Editorial

Acute kidney injury in acute respiratory distress syndrome: why ventilator settings matter

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Acute respiratory distress syndrome (ARDS) is an inflammatory syndrome and is associated with a mortality of around 40% (1). This mortality is largely attributed to the multisystem organ failure (MSOF) that ensues after the development of ARDS. Sub-optimal ventilator strategies propagate alveolar capillary membrane damage potentiating an inflammatory response which in turn can worsen the MSOF (2). Patients with higher levels of circulating pro-inflammatory cytokines have been found to have higher mortality (3). Sub-optimal conventional ventilation can worsen MSOF by day 3, with the kidneys being the most affected organs (2). The prevalence of acute kidney injury (AKI) in critically ill patients is estimated to be around 30% (4) and is associated with poor outcomes (5). This percentage further increases to around 45% in patients with ARDS (6). Patients with ARDS who develop AKI have a higher hospital mortality rate than those without AKI (6). Over the years, there has been increasing body of evidence linking mechanical ventilation and ARDS as independent risk factors for developing AKI in addition to well known risk factors like age, diabetes, cardiac and hepatic dysfunction (6,7). Various mechanisms postulated for development of AKI include hemodynamic, neurohormonal and metabolic derangements (8-10). Increased intrathoracic pressure due to ventilator leads to decreased cardiac output, subsequently leading to decreased renal perfusion. In addition, low oxygen saturation and hypercapnia targets used in ARDS management leads to increases in diuresis and in renal resistive indices (11). These ultimately lead to decrease in glomerular filtration rate (GFR) and subsequently AKI. The delay in ARDS and subsequent AKI is around 2 days. This is detected by the rise in routinely used markers of kidney injury like BUN, creatinine and decrease in urine output. However, these biomarkers are seen after the injury has already taken place. Several biomarkers have been evaluated to detect the renal stress before the onset of functional change (12) and may help identify at risk kidneys. There is paucity of data regarding the causality of AKI with independent ventilator associated parameters like PEEP, tidal volume, driving pressure and respiratory system compliance. In ARMA trial, patients who had a low tidal volume and limited plateau pressure had a greater number of days without renal failure (13). Development of AKI has been independently associated with age, a history of diabetes mellitus and arterial pH on day 1 of ARDS and no association between development of AKI and low tidal volume ventilation, limited plateau pressure, and PEEP level (14).

In the current era of targeting mechanical ventilation to decrease the deleterious effects of VILI, it becomes imperative to study the effects of individual components of ventilator mechanics on other organs. In this issue of *Annals of Translational Medicine*, Leite and colleagues present the results of a large retrospective study assessing the ventilator related parameters associated with subsequent development of AKI in mechanically ventilated patients. Using a large

database, the authors concluded that respiratory system compliance and PEEP are the only respiratory related variables that had a direct causation with the development of severe AKI. On further using mediation analysis only PEEP mediated a small effect on respiratory system compliance (Csr) on severe AKI. Compliance largely is an intrinsic property of the injured lung and poor Crs represents higher disease severity. This in turn would lead to higher chances of MOSF including AKI. The authors also conclude that PEEP is associated with AKI, however, hemodynamic changes from PEEP did not mediate the effect. We know from the animal and human studies that PEEP dampens the inflammatory cascade by preventing atelectrauma and biotrauma (15,16). The effects of PEEP could however be explained by using the concept of mechanical power. Gattinoni and colleagues proposed a concept of using mechanical power equation to estimate the contribution of the different ventilator-related causes of lung injury and of their variations (17). This equation uses respiratory rate, tidal volume, PEEP, respiratory system elastance, inspiratory-to-expiratory time ratio and airway resistance to calculate the mechanical power transferred to lungs by the ventilator. PEEP may decrease lung inhomogeneity and decrease atelectrauma, however it can also increase the ventilator pressure load. When it causes a greater rise in pressure load it may lead to VILI, which in turn can lead to AKI. The authors also mention the crosstalk theory between organs where worsening lung function can lead to worsening AKI and worsening AKI could lead to worsening lung function. Clemens et al. explored this bidirectional pathway in their study and found strong evidence of reciprocal risk of AKI and ARDS in critically ill burn patients (18).

Despite evolving knowledge of various pathophysiological mechanisms that contribute to AKI in mechanically ventilated patients, little data has emerged in regards to the contribution of individual ventilator parameters like PEEP, tidal volumes, driving pressure and plateau pressures. Long term effects of permissive hypercapnia and hypoxemia on kidneys are still not understood properly. An interesting concept would be to extrapolate the mechanical power equation and see if it can predict the development of AKI. As our understanding about the crosstalk between organs evolve, there is little doubt about the reciprocal relationship between kidneys and lungs. Treating one organ at the expense of other organ might be short sighted. Therefore, larger studies are needed to look into novel concepts such as "pneumo-renal syndrome", identify at risk kidney and mitigate risk factors for prevention of AKI. Based on the current available evidence the appropriate way to prevent AKI in ARDS patients is by using lung protective ventilation, balanced resuscitation, preventing fluid overload and avoidance of nephrotoxic medications. Because of our limited understanding, our ability to prevent and treat ARDS associated AKI is also limited. Therefore, future clinical trials focusing on the ARDS-AKI relationship, especially the effects of individual ventilator parameters are warranted.

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Footnote

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