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UNDERSTANDING THE DISEASE

Cardiogenic shock in severe ARDS: the role of cardiorespiratory extracorporeal life support

Vasileios Zochios[1,2*], Joseph M. Brewer[3] and Hakeem Yusuff[1,4,5]

The mortality of patients with acute respiratory distress syndrome (ARDS) remains unacceptably high despite evidence-based interventions [1]. One of the contributors to mortality in severe ARDS is cardiovascular dysfunction, which occurs in a substantial proportion of patients [2].

When conventional hemodynamic support measures including prone positioning and vasoactive drugs fail to restore end-organ perfusion, extracorporeal life support (ECLS) may be considered in select patients without established multiple organ failure (Fig. 1). However, there is currently lack of data to determine which ARDS clinical phenotypes are likely to benefit from ECLS, the most effective ECLS mode and configuration, or the optimal timing of ECLS application (Fig. 1B). This "Understanding the Disease" article provides an overview of ECLS modalities and configurations that can be utilized to support distinct cardiogenic shock phenotypes in the setting of severe ARDS.

Pathophysiology of cardiogenic shock phenotypes in ARDS

RV failure

Right ventricular (RV) injury is the most common cause of hemodynamic failure in ARDS and refers to a spectrum of dynamic changes in dimensions and/or function of the RV (RV dilatation/dysfunction/failure) and/or intolerance to elevated RV afterload (RV limitation) [3, 4]. The main mechanism of RV injury in ARDS is acutely elevated RV afterload which is multifactorial, often caused by hypoxemia and hypercapnic acidemia causing pulmonary arterial vasoconstriction, and an increase in the pressure opposing RV ejection [5]. Compression of intra-alveolar capillaries due to elevated transpulmonary driving pressure required to maintain tidal ventilation in ARDS may lead to increased West zone 1 or 2 (non-zone 3) conditions and further increases in RV afterload [6]. A negative diastolic interaction between the RV and left ventricle (LV) due to elevated RV end-diastolic pressure may limit LV cardiac output eventually causing coronary hypoperfusion, myocardial ischemia, and shock [3–5].

Left/biventricular failure

Left ventricular or biventricular myocardial dysfunction and shock may occur in patients with ARDS secondary to sepsis-induced or inflammatory cardiomyopathy in the context of bacterial or viral infections. In these cases, myocardial depression may be caused by direct myocardial injury and complex signaling within myocytes or immune-mediated injury [7].

Mixed shock

A common shock phenotype in ARDS which may affect one or both ventricles is mixed shock which is subdivided into three subphenotypes: *cardiogenic-vasoplegic shock,* when cardiogenic shock is complicated by maladaptive vasodilation; *vasoplegic-cardiogenic shock,* when primary microvascular and systemic vasodilation are complicated by myocardial depression; and *primary mixed shock*, when a primary systemic insult causes both low cardiac output and vasodilation [8].

Extracorporeal life support in ARDS with cardiogenic shock

Respiratory ECLS: VV ECMO and ECCO$_2$R

In venovenous (VV) extracorporeal membrane oxygenation (ECMO), central venous blood is drained from the

*Correspondence: vasileios.zochios@nhs.net
[1] University Hospitals of Leicester National Health Service Trust, Glenfield Hospital Extracorporeal Membrane Oxygenation Unit, Glenfield, Leicester, UK
Full author information is available at the end of the article

superior and/or inferior vena cava through large-bore cannulas, circulated through an extracorporeal membrane lung for oxygenation and carbon dioxide (CO_2) removal, and subsequently re-infused into the right atrium. In patients with ARDS and hemodynamic instability requiring VV ECMO, correction of hypoxemia and hypercapnic acidemia, together with ultra-lung-protective ventilation, may improve systemic perfusion and thereby provide indirect cardiac support, obviating the need for mechanical circulatory support. This effect can be attributed to RV unloading through reversal of hypoxic and/or hypercapnic pulmonary vasoconstriction, together with a reduction in the downstream pressure opposing RV ejection (non-zone 3 conditions, where alveolar pressure exceeds left atrial pressure) [9]. Extracorporeal CO_2 removal ($ECCO_2R$) is another distinct respiratory ECLS mode which can reverse hypercapnia (at low extracorporeal blood flows) allowing for a reduction in the intensity of invasive ventilation and theoretically unloading the RV in ARDS [10]. It does not improve oxygenation and international clinical practice guidelines advise against the use of $ECCO_2R$ outside randomized controlled trials because of the absence of demonstrated outcome benefit and the potential for harm [11].

Cardiac ECLS: VA ECMO

Peripheral venoarterial (VA) ECMO typically entails the placement of a drainage cannula in a peripheral vein (e.g., femoral vein) and a return cannula in a peripheral artery (e.g., femoral artery) (Fig. 1B) [10]. VA ECMO primarily provides cardiac support (through right atrial drainage, augmentation of RV and LV perfusion, and maintenance of systemic circulatory flow) and also contributes variably to gas exchange by facilitating oxygenation and carbon dioxide clearance (Fig. 1B). The concomitant ejection of blood from the LV and the retrograde extracorporeal flow delivered into the aorta during peripheral VA ECMO establishes a so-called "dual circulation," characterized by two opposing blood flows [12]. In patients with ARDS, in whom native pulmonary gas exchange is severely impaired, the LV may eject deoxygenated blood into the systemic circulation (including carotid and coronary arteries) proximal to the anatomical point at which the native LV output and the retrograde extracorporeal flow of oxygenated blood mix (differential oxygenation) [12].

In ARDS complicated by refractory cardiogenic shock, VA ECMO may represent an appropriate ECLS modality, provided that adequate gas exchange can be maintained under lung-protective ventilation (fraction of inspired oxygen < 60%, tidal volume 6–8 mL/kg predicted body weight, and driving pressure < 15 cmH_2O). If this cannot be achieved, reconfiguration from VA ECMO to an alternative modality (e.g., VVA ECMO) may be required.

Cardiorespiratory ECLS: VVA ECMO and VP ECMO

In patients with ARDS and refractory cardiogenic or mixed shock, cardiorespiratory ECLS provides direct mechanical circulatory and respiratory support (via augmentation of blood flow and extracorporeal oxygenation and carbon dioxide clearance, respectively), either as an initial strategy or as a rescue technique following conversion from VV or VA ECMO. Commonly utilized cardiorespiratory ECLS modalities include venopulmonary (VP) and venovenoarterial (VVA) ECMO.

In VP ECMO, the inflow bypasses the RV, and therefore, the extracorporeal contribution to systemic oxygenation is independent of RV function [13]. In patients with RV failure, VP ECMO offers direct circulatory support (right atrial drainage and augmentation of pulmonary blood flow) and efficient respiratory support (carbon dioxide clearance and return of oxygenated blood into the pulmonary artery) [13] (Fig. 1B). VP ECMO can either be applied from the outset (providing RV protection and mitigation of /progression of RV injury) or as mode conversion from VV ECMO in patients with ARDS and RV failure refractory to conventional measures (Fig. 1A). However, its use must be carefully managed, particularly when high ECMO flows are required to support failing cardiorespiratory physiology [13]. The potential adverse effects of elevated VP ECMO flows on the pulmonary vascular bed should be investigated in future clinical studies. A commonly employed VP ECMO cannulation strategy during the coronavirus disease 2019 (COVID-19) pandemic was single-site access via the right internal jugular vein using a dual-lumen cannula (ProtekDuo, LivaNova, London, UK) (Fig. 1B). Early application of this approach in COVID-19-related ARDS has been linked to improved survival, particularly when integrated into a comprehensive bundle of mechanical circulatory, ventilatory, and pharmacological interventions [14]. In this configuration, the proximal outer cannula drains blood from the right atrium, while the distal inner cannula returns oxygenated blood into the pulmonary artery, distal to the tricuspid and pulmonary valves (Fig. 1B). Drainage of the right atrium reduces RV preload and systemic venous congestion, thereby unloading the RV. In addition, the single-site configuration facilitates greater patient mobility and rehabilitation (Fig. 1B). However, insertion of the dual-lumen cannula requires considerable expertise and

A

CARDIAC CHAMBER IMPAIRED	RIGHT VENTRICLE	MIXED (RIGHT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)	LEFT VENTRICLE	MIXED (LEFT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)	LEFT AND RIGHT VENTRICLE	MIXED (LEFT AND RIGHT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)
CLINICAL PRESENTATION	SCAI Shock category B or C* Multimodal monitoring: physical examination, biochemical markers, echocardiography, invasive hemodynamics					
PREFERRED HEMODYNAMIC EFFECTS OF VASOACTIVE THERAPY**	• Positive inotropy • Positive chronotropy • Systemic vasoconstriction • Pulmonary vasodilation	• Positive inotropy (caution with inodilators if primary vasodilation) • Positive chronotropy • Systemic vasoconstriction • Pulmonary vasodilation	• Positive inotropy • Lusitropy • Systemic vasoconstriction	• Positive inotropy • Lusitropy • Systemic vasoconstriction	• Positive inotropy • Lusitropy • Positive chronotropy • Systemic vasoconstriction • Pulmonary vasodilation	• Positive inotropy (caution with inodilators if primary vasodilation) • Positive chronotropy • Systemic vasoconstriction • Pulmonary vasodilation
PRONE POSITIONING (IF F_IO_2 > 0.6 TO ACHIEVE P_AO_2/F_IO_2 > 150 MMHG OR 20KPA)	✓ Yes	✓ ! Yes (caution in patients with primary vasodilation)	? May be considered	? May be considered (limited hemodynamic benefit)	✓ ! Yes (if predominantly RV failure/ dysfunction)	? May be considered (limited hemodynamic benefit)

B

CARDIAC CHAMBER IMPAIRED	RIGHT VENTRICLE	MIXED (RIGHT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)	LEFT VENTRICLE	MIXED (LEFT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)	LEFT AND RIGHT VENTRICLE	MIXED (LEFT AND RIGHT VENTRICLE + PRIMARY OR MALADAPTIVE VASODILATION)
CLINICAL PRESENTATION	SCAI Shock category D or E* Multimodal monitoring: physical examination, biochemical markers, echocardiography, invasive hemodynamics					
SUGGESTED MECHANICAL SUPPORT MODALITY	V-P ECMO (Protek-Duo/ Dual site), V-A ECMO, V-VA ECMO	V-P ECMO (Protek-Duo/ Dual site), V-A ECMO, V-VA ECMO	V-A ECMO, V-VA ECMO	V-A ECMO, V-VA ECMO	V-A ECMO, V-VA ECMO	V-A ECMO, V-VA ECMO

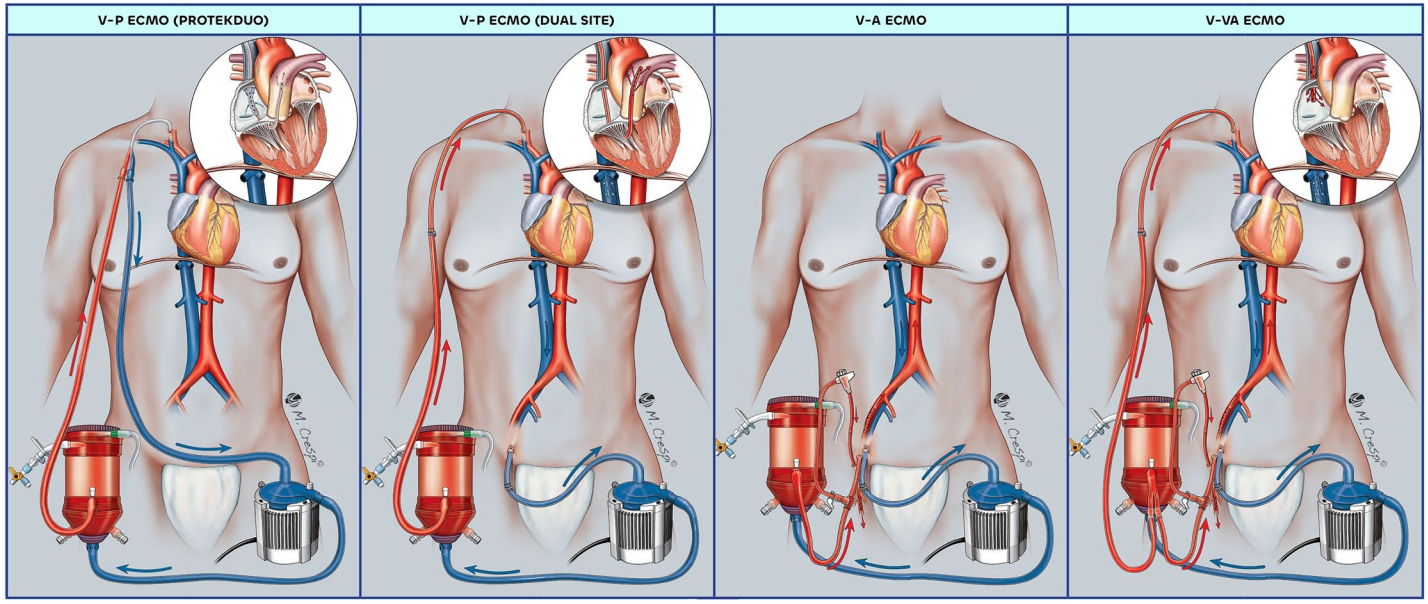

Fig. 1 (See legend on next page.)

VENOPULMONARY ECMO	VENOARTERIAL ECMO	VENOVENOARTERIAL ECMO
Advantages	Advantages	Advantages
• Provides contractile RV support and respiratory support • RV unloading • Preserves pulmonary blood flow	• Quicker to deploy (peripheral configuration) • Unloads RV • Provides systemic support	• Supports both RV and LV • Can be modified depending on the clinical course • Can be used in the context of severe pulmonary hypertension
Disadvantages	Disadvantages	Disadvantages
• Technically more difficult to deploy – requires TEE +/- x-ray • Does not support the LV/ may worsen function • High pulmonary artery pressures possible in the setting of chronic severe pulmonary hypertension and high ECMO flows	• Risk of limb ischemia (peripheral configuration) • Risk of differential gas exchange	• Multiple cannulation sites • Complications associated with arterial cannulation (limb ischemia)

Fig. 1 Proposed conventional and ECLS management approach to different cardiogenic shock phenotypes in severe ARDS requiring extracorporeal life support. **A** Principles of cardiorespiratory conventional management in patients with severe ARDS and SCAI Shock Stage B or C (RV-dominant, LV-dominant, biventricular, and mixed shock) requiring prone positioning and pharmacological therapies to augment blood flow. It should be noted that prone positioning improves hemodynamics mainly through RV unloading as a result of alveolar recruitment, improvement in gas exchange, and a reduction in transpulmonary pressure. In cases of mixed shock with primary vasodilation or LV failure, prone positioning may worsen hemodynamics or have a neutral effect, respectively. * SCAI Shock Stages classification [16]: SCAI A: hemodynamically stable at risk of cardiogenic shock (normal physical examination and biochemical markers, SBP > 100 mmHg, CI > 2.5 L/min/m^2); SCAI B: hemodynamic instability without hypoperfusion (warm-well perfused and normal lactate, SBP < 90 mmHg); SCAI C: hypoperfusion requiring pharmacologic or mechanical intervention beyond volume loading (cold and clammy, lactate ≥ 2 mmol/L, CI < 2.2 L/min/m^2); SCAI D: failure to stabilize with initial strategy to restore perfusion (lactate rising and persistently > 2 mmol/L, deteriorating renal/liver function, requiring escalating doses of vasoactives and ECLS); SCAI E: refractory shock and impeding circulatory collapse (lactate > 8 mmol/L, profound hypotension despite maximal hemodynamic support) [16]. ** Cardiovascular targeting and examples of commonly used vasoactive drugs: *positive inotropy* (epinephrine, milrinone, dobutamine, norepinephrine); *positive chronotropy* (epinephrine, dobutamine, dopamine, milrinone, norepinephrine); *systemic vasoconstriction* (norepinephrine, vasopressin); *lusitropy* (milrinone, dobutamine); *pulmonary vasodilation* (inhaled nitric oxide, inhaled iloprost, systemic epoprostenol). **B** ECLS modes and configurations which could potentially be utilized in cases of ARDS with SCAI Shock Stage D or E refractory to conventional measures or from the outset at presentation. The hyphen ("**-**") in V-A, V-P, and V-VA ECMO indicates "membrane lung" [10]. V-A ECMO: drainage of venous blood from the right femoral vein and return of oxygenated blood into the right femoral artery; V-P ECMO (single-site dual-lumen ProtekDuo cannula): drainage of venous blood from the right atrium and return of oxygenated blood into the pulmonary artery; V-P ECMO (dual-site cannulation): drainage of venous blood from the right femoral vein and return of oxygenated blood into the pulmonary artery; V-VA ECMO: drainage of venous blood from the right femoral vein and return of oxygenated blood into the right internal jugular vein and right femoral artery. *ARDS* acute respiratory distress syndrome, *CI* cardiac index, *ECLS* extracorporeal life support, *ECMO* extracorporeal membrane oxygenation, F_iO_2 fraction of inspired oxygen, *LV* left ventricle, P_aO_2 partial pressure of oxygen in arterial blood, *RV* right ventricle, *SCAI* society for cardiovascular angiography and interventions, *SBP* systolic blood pressure, *VA ECMO* venoarterial extracorporeal membrane oxygenation, *VP ECMO* venopulmonary extracorporeal membrane oxygenation, *VVA ECMO* venovenoarterial extracorporeal membrane oxygenation

advanced imaging (transesophageal echocardiography and fluoroscopic guidance), which may restrict its use to high-volume specialist centers.

VVA ECMO using a V-VA configuration (Fig. 1B) provides both respiratory and hemodynamic support and may be initiated as the primary mode or result from conversion of VV or VA ECMO when evolving cardiorespiratory failure necessitates combined support (Fig. 1B) [15]. VVA ECMO can be dynamically adjusted to the patient's clinical course to provide greater cardiac or respiratory support and may represent the ECLS modality of choice for patients with septic cardiomyopathy (single-ventricular failure, biventricular failure, or mixed shock) in the setting of severe ARDS.

Current evidence for cardiorespiratory ECLS is largely observational, underscoring the need for prospective investigations and large-scale registry studies to determine whether these modalities confer clinically meaningful outcome benefits.

The relative advantages and disadvantages of ECLS modalities for supporting patients with ARDS and cardiogenic shock are presented in Fig. 1B.

Conclusion

A high proportion of patients with severe ARDS develop hemodynamic failure which carries high mortality. Until large registry or randomized studies address this important problem area, a personalized application of cardiorespiratory ECLS based on sound physiology and clinical phenotyping may reduce mortality when applied early as a bridge to heart and lung recovery (Fig. 1).

Author details

[1] University Hospitals of Leicester National Health Service Trust, Glenfield Hospital Extracorporeal Membrane Oxygenation Unit, Glenfield, Leicester, UK. [2] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK. [3] Nazih Zuhdi Transplant Institute, Advanced Cardiac Care, Specialty Critical Care and Acute Circulatory Support Service, Integris Baptist Medical

Center, Oklahoma City, USA. [4] Department of Respiratory Sciences, University of Leicester, Leicester, UK. [5] National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK.

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Declarations

Conflicts of interest
VZ is the chair, HY co-chair, and JMB is a member and collaborator of the Protecting the Right Ventricle Network (PRORVNet). VZ reports honoraria for education from Mitsubishi Tanabe Pharma Europe, outside the submitted work. HY is a member of the advisory board for AOP Health.

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