days)	17 (10–35)	19 (10–41)	12 (7–25)	0.01
IMV duration (days)	25 (13–46)	32 (18–54)	7 (4–18)	< 0.01
Failed extubation (%)	24 (9.5)	13 (6.5)	11 (20.4)	< 0.01
Tracheostomy (%)	123 (48.6)	112 (56.3)	11 (20.4)	< 0.01
ICU-LOS (days)	32 (18–56)	37 (22–63)	19 (13–32)	< 0.01
Hospital survival (%)	193 (76.0)	144 (72.0)	49 (90.7)	< 0.01
EQ-5D-5L	9 (7–11)	10 (9–12)	8 (7–10)	0.03
EQ-VAS	75 (60–80)	75 (60–80)	75 (60–85)	0.63

Data are presented as numbers of cases (%) or median (interquartile range)

CTRL group without extubation during ECMO, *EXT* group with extubation during ECMO, *EQ-5D-5L* EuroQol-5 dimension self-assessed, health-related, quality of life questionnaire presented as a level summary score, *EQ-VAS* EuroQol vertical visual analog scale for self-rated health, *ICU* intensive care unit, *LOS* length of stay

EXT group was associated with a lower risk of 150-day all-cause mortality (OR 0.23–0.32; $p < 0.05$), independently of the key clinical covariates and confounding adjustment method (Fig. 2; Additional file 1: Fig. S1). EXT group associated with lower risk of nosocomial infection and VAP in the unadjusted analysis. However, these associations were highly dependent on the ICU length of stay, which was shorter in the EXT group (Table 4) and lost their statistical significance in the adjusted models (Fig. 2). Notably, EXT group was also associated with decreased risk of tracheostomy, independently of the adjustment method (Fig. 2).

Discussion

In the present study, the safety and feasibility of a standardized approach for extubation during ECMO in severe ARDS were evaluated. This consisted of a daily assessment of clinical and gas exchange criteria based on an Extracorporeal Life Support Organization guideline [11], with extubation during ECMO after validation by a dedicated intensive care medicine specialist. Using this approach, 21% of patients with severe ARDS could be extubated during ECMO support.

To evaluate the safety of our standardized approach for extubation during ECMO in severe ARDS, we analyzed ECMO-related complications, major adverse events, nosocomial infections in the ICU, and main clinical outcomes. Extubation during ECMO did not

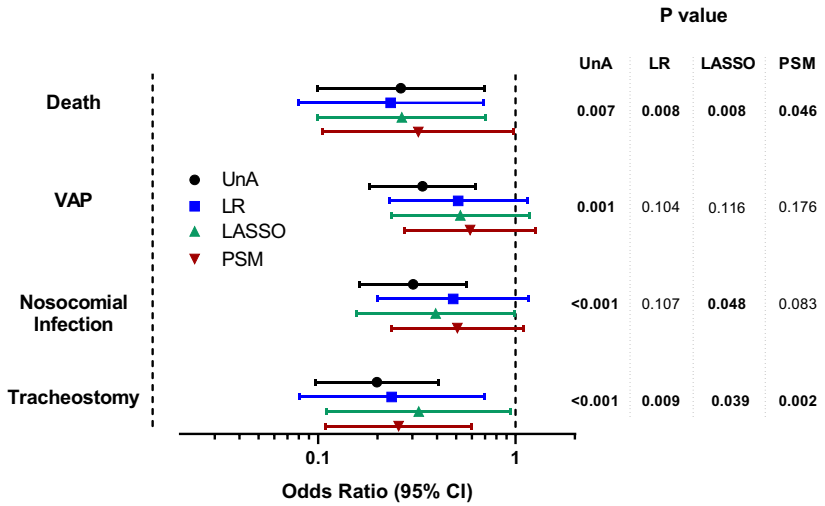

Fig. 2 Unadjusted (UnA) and adjusted study of clinical outcomes. Standard logistic regression (LR), least absolute shrinkage and selection operator (LASSO) logistic regression and logistic regression after propensity-score matching (PSM) were used to assess clinical outcomes in EXT group with CTRL group as reference, presented as odds ratio with their respective 95% confidence intervals. VAP, ventilator-associated pneumonia. Corresponding P-values are given on the right

associate with an increased incidence of major adverse events. This could be related, at least in part, to the fact that extubation during ECMO was associated with shorter ECMO runs, a well-established determinant of ECMO-related complications [17]. Of note, one case of non-fatal accidental ECMO decannulation occurred in the EXT group, 5 days after a failed extubation attempt, when the patient was on IMV under light sedation. An accidental decannulation requiring emergent intubation and brief cardiopulmonary resuscitation was also reported in a case series on the use of ECMO instead of IMV in ARDS by Hoeper et al. [10]. This underscores the importance of providing ECMO in centers with extensive experience for the immediate correct management of ECMO-related complications [18, 19]. Failed extubation rate was higher in the EXT group when compared with the CTRL group. Objective criteria for patient extubation under ECMO support are not clearly established and are based on expert recommendations from experienced centers [1, 2, 11, 20], and further studies are warranted to better define patient selection for this weaning strategy in severe ARDS. A higher incidence of cannula-associated deep vein thrombosis was observed in the EXT group. During ECMO support, higher platelets with similar systemic anticoagulation levels (as evaluated by the aPTT) could eventually have contributed, at least in part, to the higher rate of cannula-associated deep vein thrombosis observed in this group. In a recent experimental study, the reduction of platelets within an in vitro ECMO test circuit was associated with lower clot stability [21]. We did not collect individual patient data on the cannulae caliber, so we cannot hypothesize if this could have contributed to the observed differences in deep vein thrombosis between groups. Regarding ECMO blood flow, it did not differ between groups during the first week of ECMO support, so it is unlikely that it has contributed to the observed differences in cannula-associated deep vein thrombosis.

Despite the low level of systemic anticoagulation used in our study, the frequency of hemorrhagic shock in the CTRL group goes in line with the results of a systematic review and meta-analysis of complications and mortality of VV ECMO for refractory acute respiratory distress syndrome [5], in which significant bleeding was reported in 10.4% of cases. In a recent study, longer duration of ECMO support and lower platelet count were identified as independent risk factors for hemorrhage in adults on ECMO [22]. Both factors were observed in the CTRL group when compared with EXT group.

During ECMO support nosocomial infections, especially ventilator-associated pneumonia, are common and associated with worse outcomes [23, 24]. Extubation during ECMO was associated with a lower incidence of nosocomial infections in the ICU, namely ventilator-associated pneumonia, with a corresponding shorter duration of antibiotic therapy and more antibiotic-free days in the ICU (%). This is likely related to the shorter IMV and ICU length of stay in this group, which are two main determinants of ICU-acquired infections [25, 26]. In two studies analyzing the feasibility of patient extubation during ECMO, mostly for cardiac support, a lower incidence of ventilator-associated pneumonia was also observed [27, 28]. Regarding patient outcome, extubation during ECMO was associated with higher hospital survival when compared with the CTRL group, which could further indicate the safety of our standardized approach for extubation during ECMO in severe ARDS.

Patients in the CTRL group presented higher SAPS II and SOFA scores at ECMO initiation, with no significant differences in PF ratio and Murray score, indicating more extrapulmonary organ dysfunctions when compared to the EXT group. This agrees with the ELSO guideline on extubation during ECMO in patients with respiratory failure [11] and the initial published experience [4, 10, 29], in which readiness for extubation depends on the absence of circulatory shock or multi-organ failure, as well as on whether the patient is awake and cooperative.

Although patients extubated during ECMO had higher baseline static RS compliance, this was no longer apparent after ECMO initiation and adjustment of IMV to lower tidal volumes. Importantly, in our study, ECMO support allowed stable and adequate arterial blood gases for extubation, even in the face of significantly reduced RS compliance and extensive bilateral pulmonary infiltrates, typically observed in severe ARDS [30]. Recently, in a case report, Schmidt et al. were able to successfully treat COVID-19-associated severe ARDS with prolonged (41 days) 'awake ECMO' [31]. Before ECMO cannulation the chest X-ray showed extensive bilateral pulmonary infiltrates, with the chest computed tomography, performed on Day 20, still presenting extensive bilateral parenchymatous condensations. Analogously, extensive bilateral pulmonary infiltrates did not preclude successful extubation before ECMO decannulation of 5 patients with COVID-19-associated severe ARDS [32]. Differences in RS compliance between CTRL and EXT groups on the day of liberation from IMV could not be explained solely by the reduction of ventilation during ECMO, being also affected by the different timing of extubation (7 (4–18) vs. 32 (18–54); $P < 0.01$), meaning probably a different ARDS phase. Moreover, the difficulty in measuring RS compliance during assisted breathing [33, 34] should also be considered when interpreting these observed differences.

In our study, high-flow nasal oxygen was routinely used immediately after extubation during ECMO, with non-invasive ventilation being restricted to selected patients with obesity or COPD. This was well tolerated, importantly contributing to the success of this weaning strategy. High-flow nasal oxygen was also the preferred (66%) oxygen therapy modality for extubated ECMO patients in a retrospective study of 12 consecutive severe ARDS patients supported with ECMO [35]. Differently, in a previous study by Crotti et al. [16] spontaneously breathing in early ARDS on ECMO (mean duration of IMV was 3 days) was found to be very difficult to manage, with high levels of PEEP through CPAP required to limit lung derecruitment and collapse. This was attributed to the huge degree of lung inflammation, parenchymal edema, and consequent alveolar collapse, with other organ dysfunctions and septic shock often complicating the clinical picture. In our study, spontaneous breathing was implemented at a later stage of ARDS (mean duration of IMV was 7 days) and in the absence of significant extrapulmonary organ dysfunctions, which could have contributed to favorable clinical outcomes. However, considering the recently published evidence in patients at high risk of extubation failure [36], as well as the median PEEP value at the time of extubation (8 cmH_2O) in the EXT group, a routine strategy of cycles of noninvasive ventilation or CPAP with a high-flow nasal cannula, to avoid possible derecruitment after extubation (unless there are contraindications or the patient does not tolerate it), could have been of value to reduce extubation failure.

Health-related quality of life evaluated 3–6 months after hospital discharge, as evaluated by the EQ-5D-5L instrument, was significantly improved in the EXT group when compared with the CTRL group, suggesting that the weaning strategy of extubation during ECMO support in severe ARDS could associate with improved patient recovery. However, further research is needed to clarify the clinical significance of these results, given that in our study no differences were detected between groups at follow-up in patient self-rated health (as evaluated by the EQ-VAS), the sample size is relatively small, there is no data on deconditioning such as limb muscle strength [37], and there is no information regarding delirium/delirium screening, all considered relevant for the potential benefits of 'awake ECMO [4].

This study has several limitations that should be addressed. It is a two-center study over 6 years, which could limit its internal and external validity. The studied groups (EXT and CTRL groups) are not well-balanced regarding baseline patient characteristics, which may have affected the group assignment and the clinical

outcomes. The observational design of the study does not infer causality, namely, it does not allow us to distinguish the impact on the clinical outcomes (e.g., mortality and nosocomial infections) of meeting the clinical and gas exchange criteria or being extubated during ECMO. Moreover, given that during the ECMO run the gas exchanges depend on the patient's interactions with the extracorporeal support, it would have been necessary to measure oxygen consumption (VO_2) and CO_2 removal (VCO_2) by the ventilator and by the ECMO circuit to understand the relative contribution of the native and the membrane lung to the gas exchanges during extubation. We also did not collect individual patient data on the timing of the first assessment for extubation after ECMO cannulation, which could have provided further information on the usual management (such as prone positioning, neuromuscular blocker agents, and sedation) after ECMO implantation. Finally, our study did not evaluate the role of ECMO initiation in ARDS patients before endotracheal intubation. Although it has been previously shown to be feasible [10, 29, 38], a recent study on 18 adults patients with COVID-19-associated severe ARDS from 4 German tertiary care ICUs did not recommend this 'awake-ECMO' approach, as a high rate of patients receiving 'awake-ECMO' were finally intubated (78%) and those subsequently intubated seem to have higher mortality than patients managed conventionally with IMV and ECMO [39].

Conclusions

A standardized approach was safe and feasible allowing extubation during ECMO in 21% of patients with severe ARDS, selecting patients who will have a shorter duration of invasive mechanical ventilation, ECMO course, and ICU stay, as well as fewer infectious complications, and high hospital survival. While it is recognized that an observational study does not imply causality, the favorable outcomes observed in the present study could set the stage for further research and stimulate high-volume ECMO centers to consider in selected patients with severe ARDS the strategy of extubation during ECMO as an integral part of their treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13613-023-01185-y.

Additional file 1. Table S1. Ventilatory, gas exchange, and extracorporeal membrane oxygenation (ECMO) parameters before and at ECMO Day 1. **Table S2.** Ventilatory, gas exchange, and extracorporeal membrane oxygenation (ECMO) parameters at liberation from invasive mechanical ventilation and at ECMO decannulation **Table S3.** Platelet count and coagulation parameters. **Table S4.** Sample characteristics before and after matching in the CTRL and EXT groups. **Table S5.** Unadjusted and adjusted analysis of the duration of ECMO, IMV and ICU length of stay**. Figure S1:** Kaplan–Meier analysis for all-cause mortality stratified by group (EXT vs CTRL) before (A) and after (B) Propensity-score Matching.

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Author contributions
All authors fulfilled the 4 criteria for attributing authorship: (i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (ii) drafting the work or revising it critically for important intellectual content; (iii) final approval of the version to be published, and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The institutional Ethics Committee reviewed and approved the study and waived the requirement for patient consent (Approval number: CES 205/2022).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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2.7. Comparative outcomes of ECMO for COVID-19 delivered in experienced European centres during successive SARS-CoV-2 variant outbreaks (ECMO-SURGES): an international, multicentre, retrospective cohort study.

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Comparative outcomes of extracorporeal membrane oxygenation for COVID-19 delivered in experienced European centres during successive SARS-CoV-2 variant outbreaks (ECMO-SURGES): an international, multicentre, retrospective cohort study

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Summary

Background To inform future research and practice, we aimed to investigate the outcomes of patients who received extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) due to different variants of SARS-CoV-2.

Methods This retrospective study included consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received ECMO for ARDS in 21 experienced ECMO centres in eight European countries (Austria, Belgium, England, France, Germany, Italy, Portugal, and Spain) between Jan 1, 2020, and Sept 30, 2021. We collected data on patient characteristics, clinical status, and management before and after the initiation of ECMO. Participants were grouped according to SARS-CoV-2 variant (wild type, alpha, delta, or other) and period of the pandemic (first [Jan 1–June 30] and second [July 1–Dec 31] semesters of 2020, and first [Jan 1–June 30] and second [July 1–Sept 30] semesters of 2021). Descriptive statistics and Kaplan-Meier survival curves were used to analyse evolving characteristics, management, and patient outcomes over the first 2 years of the pandemic, and independent risk factors of mortality were determined using multivariable Cox regression models. The primary outcome was mortality 90 days after the initiation of ECMO, with follow-up to Dec 30, 2021.

Findings ECMO was initiated in 1345 patients. Patient characteristics and management were similar for the groups of patients infected with different variants, except that those with the delta variant had a younger median age and less hypertension and diabetes. 90-day mortality was 42% (569 of 1345 patients died) overall, and 43% (297/686) in patients infected with wild-type SARS-CoV-2, 39% (152/391) in those with the alpha variant, 40% (78/195) in those with the delta variant, and 58% (42/73) in patients infected with other variants (mainly beta and gamma). Mortality was 10% higher (50%) in the second semester of 2020, when the wild-type variant was still prevailing, than in other semesters (40%). Independent predictors of mortality were age, immunocompromised status, a longer time from intensive care unit admission to intubation, need for renal replacement therapy, and higher Sequential Organ Failure Assessment haemodynamic component score, partial pressure of arterial carbon dioxide, and lactate concentration before ECMO. After adjusting for these variables, mortality was significantly higher with the delta variant than with the other variants, the wild-type strain being the reference.

Interpretation Although crude mortality did not differ between variants, adjusted risk of death was highest for patients treated with ECMO infected with the delta variant of SARS-CoV-2. The higher virulence and poorer outcomes associated with the delta strain might relate to higher viral load and increased inflammatory response syndrome in infected patients, reinforcing the need for a higher rate of vaccination in the population and updated selection criteria for ECMO, should a new and highly virulent strain of SARS-CoV-2 emerge in the future. Mortality was noticeably lower than in other large, multicentre series of patients who received ECMO for COVID-19, highlighting the need to concentrate resources at experienced centres.

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Research in context

Evidence before this study

Data from retrospective cohorts of patients with COVID-19 treated with extracorporeal membrane oxygenation (ECMO) during the first few weeks of the pandemic revealed that despite longer ECMO runs and intensive care unit (ICU) length of stay, the mortality of patients with COVID-19 supported by ECMO was similar to that reported in the EOLIA trial and in other large retrospective series of ECMO for non-COVID-19 acute respiratory distress syndrome (ARDS). However, less favourable outcomes were reported in patients treated from July to December, 2020, and a strong effect of patient volume and ECMO centre experience has been noted in most multicentre cohorts published so far, which included almost exclusively patients infected with the wild-type strain of SARS-CoV-2. We aimed to identify all available evidence on the outcomes of patients who received ECMO for severe COVID-19 according to the different SARS-CoV-2 variants, during successive waves of the pandemic. We searched PubMed for articles published in any language in peer-reviewed journals from Jan 1, 2020, up to Aug 8, 2022, with the terms "extracorporeal membrane oxygenation" and either "COVID-19" or "severe acute respiratory syndrome coronavirus 2", and focused on large, multicentre cohort studies that included at least 200 patients treated with ECMO. We found 15 studies, but none of them reported patient outcomes after infection with different variants of SARS-CoV-2.

Added value of this study

Our multicentre, international, retrospective study included 1345 patients who received ECMO in 21 experienced centres in eight European countries. Patient characteristics and management were similar across different variants of SARS-CoV-2, except that the delta group had a younger age and fewer comorbidities than did the groups for other variants. We found that crude 90-day mortality did not differ between variants and was 15–25% lower than the in-hospital mortality reported in other large COVID-19 series. Independent predictors of mortality were age, immunocompromised status, a longer time from ICU admission to intubation, need for renal replacement therapy, and higher Sequential Organ Failure Assessment haemodynamic component score, partial pressure of arterial carbon dioxide, and lactate concentration before ECMO. After adjusting for these variables, mortality was significantly higher with the delta variant than with other variants of SARS-CoV-2.

Implications of all the available evidence

Adjusted mortality of patients with COVID-19-related ARDS treated with ECMO was higher for those infected with the delta variant, who were younger and had fewer comorbidities at ECMO initiation. The higher virulence and poorer outcomes associated with the delta strain might relate to higher viral load and increased inflammatory response syndrome in infected patients, reinforcing the need for a higher rate of vaccination in the population and updated selection criteria for ECMO, should a new and highly virulent strain of SARS-CoV-2 emerge in the future. Mortality in our series of patients treated in experienced ECMO centres was noticeably lower than that in other large multicentre series of patients receiving ECMO for COVID-19, underlying the need to concentrate resources at experienced centres, especially during pandemics that impose substantial burdens on health-care systems.

Introduction

The global pandemic of SARS-CoV-2 started in January, 2020, with the most serious forms of the disease rapidly evolving to severe acute respiratory distress syndrome (ARDS). Based on positive results from randomised controlled trials,[1–3] and a meta-analysis of individual patient data[4] done in non-COVID-19-related ARDS, extracorporeal membrane oxygenation (ECMO) was recommended for patients with COVID-19 who had profound hypoxaemia or high thoracic pressures despite lung-protective mechanical ventilation, including prone positioning.[5–7] Single-centre[8] and multicentre international cohorts[5,9–11] showed that despite longer ECMO runs and length of stay in the intensive care unit (ICU), the mortality of patients with COVID-19 who were treated with ECMO during the first few weeks of the pandemic was similar to that reported in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[1] and in other large retrospective series of ECMO for non-COVID-19 ARDS.[12–14] However, these encouraging results were challenged by less favourable outcomes in patients treated after July, 2020. For example, the 90-day mortality increased from 36% to 48% between the first and second waves of COVID-19 in patients admitted to hospital at Sorbonne University, Paris, France.[15] Similar increases in mortality were reported in the large cohort of the Extracorporeal Life Support Organization (ELSO)[9] and in patients treated in Spain and Portugal.[16] The reasons for this increase in mortality are still unclear and the respective effects of specific SARS-CoV-2 strains responsible for ARDS, ECMO centre experience, patient characteristics, and patient management have not yet been investigated in detail in large, multicentre cohorts.

The primary objective of this multicentre, international, retrospective study was to analyse, according to different SARS-CoV-2 variants, the characteristics and 90-day mortality of patients with COVID-19 who received ECMO in experienced European centres. Secondary objectives were to report the evolving characteristics, management, and outcomes of these patients during the first 2 years of the pandemic and to determine independent risk factors for mortality.

Methods

Study design and participants

The ECMO-SURGES study was a multicentre, retrospective cohort study done in 21 medium-volume (15–30 venoarterial ECMO [VA-ECMO] or venovenous ECMO [VV-ECMO] cases per year) to high-volume (>30 cases per year) experienced ECMO centres[17] across eight European countries (Austria, Belgium, England, France, Germany, Italy, Portugal, and Spain). Centres were invited to participate if they had an ECMO programme established for at least 5 years and were currently caring for patients with COVID-19 on ECMO. All participating ICUs obtained institutional review board approval in accordance with their local regulations.

All consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received VA-ECMO or VV-ECMO for severe ARDS from Jan 1, 2020, to Sept 30, 2021, were included retrospectively. Patients receiving ECMO for isolated refractory cardiogenic shock were excluded. The end of follow-up was Dec 30, 2021.

Time periods and SARS-CoV-2 variants

We defined four periods during the study: Jan 1–June 30, 2020 (first semester of 2020, S1-2020); July 1–Dec 31, 2020 (second semester of 2020, S2-2020); Jan 1–June 30, 2021 (first semester of 2021, S1-2021); and July 1–Sept 30, 2021 (second semester of 2021, S2-2021). SARS-CoV-2 variants were classified as wild type, alpha (B.1.17), delta (B.1.617.2), or other variants. This latter group combined the gamma (P.1), beta (B.1.351), mu (B.1.621), and B.1.160 variants. Because sequencing was not routinely done during the first and second waves of the pandemic, all patients treated before Oct 31, 2020 (when the alpha variant was first reported in England) were considered to have the wild-type variant. When SARS-CoV-2 variant sequencing was not done, patients were categorised as having the predominant variant in the country at the date of admission to the ICU according to the European Centre for Disease Prevention and Control, which reported the number of cases per week and per country in Europe on a weekly basis.

Data collection

We collected patient information on age, sex, body-mass index, comorbidities, SARS-CoV-2 vaccination status, haemodynamic component of the Sequential Organ Failure Assessment (SOFA) score, and dates of first symptom(s) and hospital and ICU admissions. Patients were defined as having an immuno-compromised status if they had haematological malignancies, had an active solid tumour or had received specific anti-tumour treatment within the previous year, had undergone solid-organ transplant, were living with HIV, or were on long-term corticosteroids or immunosuppressants. Additionally, we collected pre-ECMO implantation information: previous rescue therapies; date of initiation of high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation; and ventilator parameters (mode, positive end-expiratory pressure [PEEP], fraction of inspired oxygen [FiO_2], respiratory rate [RR], tidal volume [V_t], plateau pressure [P_{plat}], arterial blood gas parameters including partial pressure of oxygen [PaO_2] and partial pressure of carbon dioxide [$PaCO_2$], and routine laboratory values). Driving pressure (ΔP) was defined as P_{plat} minus PEEP, and mechanical power (J/min) was calculated using the equation:[18]

$$\text{Mechanical power} = 0{\cdot}098 \times V_t \times RR \times (\text{peak pressure} - 1/2 \times \Delta P)$$

If not specified, peak pressure was considered equal to plateau pressure.

Outcomes

Patient status was recorded 90 days after ECMO initiation. For patients who were still alive at day 90, the following states were defined: on ECMO; on mechanical ventilation and weaned off ECMO; still in hospital and weaned off ECMO and mechanical ventilation; in a rehabilitation centre; or back at home. Causes of death, in-ICU and in-hospital death rates, and the time spent on ECMO, on mechanical ventilation, in the ICU, and in hospital were also noted. Data on mechanical ventilation parameters and other adjuvant therapies were collected on days 1 and 3 after ECMO initiation. ECMO-related complications and organ dysfunction included clogged circuit or membrane, ECMO circuit change, heparin-induced thrombocytopenia, major

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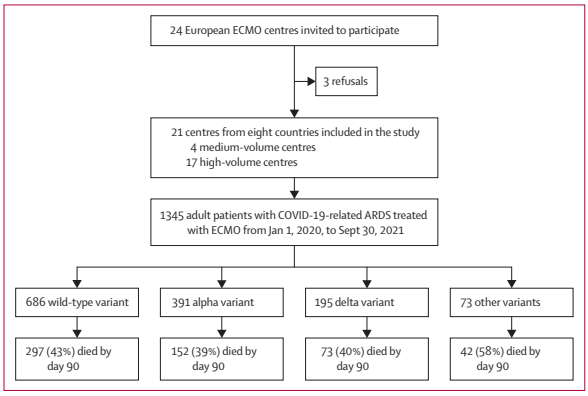

Figure 1: **Study flowchart**
ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation.

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See Online for appendix

For more on the **Extracorporeal Life Support Organization** see https://www.elso.org/

For more on the **European Centre for Disease Prevention and Control COVID-19 reporting** see https://www.ecdc.europa.eu/en/covid-19

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Age, years	53 (44–59)	54 (46–60)	53 (45–58)	46 (37–55)	55 (49–62)	<0·0001
Sex	..	..	..	..	..	0·261
Male	1035 (77%)	540 (79%)	300 (77%)	143 (73%)	52 (71%)	..
Female	310 (23%)	146 (21%)	91 (23%)	52 (27%)	21 (29%)	..
Body-mass index, kg/m²	30 (27–35)	29 (26–34)	31 (27–37)	31 (28–35)	31 (27–36)	0·017
SOFA cardiovascular component ≥3	573 (53%)	323 (56%)	145 (50%)	75 (51%)	30 (43%)	0·083
COVID-19 vaccination status	..	..	..	..	..	0·0005
1 vaccine dose	24 (2%)	0	5 (1%)	15 (8%)	4 (5%)	..
2 vaccine doses	17 (1%)	0	3 (1%)	12 (6%)	2 (3%)	..
Comorbidities						
Hypertension	555 (41%)	299 (44%)	166 (42%)	55 (28%)	35 (48%)	0·0008
Diabetes	327 (24%)	193 (28%)	89 (23%)	27 (14%)	18 (25%)	0·0005
Ischaemic cardiomyopathy	76 (6%)	41 (6%)	24 (6%)	7 (4%)	4 (5%)	0·589
Chronic respiratory disease*	158 (12%)	77 (11%)	52 (13%)	15 (8%)	14 (19%)	0·045
Immunocompromised†	84 (6%)	41 (6%)	23 (6%)	12 (6%)	8 (11%)	0·407
Pregnant	22 (2%)	7 (1%)	9 (2%)	6 (3%)	0 (0%)	0·102
Time from first symptoms to hospital admission, days	6 (3–8)	6 (3–8)	5 (3–8)	6 (4–8)	6 (3–8)	0·383
Time from ICU admission to intubation, days	1 (0–4)	0 (0–3)	1 (0–5)	1 (0–3)	3 (1–6)	<0·0001
Time from intubation to ECMO, days	4 (1–8)	4 (2–8)	3 (1–7)	4 (1–8)	4 (1–7)	0·017
Retrieval on ECMO by MERT from another hospital	857 (64%)	434 (63%)	252 (64%)	132 (68%)	39 (53%)	0·185
High-flow nasal oxygen	675 (50%)	310 (45%)	199 (51%)	114 (58%)	52 (71%)	<0·0001
Duration, days	1 (0–4)	1 (0–4)	2 (0–5)	1 (0–4)	3 (1–6)	<0·0001
Non-invasive ventilation	567 (42%)	229 (33%)	197 (50%)	100 (51%)	41 (56%)	<0·0001
Duration, days	1 (0–4)	0 (0–3)	1 (0–4)	2 (0–5)	3 (1–6)	0·0009
Ventilation parameters						
FiO_2	100 (100–100)	100 (100–100)	100 (100–100)	100 (95–100)	100 (100–100)	0·581
PEEP, cm H_2O	12 (10–14; n=1157)	12 (10–14; n=608)	12 (10–14; n=327)	12 (10–15; n=162)	12 (10–14; n=60)	0·361
Tidal volume, mL/kg PBW	6·1 (5·5–6·9; n=1068)	6·1 (5·6–7·0; n=569)	6·1 (5·4–6·9; n=303)	6·3 (5·7–7·2; n=151)	6·1 (5·5–7·0; n=56)	0·215
Respiratory rate, breaths per min	26 (23–30; n=1077)	26 (23–30; n=587)	26 (22–30; n=291)	25 (22–28; n=141)	28 (25–30; n=58)	0·0038
Driving pressure, cm H_2O‡	18 (15–22; n=1050)	18 (15–22; n=545)	18 (15–21; n=303)	16 (14–20; n=145)	19 (16–22; n=57)	0·0060
Static compliance, mL/cm H_2O	22·5 (17·5–29·7; n=994)	22·5 (17·6–30·0; n=519)	23·0 (16·9–28·3; n=284)	25·0 (18·5–32·3; n=137)	20·7 (15·2–23·8; n=54)	0·0046
Mechanical power, J/min§	21·7 (17·6–25·9; n=939)	22·1 (18·2–26·3; n=513)	20·9 (17·1–25·2; n=254)	21·1 (16·8–25·7; n=120)	22·2 (17·5–26·4; n=52)	0·086

(Table 1 continues on next page)

bleeding, ischaemic or haemorrhagic stroke, renal replacement therapy, proven pulmonary embolism, pneumothorax, ventilator-associated pneumonia, and bacteraemia. Major bleeding was defined as requiring at least 2 units of packed red blood cells for an obvious haemorrhagic event, an event necessitating a surgical or interventional procedure, an intracerebral haemorrhage, or any other bleeding event leading to death.

Statistical analysis

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for reporting cohort studies. All consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received ECMO at the 21 centres during the study period were included, and no sample size calculation was performed. Details of the statistical analyses are provided in the appendix (pp 2–5).

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
(Continued from previous page)						
Last blood gas values pre-ECMO						
pH	7·32 (7·24–7·38)	7·31 (7·23–7·39)	7·33 (7·25–7·39)	7·32 (7·25–7·38)	7·34 (7·28–7·38)	0·283
PaO_2/FiO_2 ratio	66 (55–80)	68 (56–81)	65 (51–80)	65 (51–80)	60 (56–67)	0·0008
$PaCO_2$, mm Hg	60 (50–71)	60 (50–74)	60 (50–70)	60 (50–70)	56 (48–64)	0·087
Arterial lactate, mmol/L	1·4 (1·0–2·0)	1·4 (1·1–2·0)	1·4 (1·0–2·0)	1·3 (1·0–2·0)	1·5 (1·2–2·1)	0·084
Bacterial coinfection	476 (35%)	219 (32%)	143 (37%)	86 (44%)	28 (38%)	0·015
Laboratory values						
White blood cell count, $\times 10^9$ cells per L	13·4 (9·4–18·1; n=1109)	12·9 (9·2–17·9; n=594)	13·2 (9·4–18·4; n=306)	14·5 (10·5–20·9; n=141)	14·0 (9·8–18·6; n=68)	0·038
Serum creatinine, µmol/L	70 (53–103; n=1117)	71 (54–109; n=604)	70 (52–98; n=301)	67 (47–96; n=143)	69 (48–111; n=69)	0·274
Serum bilirubin, µmol/L	7 (5–13; n=1041)	7 (5–13; n=559)	7 (4–13; n=283)	8 (5–13; n=131)	7 (5–11; n=68)	0·678
Platelet count, $\times 10^9$ per L	257 (186–342)	249 (178–339)	255 (195–339)	276 (212–360)	240 (171–317)	0·037
Rescue therapy pre-ECMO						
Neuromuscular blockade	1278 (95%)	648 (94%)	370 (95%)	188 (96%)	72 (99%)	0·387
Prone positioning	1203 (89%)	603 (88%)	357 (91%)	179 (92%)	64 (88%)	0·208
Inhaled nitric oxide	371 (28%)	192 (28%)	100 (26%)	49 (25%)	30 (41%)	0·044
Recruitment manoeuvres	334 (25%)	166 (24%)	96 (25%)	58 (30%)	14 (19%)	0·269
Almitrine	20 (1%)	11(2%)	3 (1%)	3 (2%)	3 (4%)	0·190
Renal replacement therapy	67 (5%)	38 (6%)	14 (4%)	10 (5%)	5 (7%)	0·399
Cardiac arrest	58 (4%)	41 (6%)	14 (4%)	3 (2%)	0	0·0040
Pneumothorax	159 (12%)	76 (11%)	49 (13%)	21 (11%)	13 (18%)	0·352

Data are median (IQR) or n (%); the number of patients for whom data were available is specified when less than the total for any group. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. ICU=intensive care unit. MERT=Mobile ECMO Retrieval Team. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. SOFA=Sequential Organ Failure Assessment. *Chronic obstructive pulmonary disease or asthma. †Patients with haematological malignancies or an active solid tumour, those who had received specific anti-tumour treatment within 1 year, those who had undergone a solid-organ transplant, HIV-positive patients, or those on long-term corticosteroids or immunosuppressants. ‡Driving pressure=plateau pressure – PEEP. §Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.

Table 1: **Patients' pre-ECMO characteristics according to SARS-CoV-2 variant**

Patient characteristics are reported as number (percentage) for categorical variables, and median (IQR) for continuous variables. Categorical variables were compared by χ^2 or Fisher's exact test, and continuous variables were compared using Student's t test or the Kruskal-Wallis rank-sum test. Kaplan-Meier overall survival curves until day 90 were computed and were compared using log-rank tests.

Baseline risk factors for death at day 90 were assessed within the whole cohort using multivariable Cox regression models. Baseline variables (ie, those obtained before ECMO initiation) included in the multivariable model were defined a priori (COVID variant and age, sex, body mass index, chronic respiratory disease, treated hypertension, diabetes mellitus, immunocompromised status, time from first symptoms to hospital admission, time from intensive care unit admission to intubation, time from intubation to ECMO, cardiac arrest, haemodynamic component of the SOFA score, renal replacement therapy, bacterial coinfection, mechanical power, pneumothorax, $PaCO_2$, PaO_2/FiO_2 ratio, lactate, platelets, recruitment manoeuvres, prone positioning, inhaled nitric oxide, and neuromuscular blockade), and no variable selection was done. Log linearity was graphically assessed for the quantitative variables' effects using restricted cubic splines. The Cox regression model was stratified on the country variable. Multiple imputations (appendix pp 3–4) were used to replace missing values (appendix pp 6–9), when appropriate. Ten copies of the dataset were created with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of the participants. Each dataset was then analysed and the results from each dataset were pooled to give a final result using Rubin's rule.[19] Hazard ratios and their 95% CIs were estimated on the final pooled dataset using Rubin's rule. Additionally, two prespecified sensitivity analyses were done: one after excluding the 84 patients for whom the variant type was missing and the other with the semester of inclusion in the study instead of the SARS-CoV-2 variant.

All analyses were computed at a two-sided alpha level of 5%. Statistical analyses were done with R version 4.2.0.

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Type of ECMO support	..	..	..	..	..	0·529
VV-ECMO	1318 (98%)	668 (97%)	384 (98%)	194 (99%)	72 (99%)	..
Femoral–jugular	1045 (78%)	539 (79%)	290 (74%)	152 (78%)	64 (88%)	..
VA-ECMO	19 (1%)	13 (2%)	5 (1%)	1 (1%)	0	..
VAV-ECMO	8 (1%)	5 (1%)	2 (0.5%)	0	1 (1%)	..
Ventilation parameters on day 1						
FiO_2	50 (40–70)	50 (40–70)	50 (40–70)	50 (40–60)	50 (40–70)	0·138
PEEP, cm H_2O	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·843
Tidal volume, mL/kg PBW	2·9 (2·0–4·2)	3·0 (2·0–4·2)	2·7 (1·9–4·1)	3·1 (2·1–4·7)	2·7 (2·0–3·6)	0·200
Respiratory rate, breaths per min	14 (10–20)	14 (12–20)	14 (10–16)	12 (12–16)	12 (10–20)	0·002
Driving pressure, cm H_2O*	12 (10–14)	12 (11–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·867
Compliance, mL/cm H_2O	15·6 (10·0–23·1)	16·7 (10·7–23·4)	15·0 (9·7–21·9)	15·9 (10·5–23·3)	14·3 (9·8–20·0)	0·097
Mechanical power, J/min†	4·7 (2·9–7·4)	5·1 (3·2–8·2)	4·4 (2·6–6·7)	4·1 (2·9–7·6)	4·0 (2·5–7·0)	0·002
Ventilation mode on day 1	..	..	..	..	..	0·0005
APRV or bilevel PAPV	288 (22%)	167 (25%)	72 (19%)	23 (12%)	26 (38%)	..
Volume control ventilation	279 (21%)	150 (22%)	72 (19%)	29 (15%)	28 (41%)	..
Pressure control ventilation	735 (56%)	350 (52%)	233 (62%)	138 (73%)	14 (21%)	..
Neuromuscular blockade on day 1	860 (67%)	440 (68%)	250 (68%)	123 (67%)	47 (64%)	0·918
Prone positioning on day 1	200 (15%)	76 (11%)	73 (19%)	38 (19%)	13 (18%)	0·0011
Inhaled nitric oxide on day 1	63 (5%)	28 (4%)	23 (6%)	10 (5%)	2 (3%)	0·514
Awake on ECMO on day 1‡	13 (1%)	2 (<1%)	6 (2%)	4 (2%)	1 (1%)	0·032
Ventilation parameters on day 3						
FiO_2	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	0·994
PEEP, cm H_2O	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·206
Tidal volume, mL/kg PBW	2·9 (1·9–4·4)	2·9 (1·9–4·3)	2·7 (1·8–4·2)	3·2 (1·9–5·0)	3·5 (2·5–5·2)	0·058
Respiratory rate, breaths per min	14 (12–20)	14 (12–20)	14 (10–18)	13 (12–16)	15 (10–20)	0·0102
Driving pressure, cm H_2O*	12 (10–14)	12 (11–14)	13 (10–14)	12 (10–15)	14 (12–15)	0·282
Compliance, mL/cm H_2O	15·8 (10·2–23·3)	16·2 (10·0–23·3)	15·0 (9·0–23·0)	16·0 (10·0–23·0)	17·2 (11·1–26·0)	0·331
Mechanical power, J/min†	4·7 (2·9–7·8)	5·0 (3·1–8·5)	4·3 (2·5–6·6)	4·4 (2·3–7·7)	6·4 (3·3–9·8)	0·0009
Neuromuscular blockade on day 3	736 (57%)	382 (58%)	221 (59%)	91 (48%)	42 (62%)	0·067
Prone positioning on day 3	286 (21%)	113 (17%)	98 (25%)	42 (22%)	33 (46%)	<0·0001
Inhaled nitric oxide on day 3	39 (3%)	19 (3%)	13 (3%)	5 (3%)	2 (3%)	0·935
Awake on ECMO on day 3‡	32 (2%)	8 (1%)	19 (5%)	5 (3%)	0	0·0015

Data are median (IQR) or n (%). APRV=airway pressure release ventilation. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. PAPV=positive airway pressure ventilation. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. VA-ECMO=venoarterial ECMO. VAV-ECMO=venoarteriovenous ECMO. VV-ECMO=venovenous ECMO. *Driving pressure=plateau pressure – PEEP. †Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure. ‡Defined as the patient being awake, cooperative, and performing rehabilitation and physiotherapy.

Table 2: **Patients' characteristics on ECMO day 1 and day 3 according to SARS-CoV-2 variant**

Role of the funding source
There was no funding source for this study.

Results

Among 24 European ECMO centres invited to participate in the ECMO-SURGES study, 21 centres (four medium-volume centres and 17 high-volume centres) from eight countries included patients with COVID-19 treated with ECMO in the study (figure 1). The main characteristics of these centres are described in the appendix (p 10). Notably, the median number of ECMO cases treated in these centres in 2019 was 40 (IQR 30–81), and a mobile rescue team was available in 18 (86%) of 21 centres before the pandemic and in 17 (81%) centres during the pandemic. Most centres followed the EOLIA entry criteria[1] to indicate ECMO. The median upper age to deny ECMO support fell from 70 years (IQR 65–70) before the pandemic to 65 years (65–65) during the pandemic, and more

contraindications to ECMO such as pre-ECMO cardiac arrest and severe immunocompromised status existed during the pandemic than before it (appendix p 10). Thus, between Jan 1, 2020, and Sept 30, 2021, 1345 patients were treated with ECMO in these centres: 324 during S1-2020, 352 during S2-2020, 496 during S1-2021, and 173 during S2-2021. Sequencing was done for 1261 (94%) of 1345 patients and the predominant variant in the country was considered for 84 patients without virus sequencing who were admitted to hospital after Oct 31, 2020. 686 (51%) of 1345 cases were infected with the wild-type variant, whereas alpha, delta, and other

	All (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Tracheostomy	693 (52%)	347 (51%)	198 (51%)	118 (61%)	30 (41%)	0·0199
Time from intubation to tracheostomy, days	19 (12–29)	20 (13–30)	19 (12–29)	17 (12–23)	20 (11–32)	0·077
Renal replacement therapy	472 (35%)	261 (38%)	124 (32%)	64 (33%)	23 (32%)	0·142
Prone positioning on ECMO	635 (47%)	327 (48%)	193 (49%)	69 (35%)	46 (63%)	0·0003
Number of sessions on ECMO	0 (0–3)	0 (0–3)	0 (0–4)	0 (0–3)	2 (0–5)	0·0008
Received COVID-19-specific treatment*						
Remdesivir	163 (12%)	98 (14%)	47 (12%)	16 (8%)	2 (3%)	0·0079
Tocilizumab	223 (17%)	90 (13%)	51 (13%)	69 (35%)	13 (18%)	<0·0001
Dexamethasone	928 (69%)	345 (50%)	342 (87%)	175 (90%)	66 (90%)	<0·0001
High-dose corticosteroids (Meduri protocol)	451 (34%)	219 (32%)	138 (35%)	61 (31%)	33 (45%)	0·1002
ECMO-related complications						
Clogged circuit or membrane requiring change	449 (33%)	205 (30%)	144 (37%)	89 (46%)	11 (15%)	<0·0001
Number of circuit change(s)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0·0047
Repeat ECMO needed after decannulation	36 (3%)	20 (3%)	8 (2%)	6 (3%)	2 (3%)	0·817
Heparin-induced thrombocytopenia	90 (7%)	35 (5%)	29 (7%)	20 (10%)	6 (8%)	0·058
Major bleeding	432 (32%)	252 (37%)	109 (28%)	53 (27%)	18 (25%)	0·0024
Ischaemic stroke	39 (3%)	15 (2%)	11 (3%)	10 (5%)	3 (4%)	0·147
Haemorrhagic stroke	98 (7%)	49 (7%)	36 (9%)	12 (6%)	1 (1%)	0·097
Pneumothorax on ECMO	202 (15%)	93 (14%)	59 (15%)	35 (18%)	15 (21%)	0·239
Pulmonary embolism	168 (12%)	79 (11%)	55 (14%)	23 (12%)	11 (15%)	0·569
≥1 antibiotic-treated ventilator-associated pneumonia	887 (69%)	421 (66%)	260 (67%)	146 (75%)	60 (82%)	0·0051
≥1 antibiotic-treated bacteraemia episode(s)	571 (44%)	288 (45%)	163 (42%)	87 (45%)	33 (45%)	0·799
Outcomes						
Lung transplant on ECMO	6 (1%)	4 (1%)	1 (<1%)	1 (1%)	0	0·899
ECMO duration, days	21 (10–40)	19 (10–36)	22 (11–43)	25 (13–43)	21 (11–36)	0·021
Mechanical ventilation duration, days	37 (21–58)	36 (21–57)	38 (21–58)	39 (25–62)	33 (22–49)	0·185
ICU length of stay, days	43 (26–63)	42 (25–63)	44 (26–63)	44 (32–68)	42 (28–61)	0·316
Hospital length of stay, days	52 (33–79)	52 (32–79)	51 (34–77)	56 (38–84)	45 (31–67)	0·127
ECMO successfully weaned	812 (60%)	400 (58%)	258 (66%)	119 (61%)	35 (48%)	0·011
ICU discharge survival	737 (55%)	374 (54%)	232 (60%)	103 (55%)	28 (40%)	0·020
Hospital discharge survival	667 (52%)	319 (50%)	226 (59%)	97 (53%)	25 (37%)	0·0023
90-day survival status	..	..	..	..	..	0·0101
Dead	569 (42%)	297 (43%)	152 (39%)	78 (40%)	42 (58%)	..
On ECMO	53 (4%)	37 (5%)	8 (2%)	8 (4%)	0	..
On mechanical ventilation and weaned off ECMO	47 (3%)	26 (4%)	11 (3%)	9 (5%)	1 (1%)	..
Still in the hospital and weaned off ECMO	89 (7%)	43 (6%)	32 (8%)	14 (7%)	0	..
In rehabilitation	120 (9%)	56 (8%)	35 (9%)	19 (10%)	10 (14%)	..
Back home	467 (35%)	227 (33%)	153 (39%)	67 (34%)	20 (27%)	..

(Table 3 continues on next page)

	All (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
(Continued from previous page)						
Cause of death (n=592)	..	..	..	..	..	0·0125
Septic shock	165 (28%)	94 (30%)	41 (26%)	19 (23%)	11 (27%)	..
Unspecified multiorgan failure	133 (22%)	73 (23%)	26 (17%)	25 (30%)	9 (22%)	..
Stroke	62 (10%)	28 (9%)	20 (13%)	12 (14%)	2 (5%)	..
Haemorrhagic shock	38 (6%)	20 (6%)	10 (6%)	6 (7%)	2 (5%)	..
Cardiovascular shock	21 (4%)	6 (2%)	5 (3%)	9 (10%)	1 (2%)	..
ECMO device failure	3 (1%)	1 (<1%)	1 (1%)	0	1 (2%)	..
Cannulation complication	9 (2%)	6 (2%)	1 (1%)	0	2 (5%)	..
Transport complication	1 (<1%)	1 (<1%)	0	0	0	..
Persistent respiratory failure other than COVID-19	46 (8%)	31 (10%)	11 (7%)	3 (4%)	1 (2%)	..
Refractory respiratory failure related to COVID-19	108 (18%)	48 (15%)	38 (25%)	10 (12%)	12 (30%)	..
Other	6 (1%)	4 (1%)	2 (1%)	0	0	..

Data are median (IQR) or n (%). ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. *Given before or during ECMO.

Table 3: **ECMO management, complications, and outcomes according to SARS-CoV-2 variant**

variants were responsible for 391 (29%), 195 (14%), and 73 (6%) cases, respectively (table 1). Among the group infected with other variants, 47 were beta, 17 gamma, three mu, and six B.1.160. The wild-type variant accounted for 100% (324/324) of the strains isolated during the first semester of 2020 and for 81% (284/352) of the strains isolated in the second semester of 2020, whereas alpha was predominant in S1-2021 (326 [66%] of the 496 strains isolated) and delta in S2-2021 (169 [98%] of the 173 strains isolated). Variant distribution and main characteristics of the population in the eight countries are provided in appendix (pp 11–12).

Table 1 summarises the main demographic and clinical characteristics of patients according to SARS-CoV-2 variant. Patients with wild-type, alpha, delta, and other variants had similar demographic characteristics, except that patients infected with the delta variant tended to be younger and have less hypertension and diabetes than those with any of the other variants. Overall, the time from ICU admission to intubation, the proportion of patients receiving non-invasive oxygenation strategies (eg, high-flow nasal oxygen and non-invasive mechanical ventilation), and the rate of pneumothorax increased over time (appendix pp 13–15). S2-2021 patients (98% [169/173] of whom were infected with the delta variant) were younger, more frequently vaccinated, and had more frequent bacterial coinfection at cannulation than patients treated during the other semesters (appendix pp 13–15). Neuromuscular blockade and prone positioning were used pre-ECMO in more than 90% of the patients, with no significant difference between variants or semesters (table 1, appendix pp 13–15).

VV-ECMO was administered to 98% of the patients, with the femoral–jugular setting being used in more than 75% of cases (table 2). All patients received ultra-protective mechanical ventilation on ECMO, which aimed to achieve decreases in FiO_2, respiratory rate, tidal volume, and driving pressure, irrespective of the variant or the time period (table 2, appendix pp 16–17). This strategy led to a substantial decrease in ventilation mechanical power (from a median of 21·7 J/min [IQR 17·6–25·9] at baseline to 4·7 J/min [2·9–7·4] on ECMO day 1). Notably, the rate of prone positioning on ECMO increased over time, with a peak number of 278 (58%) of 495 patients being proned during S1-2021 (appendix pp 18–19). Remdesivir treatment decreased over time, with only 12 (7%) of 173 patients receiving this drug during S2-2021. By contrast, the use of tocilizumab and dexamethasone (given before or during ECMO), increased over time (appendix pp 18–19). Of 686 patients with the wild-type variant, only 345 (50%) received dexamethasone and 90 (13%) received tocilizumab, compared with 175 (90%) and 69 (35%) of 195 patients with the delta variant, respectively (table 3).

The rate of clogged circuit or membrane requiring change increased over time, with the highest rate (46%) reported in patients with the delta variant, whereas massive bleeding was most frequently reported in patients with the wild-type strain (37%, p=0·0024; table 3) and during S2-2020 (appendix pp 18–19). The highest rates of ventilator-associated pneumonia were reported in patients with the delta variant (146 [75%] of 195) and in those with other variants (60 [82%] of 73). Of note, rates of ischaemic and haemorrhagic stroke and of bacteraemia were similar between periods and variants (table 3, appendix pp 18–19).

Complete 90-day post-ECMO survival status was available for all patients. 90-day mortality was 42% (569 of 1345 patients died) overall, and 43% (297/686) in patients with wild-type SARS-CoV-2, 39% (152/391) in those with the alpha variant, 40% (78/195) in those with the delta variant, and 58% (42/73) in those with other variants, respectively (log-rank test p=0·008; figure 2A). When compared with other semesters, patients treated during

S2-2020 had the highest 90-day mortality (50% [175/352 died] *vs* 40% [393/993 died] in other semesters [S1-2020: 39% (125/324); S1-2021: 40% (199/496; S2-2021: 40% (69/173], log-rank test p=0·018; figure 2B) and the lowest rates of successful ECMO weaning, ICU survival, and hospital survival. Patients with the delta variant had longer ECMO runs than did those with all other types of variant, despite similar lengths of stay in the ICU and hospital (table 3).

Factors associated with higher mortality according to multivariable analysis are reported in table 4. Age, immunocompromised status, and a longer time between ICU admission and intubation were significantly associated with mortality. Patients needing renal replacement therapy, and those with higher SOFA haemodynamic component score, $PaCO_2$, and lactate concentration before ECMO also had an increased risk of death. After adjusting for these specific variables, the delta variant was associated with a higher likelihood of death, with the wild-type strain as the reference (table 4). Moreover, similar mortality risk factors were found in the two sensitivity analyses, when the model accounted for the semester of inclusion in the study instead of the SARS-CoV-2 strain (appendix p 20), or when excluding patients for whom the variant type was missing (appendix p 21). Kaplan-Meier survival estimates according to tertiles of age, $PaCO_2$, and pre-ECMO time from ICU admission to intubation, and according to whether or not patients received renal replacement therapy, are provided in figure 3 and the appendix (p 22).

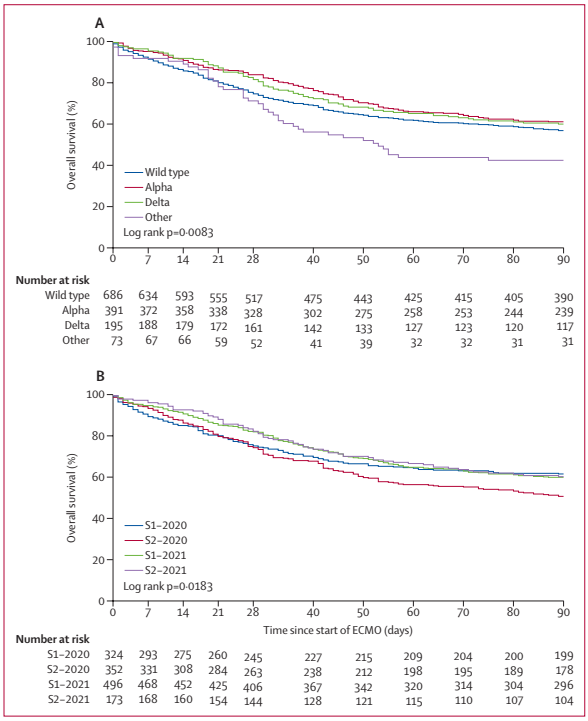

Figure 2: **Survival probability at 90 days according to (A) SARS-CoV-2 variant or (B) study period**
ECMO=extracorporeal membrane oxygenation.

Discussion

This study, reporting the characteristics and outcomes of 1345 patients who received ECMO for severe COVID-19 in 21 experienced European centres, showed no crude difference in 90-day mortality in patients infected with the wild-type, alpha, and delta SARS-CoV-2 variants, which were the three successive dominant viral strains from early 2020 to the second semester of 2021. Notably, mortality was 10% higher (50%) in the second semester of 2020 than in other periods, when the wild-type variant was still dominant. Factors independently associated with 90-day mortality were age, immunocompromised status, longer time between ICU admission and intubation, higher $PaCO_2$ and lactate concentrations, cardiovascular failure, and need for renal replacement therapy at ECMO initiation. After adjusting for these covariates, mortality was higher for patients infected with the delta variant with the wild-type strain as the reference.

Only a few large, multicentre studies[5,9–11,20,21] have reported the outcomes of patients who received ECMO for severe COVID-19. In the international ELSO Registry,[9] in-hospital mortality was 50% among the 4812 patients with COVID-19 who received ECMO, and peaked at 59% for patients treated in less experienced centres in the second semester of 2020. In Germany, the overall in-hospital mortality was 68% among 3397 patients with COVID-19 supported with VV-ECMO from March, 2020, to May, 2021.[21] This high in-hospital mortality was attributed to patients' older mean age (57 years [SD 11]) and to the absence of regulations for ECMO use in the country.[21] Notably, the actual 90-day mortality might have been higher than the reported in-hospital mortality in these series.[9,10,20,21] Additionally, the vast majority of these patients were treated in 2020, when the wild-type SARS-CoV-2 strain was dominant, and no data have previously been reported regarding ECMO patient outcomes after infection with other SARS-CoV-2 variants.

Indeed, infections with the alpha and delta variants of SARS-CoV-2 have been associated with increased transmission, more severe disease, and poorer clinical outcomes compared with the wild-type strain.[22–25] In a large epidemiological study in the US state of Washington, significantly more hospital admissions were reported for infections with the alpha, beta, gamma, or delta strains than with the wild-type variant, with the highest rates associated with the beta and gamma subtypes.[26] Higher

	Multivariable HR (95% CI)	p value
Age, years	1·05 (1·04–1·06)	<0·0001
Male sex	0·97 (0·77–1·22)	0·807
Body-mass index, kg/m²	1·00 (0·98–1·01)	0·736
Chronic respiratory disease	1·19 (0·92–1·54)	0·195
Hypertension	0·94 (0·78–1·14)	0·527
Diabetes mellitus	1·06 (0·86–1·30)	0·604
Immunocompromised status	1·59 (1·16–2·19)	0·004
Variant	..	0·027
Wild type	..	..
Alpha	0·92 (0·75–1·13)	..
Delta	1·31 (1·00–1·73)	..
Other	1·37 (0·97–1·95)	..
Time from first symptoms to hospital admission, per 1 day	0·99 (0·97–1·01)	0·492
Time from ICU admission to intubation, per 1 day	1·05 (1·02–1·07)	0·0002
Time from intubation to ECMO, per 1 day	1·01 (0·99–1·03)	0·330
Pre-cannulation		
Cardiac arrest	1·04 (0·68–1·63)	0·820
Cardiovascular component of the SOFA score ≥3	1·30 (1·05–1·60)	0·016
Renal replacement therapy	1·55 (1·10–2·17)	0·012
Bacterial coinfection	1·00 (0·82–1·21)	0·928
Mechanical power* (n=939)	1·02 (1·00–1·03)	0·058
Pneumothorax	1·25 (0·96–1·63)	0·096
$PaCO_2$, mm Hg	1·01 (1·00–1·01)	0·011
PaO_2/FiO_2 ratio	1·00 (1·00–1·00)	0·506
Lactate concentration, mmol/L	1·10 (1·02–1·19)	0·011
Platelet count, × 10^9 per L	1·00 (1·00–1·00)	0·382
Recruitment manoeuvres	1·24 (0·95–1·60)	0·109
Prone positioning	1·02 (0·75–1·37)	0·904
Inhaled nitric oxide	1·03 (0·84–1·27)	0·799
Neuromuscular blockade	1·01 (0·65–1·59)	0·944

ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. HR=hazard ratio. ICU=intensive care unit. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. SOFA=Sequential Organ Failure Assessment. *Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure − 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.

Table 4: **Predictive factors associated with 90-day mortality in critically ill adults with COVID-19 treated with ECMO**

viral load and increased inflammatory response syndrome have been suggested as potential mechanisms conferring higher virulence to these strains and poorer outcomes in infected patients.[22–25] However, in the most severe forms of COVID-19, patient selection for ECMO, their characteristics at ECMO initiation, and different management and treatments during hospitalisation might also affect outcomes.[9,15,16] In our series, infection with the delta variant was independently associated with higher mortality, with the wild-type strain being the reference in this comparison. However, patients with the delta variant were younger and had fewer comorbidities at ECMO initiation than did those with the other variants. Since the vaccination campaign prioritised the oldest members of the population in all European countries in 2021, it might be speculated that younger patients were less protected than their older counterparts against severe forms of COVID-19 during the delta wave. Indeed, the rate of vaccination remained very low in our patients with COVID-19 on ECMO throughout 2021, with less than 8% of patients with the delta variant having received at least one shot of the vaccine. However, these patients had more frequent ventilator-associated pneumonia and clogged ECMO membrane requiring circuit change during ECMO support than those with all other variant types. These complications might relate to patients' immunosuppressive state, affecting both the innate and adaptive immune systems,[27,28] and to the intense activation of coagulation,[29] which frequently occur during COVID-19, and also to the longer time spent on ECMO.

The higher mortality observed in the second semester of 2020 parallels that reported in previous ECMO series.[9,15,16] In Spain and Portugal,[16] hospital mortality increased (from 41% to 60%) during the second semester of 2020, during which patients being treated with ECMO were older, had more comorbidities and bacterial coinfection at baseline, and were less likely to be treated at a high-volume centre compared with patients treated previously. Their time between admission to the ICU and ECMO start was also longer. In the ELSO Registry,[9] in-hospital mortality increased from 37% before to 52% after May 1, 2020. Patients treated later in 2020 had more frequent diabetes, pre-existing heart disease, immunocompromised status, bacterial pneumonia, and bloodstream co-infection and use of corticosteroids before ECMO than those treated earlier in 2020. They were also more likely to have received non-invasive ventilation before ECMO and had a shorter duration of invasive ventilation before ECMO than those treated earlier in 2020. In our series, the severity of respiratory disease and patient management under ECMO were similar between periods, while the recourse to non-invasive ventilation and steroids increased after June, 2020, and remained constant thereafter. A potential cause of poorer outcomes in the second semester of 2020 might relate to patients' older age and more frequent comorbidities such as diabetes and hypertension. Our multivariable analysis of factors associated with mortality revealed that the time from ICU admission to intubation, a surrogate for the duration of non-invasive respiratory support, which increased significantly in most ECMO series after June, 2020, was a stronger predictor of poor outcome than the time on mechanical ventilation before ECMO. Notably, time on non-invasive respiratory support

was the longest for patients with less common SARS-CoV-2 strains, who had the highest mortality. Indeed, patients who did not improve on non-invasive oxygenation support might have suffered greater self-inflicted lung injury[30] due to strong respiratory efforts and important swings of transpulmonary pressure, which could also explain the increased rate of pneumothorax in the later three semesters of our study. Therefore, the duration of non-invasive respiratory support might be an important consideration in patient selection for ECMO in this context, and warrants further investigation.

Our study has several strengths. First, viral identification was obtained in 94% of cases. Second, we provide details on the ventilatory and general ICU management of our patients in the days following ECMO initiation. Third, patient selection and management was similar in our units over time and variants, with the use of ultraprotective mechanical ventilation under ECMO, with low volume and pressures resulting in very low mechanical power.[13] Fourth, we collected patient outcomes at 90 days (not just in-hospital mortality) in some of the most experienced ECMO centres in Europe, which minimised the volume–outcome effect that had been reported for both patients without COVID-19[17] and those with COVID-19[5,9,16] supported by ECMO. Indeed, the overall 90-day mortality we report here is in line with that of previous non-COVID-19 cohorts of patients with ARDS supported with ECMO.[1,12–14] This mortality rate is also 15–25% lower than the in-hospital mortality observed in recent large COVID-19 series,[9,10,21] despite lower levels of PaO_2 and FiO_2 at baseline.

Our study has also several limitations. First, some patients were still under ECMO or mechanical ventilation at the end of follow-up and mortality might have been higher at later timepoints. Second, we did not evaluate long-term health-related quality of life and other sequelae of COVID-19, which might persist for a long time.[31] Third, we did not collect data after infection with the omicron variant of SARS-CoV-2, which emerged in November, 2021, and has been associated with less severe disease than earlier variants of the virus.[32] Fourth, we inferred the variant based on chronology and geography, and not through direct testing, in 84 (6%) of 1345 patients. Fifth, the calculation of adjusted hazard ratios for mortality among SARS-CoV-2 strains was based on key prognostic factors included in our database, and could have been biased by residual confounders that were not accounted for in our multivariable model. Of note, the hazard ratios associated with these factors should be interpreted with caution because they do not represent the same time of causal effect as that of SARS-CoV-2 strains.[33] Sixth, the strain on health-care systems and ICU resource constraints might have differed during the study period and between countries, leading to differential selection criteria for ECMO or patient management. Lastly, our study was conducted in high-volume European ECMO centres, which might limit the generalisability of our results to centres in other regions of the world.

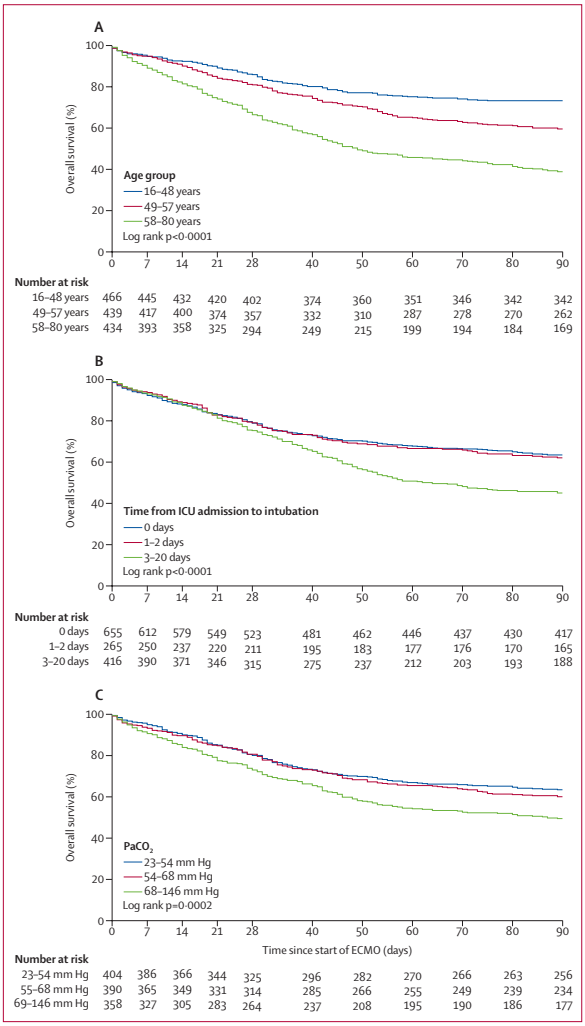

Figure 3: **Kaplan-Meier survival estimates according to tertiles of (A) age, (B) time from ICU admission to intubation, and (C) pre-ECMO $PaCO_2$**

ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. $PaCO_2$=partial pressure of arterial carbon dioxide. The number of patients censored at each timepoint on all Kaplan-Meier curves was 0, until the final timepoint (90 days) when all patients were censored.

In conclusion, adjusted mortality of patients with COVID-19 treated with ECMO in experienced centres in Europe was higher for those infected with the delta variant, who were younger and had fewer comorbidities at ECMO initiation. The 42% 90-day mortality reported here is lower than that reported for other large series of patients with COVID-19-related ARDS supported with ECMO and in line with cohorts of non-COVID-19 patients on ECMO. This observation reinforces the need to concentrate ECMO resources at experienced ECMO centres in a hub-and-spoke model, especially during pandemics that impose substantial constraints on health-care systems.[11,34,35]

Contributors

All authors were involved in data generation. MS, DH, and AC had direct access to and verified the data. MS, DH, and AC were involved in analysis of the data. MS, DH, and AC wrote the manuscript. All authors contributed to revisions to the manuscript, and read and approved the final version. AC takes responsibility for the integrity of the work as a whole, from inception to published article. AC was responsible for the decision to submit the manuscript for publication. All authors have seen and approved the final text.

Declaration of interests

MS reports lecture fees from Getinge, Drager, and Xenios, outside of the submitted work. AM-D reports grants from Addmedica, Baxter, Ferring, Fisher & Paykel, and Philips, and personal fees from Air Liquide, outside of the submitted work. PSc reports lecture fees from Getinge and scientific grants from the European Society of Intensive Medicine (ESICM) and the European Commission (Horizon 2020 Fast Track to Innovation; NCT04115709), and has co-organised an ARDS fellowship for the ESICM sponsored by Medtronic. BL reports fees from Abiomed, Getinge, Baxter, Novartis, Sanofi, Amomed, and Orion, outside of the submitted work. GG has received personal fees (payment for lectures) from Getinge, Draeger Medical, Biotest, GSK, Pfizer, Fisher & Paykel, and Cook Medical, and research grants from MSD and Fisher & Paykel. CG reports fees from Xenios, outside of the submitted work. JR reports lecture fees from Werfen and Gilead, and advisory fees from Medtronic, outside of the submitted work. AC reports grants from Getinge, and personal fees from Getinge, Baxter, and Xenios, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data reported in this Article will be shared after de-identification (text, tables, figures, and appendix), beginning 6 months and ending 2 years after Article publication, to researchers who provide a methodologically sound proposal and after approval by the internal scientific committee. Proposals should be addressed to alain.combes@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

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3. ECMO no Choque Cardiogénico

3.1. ECMO for drug-refractory electrical storm without a reversible trigger: a retrospective multicentric observational study.

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ORIGINAL ARTICLE

ECMO for drug-refractory electrical storm without a reversible trigger: a retrospective multicentric observational study

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Abstract

Aims Drug-refractory electrical storm (ES) is a life-threatening medical emergency. We describe the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) in drug-refractory ES without a reversible trigger, for which specific guideline recommendations are still lacking.

Methods and results Retrospective observational study in four Iberian centres on the indications, treatment, complications, and outcome of drug-refractory ES not associated with acute coronary syndromes, decompensated heart failure, drug toxicity, electrolyte disturbances, endocrine emergencies, concomitant acute illness with fever, or poor compliance with anti-arrhythmic drugs, requiring VA-ECMO for circulatory support. Thirty-four (6%) out of 552 patients with VA-ECMO for cardiogenic shock were included [71% men; 57 (44–62) years], 65% underwent cardiopulmonary resuscitation before VA-ECMO implantation, and 26% during cannulation. Left ventricular unloading during VA-ECMO was used in 8 (24%) patients: 3 (9%) with intraaortic balloon pump, 3 (9%) with LV vent, and 2 (6%) with Impella. Thirty (88%) had structural heart disease and 8 (24%) had an implantable cardioverter-defibrillator. The drug-refractory ES was mostly due to monomorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) (59%), isolated monomorphic VT (26%), polymorphic VT (9%), or VF (6%). Thirty-one (91%) required deep sedation, 44% overdrive pacing, 36% catheter ablation, and 26% acute autonomic modulation. The main complications were nosocomial infection (47%), bleeding (24%), and limb ischaemia (21%). Eighteen (53%) were weaned from VA-ECMO, and 29% had heart transplantation. Twenty-seven (79%) survived to hospital discharge (48 (33–82) days). Non-survivors were older [62 (58–67) vs. 54 (43–58); $P < 0.01$] and had a higher first rhythm disorder-to-ECMO interval [0 (0–2) vs. 2 (1-11) days; $P = 0.02$]. Seven (20%) had rehospitalization during follow-up [29 (12–48) months], with ES recurrence in 6%.

Conclusions VA-ECMO bridged drug-refractory ES without a reversible trigger with a high success rate. This required prolonged hospital stays and coordination between the ECMO centre, the electrophysiology laboratory, and the heart transplant programme.

Keywords Antiarrhythmic drugs; Catheter ablation; Electrical storm; Extracorporeal membrane oxygenation; Heart transplantation

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Introduction

Drug-refractory electrical storm (ES) is a life-threatening medical emergency with high mortality. An ES is characterized by ≥3 ventricular arrhythmia episodes [ventricular tachycardia (VT) or ventricular fibrillation (VF)] over 24 h, each requiring therapeutic intervention (including ≥3 appropriate implantable cardioverter defibrillator (ICD) shocks), or an incessant VT lasting ≥12 h. If ES persists despite classical anti-arrhythmic drugs, then it is defined as drug-refractory ES.[1] Haemodynamic instability can complicate drug-refractory ES, profoundly impacting patient management and definitive treatment.[1,2]

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a short-term mechanical circulatory support modality that conveys immediate biventricular and respiratory support.[3] By restoring haemodynamics and tissue perfusion in patients with circulatory collapse, VA-ECMO can bridge patients with drug-refractory ES complicated by cardiogenic shock to definitive treatment, as well as enables optimization of antiarrhythmic drugs and catecholamine weaning, all of which may contribute to ending ES.[1,4–7]

VA-ECMO has been successfully used for drug-refractory ES with reversible triggers such as acute coronary syndromes,[8] decompensated heart failure,[9] drug toxicity,[10] electrolyte disturbances,[11] thyrotoxicosis,[12] and concomitant acute illness with fever.[9] However, reversible causes of ES are identified in only 10% of patients.[13] In patients with drug-refractory ES without a reversible trigger severe underlying structural heart disease is frequently present, requiring a complex multidisciplinary treatment approach that might include deep sedation and invasive mechanical ventilation, mechanical circulatory support, overdrive pacing, acute autonomic modulation, optimization of antiarrhythmic drug therapy, electrophysiologic study and catheter ablation, and emergency heart transplantation.[2,9] In this specific context, VA-ECMO could potentially be a valuable option in hemodynamically unstable patients as a bridge to definitive treatment, but data are still limited.

Attending to the lack of specific guideline recommendations, we conducted a retrospective observational study in 4 Iberian centers on the indications, definitive treatment, complications, and outcomes of patients requiring VA-ECMO for circulatory support in drug-refractory ES without a reversible trigger.

Methods

Study population

A retrospective, multicentric, and observational 11 year (from March 2012 to October 2023) study in four Iberian ECMO centres [São João University Hospital Centre, Porto, Portugal; Hospital Álvaro Cunqueiro, Vigo (Pontevedra), Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; and Juan Canalejo Hospital, A Coruña, Spain] on the indications, definitive treatment, complications, and outcomes of adult patients requiring VA-ECMO for circulatory support in drug-refractory ES without a reversible trigger. The study complies with the Declaration of Helsinki, and the institutional Ethics Committee reviewed and approved the study, waiving the requirement for patient consent (approval number: CES 119/2023).

ES was diagnosed using the definition from the most recent European Society of Cardiology guidelines.[1] Drug-refractory ES complicated by circulatory collapse was defined as ventricular arrhythmia with circulatory failure, as attested by sustained hypotension, low cardiac index (<2.2 L/min/m^2), and tissue hypoxia, despite the infusion of high-dose catecholamines, adequate intravascular volume, and maximal drug management. The ECMO centre medical team in conjunction with a clinical arrhythmology specialist team managed the drugs administered to control ES. Amiodarone, lidocaine, and external electrical shocks were the first-line medical treatments. Exclusion criteria were (i) the presence of a reversible trigger such as acute coronary syndromes, decompensated heart failure, drug toxicity, electrolyte disturbances, endocrine emergencies (e.g., thyrotoxicosis), concomitant acute illness with fever, or poor compliance with anti-arrhythmic drugs; (ii) ES following cardiotomy; (iii) VA-ECMO during cardiopulmonary resuscitation (CPR) with no shockable rhythm; (iv) ES onset after starting VA-ECMO; and (v) VA-ECMO instituted for the purpose of catheter ablation in elective high-risk procedures. Acute ischaemic heart disease was ruled out by coronary angiography, with the measurement of fractional flow reserve (FFR) for direct evaluation of the haemodynamic relevance of coronary artery stenoses in doubtful cases. We could perform cardiac MRI in 7 (20%) patients during the hospital stay, which did not identify other potentially reversible triggers for the ES. The haemodynamic instability associated with drug-refractory ES, the presence of an ICD in some patients, and the fact that the ECMO equipment is not MRI compatible, importantly limited the performance of MRI in our patients.

Mechanical circulatory support

The ECMO circuits used were heparin-coated and consisted of two cannulae, an integrated centrifugal pump, and a polymethylpentene membrane oxygenator with 3/8" connecting tubes (e.g., HLS Set Advanced 7.0 from Maquet-Cardiopulmonary-AG; Hirrlingen, Germany). Cannulation procedures were performed either percutaneously or by surgical cutdown at the bedside, depending on local expertise. A

20558822, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ehf2.14756 by Universidade do Porto, Wiley Online Library on [05/03/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

femoral vein was cannulated with a 23-Fr to 25-Fr cannula for blood outflow from the right atrium, and a common femoral artery was cannulated with a 15-Fr to 17-Fr cannula for retrograde blood inflow to the descending aorta with an anterograde distal perfusion 7-Fr catheter in the ipsilateral superficial femoral artery to prevent limb ischaemia. Left ventricular unloading was used during VA-ECMO support at the Centre's discretion using either an intraaortic balloon pump, LV vent, or Impella® 2.5. Goal ECMO flows were set to maintain a cardiac index greater than 2.0. Systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time (aPTT) of 1.5 normal. The heat exchanger was used to maintain normothermia. Cannula position was regularly assessed by chest X-ray and echocardiography. All patients had invasive arterial pressure monitoring and intensivists with two-dimensional echocardiography and pulsed Doppler training were available 24/7. Echocardiography was performed before VA-ECMO implantation, daily until the successful weaning from VA-ECMO, and just before ICU discharge for (i) evaluation of LV systolic function (e.g., ejection fraction using the Simpson Method) and cardiac index calculation; (ii) estimation of biventricular filling pressures; (iii) measurement of parameters associated with successful weaning from VA-ECMO (e.g., LV outflow tract velocity time integral, lateral mitral annulus peak systolic velocity); and (iv) detection of VA-ECMO complications (e.g., cardiac tamponade). The pulmonary artery catheter was only used for haemodynamic monitoring in selected cases, namely, heart transplantation.

Specific therapies for drug-refractory electrical storm

Patients with drug-refractory ES and VA-ECMO support were treated with one or more different techniques based on the type of ventricular arrhythmia and the presence of underlying structural heart disease. When present, the clinical arrhythmology specialist team carried out ICD interrogation, and device reprogramming was performed accordingly. Deep sedation and invasive mechanical ventilation were used to directly suppress ventricular arrhythmias and to bridge definitive treatment.[13] Overdrive pacing was used to temporarily suppress slow recurrent/incessant ventricular tachycardia (VT), especially caused by the R-on-T phenomenon.[14] In selected cases, acute autonomic modulation under deep sedation was performed to decrease sympathetic tone using stellate ganglion blockade or cervicothoracic epidural blockade.[15,16] The decision to perform an electrophysiologic study (EPS) and catheter ablation was made by the clinical arrhythmology specialist team on a case-by-case scenario when VA-ECMO weaning was precluded by persistent ES.[17,18] Patients with multiple arrhythmic foci, LV thrombus, or clinical evidence of hypoxic–ischaemic encephalopathy were not considered eligible for EPS. Whenever catheter ablation was not successful and in patients with advanced heart failure with a low probability of cardiac recovery, emergency heart transplantation was prioritized, provided the absence of contraindications.

Outcomes

The primary outcome of the study was hospital mortality. Secondary outcomes included VA-ECMO duration, bridge-to-heart transplant, intensive care unit (ICU) length of stay, and VA-ECMO associated complications (i.e., bleeding, stroke, limb ischaemia, thrombosis, cardiac tamponade, and nosocomial infection). Rehospitalization and ES recurrence after hospital discharge were also described.

Statistical analysis

Categorical variables are presented as numbers (%) and continuous variables as median (interquartile range). The Kolmogorov–Smirnov test was used to assess the actual distribution of continuous variables. Comparisons between survivors and non-survivors were performed using the Mann–Whitney *U* test for non-normally distributed variables (age, time from hospital admission to ICU admission, time from hospital admission to VA-ECMO cannulation, time from first rhythm disorder to VA-ECMO cannulation, ICU length of stay, hospital length of stay, and lactate), and the independent samples *t*-test for normally distributed variables (VA-ECMO duration, SOFA score). For categorical variables, comparisons between survivors and non-survivors were performed using the chi-square test. For statistical analysis, SPSS Version 27 (IBM Corporation) was used.

Results

Baseline characteristics of the study population

During the period of the study, 34 (6%) out of 552 patients with VA-ECMO for cardiogenic shock were included in the four ECMO centres for drug-refractory ES without a reversible trigger (*Table* 1): 17 in São João University Hospital Centre (Porto, Portugal), 7 in Hospital Álvaro Cunqueiro (Vigo, Spain), 5 in Juan Canalejo Hospital (A Coruña, Spain), and 5 in Hospital Universitari Vall d'Hebron (Barcelona, Spain). Median age was 57 (44–62) years, with male predominance (71%). Most patients presented at least one cardiovascular risk factor (27; 79%). Regarding previous medical history, no patient had atrial fibrillation, while heart failure was present in about half of the patients (44%; all in New York Heart Association (NYHA) class II or III), 21% had previ-

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Table 1 Baseline characteristics of extracorporeal membrane oxygenation-rescued electrical storm patients according to hospital survival status

Characteristic	All Patients	Survivors	Non-survivors	*P*
n	34	27 (79)	7 (21)	-
Age, year	57 (44–62)	54 (43–58)	62 (58–67)	<**0.01**
Male	24 (71)	18 (67)	6 (86)	0.69
Cardiovascular risk factors				
Dyslipidaemia	20 (59)	14 (52)	6 (86)	0.61
Overweight	18 (53)	14 (52)	4 (57)	0.89
Hypertension	14 (41)	11 (41)	3 (43)	0.95
Smoking	10 (29)	6 (22)	4 (57)	0.21
Diabetes mellitus	9 (26)	5 (18)	4 (57)	0.14
Previous medical history				
Heart failure	15 (44)	10 (37)	5 (71)	0.34
Ventricular arrhythmias	7 (21)	4 (15)	3 (43)	0.21
Antiarrhythmic medication	17 (50)	13 (48)	4 (57)	0.81
Implantable cardioverter-defibrillator	8 (24)	5 (18)	3 (43)	0.31
Underlying aetiology of ES				
Ischaemic cardiomyopathy	18 (53)	13 (48)	5 (71)	0.56
Non-ischaemic dilated cardiomyopathy	6 (18)	4 (15)	2 (29)	0.49
Myocarditis	5 (15)	5 (18)	0 (0)	0.26
Hypertrophic cardiomyopathy	1 (3)	1 (4)	0 (0)	0.61
Idiopathic/structurally normal heart	4 (11)	4 (15)	0 (0)	0.32

Results are expressed as *n* (%) or median (interquartile range).
ES, electrical storm.

ous ventricular arrhythmias, and 24% had an ICD. Half of the patients (50%) had at least one chronic antiarrhythmic drug: (i) beta-blocker alone (10; 29%); (ii) beta-blocker and amiodarone combination (6; 18%); or (iii) diltiazem (one; 3%). Structural heart disease was present in 30 (88%) patients: 18 (53%) patients had ischaemic cardiomyopathy, 6 (18%) non-ischaemic dilated cardiomyopathy, 5 (15%) myocarditis, and 1 (3%) hypertrophic cardiomyopathy. Four (11%) patients had structurally normal hearts.

No significant differences were detected between groups in the baseline characteristics of patients except for age, with non-survivors being significantly older when compared with survivors [62 (58–67) vs. 54 (43–58); $P < 0.01$].

Pre-extracorporeal membrane oxygenation characteristics and management of drug-refractory electrical storm

Patients with drug-refractory ES were admitted to the ICU 1 (0–7) days after hospital admission, 13 (38%) of whom had direct ICU admission. Of note, the interval between the first rhythm disorder and ECMO implantation was shorter in survivors when compared to non-survivors [0 (0–2) vs. 2 (1–11) days; $P = 0.02$]. Thirteen (38%) patients were cannulated by the mobile ECMO team in the referring centres (*Table* 2, *Table* 3, and *Figure* 1).

The ES was mostly due to monomorphic VT and ventricular fibrillation (VF) in 20 (59%), isolated monomorphic VT in 9 (26%), polymorphic VT in three (9%), or VF in two (6%) patients. About two-thirds of patients (65%) underwent cardiopulmonary resuscitation prior to ECMO, and 26% during cannulation. At ICU admission, SOFA score and blood lactate were 8 (5–10) and 4.4 (2.0–8.3) mmol/L, respectively. Regarding the use of antiarrhythmic drugs before VA-ECMO cannulation, amiodarone was administered in 33 (97%), lidocaine in 22 (65%), and beta-blockers in 19 (56%) patients. Before VA-ECMO implantation 21 (62%) patients required inotropes. Severe left ventricular dysfunction (left ventricular ejection fraction (LVEF) < 30%) was present in 29 (85%) patients, two (6%) patients had moderate LV dysfunction (LVEF 30–40%), two (6%) mild LV dysfunction (LVEF 41–50%), and one (3%) presented preserved LV function (LVEF >50%).

VA-ECMO was initiated in 32 (94%) patients due to circulatory collapse (one during the EPS), and in two (6%) due to haemodynamic instability just before the EPS. Regarding the management of drug-refractory ES during VA-ECMO, 31 (91%) patients required deep sedation and invasive mechanical ventilation, 15 (44%) overdrive pacing, 12 (36%) EPS and catheter ablation, and 9 (26%) acute autonomic modulation. Left ventricular unloading during VA-ECMO was used in 8 (24%) patients: 3 (9%) with intraaortic balloon pump, 3 (9%) with LV vent, and 2 (6%) with Impella.

Outcome

Complications during VA-ECMO were frequently observed: nosocomial infection (47%), bleeding (24%), limb ischaemia (21%), cardiac tamponade (12%), thrombosis (9%), and stroke (3%). Of the four cases of cardiac tamponade, one complicated endomyocardial biopsy for suspected acute myocarditis, three occurred post-cardiotomy (emergent heart transplantation in one case and coronary artery bypass grafting

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Table 2 Pre-extracorporeal membrane oxygenation characteristics of electrical storm patients according to hospital survival status

Characteristic	All Patients	Survivors	Non-survivors	*P*
n	34	27 (79)	7 (21)	-
Hospital to ICU, days	1 (0–7)	1 (0–8)	2 (0–7)	0.45
Hospital to ECMO, days	3 (1–8)	3 (1–8)	6 (3–24)	0.13
First rhythm disorder-to-ECMO interval, days	1 (0–2)	0 (0–2)	2 (1–11)	**0.02**
Type of ES				
Monomorphic VT and VF	20 (59)	15 (56)	5 (71)	0.71
Isolated monomorphic VT	9 (26)	8 (30)	1 (14)	0.52
Polymorphic VT	3 (9)	2 (7)	1 (14)	0.61
VF	2 (6)	2 (7)	0 (0)	0.47
Cannulation by mobile ECMO team	13 (38)	9 (33)	4 (57)	0.46
CPR prior to ECMO	22 (65)	18 (67)	4 (57)	0.82
ECMO cannulation during CPR	9 (26)	8 (30)	1 (14)	0.52
At VA-ECMO cannulation				
SOFA	8 (5–10)	9 (6–10)	6 (5–10)	0.52
Lactate, mM	4.4 (2.0–8.3)	3.5 (1.4–8.5)	5.0 (2.3–6.7)	0.59
Before ECMO cannulation				
Drugs administered				
Amiodarone	33 (97)	26 (96)	7 (100)	0.95
Lidocaine	22 (65)	16 (59)	6 (86)	0.56
Beta-blockers	19 (56)	14 (52)	5 (71)	0.63
Inotropes	21 (62)	15 (56)	6 (86)	0.50
Left ventricular ejection fraction				
>50%	1 (3)	1 (4)	0 (0)	0.61
40–50%	2 (6)	2 (7)	0 (0)	0.47
30–40%	2 (6)	2 (7)	0 (0)	0.47
<30%	29 (85)	22 (82)	7 (100)	0.74

Results are expressed as *n* (%) or median (interquartile range).
CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ES, electric storm; IMV, invasive mechanical ventilation; SOFA, Sequential Organ Failure Assessment; SR, sinus rhythm; VF, ventricular fibrillation, VT, ventricular tachycardia.

Table 3 Outcomes of extracorporeal membrane oxygenation-rescued electrical storm patients according to hospital survival status

Characteristic	All Patients	Survivors	Non-survivors	*P*
n	34	27 (79)	7 (21)	-
Management of drug-refractory ES during ECMO				
Deep sedation and IMV	31 (91)	25 (93)	6 (86)	0.90
Overdrive pacing	15 (44)	9 (33)	6 (86)	0.16
Electrophysiologic study and catheter ablation	12 (36)	8 (30)	4 (57)	0.37
Acute autonomic modulation	9 (26)	5 (18)	4 (57)	0.14
Complications during ECMO				
Nosocomial infection	16 (47)	13 (48)	3 (43)	0.88
Bleeding	8 (24)	8 (30)	0 (0)	0.16
Limb ischaemia	7 (21)	4 (15)	3 (43)	0.21
Cardiac tamponade	4 (12)	4 (15)	0 (0)	0.32
Thrombosis	3 (9)	2 (7)	1 (14)	0.61
Stroke	1 (3)	1 (4)	0 (0)	0.61
Outcomes				
ECMO weaning	18 (53)	18 (67)	0 (0)	**0.04**
Bridge to heart transplantation	10 (29)	9 (33)	1 (14)	0.44
ECMO duration, days	10 (6–18)	10 (6–19)	12 (5–13)	0.50
ICU LOS, days	28 (15–40)	30 (15–43)	22 (14–40)	0.93
Hospital LOS, days	48 (33–82)	52 (36–101)	40 (16–69)	0.11

Results are expressed as *n* (%) or median (interquartile range).
ECMO, extracorporeal membrane oxygenation; ES, electric storm; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay.

in the two others); all required emergent sternotomy (*Table* 3 and *Figure* 1). In five (15%) patients, major bleeding led to a transfusion of two or more red blood cell units; there were no cases of fatal bleeding. All cases of acute limb ischaemia were associated with femoral arterial cannulation, 4 (12%) required surgical thromboembolectomy, with no cases of amputation. No significant differences were detected between survivors and non-survivors in the incidence of ECMO-related complications *Figure* 2.

Eighteen (53%) patients were successfully weaned from VA-ECMO and 10 (29%) patients were bridged to heart transplantation. Twenty-seven (79%) patients survived hospital

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Figure 1 Flow chart of the study. AAM, acute autonomic modulation; CA, catheter ablation; EPS, electrophysiologic study; ES, electric storm; OP, overdrive pacing; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

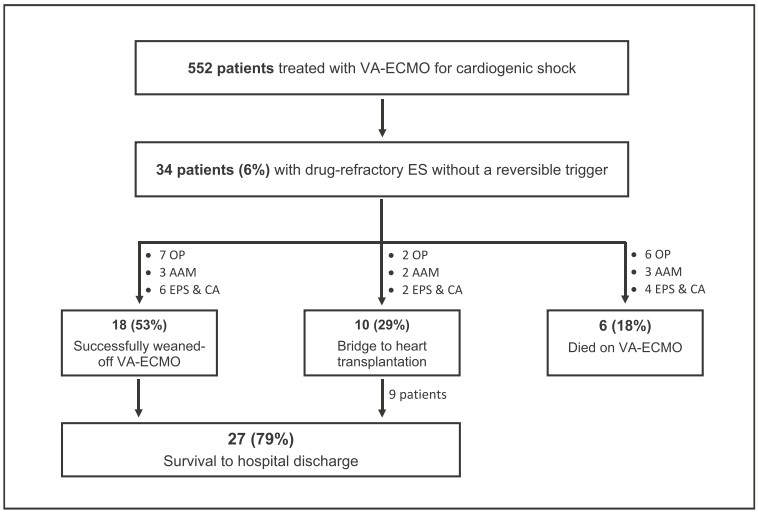
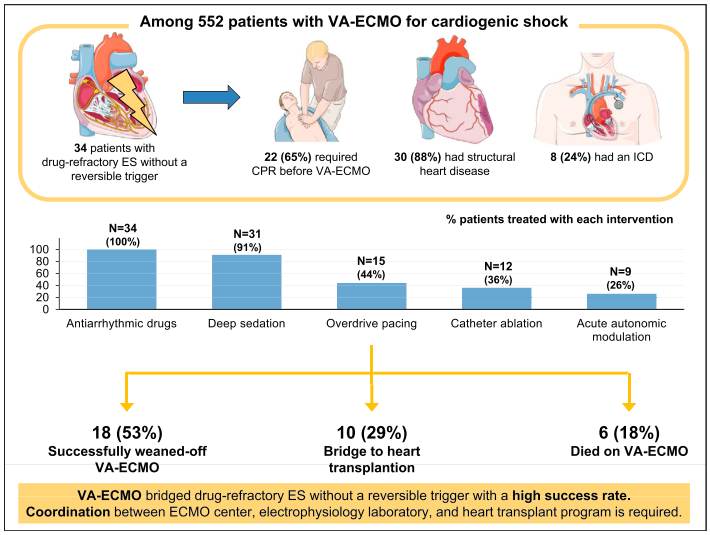


Figure 2 Visual graph of the study. CPR, cardiopulmonary resuscitation; ICD, implantable cardioverter defibrillator; ES, electric storm; VA-ECMO, venoarterial extracorporeal membrane oxygenation.



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discharge, 6 patients died on VA-ECMO, and 1 patient died post-emergent heart transplant. Patients had prolonged ICU and hospital length of stay [28 (15–40) and 48 (33–82) days, respectively].

During follow-up after hospital discharge [29 (12–48) months], all patients were alive 1 year post-ICU admission (including the 9 patients submitted to emergent heart transplantation that survived hospital discharge) and 7 (20%) patients had rehospitalization, with ES recurrence in two (6%) cases. Four patients (12%) died after hospital discharge during follow-up, three from a non-cardiovascular cause.

Discussion

In the present observational multicentric study, we describe the indications, definitive treatment, complications, and outcome of 34 patients from four Iberian centres requiring VA-ECMO for circulatory support in drug-refractory ES without a reversible trigger. Most patients (88%) had structural heart disease and 8 (24%) had an ICD. Eighteen (53%) patients were successfully weaned off VA-ECMO and 29% were bridged to emergent heart transplantation. Twenty-seven (79%) patients survived hospital discharge. Notably, survivors were younger and had a shorter time interval between the first rhythm disorder and ECMO initiation.

VA-ECMO is increasingly used as a life-saving therapy for patients with refractory cardiogenic shock,[3,19] but its use in drug-refractory ES still lacks clear guidelines and solid evidence.[2,13] During the 11 year period of our study, drug-refractory ES without a reversible trigger was a rare indication for VA-ECMO, representing only 6% of all cases of VA-ECMO for cardiogenic shock from our 4 ECMO centres. In fact, previous studies focus on case reports or single-centre cohorts of ECMO-rescued ES patients.[5,20–22] More recently a study included 83 adult patients from two French tertiary care centres with drug-refractory ES and treated with VA-ECMO.[23] Of note, most patients (61%) had a reversible trigger for drug-refractory ES such as acute myocardial infarction with ST elevation, with 52% of patients undergoing angioplasty or surgical revascularization. This could explain, at least in part, the low use of catheter ablation as a definite treatment for drug-refractory ES when compared with our study (14 vs. 36%) in which patients with a reversible trigger were not included and most patients presented structural heart disease.

Although our patients were critically ill with high SOFA scores and blood lactate levels at ICU admission, and 65% underwent cardiopulmonary resuscitation prior to ECMO and 26% during cannulation, a high success rate was attained. This compares favourably with previous cohorts, in which ischaemic cardiomyopathy requiring emergent revascularization was the trigger for drug-refractory ES in most patients.[5,23] In fact, mortality rates remain at 40% to 50% when cardiogenic shock complicates acute myocardial infarction, and the routine use of VA-ECMO was shown not to be superior to supportive care alone in a recent multicentric randomized clinical trial.[24] In our study, survivors were younger and had a shorter time between the first rhythm disorder and ECMO initiation. Age $<$50 years has been previously shown to be an independent protective factor with 6 month survival in drug-refractory ES treated with VA-ECMO, regardless of the underlying cause.[23] Regarding the shorter time between the first rhythm disorder and ECMO initiation in survivors, it could suggest that VA-ECMO should be considered early in drug-refractory ES before multiple organ failure ensues.

Beyond haemodynamic support and tissue perfusion, VA-ECMO enables adequate levels of anti-arrhythmic drugs to be attained, rapid weaning off the catecholamine, and the reduction of myocardial oxygen consumption, all of which may contribute to ending the ES.[3,13,23] VA-ECMO could also provide a bridge to acute autonomic modulation procedures such as percutaneous stellate ganglion block and cervicothoracic epidural nerve blocks, which are now recommended by the European Guidelines (Class IIb, LOE B).[1] Additionally, VA-ECMO has been previously shown to allow the successful catheter ablation of ventricular arrhythmias in hemodynamically unstable patients.[25,26] Accordingly, in our study, in which acute autonomic modulation and catheter ablation were frequently used, 18 (53%) patients were successfully weaned from VA-ECMO. Of note, 13 (38%) of our patients were rescued by the mobile ECMO team from referring hospitals, allowing safe inter-hospital transfer to a specialized centre with a high-volume ECMO programme, an electrophysiology laboratory, and a heart transplant programme. This could be particularly relevant given that ES management is complex and requires a multidisciplinary approach and well-defined protocols and networks to guarantee proper patient care.[13]

VA-ECMO has been previously reported as a bridge to successful heart transplantation in refractory ES.[20] In our study, emergent heart transplantation was required for the definitive treatment of drug-refractory ES in about one-third of patients, with a 1 year survival of 90%. In a recent multicenter study from 11 French centers that included 45 patients transplanted for refractory ES, the reported 1 year survival was 69%.[27] In this study, 62% of patients were in cardiogenic shock, and mechanical circulatory support was used as a bridge to cardiac transplantation in 49%. Interestingly, when compared with a previous cohort of drug-refractory ES treated with VA-ECMO, the rate of heart transplantation in our study was higher (11% vs. 30%).[23] This could possibly be related to the fact that, in that cohort, about two-thirds of patients had a reversible trigger for drug-refractory ES.

Although a high success rate was achieved, our patients required prolonged ICU and hospital stays with frequent ECMO-associated complications such as bleeding, acute limb ischaemia, and cardiac tamponade. These results highlight

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the importance of high-volume centres with 24/7 cardiac surgery availability for the successful management of complications during VA-ECMO.[28,29]

Our study has several limitations. The relatively low number of patients and ECMO centers included in the study limits its external validity and generalisability of the results. The 4 Iberian centers that participated in the study had significant experience managing VA-ECMO-associated complications and referring patients to the electrophysiology laboratory and heart transplant programme. Given our study's retrospective and observational design, we cannot attribute to the use of VA-ECMO the high success rate observed in managing drug-refractory ES complicated by cardiogenic shock. Namely, we did not compare the outcomes of our study to those of patients with a similar clinical presentation not treated with VA-ECMO. Although it could have been relevant to aid in interpreting the results of which patient phenotype is more likely to benefit from early cannulation to VA-ECMO and/or its complications, multivariant analysis was not performed given the relatively small sample size of the study and the low number of events (e.g., limb ischaemia and cardiac tamponade).

Conclusion

VA-ECMO bridged drug-refractory ES without a reversible trigger with a high success rate. This required prolonged hospital stays with the management of frequent ECMO-associated complications, as well as the coordination between the ECMO centre, the electrophysiology laboratory, and the heart transplant programme.

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Conflict of interest

None declared.

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3.2. Cardiac Tamponade Complicating Extracorporeal Membrane Oxygenation: An ELSO Registry Analysis.

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Original Article

Cardiac Tamponade Complicating Extracorporeal Membrane Oxygenation: An Extracorporeal Life Support Organization Registry Analysis

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Objectives: Cardiac tamponade is a potentially life-threatening complication during extracorporeal membrane oxygenation (ECMO). In this study, the authors assessed the incidence, patient characteristics, and risk factors for mortality of cardiac tamponade during ECMO.
Design: The authors queried the Extracorporeal Life Support Organization (ELSO) Registry from 1997 to 2021 for all adults with cardiac tamponade as a reported complication during ECMO.
Participants: Cardiac tamponade was reported in 2,176 (64% men; 53.8 ± 0.33 years) of 84,430 adults (2.6%).
Measurements and Main Results: Venoarterial ECMO was the main configuration (78%), followed by venovenous ECMO (VV ECMO) (18%), for cardiac (67%), pulmonary (21%) support, and extracorporeal cardiopulmonary resuscitation (ECPR) (12%). Percutaneous cannulation was performed in 51%, with the femoral vein and femoral artery as the most common sites for drainage and return cannulae, with dual-lumen cannulae in 39% of VV ECMO. Hospital survival was lower (35% *v* 49%; $p < 0.01$) when compared with that of all adults from the ELSO Registry. In multivariate analysis, age, aortic dissection and/or rupture, COVID-19, ECPR, pre-ECMO renal-replacement therapy, and prone position are associated with hospital mortality, whereas ECMO for pulmonary support is associated with hospital survival. Similarly, renal, cardiovascular, metabolic, neurologic, and pulmonary complications occurred more frequently in nonsurvivors.
Conclusions: Cardiac tamponade is a rare complication during ECMO that, despite being potentially reversible, is associated with high hospital mortality. Venoarterial ECMO is the most common configuration. ECMO for pulmonary support was associated with higher survival, and ECPR was associated with higher mortality. In these patients, other ECMO-related complications were frequently reported and associated with hospital mortality.
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Key Words: acute respiratory distress syndrome; cardiac tamponade; Extracorporeal Life Support Organization; extracorporeal membrane oxygenation; registry

CARDIAC TAMPONADE, consisting of the compression of all cardiac chambers due to increased pericardial pressure, is a potentially life-threatening complication during extracorporeal membrane oxygenation (ECMO). Risk factors for cardiac tamponade are frequently present in patients under ECMO support, which are related to the underlying disease (eg, recent cardiac surgery, acute myocardial infarction, myocarditis, cardiopulmonary resuscitation), and to the

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extracorporeal technique itself (eg, cannulation-related cardiovascular perforation, systemic anticoagulation).[1-5]

Extracorporeal membrane oxygenation might also impact the clinical presentation and the therapeutic approach of cardiac tamponade. Typical hemodynamic findings of cardiac tamponade are less likely to appear in patients under venoarterial ECMO (VA ECMO), potentially delaying its diagnosis and treatment.[6] Cardiac tamponade also has been described as a complication of venovenous ECMO (VV ECMO).[1,2]

Despite the potential risk of cardiac tamponade associated with ECMO support, data on this association are limited, being mainly limited to old series, single-center studies, and case reports.[1,3,6-8] In the present study, the authors queried the Extracorporeal Life Support Organization (ELSO) Registry for all adults with cardiac tamponade as a reported complication during the ECMO run to assess the incidence, patient characteristics, and risk factors for mortality of cardiac tamponade complicating ECMO.

Methods

Data Source

The international ELSO Registry includes data voluntarily reported from more than 400 centers, including patient clinical characteristics, circuit components, cannulation configurations, and clinical outcomes.[9,10] Clinical diagnoses and comorbidities are reported with the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes. Studies using the ELSO database are exempt from local Institutional Review Board approval, as the data are deidentified. To ensure that the data were analyzed as it was originally intended, the manuscript was analyzed by the ELSO Scientific Oversight Committee before journal submission.

Study Population, Covariates, and Outcomes

The authors included adults (≥18 years old) receiving ECMO support from January 1, 1997, through July 31, 2021, with cardiac tamponade as a reported complication (Codes 541 and 544) during the ECMO run. Available variables considered in the analysis included the year of ECMO support, baseline demographics, primary diagnosis, comorbidities, ECMO support type, pre-ECMO support (namely mechanical circulatory support), gas exchange parameters (pH, partial pressure of oxygen in arterial blood, and partial pressure of carbon dioxide in arterial blood), basic ventilator parameters (fraction of inspired oxygen, positive end-expiratory pressure and peak inspiratory pressure), ECMO type, cannulation site strategy, duration of ECMO support, the reason for ECMO discontinuation, hospital survival, and other ECMO-related complications.

Statistical Analysis

Categorical variables are presented as numbers (%), and continuous variables as mean ± SEM mean. In Tables 1 to 4, comparisons between groups (survivors versus nonsurvivors) were performed using an independent *t* test for continuous variables, whereas the χ^2 test was used for categorical variables. In Table 5, the independence of baseline patient characteristics (age, acute myocardial infarction, aortic dissection or rupture, and COVID-19 as primary diagnosis), ECMO support type (pulmonary and extracorporeal cardiopulmonary resuscitation [ECPR]), pre-ECMO support (renal-replacement therapy and prone position) in-hospital survival was tested using multivariate binary logistic regression. Similarly, in Table 6, the independence of ECMO-related complications (renal, hemorrhagic, cardiovascular [other than cardiac tamponade], metabolic, neurologic, pulmonary, and limb) in-hospital survival was tested using multivariate binary logistic regression. A Holm-Bonferroni sequential correction was used in multivariate regressions (Tables 5 and 6) to reduce the risk of type I error due to multiple hypothesis testing. A p value of 0.05 was selected to determine statistical significance. For statistical analysis, SPSS Version 27 (IBM SPSS, Inc) was used.

Results

Pre-ECMO Characteristics of Patients

Among 84,430 adults treated with ECMO between 1997 and July 2021, cardiac tamponade was reported in 2,176 (2.6%). The number of reported cases consistently increased over time (Fig 1, A), with the percentage of all-comers in the ELSO Registry with cardiac tamponade complicating ECMO increasing from 1997 to 1998 and 2001 to 2002, and progressively decreasing thereafter (Fig 1, B). The baseline characteristics of patients with cardiac tamponade complicating ECMO are detailed in Table 1. Male predominance was like that observed in the ELSO Registry in the same period (64%). The most common indications for ECMO support were circulatory failure (45%), respiratory failure (8%), and cardiac arrest (4%). The most frequently encountered comorbidities were ischemic (20%) and valvular (11%) heart disease, atrial fibrillation (9%), hypertension (8%), diabetes mellitus (8%), and dyslipidemia (6%).

When compared with survivors, nonsurvivors were older, more frequently had aortic dissection and/or rupture or COVID-19 as the primary diagnosis, and had a higher incidence of ischemic heart disease as a comorbidity (Table 1). In multivariate analysis, age, aortic dissection and/or rupture, and COVID-19 as the primary diagnosis remained independent predictors of hospital mortality (Table 5). Patients >65 years presented a mortality of 75%, whereas in patients <65 years, mortality was 61% ($p < 0.01$).

Supportive Care and Therapies Before and at ECMO Initiation

In patients with cardiac tamponade, ECMO was initiated for cardiac support in 67%, pulmonary support in 21%, and ECPR in 12% (Table 2). The proportion of ECMO for pulmonary support was initially higher (43% in the 1997-1998 period), but stabilized at ∼20% from the 2007-2008 period onward

Table 1
Baseline Characteristics of Patients With Cardiac Tamponade Complicating ECMO

Baseline Characteristics	All	Survivors	Nonsurvivors	p Value
N (%)	2,176 (2.6)	756 (35)	1,400 (65)	-
Age, mean ± SEM, y	53.8 ± 0.33	50.2 ± 0.57	55.8 ± 0.40	< 0.01*
Male sex, n (%)	1,369 (64)	483 (35)	886 (65)	0.76
Primary diagnosis, n (%)				
Circulatory failure	961 (45)	334 (35)	627 (65)	0.79
Shock	301 (14)	112 (37)	189 (63)	0.40
Cardiogenic shock	287 (13)	104 (36)	183 (64)	0.65
Acute myocardial infarction	121 (5.6)	31 (26)	90 (74)	0.02
Postcardiotomy	103 (4.8)	40 (39)	63 (61)	0.41
Aortic dissection/rupture	49 (2.3)	9 (18)	40 (82)	0.01*
Heart transplant	35 (1.6)	16 (46)	19 (64)	0.18
Valvular heart disease	31 (1.4)	9 (29)	22 (71)	0.48
Pulmonary embolism	23 (1.1)	8 (35)	15 (65)	0.98
Acute myocarditis	11 (0.5)	5 (45)	6 (55)	0.47
Respiratory failure	163 (7.6)	51 (31)	112 (69)	0.29
Acute respiratory failure	47 (2.2)	18 (38)	29 (62)	0.64
COVID-19	44 (2.0)	7 (16)	37 (84)	< 0.01*
ARDS	39 (1.8)	12 (31)	27 (69)	0.57
Chronic respiratory failure	33 (1.5)	14 (42)	19 (58)	0.37
Cardiac arrest	82 (3.8)	23 (28)	59 (72)	0.17
Comorbidities				
Ischemic heart disease	432 (19.9)	127 (29)	305 (71)	< 0.01*
Valvular heart disease	247 (11.4)	80 (32)	161 (65)	0.52
Atrial fibrillation	199 (9.1)	76 (38)	122 (61)	0.30
Hypertension	186 (8.5)	63 (34)	120 (65)	0.85
Diabetes mellitus	168 (7.7)	51 (30)	116 (69)	0.20
Dyslipidemia	133 (6.1)	45 (34)	88 (66)	0.76
Chronic respiratory disease	105 (4.8)	37 (35)	67 (64)	0.91
Chronic kidney disease	98 (4.5)	36 (37)	62 (63)	0.72
Obesity	92 (4.2)	30 (33)	62 (67)	0.61
Smoking	47 (2.2)	14 (30)	33 (70)	0.44

NOTE. Data are presented as numbers of cases (%) or mean ± SEM. In survivors and in nonsurvivors, column percentages reflect the fraction of patients with each characteristic.
Abbreviations: ARDS, acute respiratory distress syndrome.
* p <0.05

through 2021. Likewise, the proportion of ECPR was initially higher (39% in the 1999-2000 period), but stabilized at ∼10% from the 2003-2004 period onwards (Fig 1, C).

Supportive care and therapies delivered before and at ECMO initiation are presented in Table 2. When compared with survivors, nonsurvivors more frequently had ECMO for ECPR and renal-replacement therapy and prone position as pre-ECMO support, all of which remained independent predictors of hospital mortality in multivariate analysis (Table 5). Differently, pulmonary support was associated with hospital survival in univariate and multivariate analyses (Tables 2 and 5).

ECMO Support Characteristics

Compared to all-comers in the ELSO registry, patients who had tamponade were more likely to have VA ECMO configuration (78% *v* 56%; p < 0.01) and less likely to have VV ECMO configuration (18% *v* 42%; p < 0.01), with no significant differences in the venovenous-arterial ECMO configuration (1.4% *v* 1.3%; p = 0.59).

Extracorporeal membrane oxygenation cannulation was performed percutaneously in 51% of patients (Table 3). The drainage cannula most commonly used was in the femoral vein (60%) of patients, whereas the most common return cannula was in the femoral artery (37%). The use of dual-lumen cannulae was reported in 7% of patients (39% of VV ECMO). Its association with cardiac tamponade was reported for the first time in 2009, progressively increasing thereafter from 2 to 38 cases/y in 2021 (p < 0.01).

ECMO-Related Complications and Outcomes

Extracorporeal membrane oxygenation–related complications other than cardiac tamponade were reported frequently (Table 4). In multivariate analysis, renal, cardiovascular, metabolic, neurologic, and pulmonary ECMO-related complications independently predicted hospital mortality (Table 6). Additionally, thrombocytopenia was reported in 4% of patients with cardiac tamponade complicating ECMO support, coagulopathy in 4%, hypothyroidism in 1%, cancer in 0.8%, and

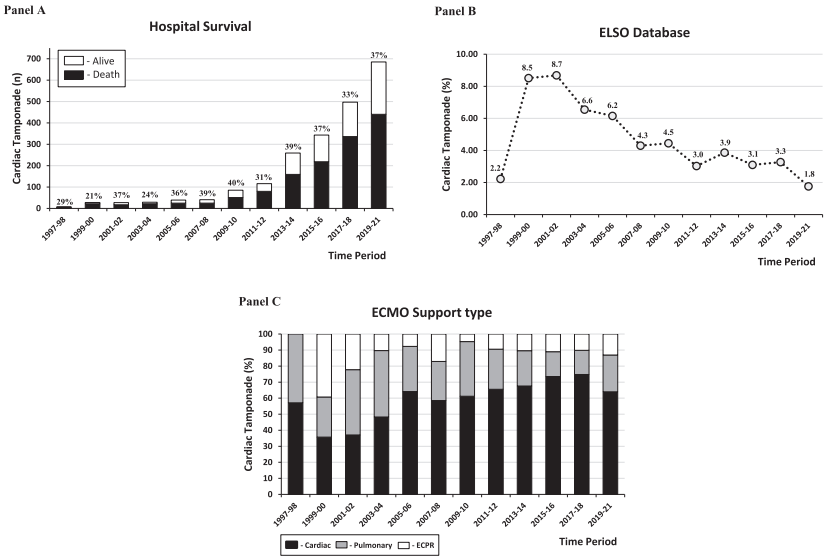

Fig 1. (A) Number of cases and hospital survival. (B) The % of cases reported in the Extracorporeal Life Support Organization Registry with cardiac tamponade complicating extracorporeal membrane oxygenation is presented. ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation. (C) The type of support of patients with cardiac tamponade complicating extracorporeal membrane oxygenation, as reported in the Extracorporeal Life Support Organization Registry between 1997 and July 2021.

Table 2
Supportive Care and Therapies Delivered Before and at ECMO Initiation

Therapies before ECMO	All	Survivors	Nonsurvivors	p Value
N (%)	2,176 (2.6)	756 (35)	1,400 (65)	-
ECMO support type, n (%)				
Cardiac	1,466 (67)	505 (34)	946 (65)	0.71
Pulmonary	458 (21)	196 (43)	260 (57)	< 0.01*
ECPR	252 (12)	55 (22)	194 (77)	< 0.01*
Pre-ECMO support, n (%)				
Vasopressors	1,419 (65)	475 (33)	930 (66)	0.09
Inotropes	1,064 (49)	362 (34)	695 (65)	0.35
Neuromuscular blockers	644 (30)	217 (34)	417 (65)	0.60
Inhaled pulmonary vasodilators	342 (16)	125 (37)	215 (63)	0.47
Renal replacement therapy	130 (6.0)	31 (24)	97 (75)	< 0.01*
Prone position	59 (2.7)	11 (19)	48 (81)	< 0.01*
Pre-ECMO mechanical circulatory support, n (%)				
Cardiopulmonary bypass	680 (31)	234 (34)	440 (65)	0.82
Intra-aortic balloon	479 (22)	172 (36)	301 (63)	0.50
Ventricular assist device	122 (5.6)	49 (40)	73 (60)	0.22
Percutaneous ventricular assist device	87 (4.0)	24 (28)	61 (70)	0.18
Pre-ECMO parameters, mean ± SEM				
RR, breaths/min	18.0 ± 0.21	18.1 ± 0.39	17.9 ± 0.25	0.64
PaO_2/F_iO_2, mmHg	199 ± 8.2	193 ± 9.7	202 ± 11.5	0.62
PIP, cmH_2O	27.7 ± 0.33	27.4 ± 0.54	27.9 ± 0.41	0.49
PEEP, cmH_2O	8.6 ± 0.15	8.5 ± 0.22	8.6 ± 0.20	0.76
pH	7.28 ± 0.004	7.28 ± 0.006	7.27 ± 0.005	0.24
$PaCO_2$, mmHg	47.0 ± 0.61	48.2 ± 1.03	46.4 ± 0.76	0.17

NOTE. Data are presented as numbers of cases (%) or mean ± SEM. In survivors and in nonsurvivors, column percentages reflect the fraction of patients with each characteristic.
Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, ECMO-assisted cardiopulmonary resuscitation; F_iO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RR, respiratory rate.
* p <0.05

Table 3
ECMO Support Characteristics in Patients With Cardiac Tamponade

Support Characteristics, n (%)	All	Survivors	Nonsurvivors	p Value
ECMO type				
VA ECMO	1,709 (78.5)	564 (74.6)	1,127 (80.5)	< 0.01*
VV ECMO	390 (17.9)	164 (21.7)	224 (16.0)	< 0.01*
VVA ECMO	31 (1.4)	10 (1.3)	21 (1.5)	0.74
ECMO cannulation				
Percutaneous	1,110 (51.0)	379 (50.1)	720 (51.4)	0.56
Dual-lumen cannula	137 (7.0)	46 (6.8)	81 (6.4)	0.75
Drainage cannula				
Femoral vein	767 (60.3)	268 (63.2)	488 (58.9)	0.14
Right atrium	251 (19.7)	74 (17.5)	172 (20.7)	0.16
Internal jugular vein	98 (7.7)	39 (9.2)	59 (7.1)	0.19
Return cannula				
Femoral artery	528 (36.9)	169 (35.1)	353 (37.8)	0.35
Aorta	310 (21.6)	107 (22.2)	196 (21.0)	0.53
Internal jugular vein	164 (11.5)	65 (13.5)	98 (10.5)	0.08
Femoral vein	162 (11.3)	57 (11.9)	104 (11.1)	0.65

NOTE. Data are presented as numbers of cases (%).
Abbreviations: ECMO-VA, venoarterial extracorporeal membrane oxygenation; ECMO-VV, venovenous extracorporeal membrane oxygenation; ECMO-VVA, venovenoarterial extracorporeal membrane oxygenation; ECPR, ECMO-assisted cardiopulmonary resuscitation.
* p <0.05

thoracic trauma in 0.6%. No significant differences were detected between survivors and nonsurvivors.

Of the patients with cardiac arrest complicating cardiac tamponade (218; 10%), 49% had VA ECMO, 46% VV ECMO, and 3% venovenous-arterial ECMO as initial configurations, with ECMO mode conversion reported in 16% of patients with initial VV ECMO configuration.

Extracorporeal membrane oxygenation run duration for patients with cardiac tamponade complicating ECMO was 258 ± 8.4 hours, 206 ± 5.5 hours in cardiac support, 484 ± 18.6 hours in pulmonary support, and 148 ± 5.6 in ECPR. Extracorporeal membrane oxygenation discontinuation was due to recovery in 46% of patients, death in 46%, direct major ECMO complications in 3%, ventricular assist device implantation in 2%, heart transplantation in 0.6%, and heart and lung transplantation in 0.1%. Hospital survival in patients with cardiac tamponade was 35% and relatively stable during the period of the study (Fig 1, A) (p = 0.74)—34% in ECMO for cardiac support, 43% for pulmonary support, and 22% in ECPR (p < 0.01). This differed from the current hospital survival rate reported in the ELSO Registry—49% for all adults, 46% in ECMO for cardiac support, 58% for pulmonary support, and 30% in ECPR (p < 0.01).[11]

Discussion

In the ELSO Registry, cardiac tamponade complicating ECMO was reported in 2,176 of 84,430 adults (2.6%) from

Table 4
Complications in Patients With Cardiac Tamponade Complicating ECMO Support

Complications, n (%)	All	Survivors	Nonsurvivors	p Value
Renal complications	1,301 (59.8)	377 (49.9)	915 (65.4)	< 0.01*
Renal-replacement therapy	1,035 (47.6)	273 (36.1)	754 (53.9)	< 0.01*
Hemorrhagic complications	1,293 (59.4)	414 (54.8)	869 (62.1)	0.01*
Surgical site bleeding	904 (41.5)	294 (38.9)	605 (43.2)	0.05
Cannulation site bleeding	320 (14.7)	83 (11.0)	235 (16.8)	< 0.01*
Cardiovascular complications	1,172 (53.9)	353 (46.7)	812 (39.9)	< 0.01*
Inotropes	759 (34.9)	232 (30.7)	526 (37.6)	< 0.01*
Cardiac arrhythmia	546 (25.1)	166 (22.0)	375 (26.8)	0.01*
Device-related complications	631 (29.0)	202 (26.7)	424 (30.2)	0.08
Metabolic complications	608 (27.9)	158 (20.9)	449 (32.1)	< 0.01*
Hyperbilirubinemia	321 (14.8)	73 (9.7)	248 (17.7)	< 0.01*
Acidosis	200 (9.2)	39 (5.2)	161 (11.5)	< 0.01*
Neurologic complications	296 (13.6)	60 (7.9)	236 (16.9)	< 0.01*
CNS infarct	146 (6.7)	36 (4.8)	110 (7.9)	< 0.01*
CNS hemorrhage	74 (3.4)	13 (1.7)	61 (4.4)	< 0.01*
Pulmonary complications	242 (11.1)	61 (8.1)	180 (12.9)	< 0.01*
Pulmonary hemorrhage	146 (6.7)	29 (3.8)	116 (8.3)	< 0.01*
Pneumothorax	118 (5.4)	39 (5.2)	79 (5.6)	0.64
Infectious complications	240 (11.0%)	95 (12.6%)	145 (10.4)	0.12
Limb complications	144 (6.6%)	38 (5.0%)	105 (7.5)	0.03*
Limb ischemia	97 (4.5%)	30 (4.0%)	66 (4.7)	0.42
Limb fasciotomy	50 (2.3%)	10 (1.3%)	40 (2.9)	0.02*

NOTE. Data are presented as numbers of cases (%).
Abbreviations: CNS, central nervous system; ECMO, extracorporeal membrane oxygenation.
* p <0.05

Table 5
Multivariate Binary Logistic Regression Model, Including Age, Aortic Dissection/Rupture, and COVID-19, as the Primary Diagnosis, Ischemic Heart Disease As Comorbidity, Pulmonary ECMO Support and ECMO-Assisted CPR, and Pre-ECMO Renal-Replacement Therapy and Prone Position, With Hospital Survival as an Outcome of Patients With Cardiac Tamponade Complicating ECMO

Hospital Survival	OR (95% CI)	p Value
Age	0.979 (0.973-0.985)	< 0.01*
Primary Diagnosis		
Aortic dissection and/or rupture	0.392 (0.187-0.821)	0.01*
COVID-19	0.294 (0.123-0.702)	< 0.01*
Comorbidity		
Ischemic heart disease	0.956 (0.746-1.225)	0.54
ECMO support type		
Pulmonary	1.351 (1.063-1.718)	0.01*
ECPR	0.534 (0.387-0.739)	< 0.01*
Pre-ECMO support		
Renal-replacement therapy	0.583 (0.386-0.880)	0.01*
Prone position	0.379 (0.189-0.758)	< 0.01*

NOTE. Results are presented as odds ratio (OR) with a correspondent 95% CI.
Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio.
* p <0.05

1997 to 2021. The reported historic (~1985-2010) rate of hemorrhagic cardiac tamponade in the ELSO Registry for cardiac ECMO, including neonatal, pediatric, and adult ECMO, was lower (1.8%).[1] The number of reported cases consistently increased over time, with the percentage of all-comers in the ELSO Registry with cardiac tamponade complicating ECMO increasing from 1997 to 1998 and 2001 to 2002 and progressively decreasing thereafter. Increasing age, aortic dissection or rupture, COVID-19 as the primary diagnosis, renal-replacement therapy, and prone position before ECMO initiation are independently associated with hospital mortality.

During ECMO support, a lack of pulsatility or arrhythmias could signal tamponade, and an echocardiogram should be obtained to assess the diagnosis. In the authors' study, most cases of cardiac tamponade occurred in patients under VA-ECMO (78%) for cardiac support (67%) and ECPR (12%). This could have been relevant to the clinical outcome given that typical hemodynamic findings of cardiac tamponade have been reported as less likely to appear in patients under VA ECMO, potentially delaying treatment.[6] In this study, around one-third of patients had undergone cardiopulmonary bypass, and around one-half underwent central cannulation. This may indicate that cardiac surgery increases the risk of cardiac tamponade in patients undergoing ECMO support, but it requires a dedicated study.[12] A relatively high rate of cardiac perforation has been reported with the use of a dual-lumen bicaval cannulae.[1,2] In the authors' study, 39% of patients with cardiac tamponade complicating VV ECMO had dual-lumen cannulae. This was first reported in 2009, progressively increasing thereafter ($p < 0.01$).

Table 6
Multivariate Binary Logistic Regression Model, Including Renal, Hemorrhagic, Cardiovascular, Metabolic, Neurologic, Pulmonary, and Limb Complications, in Patients With Cardiac Tamponade Complicating ECMO Support, With Hospital Survival as an Outcome

Hospital Survival	OR (95% CI)	p Value
ECMO-related complications		
Renal	0.640 (0.528-0.776)	< 0.01*
Hemorrhagic	0.870 (0.721-1.050)	0.15
Cardiovascular	0.790 (0.652-0.958)	0.02*
Metabolic	0.742 (0.591-0.932)	0.01*
Neurologic	0.470 (0.347-0.637)	< 0.01*
Pulmonary	0.653 (0.478-0.893)	< 0.01*
Limb	0.727 (0.490-1.077)	0.11

NOTE. Results are presented as odds ratio (OR) with correspondent 95% CI.
Abbreviations: ECMO, extracorporeal membrane oxygenation; OR, odds ratio.
* p <0.05

Only 18% of patients with cardiac tamponade complicating ECMO had VV ECMO, compared with 42% of patients with this configuration in the ELSO Registry in the same period, and ECMO for pulmonary support was independently associated with hospital survival in multivariate analysis. Of note, when circulatory collapse complicates cardiac tamponade during VV ECMO, conversion to VA ECMO should be considered as a bridge for timely correction of the underlying cause.[3,7] In the ELSO Registry, ECMO mode conversion was reported only in 16% of adult patients with initial VV ECMO configuration, in whom cardiac tamponade was associated with cardiac arrest. Although VV ECMO to VA ECMO conversion should be considered when cardiac arrest complicates VV ECMO, this has not been described consistently outside the specific clinical context of cardiac tamponade.[3,7] In a recent single-center retrospective study, the conversion rate from VV ECMO to VA ECMO in 219 VV ECMO adult patients was 21%, the main indication for conversion being right ventricular failure (65%) and cardiogenic shock (26%), with no cases of cardiac arrest.[13] In another single-center study that included 78 patients with COVID-19 requiring VV ECMO, 14 (18%) were converted from VV ECMO to VA ECMO or hybrid ECMO.[14] Once again, the reasons for the ECMO mode configuration did not include cardiac arrest—inadequate drainage (35.7%), inadequate perfusion (14.3%), myocardial infarction (7.1%), hypovolemic shock (14.3%), cardiogenic shock (14.3%) and septic shock (7.1%).

The extracorporeal technique requires a balanced decision to titrate systemic anticoagulation to prevent thrombotic complications while avoiding bleeding complications.[15-18] Coagulation and hematologic risk factors were also present in the study population (coagulopathy [4%] and thrombocytopenia [4%]), which eventually could have contributed to the risk for cardiac tamponade. Thrombocytopenia previously has been shown to be associated with ECMO support.[19,20] Additionally, other risk factors for cardiac tamponade were also reported in a small percentage of patients, such as hypothyroidism (1.2%), cancer (0.8%), and thoracic trauma (0.2%). Given that it was not part of the predefined analysis, data from the global ELSO Registry on the frequency of hypothyroidism, cancer, and

thoracic trauma could not be compared with the authors' study population.

Compared with all adults from the ELSO Registry in the same period, cardiac tamponade complicating ECMO was associated with lower hospital survival for all types of support—cardiac, pulmonary, and ECPR ($p < 0.01$). These results are particularly relevant, given that data on the outcomes of adult patients with cardiac tamponade complicating ECMO are limited to case reports and case series.[1,6,7,21] Complications in addition to cardiac tamponade (namely renal, cardiovascular, metabolic, neurologic, and pulmonary) were observed frequently after ECMO initiation, and independently associated with hospital mortality. This highlights the importance of high-volume centers with 24-hour, 7 days a week cardiac surgery availability for the successful management of ECMO-related complications.[7,22-24]

To clarify the specific contribution of cardiac tamponade to the mortality risk factors in patients on ECMO, the authors compared their results with previous studies. Age and pre-ECMO renal-replacement therapy have been previously associated with mortality in patients on ECMO.[25,26] In the study by Marie et al., patients on ECMO older than 65 years had increased mortality (75% *v* 48%; $p < 0.01$), which correlated with the finding of increased mortality of this patient subgroup in this study (75% *v* 61%; $p < 0.01$).[25] Haneya et al. reported higher mortality in patients on ECMO requiring pre-ECMO renal- replacement therapy (72% *v* 47%; $p < 0.01$), which also was observed in this study on cardiac tamponade (75% *v* 64%; $p < 0.01$).[26] Data from the global ELSO Registry consistently showed higher mortality for adult ECPR (70%), whereas pulmonary ECMO was associated with higher survival (58%) compared to cardiac ECMO (46%) ($p < 0.01$).[11,25,26] This could indicate that these risk factors do not interact with cardiac tamponade in the mortality risk in patients on ECMO. Cardiac tamponade complicating aortic dissection and/or rupture has been previously associated with the need for ECMO support and a worse prognosis.[27] Regarding COVID-19 requiring ECMO, the incidence of bleeding complications was high and associated with mortality, with cardiac tamponade described as a potential complication of severe myopericarditis.[28,29] In the authors' study, the prone position was associated with increased hospital mortality (81% *v* 65%; $p < 0.01$), which varied from prior reports.[30,31] Namely, in a retrospective single-center study over 8 years, Petit et al. showed lower 90-day mortality in patients with prone positioning during ECMO (20% *v* 42%, $p < 0.01$).[31] This could indicate a specific contribution of cardiac tamponade to the mortality risk in this patient population. Timely diagnosis of cardiac tamponade requires a high index of suspicion in the setting of prone positioning; delays in recognition of tamponade may lead to a worse prognosis.[32]

Data on cannula size could not be obtained from the ELSO Registry, so a possible association with tamponade risk could not be ascertained. Of note, it has been suggested that the guidewires used in ECMO cannula packages may be more prone to cardiovascular perforation.[33] Most ECMO packages contain soft, flexible guidewires as opposed to more stiff guidewires often used in interventional cardiology procedures. Flexible guidewires have a greater chance of intravascular or intracardiac 'looping' that directs the dilators and cannulae toward the vascular or cardiac wall, with an increased risk of perforation.[34] Another limitation that must be accounted for in the present study related to the lack of information on the timing of cardiac tamponade diagnosis. In fact, the authors could not determine whether cardiac tamponade had already been present in emergent cannulations, such as in the case of ECPR, for an unknown cause. In the present study, data on coagulation are not presented. This represents a major limitation to this study, given that the therapeutic anticoagulation levels and the complex coagulopathy associated with ECMO (which includes an acquired von Willebrand syndrome, platelet dysfunction, and activation of fibrinolysis) are established risk factors for bleeding complications in patients requiring ECMO.[35-37]

Conclusion

In conclusion, cardiac tamponade was a rare complication of ECMO support in adults, and was associated with lower hospital survival compared to all-comers in the ECMO registry. VA ECMO was the most common configuration. ECMO for pulmonary support was associated with higher survival, and ECPR was associated with higher mortality. In these patients, other ECMO-related complications frequently were reported and associated with hospital mortality.

Declaration of competing interest

None.

CRediT authorship contribution statement

Carla Basílio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Marc Anders:** Data curation, Validation, Writing – review & editing. **Peter Rycus:** Data curation, Supervision, Validation, Writing – review & editing. **José Artur Paiva:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Roberto Roncon-Albuquerque:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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3.3. Scrutinizing the Role of VA-ECMO: Has Clinical Practice Outpaced the Evidence?

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Scrutinizing the Role of Venoarterial Extracorporeal Membrane Oxygenation: Has Clinical Practice Outpaced the Evidence?

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ABSTRACT: The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) for temporary mechanical circulatory support in various clinical scenarios has been increasing consistently, despite the lack of sufficient evidence regarding its benefit and safety from adequately powered randomized controlled trials. Although the ARREST trial (Advanced Reperfusion Strategies for Patients with Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation) and a secondary analysis of the PRAGUE OHCA trial (Prague Out-of-Hospital Cardiac Arrest) provided some evidence in favor of VA-ECMO in the setting of out-of-hospital cardiac arrest, the INCEPTION trial (Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest) has not found a relevant improvement of short-term mortality with extracorporeal cardiopulmonary resuscitation. In addition, the results of the recently published ECLS-SHOCK trial (Extracorporeal Life Support in Cardiogenic Shock) and ECMO-CS trial (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) discourage the routine use of VA-ECMO in patients with infarct-related cardiogenic shock. Ongoing clinical trials (ANCHOR [Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock, NCT04184635], REVERSE [Impella CP With VA ECMO for Cardiogenic Shock, NCT03431467], UNLOAD ECMO [Left Ventricular Unloading to Improve Outcome in Cardiogenic Shock Patients on VA-ECMO, NCT05577195], PIONEER [Hemodynamic Support With ECMO and IABP in Elective Complex High-risk PCI, NCT04045873]) may clarify the usefulness of VA-ECMO in specific patient subpopulations and the efficacy of combined mechanical circulatory support strategies. Pending further data to refine patient selection and management recommendations for VA-ECMO, it remains uncertain whether the present usage of this device improves outcomes.

Key Words: extracorporeal membrane oxygenation ■ heart failure ■ heart-lung machine ■ shock, cardiogenic

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Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a mechanical circulatory support (MCS) modality capable of temporary replacement of heart and lung function. Its historical development is summarized in Figure S1. The basic concept involves the drainage of central venous blood into an extracorporeal tubing system, oxygenation and decarboxylation within a respiratory unit, and return of arterialized blood into the patient's vasculature (Figure 1). The circuit is powered by a centrifugal pump providing adjustable flow rates of up to 6.0 L/min. Central cannulation potentially allows for direct cannula positioning into the pulmonary artery, left

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STATE OF THE ART

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
CA	cardiac arrest
CPR	cardiopulmonary resuscitation
CS	cardiogenic shock
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
ELSO	Extracorporeal Life Support Organization
HR	hazard ratio
IABP	intra-aortic balloon pump
IFN-γ	interferon gamma
IL	interleukin
LV	left ventricle
MCS	mechanical circulatory support
NR	nonrandomized
OHCA	out-of-hospital cardiac arrest
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
ROSC	return of spontaneous circulation
VA-ECMO	venoarterial extracorporeal membrane oxygenation
VT	ventricular tachycardia

ventricle (LV), or ascending aorta. By contrast, peripheral percutaneous cannulation requires less infrastructure and can be implemented rapidly in case of circulatory collapse, even in out-of-hospital settings.[1]

According to the current American Heart Association and European Society of Cardiology guidelines, VA-ECMO or other MCS, without a specific recommendation which device to prefer, should be considered for selected patients in severe cardiogenic shock (CS; Table 1).[2–9] Other contemporary application scenarios include VA-ECMO–assisted resuscitation for refractory cardiac arrest (CA; extracorporeal cardiopulmonary resuscitation [ECPR]), and VA-ECMO–protected high-risk procedures such as percutaneous coronary interventions (PCI) or catheter ablation of ventricular tachycardias (VTs; Table 1).[10–13] Over the past 15 years, the number of VA-ECMO centers has more than quadrupled and its use has increased approximately 8-fold according to data from the Extracorporeal Life Support Organization (ELSO) registry.[14] Contradicting these developments is the scarcity of high-quality evidence supporting VA-ECMO use for an expanding list of indications. Current guideline recommendations are largely based on retrospective studies, often without any or adequate control groups, and meta-analyses of nonrandomized data.[15] So far, only one randomized controlled trial (RCT) has provided evidence in favor of VA-ECMO in a highly selected scenario of refractory cardiopulmonary resuscitation.[16] On the other hand, given (1) the results of the ECLS-SHOCK (Extracorporeal Life Support in Cardiogenic Shock),[17] ECMO-CS (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock),[18] and INCEPTION (Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest)[19] trials, (2) stagnating in-hospital mortality of patients undergoing VA-ECMO, and (3) the technical complexity, (4) resource intensity, (5) costs, and (6) severity of potential complications, as well, it is questionable to what extent the widespread use of VA-ECMO is justified at this stage.

In this narrative review, we discuss the strengths and limitations of the available data regarding efficacy, associated risks, and management strategies of VA-ECMO use in CS and other contemporary application scenarios such as ECPR and VA-ECMO–facilitated high-risk procedures, focusing on RCTs and large/matched prospective or retrospective studies. We aim to elaborate the remaining gaps in evidence (Table 2), provide an overview of ongoing clinical trials (Table 3), and highlight key questions for future research endeavors.

VA-ECMO IN CS

CS is defined as end-organ hypoperfusion resulting from primary ventricular dysfunction.[2] Current guidelines recommend short-term MCS as a bridge to recovery, treatment of the cause of CS, durable MCS implantation, heart transplantation, or decision-making in selected patients showing persistent signs of hemodynamic instability despite optimal therapy (class IIa, level of evidence C [European Society of Cardiology], level of evidence B-NR [American Heart Association]).[2,3,8,20] However, the diagnostic criteria for CS do not account for the pathogenesis, nor do they capture the extent of hemodynamic compromise, and are therefore insufficient for identifying candidates who are likely to benefit from MCS. The 2019 Society for Cardiovascular Angiography and Interventions consensus statement suggested a more granular description of patients with CS according to the requirement of medical and mechanical circulatory support, the response to initial treatment, and the presence of circulatory collapse and CA.[21] As such, this classification, which is partly subjective, is not intended to guide clinical decision-making regarding the application of MCS. Outcome prediction tools such as the SAVE (Survival after VA-ECMO) and ENCOURAGE scores may allow for improved patient selection, but decision-making regarding VA-ECMO initiation, maintenance, deescalation, complication management, and destination concepts still represents a major challenge for cardiovascular intensive care teams.[22–24] The available evidence on VA-ECMO support in CS is summarized in the next sections.

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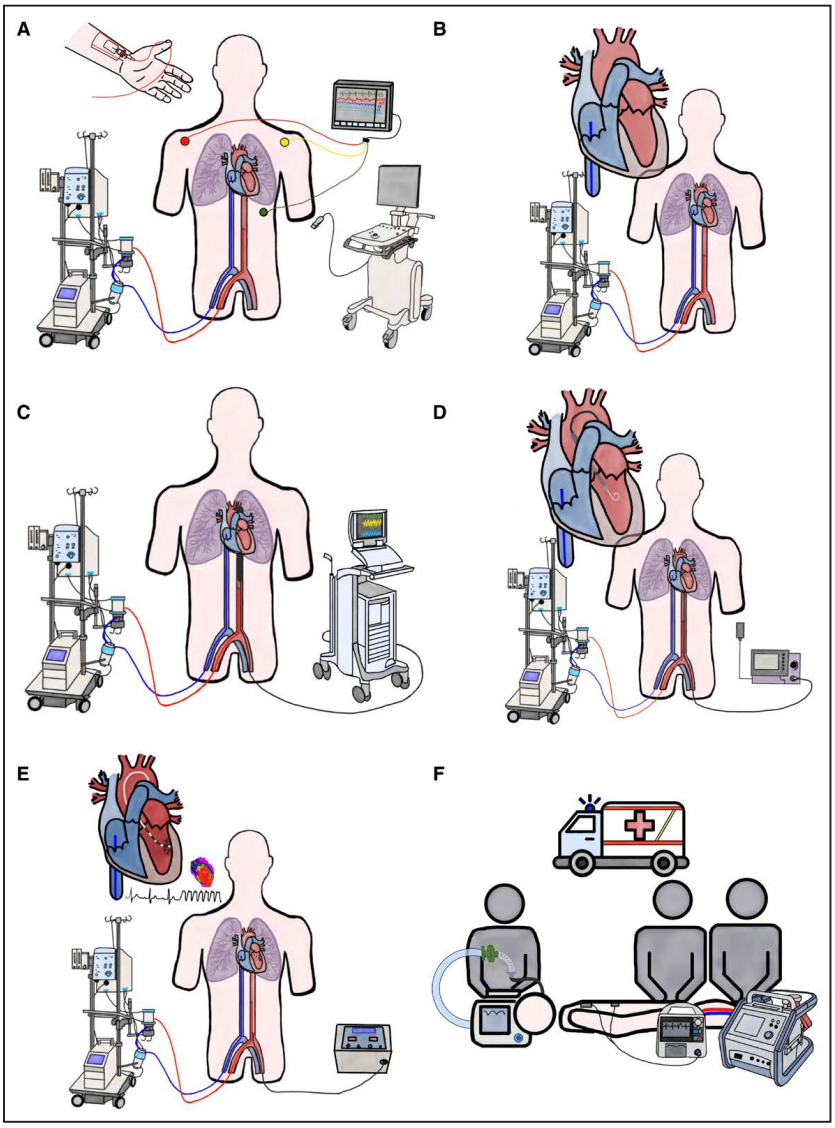

Figure 1. The VA-ECMO device.
A, Basic intensive care monitoring during VA-ECMO (venoarterial extracorporeal membrane oxygenation, device shown in left lower corner) including advanced hemodynamic monitoring and bedside echocardiography (right lower corner). **B**, Peripheral insertion of VA-ECMO (device shown in left lower corner) cannulae through femoral artery (outflow cannula, red line) and femoral vein (inflow cannula, blue line). **C**, Combined mechanical circulatory support using VA-ECMO (device shown in left lower corner) and intra-aortic balloon pump (IABP, external controller shown on the right). **D**, Combined mechanical circulatory support using VA-ECMO (device shown in left lower corner) and Impella (Impella pump shown in left upper corner, external controller shown in right lower corner). **E**, VA-ECMO–facilitated ablation of ventricular tachycardia (catheter placement shown in left upper corner, electrophysiological transmission unit shown in right lower corner). **F**, Extracorporeal cardiopulmonary resuscitation setup including portable ventilator (left lower corner), external defibrillator (central), and portable VA-ECMO device (right lower corner).

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Table 1. Guideline Recommendations for the Use of Short-Term Mechanical Circulatory Support

Clinical scenario	Guideline	Recommendation	Class of recommendation	Level of evidence
Cardiogenic shock	2021 ESC acute and chronic heart failure[2]	Short-term MCS should be considered in patients with CS as a BTR, BTD, BTB. Further indications include treatment of the cause of CS or long-term MCS or transplantation.	IIa	C
	2022 AHA/ACC/HFSA heart failure guidelines[3]	In patients with CS, temporary MCS is reasonable when end-organ function cannot be maintained by pharmacological means to support cardiac function.	IIa	B-NR
		In patients with advanced HFrEF and hemodynamic compromise and shock, temporary MCS, including percutaneous and extracorporeal ventricular assist devices, are reasonable as a "bridge to recovery" or "bridge to decision."	IIa	B-NR
Cardiogenic shock	2021 ESC acute and chronic heart failure[2]	IABP may be considered in patients with CS as a BTR, BTD, BTB, including treatment of the cause of CS (ie, mechanical complication of acute MI) or long-term MCS or transplantation.	IIb	C
Cardiogenic shock	2021 ESC acute and chronic heart failure[2]	IABP is not routinely recommended in post-MI CS.	III	B
Cardiogenic shock in patients with ACS	2023 ESC ACS[4]; 2018 ESC/EACTS on myocardial revascularization[5]	In selected patients with ACS and severe/refractory CS, short-term MCS may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.	IIb	C
Cardiogenic shock in patients with ACS	2018 ESC/EACTS on myocardial revascularization[5]	Routine use of IABP in patients with CS due to ACS is not recommended.	III	B
Cardiogenic shock in patients with ACS	2023 ESC ACS[4]	The routine use of an IABP in patients who have ACS with CS and without mechanical complications is not recommended.	III	B
	2013 ACCF/AHA STEMI[8]	The use of IABP counterpulsation can be useful for patients with CS after STEMI who do not quickly stabilize with pharmacological therapy.	IIa	B
Cardiogenic shock in patients with NSTEMI	2020 ESC NSTEMI[7]	For NSTEMI-ACS–related mechanical complications, the use of IABP should be considered.	IIa	C
High-risk pulmonary embolism	2019 ESC pulmonary embolism[9]	ECMO may be considered in combination with surgical embolectomy or catheter-directed treatment, in refractory circulatory collapse or cardiac arrest.	IIb	C
Electrical storm	2022 ESC Ventricular Arrhythmias[12]	Institution of MCS may be considered in the management of drug-refractory electrical storm and CS.	IIb	C
ECPR	2021 ERC Adult Advanced Life Support[10]	We suggest that ECPR may be considered as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings in which it can be implemented.	Weak recommendation	Very low certainty of evidence
	2019 AHA Focused Update on Advanced Cardiovascular Life Support[11]	ECPR may be considered for selected patients as rescue therapy when conventional CPR efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers	IIb	C-LD

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; BTB, bridge to bridge; BTD, bridge to decision; BTR, bridge to recovery; CPR, cardiopulmonary resuscitation; CS, cardiogenic shock; EACTS, European Association for Cardio-Thoracic Surgery; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ERC, European Resuscitation Council; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; MI, myocardial infarction; NR, nonrandomized; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

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Mortality Among Patients in CS Who Are Receiving VA-ECMO.

Although the use of VA-ECMO is increasing steadily, multiple retrospective observational studies have demonstrated that survival rates remain poor.[25–28] An ELSO registry analysis found a 58% in-hospital mortality rate among 3846 patients receiving VA-ECMO for CS.[22] A meta-analysis including 10 276 patients on VA-ECMO support for acute myocardial infarction–related cardiogenic shock (AMI-CS) more recently reported an overall pooled mortality estimate of 58%.[29] CS is, however, a complex disease comprising heterogeneous subtypes with substantial differences regarding demographics, hemodynamics, patient management, and other variables. This is reflected by the differences in in-hospital mortality estimates associated with various underlying CS pathogeneses.[30,31]

VA-ECMO Versus Conservative Care in CS

Retrospective studies focusing on VA-ECMO for AMI-CS and other types of CS are largely limited by statistical power, single-arm design, and inconsistent, nonstandardized use of additional MCS devices (Table S1).[22,32–35] Thus

Table 2. Remaining Gaps in Evidence

Efficacy of VA-ECMO
1. Which patient subgroup benefits from VA-ECMO? (eg, acute decompensated heart failure vs right ventricle failure)
2. Which criteria should be applied for identifying those patients?
3. What is the optimal timing of VA-ECMO initiation?
4. What is the overall performance of available risk stratification models for the use of VA-ECMO?
5. What are key predictors of VA-ECMO success and failure?
6. How can cost-effectiveness of VA-ECMO treatment be improved? Threshold for the use of VA-ECMO?
7. What are the advantages and disadvantages of VA-ECMO compared to other MCS devices in head-to-head comparative trials?
Safety of VA-ECMO
1. How can complications be prevented, recognized, and managed most effectively?
2. What is the optimal cannulation and decannulation strategy?
3. How can anticoagulation be optimized, especially considering different therapeutic targets, agents, and combination therapy?
4. Do technical innovations (eg, reduction in cannula and oxygenator thrombogenicity, value of antimicrobial coatings, solutions for safe VA-ECMO implantation and explantation) translate to improved outcomes?
Patient management
1. What is the superior mechanical and nonmechanical ventilation strategy?
2. How can fluid management be optimized (eg, regarding target balance and the role of renal replacement therapy)?
3. Which agents and dosing algorithms should be used for inotropes, vasopressors, and sedatives?
4. What are the optimal transfusion thresholds for red blood cells, platelets, and plasma?
5. What is the role of advanced monitoring techniques (eg, continuous electroencephalography)?
Venting
1. Does concomitant MCS-based left ventricle unloading improve outcomes, and if yes, what criteria should be used for additional MCS initiation?
2. Which venting strategy (eg, active vs passive, should be used in specific scenarios?
3. What is the optimal timing of left ventricle venting?
Weaning
1. What are predictors of successful and unsuccessful weaning?
2. What is the role of adjunctive interventions, such as vasoactive medication or device upgrades during liberation?

MCS indicates mechanical circulatory support; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

far, 4 trials have generated prospective randomized evidence regarding the outcomes of VA-ECMO compared with standard of care in CS. In the first study by Brunner et al,[36] 42 patients with AMI-CS were randomly assigned, 21 of whom received VA-ECMO therapy. The primary end point, left ventricular ejection fraction 30 days after implantation, was similar between the VA-ECMO and control group. The 1-year mortality rate was 38% among patients in the standard-of-care group and 19% among patients who underwent VA-ECMO (P=0.31).[37] Ostadal et al[18] published another RCT evaluating the efficacy and safety of immediate VA-ECMO versus early conservative therapy in 117 participants treated for rapidly deteriorating or severe CS (roughly corresponding to Society for Cardiovascular Angiography and Interventions stages D/E) with ST-segment–elevation myocardial infarction (50.4%) being the most common underlying cause. Twenty-three of 59 patients (39%) in the conservative arm received VA-ECMO per study protocol for progressing shock defined as a rise in arterial lactate by ≥3 mmol/L compared with the lowest value during the preceding 24 hours. The primary composite end point of death, resuscitated CA, and implementation of another circulatory assist device at 30 days occurred in 63.8% in the VA-ECMO arm and in 71.2% of patients in the control arm (hazard ratio [HR], 0.72 [95% CI, 0.46–1.12]). There was no significant difference in 30-day all-cause mortality, distribution of cerebral performance category scores, or the rate of serious adverse events (risk difference, −0.7 [95% CI, −18.4 to 17.0]). Main limitations result from the use of bail-out MCS for a substantial proportion of patients in the early conservative arm, the use of a trial-specific definition of severe CS (making future cross-study comparisons challenging), and its sample size. Despite these limitations, the results of the ECMO-CS trial at least suggest that a potential survival benefit with VA-ECMO support is not likely to be substantial. The ECLS-SHOCK trial published in August 2023 by Thiele et al[17] evaluated outcomes with VA-ECMO compared with optimal medical therapy in 420 patients with AMI-CS. Main eligibility criteria were myocardial infarction within 12 hours before inclusion, persistent hypotension or need for catecholamines to maintain adequate blood pressure, arterial lactate of >3mmol/L, clinical signs of organ hypoperfusion, and planned coronary revascularization. Approximately 78% of patients were resuscitated before randomization, whereas 51.6% were classified as Society for Cardiovascular Angiography and Interventions shock C at randomization. In the control group, VA-ECMO was initiated in 26 patients mainly because of refractory CA or persistent CS, and other forms of MCS in 15.4% of the remaining 182 patients without VA-ECMO. A relatively low rate of 5.8% of patients randomly assigned to the VA-ECMO arm received another MCS device for LV decompression. The primary end point, 30-day all-cause mortality, occurred in 47.8% in the VA-ECMO group and in 49.0% in the control group (relative risk, 0.98 [95% CI, 0.80–1.19]). Main secondary outcome parameters, such as poor neurological outcome (cerebral performance category 3/4; 24.8% versus 22.6%), repeat revascularization (8.6% versus 10.6%), and renal replacement therapy (8.1% versus 13.9%) were also not significantly different between both groups. On the other hand, VA-ECMO was associated with a significantly higher risk of moderate or severe bleeding complications (relative risk, 2.44 [95% CI,

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Table 3. Ongoing and future trials on VA-ECMO support

Clinical trial	Identifier	Estimated enrollment	Interventional group	Control group	Primary outcome	Estimated completion date
Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock (ANCHOR)	NCT04184635	400	VA-ECMO + IABP	Optimal medical treatment	Treatment failure at day 30	October 2025
Left Ventricular Unloading to Improve Outcome in Cardiogenic Shock Patients on VA-ECMO (UNLOAD ECMO)	NCT05577195	198	VA-ECMO + Impella	VA-ECMO only	Time to death from any cause within 30 days after randomization	December 2025
Impella CP With VA ECMO for Cardiogenic Shock (REVERSE)	NCT03431467	96	VA-ECMO + Impella CP	VA-ECMO only	Recovery from cardiogenic shock	January 2025
Effects of Induced Moderate Hypothermia on Mortality in Cardiogenic Shock Patients Rescued by Veno-arterial ExtraCorporeal Membrane Oxygenation (HYPO-ECMO)	NCT02754193	334	Targeted hypothermia 33–34 °C	Targeted normothermia 36–37 °C	30-day all-cause mortality	November 2019
Extracorporeal Membrane Oxygenation in the Therapy for Refractory Septic Shock With Cardiac Function Under Estimated (ECMO-RESCUE)	NCT05184296	64	VA-ECMO within 6 h of enrollment	Conventional therapy	30-day survival rate	May 2025
Cardiac Arrest Extra Corporeal Oxygenation Membrane (CAREECMO)	NCT03352999	50	Fast-track access to VA-ECMO	N/A	Number of survivors without neurological sequelae (DRS scale from 0 to 6) at 12 mo	December 2023
LEVOSIMENDAN to Facilitate Weaning From ECMO in Severe Cardiogenic Shock Patients (LEVOECMO)	NCT04728932	206	Levosimendan	Placebo	Time to successful ECMO weaning within 30 days after randomization	November 2024
Interest of Levosimendan in Reducing Weaning Failures of Extra Corporeal Life Support – ECLS (Weanilevo)	NCT04158674	210	Levosimendan	Placebo	ECLS withdrawal failure	February 2024
Reduced Anticoagulation Targets in ECLS (RATE)	NCT04536272	330	Group 2: 1.5-2 times baseline aPTT* Group 3: Low molecular weight heparin guided by weight and renal function.*	Group 1: Heparin administration with a target of 2-2.5 times baseline aPTT*	Hemorrhagic complications, severe thrombembolic complications, 6-mo mortality	March 2024
Prediction of Weanability, Survival and Functional Outcomes After ECLS (PRECISE-ECLS)	NCT05444764	800	VA- or VV-ECMO	N/A	Quality of life (EQ-5D), mortality, weaning success	March 2024
Left Ventricular Physiological Effects of Veno-Arterial Extracorporeal Membrane Oxygenation Support During Cardiogenic Shock	NCT05426083	200	VA-ECMO	N/A	Pressure-volume loops at the highest and the lowest level of VA-ECMO support	July 2025
Impact of Adrenoreceptor Expressions on Inflammatory Pattern in Refractory Cardiogenic Shock Under VA ECMO (ADRECMO)	NCT03327493	48	Biological and clinical assessment in patients under refractory cardiogenic shock receiving ECLS (day 0, day 3, "ECLS weaning" day)	N/A	Change plasma cytokines (TNF-α, IFN-γ, IL-4, IL-12, IL-1, IL-6, IL-10), adrenoreceptors, lymphocytes	May 2022
Venous Oxygen Saturation During ECMO Support (ECMOxygen)	NCT04934566	52	Measurement of SmVo2, SVo2, and ScVo2 at 3 different sites	N/A	Intraclass correlation coefficient between $SECMO_{O_2}$ and $ScVo_2$ in the initial assist condition of 2–3 L/min (after 30 min of stability)	June 2023
Transcatheter Aortic Valve Replacement With Extracorporeal Life System Support	NCT04160624	200	TAVR under ECLS	TAVR without ECLS	Major adverse cardiac event	December 2020
Hemodynamic Support With ECMO and IABP in Elective Complex High-risk PCI (PIONEER)	NCT04045873	306	VA-ECMO + IABP	IABP only	MACCE at periprocedure, in-hospital, or within a 30-day follow-up post discharge	June 2024
Post-Surgery Extracorporeal Life Support (PC-ECLS)	NCT04330651	500	ECLS	N/A	1-mo, 1-y, 5-y survival	January 2029

(*Continued*)

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Table 3. Continued

Clinical trial	Identifier	Estimated enrollment	Interventional group	Control group	Primary outcome	Estimated completion date
Validation of Continuous Transcutaneous Carbon Dioxide Monitoring in VA-ECMO Patients	NCT04445909	30	VA-ECMO	N/A	Agreement between transcutaneous carbon dioxide partial pressure measurement and arterial carbon dioxide partial pressures	July 2023
Impact of a VA-ECMO in Combination With CytoSorb in Critically Ill Patients With Cardiogenic Shock (ECMOsorb)	NCT05027529	54	VA-ECMO + Cytokine hemoadsorption system (CytoSorb Adsorber)	VA-ECMO only	Change in inotropic score after 72 h	December 2024

aPTT indicates activated partial thromboplastin time; DRS, disability rating scale; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IFN-γ, Interferon gamma; IL, interleukin; LMWH, low-molecular-weight heparin; MACCE, major adverse cardiac and cerebrovascular events; N/A, not applicable; $ScVo_2$, central venous oxygen saturation; $SmVo_2$, mixed venous oxygen saturation; SVo_2, venous oxygen saturation; TAVR, transcatheter aortic valve replacement; TNF-α, tumor necrosis factor alpha; VA-ECMO, venoarterial extracorporeal membrane oxygenation; and VV-ECMO, venovenous extracorporeal membrane oxygenation.

*Groups 1 and 2 received unfractionated heparin and Group 3 received LMWH.

1.50–3.95]), and peripheral vascular complications requiring intervention (relative risk, 2.86 [95% CI, 1.31–6.25]). Considering that the patients for this trial were almost exclusively recruited at German tertiary centers, the results may not be generalizable to other health care systems where the proposed criteria for VA-ECMO initiation vary from the eligibility criteria of this trial. The fourth RCT named EURO SHOCK has unfortunately been terminated due to slow enrollment after the inclusion of only 35 of the 428 planned participants.[38] In an individual-patient data meta-analysis including patients with AMI-CS from all 4 above-mentioned RCTs, the intention-to-treat analysis showed no significant benefit on 30-day mortality in patients receiving VA-ECMO support compared with the optimal medical therapy alone (46% versus 48%; odds ratio [OR], 0.93 [95% CI, 0.66–1.29]).[39] In the as-treated analysis, no significant difference in 30-day mortality was observed as well (46% versus 48.0%; OR, 0.92 [95% CI, 0.66–1.28]). In none of the prespecified subgroups (age <65 versus ≥65 years, male versus female, arterial lactate <5 versus ≥5 mmol/L, CA before randomization versus no CA before randomization, ST-segment–elevation myocardial infarction versus non–ST-segment–elevation myocardial infarction, anterior myocardial infarction versus myocardial infarction at other location, TIMI flow after PCI 0/1 versus 2/3) did VA-ECMO therapy improve 30-day survival.

VA-ECMO Versus IABP Support in CS

In a meta-analysis by Ouweneel et al[40] on the basis of 13 observational studies, VA-ECMO showed a 33% higher 30-day survival than intra-aortic balloon pump (IABP) in CS, but no difference compared with TandemHeart/Impella. In the absence of RCTs, available retrospective studies and meta-analyses suggest potentially improved survival with VA-ECMO compared with IABP in the setting of CS.[40–42] Given the lack of any mortality benefit of IABP, the comparator in the current 4 RCTs was always standard of care, excluding IABP or other devices.

VA-ECMO Versus Impella Support in CS

Maini et al[43] reported that VA-ECMO support is associated with lower survival in CS compared with Impella. This was based on a retrospective analysis of 1188 patients who were treated with either a percutaneous cardiac assist (n=883) or VA-ECMO/LV assist device (n=305). By contrast, mortality rates were similar between patients treated with VA-ECMO and Impella in a Swedish retrospective study after adjusting for the SAVE score.[44] A propensity-matched analysis of 128 patients with AMI-CS published by Karami et al[45] reported no significant difference in 30-day mortality rate between patients receiving VA-ECMO or Impella support, although Impella was associated with a lower risk of system-related complications. Accordingly, the nonrandomized prospective yet underpowered trial published by Garan et al[46] found no significant difference regarding short- and long-term survival using Impella (n=11) compared with VA-ECMO alone (n=16), showing an in-hospital mortality of 36.4% versus 50.0%. In summary, the available evidence does not point toward a significant survival benefit for Impella or VA-ECMO support in CS.[44–47] Whether the respective hemodynamic advantages outweigh the device-related risks in specific patient subgroups, such as patients experiencing predominant right ventricle failure, remains to be determined.

VA-ECMO in Postcardiotomy CS

VA-ECMO is deployed in 0.4% to 3.7% of patients undergoing cardiac surgery for postcardiotomy CS.[48] Especially in the case of intraoperative MCS initiation, central cannulation or mixed/dynamic VA-ECMO configurations are more frequently used than in other clinical scenarios.[49] In addition, the patient's preoperative condition, use of

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other MCS devices and cardiopulmonary bypass, and specific procedure-related complications, as well, contribute to the complexity of this patient population. Several large retrospective studies (Table S2) have identified risk factors associated with in-hospital mortality, including age,[49,50] lactate level,[50] renal function,[50] and preoperative cardiac arrest,[49] which should be considered during the decision-making process for VA-ECMO according to the 2020 European Association for Cardio-Thoracic Surgery/ELSO/Society of Thoracic Surgeons/American Association for Thoracic Surgery consensus document.[51] At present, the in-hospital mortality rate associated with the use of VA-ECMO for postcardiotomy CS is ≈60% even in experienced centers.[48,49]

Timing of VA-ECMO Initiation in CS

In a registry analysis including 362 patients with refractory CS, Lee et al[52] found a 47% lower risk of 30-day mortality when VA-ECMO was inserted early rather than later after shock onset in a weighted Cox model analysis. Regarding VA-ECMO initiation in relation to PCI, a retrospective study by Choi et al[53] suggests improved outcomes in those patients receiving VA-ECMO before revascularization. A meta-analysis on the basis of observational data involving 1352 patients undergoing MCS for AMI-CS (IABP: n=956, Impella: n=203, VA-ECMO: n=193) found that VA-ECMO initiation before PCI was associated with a significantly lower risk of mortality.[54] By contrast, aggressive CS management with early VA-ECMO initiation did not translate to improved outcomes in the individual-patient data meta-analysis of AMI-CS trials.[39] These findings call for a more vigorous assessment of timing in clinical trial protocols also in studies involving CS pathogeneses other than myocardial infarction, keeping in mind the association of VA-ECMO and increased LV afterload.[55]

In theory, VA-ECMO offers effective and flexible short-term MCS in a variety of CS scenarios. However, its steadily growing use for CS treatment without appropriate evidence deserves attention, considering the recommendation downgrade of IABP support in patients with AMI-CS (class III, level of evidence B) on the basis of the IABP-SHOCK II trial results (Intraaortic Balloon Pump in Cardiogenic Shock II).[2,4,56] The ECLS-SHOCK trial similarly challenges current practice and guideline recommendations that at present support the use of VA-ECMO for AMI-CS. Although generating randomized evidence in this setting is challenging, trials focusing on other CS pathogeneses (eg, acute decompensated heart failure, valvular heart disease, fulminant myocarditis, or acute right ventricle failure) and optimal complication management are urgently needed. Until more data and technological advances allow for effective prevention and countermeasures of the adverse effects associated with VA-ECMO, which likely outweigh some of its clinical benefits, and specific subpopulations are identified, in whom VA-ECMO therapy translates to improved outcomes, redefining the role of this device for treatment of AMI-CS and CS in general seems inevitable.

STRATEGIES FOR LV UNLOADING DURING VA-ECMO

Several active and passive LV unloading strategies have been developed to mitigate LV distension and to prevent secondary myocardial damage, and pulmonary congestion, as well, during VA-ECMO (Figure 2).[1,57] The hemodynamic concept of LV venting modalities is based on the reduction of LV afterload or LV preload, thereby decreasing LV end-diastolic volume, LV end-diastolic pressure, left atrial pressure, and mean pulmonary artery pressure.[57]

LV Unloading Without Additional MCS

Titrating VA-ECMO flow as low as clinically acceptable should be the first approach to alleviate LV afterload.[58] Venting options without the need for additional MCS implantation include inotropes, atrial septostomy, pulmonary artery or left atrial (LA) cannulation with drainage into the venous VA-ECMO line, or direct drainage of the LV cavity.[59–63] The EARLY-UNLOAD (Early Left Atrial Septostomy Versus Conventional Approach After Venoarterial Extracorporeal Membrane Oxygenation) single-center RCT published by Kim et al[64] investigated the efficacy of routine LV preload reduction using LA cannulation within 12 hours after VA-ECMO initiation compared with conventional VA-ECMO management. In the control group, LA cannulation was permitted as a rescue strategy in case of increased LV afterload, which was performed in 29 of 58 patients a median of 21.8 hours after VA-ECMO initiation. The 30-day all-cause mortality rate was similar among patients receiving routine LA cannulation versus control (46.6% versus 44.8%; HR, 1.02 [95% CI, 0.59–1.74]), but also the as-treated analysis did not show a relevant survival benefit of routine active LA venting (HR, 1.67 [95% CI, 0.92–3.05]). Given the hemodynamic implications of various active unloading techniques, these findings may not be generalizable to MCS-based venting options. Key studies analyzing the IABP (Figure 1C) or Impella device (Figure 1D) for LV unloading will be discussed in the next 2 sections.

Combining VA-ECMO With IABP Support

The rationale of combining VA-ECMO and IABP is the moderation of retrograde flow toward the LV during diastole and support of native LV output through balloon deflation during systole, while providing more powerful circulatory support compared with IABP alone (Figure 1C).[57,65] The available retrospective studies on

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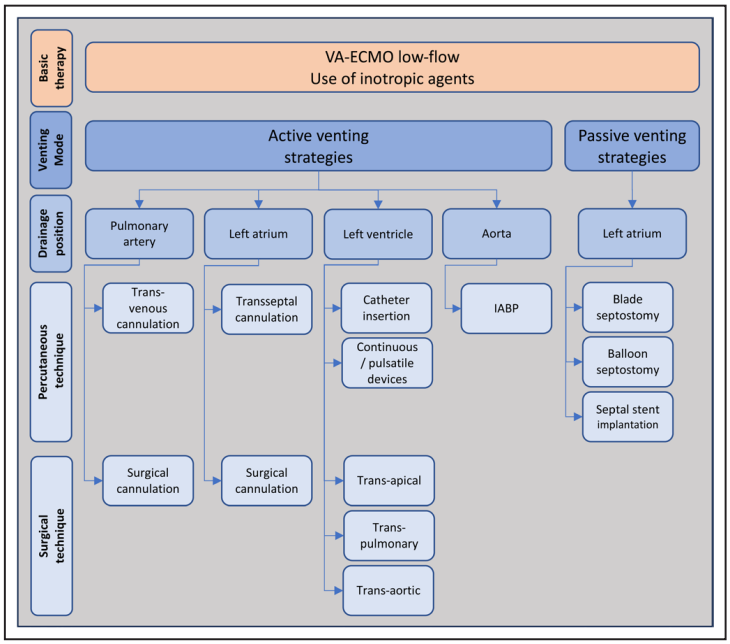

Figure 2. Strategies for left ventricular unloading during VA-ECMO.
Classification of decompression strategies during VA-ECMO support on the basis of current clinical practice. Active venting approaches directly depend on a pump`s action and imply left ventricular decompression by drainage through an additional venous line, which is incorporated through "y" connection into the VA-ECMO circuit, continuous or pulsatile pump devices, which are inserted across the aortic valve and eject left ventricular preload antegrade into the aorta, or indirect negative pressure afterload reduction by intra-aortic balloon pumping. The passive approach uses the pressure gradient between left and right atrium to reduce left ventricular preload. Whereas the latter comprises different percutaneous techniques to disrupt the interatrial septum, active venting strategies have been developed for 4 anatomical sites, namely the pulmonary artery, left atrium, left ventricle, and aorta, whereby each of these 4 positions can be accessed by either surgical or percutaneous techniques (modified according to Lüsebrink et al, 2022[57]). VA-ECMO indicates venoarterial extracorporeal membrane oxygenation; and IABP, intra-aortic balloon pump.

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combined VA-ECMO+IABP support yielded heterogeneous results (Table S3). The data from these studies should be interpreted with caution, considering the variability of inclusion criteria and incomplete information regarding the sequence of IABP and VA-ECMO implementation. In a propensity-matched single-center analysis of 126 patients, most of which underwent MCS for AMI-CS, Bréchot et al[66] found a trend toward reduced intensive care unit mortality and lower risk of pulmonary edema in patients receiving VA-ECMO and IABP. Furthermore, a large nationwide study from Japan indicated higher survival and weaning rates in a mixed cohort of patients with CS who received IABP within 24 hours after VA-ECMO initiation, although undetected differences in CS severity at baseline may have inflicted a selection bias.[67] In addition, in a multicenter analysis of 228 propensity-matched patients experiencing CS after cardiac surgery, weaning rates and in-hospital mortality were not significantly different between patients receiving VA-ECMO+IABP versus VA-ECMO alone.[68] A large meta-analysis including patients with different CS pathogeneses also found no significant mortality benefit of concomitant IABP use in postcardiotomy CS, whereas the survival rate in patients with AMI-CS receiving IABP was higher compared with VA-ECMO alone.[69] In another large meta-analysis of 3997 patients from 17 observational studies, the mortality rate was significantly lower among 1696 patients who received LV unloading (IABP 91.7%, Impella 5.5%) while receiving VA-ECMO support.[70]

In selected patients with CS, there might be a benefit in using IABP for LV decompression during VA-ECMO support at a relatively low additive risk.[37,57,66,67,70,71] The ANCHOR trial (Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock; NCT04184635), the first adequately powered RCT comparing VA-ECMO combined with IABP and optimal medical treatment alone in patients with AMI-CS, is currently underway (Table 3). Although this RCT is not specifically designed to prove

an additive effect of IABP support, it will potentially clarify if LV venting can overcome some of the limitations of VA-ECMO therapy to facilitate better outcomes. Of note, in the ANCHOR trial, the use of VA-ECMO support in the control arm is counted as an end point, therefore introducing bias. Furthermore, RCT-based evidence is needed to determine the efficacy and safety of combined MCS in patients with CS of nonischemic pathogenesis.

Combining VA-ECMO With Impella Support

In contrast to the IABP, Impella devices directly increase cardiac output by providing a flow of 2.5 L/min (Impella 2.5) to maximally 5.5 L/min (Impella 5.5 Smart Assist) from the LV cavity to the aortic root. They are therefore considered a potential alternative for more potent LV unloading during VA-ECMO therapy (Figure 1D). Impella support during VA-ECMO has been shown to decrease LV end-diastolic diameter,[1,72] pulmonary capillary wedge pressure,[73] and systolic pulmonary artery pressure,[74] as well, and may, in theory, be effective in preventing lung injury, LV dilatation, and stasis, and supporting myocardial recovery, as well.[47,57,70,75] The main downsides of the Impella are a considerable rate of hemolysis and access site complications, the necessity of surgical implantation for larger Impella pumps (Impella 5.0 and 5.5), and substantial device costs.[47]

At present, there is no randomized evidence informing outcomes of the "ECMELLA" concept (VA-ECMO+Impella) in CS (Table S4). The most convincing results regarding this MCS combination, so far, were produced by a retrospective multicenter analysis of 510 propensity-matched adult patients with CS.[76] Schrage et al[76] found a 30-day mortality rate of 58.3% among patients receiving VA-ECMO and Impella support compared with 65.7% among those treated with VA-ECMO alone (HR, 0.79 [95% CI, 0.63–0.98]), with a similar benefit in the AMI-CS and nonischemic CS subgroups. Severe bleeding, access site-related ischemia requiring intervention, renal replacement therapy, and hemolysis were detected more frequently in the ECMELLA group. In a subanalysis of 76 patients receiving delayed LV unloading (Impella upgrade >2 hours after VA-ECMO initiation) who were matched with 76 controls, no significant difference between 30-day mortality was detected. In a prospective single-arm study including 69 patients treated with ECMELLA, the interval between CS onset and initiation of the first MCS device independently predicted survival with approximately half of the patients receiving VA-ECMO support before Impella implantation.[75] All patients surviving to 6 months reported good neurological function.[75] Last, in a recent meta-analysis including a total of 11 137 patients, ECMELLA was only associated with reduced early mortality when selecting for propensity-matched studies.[77]

In summary, the current evidence does not suggest a benefit of routine LA cannulation for LV venting, whereas the ECMELLA concept and VA-ECMO+IABP combination seem to be associated with promising outcomes. Considering some fundamental limitations of the underlying nonrandomized studies on MCS-based LV unloading, the results of the ongoing randomized ANCHOR (NCT04184635), REVERSE (Impella CP With VA ECMO for Cardiogenic Shock; NCT03431467), and UNLOAD ECMO (Left Ventricular Unloading to Improve Outcome in Cardiogenic Shock Patients on VA-ECMO; NCT05577195) trials may clarify if the hemodynamic effects of Impella or IABP for active LV venting outweigh the additional device-related risks and high cost (Table 3). Information regarding criteria for MCS upgrade, downgrade, weaning, and complication management is still limited. At present, LV venting is mainly used in advanced CS stages on the basis of nonvalidated criteria of progressive LV dysfunction and pulmonary congestion, indicated by decreasing arterial waveform pulsatility, echocardiographic assessment of LV contractility and dimensions, aortic valve opening, LV outflow tract velocity time integral, radiographic imaging, and pulmonary arterial catheterization.[1,58] Proposed criteria for the escalation of VA-ECMO support to ECMELLA or venoarterial-venous ECMO configuration are summarized in Table S5. Until more data are available to formulate specific recommendations for LV unloading, it remains uncertain whether this approach translates to improved outcomes.[47]

VA-ECMO–FACILITATED NONEMERGENT HIGH-RISK PCI

Interventional treatment of complex coronary artery disease carries the risk of procedure-related transient reduction of myocardial oxygen supply, which may lead to hemodynamic compromise, especially in patients with impaired left ventricular ejection fraction and those undergoing left main or last patent vessel PCI. The landmark study on prophylactic use of periprocedural VA-ECMO support was published in 1993 by Teirstein et al.[78] Compared with the control group without MCS, patients who underwent VA-ECMO–assisted high-risk PCI had similar procedural success and mortality rates despite lower left ventricular ejection fraction at baseline and significantly higher incidence of VA-ECMO–related complications. On the other hand, fewer deaths occurred among patients with left ventricular ejection fraction <20% who received VA-ECMO support.

Considering the substantial limitations of the few published studies and case series (Table S6), the putative benefit of VA-ECMO to facilitate complete coronary revascularization and improved long-term outcomes remains to be substantiated. Data from the ongoing PIONEER trial (Hemodynamic Support With ECMO and IABP in Elective Complex High-risk PCI; NCT04045873)

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focusing on the efficacy and safety of combined VA-ECMO and IABP support during high-risk PCI might allow for more evidence-based patient selection in the future (Table 3). However, both the interventional and control arm will receive IABP support as per study protocol, which could obscure some of the VA-ECMO–related risks. Although Impella pumps have superseded VA-ECMO as the preferred device for prevention and management of hemodynamic deterioration during high-risk PCI in many European and US centers, the evidence for this strategy is rather scarce.[47] Future trials should analyze the advantages and disadvantages of VA-ECMO support compared with standard-of-care and other MCS devices, particularly regarding the patient's clinical status, setup times, implantation timing, and associated costs.

VA-ECMO–FACILITATED ABLATION OF VT

Catheter ablation has become an established treatment option for recurrent VT.[79] Patients with impaired LV function are at high risk of hemodynamic instability and subsequent end-organ hypoperfusion during VT induction, which is necessary for most activation and substrate mapping techniques in electrophysiological studies but is also associated with increased mortality.[80] To address this concern, periprocedural MCS using VA-ECMO has been proposed to enable VT ablation, and mapping and programmed stimulation, as well, in selected high-risk patients (class IIa/IIb, level of evidence B-NR; Figure 1E).[13]

The literature regarding VA-ECMO–facilitated VT ablation is sparse overall and limited to retrospective studies (Table S7). Carbucicchio et al[81] achieved hemodynamic stabilization in 19 patients after induction of nontolerated VTs by increasing the VA-ECMO flow rate from 1 L/min at stand-by to a rate necessitated for maintaining a mean arterial pressure of 60 to 70 mm Hg. The authors reported successful ablation of all VT morphologies in 52% of the patients. Since this pioneer study, multiple single-center case series have shown relatively high probability of procedural success and survival to discharge with an acceptable rate of complications related to VA-ECMO support (Table S7). Of note, 1 study reported a mortality rate of 76% when rescue VA-ECMO support was initiated for acute hemodynamic deterioration during catheter ablation.[82]

The available data indicate the feasibility and acceptable success rates of elective VA-ECMO–assisted VT ablation. Whether long-term mortality improves after successful VT ablation and whether these vulnerable patients, especially those experiencing electrical storm or ventricular fibrillation, benefit from more potent circulatory support provided by VA-ECMO compared with other MCS devices, remains to be determined by future trials. Until this evidence is available, patient selection relies on expert assessment and risk prediction tools such as the PAINESD Score,[83] which have not been validated in an RCT so far.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

Striving to improve long-term survival with good neurological function, CA treatment concepts revolve around strategies to minimize no-flow/low-flow duration. If conventional cardiopulmonary resuscitation (CPR) efforts do not achieve return of spontaneous circulation (ROSC), VA-ECMO is capable of effectively restoring circulation in pre- and in-hospital settings, thereby stabilizing patients with CA for management of the underlying causes and evaluation of destination treatment options (Figure 1F).

Two important registry analyses found no difference in mortality comparing ECPR with conventional CPR,[84,85] whereas others have shown that ECPR correlates with lower mortality rates in patients with CA (Tables S8–S10). A recent meta-analysis found that patients treated with ECPR had higher rates of survival with favorable neurological outcomes compared with conventional resuscitation.[86] Multivariate regression analysis indicated that ECPR, and initial shockable rhythm, younger age, and shorter low-flow time, as well, are associated with survival.[87–89] In addition to these factors, observational analyses have identified body weight, pH, and arterial lactate at admission, and timing intervals (CA and admission to VA-ECMO initiation), as well, to inversely correlate with outcome.[90–94]

ECPR in Out-of-Hospital CA

Three landmark RCTs assessed the efficacy and safety of ECPR in out-of-hospital cardiac arrest (OHCA) (Table S8). The single-center ARREST trial (Advanced Reperfusion Strategies for Patients with Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation) was designed to investigate survival to discharge in 174 patients undergoing OHCA from refractory ventricular fibrillation. The study was terminated after randomization of 30 participants when a predefined threshold for efficacy was crossed in the first interim analysis. Among patients randomly assigned to receive in-hospital ECPR, 43% survived to 6 months with good neurological function, whereas, in the control group receiving conventional advanced cardiac life support, no patient survived to 3 months (P=0.0063).[16] Most patients undergoing ECPR exhibited signs of organ failure, respiratory events, and trauma associated with CPR, with no unexpected device-related serious adverse events. Of note, this trial was conducted on the basis of a thoroughly designed emergency care platform integrating several public health stakeholders, which may impede the implementation of such complex protocols in other regions.

The PRAGUE OHCA trial (Prague Out-of-Hospital Cardiac Arrest) was conceptualized in 1 metropolitan VA-ECMO center in conjunction with local emergency medical services. In its invasive strategy group (n=124),

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mechanical compression was initiated, followed by periarrest transport to a cardiac center for ECPR and immediate invasive assessment and treatment, whereas conventional advanced cardiac life support was continued on-site in the standard strategy group (n=132).[95] A total of 256 patients completed the trial. In the main analysis, 39 patients (31.5%) in the invasive strategy group versus 29 (22.0%) in the standard strategy group survived to 180 days with good neurological outcome (OR, 1.63 [95% CI, 0.93–2.85]), rendering this a neutral trial. In a secondary analysis, patients were pooled into 3 groups regardless of their original randomization assignment: (1) patients who achieved prehospital ROSC and thus were not candidates for ECPR (n=83), (2) patients without prehospital ROSC despite prolonged advanced cardiac life support who did not receive ECPR (n=81), and (3) all patients who received ECPR after arrival at the hospital (n=92). The overall 180-day survival was 61.5% in patients with prehospital ROSC, 1.2% in patients without prehospital ROSC treated with conventional advanced cardiac life support, and 23.9% in patients without prehospital ROSC treated with ECPR (log-rank $P<0.001$), respectively. After adjustment for covariates, ECPR was associated with a lower risk of 180-day mortality (HR, 0.21 [95% CI, 0.14–0.31]).[96] Of note, bleeding complications were more frequently observed in patients receiving ECPR (44% versus 6.1%/ 8.3%).

Last, in the recently published multicenter INCEPTION trial conducted in the Netherlands, which focused on early ECPR for refractory OHCA in patients who had initial ventricular arrhythmia, bystander CPR, and did not have a ROSC within 15 minutes after CPR had been initiated, 70 patients were assigned to receive ECPR and 64 to receive conventional CPR.[19] The primary outcome (ie, survival with a favorable neurological outcome at 30 days) occurred in 14 (20%) patients in the ECPR group compared with 10 (16%) in the conventional CPR group (OR, 1.4 [95% CI, 0.5–3.5]). Although the number of serious adverse events per patient were similar in both groups, major bleeding events were reported in 16%, VA-ECMO circulation failure in 13%, and limb ischemia in 6% of patients undergoing ECPR, respectively. Suverein et al[19] concluded that there may be a potential of ECPR in an appropriate setting but that the reproduction of such superior results is not self-evident when ECPR is pragmatically implemented, even in cardiothoracic centers where providers are experienced in its use.

Given various disparities in patient baseline characteristics and study design, the principal factors contributing to diverging outcomes in these 3 RCTs remain speculative. Although the ARREST and INCEPTION trials only included patients with initial shockable rhythm, 38% of patients undergoing ECPR in the PRAGUE OHCA trial had initial asystole or pulseless electrical activity.[96] Another potential influencing variable may have been the median interval from cardiac arrest/emergency call to the start of VA-ECMO flow, which was 61 minutes in the PRAGUE OHCA trial,[96] 59 minutes in the ARREST trial,[16] and 74 minutes in the INCEPTION trial.[19]

ECPR in In-Hospital CA

As expected, no-flow/low-flow times before ECPR initiation are shorter in patients experiencing in-hospital CA, which presumably contributed to better outcomes in most comparative studies of in-hospital CA versus OHCA patients who underwent ECPR (Table S10). Studies focusing on in-hospital CA consistently demonstrated improved survival using ECPR compared with conventional CPR (Table S9), also shown by a recent meta-analysis by Low et al.[97] An early propensity-matched analysis of 172 patients with CA of mixed pathogenesis showed lower 1-year mortality in patients receiving ECPR.[98] This finding was reproduced by Shin et al[99] who reported 2-year survival with favorable neurological outcome of 20% receiving ECPR as opposed to 5% in matched patients receiving conventional CPR, and by Blumenstein et al[100] who found improved 30-day and 1-year survival using ECPR.[100] However, evidence from RCTs explicitly focusing on in-hospital CA is missing.

In summary, ECPR may increase the chances of survival with good functional status in select populations and appropriate settings. However, given the contradictory results of the ARREST and the much larger PRAGUE OHCA and the multicenter INCEPTION trials, the selection of promising ECPR candidates, the exact timing of ECPR (including no-flow/low-flow times and event-to-ECPR initiation), the structural and organizational requirements, and risk factors associated with mortality in CA require further validation.[10,11,86,87] Successful delivery of ECPR necessitates a meticulously orchestrated system of care, including emergency medical services, on-site or mobile ECMO teams, appropriately staffed and equipped emergency departments with adjacent PCI facilities, and experienced intensive care units for optimal postresuscitation care.[101] Due to the immense resources needed to set up and maintain ECPR programs, socioeconomic and ethical aspects must be considered, making ECPR one of the most ambitious endeavors in modern emergency medicine. Future studies should include valid economic evaluations to inform about ECPR's cost-efficacy. Whether the technological and political framework will allow for the development of ECPR networks and improved survival outside of clinical trials remains to be seen.

COMPLICATIONS ASSOCIATED WITH VA-ECMO SUPPORT

Bleeding

Current ELSO guidelines recommend the routine use of anticoagulation during VA-ECMO support to minimize the risk of thromboembolic events or oxygenator failure.[26,102]

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Balancing thromboembolic and bleeding risk, however, is a complex endeavor, considering the high prevalence of thrombocytopenia and frequent need for concomitant antiplatelet therapy after PCI.[103] According to ELSO registry data and adverse event analyses from large trials, the risk of major bleeding events during VA-ECMO is ≈30%, with cannulation site bleeding reported in up to 19% of adult patients.[17,18,25,26,39,78,95,96] Moderate to severe bleeding (Bleeding Academic Research Consortium 3–5) was significantly more frequent in patients undergoing VA-ECMO compared with controls in the recent meta-analysis of randomized trials (OR, 2.44 [95% CI, 1.55–3.84]).[39] Compared with VA-ECMO alone, additional MCS with Impella or IABP is associated with an even greater bleeding risk of up to 45% in some retrospective studies.[76,77,104] Patients undergoing ECPR are significantly more likely to experience bleeding complications (OR, 4.84 [95% CI, 1.91–12.24]).[97] In some patients, uncontrolled bleeding may require a (temporary) discontinuation of anticoagulation, which underlines the need for an individualized assessment of thromboembolic and bleeding risk.

Hemolysis

Hemolysis occurs in ≈5% to 20% of patients undergoing VA-ECMO owing to shear stress within the extracorporeal circuit and blood pump.[33,76,79] The incidence of hemolysis is even higher in patients receiving ECMELLA, who experience this complication in 28% to 58% of cases according to several large studies (Table S4).

Limb Ischemia

Restricted distal limb perfusion after the obstruction of the arterial lumen by the outflow cannula (sheath size 17–21F) remains a concern in peripherally cannulated patients despite routine insertion of an additional antegrade cannula (5–7F) in most centers.[18,26,33] The reported incidence of limb ischemia ranges from 5% to 17%,[17,18,33,39,41,90,105–109] but might be even higher in patients undergoing ECMELLA and ECPR.[76,77,100]

Abdominal Compartment Syndrome

Massive ascites, intraperitoneal and retroperitoneal bleeding, bowel ischemia, or infection may increase intra-abdominal pressure and thus impede venous VA-ECMO return.[110,111] Monitoring bladder pressure in patients at risk of abdominal compartment syndrome is essential to initiate noninvasive countermeasures or decompressive laparotomy in time.[111]

Infection

Local infection at the vascular access site is reported in ≈10% to 20% of patients undergoing VA-ECMO.[23,33] Sepsis occurs in 10% to 30% of cases, and even more frequently in the ECMELLA setting.[18,26,73,76,107,112]

Neurological Complications

In an ELSO database analysis of 4522 patients undergoing VA-ECMO, 15% experienced neurological complications correlating with poor outcomes. Ischemic stroke was reported in 3.6%, and intracerebral bleeding in 1.8%.[113] In a recent retrospective multicenter study, the incidence of intracranial hemorrhage was even higher at 12% with an associated in-hospital mortality rate of 81%.[114]

Kidney Injury

The proportion of patients receiving VA-ECMO who experience acute kidney injury is high, ranging from 12% reported by the ELSO up to 56% among clinical trial participants.[25–27,35,68,74,76,104,109,115] In a meta-analysis of observational studies of 1866 patients undergoing VA-ECMO, 46% underwent renal replacement therapy.[109] However, renal failure is most likely not causal to the device itself but rather a result of the underlying disease. In the ECLS-SHOCK trial there was no improvement in renal function as measured by the estimated glomerular filtration rate.

Harlequin Syndrome

Retrograde VA-ECMO flow involves complex alterations of the patient's hemodynamics. An unfavorable ratio between retrograde flow, oxygenation level of blood from outflow cannula, myocardial contractility, and oxygenation level of blood ejected from recovering LV can cause the "Harlequin syndrome," characterized by upper body and coronary hypoxia.[1] Differential oxygenation has been reported in up to 8.8% of VA-ECMO–treated patients.[116] Right radial oxygen saturation monitoring and increased vigilance regarding pulmonary gas exchange has become standard practice to detect this complication early.[1] Upgrading VA-ECMO using an additional jugular outflow cannula, thereby converting the circuit to a veno-arterial-venous ECMO configuration, offers a potential solution to this type of complication.

Insufficient LV Unloading

Increased LV afterload owing to retrograde aortic flow may result in progressive LV distension, deterioration of contractile function, high oxygen demand, and subsequent pulmonary congestion. Pulmonary edema during VA-ECMO has been observed in up to 74%, and LV dilation in up to 15%,[34,104] but data on incidence overall are limited, considering the variability in local practices

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and inclusion criteria of clinical trials on LV decompression.[76] However, the vicious cycle of increased LV afterload, insufficient LV unloading, and severe pulmonary congestion seems to be limiting prognosis in a relevant proportion of patients receiving VA-ECMO treatment and warrants further RCT-based research.[1]

Overall, a comprehensive analysis of VA-ECMO–associated risks remains challenging due to the multitude of factors involved in their pathogenesis and the difference of survival rates, which influences the time at risk for experiencing adverse events. Furthermore, risk analysis is often limited by inconsistent reporting and lack of standardization of adverse events. The development of effective prevention and treatment algorithms relies on more comprehensive and consistent reporting in future RCTs. The above-mentioned VA-ECMO–related complications underline the complexity and resource intensity of patient management and the importance of experienced multidisciplinary intensive care teams, as well.[1]

COST-EFFICACY

Studies evaluating the costs directly associated with the VA-ECMO device estimated those costs to amount to 6% to 11% of total in-hospital expenses compared with a much larger fraction required for general intensive care unit cost, including medication and personnel.[117,118] Determining cost-efficacy of advanced CS treatment options is particularly challenging considering differences in MCS device costs and lacking robust data regarding outcomes and country-specific reimbursement schemes. Whether the substantial resources needed for running a modern VA-ECMO program ultimately contribute to survival and quality of life has to be evaluated in future trials.

FUTURE DIRECTIONS

The presented outline of the current literature on VA-ECMO support highlights the most important remaining gaps in evidence (Table 2). However, there are enormous financial and organizational challenges in performing clinical trials with critically ill patients, and RCT-derived data will likely remain limited in the foreseeable future (Table S11). Until data from (head-to-head) RCTs and other high-quality trials allow for a fuller understanding of benefits, associated risks, and optimal management of VA-ECMO, guidelines may have to be adjusted to advise against routine use of this device for AMI-CS and potentially also other CS scenarios. Awaiting further evidence, VA-ECMO application should be limited to patients with a reasonable long-term prognosis or a high chance of successful bridging to durable assist device implantation or heart transplantation on the basis of updated consensus statements and standard operating procedures in experienced ECMO centers.

CONCLUSION

Driven by a strong therapeutic rationale, the use of VA-ECMO in various clinical scenarios, such as advanced CS, ECPR, and high-risk interventional procedures, has been increasing rapidly. Novel evidence from the ECLS-SHOCK trial and an individual-patient data meta-analysis does not support the routine use of VA-ECMO for AMI-CS, which contradicts current practice and guideline recommendations and questions the overall concept of MCS in CS. In addition, RCT-based results regarding the efficacy of ECPR are heterogeneous, highlighting the challenges of implementing such complex treatment strategies outside of clinical trials. The results of the ANCHOR (NCT04184635) trial on CS, UNLOAD ECMO (NCT05577195) and REVERSE (NCT03431467) trials on LV unloading, and the PIONEER (NCT04045873) trial on VA-ECMO–facilitated PCI may further elucidate the efficacy and safety of VA-ECMO support alone and in combination with other MCS devices, as well. Until then, considering the current state of evidence, stagnating in-hospital mortality, resource intensity, and severity of potential complications, the role of VA-ECMO in different application scenarios may have to be reevaluated. Given the growing number of critically ill patients requiring advanced hemodynamic support, intensivists and clinical scientists must strive for a better understanding of optimal device function and patient selection for VA-ECMO support. The central goal remains to improve long-term outcomes.

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Supplemental Material

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4. ECMO na Paragem Cardiorrespiratória Refratária

4.1. An integrated program of ECMO assisted cardiopulmonary resuscitation and uncontrolled DCD in refractory cardiac arrest.

Roncon-Albuquerque R Jr, Gaião S, Figueiredo P, Príncipe N, Basílio C, Mergulhão P, Silva S, Honrado T, Cruz F, Pestana M, Oliveira G, Meira L, França A, Almeida-Sousa JP, Araújo F, Paiva JA. *Resuscitation* 2018; 133: 88-94. DOI: 10.1016/j.resuscitation.2018.10.016.

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Clinical paper

An integrated program of extracorporeal membrane oxygenation (ECMO) assisted cardiopulmonary resuscitation and uncontrolled donation after circulatory determination of death in refractory cardiac arrest

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ABSTRACT

Aim: To assess the feasibility of an integrated program of extracorporeal cardiopulmonary resuscitation (ECPR) and uncontrolled donation after circulatory determination of death (uDCDD) in refractory cardiac arrest (rCA).
Methods: Single center, prospective, observational study of selected patients with in-hospital (IHCA) and out-of-hospital (OHCA) rCA occurring in an urban area of ~1.5 million inhabitants, between October-2016 and May-2018. 65 year old or younger patients without significant bleeding or comorbidities with witnessed nonasystolic cardiac arrests were triaged to ECPR if they had a reversible cause and high quality CPR lasting < 60 min. Otherwise they were considered for uDCDD after a ten minute no touch period using normothermic regional perfusion.
Results: 58 patients were included, of which 41 (71%) were OHCA and 18 (31%) had ECPR initiated. Median age was 52 (IQR 45–56) years. Cannulation was successful in 49/58 (84%) cases. Compared to ECPR, patients referred for uDCDD were more frequently OHCA (90 vs. 28%), had bystander CPR (28 vs. 83%) and prolonged low-flow period (40 (35–50) vs. 60 (49–78) min). Survival to hospital discharge with full neurological recovery (cerebral performance category 1) occurred in 6/18 (33%) ECPR patients. uDCDD resulted in transplantation of 44 kidneys.
Conclusions: An integrated program for rCA consisting of a formal pathway to uDCDD referral in ECPR ineligible patients is feasible. ECPR-referred patients had a reasonable survival with full neurologic recovery. Successful kidney transplantation was achieved with uDCDD.

A Spanish translated version of the abstract of this article appears as Appendix in the final online version at: https://doi.org/10.1016/j.resuscitation.2018.10.016.

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Introduction

Resuscitation guidelines recommend that for refractory cardiac arrest (rCA), termination of resuscitation rules may require integration with guidance on suitability for extracorporeal membrane oxygenation (ECMO) assisted cardiopulmonary resuscitation (E-CPR) or uncontrolled donation after circulatory determination of death (uDCDD) [1,2].

In settings where it can be rapidly implemented (e.g. within 1 h of collapse), ECPR may be considered when there is a witnessed cardiac arrest with bystander CPR, potentially reversible cause, and little co-morbidity [1,3]. Although observational studies showed promising results when ECPR is used as a rescue therapy for IHCA [4–6], results for OHCA are more guarded [7–10]. Whenever a decision is made to terminate CPR in rCA, uDCDD referral should be considered after death determination [11]. uDCDD has shown to provide a valuable expansion of the number of donor organs, most commonly kidneys, available for transplantation in several European countries [12–14]. In this case, normothermic regional perfusion (nRP), consisting in a modified bypass extracorporeal circulation with membrane oxygenation for selective abdominal organ preservation *in situ,* is being increasingly used to minimize the unavoidable warm ischemic damage [15]. nRP has been shown in preliminary reports to be the most effective in situ perfusion technique to reduce the detrimental effects of warm ischemia, namely decreasing primary graft dysfunction [16], delayed graft function rates [17,18] and improving long-term graft function [18–20] in renal transplantation.

ECPR and uDCDD have limited current integration secondary to high resource and training requirements [21] and limited development of uDCDD programs. When both uDCDD and ECPR are available for rCA patients, uDCDD should only be deployed if ECPR is contraindicated or futile [22,23]. Experience integrating these two techniques is lacking and opportunities for organ procurement are therefore missed [24].

In order to assess the feasibility of an integrated program of ECPR and uDCDD of selected patients with rCA, we developed a management protocol consisting in a formal pathway of uDCDD referral for ECPR ineligible patients, in a university teaching hospital serving an urban area of ~1.5 million inhabitants.

Methods

This is a prospective pilot study of a management protocol consisting of a formal pathway of uDCDD referral in ECPR ineligible patients with rCA carried out between October-2016 and May-2018. This study was an initiative of the Portuguese Ministry of Health aiming to improve the responsiveness to rCA in the Porto urban area (~1.5 million inhabitants), with the development of a collaborative protocol between the Portuguese Institute for Blood and Transplantation, the National Institute of Medical Emergency and the ECMO center of Hospital São João. An institutional protocol with inclusion criteria for ECPR was approved by the Ethics Committee of São João Hospital Centre and Faculty of Medicine of Porto. All uDCDD procedures were performed in accordance with the Portuguese Government regulations (Dispatch nº 14341/2013 in Diário da República, 2nd Grade - Nº 215, 6th November 2013) and the recommendations of the Portuguese Institute for Blood and Transplantation, as described in the uDCDD operation manual (available at URL: www.ipst.pt/files/TRANSPLANTACAO/Paragem_Cardiocirculatoria.pdf). Portugal has a contracting out system of presumed consent for organ donation (Decree Law nº 244/94, of the 22nd of April), with explicit consent for donation not required but being presumed if the person has not objected during life through registration in the National Registry for Non-Donors (RENNDA). The Ethics Committee of São João Hospital Centre and Faculty of Medicine of Porto approved the study and waived the requirement for patient consent.

Setting and population

The study was performed at São João Hospital Centre (Porto, Portugal), a 1100-bed university teaching hospital with an ECMO case volume of 80–100 patients/year and an Extracorporeal Life Support Organization (ELSO) member (Center 227). The São João Hospital Centre is also a referral center for acute coronary syndromes, with a Cardiac Catheter Laboratory available 24/7. Before the start of this program, the Hospital São João had a preliminary experience with uDCDD and nRP, having performed 5 kidney transplants from 3 uDCDD donors with refractory OHCA between January-2016 and September-2016. Our ECMO Center had also previous experience with ECPR, having performed this technique on a regular basis since 2014, almost exclusively for refractory IHCA.

The National Institute of Medical Emergency (INEM) is the provider of prehospital emergency care in Portugal. The four physician-led medical vehicles from INEM operating in the Porto urban area were included in the study: Matosinhos Local Health Unit, Porto Hospital Center, São João Hospital Center and Vila Nova de Gaia/Espinho Hospital Center. For patients with suspected CA, emergency ambulances from INEM with trained nurses and emergency medical technicians, equipped with automated defibrillators, co-responded across parts of the Porto urban area.

The study flowchart is presented in Fig. 1. Patients with OHCA or IHCA were eligible for the study if the following criteria were met: *i*) 18–65 years of age; *ii*) no asystolic unwitnessed CA; *iii*) absence of major bleeding; *iv*) absence of known or suspected significant comorbidities; *v*) > 30 min of persistent cardiac arrest and *vi*) ECMO team available for immediate cannulation at Hospital São João. Patients known to have pre-existing neurological disability or co-morbidities causing limitations in activities of daily living such as advanced heart failure, severe chronic airways disease, liver cirrhosis, renal failure on dialysis and malignancy, were not considered eligible for ECPR. Patients with known uncontrolled hypertension or diabetes mellitus, or chronic kidney disease were not eligible for uDCDD.

In OHCA, patients were transferred by ambulance directly to the Hospital São João Emergency Department if no ROSC was achieved after 5–10 minutes of advanced life-support (ALS) in the field. Prior to this study, resuscitation in OHCA was typically ceased in the field after 30 min of ALS, unless compelling reasons to continue were present. Standard ALS was continued during patient transfer by ambulance to the Hospital São João Emergency Department under uninterrupted mechanical chest compressions (Lucas™ 2.1 Chest Compression System, Lund, Sweden) (except for defibrillation or pulse checks when indicated), ventilation (~10 breaths. min^{-1}) via an endotracheal tube with 100% oxygen and injection of intravenous adrenaline (1 mg every 4 min). In VF/pVT, a single dose of intravenous amiodarone 300 mg was administered after a total of three shocks, with a further dose of 150 mg being considered after five shocks. When available, waveform capnography was use for confirming tracheal tube placement, monitor CPR quality and potentially identify ROSC during CPR. Patients with OHCA achieving ROSC *'en route'* before admission to the Hospital São João Emergency Department were not included in the study.

The decision to start ECPR was made by a senior critical care physician of our ECMO Program: in out-of-hospital rCA this decision took place in the Emergency Department at hospital admission, while in-hospital rCA the decision was made where rCA occurred (e.g. coronary catheterization laboratory, emergency department, intensive care unit (ICU)). ECPR was initiated when all the following criteria were present: *i*) reversible cause for CA suspected; *ii*) high-quality CPR provided (immediate CPR provided by bystanders or by emergency team, with ALS initiated within 10 min of collapse); and *iii*) ECPR able to be implemented within 60 min of collapse. A reversible cause for CA was presumed whenever the first documented rhythm was ventricular fibrillation or pulseless ventricular tachycardia (VF/pVT) or when a reversible cause for CA was previously documented or highly suspected

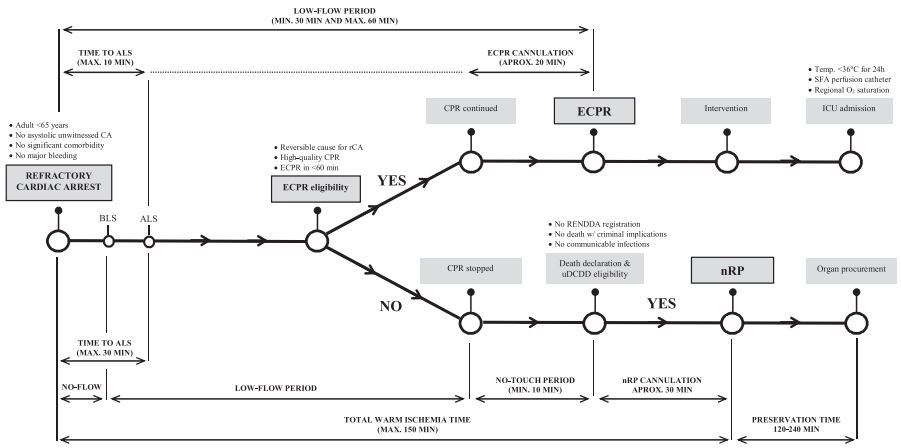

Fig. 1. Study flowchart. ALS, advanced life support; BLS, basic life support; CA, cardiac arrest; CPR, cardiopulmonary ressuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, ECMO-assisted cardiopulmonary ressuscitation; ICU, intensive care unit; nRP, normothermic regional perfusion; rCA, refractory cardiac arrest; RENNDA, national registry for non-donors; SFA, superficial femoral artery; uDCDD, uncontrolled donation after circulatory determination of death.

(e.g. pulmonary embolism, acute drug intoxication).

In patients included in the study but not fulfilling criteria for ECPR, death declaration was performed after the decision to stop CPR by the emergency physician. In this context, death declaration required the documentation of asystole or absence of mechanical ventricular activity in transthoracic echocardiography at the end of a mandatory minimum 10 min 'no-touch' period. The Organ Donation and Transplant Coordination Office was then contacted by the emergency physician, and uDCDD referral pursued if the patient was not registered in RENNDA and the following criteria were met: *i*) ALS initiated within 30 min of collapse; *ii*) hospital admission within 120 min of collapse; *iii*) absence of known or suspected death with criminal implications; and *iv*) no known or suspected communicable infections.

Treatment protocols and outcomes

The supplemental methods section of the Supplementary Material provides a detailed description of: *i*) the technique of extracorporeal support used in ECPR and uDCDD protocols and *ii*) measured outcomes.

Statistical analysis

Statistical analysis was performed using SPSS (Version 25.0, SPSS Inc.; Chicago (Illinois) USA). Numerical data were analyzed using Student's *t*-test or Mann-Whitney test as appropriate. Proportions were analyzed with chi-square test. Statistical significance was considered when $p < 0.05$.

Results

Baseline characteristics of cardiac arrest patients (table 1, suppl. Tables 1, 2 and fig. 2)

Over the 20-month period of the study, 221 patients with CA (170 OHCA and 51 IHCA) were treated in the Hospital São João. The 58 patients with rCA (41 OHCA and 17 IHCA) were included in analysis. This corresponded to 26% of all CA treated in the Hospital São João: 24% of all OHCA and 33% of all IHCA. Over the same period, the ECMO Program at Hospital São João treated 151 patients with extracorporeal support: *i*) 71 veno-venous ECMO for respiratory failure; *ii*) 22 veno-arterial ECMO for cardiogenic shock; *iii*) 18 ECPR for rCA; and *iv*) 40 nRP for uDCDD. Hospital admission occurred during normal working hours (from 8am to 5 pm, Monday to Friday) in 21 cases (36%), during weekdays after normal working hours (from 5 pm to 8am) in 25 cases (43%) and during weekends in 12 cases (21%). Baseline characteristics of these patients are shown in Table 1.

The initial CA rhythm in ECPR patients was VF/pVT in 9 (50%) cases, asystole in 4 cases and pulseless electrical activity (PEA) in 5 cases. The initial CA rhythm in the uDCDD group was VF/pVT in 21

Table 1
Baseline characteristics of patients with refractory cardiac arrest included in the study.

	All	ECPR	uDCDD	*p* =
N (%)	58	18 (31)	40 (69)	–
Age, years (IQR)	52 (45-56)	52 (45-55)	52 (44-57)	0.70
Male, n (%)	46 (79)	11 (61)	35 (88)	**0.04**
Cardiovascular risk factors				
Dyslipidemia, n (%)	15 (26)	8 (44)	7 (18)	**0.05**
Hypertension, n (%)	11 (19)	4 (22)	7 (18)	0.72
Diabetes mellitus, n (%)	6 (10)	3 (17)	3 (8)	0.36
Prior ischemic heart disease, n (%)	5 (9)	2 (11)	3 (8)	0.64
Congestive heart failure, n (%)	2 (3)	0 (0)	2 (5)	1.00
Location of cardiac arrest				
Out of hospital, n (%)	41 (71)	5 (28)	36 (90)	< **0.001**
In hospital, n (%)	17 (29)	13 (72)	4 (10)	< **0.001**
Initial rhythm				
VF / pVT, n (%)	30 (52)	9 (50)	21 (52)	0.86
Asystole, n (%)	15 (26)	4 (22)	11 (28)	0.76
PEA, n (%)	13 (22)	5 (28)	8 (20)	0.52
Arrest etiology				
Ischemic heart disease, n (%)	39 (67)	13 (72)	26 (65)	0.76
Cardiomyopathy, n (%)	3 (5)	1 (6)	2 (5)	1.00
Pulmonary embolism, n (%)	3 (5)	0 (0)	3 (8)	0.55
Respiratory, n (%)	2 (3)	1 (6)	1 (3)	0.53
Other, n (%)	11 (19)	3 (17)	8 (20)	0.76

Data is presented as number of cases (%) or median (IQR, interquartile range). PEA, pulseless electric activity; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia.

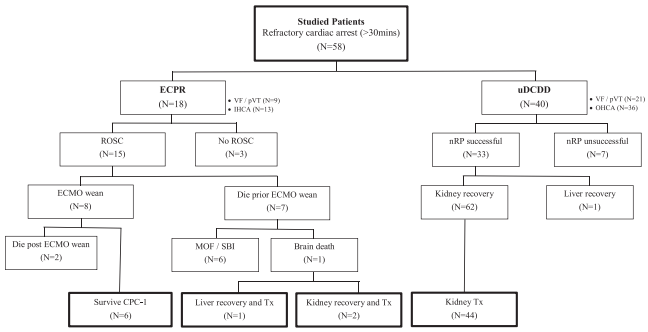

Fig. 2. Outcome of 58 patients with refractory cardiac arrest. CPC, cerebral performance category; ECMO, extracorporeal membrane oxygenation; ECPR, ECMO-assisted cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; MOF, multiple organ failure; nRP, normothermic regional perfusion; OHCA, out-of-hospital cardiac arrest; ROSC; return of spontaneous circulation; SBI, severe brain injury; Tx, transplantation; uDCDD, uncontrolled donation after circulatory determination of death; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia.

(52%) cases, asystole in 11 (28%) cases and PEA in 8 (20%) cases.

Refractory cardiac arrest details and initial management (Table 2 and Suppl. Table 3)

Patients referred for uDCDD presented initial no-flow (time period of cardiac arrest immediately after collapse without compressions being performed) much more frequently when compared to patients referred for ECPR (72 vs. 17%). ALS was initiated immediately after collapse in 83% of ECPR patients, while in uDCDD group this only occurred in 21% of cases. uDCDD group presented with a prolonged low-flow time when compared with ECPR patients. This resulted in significantly lower time from collapse to ECPR initiation when compared to the time from collapse to nRP initiation in uDCDD ().

ECPR patients presented with a less severe lactic acidosis when compared to uDCDD group. No significant differences were detected in the initial serum values of high-sensitivity cardiac troponin I, creatinine and aspartate aminotransferase between ECPR and uDCDD groups.

Table 2
Refractory cardiac arrest details and initial management.

	All (N = 58)	ECPR (N = 18)	uDCDD (N = 40)	*p* =
Initial no-flow, min	3.5 (0–10)	0 (0–0)	5 (0–10)	< **0.001**
Time from collapse to ALS, min	5 (0–19)	0 (0–0)	14 (5–20)	< **0.001**
Low–flow time, min	55 (40–68)	40 (35–50)	60 (49–78)	**0.003**
Collapse to ER admission, min	53 (0–70)	0 (0–5)	64 (49–78)	< **0.001**
Collapse to ECPR or nRP initiation, min	90 (50–108)	40 (35–55)	100 (90–115)	< **0.001**
Laboratory values				
pH	7.02 (6.80–7.10)	7.10 (7.03–7.20)	6.92 (6.77–7.03)	**0.04**
pO_2, mmHg	238 (82–389)	115 (79–280)	254 (97–462)	0.27
pCO_2, mmHg	38 (23–46)	41 (31–52)	33 (18–44)	0.22
HCO_3^-, mEq/L	11 (8–19)	19 (16–19)	9 (7–11)	**0.005**
Lactate, mEq/L	10.2 (5.3–15.2)	5.9 (4.3–8.9)	13.1 (8.5–15.9)	**0.008**
TnI-hs, µg/dL	165 (39–558)	53 (24–4847)	234 (67–546)	0.24
Creatinine, mg/dL	1.08 (0.92–1.32)	1.04 (0.90–1.25)	1.14 (0.97–1.40)	0.10
AST, UI/L	193 (92–446)	276 (92–706)	164 (101–440)	0.77
Initial ECPR or nRP parameters				
Blood flow, lpm	2.6 (2.5–3.0)	3.0 (2.7–3.0)	2.5 (2.0–2.6)	**0.002**
Sweep, lpm	5.0 (2.0–6.0)	2.0 (2.0–4.0)	6.0 (5.5–9.5)	< **0.001**

Data is presented as median (IQR). ALS, advanced life support; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation; ECPR, ECMO-assisted cardiopulmonary resuscitation; ER, emergency room; nRP, normothermic regional perfusion; TnI-hs, high-sensitivity troponin I; uDCDD, uncontrolled donation after circulatory determination of death.

ECPR outcomes, management and complications (Table 3 and Suppl. Table 4)

Cannulation was successfully achieved in 16 (89%) patients, being performed mainly in the Emergency Department. Three patients with rCA referred for ECPR did not achieve ROSC: in 2 patients ECMO cannulation was unsuccessful while in one patient cardiac arrest subsisted after ECMO initiation ().

Of the 16 ECPR patients in which cannulation was successful, 14 (88%) underwent a subsequent intervention to treat their underlying pathology. Namely, percutaneous coronary intervention was performed in 9 (56%) patients after coronary angiography. Emergent surgery for cardiac tamponade was performed in 2 patients (complicating left ventricle perforation in one case and suspected aortic dissection in the other case), antidote administration was performed in 1 patient with acute digoxin intoxication, severe hypokalemia correction was made in 1 patient and refractory hypoxemia was corrected after ECPR initiation in 1 patient with severe ARDS. Regarding the 2 ECPR patients successfully cannulated in which no specific intervention was subsequently performed, primary cardiomyopathy was suspected in both cases after an inconclusive initial diagnostic workup.

Bleeding requiring blood transfusion (50%) was the main complication associated to ECPR, although no cases of uncontrolled hemorrhagic shock were observed. Peripheral vascular issues requiring vascular surgery intervention were observed in 4 (22%) occasions: *i*) artery repair for a femoral pseudoaneurysm and arteriovenous fistula (n = 1); *ii*) thrombectomy by Fogarty's catheter for acute limb ischemia (n = 1); *iii*) thrombectomy by Fogarty's catheter and surgical fasciotomy for acute limb ischemia with associated compartment syndrome (n = 1); and *iv*) traumatic below knee amputation (n = 1). Acute renal failure requiring renal replacement therapy was present in 3 (17%) patients.

All ECPR survivors presented CPC score 1 at hospital discharge. ECPR survivors presented higher ICU and hospital lengths of stay, when compared to non-survivors. In this later group, ECMO wean was achieved only in 2 patients. Regarding ECPR non-survivors in which cannulation was achieved (n = 10), severe hypoxic-ischemic encephalopathy was observed in 8 patients and 2 patients presented with irreversible multiple organ failure.

uDCDD outcomes, management and complications (Table 4)

In uDCDD, prolonged low-flow time and protracted time from collapse to nRP initiation were observed. Differently from ECPR group, a high rate of unsuccessful percutaneous cannulation (40%) for nRP was

Table 3
ECPR outcomes, management and complications.

	All (N = 18)	Survivors (N = 6)	Non-Surv. (N = 12)	p =
IHCA / OHCA	13 / 5	4 / 2	9 / 3	1.00
Low-flow time, min	40 (35–50)	36 (30–45)	50 (35–60)	0.30
Collapse to ECPR initiation, min	40 (35–55)	36 (35–45)	50 (35–60)	0.35
ECPR cannulation successful, n (%)	16 (89)	6 (100)	10 (83)	0.53
Location of ECPR cannulation				
Emergency Department, n (%)	12 (67)	3 (50)	9 (75)	0.34
Coronary catheterization laboratory, n (%)	5 (28)	2 (33)	3 (25)	1.00
Intensive Care Unit, n (%)	1 (6)	1 (17)	0 (0)	0.33
ROSC, n (%)	15 (83)	6 (100)	9 (75)	0.52
Subsequent Intervention, n (%*)	14 (88)	6 (100)	8 (67)	0.26
Coronary angiogram, n (%*)	12 (75)	4 (67)	8 (80)	0.60
PCI, n (%*)	9 (56)	4 (67)	5 (50)	0.63
Cardiac surgery, n (%*)	2 (12)	0 (0)	2 (20)	0.50
Antidote administration, n (%*)	1 (6)	1 (17)	0 (0)	0.38
Severe hypokalemia correction, n (%*)	1 (6)	0 (0)	1 (10)	1.00
Refractory hypoxemia correction, n (%*)	1 (6)	1 (17)	0 (0)	0.38
Complications				
Bleeding, n (%)	9 (50)	3 (50)	6 (50)	1.00
Peripheral vascular issues, n (%)	4 (22)	2 (33)	2 (17)	0.57
Renal replacement therapy, n (%)	3 (17)	1 (17)	2 (17)	1.00
Median time on ECMO, days (IQR)	4 (1–6)	5 (3–7)	3 (0–5)	0.31
Wean off ECMO, n (%)	8 (44)	6 (100)	2 (17)	**0.002**
Median time in ICU, days (IQR)	5 (2–10)	16 (8–28)	5 (1–5)	**0.003**
Median hospital LOS, days (IQR)	5 (2–13)	29 (16–40)	5 (1–5)	**0.001**
CPC-1, n (%)	6 (33)	6 (100)	–	–

Data is presented as n (%) or median (IQR). CPC-1, cerebral performance score 1; ICU, intensive care unit; LOS, length of stay; IHCA, in-hospital cardiac arrest; Non-Surv., non-survivors; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ROSC, return to spontaneous circulation. * from the number of correspondent ECPR patients with ECMO cannulation successful.

observed in our first 10 uDCDD cases, performed in the initial 3-month period of the study. After this initial period, we shifted to a surgical approach for uDCDD cannulation, which allowed us to substantially increase our cannulation success rate. In fact, at the end of the study period, nRP was successfully implemented in 33 (82%) uDCDD cases, 23 (100%) in the group with successful kidney transplantation and 10 (59%) in the group in which kidney transplantation was not achieved. Regarding other potential major complications, no cases of uncontrolled hemorrhagic shock during cannulation or after nRP initiation and no cases of nRP withdrawal due to cardiac or cerebral resuscitation were observed.

nRP duration was 3.0 (3.0–3.6) h. Of the 80 potential kidney transplants from 40 uDCDD cases, 64 kidneys were procured and 44 kidneys were effectively transplanted: *i*) in 7 cases (n = 14) cannulation was not successful; *ii*) 7 cases (n = 14) presented inadequate macroscopic kidney appearance (including initial perfusion characteristics); *iii*) in 2 cases (n = 4) the result of pre-implantation biopsy was unfavorable; *iv*) in 2 cases (n = 2) a prolonged cold ischemia period was observed at the time of the second kidney transplant; and *v*) unexpected unavailability of surgical room was observed in 1 case (n = 2). Regarding the 44 kidney transplants, primary non-function was observed in 4 (9.1%) cases, while delayed graft function was present 30 (68%) kidney transplants. Estimated glomerular filtration rate at third month post-transplantation was 55.4 ml/min/1.73m^2 ().

Table 4
Normothermic regional perfusion outcomes.

	All (N = 40)	Kidney Tx (N = 23)	No Kidney Tx (N = 17)	p =
Low-flow time, min	60 (49–77)	55 (45–70)	67 (58–80)	0.15
Collapse to nRP initiation, min	100 (90–115)	100 (90–118)	102 (100–108)	0.68
nRP cannulation successful, n (%)	33 (82)	23 (100)	10 (59)	**0.001**
nRP duration, hours (IQR)	3.0 (3.0–3.6)	3.3 (3.0–3.7)	3.0 (3.0–3.0)	0.25
Procured kidneys, n (%)	64	46 (72)	18 (28)	< **0.001**

Data is presented as n (%) or median (IQR). nRP, normothermic regional perfusion; uDCDD, uncontrolled donation after circulatory determination of death.

Discussion

The present study is the first report of an integrated program for rCA consisting in a formal pathway of uDCDD referral in ECPR ineligible patients, allowing a rapid triage of both out-of-hospital and in-hospital rCA to uDCDD. In the 20-month period of the study, 18 patients with rCA were referred for ECPR. This compares well with the CHEER trial, a single center prospective observational study of a treatment protocol including ECPR for rCA in an urban area ~4 million inhabitants, in which 26 patients were treated over a 32-month period [8]. In most of our ECPR patients, rCA was witnessed, immediate high-quality CPR provided and ECPR was implemented within 60 min of collapse, all ECPR survivors having received a subsequent intervention to treat the underlying cause. This agrees with the most recent recommendations on the timing, selection and management of ECPR patients [1,3,7]. Accordingly, our rate of survival to hospital discharge of 33% was similar to the one reported by the ELSO registry [25]. Although complications such as severe neurological insult, multiorgan failure and/or bleeding were frequent in ECPR patients, non-survivors had a short length of stay while all survivors were discharged with excellent neurological outcomes. This is similar to other recent ECPR reports [8,26,27].

Aiming to shorten time from collapse to ECPR initiation, we adopted a 'scoop and run' strategy in OHCA, with immediate patient transport under mechanical CPR to our emergency department for cannulation by critical care physicians. In this regard, the encouraging results of a protocol consisting in early transport to a cardiac catheterization laboratory of patients with refractory OHCA and VF/pVT for timely ECPR cannulation and revascularization could represent a valuable alternative in this patient subset [28]. Recently, a 'stay and treat' philosophy using a mobile ICU to initiate ECPR on scene of the OHCA has also been

shown to be a viable option, allowing reduction of the low-flow time, with similar ECPR initiation times, success and complications rates compared to in-hospital ECPR [29]. Nevertheless, the best strategy to shorten the time from collapse to ECPR initiation in refractory OHCA remains to be proven and may be dependent on variables that are unique to each community [7].

uDCDD was performed in 40 (69%) patients with rCA not fulfilling criteria for ECPR. Patients with rCA referred for uDCDD had predominantly OHCA with initial no-flow, importantly limiting ECPR eligibility. In fact, recent reports describe low skill levels of the Portuguese population on basic life support [30] and low bystander CPR rates in OHCA [31]. At our institution, during the time period of the study, 114 kidneys were procured from brain-dead donors and 62 kidneys from uDCDD, the later corresponding to 35% of the kidney donor pool. These results are encouraging if we consider that Spain, a country with ~46 million inhabitants and with the largest uDCDD experience, had 123 uDCDD donors in 2016 corresponding to 6% of the deceased donor pool [15]. In our study, the conversion rate of potential into utilized donors, the conversion rate of procured into transplanted kidneys, as well as the outcomes of the transplanted kidneys is in line with previous series [18,32–34]. Of note, successful procurement and transplantation of 2 kidneys and 1 liver was achieved in a patient with brain death following ECPR, further strengthening the potential of our rCA program for organ transplantation. Accordingly, previous reports have described a rate of 20–30% of brain death in ECPR patients, of which ~50% could donate organs [35,36].

In our study, ECPR cannulation was performed percutaneously by critical care physicians with a high success rate, in agreement with previous reports [8,37]. Percutaneous cannulation for ECPR by interventional cardiologists [28] or emergency physicians [27] was also shown to be a valuable option. More recently, a hybrid approach, where cutdown is used to rapidly expose the femoral vessels, vessel access is performed through a distal percutaneous Seldinger technique, and the cutdown site is quickly sutured closed, has also been suggested [29]. Differently, in uDCDD group, a high rate of unsuccessful percutaneous cannulation for nRP was observed in the first 3-month period of our study. We have therefore shifted to a surgical approach, allowing us to achieve a high cannulation success rate at the end of the study.

The development of a successful integrated program for ECPR or uDCDD in rCA does not solely rely on technical knowledge and skills, but also on a well-developed logistical plan to allow for efficient activation once a potential candidate is identified [13,38]. In our study, rCA occurred during normal working hours only in about one-third of all cases, highlighting the importance of having a dedicated team available 24/7. ECPR presents the additional challenge of requiring trained in-house physicians for immediate cannulation. In this regard, the development of an integrated program of ECPR and uDCDD serving a large urban area allowed us to achieve a high case volume.

Finally, several limitations of our study should specifically be addressed. Firstly, the study was carried out in only one center, which limits the external validity of the results. Secondly, although the potential of utilizing uDCDD donors is substantial, uDCDD programs have only been developed in a minority of European countries, mainly due to considerable technical and organizational challenges, as well as to ethical and legal constraints [13,22]. Thirdly, despite favorable international experience [13,15], liver and lung transplantation from uDCDD were not performed in our study due to logistic constraints.

In conclusion, an integrated program for rCA consisting in a formal pathway of uDCDD referral in ECPR ineligible patients is feasible, allowing a rapid triage of both out-of-hospital and in-hospital rCA to uDCDD. Additionally, ECPR survival and kidney transplantation rates were promising. Patients with rCA referred for uDCDD were predominantly OHCA with initial no-flow and prolonged low-flow period.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2018.10.016.

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