

Lung–Kidney Cross-Talk in the Critically Ill Patient

Faeq Husain-Syed^{1,2}, Arthur S. Slutsky^{3,4}, and Claudio Ronco¹

¹Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute of Vicenza, San Bortolo Hospital, Vicenza, Italy; ²Division of Pulmonology, Nephrology and Critical Care Medicine, Department of Internal Medicine II, University Clinic Giessen and Marburg–Campus Giessen, Giessen, Germany; ³Keenan Research Center for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; and ⁴Interdepartmental Division of Critical Care Medicine, Departments of Medicine, Surgery, and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Abstract

Discoveries have emerged highlighting the complex nature of the interorgan cross-talk between the kidney and the lung. Vascular rigidity, neurohormonal activation, tissue hypoxia, and abnormal immune cell signaling have been identified as common pathways leading to the development and progression of chronic kidney disease. However, our understanding of the causal relationships between lung injury and kidney injury is not precise. This review discusses a number of features and mechanisms of renal dysfunction in pulmonary disorders in relation to respiratory acidosis, impaired gas exchange, systemic congestion, respiratory support/replacement therapies, and other issues relevant to the clinical care of these patients. Biotrauma due to injurious ventilatory strategies can lead to the release of mediators into the lung, which may then translocate

into the systemic circulation and cause end-organ dysfunction, including renal dysfunction. Right ventricular dysfunction and congestive states may contribute to alterations of renal perfusion and oxygenation, leading to diuretic resistance and recurrent hospitalization. In patients with concomitant respiratory failure, noninvasive ventilation represents a promising treatment option for the correction of impaired renal microcirculation and endothelial dysfunction. In patients requiring extracorporeal membrane oxygenation, short- and long-term monitoring of kidney function is warranted, as they are at highest risk of developing acute kidney injury and fluid overload.

Keywords: acute kidney injury; extracorporeal membrane oxygenation; lung injury; mechanical ventilation; noninvasive ventilation

Advances have changed our perception of the interorgan cross-talk between the kidneys and the lungs. Although the generic term “pulmonary–renal syndromes” can designate any impairment affecting the lungs and the kidneys, it typically implies rare disease entities involving alveolar lung hemorrhage. This is often manifest as rapidly progressive glomerulonephritis associated with fulminant pulmonary capillaritis, with the more subtle forms detectable only by imaging and invasive measurements. Other frequent entities include sarcoidosis and bronchiectasis/cystic fibrosis associated with glomerular and tubulointerstitial diseases and hyponatremia. These conditions occur

in conjunction with various pulmonary disorders, whether due to nonosmotic vasopressin stimulation (e.g., blood gas disturbances, pneumonia, mechanical ventilation [MV]), ectopic production (paraneoplastic syndrome), or altered osmoregulation. However, there are numerous other pulmonary–renal interactions, many of which are more common but have not yet been structurally characterized. It is these latter interactions, which are the focus of this review.

Renal injury can affect the lung by altering acid–base or fluid balance. In addition, in acute (1) and chronic settings (2), the kidneys can play a causal and modulatory role in pulmonary disorders

via production and/or decreased clearance of mediators (3). In the critically ill, underlying lung injury (most commonly as the acute respiratory distress syndrome [ARDS]) and its treatment can worsen renal performance via multiple mechanisms including impact on hemodynamics, biotrauma, neurohormonal dysregulation, cell signaling pathways, and remote oxidative stress; and these may be amplified when injurious forms of MV are applied (4).

Many disorders such as chronic obstructive pulmonary disease (COPD) represent multidimensional diseases. Here, the inflammatory substrate is of special interest and has led to a view that chronic respiratory

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Correspondence and requests for reprints should be addressed to Arthur S. Slutsky, M.D., St. Michael's Hospital, 30 Bond Street, Toronto, ON, M5B 1W8 Canada. E-mail: slutsky@smh.ca

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disorders contribute to both airway and systemic inflammation. Albuminuria, hyperinflation, exercise intolerance, exacerbations, and comorbidities have all been shown to be strong predictors of mortality in COPD (5). Kidney disease is a common finding in patients with chronic pulmonary disorders, and its relevance to the disproportionate burden of cardiovascular disease in these patients merits further investigation. Polypharmacy is frequent, and impaired renal clearance of drugs may increase adverse reactions. In addition, renal impairment may be underestimated in pulmonary disorders, as an absolute increase in serum creatinine may be blunted because of decreased muscle mass.

Identification of the mechanisms and modifiable risk factors related to renal impairment in patients with pulmonary disease may help the clinician manage these conditions. This is especially important with respect to the hemodynamic and fluid needs, particularly in the critically ill. This review addresses the renal physiology most germane to patients with pulmonary compromise, with a goal of providing a broader context in which to view lung–kidney interactions.

Hypercapnia and Renal Acidification Response

The lung is the origin of the oxygen transport chain, playing a pivotal role in maintaining oxygen delivery and carbon dioxide (CO₂) elimination. The regulation of systemic acid–base balance is an integrative and dynamic process involving gas exchange, exogenous factors, and metabolism in constant interplay with renal acidification mechanisms. Blood gas disturbances and renal acidification responses are the most physiologically obvious pulmonary–renal interactions, and their assessment is important in screening and detecting renal disease.

In the early phase of hypercapnia, extrarenal factors are important in buffering pH, although evidence exists of renal adjustments even during this early phase (6). This is in contrast to chronic hypercapnia, where the kidney plays the major player in stabilizing pH, and renal acidification mechanisms are important for changes in P_{CO₂}. In chronic hypercapnia, increases in plasma bicarbonate may result in a stepwise increase in P_{CO₂} without a perceptible delay. This is in contrast to acute

respiratory failure, which may lead to full-blown decompensation of acid–base homeostasis, necessitating MV.

In ARDS, lung-protective ventilation is the standard of care, having demonstrated a 9% absolute decrease in mortality (7). Although it can lead to concomitant permissive hypercapnia, lung-protective ventilation does not necessarily lead to hypercapnic acidosis. Acidosis has often been associated with hemodynamic alterations and potential cellular adverse effects (8–10), albeit the role of acidosis with concomitant hypercapnia in pulmonary recovery after acute lung injury is an area of active study (11). Patients with preserved renal function may develop metabolic alkalosis, in particular when the correction of hypercapnia occurs rapidly (e.g., with extracorporeal lung support). However, it is not known to what extent renal insufficiency of variable severity limits the renal response.

In the setting of chronic respiratory acidosis (as a consequence of impaired pulmonary reserve, e.g., hypercapnic COPD), renal compensation is more crucial, with its effect on ammoniogenesis and titratable acidity production. Here, bicarbonate levels are inversely related to survival, and concomitant renal impairment is predictive of exacerbation and death (12). Miller and colleagues demonstrated that patients with a lower urea concentration at baseline had improved pH within 1 hour and were more likely to have a good outcome when undergoing noninvasive ventilation (NIV) for hypercapnic exacerbation of COPD (13). In contrast, patients with end-stage renal disease cannot mount a renal response to chronic hypercapnia, and thus are more likely to develop hypercapnia-induced acidosis.

It has been reported that 35–60% of patients undergoing MV in the context of multiorgan failure require renal replacement therapy (RRT) (14). The integration of CO₂ removal systems may represent a promising therapeutic option in patients with respiratory failure and concomitant respiratory acidosis, including patients who are at risk of NIV failure (15). This therapeutic program will facilitate the application of a lung-protective strategy (*see THE KIDNEY DURING EXTRACORPOREAL MEMBRANE OXYGENATION*) and mimic the homeostatic regulation of the lungs, while the correction of hypercapnic acidosis may improve hemodynamics (16).

Blood Gas Disturbances and Renal Blood Flow

Systemic blood flow is controlled by the cardiovascular system, with local mechanisms regulating regional blood flow and hence oxygen delivery to individual organs. In the kidney, myogenic and tubuloglomerular feedback mediate the autoregulation of renal blood flow (RBF). The kidneys have a high rate of oxygen consumption per gram of tissue, second only to that of the heart, making the kidneys exquisitely sensitive to hypoxic injury (17). Renal oxygen consumption depends on a complex interplay of factors, including metabolic activity (e.g., increased demand due to renal compensatory mechanisms against systemic hypercapnia), that affect glomerular filtration rate (GFR), glomerulotubular balance, and sodium reabsorption (18). Well-known neurohormonal regulators (angiotensin II, nitric oxide, adrenergic nerves) orchestrate vasoreactivity and determine the balance between oxygen and metabolic substrate supply/demand.

Blunted or absent renal vasodilatory responses may impact renal compensatory mechanisms and the evolution of renal disease. Despite its clinical relevance, the relationship between impaired gas exchange and RBF has received little attention. Patients with chronic respiratory disorders often have fluid retention with edema and/or pulmonary congestion (19). The mechanisms underpinning fluid retention have not been fully elucidated, but the most common pathophysiologic finding is decreased RBF, usually accompanied by a reduced ability to excrete sodium (20). Underrecognition of concomitant renal insufficiency and impaired right ventricular (RV) function may be more common than generally recognized and is discussed later.

Although somewhat variable, hypoxemia (Sa_{O₂}, ~83–87%) reduces RBF in a dose-dependent manner (18, 21) by a number of mechanisms, including stimulation of adrenergic nerves and disturbances in nitric oxide metabolism (20). Hyperoxemia (100% oxygen; Sa_{O₂}, 98–99%) causes an increase in RBF, albeit not in a consistent manner (18). Hypercapnia and its vasodilator consequences lead to decreased systemic vascular resistance and systemic blood pressure with subsequent

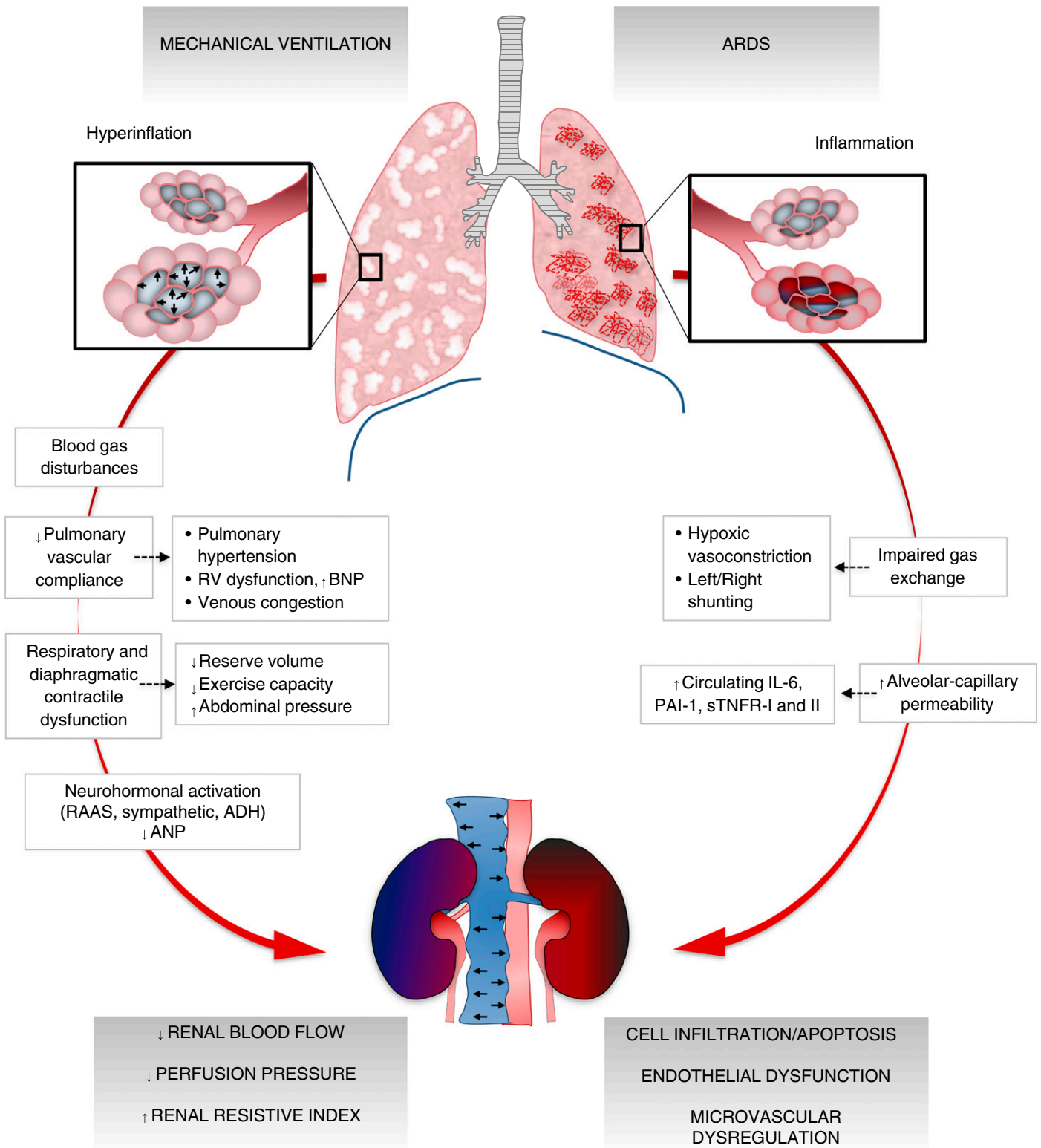


Figure 1. Lung injury and the kidney. Multiple dependent pathways in the setting of acute pulmonary disorders elevate the risk of acute kidney injury. Shown are the possible hemodynamic, neurohormonal, proinflammatory, and proapoptotic consequences of both hyperinflation and lung inflammation on renal function, and their clinical features. ↑ = increase of; ↓ = decrease of; ADH = antidiuretic hormone; ANP = A-type natriuretic peptide; ARDS = acute respiratory distress syndrome; BNP = B-type natriuretic peptide; PAI-1 = plasminogen activator inhibitor-1; RAAS = renin-angiotensin-aldosterone system; RV = right ventricular; sTNFR = soluble tumor necrosis factor receptor.

that ADH secretion was responsible for a decrease in free water clearance during antidiuresis (32, 38, 48). However, subsequent investigators could not confirm these findings, and an increase in urine osmolality has not been generally reported (48, 49).

Another putative mechanism for decreased renal function and fluid and salt retention in ventilated patients is a sympathetically mediated increase in renin activity, which decreases GFR by both decreasing RBF and stimulating aldosterone (32, 38, 49, 50). Other observations suggest an inverse relationship between plasma ANP, which has potent diuretic and natriuretic properties, and airway pressures during MV, due to reduced venous return and decreased right atrial pressure (42). Here, early RV preload adjustment by fluid administration (42) and/or ANP infusion (32) may improve renal function.

Lung Injury and the Kidney

Lung-protective ventilation is the current standard of care for patients with ARDS, having demonstrated a 9% absolute reduction in mortality (7) by minimizing ventilator-induced lung injury due to pulmonary overdistension (barotrauma and volutrauma), repetitive alveolar collapse (atelectrauma), and biotrauma. Biotrauma is a relatively newly described mechanism of lung injury in which overdistension and/or atelectrauma cause the release of a variety of mediators (e.g., IL-6 and IL-8, tumor necrosis factor [TNF]- α , monocyte chemoattractant protein-1, nitric oxide synthase, type III procollagen, and adhesion molecules [e.g., vascular cell adhesion molecule-1]) (4, 35). Importantly, these mediators as well as mediators involved in coagulation and cell adhesion (35) can translocate into the systemic circulation, especially under conditions of increased alveolar-capillary permeability, and potentially lead to distant end-organ dysfunction, including AKI (Figure 1) (4, 51). Secondary analysis from the ARDS Network trial showed that elevated levels of IL-6, type I and II soluble TNF receptors, and plasminogen activator inhibitor-1 were independently associated with AKI (52).

There is also experimental evidence that injurious ventilatory strategies can induce renal epithelial cell apoptosis (51) and dysregulation of extracellular ligands that help control renal vascular tone and epithelial/endothelial integrity (53). In a rabbit model of acid aspiration-induced

lung injury, Imai and colleagues (51) demonstrated that an injurious ventilatory strategy led to increased rates of terminal deoxynucleotidyltransferase dUTP nick end labeling-positive renal cells, which indicated apoptosis, along with elevated biochemical markers, which indicated renal dysfunction. Furthermore, the induction of apoptosis was increased in renal tubular cells incubated with plasma from rabbits ventilated by the injurious strategy compared with the control strategy. This increase in apoptosis was attenuated by a fusion protein that blocked Fas ligand. Finally, in patients with ARDS, they found a significant correlation between changes in soluble Fas ligand level and changes in creatinine level. Thus, although not conclusive, these data provided a plausible link between ventilatory strategy, biotrauma, circulating mediators, and renal dysfunction.

AKI and the Lung

At the cellular level, the renal tubular epithelium plays a fundamental role in regulating the inflammatory processes (3). During AKI, it represents a major site of cell injury and death, catalyzing circulating mediators in local and systemic inflammation/oxidative stress via a number of mechanisms, including epigenetic processes. The lung is highly susceptible to injury because of its extensive capillary network, and AKI has been shown to impact lung function (Figure 2) (e.g., up-regulation of cytokine production, deranged nitric oxide metabolism, leukocyte trafficking, increased vascular permeability, pulmonary hemorrhage, and reduced expression of pulmonary epithelial sodium channels, sodium-potassium ATPase, and aquaporin 5, which are essential for alveolar water clearance) (1). IL-6 is probably the best described proinflammatory mediator of lung injury after AKI, with supporting data from both human and animal studies (54).

Experimental studies highlight the systemic release of damage-associated molecular patterns originating from necrotic renal cells (55), and caspase-dependent, tumor necrosis factor receptor 1-mediated lung apoptosis and microvascular barrier dysfunction (56). Perhaps the most compelling evidence linking the lung and kidney is that both organs appear to have similar water and salt channels, and furosemide can prevent

active alveolar fluid secretion by inhibiting sodium-potassium-chloride cotransporter 1—possibly explaining the rapid and diuresis-independent action of furosemide in pulmonary edema (57).

In summary, MV can alter cardiopulmonary and systemic hemodynamics, and stimulate the neurohormonal system. There is a bidirectional interaction between lung injury and AKI, mediated by several pathophysiologic, molecular, and cellular mechanisms. Therefore, MV should aim to maintain renal function with a lung-protective strategy.

The Kidney and RV Function

The association between cardiac failure and renal impairment, summarized under the term “cardiorenal syndromes,” has gained wide recognition (58). Interest is fueled by the independent predictive role of worse renal impairment in worse cardiac prognosis. The right ventricle has historically received less attention than the left, probably because of its smaller mass, its role in pumping blood to only one organ, and because the morbidity and mortality associated with left ventricular disease are clinically more apparent (59). RV failure includes a large range of clinical conditions from preserved cardiac output and aerobic exercise capacity with increased RV end-diastolic volume and wall thickness (with raised diastolic filling pressures), to low-output states with small RV volume at rest. The right ventricle is affected by and contributes to disease processes such as pulmonary hypertension, caused by a variety of left heart diseases and pulmonary vascular diseases, resulting in limited exercise capacity via loss of vascular distensibility and/or recruitability. RV function during MV and particularly in ARDS has been extensively studied (43, 60, 61).

Renal failure in the setting of heart failure has traditionally been thought to be a result of diminished RBF due to low-output failure. However, findings illustrate that CVP as a surrogate for RV impairment is one of the most important hemodynamic determinants for worsening renal function, and is associated with high mortality (44). Animal studies have shown that venous congestion can decrease renal perfusion pressure and oxygen delivery by increasing intracapsular pressure via formation of renal interstitial edema (renal compartment

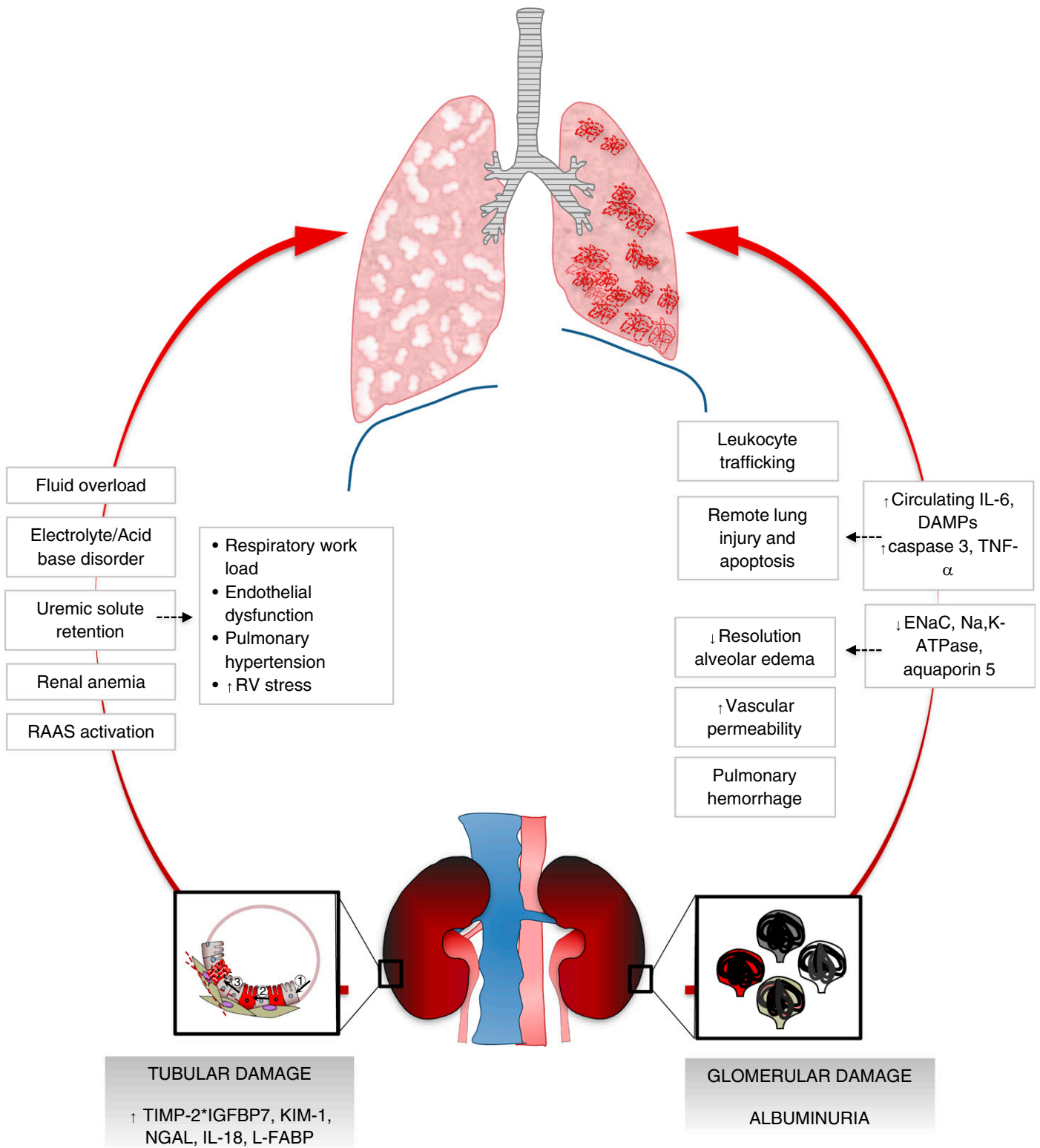


Figure 2. Acute kidney injury and the lung. Acute kidney injury can initiate and perpetuate lung injury via multiple dependent pathways. Shown is the potential multifaceted impact of renal failure on pulmonary function and the current biomarkers to detect renal tubular and glomerular damage. ↑ = increase of; ↓ = decrease of; DAMP = damage-associated molecular pattern; ENaC = epithelial sodium channel; IGFBP7 = insulin-like growth factor-binding protein-7; KIM-1 = kidney injury molecule-1; L-FABP = liver-type fatty acid-binding protein; NGAL = neutrophil gelatinase-associated lipocalin; RAAS = renin-angiotensin-aldosterone system; RV = right ventricular; TIMP-2 = tissue inhibitor of metalloproteinase-2; TNF = tumor necrosis factor.

syndrome) (62). Renal autoregulation may become impaired due to decreased availability of nitric oxide, which impairs tubuloglomerular feedback (44).

Consistent with the alterations in renal hemodynamics caused by blood gas disturbances, experiments in animal models demonstrate rapid and profound decreases in RBF and GFR, and increased avidity of the kidney for sodium (which may increase renal oxygen consumption and susceptibility to renal tissue hypoxia) in response to venous obstruction (62). These effects are rapidly reversed with relief of venous obstruction. In addition, diffuse neurohormonal activation occurs via multiple mechanisms (renin–angiotensin–aldosterone system, sympathetic nervous system, ADH, and endothelin system), leading to an overall vasoconstrictive state, which promotes sodium and water retention. This in turn leads to increased pulmonary congestion, pulmonary hypertension, and RV overload impacting left ventricular filling. The subsequent increase in CVP is transmitted to the kidneys and leads to a positive feedback loop that may culminate in either renal or cardiac decompensation, depending on organ functional reserve (63).

Diminished diuretic response represents an early clinical phenomenon that can be improved by preload reduction, either by using sequential nephron blockade or ultrafiltration (47). However, the impact of backward failure on renal function may not be confined to increased CVP, but includes a broader spectrum of mechanisms (e.g., increased gut endotoxin absorption with increased production of proinflammatory cytokines [e.g., TNF- α], associated with sodium retention, renal hypertrophy, and nephropathy) (45). Importantly, preconditioning resulting from repeated episodes of self-limited hemodynamic renal insults may increase the kidney's ability to recover (64). Recapitulating these mechanisms by drugs or other interventions may represent future therapeutic options to improve organ recovery after injury.

Fluid Balance and the Kidney

Conservative fluid administration during the first days of ICU hospitalization is a cornerstone of management to ensure adequate organ perfusion and to preserve normal diuresis. Studies have highlighted

the importance of the timing and amount of intravenous fluid administration in critically ill and ventilated patients (65, 66). This has challenged the dogma that fluids are “good” for the kidneys, but “bad” for the lungs. The concern remains for the lungs, because excess fluid is associated with worsening oxygenation, fewer ventilator-free days, and longer ICU stays (66). As for the kidneys, excess fluid administration during a critical episode cannot prevent new AKI or alter severity or renal recovery of AKI, although it does lead to increased rates of RRT (67). Thus, the optimum strategy is likely one that addresses early reversal of shock but avoids fluid overload, particularly in patients with existing lung injury.

In summary, RV dysfunction and congestion can contribute to alterations in renal perfusion, leading to diuretic resistance and recurrent hospitalization. Further studies are needed to evaluate the acceptable therapeutic management window of both RV filling pressure and CVP with respect to kidney function. Early reversal of shock is beneficial; however, fluid overload should be avoided, particularly in patients with ARDS.

Interventions and Adjuncts Targeting the Lung

Inhaled Nitric Oxide

Patients have received inhaled nitric oxide (iNO) for refractory hypoxemia and as a selective pulmonary vasodilator to treat pulmonary hypertension, as it improves ventilation–perfusion matching and reduces pulmonary vascular resistance without inducing systemic hypotension. The Lung Safe Study (68) indicated that approximately 6% of patients with ARDS still receive iNO, despite strong evidence that it does not improve clinical outcomes (69). Meta-analyses suggest that iNO increases the risk of renal dysfunction in patients with ARDS (70). Although the exact mechanisms of iNO-related renal dysfunction remain unclear, they appear to be dose dependent and associated with prolonged use of iNO. In healthy volunteers, iNO induces transient natriuresis, which cannot be explained by hemodynamic alterations (71). Animal studies and human studies have suggested systemic biochemical effects outside the pulmonary vasculature. These include

increased plasma concentrations of the stable by-products nitrate, nitrogen dioxide, and cyclic guanosine monophosphate, which may cause protein nitrosylation and raise the oxidative load, leading to renal tubular apoptosis (69, 70, 72). Thus, renal function should be monitored in the critically ill patient during iNO therapy.

Prone Position

Maintaining a patient prone rather than supine for a minimum of 16 h/d improves oxygenation in mechanically ventilated patients with ARDS, and reduces mortality, likely by further preventing ventilator-induced lung injury (73). In hemodynamically stable patients with ARDS without abdominal hypertension, assumption of the prone position does not worsen renal function and perfusion as long as cardiovascular function remains stable (74).

The Kidney during NIV

NIV is a form of assisted MV in which ventilation is delivered without using an endotracheal tube. As such, it helps prevent many problems associated with intubation (including nosocomial pneumonia) and complications of sedation, and may mitigate ventilator-induced acute lung injury. Decreased renal function can impact the success of NIV. Immune depression and disturbances in acid–base and volume homeostasis lead to a decrease in pulmonary compliance and increased work of breathing, thereby leading to NIV failure (Figure 2) (75, 76).

NIV supports spontaneous breathing/lung function, alleviates respiratory muscle/diaphragmatic workload, and may abrogate inflammatory responses in patients with muscle wasting (77). This is important because muscle wasting and inflammation may represent a crucial interface between chronic pulmonary disorders and chronic kidney disease that predisposes the patient to reduced physical performance, increased risk of complications, reciprocal dysfunction, and progression to chronic disease. Clinical trials have described the benefits of NIV beyond the respiratory system (78, 79). The use of NIV for a sustained reduction of hypercapnia in patients with stable COPD significantly improved survival (80). In sleep apnea, worsening nocturnal desaturations lead to declines in GFR (81) via induction of oxidative stress (82), activation of the

sympathetic nervous system, and up-regulation of the renin-angiotensin-aldosterone system (81), resulting in an inflammatory response and endothelial dysfunction, which are also ultimately involved in chronic kidney disease progression (83).

The functional correlate of systemic inflammation and endothelial dysfunction is glomerular hyperfiltration, and the use of NIV may attenuate these deleterious effects in obstructive sleep apnea and heart failure (78, 79). Increased residual volume is strongly associated with important patient-centered outcomes, such as dyspnea and exercise capacity, and may be more relevant in predicting cardiac and kidney function than in estimating the severity of airflow obstruction (84, 85).

In summary, NIV may represent a promising treatment option for correcting impaired renal microcirculation and endothelial dysfunction in susceptible patients, and should be further investigated.

The Kidney during Extracorporeal Membrane Oxygenation

There has been increasing interest in extracorporeal lung support (ECLS), as both full support to the failing heart or lungs, or partial support. ECLS can be subcategorized depending on the route of access (e.g., venoarterial [va], venovenous [vv], and arteriovenous), and on the blood flow rate through the gas exchanger. For example, CO₂ removal through the extracorporeal circuit with relatively low flow rates (~0.5–1.0 L) can remove CO₂, allowing lower ventilation pressures (86). From a theoretical point of view, a decrease in MV in combination with improvement in blood gas disturbances is associated with an improvement in peripheral gas exchange, systemic hemodynamics, and organ perfusion. Despite the increased interest in ECLS, the evidence supporting its role in improving clinical outcomes is relatively weak.

The incidence of AKI in patients requiring extracorporeal membrane oxygenation (ECMO) exceeds 70%, and approximately 50% undergo RRT (87). Patients with severe AKI have increased time on MV, increased ECMO duration, and increased mortality compared with those without AKI (88). The major mechanisms ascribed to renal injury are renal hypoperfusion, prolonged prehypoxemia and ischemia-reperfusion

injury after ECMO initiation, blood contact with the artificial membrane, static blood flow in va-ECMO, hemodynamic fluctuations, and malposition of the cannula with venous obstruction/arterial underperfusion and iatrogenic plaque rupture leading to (cholesterol) embolism. Selected mechanisms are discussed in detail.

Hemolysis is an important complication during ECLS, with erythrocyte fragmentation being caused by the combination of shear stress, air–fluid interface, excessive negative pressure, wall impact forces, and properties of nonendothelialized surfaces (88). Catalytic iron, formation of obstructive casts, and reduced NO bioavailability may impact vascular responses and multiorgan system function (Figure 3) (89, 90). The exposure of blood to the artificial surfaces can cause a hypercoagulable state and may reflect ongoing renovascular processes such as microvascular dysfunction and endothelial damage, leading to decreased renal oxygen supply. Hemorrhagic complications are the most commonly reported adverse events.

The critically ill patient presents with a narrow window for fluid balance, as either extreme can worsen cardio-renal or pulmonary function. The initiation of ECMO can cause rapid hemodynamic fluctuations due to issues of biocompatibility of the membrane oxygenators, entailing ischemia- and reperfusion-associated AKI or further unmasking intravascular volume depletion that is more pronounced in septic patients, due to increased capillary leakage (91).

Patients receiving ECMO are subject to fluid overload, as fluid is administered to ensure sufficient preload for centrifugal pumps. Accumulated extravascular water causing interstitial overload and concomitant hypotension may be associated with decreased tissue perfusion, decreased oxygenation, and increased extravascular lung water volume. Conversely, prolonged AKI and fluid overload may perpetuate lung inflammation, and are associated with longer ECMO dependence and higher mortality (92, 93). Animal models of ECMO have suggested that RRT may reduce pulmonary and systemic inflammation beyond the beneficial effects of restrictive fluid management (94).

vv-ECMO and va-ECMO differ with respect to their impact on hemodynamics.

Whereas vv-ECMO maintains native pulsatile cardiac output with less variation in RBF, the cardiac output in va-ECMO is a mixture of native cardiac flow (i.e., pulsatile) and ECMO pump flow (i.e., nonpulsatile). Because the blood flow during va-ECMO bypasses the lungs, there is a higher risk of systemic embolization. The nonphysiological nature of continuous flow results in increased diastolic flow and pressure, and lower peak systolic pressure, with dampening of pulsatility and increased laminar flow (95). Stasis could be a consequence, which in turn could result in vascular occlusion (Figure 3). Adverse renal effects of nonpulsatile blood flow may include altered endothelial integrity with accelerated edema formation as one of the most striking clinical presentations (96), increased activity of the renin-angiotensin-aldosterone system, and maintenance of impaired cortical RBF with prolonged end-organ recovery compared with pulsatile blood flow (97). It is still a matter of debate whether continuous blood flow affects long-term renal function and histology.

In summary, extracorporeal heart and lung support differ significantly in their pathophysiology and demand correspondingly different approaches. In patients requiring ECMO, short- and long-term monitoring of kidney function is warranted, as they are at high risk of developing AKI and fluid overload. Future studies will evaluate whether early extracorporeal fluid removal in terms of renal support therapy before replacement therapy will improve outcomes.

Predicting Renal Outcomes in Acute Pulmonary Disorders

Diagnosing AKI presents different challenges, particularly in the ICU setting. The current definition of AKI endeavors to detect kidney dysfunction based on urinary output and/or changes in serum creatinine level. However, the clinical classification is limited because it underestimates the degree of glomerular and/or tubular damage, and lacks the sensitivity and specificity to detect AKI in real time. Serum creatinine levels may take 2–3 days to increase above the defined threshold, and interventions administered at the time of AKI diagnosis, based on elevated creatinine

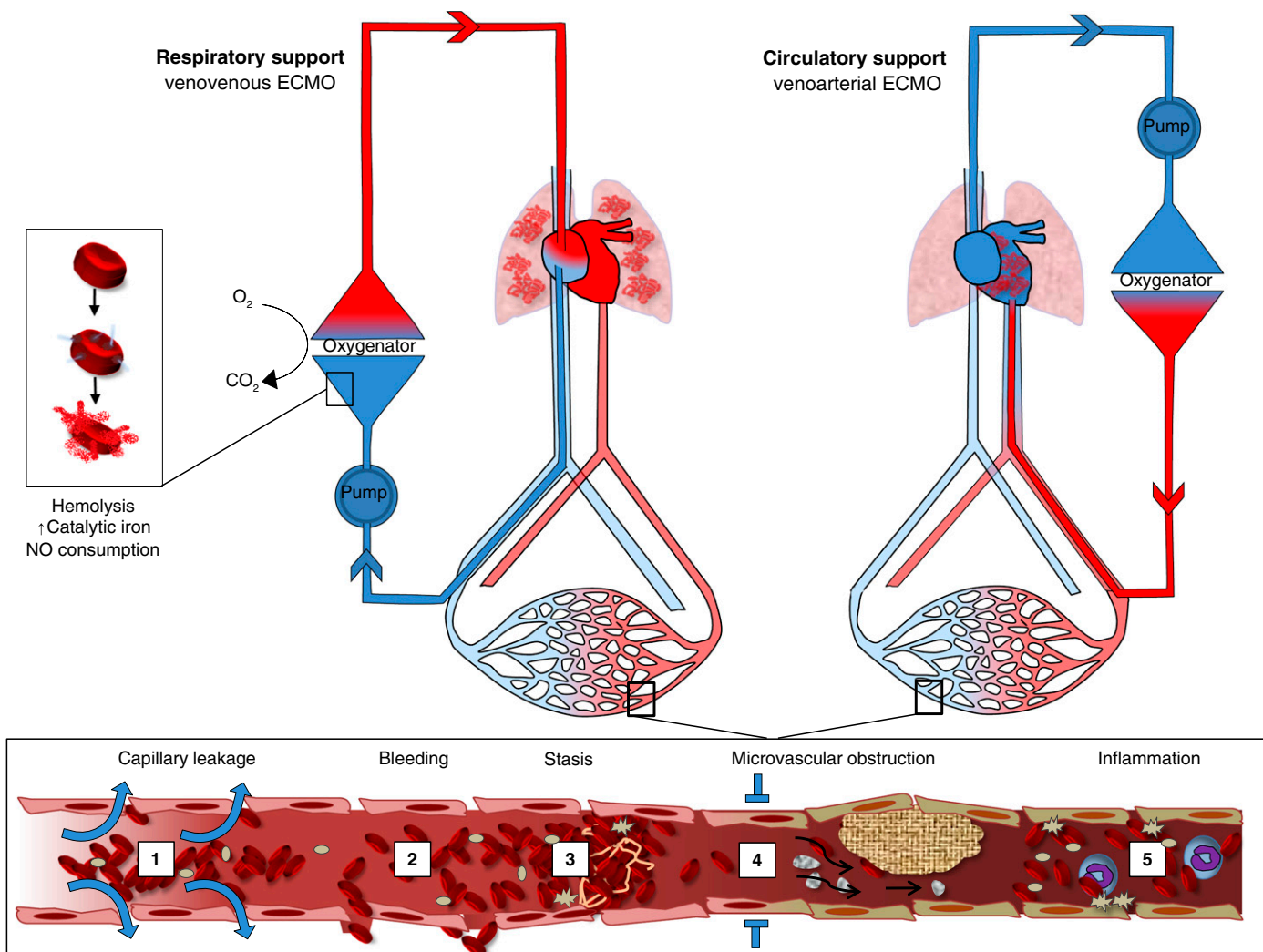


Figure 3. The kidney during extracorporeal membrane oxygenation (ECMO). Acute kidney injury often occurs as a part of multiorgan failure and can be aggravated by exposure to ECMO support. Shown is a synopsis of potential challenges that may impact renal microvascular flow in patients undergoing venovenous and venoarterial ECMO, including (1) capillary leakage, (2) bleeding, (3) blood stasis, (4) microvascular obstruction (caused by thrombosis, cholesterol emboli, clotting, and/or tissue edema), and (5) inflammation. ↑ = increase of.

levels, may not be effective. Furthermore, factors such as hydration and reduction in muscle bulk, coupled with reduced creatinine generation further confound the diagnosis, which may lead to an overestimation of renal function.

The concept of subclinical AKI through identification of damage markers in patients who do not fulfill current consensus criteria (“biomarker-positive but creatinine-negative” AKI) has implications for therapy (98). A number of emerging tubular damage biomarkers [e.g., tissue inhibitor of metalloproteinase 2 and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7]), kidney injury molecule-1, neutrophil gelatinase-

associated lipocalin, IL-18, and liver-type fatty acid-binding protein] have been identified (99, 100). They can be used to detect renal tubular damage and suggest an increased risk for AKI, the occurrence of AKI, or at least the presence of acute kidney stress—a term proposed to describe the phase preceding AKI (Figure 4) (101). During cellular injury, down-regulation of the cell cycle occurs early, helping preserve cellular energetics and metabolic function, and preventing cell division with damaged DNA until the DNA damage is repaired (99). Urinary [TIMP-2]*[IGFBP7] is of special interest, as it is involved in G₁ cell cycle arrest and might measure “renal stress” at the cellular

level before damage occurs. None of the biomarkers have been extensively investigated in acute pulmonary disorders. Moreover, there are relatively few biomarkers that link the lung and kidney; this represents an important area for further research.

Ideally, early detection of renal damage and hence early treatment may improve outcomes; however, serum creatinine may not increase above normal until more than 50% of renal function is lost. In addition, in clinical scenarios that compromise renal hemodynamics (e.g., venous congestion, intraabdominal hypertension), the patient can theoretically develop clinical renal dysfunction with elevated creatinine even if

tubular damage has not occurred. During this time, optimization of ventilator settings, RV function, and/or fluid removal might restore GFR. Here, the evaluation of clinical criteria in combination with biomarkers may identify different phenotypes of renal dysfunction and/or the patient at risk for increased susceptibility to future injuries (102).

Conclusions

The awareness of multifaceted kidney and lung interactions has increased

considerably. We have summarized current concepts linking the pathogenesis of renal dysfunction in acute pulmonary disorders. Patients with acute or chronic pulmonary or renal dysfunction often have unique management challenges, and clinicians require in-depth understanding of cardio-pulmonary-renal physiology to break the vicious cycle in the early phase of lung-kidney cross-talk to prevent multiorgan dysfunction. It is hoped that this understanding will lead to earlier recognition and

treatment, and improve the outcomes of patients with these disorders. ■

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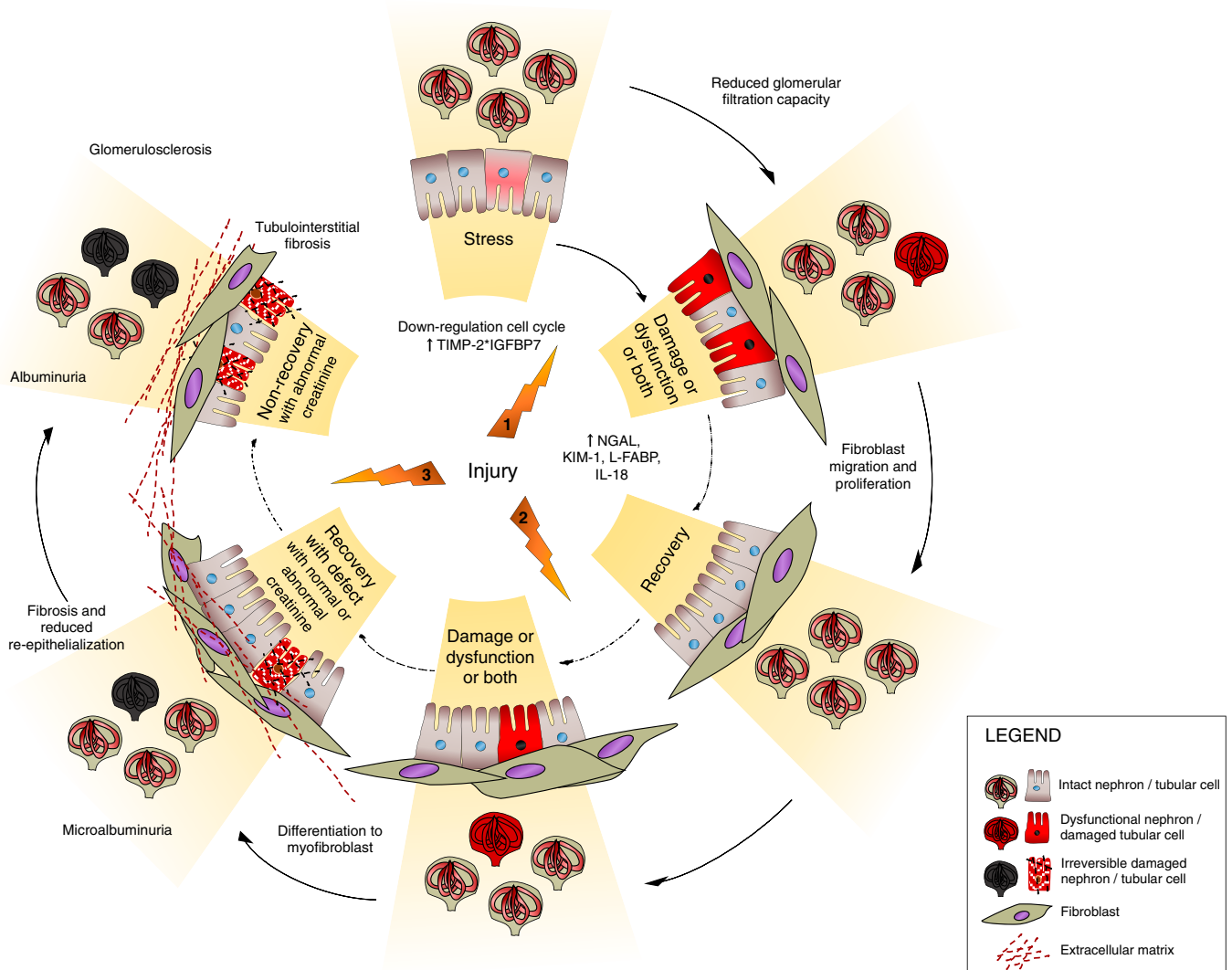


Figure 4. The acute kidney injury clock. The spectrum of kidney injury can vary from biomarker-positive tubular stress to tubular damage, renal dysfunction with elevated creatinine level, reduced glomerular filtration capacity, and tubular recovery, potentially progressing to chronic organ failure. Because the kidney permits a degree of physiologic reserve that allows the maintenance of normal organ function in any given injury, a recovery with defect may not be detectable. In this scenario, the evaluation of clinical criteria in combination with biomarkers may identify the patient at risk for increased susceptibility to future injuries. ↑ = increase of; IGFBP7 = insulin-like growth factor-binding protein-7; KIM-1 = kidney injury molecule-1; L-FABP = liver-type fatty acid-binding protein; NGAL = neutrophil gelatinase-associated lipocalin; TIMP-2 = tissue inhibitor of metalloproteinase-2.

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