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RESEARCH **REVIEW ARTICLE**

Acute Kidney Injury in ARDS: Insights into Physiology and Pathology

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ABSTRACT

Acute kidney injury is a commonly encountered problem in critically ill patients. It is often part of the multi-system organ failure syndrome, where other organs, such as the lungs, are involved. In the intensive care unit patient, primary pathology in one organ can affect other organs, and systemic illness can affect multiple organs at the same time. In this review article, we closely examine the definition and stages of dysfunction in the lungs and kidneys and the relationship between the physiology and pathology of these two organs as they interact and affect each other in critically ill patients. We also seek to understand the effects common intensive care unit interventions have on both those organs, with a special emphasis on external life support devices such as mechanical ventilation, dialysis, and extracorporeal membranous oxygenation.

KEYWORDS - AKI, ARDS, pulmonary, renal, mechanical ventilation

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AKI/ARDS DEFINITION

Acute respiratory distress syndrome (ARDS) is a type of acute progressive hypoxemic respiratory failure characterized by acute severe difficulty in breathing and low oxygen levels. Individuals with ARDS display widespread bilateral opacities on lung images (such as lung radiography or thoracic computed tomography), along with hypoxemia. ARDS was first described in 1967 when Asbaugh et al. observed acute respiratory distress in 12 patients (1). Subsequently, the definition of ARDS has undergone several revisions. The current definition of ARDS is based on the criteria established in the Berlin definition of 2012 (2). The key components of the Berlin definition are as follows:

1. Timing: ARDS is defined as the development of new or worsening respiratory symptoms within one week of a known clinical event.
2. Radiographic Findings: Bilateral infiltrates on chest X-ray or thoracic computed tomography (CT) which should not explained by atelectasis or nodules.
3. Exclusion of Cardiac Causes: In patients without an obvious inciting event for ARDS, it is important to confirm that heart failure or volume overload cannot fully explain the observed pulmonary edema. Additional tests, such as echocardiography, may be necessary to rule out cardiac causes.
4. Severity Grading: This definition introduced a categorization of ARDS severity based on the ratio of partial arterial pressure of oxygen to fraction of oxygen in the inspired air, the so-called PF ratio (PaO2/FIO2). The positive end-expiratory pressure (PEEP) level should be at least 5 cm H2O. The severity grades are as follows:
    a. Mild ARDS: P/F ratio between 200-300 mmHg
    b. Moderate ARDS: P/F ratio between 100-200 mmHg.
    c. Severe ARDS: P/F ratio less than 100 mmHg.

Acute kidney injury (AKI) is a sudden, often reversible decline in kidney function, often assessed by the glomerular filtration rate (GFR). AKI can occur up to 35% of the time in individuals with ARDS (3). When occurring together, AKI and ARDS predict worse outcomes, including higher mortality and longer hospital stays. In previous investigations of AKI acquired in hospitals and intensive care units (ICUs), a major challenge was the absence of a standardized definition (4). Until 2004, tens of definitions for AKI circulated, making it difficult to validate diagnostic and therapeutic interventions (5).

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) society developed evidence-based and clinically relevant guidelines, incorporating a modified definition that is now widely used (6). The definition and staging of AKI according to KDIGO criteria are as follows:

1. Definition:
    a. An increase in serum creatinine (Cr) by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours, or
    b. An increase in Cr to ≥1.5 times baseline within the prior week or
    c. Urine volume <0.5 mL/kg/hour for 6 consecutive hours (oliguria)
2. Staging:
    a. Stage 1: Increase in serum creatinine to 1.5-1.9 times baseline or ≥0.3 mg/dL (≥26.5 µmol/L) increase within 48 hours, or urine output <0.5 mL/kg/hour for 6-12 hours
    b. Stage 2: Increase in serum creatinine to 2.0-2.9 times baseline, or urine output <0.5 mL/kg/hour for ≥12 hours
    c. Stage 3: Increase in serum creatinine to ≥3.0 times baseline, or serum creatinine ≥4.0 mg/dL (≥353.6 µmol/L), or the initiation of renal replacement therapy, or urine output <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours

Despite the successful implementation of the 2012 KDIGO criteria for AKI, there are limitations. These criteria do little to specify the underlying cause of AKI, which is crucial for tailored diagnosis and treatment. Reliance on serum creatinine has drawbacks as it can be affected by non-renal diseases (7), indicates kidney function decline late, and may lead to underestimating the impact of AKI on systemic diseases (8). Additionally, oliguria, an early indicator of AKI, is less easily studied (9).

HOW DO KIDNEYS AND LUNGS COMMUNICATE?

The physiological pH is maintained by the interaction between the respiratory and renal physiology, leading to an acid-base balance (10). This depends on the synergy between the lungs and kidneys, such that if one organ is affected, the other will have to compensate (11). On the other hand, the control of systolic and diastolic pressure and volume homeostasis are delicately regulated through the renin-angiotensin-aldosterone system (RAAS). Lungs and kidneys are interconnected as agents released from one damaged organ affect the other.

Hypoxemia often results in injury to the kidneys due to their high oxygen consumption, which in turn causes further impairment of renal vasodilatory response to hypoxia. Hypoxemia decreases Renal Blood Flow (RBF) by stimulating adrenergic nerve endings and disturbing nitric oxide metabolism (12). On the other hand, Hypercapnia leads to a drop in systemic vascular resistance and systemic pressure due to the activation of hormonal pathways, volume retention including salt and water, and a drop in renal blood flow and filtration rate (GFR) (13). Those effects are often reversible, particularly seen after the resolution of CO2 retention, which proves the significance and effect of CO2 in regulating Renal Blood Flow (14).

PULMONARY RENAL SYNDROME

Pulmonary-renal syndromes (PRS) are a constellation of disorders characterized by a combination of rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH) (15). The underlying pathological pattern often seen in PRS is vasculitis involving small vessels such as arterioles, venules, and often capillaries (16). PRS is not a homogenous entity but is observed as a presentation associated with a wide spectrum of illnesses, including several forms of systemic vasculitis, both primary and secondary, and connective tissue diseases, including systemic lupus erythematosus (17). Specifically, the term "pulmonary renal vasculitis syndrome" describes a subset of PRS that manifests as a syndrome of DAH complicating acute glomerulonephritis, which often results in life-threatening systemic vasculitis necessitating urgent and aggressive forms of therapy (18). Prompt diagnosis is crucial in pulmonary renal syndromes due to the potential for rapid development of respiratory failure and end-stage renal failure. Diagnostic evaluation involves radiology (chest X-ray and CT), bronchoscopy with broncho-alveolar lavage, laboratory testing (serology, urine analysis), and histology through renal or lung biopsy, which helps identify the underlying etiology and guide appropriate treatment strategies (19). The most effective treatment approach depends on the underlying disease, making individualized care essential. Initially, a combination of glucocorticoids, immunosuppression, and plasmapheresis is commonly employed. Supportive measures, including transfusions, mechanical ventilation, and renal replacement therapy, are provided as necessary (17). Additionally, broad-spectrum antimicrobial treatment is often administered temporarily until further investigations rule out infection (20).

KIDNEY AND MECHANICAL VENTILATION

Mechanical ventilation is the cornerstone for the management of a wide variety of respiratory diseases, including ARDS. New evidence suggests that kidneys are affected by mechanical ventilation more than was initially discovered (21,22). AKI affects 25–60% of patients with ARDS who are on mechanical ventilation (23). Thus, it is a common and serious consequence of ARDS. Moreover, when AKI develops concurrently with ARDS, mortality rates increase dramatically, and in this population, shock is the most common cause of death (3). In fact, studies have demonstrated that the leading cause of mortality in patients with ARDS is often multi-organ failure caused by sepsis or other causes rather than hypoxemia by itself (24). Therefore, it is crucial to understand the pathophysiology and explore possible strategies to decrease the risk of developing kidney injury during mechanical ventilation.

Acute kidney injury in ARDS patients can be attributed to three main mechanisms. Firstly, hypercapnia and severe hypoxemia (PaO2 <40 mmHg) negatively impact renal blood flow, potentially due to reduced activity of mediators such as angiotensin II, nitric oxide, endothelin, and bradykinin (25–30). However, mild hypoxemia wasn't found to be associated with a drop in renal blood flow unless associated with hypercapnia (31). The effect of moderate hypoxemia on blood flow to the kidneys remains inconclusive (31,32).

Hypercapnia alone, even without hypoxia, is associated with a drop in renal blood flow to the kidneys (33), possibly through sympathetic nervous system stimulation leading to renal artery vasoconstriction (34), as well as direct vasoconstriction of the renal artery (31). Secondly, mechanical ventilation alters thoracic cavity pressures, resulting in decreased cardiac output and subsequent reduction in blood flow. Ventilation, particularly when using high positive end-expiratory pressure (PEEP), increases intrathoracic pressure, leading to decreased cardiac preload and renal blood flow (35,36).

Finally, the theory of biotrauma has gained traction as a potential contributor to acute kidney injury. This hypothesis suggests that inflammatory mediators released from the lungs during mechanical ventilation may affect renal blood flow (37). Limited studies have investigated this hypothesis and the development of AKI. One in vivo animal study demonstrated that certain ventilatory strategies increased renal epithelial cell apoptosis, with soluble FAS ligand playing

a role in AKI development (38). Another clinical study observed that locally stressful mechanical ventilation strategies can lead to the release of local and systemic cytokines, with IL-6 having a predominant effect on AKI development (39). Interestingly, both studies showed that using a strategy of lung-protective ventilation can lead to a decreased incidence of AKI (39).

In addition to ARDS, AKI is frequently observed during sepsis among critically ill patients. Sepsis is characterized by hyperdynamic circulation, altered blood flow -though not always in the ischemic range- and a sharp decline in GFR (40). The pathophysiology of septic-AKI is extremely complicated and includes tubular cell secretion of cytokines, inflammation, oxidative stress, and microvascular dysfunction.

When mechanical ventilation is used, several strategies have been proposed to decrease the chance of complications and improve outcomes. Those strategies are the mainstay in managing ARDS, as other interventions, including pharmacological ones, often provide limited benefit and are not supported by evidence.

The implementation of a conservative approach to lung management in individuals experiencing ARDS, provided there are no contraindications, leads to notably reduced ICU mortality, 28-day mortality, in-hospital mortality, and the occurrence of new non-respiratory organ failure compared to conventional oxygenation therapy (41). The National Heart, Lung, and Blood Institute (NHLBI) also supports the use of lung-protective strategies, which involve maintaining plateau pressures below 30 cmH2O. To meet this requirement, tidal volumes are reduced, often resulting in mild hypercapnia.

Notably, this observed respiratory acidosis can be independently associated with decreased lung injury (42). The mechanism behind the reduced mortality rates and lung injury associated with lung-protective strategies is thought to involve the reduction of inflammatory factors such as IL-6 and IL-8, which play a role in lung injury (39,42–44). However, especially in patients facing critical illness, concerns related to the negative effects of hypoxemia may take precedence over those associated with hyperoxemia.

Another ventilation strategy with proven mortality benefits is using higher positive end-expiratory pressure (PEEP) levels to maintain open collapsible alveoli and improve gas exchange throughout the lungs (45). High PEEP also helps prevent atelectrauma, defined as alveolar trauma resulting from repeated collapse and reopening.

KIDNEYS AND EXTRACORPOREAL MEMBRANOUS OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is a temporary intervention deployed in cardiac and respiratory failure incidents as a bridge to more definitive therapy (46). Venoarterial (VA) ECMO is used mainly for pure cardiac or mixed cardiac and respiratory failure. In contrast, venovenous (VV) ECMO is used for isolated respiratory failure with intact or adequate cardiac function (47). AKI observed while using ECMO is often attributed to multivariable causes, including sepsis, high intravascular pressure, interruption of normal renal blood flow, and increased extravascular lung edema with impaired gas exchange (48)

Patients on ECMO who develop AKI requiring renal replacement therapy (RRT) showed a significantly increased mortality rate when compared to non-RRT patients. They were significantly less likely to be successfully weaned off ECMO. (49). Close to 50% of patients on VA ECMO will need RRT support at some point in the treatment course. Some patients' attributes can be associated with a higher risk of needing RRT, including low albumin levels and shock status postoperatively. Worse outcomes, in general, were observed for this cohort of patients, with about twice the duration of ECMO support needed and about one-third the survival rate when compared to the cohort of patients not requiring RRT.

When RRT is needed, evidence suggests that early utilization of RRT may be associated with fewer complications such as volume overload and metabolic acidosis, and it may promote recovery from the systemic inflammatory response, potentially by clearance of large molecules such as inflammatory cytokines, especially when high flux filters are used. Aggressive volume management and maintaining euvolemia remain crucial to successful outcomes after ECMO (49,50).

AUTHORS' CONTRIBUTION

Baha Al-Abid: Study conception and design, supervisor, critical review of the manuscript. Anas Odeh: writing and review the manuscript Moath Bani Salem : writing and review the manuscript.Omar AbuHaltem: writing and review the manuscript.Haitham Al-ayyat: coordinating, review and editing the manuscript

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