

A Protective Kidney-Lung Approach to Improve Outcomes in Mechanically Ventilated Patients



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Key Words

Acute kidney injury · Acute respiratory distress syndrome · Fluid overload · Mechanical ventilation

Abstract

There is increasing evidence that deleterious interactions between the lung and the kidney may be partly responsible for the multiorgan failure and high mortality seen in patients with acute respiratory distress syndrome. Lung protective strategies can reduce many of the adverse mechanistic and biological effects of mechanical ventilation. However, the key modifiable mediators are yet to be defined for the titration of balance between protective ventilation settings and distant organ function. Disparate but complementary mechanisms that may be involved in acute lung–kidney interactions will be discussed. A kidney–lung protective strategy in patients on mechanical ventilation is a potential approach that should be exploited to improve outcomes in critically ill patients.

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Introduction

Several efforts have been made in the last decade to address the unacceptably high mortality in patients with acute respiratory distress syndrome (ARDS). Numerous studies suggest that ARDS mortality is declining to 25–40% mainly not only as a result of improved understanding of its pathophysiology and improvements in supportive care but also due to the implementation of lung protective ventilation strategies [1, 2]. However, we believe there is room for improvement. A multidisciplinary approach is needed as preventive strategies can be implemented at various stages: during the onset of the predisposing factors, at the onset of ARDS and during mechanical ventilation. The predominant cause of death in ARDS is not hypoxemia, which is one of the defining criteria of ARDS, but multiorgan failure [3]. It is well documented that acute kidney injury (AKI) is the most common organ dysfunction in ARDS patients and that in the presence of AKI the mortality rate increases to more than 40%, with the rate **rising with AKI severity** [4, 5]. Therefore, new therapies that can reduce the morbidity and mortality in AKI are

urgently needed. Mechanical ventilation is a life-saving procedure, but it also has many adverse mechanistic and biological effects, and may affect the function of remote organs, including the kidney [6]. We review 4 disparate but complementary mechanisms that may contribute to the adverse outcome in ARDS patients with evidence of renal failure; these mechanisms include fluid overload (FO), cardiogenic pulmonary edema, non-cardiogenic pulmonary edema (and its association with uremic lung and acute lung injury) and, finally, mechanical ventilation in ARDS. Clear understanding of the factors influencing kidney–lung interactions in patients undergoing mechanical ventilation will encourage physicians to explore and develop new strategies for managing critically ill patients.

Fluid Overload

There is convincing data highlighting cumulative fluid balance as an important vital sign in critically ill patients. Pediatric nephrologists were the first to identify the degree of FO as an independent variable associated with the number of ventilator days and mortality [7, 8], and it was established that children with AKI should not be allowed to develop more than 10% of FO because of the devastating outcomes associated with it [9]. In 2001, Goldstein et al. [7] were the first to assume that ‘...in some cases, continuous veno-venous hemofiltration may be a prevention, rather than a treatment, for worsening degrees of FO’ and ‘early initiation of continuous veno-venous hemofiltration to allow for sufficient blood product and nutrition administration, while preventing FO, may improve patient survival’. These findings were followed by multiple reports highlighting the importance of FO in adult intensive care and its association with increased morbidity and mortality [10]. Survivors can be separated from potential non-survivors simply by the degree of FO present on the day of admission and during intensive care unit stay [11]. Bioelectrical impedance vector analysis is an emerging tool to assess total body water in critically ill patients, and recent literature encourages further testing and validation [11, 12].

Cardiogenic Pulmonary Edema

The association between cardiac failure and renal impairment, summarized under the umbrella term cardio-renal syndromes, has gained wide recognition over the last decade [13]. The degree of renal impairment has

been shown to be an independent predictor of cardiac prognosis. In type 3 cardiorenal syndrome, AKI can depress cardiac function by several pathophysiological mechanisms other than FO and electrolyte or acid–base disturbances, for example, upregulation of proinflammatory and pro-apoptotic pathways, endothelial dysfunction, myocardial cell infiltration and neurohormonal activation. Systolic/diastolic dysfunction and ventricular arrhythmias are much more frequent in the setting of AKI, and can lead to pulmonary congestion and impairment of the alveolar capillary barrier function, irrespective of intravascular volume [14]. By definition, ARDS is a pulmonary edema that is not fully explained by cardiac failure, though there may be a role of left ventricular dysfunction – in particular of right ventricular dysfunction – considering the high incidence of pulmonary hypertension in ARDS [15]. Venous congestion, as a surrogate for right ventricular impairment, is one of the most important hemodynamic determinants of worsening renal function and is associated with higher mortality [16, 17]. Experimental models suggest that venous congestion is likely to decrease renal perfusion pressure and oxygen delivery by increasing intracapsular pressure due to the formation of renal edema, which aggravates the renal impairment [18]. This in turn leads to increased pulmonary congestion, pulmonary hypertension, right ventricular overload and reduces left ventricular filling. The consequent increase in central venous pressure is transmitted to the kidney, leading to a positive feedback loop that may culminate in cardiac, pulmonary or renal decompensation, depending on the functional reserve of the respective organs [19].

Noncardiogenic Pulmonary Edema

It has been recognized for a very long time that lung injury in renal failure has special features. In 1951, Bass et al. [20] described the uremic lung by its ‘central butterfly’ appearance in the radiograph and associated it with left ventricular failure and advanced kidney disease, but new findings indicate a direct interaction of the lung and the kidney. Unlike cardiogenic pulmonary edema, which is the result of increased capillary hydrostatic pressure and thus theoretically transudative, the uremic lung is characterized by a capillary leak-induced protein-rich pulmonary exudate in the absence of FO [21]. With the introduction of dialysis, the classic presentation of the uremic lung has become rare, although the underlying mechanisms are still operative in ARDS.

Rabb et al. [22] showed in their rodent model that ischemic AKI can lead to increased pulmonary vascular permeability, cellular apoptosis, alveolar hemorrhage, leukocyte trafficking and alterations in pulmonary gene/protein expression [23]. Delayed recovery of kidney function can impair resolution of lung inflammation post AKI [24]. It is assumed that proinflammatory markers released mostly from necrotic renal tubular cells follow the circulation into the large microcapillary network of the lung and mediate these histological changes. At a cellular level, AKI leads to reduced expression of epithelial sodium channel, sodium-potassium ATPase and aquaporin 5, all which are essential for alveolar water clearance [22]. Similar mechanisms have been demonstrated in experimental cardiogenic pulmonary edema, including an active augmentation through epithelial chloride secretion (sodium-potassium-chloride cotransporter 1 and cystic fibrosis transmembrane conductance regulator) and secondary fluid flux into the alveolar space [25]. Perhaps the most compelling evidence of lung–kidney interactions is that both organs appear to have similar water and salt channels, and amiloride can reproduce alveolar fluid by inhibition of epithelial sodium channel while furosemide can prevent active alveolar fluid secretion by inhibition of sodium-potassium-chloride cotransporter 1. This may represent a possible explanation for the rapid and diuresis independent action of furosemide in lung edema, independent of its vasodilating activity. Patients with cardiogenic edema can theoretically improve rapidly with fluid removal, while patients with non-cardiogenic pulmonary edema improve little, if at all. In clinical practice, however, most patients fall between the 2 categories, and the concept of keeping the patient ‘empiric’ is probably better than letting him be ‘overfilled’.

Mechanical Ventilation and ARDS

Mechanical ventilation can be a lifesaving procedure in many clinical settings; however, it can have an adverse impact on hemodynamics and induce systemic inflammation, particularly in patients with injured lungs and kidneys. Mechanical ventilation increases intrathoracic pressure and pulmonary vascular resistance, which may lead to pulmonary hypertension, right ventricular dysfunction and venous congestion. The importance of venous congestion in relation to worsening renal function was reviewed earlier. Physiological studies suggest that the use of positive end-expiratory pressure can activate the neurohormonal system in different ways (via the sympathetic nervous system or disturbances in antidiuretic

hormone secretion or the renin–angiotensin system) to further reduce renal blood flow and impede free water clearance and sodium excretion [26, 27]. Hypercapnia and hypoxemia, among other factors, compromise renal blood flow and have been investigated in healthy populations and patients with chronic obstructive pulmonary disease [28, 29]. Analogous to ‘traditional’ renal physiological studies [30], Darmon et al. [31] exposed mechanically ventilated ARDS patients without renal failure to different oxygen levels. Patients were studied at baseline (arterial saturation 96%), then with arterial oxygenation values of 88–90% (mild hypoxemia) and 98–99% (high oxygenation). While hemodynamic parameters and blood lactate level did not change during the procedure, creatinine clearance increased during mild hypoxemia and was accompanied by increase in diuresis and the renal resistive index. Clearly, more data are needed to understand the complex pathophysiology of both organs in the setting of mechanical ventilation. Is there a kidney–lung protective strategy? And if so, when does mechanical ventilation become injurious to the kidneys or to other organs? For instance, is there an optimal positive end-expiratory pressure level at which ventilation needs are met and renal function is preserved, will any deviation upset the balance?

What we learned from the seminal studies of the ARDSNet group is that compared to patients ventilated with high tidal volumes those ventilated with lower tidal volumes had a 9% absolute decrease in mortality with more ventilator-free days, less trauma to the injured lungs and less inflammation [32] and less organ failure [33] (especially a markedly reduced incidence of renal failure). Ventilation with high tidal volumes may increase alveolar vascular permeability and thereby increase the risk of proinflammatory mediators translocating into the systemic circulation and causing end-organ damage. Liu et al. [34] demonstrated in a secondary analysis of 876 patient from the ARDS Network trial that elevated levels of interleukin-6, types I and II soluble tumor necrosis factor receptors and plasminogen activator inhibitor-1 were independently associated with AKI. Besides, there is experimental evidence that ventilation with high tidal volumes can induce renal epithelial cell apoptosis [35] and dysregulation of extracellular ligands that help control renal vascular tone and epithelial/endothelial integrity [36, 37]. For improved management on a ventilator, one of the approaches that should be considered to reduce multiorgan damage is to have more invasive monitoring and attention to hemodynamics, which may decrease kidney injury [38].

Conclusions

Awareness of the multifaceted kidney and lung interactions has increased considerably. Cumulative fluid balance in critically ill patients has to be avoided, not just to prevent static edema but also to decrease edema genesis in those with acute lung injury because of the damaged alveolar capillary barrier. Venous congestion is an important mediator of the cardio-pulmonary-renal axis and may contribute to the poor outcomes associated with ARDS. Decrease in renal function can lead to acute lung injury via multiple biological mechanisms, including downregulation of lung water and salt channels. In the setting of lung-injurious ventilation, mechanical ventilation can be instrumental in amplifying distant organ damage by facilitating the translocation of proinflammatory mediators into the systemic circulation. The implementation of lung-protective ventilation is necessary in patients with ARDS, not just to protect the lungs but to protect the kidneys as well. However, many issues remain unresolved, including the optimal ventilation settings to

facilitate lung and distant organ function. To conclude, we believe that there is a kidney–lung protective strategy in mechanical ventilation, and only multidisciplinary care can address the unique needs of patients with ARDS.

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