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Research Article

Impact of Low Tidal Volume Ventilation on Inflammatory Biomarkers in Sepsis-Induced ARDS

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Abstract: Sepsis-induced acute respiratory distress syndrome (ARDS) is characterized by excessive pulmonary and systemic inflammation, contributing to high morbidity and mortality. Mechanical ventilation is a lifesaving intervention but may exacerbate inflammatory injury through ventilator-induced lung damage. This prospective interventional study evaluated the impact of low tidal volume ventilation on inflammatory biomarker profiles in patients with sepsis-induced ARDS. A total of 168 mechanically ventilated patients were allocated to either low tidal volume ventilation (6 mL/kg predicted body weight) or conventional ventilation (10 mL/kg). Plasma levels of interleukin-6, tumor necrosis factor-α, interleukin-8, and C-reactive protein were measured at baseline and after 72 hours. Patients receiving low tidal volume ventilation demonstrated a significant reduction in interleukin-6 (from 214.6 ± 78.3 pg/mL to 132.9 ± 55.4 pg/mL; $p < 0.001$) and tumor necrosis factor-α ($p = 0.002$) compared to the conventional group. Improved oxygenation indices and reduced ventilator days were also observed. These findings indicate that lung-protective ventilation attenuates systemic inflammation in sepsis-induced ARDS. This study provides novel biomarker-based evidence supporting the immunomodulatory benefits of low tidal volume strategies beyond their established physiological advantages.

Keywords: sepsis-induced ARDS; low tidal volume ventilation; inflammatory biomarkers

Introduction: Sepsis remains a major global health challenge and is a leading precipitant of acute respiratory distress syndrome, a severe form of hypoxemic respiratory failure associated with diffuse alveolar damage and dysregulated inflammation. Sepsis-induced ARDS is distinguished by heightened systemic cytokine release, endothelial dysfunction, and increased alveolar-capillary permeability, resulting in impaired gas exchange and multiorgan involvement. Despite advances in supportive care, mortality rates remain unacceptably high, underscoring the need for optimized therapeutic strategies.[1-3]

Mechanical ventilation is central to the management of ARDS, providing essential respiratory support during acute lung injury. However, inappropriate ventilatory settings

can amplify lung damage through excessive alveolar stretch, cyclic atelectasis, and biotrauma. Ventilator-induced lung injury has been increasingly recognized as a contributor to systemic inflammation, propagating cytokine release beyond the lungs and exacerbating organ dysfunction in septic patients.[4-5]

Low tidal volume ventilation emerged as a lung-protective strategy designed to minimize volutrauma and barotrauma by limiting alveolar overdistension. While its survival benefit in ARDS is well established, the biological mechanisms underlying this benefit continue to be explored. Experimental and clinical evidence suggests that lung-protective ventilation may reduce the release of pro-inflammatory mediators, thereby attenuating the systemic inflammatory response associated with sepsis.[6-7]

Inflammatory biomarkers such as interleukin-6, tumor necrosis factor-α, and interleukin-8 play a pivotal role in the pathophysiology of sepsis-induced ARDS. Elevated levels of these cytokines correlate with disease severity, ventilator dependence, and mortality. Monitoring changes in these biomarkers provides insight into the inflammatory burden and the biological impact of therapeutic interventions. However, prospective data directly linking ventilatory strategies to biomarker modulation in sepsis-induced ARDS remain limited.

Most available studies evaluating low tidal volume ventilation have focused primarily on clinical outcomes such as mortality, ventilator-free days, and oxygenation indices. While these endpoints are clinically important, they provide limited understanding of the underlying inflammatory processes. Biomarker-based evaluation offers an opportunity to elucidate mechanistic pathways and refine personalized ventilation strategies for septic patients.[8-12]

In low- and middle-income settings, sepsis-induced ARDS often presents with advanced disease severity, delayed intervention, and limited access to adjunctive therapies. Understanding how modifiable factors such as ventilatory parameters influence inflammatory pathways is particularly relevant in these contexts. Evidence demonstrating biomarker modulation through low-cost interventions such as ventilator adjustment could have significant clinical implications.

This prospective study was designed to evaluate the effect of low tidal volume ventilation on systemic inflammatory biomarkers in patients with sepsis-induced ARDS. By integrating biochemical and physiological outcomes, the study aims to provide novel evidence supporting the immunomodulatory role of lung-protective ventilation strategies and to inform evidence-based critical care practices.

Methodology: This prospective interventional study was conducted at Government Khawajah Muhammad Safdar Medical College over a 14-month period from February 2023 to March 2024. Adult patients aged 18 years or older admitted with sepsis-induced ARDS requiring invasive mechanical ventilation were consecutively enrolled. Sepsis and ARDS were diagnosed according to internationally accepted clinical and radiological criteria. Verbal informed consent was obtained from the patient's legally authorized representative prior to enrollment.

Patients were allocated into two ventilation strategy groups based on the initial ventilatory protocol applied within the first six hours of ARDS diagnosis. The low tidal volume group received ventilation at 6 mL/kg predicted body weight with plateau pressures maintained below 30 cm H_2O, while the conventional ventilation group

received tidal volumes of 10 mL/kg with standard pressure limits. Positive end-expiratory pressure and fraction of inspired oxygen were adjusted according to standardized oxygenation targets in both groups.

Sample size calculation was performed using Epi Info software, assuming a mean difference of 60 pg/mL in interleukin-6 levels between groups, a standard deviation of 120 pg/mL, a 95% confidence interval, and 80% statistical power. The minimum required sample size was calculated as 154 patients; a total of 168 patients were included to compensate for early mortality and incomplete sampling.

Blood samples were collected at baseline (within 6 hours of ventilation initiation) and after 72 hours. Plasma concentrations of interleukin-6, tumor necrosis factor-α, interleukin-8, and C-reactive protein were measured using standardized enzyme-linked immunosorbent assay techniques. Clinical data collected included oxygenation indices, ventilator days, intensive care unit length of stay, and in-hospital mortality.

Inclusion criteria comprised confirmed sepsis, diagnosis of ARDS, and requirement for invasive mechanical ventilation. Exclusion criteria included pre-existing chronic lung disease, immunosuppressive therapy, pregnancy, advanced liver disease, and expected survival less than 24 hours. Statistical analysis was performed using independent t-tests, paired t-tests, and multivariate linear regression. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Low Tidal Volume (n = 84)	Conventional Ventilation (n = 84)
Age (years)	56.2 ± 14.1	55.7 ± 13.6
Male (%)	49 (58.3)	51 (60.7)
APACHE II score	22.8 ± 5.3	23.1 ± 5.1
PaO_2/FiO_2 ratio	148.6 ± 32.4	146.9 ± 30.8

This table shows comparable baseline severity and demographic characteristics between groups.

Table 2. Changes in Inflammatory Biomarkers at 72 Hours

Biomarker	Low Tidal Volume	Conventional Ventilation	p-value
Interleukin-6 (pg/mL)	132.9 ± 55.4	198.7 ± 69.2	<0.001
TNF-α (pg/mL)	41.3 ± 16.8	57.6 ± 19.1	0.002
Interleukin-8 (pg/mL)	89.5 ± 34.2	121.4 ± 40.7	0.001

Biomarker	Low Tidal Volume	Conventional Ventilation	p-value
CRP (mg/L)	86.2 ± 28.5	112.7 ± 35.4	0.003

This table demonstrates significantly lower inflammatory biomarker levels in the low tidal volume group.

Table 3. Clinical Outcomes

Outcome	Low Tidal Volume	Conventional Ventilation	p-value
Ventilator days	7.4 ± 3.1	10.2 ± 4.5	<0.001
ICU stay (days)	9.8 ± 4.2	13.1 ± 5.6	0.002
28-day mortality (%)	29.8	42.9	0.041

This table highlights improved clinical outcomes associated with low tidal volume ventilation.

Discussion: The results of this prospective study demonstrate that low tidal volume ventilation significantly attenuates systemic inflammatory responses in patients with sepsis-induced ARDS. Patients managed with lung-protective ventilation exhibited marked reductions in key pro-inflammatory cytokines, including interleukin-6, tumor necrosis factor-α, and interleukin-8. These findings provide mechanistic insight into the biological benefits of low tidal volume strategies beyond their established effects on lung mechanics.[13-15]

Interleukin-6 plays a central role in the inflammatory cascade of sepsis and has been consistently associated with disease severity and mortality. The substantial reduction in interleukin-6 levels observed in the low tidal volume group suggests that minimizing alveolar overdistension reduces cytokine spillover from the lungs into systemic circulation. This supports the concept of biotrauma as a modifiable contributor to systemic inflammation in mechanically ventilated patients.[16-17]

The observed decrease in tumor necrosis factor-α further underscores the immunomodulatory effect of lung-protective ventilation. Tumor necrosis factor-α is a key mediator of endothelial activation and capillary leak, processes that are central to ARDS pathophysiology. Attenuation of this cytokine may partially explain the improved oxygenation and reduced ventilator dependence noted in the low tidal volume group.[18-19]

Interleukin-8, a potent neutrophil chemoattractant, was also significantly lower in patients receiving lung-protective ventilation. Reduced neutrophil recruitment may limit ongoing alveolar injury and contribute to faster resolution of lung inflammation. The concomitant reduction in C-reactive protein reflects a broader

dampening of the systemic inflammatory response.[20]

Clinical outcomes observed in this study align with biomarker findings. Reduced ventilator days, shorter intensive care unit stays, and lower mortality rates in the low tidal volume group suggest that inflammatory modulation translates into meaningful clinical benefit. These outcomes are particularly relevant in sepsis-induced ARDS, where prolonged ventilation and ICU stay are associated with high complication rates.

The strengths of this study include its prospective design, standardized ventilation protocols, and integration of biochemical and clinical outcomes. Limitations include the single-center setting and lack of long-term follow-up beyond hospital discharge. Future studies incorporating multicenter cohorts and longitudinal biomarker assessment are warranted.

Overall, the findings reinforce the role of low tidal volume ventilation as both a lung-protective and immunomodulatory intervention in sepsis-induced ARDS. Incorporating biomarker-guided evaluation may further optimize ventilatory strategies and patient outcomes.

Conclusion: Low tidal volume ventilation significantly reduces systemic inflammatory biomarkers and improves clinical outcomes in sepsis-induced ARDS. This study provides novel prospective evidence supporting the immunomodulatory role of lung-protective ventilation strategies. The findings address a critical mechanistic gap and reinforce the importance of ventilation optimization in septic critical care.

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