Impact of acute kidney injury on lung injury

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CLASSIC ANIMAL MODELS of critical illness have focused on injury of a single end-organ, with the goal of better understanding and attenuating that injury, and ultimately developing novel disease-focused therapies. For example, acute lung injury (ALI) can be induced in animal models by administration of endotoxin or hydrochloric acid, exposure to hyperoxic conditions, and the use of injurious, high tidal volume ventilation. Although these models have their limitations (9), they have been critical for the development of life-saving therapies, for example, a low tidal volume (LTV), lung-protective strategy for the treatment of ALI (10). However, it is clear from humans that injury of one organ frequently impacts other organs. Indeed, this entity is commonly referred to as multiple organ dysfunction syndrome and is associated with high morbidity and mortality. Although this phenomenon of “cross talk” has widespread recognition, animal models frequently do not reproduce this effect, nor has this effect been studied to a wide extent in these models.

Several studies suggest that ALI has deleterious effects on other organs, including the kidney (reviewed in Ref. 7). In patients with ALI, the mortality rate of those who develop acute kidney injury (defined as a 50% rise in creatinine) is 58% compared with 28% in those who do not develop acute kidney injury (8). In a rabbit model of acid aspiration and injurious ventilation, increased apoptosis was observed in the kidney and small intestine (5). Plasma isolated from these rabbits led to increased apoptosis of renal tubular epithelial cells when cocultured in vitro. Furthermore, in patients with ALI, changes in soluble Fas ligand levels are associated with changes in renal function as measured by serum creatinine (1, 5), suggesting that lung injury results in activation of proapoptotic signals that may lead to cell death in several tissue compartments, including the kidney.

Similarly, several animal studies have suggested that acute kidney injury is associated with subsequent lung injury. Bilateral ischemia-reperfusion kidney injury is associated with increased lung vascular permeability and an increase in the lung wet/dry ratio as well as inflammation with neutrophil infiltration (2, 11). At a molecular level, kidney injury stimulates an increase in lung expression of markers of inflammation, including messenger RNA for tumor necrosis factor-α and intracellular adhesion molecule-1. Furthermore, attenuation of kidney injury by treatment with α-melanocyte stimulating hormone concomitantly reduces lung injury, including expression of these inflammatory markers (2).

Recently, Dodd-o et al. (3) assessed the impact of acute kidney injury on ventilator-induced lung injury (VILI). They hypothesized that acute kidney injury might have a differential impact on animals ventilated with a lung-protective, LTV ventilation strategy and with an injurious ventilation strategy. The authors carefully controlled the hemodynamics of these animals with appropriate volume resuscitation. They controlled the acid/base status by modulating the ventilator dead space to prevent overventilation of the high tidal volume (HTV)-treated animals and by selection of the composition of resuscitation fluids to avoid hyperchloremic metabolic acidosis. Mice underwent bilateral renal artery cross-clamping for 30 min to induce relatively severe acute kidney injury or sham surgery; 22 h after acute kidney injury, they were reanesthetized and allowed to spontaneously ventilate or were ventilated with LTV or HTV (7 or 30 ml/kg, respectively). Importantly, both ventilation strategies were associated with some lung injury compared with the animals that were allowed to spontaneously ventilate. In addition, since this was a study of the impact of acute kidney injury on the lung, animals were not subjected to another pulmonary insult (e.g., acid aspiration), as is frequently done in studies of VILI.

The authors showed that among animals ventilated with an LTV strategy, those with acute kidney injury had more Evans blue dye extravasation in the lung compared with controls. This difference was associated with poorer oxygenation, but not with an increase in protein, total or polymorphonuclear cell (PMN) content of the bronchoalveolar lavage (BAL) fluid. In contrast, in animals ventilated with an HTV strategy, acute kidney injury did not worsen ALI compared with control animals, as measured by Evans blue dye extravasation, oxygenation, BAL protein, or BAL total cell content. However, animals with acute kidney injury had fewer PMNs in the BAL fluid than control animals, suggesting reduced air space inflammation. This result is similar to the findings of Zarbock and colleagues (12), who demonstrated that uremic PMNs are not recruited to the lung as efficiently as non-uremic PMNs following ALI. It should be noted that animals treated with HTV had more lung injury compared with animals treated with LTV or allowed to spontaneously ventilate. Thus, in these experimental studies in mice, acute kidney injury may attenuate the impact of injurious, HTV ventilation, whereas acute kidney injury seems to exacerbate the impact of a relatively noninjurious LTV strategy.

How does kidney injury impact lung injury? The article by Dodd-o et al. (3) does not shed any mechanistic insight into this question. Zarbock et al. (12) have suggested that uremic PMNs play a critical role in protection from acid-induced ALI following acute kidney injury. These PMNs have reduced L-selectin cell surface expression, and, therefore, recruitment of these PMNs to sites of injury and inflammation (e.g., the lung) may be reduced. However, why there would be a differential effect in animals treated with LTV and HTV in the article by Dodd-o is unclear. Hoke et al. (4a) have recently demonstrated that the injured kidney plays two important and distinct roles in the generation of systemic inflammation: cytokine generation as well as clearance of systemic

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cytokines. They compared cytokine profiles in animals after bilateral ischemia-reperfusion injury and after bilateral nephrectomy and demonstrated distinct differences in these profiles. Nonetheless, both forms of acute kidney injury were associated with subsequent ALI. Subsequent work by the same group with IL-6 knockout mice and a neutralizing antibody to IL-6 suggests that IL-6 plays a critical role in the pathogenesis of ALI (6). Further studies to explore the impact of these systemic cytokine disturbances on distant organ function are needed.

The current study highlights the complex interaction of acute kidney injury with other organ systems. Distant organ injury may be complicated by direct organ injury (e.g., acid aspiration or injurious ventilation strategies) as well as by “best supportive care” required for those organs (e.g., mechanical ventilation). Further studies to understand the mechanisms by which acute kidney injury affects the lung will be critical to developing therapies to prevent distant end-organ damage and to potentially reduce the morbidity and mortality associated with multisystem organ failure.

REFERENCES