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Review

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Management of Acute Kidney Injury in the Setting of Acute Respiratory Distress Syndrome: Review Focusing on Ventilation and Fluid Management Strategies

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Abstract

Acute respiratory distress syndrome (ARDS) is a major cause of mortality in adults with acute hypoxic respiratory failure and can predispose those afflicted to develop acute kidney injury (AKI). In the setting where AKI and ARDS overlap, incidence of mortality, length of intensive care unit stay, and complexity of management increases drastically. Lung protective ventilation strategy and conservative fluid management are the main focus of therapy in patients with ARDS, but have major implications on renal function. This review aims to provide concise discussion of pathophysiology, ventilation, and fluid management strategies as it relates to AKI in the setting of ARDS.

Keywords: Acute respiratory distress; Acute kidney injury; Acute lung injury; Ventilation strategy

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by severe hypoxemia due to respiratory failure that was first described as the "shock lung" by military clinicians in Vietnam in the 1960s [1]. This heterogeneous pathology is now understood to be the cause of death in nearly 200,000 people in the USA each year [2]. While there are many complications that results from ARDS, the development of an acute kidney injury (AKI) is common and can be fatal in these patients. Over the past decade, significant advances have been made to understand the pathophysiology of ARDS and complications such as AKI. This article discusses the management of AKI in the setting of ARDS, and highlights its epidemiology, pathophysiology and treatment strategies for internists and intensivists alike.

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Definitions

Acute lung injury (ALI) has been defined as acute lung disease that consists of acute hypoxemic respiratory failure, specifically with ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) of less than 300 mm Hg with bilateral pulmonary infiltrates due to pulmonary and non-pulmonary risk factors, and which is not due to left atrial hypertension as per the American/European Consensus Conference definition [2, 3]. This definition created a distinction between ALI and ARDS based on PaO_2/FiO_2 ratio with ARDS categorized as being < 200 mm Hg and thus more severe. ARDS was redefined in 2012 and clarifies several uncertain areas not explained by the American/European Consensus conference definition [4]. As per the Berlin definition, ARDS can be diagnosed once cardiogenic pulmonary edema and alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates have been excluded [5]. The Berlin definition of ARDS requires that for the diagnosis to be present all the criteria listed in Table 1 [5] must be present.

For the sake of clarity, this review uses ALI and ARDS interchangeably as to include all patients with a PaO_2/FiO_2 less than 300 mm Hg. In our discussion of AKI, Kidney Disease: Improving Global Outcomes (KDIGO) recommendations for classification of AKI, AKI is defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h, or an increase of serum creatinine to ≥ 1.5 times the baseline, which is known to have occurred in the patient within the last 7 days, or a decrease in urine volume of < 0.5 mL/kg/h for 6 h [4]. The literature we review here includes articles published after 2012 and uses KDIGO recommendations for classification for AKI.

Epidemiology

ARDS has a huge impact on mortality. The Kings County Lung Injury Project (KCLIP) studied the incidence and out-

Table 1. Diagnostic Criteria for Diagnosis of ARDS (Adapted From the Berlin Definition [5])

Timing: Respiratory symptoms must have an onset within 1 week of known primary insult.
Chest imaging: Includes bilateral opacities not fully explained by effusions, lobar collapse, lung collapse, or nodules on chest X-ray or computed tomographic scan.
Cause of edema: Not fully explained by cardiac cause or fluid overload states with evidence from objective assessment and diagnostic tools required (i.e., echocardiography).
Severity assessment of hypoxemia using ratio of arterial oxygen tension to fraction of inspired oxygen:
Mild: PaO_2/FiO_2 > 200 mm Hg but ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Moderate: PaO_2/FiO_2 > 100 mm Hg but ≤ 200 mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Severe: PaO_2/FiO_2 ≤ 100 mm Hg with PEEP or CPAP ≥ 5 cmH_2O

comes of ALI and had emphasized 75,000 deaths from ALI in the USA each year [6]. These data are comparable to deaths from human immunodeficiency virus (HIV) and breast cancer [6]. Studies have also shown that patients with ARDS who develop AKI demonstrate increased all-cause mortality. Cooke et al found that the relative risk of death from ARDS in patients with oliguric renal failure was 1.97, where oliguric renal failure was defined as production of ≤ 500 mL of urine in a 24-h period and a serum creatinine of ≥ 2.0 on the day of onset [6]. As seen in the ARDSNet trial, patients with AKI and ARDS had close to 2 times the mortality of that seen with ARDS alone (58% among subjects with AKI compared to 28% without AKI ($P < 0.001$)) [7]. Newly theorized risk stratified scoring systems have found patients with severe ARDS with hypertension, elevated aspartate aminotransferase levels, and elevated D-dimers had higher risk of developing AKI, and higher risk of mortality [8]. Unfortunately, to gauge a proper understanding of epidemiological trend across multiple studies is difficult as there are multiple barometers of AKI utilized that differ from KDIGO recommendations.

Pathophysiology

The exact underlying mechanism for AKI in patients with ARDS is an area of intense research, because it is not yet clearly understood. Previous studies have demonstrated that AKI in the setting of ARDS tremendously increases mortality [9]. Adult studies in patients with ARDS have found that 35% patients end up developing AKI [10]. In one study by Darmon et al, the mortality in patients who have ARDS and AKI was 42.3%, while that in patients without AKI was 20% [11].

There have been some studies that attempt to explain the pathophysiology of AKI in ARDS. The three main possible mechanisms are mechanical ventilation, hypoxemia and systemic inflammation [11]. However, among these three factors, mechanical ventilation appears to be the most significant event. Mechanical ventilation leads to a cascade of events in multiple organs, including kidney, which eventually leads to AKI thus increasing mortality. There have also been multiple studies that showed that mechanical ventilation can independently cause AKI [12-14].

In one study in a pediatric population, multiple aspects of mechanical ventilation were evaluated as potentially increasing risk for AKI in ARDS: peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), mean airway pressure (MAP) and tidal volume (TV). However, only PEEP was independently associated when adjusted for potential confounders. This association has been reported in multiple previous studies as well [15]. A systematic review and meta-analysis by van Der Akker and his team showed the mechanical ventilation in patients with ARDS increases the risk of developing AKI by almost 3 times. But this analysis failed to identify association of PEEP or TV with AKI [14]. Evidence also indicated that barotrauma caused by high pressure ventilation, not only has potential to injure the lung, but also causes systemic inflammation and organ dysfunction due to release of inflammatory cytokines. Several cytokines such as tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), interleukin-1B (IL-1B), IL-6, and IL-8 have been identified with higher rates of AKI [7, 16, 17].

In an experimental lung model, Imai and his team found that high alveolar pressures, which occur in the setting of high PEEP, increase incidence of programmed cell death in renal tubules, which might lead to AKI [18]. The consequence of these elevated pressure alter the hemodynamic of the heart, which in turn affects the homeostasis of the kidney. Positive pressure ventilation decreases venous return to the heart, which alters the cardiac preload, pulmonary vascular resistance and afterload to the right side of the heart. All these hemodynamic changes eventually lead to decreased perfusion to all the organs in the body, especially kidneys, leading to reduced glomerular filtration rate (GFR) and AKI [19].

Ventilation Strategies of ARDS and AKI

Breakthrough studies have shown the benefits of low TV ventilation strategies in the treatment of ARDS. ARDSNet trials performed in the 2000s pivoted the change in the ventilation management of patients in ARDS [20]. Low TV ventilation, described as 6 mL/kg TV based on ideal body weight, decreased mortality, duration of intensive care unit (ICU) days, duration of ventilation, and incidence of non-pulmonary organ injury [20]. In one of the studies, non-pulmonary organ injury defined renal failure as serum creatinine concentration of at least 2 mg/dL. Onset of renal failure took longer in low TV ventilation strategy when compared to traditional TV ventila-

tion (P = 0.005) [20]. Benefits of low TV ventilation strategy are seen with mild hypercarbia which can be renal protective but can be complicated with exacerbation of severe metabolic acidosis leading to hemodynamic instability [21]. Studies have demonstrated that higher TVs were associated with increased levels of TNF-α, IL-1B, IL-6, and IL-8, with higher rates of AKI or higher number of days with AKI [22]. Moreover, animal models have shown that exposure to moderate hypercapnia ($PaCO_2$ 80 - 100) is more favorable with less inflammatory injury than animals with severe hypercapnia ($PaCO_2$ of 130 - 150) due to the inhibition of NF-kB expression during increasing levels of hypercapnia [23].

There is still mounting evidence to suggest that increasing deleterious effects of lung dysfunction, its treatment strategies, and subsequent kidney injury explains the natural progression of multi-organ failure seen in critically ill patients. Elevated PEEP, well documented to be beneficial in ARDS management, can also alter hemodynamic changes as it relates to venous return, cardiac afterload, thus decreasing cardiac output along with renal blood flow [15]. Cardiorenal interactions studied by Annat et al has shown that increasing PEEP (PEEP of greater than 10 cm H_2O) leads to significant reductions in urinary output, renal blood flow, sodium excretion, and potassium excretion [21]. These changes were reversed when PEEP was withdrawn. In contrast, studies have also shown ventilation using higher volume and low levels of PEEP lead to increase epithelial injury in nephrons due to a correlation between Fas ligand changes and serum creatinine changes [18]. A large meta-analysis performed in 2013 exhibited a 3-fold increase in the risk of AKI in both ARDS and mechanical ventilation [24, 25]. Data have shown independent associations between ARDS and mechanical ventilation to AKI [24]. Thus these studies have proposed that ARDS and mechanical ventilation be listed as risk factors of AKI. A secondary analysis of a multi-center observational study has shown that the presence of AKI was associated with prolonged duration of mechanical ventilation [25]. Patients who received higher TVs on day 1 to 3 upon intubation for ARDS had significantly higher risk of renal nonrecovery [26]. Comparatively, use of lower TVs over the first 3 days of patients diagnosed with ARDS was significantly associated with renal recovery [26]. Long-term consequences of ventilation strategies in the treatment of ARDS to renal physiology remain to be determined [11].

Fluid Management in ARDS and Renal Perfusion

Often patients with ARDS are given liberal amounts of fluids for management of the underlying cause of systemic injury (e.g. sepsis, trauma, other organ pathology). Initial phases of these conditions necessitate large volume resuscitation in order to achieve and maintain hemodynamic stability [24]. After the return of hemodynamic stability, administration of additional volume has been shown to be detrimental [27]. Inability to preserve lower fluid balance after hemodynamic stability was found to be an independent mortality risk factor in patients who developed ALI in the setting of septic shock [27]. Compared to the use of liberal fluid strategies, conservative use of normal saline by achieving a negative fluid balance improved oxygenation index, lung injury as well as decreased length of stay in the ICU [28]. Increased renal perfusion with liberal fluid management did not offset the worsening of lung function. There was also less reported use of dialysis in the first 60 days with the conservative fluid strategies. This trial, also known as Fluid and Catheter Treatment Trial (FACTT) study, also showed that administration of intravenous (IV) fluids to shock-free patients did not lead to improvement of kidney function, but only lead to delay in the resolution of lung injury [28]. Overall, the results of this study favored the use of a conservative fluid strategy for critically ill patients with ARDS.

Continuous renal replacement therapy (CRRT) in ARDS

CRRT has been used as a modality for renal support in critically ill patients in the ICU setting [29]. Continuous venovenous hemofiltration (CVVH) is a CRRT that combines clearance, diffusion, and convection, allowing for the extraction of fluids and electrolytes from a patient's blood [30]. This modality has been useful in removing key humoral mediators of systemic inflammatory response by convection and absorption. Studies have shown the existence of therapeutic benefits of CRRT in patients with ARDS [31]. With the compromised alveolar-capillary barrier function in patients with ARDS, CRRT is beneficial for extracorporeal treatment in maintaining goals for conservative fluid strategy [29]. CRRT is also beneficial in eliminating inflammatory mediators that contribute to the pathogenesis of ARDS. As discussed above, TGF-β1 is a key mediator for impeding development ARDS in patients [32]. TGF-β1 concentrations have been reported to be substantially elevated in lung fluids in patients with ALI and ARDS [33, 34]. Studies have also shown that after initiation of CRRT, TGF-β1 concentrations decreased and were associated with clinical improvement of outcomes in patients based on PaO_2/FiO_2 ratios [29]. Data support findings which show that decreased TGF-β1 concentrations are associated with more ventilator-free days and ICU-free says [35]. Use of CRRT, when initiated early, is associated with a 28% mortality risk reduction in patients with AKI in the ICU setting [36]. This statistic was not reproduced in the setting of severe ARDS due to influenza A. In a study looking at the outcomes of AKI in patients with severe ARDS due to influenza A, the need for CRRT was associated with increased mortality [26]. In this population, vasopressor use and duration was associated with CRRT utilization and with increased mortality [37].

However, due to the limitations underlying the results of these studies, conclusions for practical use warrants reexamination. There still exists variability in the defining ARDS in subset of studies as many still use the 1994 American-European consensus definition for ARDS, as opposed to the most current Berlin ARDS definition [29]. Several inflammatory markers are involved in the development of ARDS in patients, not all of which have been examined with CRRT. Overall, multifactorial benefit with the use of CRRT for the

treatment of AKI in the setting of ARDS does merit discussion.

Conclusions

AKI in conjunction with ARDS increases mortality drastically. Modalities used to treat ARDS also have a pronounced effect in causing kidney injury. This review aims to provide a concise understanding on the intricacies of managing AKI in the setting of primary ARDS as it relates to low TV ventilation and fluid restriction strategies for internists and intensivists alike. Future studies that focus on the cause of death in patients with AKI with ARDS may improve the overall care in this critically ill population.

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Conflict of Interest

The authors have no conflict to disclose.

Author Contributions

VU and MS conceived the presented idea and wrote the initial draft with the support from AA, MH, RM, and TV, whom were involved in literature review, critical analysis, and in reviewing and editing the final manuscript.

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