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Lung injury in myocardial infarction-associated cardiogenic shock supported by venoarterial extracorporeal membrane oxygenation: a scoping review

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Abstract

Background Acute lung injury and acute respiratory failure are frequent complications of cardiogenic shock and are associated with increased morbidity and mortality. Even with increased use of temporary mechanical circulatory support, such as venoarterial extracorporeal membrane oxygenation (VA-ECMO), acute lung injury related to cardiogenic shock continues to have a determinantal effect on patient outcomes.

Objectives To summarize potential mechanisms of acute lung injury described in patients with cardiogenic shock supported by VA-ECMO and determine current knowledge gaps.

Methods We searched literature from January 1st, 2010, to December 31st, 2023, using MEDLINE, EMBASE, and Web of Science databases on February 27th, 2024. The search strategy was split into two main domains: (a) cardiogenic shock and ECMO and (b) Acute respiratory failure and ECMO.

Results The search yielded 2246 citations. After 743 duplicates were removed, 1465 citations remained. Of these studies, 1456 were excluded based on the exclusion criteria, leaving the final eight studies we included in our scoping review. We identified disruption of the pulmonary blood flow in patients with cardiogenic shock, with cardiac arrest being an extreme form of cardiogenic shock. Placing the patient on VA-ECMO could intensify this process of lung injury.

Conclusion Acute lung injury in patients with cardiogenic shock, especially when supported by VA ECMO, is a significant complication that is associated with increased morbidity and mortality. There is a limited understanding of the underlying mechanisms that could represent opportunities for future research to mitigate its development and provide the best approach to protecting and monitoring lung function.

Keywords Cardiogenic shock, Acute respiratory failure, Lung injury, Extracorporeal membrane oxygenation

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Introduction

Cardiogenic shock has a high in-hospital mortality (>40%) despite recent advances in supportive interventions [1–3]. In-hospital mortality dramatically increases as patients' clinical condition deteriorates based on the Society for Cardiovascular Angiography and Intervention (SCAI) classification, which ranges from 3% in SCAI stage A up to 67% in SCAI stage E [4]. Similarly, the need for invasive mechanical ventilation increases from 5.6% in SCAI stage A to 75% in SCAI stage E. In an analysis of a national registry of acute myocardial infarction with cardiogenic shock, acute respiratory failure was present in 57% of patients [5].

Impairment of left ventricular systolic and diastolic function leads to increased left atrial pressure, which increases pulmonary capillary hydrostatic pressure. Subsequently, increased fluid filtration into the lung parenchyma exceeds the lymphatic system's ability to remove fluid [6]. As a result, the lungs become edematous, noncompliant, and have impaired gas exchange capability. In ischemic-perfusion scenarios, as are seen after cardiac arrest, there are varying degrees of non-cardiogenic pulmonary edema. Chest imaging manifests a continuum from mild infiltration to diffuse opacification, as is seen with acute respiratory distress syndrome. However, ischemia/perfusion remains a diagnosis of exclusion, as there are no currently well-defined criteria for ischemic-perfusion injury [7].

With the recent advances in mechanical circulatory support technology, there has been expanded use of VA-ECMO as a supportive intervention in patients with cardiogenic shock and cardiac arrest [8]. VA-ECMO has the advantage of rapid deployment at the bedside, providing bi-ventricular cardiac and respiratory support. Hence, it maintains peripheral organ perfusion and prevents multi-organ dysfunction. However, one of the challenges of peripheral VA-ECMO is that the blood flow in non-physiological patterns which predisposes the patient to many complications such as limb ischemia, left ventricular distension, intra-cardiac thrombosis, cerebrovascular accidents, and pulmonary complications such as pulmonary edema and hemorrhage [9].

The purpose of our scoping review was to summarize potential mechanisms of acute lung injury in patients with cardiogenic shock supported by VA-ECMO and determine what knowledge gaps currently exist. We also aimed to highlight the studies that have been published related to this topic.

Methods

To address our questions, we comprehensively reviewed the literature using the farmwork described by Peters and colleagues [10]. We searched literature from January 1st, 2010-December 31st, 2023, using MEDLINE, EMBASE, and Web of Science databases on February 27th, 2024. The search strategy was split into two main domains: (a) cardiogenic shock and ECMO (b) Acute respiratory failure and ECMO. Keywords and MeSH terms relating to these categories were used to optimize the database search. We searched with keywords and MeSH terms "acute respiratory failure" or acute lung injury" AND "cardiogenic shock" OR "cardiac arrest" AND "Extracorporeal membrane oxygenation" OR "ECMO" OR "ECLS". The results were duplicated and uploaded to Covidence.

Inclusion criteria

The inclusion criteria were applied using the population, intervention, comparator, and study design approach [10]. We included (1) randomized controlled trials, observational studies, and review papers; (2) adult studies (>18 years); (3) Studies of acute respiratory failure and cardiogenic shock. The search was limited to the English language.

Exclusion criteria

We excluded (1) editorials, commentaries, and case reports, (2) studies focusing on acute respiratory failure and the use of venovenous ECMO, and (3) studies of the pediatric population.

Study selection and data extraction

Two authors screened all relevant articles to assess the literature results for eligibility. A third reviewer resolved any disagreements on the inclusion/exclusion of the literature. The Covidence platform was used to streamline the review process. Articles meeting inclusion criteria were retrieved, and the full text was reviewed. References of included studies were screened and included based on inclusion and exclusion criteria. Extracted data included authors, article title, publication date, journal name, article type, objectives, methods, and key findings.

Results

The search yielded 2246 citations. After 743 duplicates were removed, 1465 citations remained. Of these studies, 1456 were excluded based on the exclusion criteria, leaving the final eight studies we included in our scoping review (Fig. 1). A summary of the included studies is described in Supplementary Table 1.

Aims and scope

Based on our search, we identified two broad conclusions. First, there is disruption of the pulmonary blood flow in patients with cardiogenic shock, with cardiac arrest being an extreme form of cardiogenic shock. Second, patients supported by VA-ECMO could experience an intensified process of lung injury. However, because of the provided gas exchange via ECMO, clinical recognition of

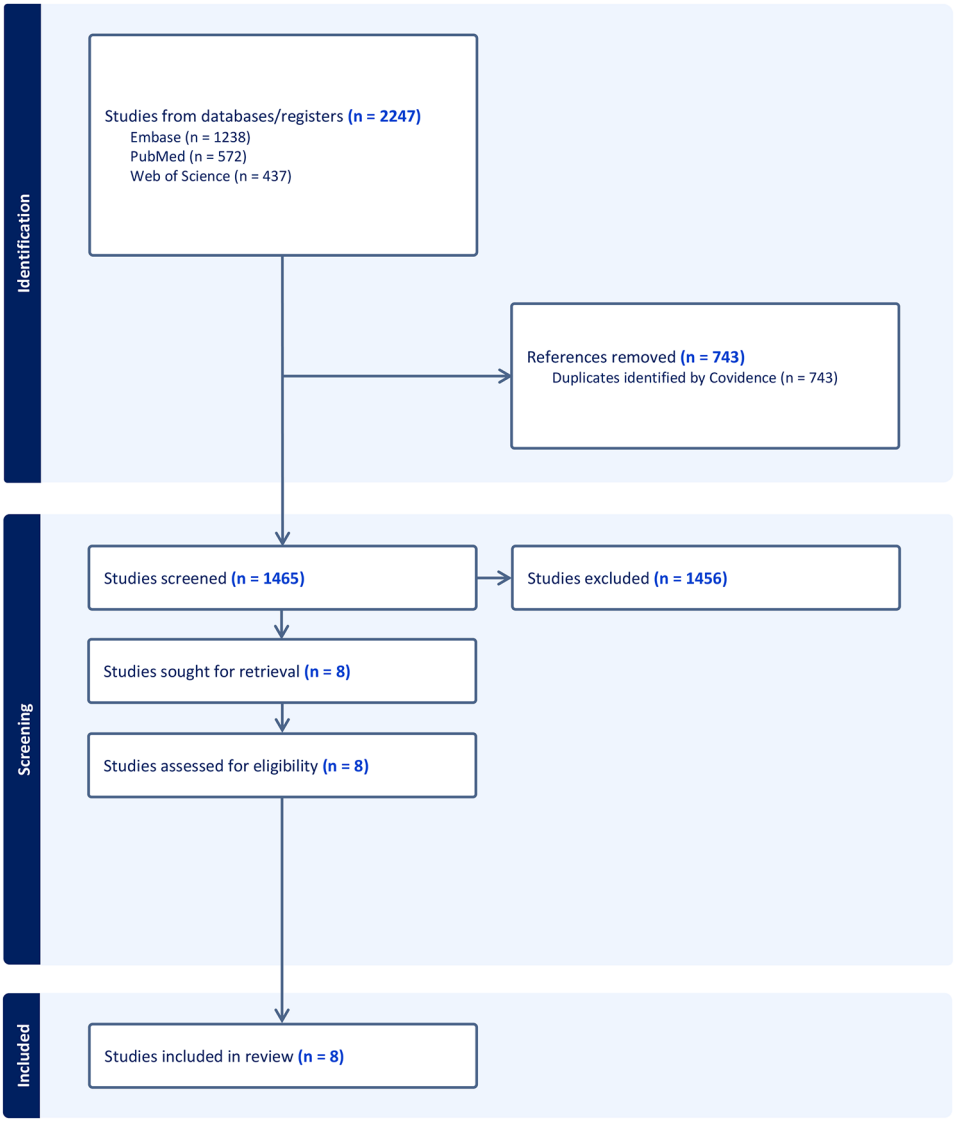

Fig. 1 PRISMA diagram for literature retrieval

this process might be overlooked, which could be associated with prolonged ECMO support and potentially worse clinical outcomes. Based on the included studies, acute lung injury during VA-ECMO support has been identified based on a constellation of clinical and/or radiographic evidence of pulmonary edema within 48 h of VA-ECMO insertion, $PaO_2/FiO_2 < 200$, and impaired lung mechanics, including compliance [11, 12].

Physiology of lung blood supply

The lung is the only organ with two circulations: pulmonary and bronchial. Pulmonary circulation's main function is gas exchange, while bronchial circulation provides oxygenated blood to the walls of the airways, pulmonary arteries, and veins. Pulmonary circulation is compliant and highly adaptive, accommodating the entire cardiac output and adjusting to multiple neuronal and humoral factors [13]. Conversely, the bronchial arteries originate from the thoracic aorta and carry an estimated 1–2% of the cardiac output, which is oxygenated blood. After passing through the lung tissues, bronchial arterial blood empties into the pulmonary veins [14].

The impairment of cardiac function in patients with cardiogenic shock and subsequent increase of the left atrial pressure leads to elevation in the pulmonary artery pressure [6]. The increase in the hydrostatic pressure in the pulmonary circulation, which surpasses the lymphatic drainage capacity, contributes to pulmonary congestion, impairment of lung compliance, and the gas exchange function. At the same time, the reduction in the bronchial circulation exposes the lung tissue to hypoperfusion and potential ischemic injury [15].

Disruption of the lung blood flow in cardiogenic shock

The pathophysiology of pulmonary congestion in the setting of cardiogenic shock could be attributed to multiple factors [16]. Fluid redistribution is a common phenomenon in patients with acute heart failure that is caused by the sudden increase in vascular stiffness [17]. The increase in the vascular stiffness of the capacitance veins leads to an increase in the preload to the poorly adaptive heart. At the same time, the increase in arterial vascular stiffness causes an increase in the cardiac afterload [18]. Subsequently, the elevated intra-cardiac pressures lead to "backward failure" with pulmonary congestion. Another mechanism is the overactivation of the neuro-hormonal pathway (renin–angiotensin–aldosterone system), which causes fluid retention [19]. In addition to the macro-circulatory impact of the cardiogenic shock, the micro-circulatory effect is equally significant. Microcirculation is the terminal vascular network of the systemic circulation (arterioles, capillaries, and venules) [20]. It has a crucial role in oxygen delivery to the tissues, regulating the blood flow in response to hemodynamic fluctuation, and plays a central role in the immune systemic response, including hemostasis [21]. In cardiogenic shock, there is an alteration of microvascular blood flow, attenuated response to hyperemia and hypoxia, and marked heterogeneity between different tissues [22, 23]. Interestingly, there is no correlation between macrovascular parameters and microvascular blood flow, a phenomenon referred to as "loss of hemodynamic coherency." [24] This impairment of the microcirculation in the end-organs, including the lung, could lead to the activation of arteriovenous shunts and the development of atelectasis and hypoxemia [25].

Molecular mechanisms of lung ischemic perfusion injury

Systemic inflammatory response is a well-documented phenomenon in patients with acute lung injury and myocardial infarction-induced cardiogenic shock, and it correlates with the severity of shock [26]. The global hypoperfusion associated with cardiogenic shock triggers tissue damage with the release of danger-associated molecular patterns (DAMPs), which triggers the activation of inflammatory cytokines and chemokines such as Interleukin-6 (IL-6) and Tumor necrosis factor (TNF)-α [27]. Pro-inflammatory mediators cause endothelial activation and impairment of the nitric oxide signaling, leading to vasodilation and increasing endothelial permeability, further exacerbating the cardiogenic shock and leading to pulmonary congestion and, eventually, multi-organ system dysfunction [28].

In extreme cases, the lung could experience ischemic perfusion injury. Lung ischemia occurs when the blood flow to the pulmonary parenchyma drops below the metabolic demands and/or decreased ventilation [29]. Perfusion leads to the production of toxic molecules that further hinder tissue perfusion. Lung ischemia activates the inflammatory response, including the immune system, complement, coagulation cascades, and endothelial dysfunction. During ischemic perfusion injury, intracellular molecules are released that activate signaling pathways such as NF-κB, mitogen-activated protein kinase (MAPK), and type-I interferon, further promoting the production of pro-inflammatory cytokines and chemokines (Fig. 2) [30]. Once the immune response is activated, areas of ischemia become infiltrated with inflammatory cells (granulocytes, dendritic, and T regulatory cells) [31]. The complement system bridges innate and adaptive immune responses that exacerbate further tissue damage directly and indirectly by amplifying the immune response [32]. The inflammatory response also leads to localized endothelial dysfunction, which activates the platelets with subsequent microvascular constriction and thrombus formation [33]. Reactive oxygen species (ROS) play a major role in the reperfusion phase, where the tissues produce a large amount of ROS that overwhelms the body's antioxidant mechanisms and leads to further cell damage and death [34].

Disruption of the lung blood flow on venoarterial extracorporeal membrane oxygenation

The retrograde blood flow from the peripheral VA-ECMO could contribute to the elevated aortic pressure and left ventricular afterload. The impaired left ventricular contractility and the increased aortic pressure correlated with the left atrial distension and subsequent pulmonary edema [35]. Pulmonary congestion compromises the lung parenchymal cell oxygenation by interstitial pulmonary edema and thickening of the alveoli-capillary barrier, compromising oxygen diffusion [36]. Another mechanism is anoxic ischemia, which can destabilize the intercellular junction, impair barrier permeability, impede alveolar fluid clearance and surfactant production, local vasoconstriction, and trigger a systemic inflammatory response (Fig. 2) [37]. In addition, bronchial arteries' blood flow could be compromised during VA-ECMO support by lack of pulsatility and deoxygenated blood, which further compromises blood supply to ischemic lung areas [38].

VA-ECMO triggers a systemic inflammatory response by exposing the blood to the biomaterial of the ECMO circuit. This response highly affects the lungs due to the extensive vasculature and abundant immune cells. The contact of the blood with the ECMO circuit triggers the activation of the intrinsic pathway with the generation of thrombin and fibrin. Thrombin stimulates the platelets and the endothelial cells to produce pro-inflammatory mediators (IL-6, TNF-α, IL-1β), which activate leukocytes and cause pulmonary vasoconstriction. Complements play a role in chemoprophylaxis as well. Also, the

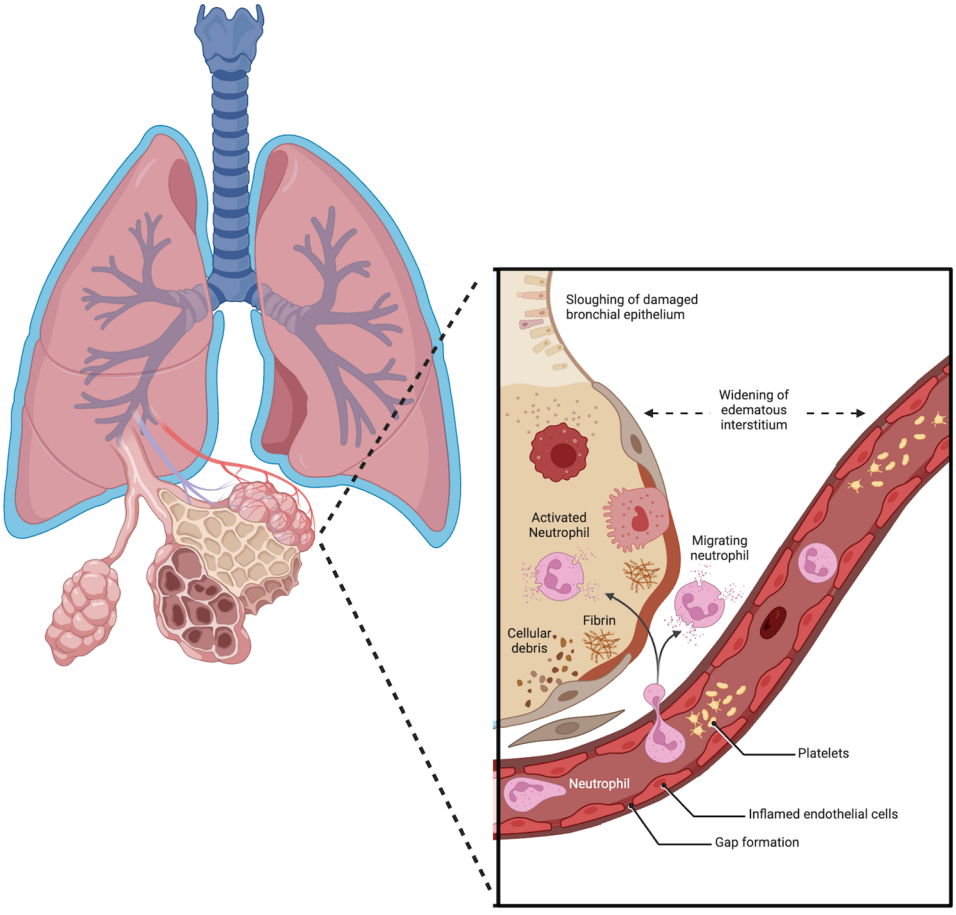

Fig. 2 Inflammation plays an important role in developing acute lung injury. Lung ischemic and disruption of physiological blood flow to the lung are important factors in patients with myocardial infarction-induced cardiogenic shock

activation of endothelial and polymorphonuclear cells triggers the production of reactive oxygen species.

Clinical implications of lung injury on venoarterial extracorporeal membrane oxygenation

The limited evidence suggests that risk factors for the development of acute lung injury could be extrapolated. Elevated lactic acid, serum creatinine, total bilirubin, prolonged mechanical ventilation before VA-ECMO implantation, and frequent blood transfusion were associated with the development of ALI during VA-ECMO support [39]. Also, one study showed that prolonged cardiac arrest, as reflected by acute brain injury, is a risk factor for ALI during VA-ECMO support [12]. Although acute lung injury occurs more frequently in peripheral VA-ECMO configuration, it has been described in central VA-ECMO as well [11]. The clinical implications of poor lung function on the clinical outcomes of VA-ECMO patients can be demonstrated by direct consequences on the lung and other organs beyond. Lung function impairment might require prolonged use of mechanical ventilation in VA-ECMO patients. This exposes the patient to the risk of ventilator-induced lung injury (VILI) as well as ventilator-associated pneumonia (VAP) [40, 41]. Until now, there has been no consensus regarding the optimal ventilator settings during VA-ECMO support, lung function monitoring, and VILI prevention. Similarly, the diagnosis of VAP in the setting of VA-ECMO is another challenge and requires a high index of suspicion coupled with microbiological confirmation [40]. The strategies of early extubation and awake ECMO might be promising in preventing both complications, but they have yet to be widely adopted. Poor lung function can predispose patients with peripheral VA-ECMO to upper body hypoxia (differential oxygenation), producing poor oxygen delivery to the cerebral and coronary circulation. This could impair heart recovery and increase the risk of cerebrovascular complications [42, 43]

In addition, even after weaning VA-ECMO and restoring the normal physiological blood flow to the lung, acute lung injury can occur. This form of injury is similar to the ischemic perfusion injury previously described. In a single-center retrospective analysis of 55 patients with cardiogenic shock supported by VA-ECMO, 27% of the

Table 1 Key gaps in the knowledge and opportunities for future research

Key Evidence Gaps
1. Currently, there is no acceptable definition for acute lung injury in patients supported by VA-ECMO.
2. Lack of understanding of the pathophysiology of acute lung injury in cardiogenic shock patients supported by VA-ECMO
3. It is unclear if there is impact of patient-related risk factors for acute lung injury include the baseline characteristics and the underlying etiology of cardiogenic shock.
4. Consistent practices are lacking to prevent acute lung injury in VA-ECMO patients, including managing mechanical ventilation, optimum ECMO flow, and left ventricular unloading.
5. Theoretical but lacking evidence regarding the impact of lung injury in ECMO patients on other organ-system dysfunctions.
6. Utilization of biomarkers and transitional research in early identification and prevention of acute lung injury in cardiogenic shock patients supported by VA-ECMO.
7. It remains unclear which management strategy has the best impact on lung recovery, i.e., pharmacological interventions such as inotropic support and protective mechanical ventilation settings vs. non-pharmacological ones such as physiological ECMO flow and left ventricular unloading.

VA-ECMO = venoarterial extracorporeal membrane oxygenation

patients developed acute lung injury upon transition to a durable mechanical circulatory support option [11]. Another study of out-hospital cardiac arrest patients who received Extracorporeal cardiopulmonary resuscitation (ECPR). Chest CT showed lung injury (hyper attenuation) in at least one lung area in 91.8% and altered lung mechanics, and the survivors had faster lung recovery compared to the non-survivors [12].

We propose continuous monitoring of lung function by using radiographic criteria and monitoring lung compliance in patients with cardiogenic shock supported by pharmacological or non-pharmacological interventions. Lung ultrasound might provide a reliable and safe diagnostic tool. Some of the studies utilized lung ultrasound to diagnose acute respiratory distress syndrome. They proposed the presence of multiple bilateral, non-homogenous B-lines in at least one area per hemithorax and the presence of subpleural consolidations [44, 45]. The lung ultrasound might be more accurate than a CT scan in detecting focal vs. diffuse lung consolidation [46]. Even more, lung ultrasound can help with a personalized approach toward titration of mechanical ventilation settings such as positive end-expiratory pressure [47]. Bronchoscopy is useful for diagnosing VAP, improving lung mechanics in specific cases, and accelerating weaning from mechanical ventilation [48]. It is feasible and safe in patients with acute lung injury, even in prone positioning [49]. It might be helpful to apply strategies for managing acute respiratory distress syndrome, such as protective lung ventilation parameters such as low tidal volume ventilation (6 cc/kg of predicted body weight) and monitoring the plateau pressure to maintain it at less than 30 cmH_2O [50]. One of the advantages of VA ECMO is that it will allow for protective ventilatory settings and might reduce the risk of ventilator-induced acute lung injury. Also, maintaining a conservative fluid management strategy when hemodynamics allow might help reduce the duration of invasive mechanical ventilation [51]. Prone positioning might benefit patients with impaired gas exchange ($PaO_2/FiO_2 < 150$) [52].

Future perspectives

There are many gaps in the knowledge regarding the ALI in cardiogenic shock patients who are supported by VA ECMO (Table 1). Despite some authors' proposed definition of the ALI, there is no acceptable universal definition by the scientific community [11, 12]. This is crucial for the early detection of ALI in cardiogenic shock, prevention, and implementation of therapeutic interventions. Even more, conducting future research to expand our understanding of the pathophysiological mechanism that leads to the development of ALI in cardiogenic shock. The disruption of lung blood flow because of the progressive shock and non-physiological flow of the peripheral VA ECMO is one of the factors that we need to understand more. However, the underlying molecular mechanism of lung inflammation and its interaction with coagulation and endothelial dysfunction is a potential target for future studies to help monitor and modulate the degree of ALI in cardiogenic shock patients. Also, it is unclear if there are preventive measures in the high-risk patient population for ALI in cardiogenic shock, especially on VA ECMO—for example, protective mechanical ventilation settings or early unloading of the left ventricle.

Limitations of the current study

The current study has multiple limitations. The most prominent is the limited number of studies reporting on acute lung injury in patients with cardiogenic shock. We conducted our literature research using commonly available scientific databases. Studies would have been included if they had been listed in the analyzed databases. Additionally, because of the lack of a standard definition of ALI in cardiogenic shock patients, there might be underreporting of this phenomenon in the literature. The effect of peripheral VA ECMO on blood gas exchange may make recognizing ALI even more difficult. Finally, very limited studies focused on the preventive and therapeutic interventions for ALI in cardiogenic shock.

Conclusions

There is a limited understanding of the mechanism and the outcomes of acute lung injury in patients with cardiogenic shock supported by VA-ECMO. Acute respiratory failure, which is a common complication of cardiogenic

shock, is associated with high morbidity and mortality. The underlying mechanisms of respiratory failure are complicated and intertwined. VA-ECMO support in cardiogenic shock adds another layer of complexity to the recovery of lung function, and the impact of lung dysfunction on heart recovery and neurological complications needs to be further elucidated. To improve outcomes, there are key research opportunities to define lung injury in the setting of VA-ECMO, mitigate ischemic-perfusion injury of the lungs, develop the best approach to protect and monitor lung function, and examine the underlying cellular and molecular mechanisms of such lung dysfunction.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04472-7.

Supplementary Material 1

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AZ conceptualization, literature search, writing, and editing MAZ writing and editing MAV literature review, writing, and editing MR writing and editing SMC conceptualization, writing, and editing.

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Data availability
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Not applicable.

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