The Effects of Prone Positioning with VV-ECMO Support in Adult Acute Respiratory Distress Syndrome Patients: A Scoping Review of the Evidence

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Abstract

Background: Acute Respiratory Distress Syndrome (ARDS) is a severe form of respiratory failure associated with high morbidity and mortality. Optimizing gas exchange while minimizing ventilator-induced lung injury (VILI) is crucial when managing ARDS patients. Lung-protective mechanical ventilation (LPV) is widely used, but variability in alveolar injury poses treatment challenges. Prone positioning and venovenous extracorporeal membrane oxygenation (VV-ECMO) have emerged as adjunct oxygenation therapies in recent years. Proning redistributes mechanical forces and improves ventilation distribution. Respiratory ECMO, or VV-ECMO, provides gas exchange support and facilitates lung-protective ventilation. However, the combined efficacy of these interventions remains unclear.

Objective: This scoping review aims to summarize the available evidence on the effects of prone positioning in adult patients with ARDS requiring VV-ECMO.

Methodology: A scoping review design was chosen to comprehensively explore the literature on VV-ECMO therapy in prone adult ARDS patients, including historical progress, current practices, and future directions. The study will utilize a rigorous search strategy across multiple electronic databases and employ specific inclusion and exclusion criteria to identify relevant articles. Screening protocols will be implemented to ensure the selection of appropriate studies. The search strategy results will be reported using a PRISMA flow diagram. Data characterization will utilize an extraction table to capture key study characteristics and findings.

Contributions: This scoping review aims to inform future evidence-based proning protocols and guidelines when utilizing VV-ECMO and to facilitate standardized practices and improved healthcare delivery for patients with ARDS. This review will enable perfusionists to proactively anticipate and manage potential complications or challenges associated with proning and combined VV-ECMO therapy. This study aims to contribute to advancing the cardiovascular perfusion field by guiding research directions and identifying current knowledge and practice gaps.

Keywords: Prone position, ARDS, acute respiratory distress syndrome, ECMO, extracorporeal membrane oxygenation, ECLS, extracorporeal life support, venovenous, VV-ECMO, adult, human.

1. Background

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening form of respiratory failure associated with capillary endothelial injury and diffuse alveolar damage.(1) Diagnosis is often made using the Berlin definition, which categorizes severity based on PaO_2/FiO_2 ratio: mild (200-300 mmHg), moderate (100-200 mmHg), and severe (≤100 mmHg).(1) Furthermore, it can be characterized by acute onset (within one week of inciting event) of hypoxemia, decreased lung compliance, diffuse lung inflammation, and bilateral opacities (increased pulmonary vascular permeability) on diagnostic imaging due to noncardiogenic pulmonary edema.(2) As ARDS progresses, increased alveolar-capillary permeability leads to the development of diffuse alveolar edema.(1) Alveolar edema interferes with respiratory gas diffusion, leading to hypoxemia.(1) The etiologies of

ARDS are diverse, with pneumonia and sepsis being the most common causes(1,3); however, it may also result from inflammatory processes such as acute pancreatitis, drug reactions, and fungal or parasite infections.(3) The COVID-19 pandemic has had a significant impact, leading to a notable increase in severe ARDS cases caused by viral pneumonia.(4) This surge created a tremendous demand for ECMO and perfusionist services while also placing a significant burden on healthcare systems and providers worldwide(4), thus emphasizing the need to further develop effective management strategies for ARDS patients.

Oxygenation strategies with ARDS are usually complicated by the heterogeneity of lung injury, a hallmark pattern of the pathology where more severely affected areas of the lungs result in deceased regional lung compliance, resulting in varying responses to management.(1) Despite advances in critical care, ARDS remains a significant health concern associated with high morbidity, mortality, and treatment costs.(1,5,6) In fact, moderate and severe cases of ARDS still carry mortality rates of 40.3% and 46.1%, respectively.(6) While no curative treatment exists for ARDS, there are supportive interventions that have gained increasing popularity based on the severity of ARDS.(7) However, even after undergoing ARDS management, survivors often experience substantial morbidity, including impaired functional ability and reduced exercise tolerance, and report cognitive and economic consequences.(7)

The primary objective in managing ARDS is to optimize gas exchange while minimizing the risk of ventilator-induced lung injury (VILI).(8) Four mechanisms contribute to the development of VILI: volutrauma (alveolar overdistension secondary to increased transpulmonary pressure); barotrauma (increased transpulmonary pressure causing alveolar rupture); atelectrauma-shearing (cyclic opening and closing of alveoli); and biotrauma (proinflammatory cytokines further promoting inflammatory cascade leading to pulmonary and extra-pulmonary injury).(2) Excessive mechanical stress from positive ventilation can cause VILI through these mechanisms, furthering lung inflammation and damage.(7) Lung-protective mechanical ventilation (LPV) plays a crucial role in mitigating the risk of VILI. The approach utilizes lower tidal volumes to predicted body weight, avoiding high plateau pressures and employing high positive end-expiratory pressures (PEEP).(7) However, the efficacy of this strategy can be compromised by the variability in alveolar injury across the lungs. While increased PEEP has been demonstrated to enhance oxygenation in affected alveoli, increased alveolar pressures also contribute to volutrauma and atelectrauma-shearing in adjacent unaffected alveoli.(1) Furthermore, supine positioning can exacerbate atelectasis and the de-recruitment of dependent lung regions.(7) To address these challenges, therapies such as proning and, in severe cases, venovenous extracorporeal membrane oxygenation (VV-ECMO) have gained increased use.(7,9)

Proning can aid in the management of ARDS through several mechanisms. Firstly, it promotes the redistribution of mechanical forces, leading to a more homogenous distribution of ventilation throughout the lungs.(5,10,11) When a patient is ventilated and prone, there is a reduced risk of tidal hyperinflation of non-dependent lung regions, mitigating volutrauma and atelectrauma-shearing of these alveoli.(11) Additionally, proning helps reverse the effects of gravitational forces and facilitates the repositioning of surrounding structures.(5,10,11) The effect is further enhanced by the greater dorsal mass of the lungs, leading to increased lung recruitment of alveolar units in prone positioning.(11) As a result, proning enhances the distribution of ventilation and perfusion, improving V/Q (Ventilation/Perfusion) matching.(5) Indeed, previous evidence has revealed improved survivability when proning patients with severe ARDS receiving LPV.(12)

Traditionally, VV-ECMO has often been recommended for severe cases of hypoxemia refractory to maximal support of conventional therapies.(13) VV-ECMO is a life-support therapy that involves diverting deoxygenated blood from systemic circulation to an extracorporeal membrane oxygenator, enabling respiratory gas exchange by oxygenating the blood and removing carbon dioxide.(7) Augmenting the function of the diseased lungs in ARDS allows for improved implementation of lung-protective ventilation measures, further reducing the risk of VILI.(4,7) The 2018 multicenter international randomized controlled trial known as ECMO to Rescue Lunge Injury in

Severe ARDS (EOLIA) found that early application of ECMO (venovenous and venoarterial were included) was not associated with a significantly reduced 60-day mortality rate when compared to the control group (no ECMO).(14) Of note, a crossover of 28% of control patients to the ECMO group may have confounded the true effect of ECMO initiation.(14) The EOLIA trial has generated controversy over the efficacy of ECMO in these situations. Consequently, ECMO has conventionally been regarded as a salvage or rescue therapy for such cases(4), as outcomes remained unclear.(3) Interestingly, more recent evidence is now supporting the early use of VV-ECMO, as it has been shown to have a clinically significant benefit.(6) This has led to increased interest in combining prone position maneuvers and VV-ECMO.(6)

In certain instances of severe ARDS, the combination of VV-ECMO and LPV may not be sufficient to adequately maintain tissue oxygenation.(15) While prone positioning can be employed for non-intubated and intubated ARDS patients, its utilization is less common once a patient has been initiated on VV-ECMO support.(9,11) Previously, there have been concerns regarding the impact of prone positioning on hemodynamic stability, cannula dislodgment, and decreased ECMO blood flows.(16) The process of proning patients on VV-ECMO can be resource-intensive and may carry substantial risk to patient stability.(16) However, emerging evidence now demonstrates that prone positioning while on VV-ECMO is safe and feasible[4] and may be associated with improved survivability.(15) These findings necessitate further related research and have prompted the following research question: "*What is the effect of prone positioning in adult patients with ARDS requiring VV-ECMO?"* After briefly examining the available literature, we determined that a scoping review would be the most effective method to gain a deeper understanding of this question. The absence of guidelines and standardization for proning patients on VV-ECMO(12) can result in significant variations in patient management. Therefore, analyzing patterns and trends through a review can provide valuable insights into the effects of this intervention, allowing clinicians to more accurately evaluate the benefit-risk ratio. This review holds great significance for the field of cardiovascular perfusion as it intends to contribute to the optimal practices in caring for adult patients with ARDS on VV-ECMO. Hence, this scoping review aims to examine the existing evidence in the literature, identify gaps in knowledge and current practices, and further elucidate the understanding and adoption of optimal care methods for these patients.

2. Methodology

Research Question

The following research question will guide this review: 'What is the effect of prone positioning in adult patients with ARDS requiring VV-ECMO support?

Study Design

A scoping review study design has been selected to facilitate a systematic investigation of the proposed research question, which plans to examine the effects of prone positioning in adult patients with ARDS requiring VV-ECMO support. A scoping review is an appropriate study design choice to effectively address a broad research question while ensuring reproducible search results through utilizing a transparent search strategy protocol.(17) By employing a rigorous scoping review design, this study aims to identify and analyze all relevant literature, including recent historical progress, current practices, and future directions in VV-ECMO therapy for prone adult ARDS patients.(17) This comprehensive approach will facilitate the identification of gaps in current knowledge and practices related to ARDS and ECMO. Additionally, it will contribute to developing a consolidated document outlining current practices and evidence surrounding the care of these critically ill patients. The target audience for this review includes cardiovascular perfusionists, ECMO specialists, and other critical care professionals working with extracorporeal circuits. Thus, a scoping review study design will facilitate an improved understanding of the effects of prone positioning in adult ARDS patients receiving VV-ECMO support, provide valuable insights, and inform and contribute to the advancement of best practices in ECMO therapy in this patient population.

Search Strategy

In order to facilitate the rigour and reproducibility of this scoping review, an optimized

search strategy has been developed, which will entail multiple processes, including literature identification and the development and application of article selection criteria and screening protocols to determine article eligibility for study inclusion.

Literature Identification & Selection Criteria

The literature identification process of the search strategy will include multiple electronic databases [PubMed, EBSCOHost, Cochrane Library, Google Scholar, and Michener EDS (electronic database system)]. A combination of keywords (ARDS, ECMO, prone, adult) and their synonyms (Appendix 1), Medical Subject Headings (MeSH) terms, and Boolean operators (AND, OR, NOT) will be optimized for each database search. Search results will be filtered according to selection criteria. Article inclusion criteria will include the following: English language; peer-reviewed; study designs including observational studies, randomized controlled trials, systemic reviews, meta-analyses, and Cochrane reviews; articles published within the last five years; adult patients (≥18 years); and patients with ARDS on VV-ECMO requiring prone positioning. Exclusion criteria will consist of patients on venoarterial (VA)-ECMO, pediatric patients (< 18 years), and narrative review articles. All relevant search results will then be pooled for article screening and selection for inclusion.

Citation Management

All citations for study inclusion will be imported into the software citation manager, *EndNote*. A shared EndNote group folder between the investigators, AB and JC, will be utilized to pool articles and facilitate subsequent screening, data extraction, and reporting.

Screening Protocol

Following literature identification, the next step of the search strategy requires screening all search results for review inclusion utilizing the defined selection criteria (listed above); thus, a specific protocol has been developed to assist with this process. The first step of screening is the removal of all duplicate articles. Next, the first pass of article screening is performed, which includes reviewing the titles and abstracts of all search results for study inclusion based on the defined inclusion and exclusion criteria. Once first-pass screening is complete, second-pass article screening can begin; the second-pass screening process will consist of a full-text review of all remaining studies for eligibility utilizing article inclusion and exclusion criteria. The primary investigators, AB and JC, will each independently complete first and second-pass article screening for all literature identified; if the primary investigators cannot make discretion for inclusion following discussion, an independent and unbiased third-party researcher is available for tie-breaking, as required. For articles excluded, reasons for exclusion will be provided. Additional resources will also be utilized during the screening process to avoid the inclusion of predatory journals, including *The Directory of Open Access Journals*, *Open Access Scholarly Publishers Association*, and *Think.Check.Submit*.(18)

Search Strategy & Screening Results Reporting

After determining the final articles included for review, the search strategy results will be transposed into a PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) flow diagram (Figure 1). A PRISMA flow diagram is designed to depict the flow of information through the different phases of the review process, mapping out the number of records identified, included, excluded, and reasons for exclusion.(19) Thus, utilizing a PRISMA flow diagram within our scoping review will enable transparency and reproducibility for the literature identification, screening, and selection reporting processes, in addition to providing an organized visual representation of the included studies and their methods for inclusion.

Data Characterization, Extraction, & Reporting

Data extraction and reporting can commence once the final articles for inclusion have been determined. To streamline the data extraction and reporting process, investigators AB and JC have devised a template table (Table 1) that will serve as a guide for extracting pertinent study characteristics. This table will facilitate the collation, summarization, and reporting of relevant study characteristics and findings, enabling data comparison and identification of knowledge or practice gaps.

The data items to be included in the table are as follows: study authors, year of publication, country of

study origin, study design, number of study participants, mean patient age, ARDS criteria and etiology, proning protocol, ECMO description, mean ECMO support time, adverse events, and main study findings. It is important to note that this template table may be subject to modification and optimization based on the results of a trial of data extraction from five included studies.

The datasets will be independently extracted and subsequently compared. In situations where discrepancies arise in the extracted data, the investigators, AB and JC, will engage in discussions to reach a consensus and resolve any discrepancies, creating a unified data extraction set. Further relevant data tables may also be developed depending on the literature findings.

Table 1. *Proposed template table for data extraction of pertinent study characteristics.*

Study & Year	Country	Study Design	n=	Mean Age	ARDS Criteria	ARDS Etiology	Proning Protocol	ECMO Circuit	Mean ECMO Time	Adverse Events	Main Findings
Study 1	-	-		-	-	-	-	-	-	-	-
Study 2	-	-		-	-	-	-	-	-	-	-
Study 3	-	-		-	-	-	-	-	-	-	-
Study 4	-	-		-	-	-	-	-	-	-	-
Study 5	-	-		-	-	-	-	-	-	-	-
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3. Limitations and Mitigation Strategies

Limitations

All study designs will have limitations in some form or another, as no study design is perfect. Scoping reviews are known to have several limitations associated with their design despite including methods to include rigour and reproducibility.(17) One potential limitation of this study design is the possibility of bias. Since scoping reviews heavily rely on the judgment and selection criteria of the investigators, this introduces the potential for biased inclusion or exclusion of articles.(20) Search results may vary widely depending on the databases researched, including lack of full-text availability.(20) Importantly, this could lead to the omission of relevant studies or the inclusion of studies with similar findings, thereby affecting the comprehensiveness and validity of this review.

Furthermore, the task of truly identifying all relevant literature may be challenging and unrealistic in nature, as scoping reviews are not intended to be absolutely comprehensive or exhaustive and are often completed due to time constraints and when systematic reviews are not feasible.(20) Thus, determining a balance of breadth and depth of analysis of the available literature is fundamental to the success of a scoping review; however, this may also be a significant challenge depending on the volume of the literature revealed with searching and is highly subject to the proposed research question.(20)

Another limitation of this review, again related to the scoping review study design, is the lack of critical appraisal of included studies, the possible inclusion of low-quality studies, and the depth of critical analysis subsequently possible. Unlike systematic reviews, which critically appraise each included study, scoping reviews aim to provide an overview of the available evidence and typically do not conduct an in-depth analysis of individual studies.(20) Consequently, complex relationships may not be thoroughly explored, and definitive conclusions may be challenging to draw and generalize.

The potential for significant heterogeneity of included studies, including their results and study designs, is another possible limitation of scoping reviews. Scoping reviews often encompass studies with diverse methodologies, populations, and interventions.(20) Such variability can pose challenges in synthesizing the findings and drawing meaningful conclusions. Thus, comparing and contrasting studies with different designs and outcomes may be difficult, potentially impacting the review's overall findings.

Lastly, another limitation of this review is that the included articles for analysis were limited to clinical trials (observational and RCT study designs), systematic reviews, and meta-analyses and did not include any grey literature. Grey literature will not be included within this scoping review for concerns of maintaining transparent literature identification and study reproducibility.

Mitigation Strategies

Several strategies can be employed to mitigate many of the limitations mentioned above. First and foremost, it is crucial to adopt transparent and predefined protocols for a scoping review; this entails clearly defining the research question, inclusion and exclusion criteria, search strategy, screening process,

and all other protocols to be utilized throughout the research.(20) By establishing these protocols in advance, the transparency and reproducibility of the review are enhanced while minimizing the risk of bias. This systematic and rigorous approach to study selection ensures a more objective evaluation. Independent review and consensus also play a vital role in reducing bias and improving the robustness of the review; to accomplish this, two independent reviewers, AB and JC, will be engaged in the screening and selection of studies, with provisions for discussion and consensus in the event of any disagreement.

A comprehensive search strategy is another critical approach to employ. A detailed search strategy involves conducting a systematic and thorough search across multiple databases, utilizing appropriate keywords, synonyms, and controlled vocabulary.(20) Doing so minimizes the risk of omitting important evidence and enhances the comprehensiveness of the review. Furthermore, providing a record of all keywords, search terms, and search results ensures transparency and reproducibility, further enhancing the review's validity. Transparent and clear reporting of study characteristics, including study design, population characteristics, and interventions, also helps mitigate limitations.(20) This strategy enables readers to assess potential diversity and heterogeneity among the included studies while facilitating comprehension of the review's findings.

Considering the heterogeneity of the included studies is also essential. Descriptive summaries, subgroup analyses, or mapping of different study characteristics and findings can address heterogeneity challenges, providing a comprehensive overview of the evidence.(20) Additionally, it is crucial to acknowledge and transparently report the limitations associated with the scoping review methodology.(20) This allows readers to understand the potential impact of these limitations on the findings and conclusions of the review.

Implementing these mitigation strategies addresses and minimizes many limitations commonly associated with scoping review study designs, thus enhancing the validity, transparency, and utility of the review's findings, allowing for a more robust summary of the evidence.

4. Conclusion

To conclude, understanding the effects of prone positioning on adult patients with ARDS on VV-ECMO is crucial for cardiovascular perfusionists. This knowledge empowers perfusionists to optimize patient management, develop evidence-based protocols, anticipate and manage complications, and actively contribute to research efforts. By acquiring this knowledge, perfusionists play an integral role in improving patient outcomes, enhancing safety, and advancing the field of cardiovascular perfusion. Ultimately, this scoping review aims to contribute to the growing evidence base in this field of study, to inform perfusion practice, and to enhance the outcomes of this patient population.

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