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Microvasc Res. Author manuscript; available in PMC 2010 January 1.

Published in final edited form as:
Microvasc Res. 2009 January ; 77(1): 8–12. doi:10.1016/j.mvr.2008.09.001.

Acute kidney injury and lung dysfunction: a paradigm for remote organ effects of kidney disease?

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Acute kidney injury (AKI) is a common problem in both tertiary care centers as well as in the developing world. AKI often arises from insults such as trauma, severe infection/sepsis, medications and contrast agents, or following major surgery. Depending on the definition of AKI employed, 7–18 % of all hospitalized patients suffer from AKI (Nash 2002, Uchino 2006), approximately 35% of patients requiring intensive care have AKI on the day of admission (Bagshaw 2008), and as many as 5% of intensive care patients have AKI severe enough to require dialysis (Uchino 2005). Even AKI that is not severe enough to require dialysis is associated with an increased mortality (Uchino 2006, Bagshaw 2008, Levy 1996, Chertow 2005). Improvements in dialysis technology- most notably continuous renal replacement therapy (CRRT) have not been proven to reduce the mortality (approximately 50%) attendant to AKI that requires renal replacement therapy (Palevsky 2008). It appears that attenuation of the filtrative function of the kidney is not the sole driving force in the deleterious effect this common ailment exerts on patient survival.

Renal failure has been shown to alter organ systems critical to patient survival, effects that likely underlie the adverse effect on survival. In particular, renal failure can affect the lungs, increasing pulmonary vascular permeability and promoting pulmonary hemorrhage (Kramer 1999). As the combination of acute lung injury and renal failure carries an astoundingly high mortality of 80%, this consequence of AKI is of great clinical significance.

An increasing body of evidence suggests that the deleterious effects of AKI on lung function could, at least in part, be due to loss of the normal balance of immune, inflammatory, and soluble mediator metabolism that attends injury of the tubular epithelium. Such dysregulation, acting at least in part on endothelia, leads to compromise of remote organ function. Kidney-lung interaction in the setting of AKI therefore constitutes not only a pressing clinical problem, but also an illuminating framework in which to consider possible mechanisms by which renal diseases exert such deleterious effects on patient outcomes, even when dialysis is provided. Other organs in which AKI can compromise function (possibly through mechanisms similar to those operating in the “uremic lung”) include the heart, GI track, bone marrow and brain.

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History and (simplified) physiology of the problem

The pathology and natural history of acute renal failure was cogently described by Bywaters and Beall in 1941 (Bywaters 1941). Four victims who had suffered crush injuries during the bombing of London were presented. Each had been entrapped for 6–12 hours, 2 were initially normotensive, all became oliguric, and all succumbed after 3–7 days with severe azotemia, oliguria, and hyperkalemia. The authors identified "degenerative changes" in the proximal tubules with intratubular casts containing desquamated tubular epithelial cells, "… an absence of changes in glomeruli," and commented on the evident lack of appropriate tubular function, with the urine resembling a "glomerular filtrate." As suggested in its initial description and myriad subsequent publications, AKI is a "disease" of the renal epithelia, and now shown to involve the endothelium as well. Disparity between the severity of tubular histology (at times modest) and the decrement in renal function (potentially severe) has spawned multiple non-exclusive hypotheses, most notable of which are regional dysregulation of renal vascular tone and "backleak" through the denuded epithelium from tubules potentially obstructed by cellular casts. Until recently, the focus has been predominantly on the failure of the kidney to excrete waste products, electrolytes such as potassium, and fluid. These aspects of renal function relate primarily to the kidney's capacity to form an adequate volume of ultrafiltrate and appropriately sequester such waste products in the tubular lumen for excretion. However, a growing body of evidence suggests that the insulted kidney not only fails to excrete appropriately, but likely plays a direct role in promoting dysfunction in remote organs- the best studied of which has been the lung. We will outline some of these pathways and the evidence supporting them.

Limitations of current supportive care

Since the advent of renal replacement therapy in the 1950s, the focus of treatment in the setting of severe AKI has been on the diffusive and convective clearance of electrolytes (such as potassium), nitrogenous waste products (such as urea), and fluid. Extracorporeal renal replacement therapies (RRT) are based on diffusive or convective clearance across semipermeable membranes. Modern approaches can provide clearance of small solutes and fluid that approaches that of the native kidney. However, these processes are purely physicochemical in nature, and do not replace the metabolic functions normally performed by the kidney. Over 50 years later, the timing of initiation of RRT, the method of delivery, and the clearance dosage remain the subjects of intense debate. Despite improvements in delivery of RRT and concurrent improvements in supportive care, the overall mortality rate remains unchanged. A recent high quality multicenter prospective study demonstrated that high dose dialysis compared to 3 times/week did not lower mortality (approximately 50% in both groups) (Palevsky et al, NEJM 2008). Moreover, such interventions, carrying as they do procedural risks, might be inappropriate in less severe AKI. This is an important consideration, as a number of studies have shown that AKI that is not severe enough to "require" dialysis under current paradigms is associated with significant increases in mortality and risk of complications (Nash 2002, Uchino 2006, Levy 1996, Chertow 2005).

Limitations of current diagnostic criteria

Our current abilities to assess renal function and renal injury are inadequate. Current definitions of AKI, commonly linked to serum creatinine and/or urine output, are likely insensitive to the severity of renal injury, leading to delayed diagnosis and underestimation of the degree of renal tubular injury. Urine output is modulated by multiple factors potentially unrelated to renal injury, while an elevation in serum creatinine reflects primarily the integrity of kidney's function as a filter. Moreover, creatinine is both secreted and filtered, and rises only in proportion to the disparity between its production (which can be increased or decreased in common clinical settings)- detection of AKI is thus both delayed and potentially confounded.

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Nonetheless, the Acute Kidney Injury Network demonstrated that an incremental serum creatinine increase of only 0.3mg/dL, considered in isolation, predicted mortality as well as the expanded definitions, such as the RIFLE class (a standardized scale of the severity of AKI), which also demonstrated a correlation with increased morbidity and mortality in a number of large scale studies (Barrantes 2008). An analysis of hospital records of 19,982 adult patients, showed that a ≥ 0.5 mg/dL increase in serum creatinine was associated with a 6.5-fold increase in the odds of death (Chertow 2005). The correlation of a (very) modest increase in a marker of filtration and a significant increase in mortality suggests that there are other aspects of renal function, not measured by current techniques, that contribute to the elevation of mortality that accompanies AKI.

The kidney as an immunomodulator

The kidneys are uniquely positioned to serve as an immunomodulatory organ. First, they receive approximately 25% of cardiac output- considerably more on a per-gram basis than the liver and clearly more than most visceral organs. The proximal tubular epithelial cells reabsorb numerous substances from the 140 liters of plasma ultrafiltrate the normal kidney produces each day, substances that include small peptides, and immune regulatory molecules as well as electrolytes and nitrogenous waste products. Proximal tubular cells also actively secrete molecules from the peritubular capillary bed into the tubular lumen- offering a mode of clearance for molecules that are not filtered at the glomerulus. Finally, proximal tubular cells are immunologically active, presenting antigen and producing a variety of inflammatory mediators and even GM-CSF when provoked (Waeckerle-Men 2007, Jevnikar 1991, Schmouder 1992, Nechemia-Arbely 2008, Wu 1984).

It is also notable that leukocytes passing through the kidney are exposed to a uniquely hostile environment. The renal medulla is severely hypertonic (~800 or more mOsm/Kg) and hypoxic (tissue PO_2 ~20 torr). Leukocytes passing through this hostile environment might well be “primed” to respond to any second signal provided by the renal endothelium; such signals might promote activation of leukocytes or changes in leukocyte adhesion molecule expression. These effects could modulate cell behavior in remote organs, with potentially deleterious effects. The injured kidney is known to modulate the activity of each of the major leukocyte lineages (Kluth 2004, Linas 1995, Ascon 2006, Singer 1993). Intriguingly, if such modulation in the mediator-rich, physicochemically hostile environment of the kidney includes neutrophil activation, it could well modulate leukocyte trafficking in a number of important organs - such as the lung - via both adhesion molecule expression and neutrophil physical characteristics, such as cytoplasmic “stiffness” (Doerschuk 1993, Wiggs 1994, Hogg 1994, Motosugi 1996).

Alveolar and interstitial fluid balance in the lungs

The pulmonary circulation is a low-pressure exchange circuit with a geometric arrangement suited to maximize contact surface area between the blood and air compartments. Right ventricular output flows down a progressively branching vascular pathway, through an alveolar capillary network which shares a common basement membrane with the alveolar epithelial cells and is in such close apposition to the pulmonary airspaces that it may properly be considered a capillary sheet. The capillary sheet then drains into the pulmonary venous circulation and left atrium. Smaller pulmonary arteries and veins pass through the pulmonary interstitial spaces, effectively “between” the alveoli. The pulmonary vasculature is far from an inert conduit, however. Pulmonary vascular tone and metabolic activity are modulated by catecholamines, cytokines, arachidonic acid metabolites, nitric oxide, and acid/base status.

Much recent work has focused on the important roles played by the pulmonary vasculature in acute lung injury/acute respiratory distress syndrome. Specifically, increases in pulmonary endothelial permeability lead to increased fluid extravasation (Lamm 1988). Such

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extravasation is not confined to the alveolar capillary sheet; in a number of models of lung injury, leakage can take place in either the pre-intermediate segment (corresponding to the precapillary pulmonary artery) or the post-intermediate segment (corresponding to the postcapillary venule). Although the pulmonary lymphatics can effectively reabsorb this fluid, acute increases in vascular permeability can result in fluid leakage that overwhelms lymphatic reabsorptive capacity, leading to increased interstitial lung water and compromised lung mechanics. This adverse chain of events is exacerbated by the compliance behavior of the pulmonary interstitium: once a critical level of interstitial water accumulates, the effective compliance for fluid accumulation increases (Miserocchi 2001). Ultimately, interstitial fluid invades the alveoli, inactivating surfactant and further compromising compliance. The compensatory mechanism for alveolar fluid reabsorbtion depends on an active regulatory process. Sodium enters the alveolar epithelium through an amiloride sensitive sodium channel and is actively transported into the interstitium by the sodium-potassium ATPase pump. Water is passively drawn down the resultant osmotic gradient to achieve equilibrium through aquaporin channels. Inhibition of the sodium channels can markedly affect alveolar fluid balance (Dematte 2000, Mathay 1996, Icard 1999, Khimenko 1994).

Modulation of epithelial channels by AKI

AKI has been shown to downregulate pulmonary epithelial Na, K ATPase, EnaC, and aquaporin 5 (Rabb 2003). This downregulation of Na, K ATPase and EnaC, in particular, could exacerbate the effects of increased pulmonary vascular permeability by decreasing active transport of fluid out of the alveoli. Parenthetically, although pulmonary fluid clearance appears less sensitive to decrements in aquaporin expression, reduced aquaporin activity has been shown to predispose to ventilator induced lung injury in an animal model (Hales 2001).

Changes in vascular permeability induced by macrophages in AKI

Other factors altering pulmonary vascular permeability seem to be macrophage mediated. Work by Kramer *et al* demonstrated the potential for renal failure to modulate pulmonary vascular permeability (Kramer 1999). In this study, rats were subjected to renal ischemia-reperfusion injury or sham operation, and allowed to recover. Rats subjected to ischemia/reperfusion injury displayed increased pulmonary vascular permeability, pulmonary alveolar hemorrhage, interstitial edema, and pulmonary vascular congestion. The macrophage pacifant CNI-1493 attenuated the increase in vascular permeability as reflected in less extravasation of Evan's blue dye.

A potential role for IL-6 in AKI related acute lung injury

Cytokine expression also plays a role in changes in pulmonary vascular integrity. Plasma IL-6 has been found to be a significant predictor of morbidity and mortality in patients with ARDS (Meduri 1995, Parsons 2005). Both IL-1b and IL-6 have roles in the induction of the synthesis of endothelial adhesion molecules and the production of other chemotactic cytokines (IL-8, and IL-9), with IL-8 being a potent chemotactic factor for neutrophils. IL-6 has been found to be predictive of patient mortality in AKI, although in that study there was no difference in respiratory, cardiac, CNS, hepatic, or hematologic failure between survivors and nonsurvivors (Simmons 2004). Recently, Klein *et al*, using an IL-6 knockout mouse model, demonstrated that IL-6 knockouts had decreased neutrophilic infiltration, myeloperoxidase activity and reduced capillary leak resulting in less pulmonary edema (Klein 2008). It appears that a significant pathway of lung injury following kidney injury could arise from cytokine dysregulation in the kidney, with subsequent activation of the lung's native immune cells.

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Activated neutrophils and acute lung injury

The lung sequesters large numbers of defensive cells with immunologic or inflammatory potential. Although a high density of inflammatory/immune cells is teleologically reasonable in view of the lung's potential attack by inhaled pathogens, the presence of a large population of potentially proinflammatory cells also creates the potential for lung damage due to induction of inflammatory responses. The clinical relevance of this concern is made clear in animal models and the profound lung injury which may attend recovery from neutropenia in patients treated for malignancies (Zarbock 2006, Kawano 1987, Rimensberger 1998, Rinaldo 1985). Notably, the pulmonary capillary sheet is configured such that leukocytes must mechanically deform to pass through to the pulmonary venous circulation. Activated neutrophils, by virtue of actin polymerization and cytoplasmic stiffening, are unable to deform adequately, and are trapped within the pulmonary circulation (Doerschuk 1993, Wiggs 1994, Hogg 1994, Motosugi 1996). Neutrophil-endothelial adhesion contributes further to such sequestration; and approximately 50% of the circulating leukocyte population can be sequestered within the pulmonary vasculature. Granulocyte macrophage colony stimulating factor (GM-CSF) knockout studies in mice have shown marked decreases in neutrophilic infiltration of the lungs in ALI models (Frossard 2002, Choi 2008). This resulted in marked decreases in cytokine production, and less pulmonary vascular leakage, effects reversed upon repletion of GM-CSF. Attenuation of NF-kB, a pro-cellular adhesion molecule induced by TNF (and potentially produced by proximal tubular cells) that promotes binding and emigration of neutrophils has been demonstrated to be protective in lung injury models, with marked decreases in cytokine production and concomitant decreases in pulmonary permeability and resultant edema (Kang 2001).

Renal dysfunction, nitric oxide metabolism, and acute lung injury

In addition to the cellular- and cytokine related effects outlined above, the derangement of nitric oxide metabolism associated with renal failure may compromise lung function. Disordered (reduced) nitric oxide metabolism in the setting of renal failure was identified almost 10 years ago (Wever 1999, Vaziri 2002). The cause of this dysregulation is not entirely clear, but asymmetric dimethyarginine (ADMA) is felt to play a significant role. ADMA is an inhibitor of endothelial nitric oxide synthase (eNOS), and shifts NO metabolism toward production of oxygen-based free radicals (Druhan 2008). Recent evidence suggests that the increase in ADMA is not due to depressed renal clearance, but rather to diminished activity of dimethylarginine dimethylaminohydrolase (DDAH), which breaks down ADMA, as well as increased activity of protein methyltransferase (PRMT) (Matsuguma 2006). This effect of renal failure on nitric oxide metabolism could also render the lung more susceptible to injury. Increased ADMA in renal failure, arising from reduced activity of DDAH and increased activity of PRMT, inhibits eNOS and shifts intraendothelial biochemistry toward the production of free radicals. High levels of exhaled nitric oxide, accompanied by evidence of lipid peroxidation, appear to correlate with ventilator induced lung injury (Broccard 2004). Inducible nitric oxide synthase knockout (iNOS) animals have been shown to suffer less ventilator induced lung injury than wild type (Peng 2005). In contrast, eNOS knockout mice displayed enhanced leukocyte- endothelium interaction and were more susceptible to ischemia-reperfusion injury (Kaminski 2004). It is reasonable-but unproven- to suspect that the ADMA-induced shift in eNOS activity from NO production to free radical production could render the "uremic lung" more susceptible to mechanical or inflammatory injury. The difference in susceptibility to injury between iNOS and eNOS knockouts might be due to differences in the animal models, but it might also be due to the differing rates of NO production and stringency of regulation displayed by these enzymes, with iNOS producing levels more conducive to lipid peroxidation. Interestingly, the "prooxidant state" characterizing uremia might also exacerbate damage due to shifts in the eNOS metabolites.

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Modulation of leukocyte or endothelial function attending renal failure could therefore either exacerbate or attenuate the severity of lung injury. The findings of Kramer *et al* that a macrophage pacifant could attenuate changes in pulmonary vascular permeability attending renal failure support the former effect, whereas Zarbock's recent finding that renal failure may exert a protective effect against acid- induced lung injury supports the latter (Kramer 2003, Zarbock 2006). Clearly, the balance between immune/inflammatory upregulation and suppression can vary between patients, pathologies, and potentially across the course of the illness.

Cardiac consequences of acute renal injury

Postoperative AKI is a serious complication after cardiac surgery and is associated with hospital mortality ranging from 9% with RIFLE class "risk" to 32% (with RIFLE class "failure") (Kuitunen 2006). These mortality rates are largely consistent with more recent studies (Lassnigg 2008), and represent a several-fold elevation in the risk of death from that expected with uncomplicated cardiac surgery (Gomes 2007).

The pathophysiology of cardiac dysfunction in the setting of acute renal injury is currently under active investigation. Analogous to the lung, the deleterious effects appear to be mediated by increased expression of leukocyte adhesion molecules, infiltration of the myocardium by the immobilized leukocytes, and cytokine expression. In the cardiac literature, leukocytes have been thought to be active in cardiac dysfunction after ischemia, with demonstrated improvements when utilizing agents that block leukocyte function or localization. IL-1 and TNF-α induce expression of ICAM-1, an intercellular adhesion molecule promoting diapedesis of leukocytes into the interstitium. Additionally, IL-1 and TNF-α depress left ventricular function and may induce cardiac myocyte apoptosis. In isolated rat hearts, a TNF-α infusion decreased left ventricular developed pressure and elicited coronary vasoconstriction, as well as leukocytic infiltration of the myocardium and myocyte apoptosis.

Renal ischemia/reperfusion in mice of even brief duration can increase IL-1 and TNF-α levels with concomitant increase in ICAM-1 expression (Kelly 2003). At 48 hours post injury, there were functional changes in cardiac physiology with increased left ventricular end diastolic volume and left ventricular end systolic volume with depressed fractional shortening of the ventricles (Kelly 2003). This investigator also detected evidence of myocardial apoptosis, as ascertained by a 10-fold increase in the number of TUNEL positive cells, at 48 hours. In contrast to some studies of AKI/ALI, renal ischemia/reperfusion injury appeared crucial to this finding: animals subjected to as little as 15 minutes of renal ischemia displayed myocardial apoptosis, whereas animals undergoing to bilateral nephrectomy did not (despite a much larger increment in creatinine). Ischemia/reperfusion animals treated with anti- ICAM-1 to block the TNF-α induced increase in leukocyte infiltration displayed attenuation of myocardial apoptosis.

Impaired cardiac function alters the delicate interdependency of the cardio-pulmonary circuit. With impaired cardiac output pulmonary vascular pressure increases, augmenting transudation of fluid into the interstitium and possibly alveoli. Such extravasation, in combination with AKI induced compromise of epithelial and endothelial pump function, may act synergistically to further compromise cardiopulmonary function.

Effects of AKI on CNS vasculature

In mice, AKI led to increased expression of glial fibrillary acidic protein (a marker of inflammation) in astrocytes in the cortex and corpus callosum, activation of microglia (brain macrophages), increased vascular permeability to blood albumin, increased levels of the proinflammatory chemokines keratinocyte-derived chemoattractant and G-CSF in the cerebral cortex and hippocampus, and decreased locomotor activity (Liu 2008). The blood-brain barrier

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was significantly altered during the AKI, which could be an important conduit for enhanced soluble inflammatory substances to enter brain parenchyma. These CNS changes could then have important effects on both sensorium as well as other organs that are modulated by neuronal activity.

Conclusion

The extrarenal effects of AKI represent a clear example of local feedback loops "driving" systemic consequences. Upregulation of cytokine production, modulation of leukocyte function, and deranged NO metabolism have been rigorously examined as regards their effects on local organ function- e.g., renal function, recovery, or progression. However, we are increasingly aware that systemic dysregulation of such modulators arising due to AKI can have serious consequences for organ systems remote from the kidney. The data for such consequences of AKI are strongest for the lungs, but accumulating for other organ systems as well. Such effects likely contribute to the poor survival of patients suffering AKI despite excellent electrolyte, acid-base, volume, and small solute clearance. Recognition of the mediators and mechanisms by which AKI leads to lung changes is important for both improving dialytic management during AKI as well as development of novel therapeutics for this frequently fatal disease.

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