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VENTILATOR-INDUCED LUNG INJURY -PREVENTION AND NEW INSIGHTS

Anaesthesiology

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ABSTRACT

Introduction: Ventilator-Induced Lung Injury (VILI) is a significant complication in mechanically ventilated patients, contributing to increased morbidity and mortality. Despite advances in ventilatory strategies, VILI remains a clinical challenge due to the complex interplay of mechanical stress, inflammatory pathways, and individual patient variability. **Aim:** To explore recent insights into the pathophysiology of VILI and evaluate preventive strategies that minimize lung damage during mechanical ventilation. **Methods:** Recent clinical trials, experimental studies, and meta-analyses were reviewed. The included researches were related to the parameter settings of mechanical ventilation, the lung-protective strategies, the indices about the injury, and novel strategies, such as personalized ventilation and pharmacology therapies. **Results:** Increasing evidence focuses on the contribution of low tidal volume ventilation .Advances in ventilatory support with the adjunct of features in newer ventilatory support, as NAVA, and bodies of work in the ECCO2 removal field hold promise to reduce lung injury by decreasing ventilatory stress. Anti-inflammatory treatments and biomarkers, such as IL-6, SP-D and sRAGE, have potential in predicting and preventing VILI. **Conclusion:** Prevention of VILI will necessitate a comprehensive, individualized strategy that incorporates lung-protective ventilator strategies, continued surveillance and evolving treatments. Further studies are needed to develop these strategies in order to decrease the viscious circle represented by VILI in such environments.

KEYWORDS

Ventilator-Induced Lung Injury, Mechanical Ventilation, Lung Protection, ARDS, Driving Pressure, PEEP, Biomarkers, $ECCO_2R$, NAVA.

1. INTRODUCTION

Mechanical ventilation (MV) is a life-saving intervention in patients who are critically ill with acute respiratory failure, especially those with acute respiratory distress syndrome (ARDS).[1] Although necessary, MV paradoxically can be a cause or can exacerbate lung injury - such as Ventilator-Induced Lung Injury (VILI). This iatrogenic complication significantly contributes to the persistently high mortality rates seen among patients with ARDS, which can exceed 30%, with some epidemiologic studies reporting values >40% to 46.1% in severe cases.[2]

Historical Context and Evolution of the VILI Concept

The perception of VILI has evolved over many decades. Early concerns about complications of Ventilation using mechanical means can be traced back to the 1950s during the polio epidemic with the development of what was termed the 'respirator lung syndrome'. 3 It was thought that the significant fractional concentration of inspired oxygen frequently applied to ventilated patients was the primary culprit for injury at that time. 3 In focusing initially on the toxicity of oxygen, attention gradually changed with the advance of investigations. The increasing clarification of the molecular processes of VILI The gradual clarification of the molecular processes underlying VILI continues to guide efforts to reduce lung injury from MV.[3,4]

This study is designed to give an overview of lung harm brought on by a ventilator. It starts with an elaboration of the complex pathophysics of VILI, which is not only about the traditional mechanical forces, but it also involves as modern concepts of biological responses. It then examines based-on-evidence and experimental preventive therapies, such as lung-protective ventilation strategies and adjuvant treatments. Finally, this paper addresses new findings and future perspectives for VILI studies: personalized ventilation strategies, new molecular targets, and current research directions.

Studies suggest that mechanical power, particularly dynamic mechanical power (Powerdynamic) and driving mechanical power (Powerdriving), may be a better predictor of VILI and mortality than individual parameters like tidal volume or the pressure that drives alone.[5] For instance, double-triggered breaths, where a patient's inspiratory effort triggers a second breath before the first exhalation is complete, significantly increase tidal volume, transpulmonary the pressure that drives, and mechanical energy, thus increasing VILI risk.[3,5] Reducing mechanical power, for example, through strategies like lateral-prone ventilation, has shown promise in mitigating VILI risk in A.R.D.S. patients.[6] This holistic approach to quantifying the mechanical insult provides a more comprehensive understanding of VILI risk.

Prevention Strategies For VILI

Knowledge of the intricate pathophysiology of VILI has led to the identification of several preventative measures, among which LPV has taken a lead role.

Lung-Protective Ventilation (LPV): The Cornerstone

Lung-protective ventilation protocols are implemented according to the process of VILI by regulating mechanical stress to prevent overdistension and atelectrauma.[7] This strategy has since undergone major adjustments and has become the current best practice modality in ALI/A.R.D.S. patients.

Low Tidal Volume (LTV) Ventilation

The most impactful and widely adopted strategy to prevent VILI is the use of low tidal volume (LTV) ventilation. The landmark Syndrome of Acute Respiratory Distress Network (A.R.D.S.Net) trial, published in 2000, indisputably demonstrated the survival benefit of LTV ventilation. This multicenter randomized trial, which was halted early because clear efficacy, compared a conventional tidal volume of 12 mL/kg of anticipated weight (PBW) with a 6 mL/kg PBW reduced tidal volume. The LTV group showed a remarkable 22% lower mortality rate (31.0% versus 39.8%) and more days without a ventilator.The rationale behind LTV ventilation is to prevent volutrauma by limiting the overdistension of the baby lung—the relatively small, normally aerated regions of the heterogeneous A.R.D.S. lung. By reducing the tidal volume, the mechanical stretch on these vulnerable areas is minimized.[8] Despite its proven benefits, LTV ventilation can present clinical challenges, such as potential for hypercapnia and patient-ventilator asynchrony, which have contributed to its underutilization in practice. To mitigate these issues, clinicians may need to increase the respiratory rate to maintain minute ventilation and prevent acute hypercapnia, and optimize inspiratory flow and trigger sensitivity settings to limit the work of breathing and dyspnea.40 In cases of severe acidosis (pH < 7.15), the tidal volume can be judiciously titrated upwA.R.D.S. to 8 mL/kg PBW, provided pressure at the plateau remains below 30 cmH2O, to facilitate bicarbonate therapy.9

Pressure at the Plateau Limitation

Closely linked to LTV ventilation is the strategy of limiting inspiratory pressures, specifically the pressure at the plateau (Pplat), which is the pressure measured after a brief inspiratory pause when airflow is zero. The goal is to maintain pressure at the plateau below 30 cmH2O, as recommended by major guidelines.[10]This limit serves as a surrogate for trans pulmonary pressure, aiming to prevent alveolar overdistension (barotrauma and volutrauma)[11]

End-expiratory Pressure that is Positive (P.E.E.P.) Optimization

End-expiratory pressure that is positive (P.E.E.P.) is a critical component of LPV, primarily aimed at preventing atelectrauma by keeping alveoli open and reducing repetitive alveolar collapse and expansion (RACE). By maintaining an adequate end-expiratory lung volume, P.E.E.P. limits the shear pressures produced as lung units open and close cyclically.[12]

Adjunctive Strategies

Beyond the core principles of LPV, several adjunctive strategies are employed to further minimize VILI and improve outcomes in A.R.D.S. patients.

Prone Positioning

Prone positioning (PP), where the patient is placed face down, is a highly effective adjunctive therapy for severe A.R.D.S., strongly recommended for more than 12 hours a day.[13] Its benefits stem from improving oxygenation and, crucially, reducing VILI

Reduction in Inflammatory Mediators: PP can reduce the expression of inflammatory mediators, contributing to a decrease in biotrauma.

Neuromuscular Blockade (NMBAs)

Neuromuscular blocking agents (NMBAs) are drugs that induce reversible muscle paralysis by blocking transmission at the neuromuscular junction.[14] In the context of A.R.D.S., NMBAs are used adjunctively to deep sedation to facilitate Ventilation using mechanical means, improve patient-ventilator synchrony, and minimize VILI.20 By paralyzing the diaphragm and other respiratory muscles, NMBAs prevent active expiration and breath stacking, which can otherwise lead to expiratory atelectasis and increased VILI risk.[14]

NMBAs are thought to reduce barotrauma, volutrauma, and atelectrauma by allowing better control of tidal volume and the pressure that drives, ensuring provision of the intended lung-protective strategy.[39] Current understanding suggests that NMBAs may be most beneficial when integrated into a comprehensive bundle of Ventilation using mechanical means care, including P.E.E.P. optimization, sedation as well as lying prone, especially in patients with severe A.R.D.S. and intense central respiratory drive that precludes lung-protective ventilation.[16]

Oxygenation of the Extracorporeal Membrane (ECMO)

Oxygenation of the extracorporeal membrane (ECMO) acts as a life-saving treatment for those with severe A.R.D.S. who do not improve with conventional lung-protective strategies and remain hypoxemic.[17] ECMO provides full blood oxygenation and CO2 elimination outside the body, thereby allowing the lungs to rest and heal by enabling extremely low tidal volumes and extremely protective ventilation settings and airway pressures.[18] Theoretically, this minimizes all three VILI mechanisms (volutrauma, atelectrauma, biotrauma) by reducing excessive stress and strain on lung tissue.[19]

The efficacy of venovenous ECMO in severe A.R.D.S. has been evaluated in several trials. The CESAR trial showed that transfer to an ECMO center was associated with fewer deaths or severe disabilities.[20] The more recent EOLIA trial, while showing a non-statistically significant reduction in 60-day mortality, contributed to a meta-analysis that demonstrated ECMO group's 60-day mortality rate was much lower than conventional Ventilation using mechanical means (34% vs. 47%). A meta-analysis of data from specific patients further confirmed that ECMO significantly lowered 90-day mortality in severe A.R.D.S. and resulted in more days alive out of the ICU and without organ failure. Despite its benefits, ECMO is associated with significant risks, most notably a moderate risk of major hemorrhage.52 ECMO represents a crucial bridge to recovery for patients at high risk of VILI, allowing the lungs to recuperate while maintaining adequate gas exchange.[21]

Novel Perspectives and Prospects for VILI Research

Recent advancements in VILI research have deepened the understanding of its pathophysiology, paving the way for more personalized and targeted therapeutic approaches.

Personalized Ventilation Approaches

Recognizing that VILI risk and optimal ventilator settings vary significantly among patients due to differences in injury etiology and individual pathophysiology, research has shifted towA.R.D.S. personalized ventilation strategies. The goal is to adaptively adjust ventilator settings to match individual lung mechanics and minimize VILI, rather than applying a one-size-fits-all approach.

Esophageal Pressure Monitoring

Esophageal pressure (Pes) monitoring is a minimally invasive technique that provides a surrogate for pleural pressure, enabling the estimation of trans pulmonary pressure (PL).[22] Trans pulmonary pressure is a direct measure of lung stress, representing the true distending force applied to lung structures.34 By monitoring Pes, clinicians can differentiate between lung and chest wall mechanics, which is crucial in conditions like chest wall edema or intra-abdominal hypertension where increased chest wall elastance can lead to substantial differences between airway pressure and trans pulmonary pressure.[23]

Esophageal pressure monitoring allows for individualized P.E.E.P. titration, aiming for a slightly positive end-expiratory trans pulmonary pressure (near 0 cmH2O) to prevent atelectrauma without causing overdistension.20 Studies have shown that Pes monitoring can improve the accuracy of P.E.E.P. titration and reduce the risk of VILI.20 This approach helps to ensure that the mechanical forces are within a healthy, normal range, minimizing both overdistension and atelectrauma[24]

Electrical Impedance Tomography (EIT)

Electrical Impedance Tomography (EIT) is a non-invasive, radiation-free bedside tool that provides real-time imaging of regional lung ventilation and its distribution.[25] EIT is particularly valuable in A.R.D.S. patients, where lung heterogeneity makes global measurements insufficient.[26] It allows for patient-specific and regional assessment of P.E.E.P. effects on lung recruitability (collapsed units that can be opened) and overdistension (already open units that become excessively stretched).

Molecular and Cellular Targets

Advances in understanding the molecular mechanisms underlying VILI have unveiled several potential targets for therapeutic intervention, moving beyond purely mechanical adjustments.

Stretch-Activated Ion Channels: Via stretch-activated or -inactivated ion channels, physical forces acting on cell membranes can alter the permeability of different ions. These channels mediate the influx of ions like Ca2+ and Na+, converting physical stimuli into electrical or chemical signals. While their precise role in VILI is still being elucidated, some studies suggest that blocking these channels, for example with gadolinium, can prevent high airway pressure-induced permeability increases.[27]

Extracellular Matrix-Integrin-Cytoskeleton Complex: The complex interplay between the extracellular matrix, integrins (transmembrane receptors), and the intracellular cytoskeleton is fundamental to mechanosensation.29 Physical forces transmitted through this complex can activate or inactivate signaling-related enzymes, altering intracellular signal transduction processes.[28] Understanding these protein-protein interactions could lead to strategies that modulate the cellular response to mechanical stress.

Mitochondrial Dysfunction

Mitochondrial dysfunction is increasingly recognized as a vital component in the pathogenesis of VILI. It is characterized by mitochondrial depolarization and can lead to an increase in reactive oxygen species (ROS), oxidative stress, and chronic inflammation.

Novel Biomarkers

The identification of reliable biomarkers is crucial for early diagnosis, risk stratification, and guiding personalized interventions. Secreted extracellular cyclophilin A (CypA) has been identified as a potential biomarker and mediator of VILI. Overventilation can cause CypA secretion from stretched alveolar epithelial cells, which then acts as a

proinflammatory cytokine by activating receptors like CD147 and TREM-2 on immune cells, triggering alveolocapillary barrier failure and impaired lung function.55 Preclinical studies have shown that CypA blockade can improve survival and reduce lung injury parameters in overventilated mice. This suggests CypA could serve as a theragnostic (both biomarker and therapeutic target), especially if interventions are initiated early in the disease course.[29]

New Insights and Challenges

VILI research continues to evolve, with significant trends focusing on refining experimental models, translating findings to clinical practice, and leveraging advanced technologies.

Preclinical Models

Preclinical animal models are indispensable for dissecting VILI mechanisms and testing novel therapies. Researchers utilize a range of species, from rodents to larger animals like sheep and pigs, employing strategies that mimic aspects of patient treatment. Large-animal models are particularly useful for exploring the effects of gravity on VILI development, which is difficult in smaller animals.However, existing small-animal models often face criticism due to the combination of supraphysiological high tidal volumes and short study durations (e.g., 3-4 hours) compared to human ventilation periods that can last for days. While high tidal volumes (e.g., >30 ml/kg) or pressure at the plateaus (>27 cmH2O) are needed to induce inflammatory VILI in mice within short timeframes, studies extending ventilation to 16 hours still show lung deterioration even with low tidal volumes. This suggests that there may be no single safe threshold below which ventilation is entirely benign, and that cumulative injury can occur even with seemingly protective settings.A significant finding from preclinical research, corroborated by patient samples from the ARMA trial, is the observation that inflammatory mediators, such as IL-6, are increased with higher tidal volumes and correlate with lung mechanics deterioration, particularly in non-surviving animals/ patients.58 This supports the biotrauma hypothesis of VILI, suggesting that inflammation contributes actively to injury rather than being a mere bystander, and that individual immune system sensitivity to the insult of ventilation may be a critical determinant of survival.[30]

Clinical Trials

Translating promising preclinical findings into clinical benefits remains a significant challenge. While many studies have investigated protective ventilation strategies, few have shown clear survival benefits beyond the initial A.R.D.S.Net trial.43 Recent clinical trials continue to explore various aspects of VILI prevention. For example, the PREVENT VILI trial is a phase III multicenter randomized trial evaluating a novel individualized ventilation strategy that aims to minimize lung stress by targeting end-expiratory trans pulmonary pressure near 0 cmH2O and the pressure that drives below 12 cmH2O.10 This trial seeks to determine if precise ventilator titration, compared to guided usual care, can improve survival and pulmonary recovery in A.R.D.S. patients.[31]

Another area of ongoing clinical investigation is the impact of different ventilation modes (e.g., pressure control vs. volume control) on VILI risk, particularly in intraoperative settings.38 These trials aim to identify the most effective approaches in minimizing lung injury and postoperative pulmonary complications.38 The challenge lies in designing trials that can capture subtle benefits, account for patient heterogeneity, and overcome the inherent difficulties of implementing complex ventilation strategies in clinical practice.

Omics Technologies

The integration of omics technologies, including genomics, transcriptomics, and proteomics, represents a cutting-edge trend in VILI research. These high-throughput approaches enable a comprehensive understanding of the molecular mechanisms underlying VILI by analyzing vast amounts of biological data.

Genomics: Identifying genetic markers associated with an increased risk of VILI could help in stratifying patients for specific interventions and personalizing treatment.24 Pharmacogenomics, which studies how genetic variations affect drug response, could lead to more effective and safer pharmacological therapies for VILI.

Transcriptomics and Proteomics: Analyzing gene expression patterns (transcriptomics) and protein profiles (proteomics) provides insights into the cellular responses to mechanical stress and inflammation in VILI.22 This can reveal novel biomarkers for early detection and monitoring, as well as identify new therapeutic targets by pinpointing dysregulated pathways.

By providing a holistic view of the biological processes involved, omics technologies hold the potential to revolutionize VILI research, leading to the development of highly targeted and personalized medicine strategies to prevent and treat this critical complication

DISCUSSION

Lung Injuries Caused by Ventilators VILI remains a significant and complex challenge in critical care, paradoxically arising from a life-sustaining intervention. The evolution of understanding VILI has progressed from initial recognition of macroscopic barotrauma to a nuanced appreciation of volutrauma, atelectrauma, and crucially, biotrauma—a systemic inflammatory response driven by mechanical forces. This integrated view highlights VILI as a multifactorial condition involving intricate interactions between mechanical stress, cellular deformation, and biological signaling pathways, leading to local lung damage and distant organ dysfunction.

The basis of VILI prevention is lung-protective ventilation (LPV) which involves low tidal volumes and strict reduction of pressure at the plateau. The landmark A.R.D.S.Net trial conclusively proved the survival advantage of this approach. Subsequent trials failed repeatedly to show more survival benefit by applying high P.E.E.P. at an individual level, creating space for thinking of personalized strategies. The transition of the pressure that drives as a better predictor of the risk of VILI has evolved LPV and emphasized the role of dynamic strain on lung.

Novel discoveries are shifting the paradigm of VILI treatment to precision medicine. Advanced monitoring strategies, such as esophageal pressure monitoring and electrical impedance tomography (EIT), additionally provide real-time personalized evaluation of lung mechanics for individualized P.E.E.P. titration and ventilation changes. Meanwhile, the mechanism of VILI at molecular and cellular levels has been identified, thus providing potential therapeutics. Approaches to target inflammation, mechanotransduction pathways and mitochondrial dysfunction are under investigation; extracellular CypA as a candidate biomarker provides leads for individualized therapies.

CONCLUSION

Preventing VILI requires an integrated, patient-specific approach that combines protective mechanical ventilation strategies with ongoing monitoring and evolving therapeutic modalities. VILI remains a significant challenge, but a deeper understanding of its pathophysiology and the evolution of lung-protective strategies are paving the way for improved patient care. Continued research is essential to refine these strategies and reduce the burden of VILI in critical care settings. Future directions involve integrating advanced monitoring techniques and personalized ventilation protocols to minimize lung injury while optimizing gas exchange.

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