Lung–Kidney Cross-Talk in the Critically Ill Patient

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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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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 (CO_2) 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_{CO_2}. In chronic hypercapnia, increases in plasma bicarbonate may result in a stepwise increase in P_{CO_2} 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 ammoniagenesis 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 CO_2 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_{O_2}, ~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_{O_2}, 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

neurohormonal activation and retention of salt and water, although this response is variable (21). Alterations in renal hemodynamics include reduction in RBF and GFR (21, 22), whether due to direct renal vasoconstriction (23) or peripheral vasodilatation–induced neurohormonal vasoconstriction, and a reduced ability to excrete sodium (19). In addition, acute hypercapnia markedly increases pulmonary vascular resistance and can lead to right ventricular dysfunction (24). Left ventricular function is well preserved, and RBF/GFR increases when hypercapnia improves (21).

Patients with COPD often have impaired renal hemodynamics. Patients with hypercapnia have lower baseline RBF than those with normocapnic hypoxemia. RBF increases with improved oxygenation, a change that is reversed by the addition of CO_2 (20), emphasizing the importance and dominance of CO_2 in regulating RBF in the presence of physiologic oxygenation levels or even hyperoxemia (21). In the hypercapnic milieu, several studies have described a loss of renal vasodilatory responses to various stimuli (e.g., dopamine [25], L-arginine [26], protein loading [23]). Whether hypercapnia leads to structural changes that render the renal vasculature less responsive is not known, and one can speculate that hypercapnia activates vasoconstrictive mechanisms that are powerful enough to withstand vasodilatory stimuli.

In the acute setting, the target for oxygenation in ventilated patients, particularly patients with ARDS, is a matter of debate. Two levels of oxygenation (Sa_{O_2}, 88–92% and >96%) were examined in a pilot trial: No differences were found in any measures of organ dysfunction (serum creatinine among others) or mortality (27). However, only a few studies have investigated the effects of blood gas disturbances on renal function in acute pulmonary disorders. Indeed, short-term mild hypoxemia (Sa_{O_2}, ~88%) in mechanically ventilated patients with ARDS without evidence of renal failure is associated with increased creatinine clearance, accompanied by increased diuresis and the renal resistive index (28). Although the causative mechanisms remain elusive, the renal response to mild hypoxemia in patients with ARDS implies impairment in some aspect of the renal compensatory response to hypoxemia. This finding may help identify patients at high risk for developing acute kidney injury (AKI), and may ultimately lead to a new recommended target Sa_{O_2} range for patients with ARDS.

In summary, acidosis and blood gas disturbances are common features of acute pulmonary compromise and impair renal function; the mechanisms remain unresolved. Tubular damage markers (*see* Predicting Renal Outcomes in Acute Pulmonary Disorders) and new diagnostic techniques may provide more dynamic measurements of renal function, including vascular responsiveness (29, 30).

The Kidney during MV

Intubation and MV are often required in critically ill patients to decrease the oxygen cost of breathing and to improve gas exchange. Paradoxically, interventions that improve the function of one organ system can have undesirable effects on others (31, 32). MV is associated with a threefold increase in the odds ratio of AKI in critically ill patients (33). Moreover, AKI impacts the duration of MV and weaning from MV, and is associated with mortality rates greater than 60% (31, 34). About 35–60% of patients with multiorgan failure undergoing MV require RRT (14). AKI in critically ventilated patients may be the result of reduced compensatory capacity of the kidneys, due to MV and/or multiple insults (e.g., ischemic, septic, nephrotoxic) in combination with preexisting renal insufficiency. Hemodynamic and hormone-induced mechanisms, and systemic inflammation through MV-associated mediator release, are associated with alterations in renal function and are discussed below. There is strong evidence of MV-induced hemodynamic alterations and systemic mediator release (33, 35).

The Kidney and Hemodynamic Alterations during MV

MV increases intrathoracic pressure and produces dynamic physiological effects that depend on a number of factors including the levels of airway pressures, inspiratory volume, and the patient's volume status (36). Positive pressure ventilation and positive end-expiratory pressure (PEEP) are associated with decreased RBF, GFR, sodium excretion, and urinary output (37–39), in contrast to ventilator modes that promote spontaneous breathing, which may better preserve renal function (Figure 1) (40, 41). With an intact cardio–pulmonary–renal axis, optimal fluid administration in accordance with intrathoracic pressure may restore cardiac and renal function (42). However, increased intrathoracic pressure can impede RV function (43) and cause renal congestion by decreasing venous return, evident as an increase in central venous pressure (CVP) and pulmonary vascular resistance (44). The impact of a dysfunctional RV is affected by afterload, and hence, increased pulmonary vascular resistance can amplify renal congestion irrespective of the intravascular volume (*see* The Kidney and RV Function).

Intraabdominal pressure (IAP) is a dynamic variable affected by diaphragmatic descent and abdominal pressure–volume characteristics. Depending on the magnitude of the positive pressure, respiratory system elastance, and preexisting abdominal pressure, MV can increase IAP and compromise microvascular blood flow (45). Analogous to systemic congestion, increased IAP can cause renal edema because of diminished venous drainage, potentially resulting in a vicious cycle that further increases IAP. The intubated patient with COPD is at particularly high risk of ventilation-induced changes in thoracic pressure due to the development of auto-PEEP, resulting in further intraabdominal hypertension (46).

A similar pathophysiology occurs in patients with ascites-induced increased IAP; paracentesis can improve renal function and diuretic response because of improved microvascular blood flow and improved intestinal absorption of diuretics (47). Intravesical pressure measurement represents a safe, rapid, and cost-effective method of diagnosing intraabdominal hypertension, and has long been used in peritoneal dialysis.

The Kidney and Neurohormonal Alterations during MV

A number of hormonal responses to MV have been studied, including antidiuretic hormone (ADH), renin, aldosterone, and A-type natriuretic peptide (ANP); however, no definitive correlation has been established between these responses and renal function during MV. On the basis of increased ADH levels during positive pressure ventilation and PEEP, early studies postulated

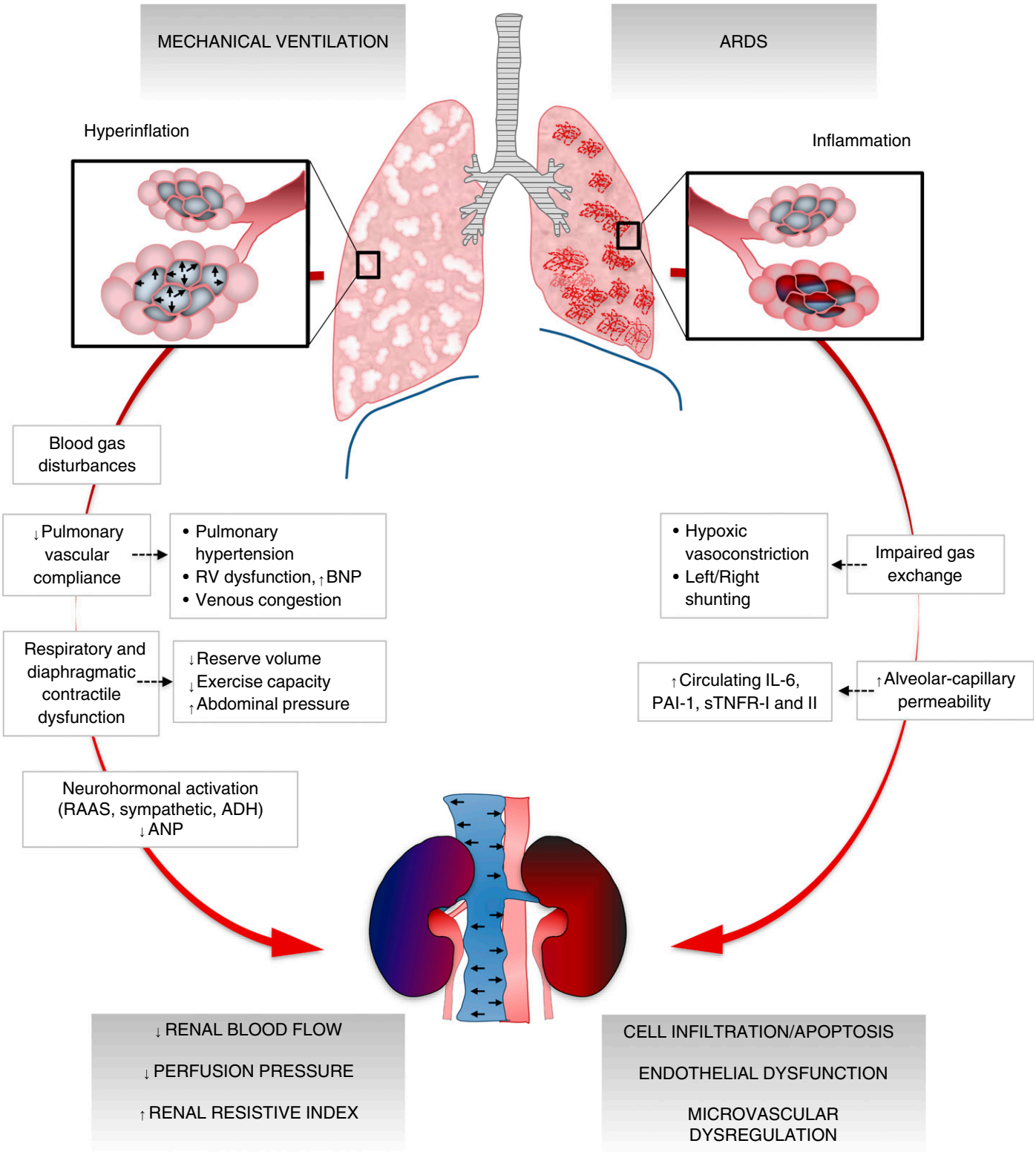

Figure 1. Lung injury and the kidney. Multiple dependent pathways in the setting of acute pulmonary disorders elevate the risk of acute kidney injury. Shown are the possible hemodynamic, neurohormonal, proinflammatory, and proapoptotic consequences of both hyperinflation and lung inflammation on renal 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 chemotactic 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

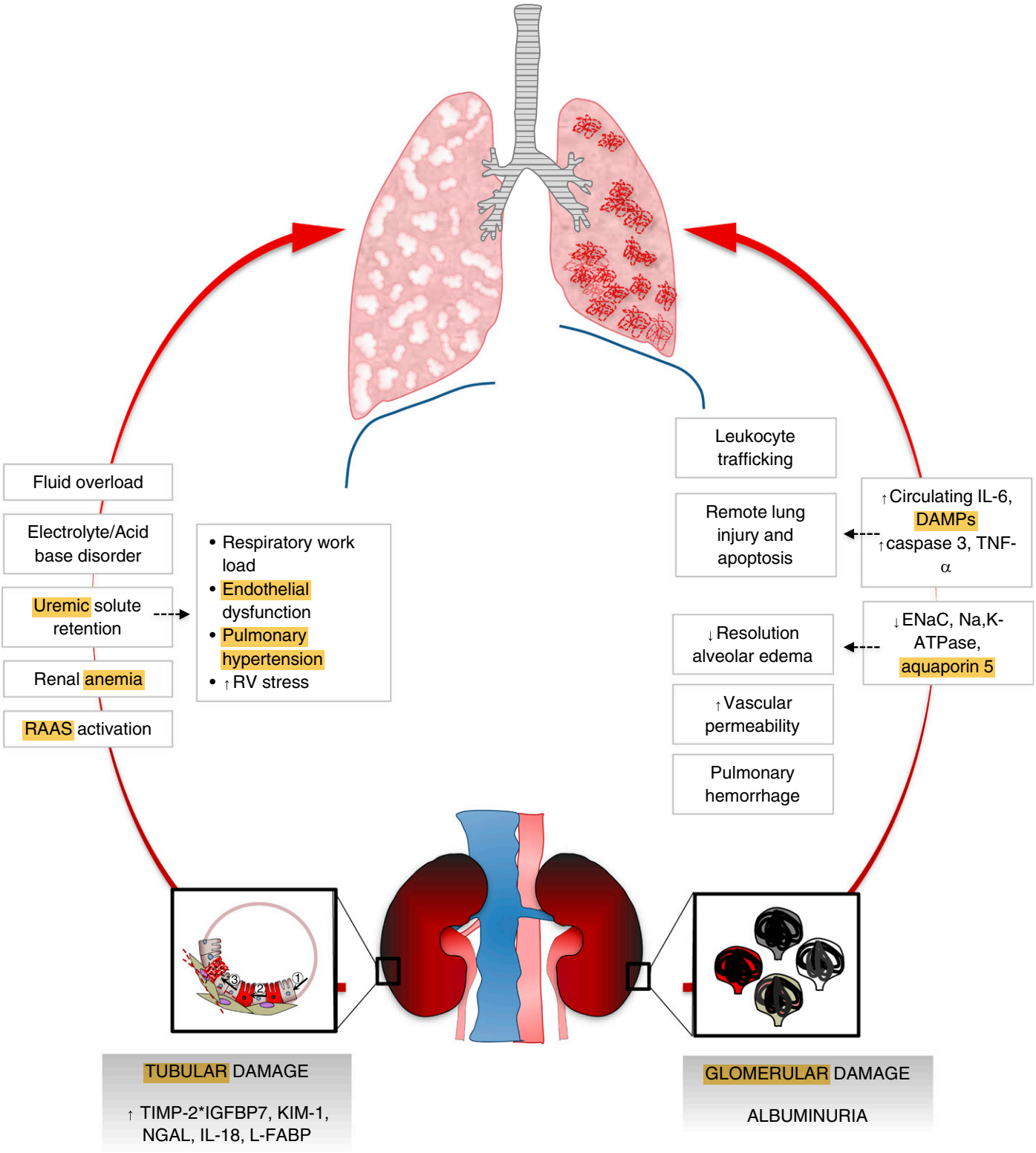

Figure 2. Acute kidney injury and the lung. Acute kidney injury can initiate and perpetuate lung injury via multiple dependent pathways. Shown is the potential multifaceted impact of renal failure on pulmonary function and the current biomarkers to detect renal tubular and glomerular damage. ↑ = increase 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, CO_2 removal through the extracorporeal circuit with relatively low flow rates (~0.5–1.0 L) can remove CO_2, 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

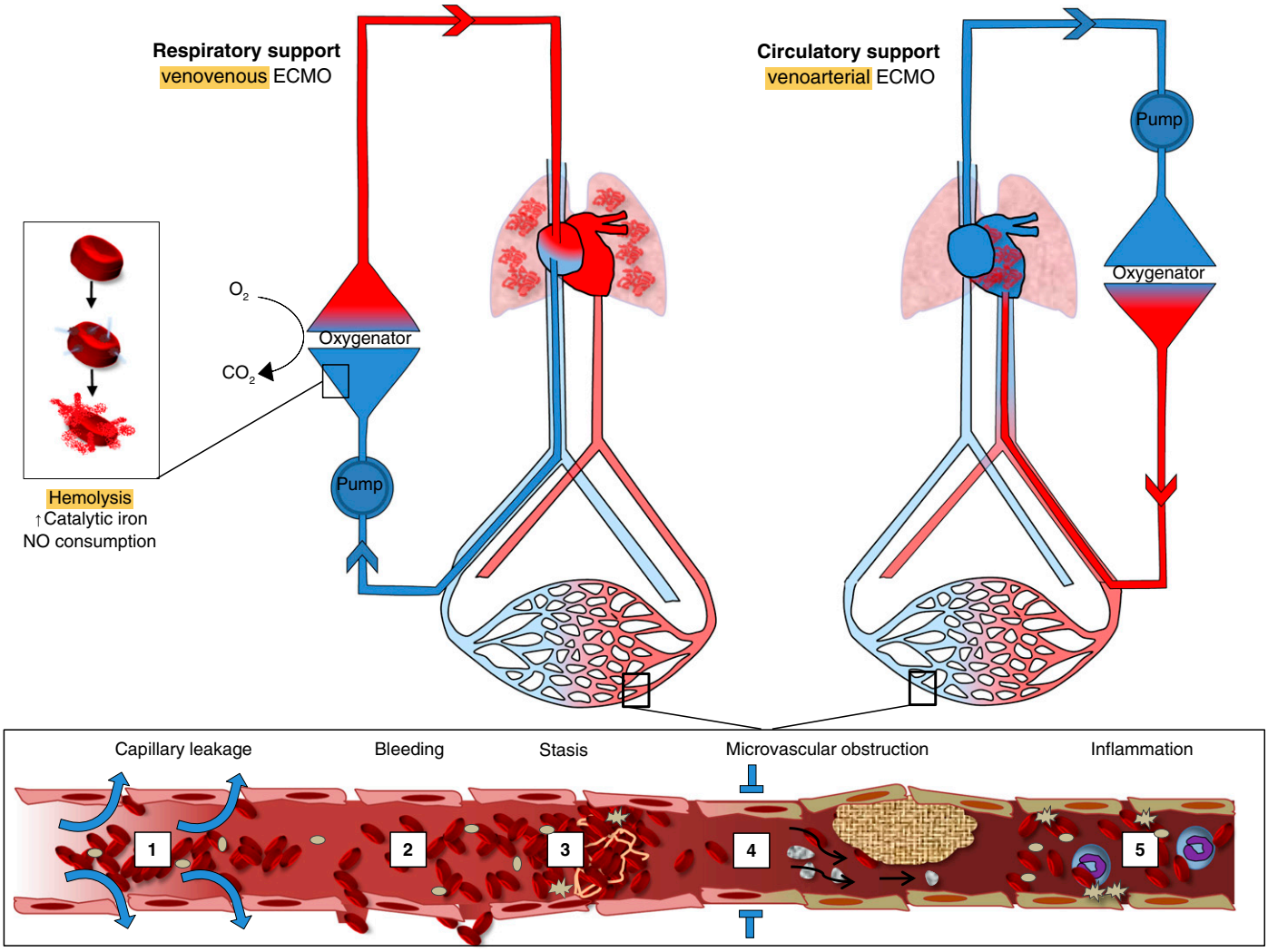

Figure 3. The kidney during extracorporeal membrane oxygenation (ECMO). Acute kidney injury often occurs as a part of multiorgan failure and can be aggravated by exposure to ECMO support. Shown is a synopsis of potential challenges that may impact renal microvascular flow in patients undergoing venovenous 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 G_1 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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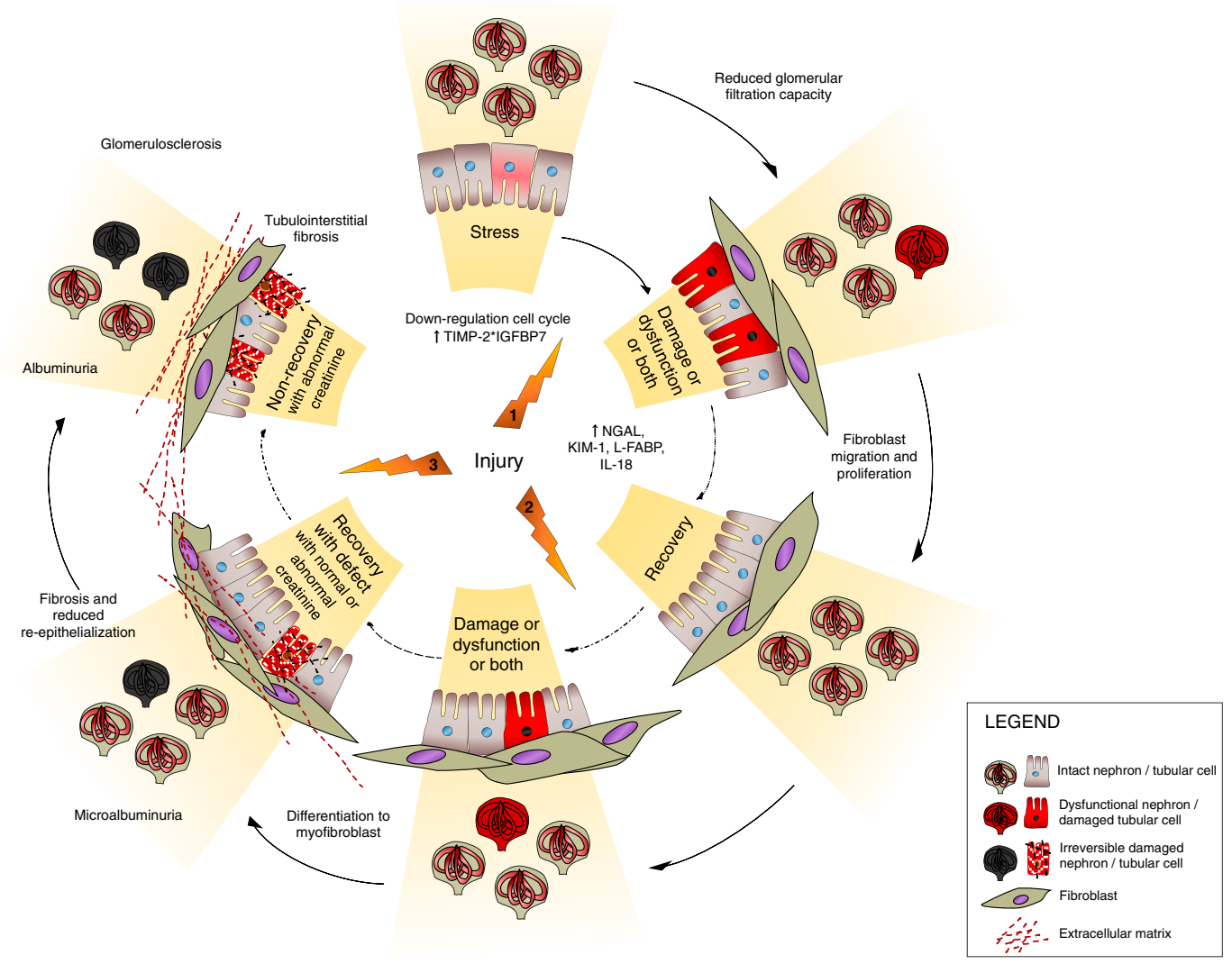

Figure 4. The acute kidney injury clock. The spectrum of kidney injury can vary from biomarker-positive tubular stress to tubular damage, renal dysfunction with elevated creatinine level, reduced glomerular filtration capacity, and tubular recovery, potentially progressing to chronic organ failure. Because 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.

References

1. Li X, Hassoun HT, Santora R, Rabb H. Organ crosstalk: the role of the kidney. *Curr Opin Crit Care* 2009;15:481–487.
2. Kooman JP, Kotanko P, Schols AM, Shiels PG, Stenvinkel P. Chronic kidney disease and premature ageing. *Nat Rev Nephrol* 2014;10: 732–742.
3. Husain-Syed F, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio–pulmonary–renal interactions: a multidisciplinary approach. *J Am Coll Cardiol* 2015;65:2433–2448.
4. Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000;284:43–44.
5. Romundstad S, Naustdal T, Romundstad PR, Sorger H, Langhammer A. COPD and microalbuminuria: a 12-year follow-up study. *Eur Respir J* 2014;43:1042–1050.
6. Madias NE. Renal acidification responses to respiratory acid–base disorders. *J Nephrol* 2010;23:S85–S91.
7. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
8. Curley G, Contreras MM, Nichol AD, Higgins BD, Laffey JG. Hypercapnia and acidosis in sepsis: a double-edged sword? *Anesthesiology* 2010;112:462–472.
9. Ismaiel NM, Henzler D. Effects of hypercapnia and hypercapnic acidosis on attenuation of ventilator-associated lung injury. *Minerva Anestesiol* 2011;77:723–733.
10. Carvalho CR, Barbas CS, Medeiros DM, Magaldi RB, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Munhoz C, Kaufmann M, Ferreira M, *et al*. Temporal hemodynamic effects of permissive hypercapnia associated with ideal PEEP in ARDS. *Am J Respir Crit Care Med* 1997;156:1458–1466.
11. Nardelli LM, Rzezinski A, Silva JD, Maron-Gutierrez T, Ornellas DS, Henriques I, Capelozzi VL, Teodoro W, Morales MM, Silva PL, *et al*. Effects of acute hypercapnia with and without acidosis on lung inflammation and apoptosis in experimental acute lung injury. *Respir Physiol Neurobiol* 2015;205:1–6.
12. Khilnani GC, Banga A, Sharma SK. Predictors of mortality of patients with acute respiratory failure secondary to chronic obstructive pulmonary disease admitted to an intensive care unit: a one year study. *BMC Pulm Med* 2004;4:12.
13. Miller D, Fraser K, Murray I, Thain G, Currie GP. Predicting survival following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease. *Int J Clin Pract* 2012;66:434–437.
14. Liu KD, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. *Clin J Am Soc Nephrol* 2008;3:578–586.
15. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, Dell'Amore A, Urbino R, Mascia L, Evangelista A, *et al*. Extracorporeal CO_2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015;43:120–127.
16. Forster C, Schriewer J, John S, Eckardt KU, Willam C. Low-flow CO_2 removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. *Crit Care* 2013;17:R154.
17. Ricksten SE, Bragadottir G, Redfors B. Renal oxygenation in clinical acute kidney injury. *Crit Care* 2013;17:221.
18. Sharkey RA, Mulloy EM, O'Neill SJ. Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. *Eur Respir J* 1998;12:653–657.
19. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. *Am J Respir Crit Care Med* 1994; 150:833–852.
20. Sharkey RA, Mulloy EM, O'Neill SJ. The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. *Chest* 1999;115:1588–1592.
21. Hemlin M, Ljungman S, Carlson J, Maljukanovic S, Mobini R, Bech-Hanssen O, Skoogh BE. The effects of hypoxia and hypercapnia on renal and heart function, haemodynamics and plasma hormone levels in stable COPD patients. *Clin Respir J* 2007;1:80–90.
22. Anand IS, Chandrashekhar Y, Ferrari R, Sarma R, Guleria R, Jindal SK, Wahi PL, Poole-Wilson PA, Harris P. Pathogenesis of congestive state in chronic obstructive pulmonary disease: studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. *Circulation* 1992;86:12–21.
23. Sharkey RA, Mulloy EM, Kilgallen IA, O'Neill SJ. Renal functional reserve in patients with severe chronic obstructive pulmonary disease. *Thorax* 1997;52:411–415.
24. Mekontso Dessap A, Charron C, Devaquet J, Aboab J, Jardin F, Brochard L, Vieillard-Baron A. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med* 2009;35:1850–1858.
25. Howes TQ, Deane CR, Levin GE, Baudouin SV, Moxham J. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. *Am J Respir Crit Care Med* 1995;151:378–383.
26. Howes TQ, Keilty SE, Maskrey VL, Deane CR, Baudouin SV, Moxham J. Effect of L-arginine on renal blood flow in normal subjects and patients with hypoxic chronic obstructive pulmonary disease. *Thorax* 1996;51:516–519.
27. Panwar R, Hardie M, Bellomo R, Barrot R, Eastwood GM, Young PJ, Capellier G, Harrigan PWJ, Bailey M; CLOSE Investigators; ANZICS Clinical Trials Group. Conservative versus liberal oxygenation targets for mechanically ventilated patients: a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2016;193:43–51.
28. Darmon M, Schortgen F, Leon R, Moutereau S, Mayaux J, Di Marco F, Devaquet J, Brun-Buisson C, Brochard L. Impact of mild hypoxemia on renal function and renal resistive index during mechanical ventilation. *Intensive Care Med* 2009;35:1031–1038.
29. Cutajar M, Thomas DL, Hales PW, Banks T, Clark CA, Gordon I. Comparison of ASL and DCE MRI for the non-invasive measurement of renal blood flow: quantification and reproducibility. *Eur Radiol* 2014;24:1300–1308.
30. Wang E, Meier DJ, Sandoval RM, Von Hendy-Willson VE, Pressler BM, Bunch RM, Alloosh M, Sturek MS, Schwartz GJ, Molitoris BA. A portable fiberoptic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. *Kidney Int* 2012;81:112–117.
31. Kuiper JW, Groeneveld AB, Slutsky AS, Plötz FB. Mechanical ventilation and acute renal failure. *Crit Care Med* 2005;33:1408–1415.
32. Pannu N, Mehta RL. Effect of mechanical ventilation on the kidney. *Best Pract Res Clin Anaesthesiol* 2004;18:189–203.
33. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care* 2013;17:R98.
34. Lombardi R, Nin N, Lorente JA, Frutos-Vivar F, Ferguson ND, Hurtado J, Apezteguia C, Desmery P, Raymondos K, Tomicic V, *et al*.; VENTILA Group. An assessment of the Acute Kidney Injury Network creatinine-based criteria in patients submitted to mechanical ventilation. *Clin J Am Soc Nephrol* 2011;6:1547–1555.
35. Kuiper JW, Vaschetto R, Della Corte F, Plötz FB, Groeneveld AB. Bench-to-bedside review: ventilation-induced renal injury through systemic mediator release—just theory or a causal relationship? *Crit Care* 2011;15:228.
36. Pinsky MR. Cardiovascular issues in respiratory care. *Chest* 2005;128 (5)(Suppl 2):592S–597S.
37. Drury DR, Henry JP, Goodman J. The effects of continuous pressure breathing on kidney function. *J Clin Invest* 1947;26:945–951.
38. Annat G, Viale JP, Bui Xuan B, Hadj Aissa O, Benzoni D, Vincent M, Gharib C, Motin J. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. *Anesthesiology* 1983;58:136–141.
39. Ueda H, Neclerio M, Leather RP, Powers SR Jr. Effects of positive end expiratory pressure ventilation on renal function. *Surg Forum* 1972;23:209–211.
40. Steinhoff H, Falke K, Schwarzhoff W. Enhanced renal function associated with intermittent mandatory ventilation in acute respiratory failure. *Intensive Care Med* 1982;8:69–74.
41. Hering R, Peters D, Zinserling J, Wrigge H, von Spiegel T, Putensen C. Effects of spontaneous breathing during airway pressure release ventilation on renal perfusion and function in patients with acute lung injury. *Intensive Care Med* 2002;28:1426–1433.

42. Ramamoorthy C, Rooney MW, Dries DJ, Mathru M. Aggressive hydration during continuous positive-pressure ventilation restores atrial transmural pressure, plasma atrial natriuretic peptide concentrations, and renal function. *Crit Care Med* 1992;20:1014–1019.
43. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP. Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. *Anesthesiology* 1990;72:966–970.
44. Anand IS. Cardiorenal syndrome: a cardiologist's perspective of pathophysiology. *Clin J Am Soc Nephrol* 2013;8:1800–1807.
45. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013;62:485–495.
46. Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. *Eur Respir J* 1996;9:1283–1292.
47. Husain-Syed F, Muciño-Bermejo MJ, Ronco C, Seeger W, Birk HW. Peritoneal ultrafiltration for refractory fluid overload and ascites due to pulmonary arterial hypertension. *Ann Hepatol* 2015;14:929–932.
48. Hemmer M, Viquerat CE, Suter PM, Vallotton MB. Urinary antidiuretic hormone excretion during mechanical ventilation and weaning in man. *Anesthesiology* 1980;52:395–400.
49. Farge D, De la Coussaye JE, Beloucif S, Fratacci MD, Payen DM. Interactions between hemodynamic and hormonal modifications during PEEP-induced antidiuresis and antinatriuresis. *Chest* 1995;107:1095–1100.
50. Payen DM, Farge D, Beloucif S, Leviel F, De La Coussaye JE, Carli P, Wirquin V. No involvement of antidiuretic hormone in acute antidiuresis during PEEP ventilation in humans. *Anesthesiology* 1987;66:17–23.
51. Imai Y, Parodo J, Kajikawa O, de Perrot M, Fischer S, Edwards V, Cutz E, Liu M, Keshavjee S, Martin TR, *et al*. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003;289:2104–2112.
52. Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, Korpak A, Thompson BT, Chertow GM, Matthay MA; National Heart, Lung, and Blood Institute ARDS Network Clinical Trials Group. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med* 2007; 35:2755–2761.
53. Koyner JL, Murray PT. Mechanical ventilation and the kidney. *Blood Purif* 2010;29:52–68.
54. Seeley EJ. Updates in the management of acute lung injury: a focus on the overlap between AKI and ARDS. *Adv Chronic Kidney Dis* 2013; 20:14–20.
55. Zhao H, Ning J, Lemaire A, Koumpa FS, Sun JJ, Fung A, Gu J, Yi B, Lu K, Ma D. Necroptosis and parthanatos are involved in remote lung injury after receiving ischemic renal allografts in rats. *Kidney Int* 2015; 87:738–748.
56. White LE, Cui Y, Shelak CM, Lie ML, Hassoun HT. Lung endothelial cell apoptosis during ischemic acute kidney injury. *Shock* 2012;38: 320–327.
57. Solymosi EA, Kaestle-Gembardt SM, Vadász I, Wang L, Neye N, Chupin CJ, Rozowsky S, Ruehl R, Tabuchi A, Schulz H, *et al*. Chloride transport–driven alveolar fluid secretion is a major contributor to cardiogenic lung edema. *Proc Natl Acad Sci USA* 2013;110:E2308–E2316.
58. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;52:1527–1539.
59. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, *et al*.; National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation* 2006;114:1883–1891.
60. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, Beauchet A, Jardin F. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med* 2001;29: 1551–1555.
61. Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. *Intensive Care Med* 2007;33:444–447.
62. Bellomo R, Prowle JR, Echeverri JE. Diuretic therapy in fluid-overloaded and heart failure patients. *Contrib Nephrol* 2010;164: 153–163.
63. Testani JM, Khera AV, St John Sutton MG, Keane MG, Wiegers SE, Shannon RP, Kirkpatrick JN. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. *Am J Cardiol* 2010;105: 511–516.
64. Stephany B, Wehbe E, Budev M. Lung transplant patients with elevated baseline pulmonary arterial pressures are more likely to recover from post-transplant acute kidney injury [abstract]. *Am J Transplant* 2015;15(Suppl 3):59.
65. Valentine SL, Sapru A, Higgerson RA, Spinella PC, Flori HR, Graham DA, Brett M, Convery M, Christie LM, Karamessinis L, *et al*.; Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network; Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet). Fluid balance in critically ill children with acute lung injury. *Crit Care Med* 2012;40:2883–2889.
66. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.
67. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yealy DM, Huang DT, Angus DC; ProCESS and ProGReSS-AKI Investigators.The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med* 2016;193:281–287.
68. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, *et al*.; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315:788–800.
69. Afshari A, Brok J, Møller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. *Cochrane Database Syst Rev* [serial on the Internet]. 2010 [accessed July 2016];7:CD002787. Available from: http://summaries.cochrane.org/
70. Ruan SY, Huang TM, Wu HY, Wu HD, Yu CJ, Lai MS. Inhaled nitric oxide therapy and risk of renal dysfunction: a systematic review and meta-analysis of randomized trials. *Crit Care* 2015;19:137.
71. Wraight WM, Young JD. Renal effects of inhaled nitric oxide in humans. *Br J Anaesth* 2001;86:267–269.
72. Goździk W, Albert J, Harbut P, Zieliński S, Ryniak S, Lindwall R, Dziegiel P, Podhorska-Okolow M, Kübler A, Frostell C. Prolonged exposure to inhaled nitric oxide transiently modifies tubular function in healthy piglets and promotes tubular apoptosis. *Acta Physiol* (*Oxf*) 2009;195:495–502.
73. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
74. Hering R, Wrigge H, Vorwerk R, Brensing KA, Schröder S, Zinserling J, Hoeft A, Spiegel TV, Putensen C. The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. *Anesth Analg* 2001;92:1226–1231.
75. Huang CC, Tsai YH, Lin MC, Yang CT, Hsieh MJ, Lan RS. Respiratory drive and pulmonary mechanics during haemodialysis with ultrafiltration in ventilated patients. *Anaesth Intensive Care* 1997;25: 464–470.
76. Prezant DJ. Effect of uremia and its treatment on pulmonary function. *Lung* 1990;168:1–14.
77. Hannink JD, van Hees HW, Dekhuijzen PN, van Helvoort HA, Heijdra YF. Non-invasive ventilation abolishes the IL-6 response to exercise in muscle-wasted COPD patients: a pilot study. *Scand J Med Sci Sports* 2014;24:136–143.
78. Nicholl DD, Hanly PJ, Poulin MJ, Handley GB, Hemmelgarn BR, Sola DY, Ahmed SB. Evaluation of continuous positive airway pressure therapy on renin–angiotensin system activity in obstructive sleep apnea. *Am J Respir Crit Care Med* 2014;190:572–580.

79. Tamura Y, Koyama T, Watanabe H, Hosoya T, Ito H. Beneficial effects of adaptive servo-ventilation therapy on albuminuria in patients with heart failure. *J Cardiol* 2015;65:412–417.
80. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, Karg O, Laier-Groeneveld G, Nava S, Schönhofer B, *et al*. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
81. Sakaguchi Y, Hatta T, Hayashi T, Shoji T, Suzuki A, Tomida K, Okada N, Rakugi H, Isaka Y, Tsubakihara Y. Association of nocturnal hypoxemia with progression of CKD. *Clin J Am Soc Nephrol* 2013;8: 1502–1507.
82. Pialoux V, Hanly PJ, Foster GE, Brugniaux JV, Beaudin AE, Hartmann SE, Pun M, Duggan CT, Poulin MJ. Effects of exposure to intermittent hypoxia on oxidative stress and acute hypoxic ventilatory response in humans. *Am J Respir Crit Care Med* 2009; 180:1002–1009.
83. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, Turin TC, Hanly PJ. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest* 2012; 141:1422–1430.
84. Watz H. Chronic obstructive pulmonary disease: when pulmonologists do something good for the heart. *Am J Respir Crit Care Med* 2016; 193:703–704.
85. Chandra D, Stamm JA, Palevsky PM, Leader JK, Fuhrman CR, Zhang Y, Bon J, Duncan SR, Branch RA, Weissfeld J, *et al*. The relationship between pulmonary emphysema and kidney function in smokers. *Chest* 2012;142:655–662.
86. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, *et al*. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO_2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent study. *Intensive Care Med* 2013;39:847–856.
87. Chen YC, Tsai FC, Fang JT, Yang CW. Acute kidney injury in adults receiving extracorporeal membrane oxygenation. *J Formos Med Assoc* 2014;113:778–785.
88. Chen H, Yu RG, Yin NN, Zhou JX. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. *Crit Care* 2014;18:675.
89. Leaf DE, Rajapurkar M, Lele SS, Mukhopadhyay B, Rawn JD, Frendl G, Waikar SS. Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery. *Kidney Int* 2015;87:1046–1054.
90. Vermeulen Windsant IC, de Wit NC, Sertorio JT, van Bijnen AA, Ganushchak YM, Heijmans JH, Tanus-Santos JE, Jacobs MJ, Maessen JG, Buurman WA. Hemolysis during cardiac surgery is associated with increased intravascular nitric oxide consumption and perioperative kidney and intestinal tissue damage. *Front Physiol* 2014;5:340.
91. Keckler SJ, Laituri CA, Ostlie DJ, St Peter SD. A review of venovenous and venoarterial extracorporeal membrane oxygenation in neonates and children. *Eur J Pediatr Surg* 2010;20:1–4.
92. Andres-Hernando A, Altmann C, Bhargava R, Okamura K, Bacalja J, Hunter B, Ahuja N, Soranno D, Faubel S. Prolonged acute kidney injury exacerbates lung inflammation at 7 days post-acute kidney injury. *Physiol Rep* 2014;2:2.
93. Schmidt M, Bailey M, Kelly J, Hodgson C, Cooper DJ, Scheinkestel C, Pellegrino V, Bellomo R, Pilcher D. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med* 2014;40:1256–1266.
94. Shi J, Chen Q, Yu W, Shen J, Gong J, He C, Hu Y, Zhang J, Gao T, Xi F, *et al*. Continuous renal replacement therapy reduces the systemic and pulmonary inflammation induced by venovenous extracorporeal membrane oxygenation in a porcine model. *Artif Organs* 2014;38: 215–223.
95. Frazier OH, Myers TJ, Westaby S, Gregoric ID. Clinical experience with an implantable, intracardiac, continuous flow circulatory support device: physiologic implications and their relationship to patient selection. *Ann Thorac Surg* 2004;77:133–142.
96. Orime Y, Shiono M, Hata H, Yagi S, Tsukamoto S, Okumura H, Nakata K, Kimura S, Hata M, Sezai A, *et al*. Cytokine and endothelial damage in pulsatile and nonpulsatile cardiopulmonary bypass. *Artif Organs* 1999;23:508–512.
97. Patel AM, Adeseun GA, Ahmed I, Mitter N, Rame JE, Rudnick MR. Renal failure in patients with left ventricular assist devices. *Clin J Am Soc Nephrol* 2013;8:484–496.
98. Haase M, Kellum JA, Ronco C. Subclinical AKI—an emerging syndrome with important consequences. *Nat Rev Nephrol* 2012;8: 735–739.
99. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, *et al*. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;17:R25.
100. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. *Clin J Am Soc Nephrol* 2015;10:147–155.
101. Katz N, Ronco C. Acute kidney stress—a useful term based on evolution in the understanding of acute kidney injury. *Crit Care* 2016;20:23.
102. Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, Chawla LS, Cruz D, Ince C, Okusa MD; ADQI 10 Workgroup. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int* 2014;85:513–521.