REVIEW ARTICLE

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Cardiovascular Consequences of Acute Kidney Injury

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Acute kidney injury is generally characterized by an abrupt rise in the serum creatinine level, decreased urinary output, or both.[1] Advances in critical care and renal replacement therapies have provided tools that can support patients through most of the immediate complications of acute kidney injury, such as uremia or hyperkalemia, which could be rapidly fatal. Yet mortality from acute kidney injury remains high. Up to 60% of patients with severe acute kidney injury who are admitted to an intensive care unit (ICU) die from the disorder[2]; the long-term risk of death associated with acute kidney injury is also increased.[3-5]

Acute kidney injury is associated with an increased risk of chronic and end-stage kidney disease[6] and has adverse effects on other organ systems, including the heart. Likewise, patients with chronic kidney disease are at high risk for acute kidney injury and adverse cardiovascular sequelae.[7-9] Accumulating evidence supports the notion that cardiovascular damage due to acute kidney injury leads to other poor outcomes,[10] independent of or intertwined with the risks associated with the development of chronic kidney disease (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[11]

Interactions between cardiac and kidney diseases have been classified as cardiorenal syndromes. A current classification[10] includes five types of cardiorenal syndromes: acute cardiac impairment leading to acute kidney injury (type 1), chronic cardiac impairment leading to kidney impairment (type 2), acute kidney injury leading to cardiac impairment (type 3), chronic kidney disease leading to cardiac impairment (type 4), and systemic conditions leading to both cardiac and kidney impairment (type 5) (Fig. S1).

In this review, we discuss the current understanding of the cardiovascular consequences of acute kidney injury (i.e., type 3 cardiorenal syndrome). We also discuss potential preventive strategies that target acute and recovery phases, with the aim of reducing the risk of subsequent adverse clinical events.

EPIDEMIOLOGIC INSIGHTS

Chronic hypertension and heart failure are risk factors for acute kidney injury and can hamper recovery from kidney injury.[12] Certain systemic conditions leading to acute kidney injury, such as sepsis, are additional potential causes of cardiovascular damage.[7]

Conversely, acute kidney injury is associated with an increased risk of death and both short-term and long-term cardiovascular complications, such as decompensated heart failure (Fig. 1). The association between acute kidney injury and long-term cardiovascular events has been observed in several large cohort studies (Table S1), although direct comparisons of risk among available studies are of limited

value, since the definition of acute kidney injury varies from study to study. In 2018, Go et al. reported a study examining the association between acute kidney injury and the risk of cardiovascular events in a large, contemporary, matched U.S. cohort of 430,159 hospitalized adults (39,153 of whom had acute kidney injury).[13] During the patients' first year after discharge, the risk of hospitalization for heart failure was increased by 44% in the group with acute kidney injury as compared with the group that did not have kidney injury. In a Canadian population-based study involving 156,690 patients who survived a hospitalization complicated by acute kidney injury, 1 in 5 patients was readmitted within 30 days, most often with heart failure.[14]

A 2017 meta-analysis of 25 studies involving a total of 254,408 patients, including 55,150 with acute kidney injury,[15] showed that the condition was associated with an 86% increase in the risk of death from cardiovascular causes (95% confidence interval [CI], 72 to 101) during a median follow-up of 1.4 years (interquartile range [IQR], 1.3 to 1.9). There was a 58% increase (95% CI, 46 to 72) in the risk of chronic heart failure during 2.9 years of follow-up (IQR, 1.7 to 3.8), a 40% increase (95% CI, 23 to 59) in the risk of acute myocardial infarction during 2.3 years of follow-up (IQR, 0.7 to 2.9), and a 15% increase (95% CI, 3 to 28) in the risk of stroke over a period of 2.7 years (IQR, 2.0 to 3.4).[15] The increased relative risk did not differ between patients with and those without chronic kidney disease, and neither status with respect to recovery of renal function nor severity of acute kidney injury was associated with a change in the risk of myocardial infarction. Such associations suggest that the long-term risk of cardiovascular

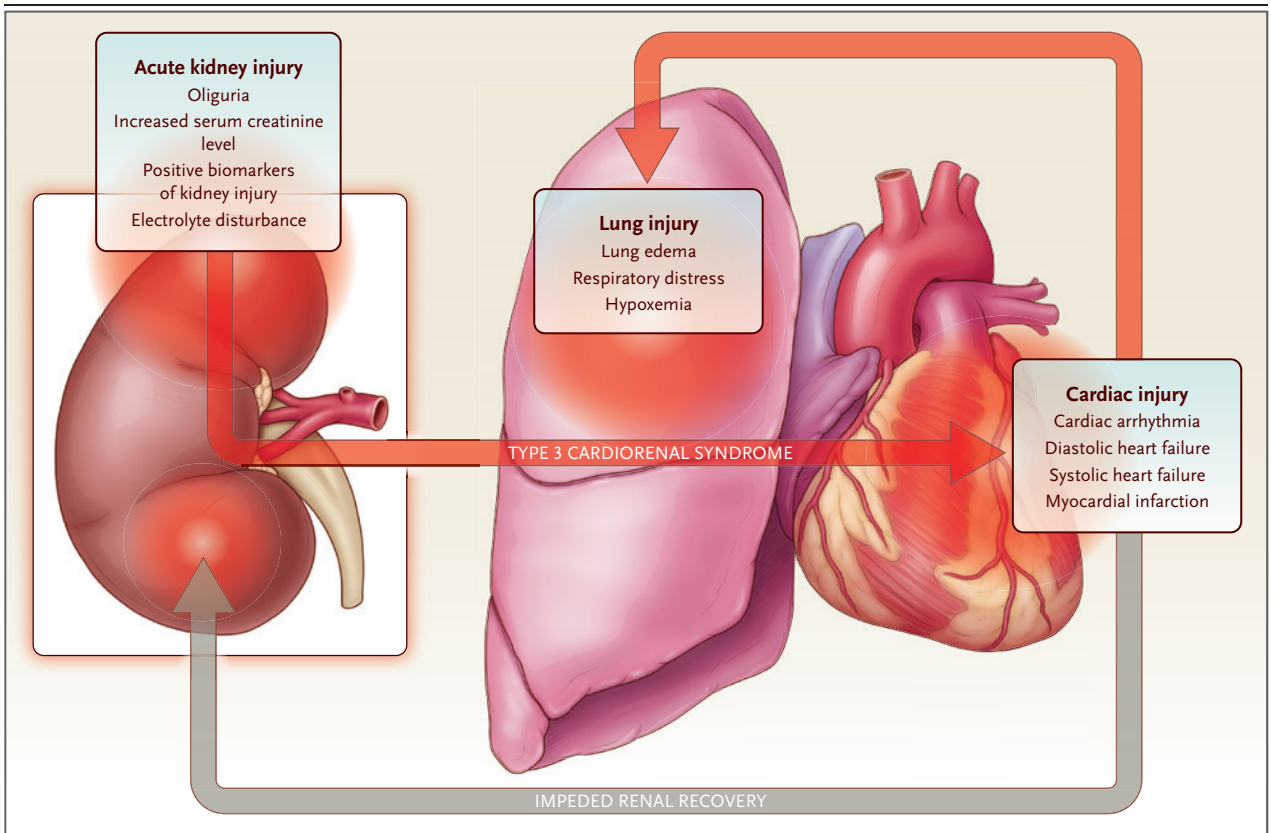

Figure 1. Cardiac and Pulmonary Consequences of Acute Kidney Injury.

Acute kidney injury has been shown to promote cardiac injury and dysfunction, defined as type 3 cardiorenal syndrome. Heart failure, in turn, can impede renal recovery. Lung injury and hypoxemia after acute kidney injury can arise both from increased capillary permeability and from increased hydrostatic capillary pressure due to heart failure.

events is associated with the acute kidney injury itself and not only with the risk of end-stage kidney disease.[16-18]

Moreover, a history of heart failure is not the sole driver of the risk of cardiovascular events. Bansal et al.[19] reported that among patients without a history of heart failure, the occurrence of acute kidney injury was associated with a 23% increase in the risk of incident heart failure (hazard ratio, 1.23; 95% CI, 1.19 to 1.27). In a sensitivity analysis that excluded patients with cardiovascular risk factors, the risk associated with acute kidney injury was 38% (hazard ratio, 1.38; 95% CI, 1.21 to 1.56).[19] The long-term burden of acute kidney injury has also been shown in a U.S. cohort of 210,895 adults without a history of heart failure.[20] Patients with community-acquired acute kidney injury had approximately twice the risk of hospitalization for new heart failure within 365 days as did patients without acute kidney injury, in an analysis controlled for baseline and clinical characteristics. In a study involving children and young adults admitted to an ICU, those with acute kidney injury in the absence of other coexisting conditions had an increased risk of death.[21] Finally, analyses of claims databases show that patients with acute kidney injury are more likely than patients without such injury to have subsequent hypertension (46.1% vs. 41.2%, P<0.001).[22] Hypertension thus appears likely to be associated with the poor cardiovascular and renal outcomes of acute kidney injury.

PATHOPHYSIOLOGY

Although the pathophysiology of cardiovascular damage after acute kidney injury is not fully understood, several factors appear to be involved (Figs. 2 and 3). The most prominent are cardiac inflammation, cardiac fibrosis, neurohormonal activation, and electrolyte disturbances.[23,24]

In some animal models, a transient episode of ischemic acute kidney injury increases plasma levels of certain circulating inflammatory mediators (e.g., tumor necrosis factor α [TNF-α], interleukin-1, interleukin-6, intercellular adhesion molecule 1, and interferon-γ).[25] Some of these cytokines exert direct cardiodepressant effects.[26] Renal ischemia induces apoptosis of cardiac muscle cells, as well as inflammation, including leukocyte infiltration, within 48 hours after reperfusion,[27,28] and blocking TNF-α limits the apoptosis.[27] In mice, acute kidney injury induces cardiac mitochondrial injury, which is associated with apoptosis and diastolic dysfunction within 72 hours and can be prevented by inhibition of dynamin-related protein 1, a protein central to mitochondrial fusion and fragmentation.[29] Experimentally induced ischemic acute kidney injury in rats affects the metabolomic profile in the heart, with altered metabolism, amino acid depletion, increased oxidative stress, and a shift toward anaerobic forms of energy production, as well as echocardiographic signs of diastolic dysfunction,[30,31] all findings that are similar to those observed after direct ischemic myocardial injury. In mice, kidney failure induced by subtotal nephrectomy increases cardiac susceptibility to ischemic–reperfusion injury and an associated down-regulation of cardiac adiponectin signaling.[32] It is difficult to generalize such preclinical insights to acute kidney injury in humans, owing to limitations and pitfalls of animal models of inflammation, such as sex- and strain-related differences in the immune responses of rodents, variable expression of some molecular markers, or the presence of factors that limit the systemic proinflammatory response.[33]

Biomarker studies in patients provide additional relevant translational insights. Several biomarkers that are up-regulated after acute kidney injury in humans have been found to be associated with an increased number of cardiovascular events, and the underlying pathways of these biomarkers may play a role in the development of cardiovascular damage. For example, neutrophil gelatinase–associated lipocalin (NGAL), a protein expressed in renal tubular epithelial cells[34] and in immune cells, was reported to be associated with the development of cardiac fibrosis after mineralocorticoid-receptor activation.[35-37] Recently, in a nested, matched, case–control study involving patients with incident heart failure, 89 of 252 circulating plasma proteins in the discovery set and 38 in the replication set were associated with heart failure.[38] Furthermore, for these validated proteins, four major pathways were involved: inflammation and apoptosis; growth, angiogenesis, and extracellular-matrix remodeling; metabolism; and the renin–angiotensin–aldosterone system.[34-38] Two of the identified proteins, insulin-like growth factor–binding protein 7 (IGF-BP7), a biomarker of cell-cycle

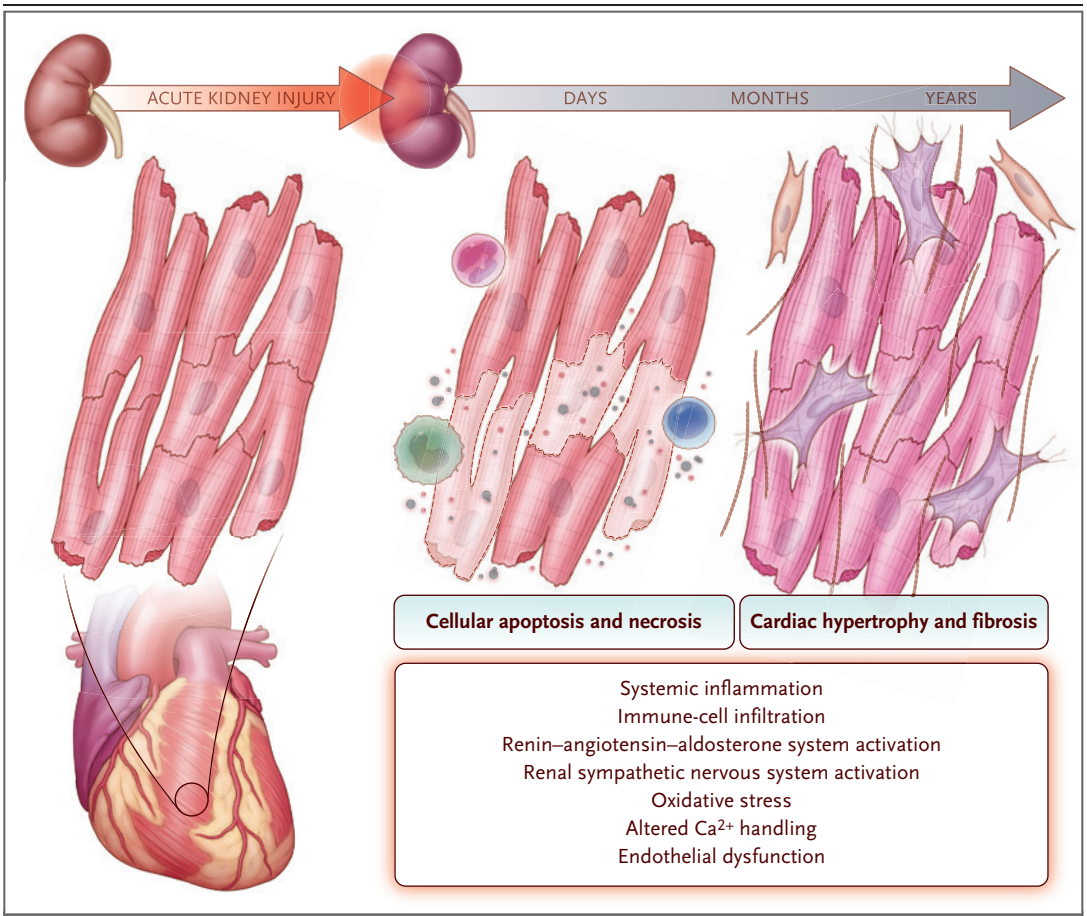

Figure 2. Pathophysiological Features of Cardiac Damage after Acute Kidney Injury.
Acute kidney injury induces structural cardiac damage, with cardiac inflammation and cellular apoptosis and necrosis developing within days after an event and cardiac fibrosis developing months or years later.

arrest, and kidney injury molecule 1 (KIM-1), are also increased during kidney injury. With the use of a complex-network approach, several biomarkers have been shown to be linked by known protein interactions, biochemical interactions, or gene regulatory pathways (including a cluster depicting inflammation or apoptosis and the renin–angiotensin–aldosterone system) involved in acute kidney injury (Fig. S2).[34-38] Such observations further support the concept of incident heart failure triggered by acute kidney injury.

Induction of the renin–angiotensin–aldosterone system is a hallmark of the cardiovascular response to acute kidney injury and appears to trigger a cardiac immune response and subsequent fibrosis.[39-41] Angiotensin II has long been recognized as a factor that mediates cardiac hypertrophy and impaired cardiac function and induces macrophage infiltration, cardiac inflammation, and myocardial fibrosis.

Activation of the renal sympathetic nervous system also contributes to cardiac injury after acute kidney injury, furthering the likelihood of endothelial dysfunction and cardiac fibrosis, as well as ventricular dysfunction.[42] Polhemus et al.[43] showed that blockage of the renal sympathetic nervous system prevented cardiac damage, in part through inhibition of angiotensin II and renal neprilysin activity. The protective effects of renal sympathetic denervation were partially reproduced by the use of bisoprolol, a β_1 antagonist.[43] The parenchymal scarring mediated by the fibrogenic response to acute kidney injury may ultimately lead to heart failure.[44]

The cardiac consequences of acute kidney injury might also be mediated by the lectin pro-

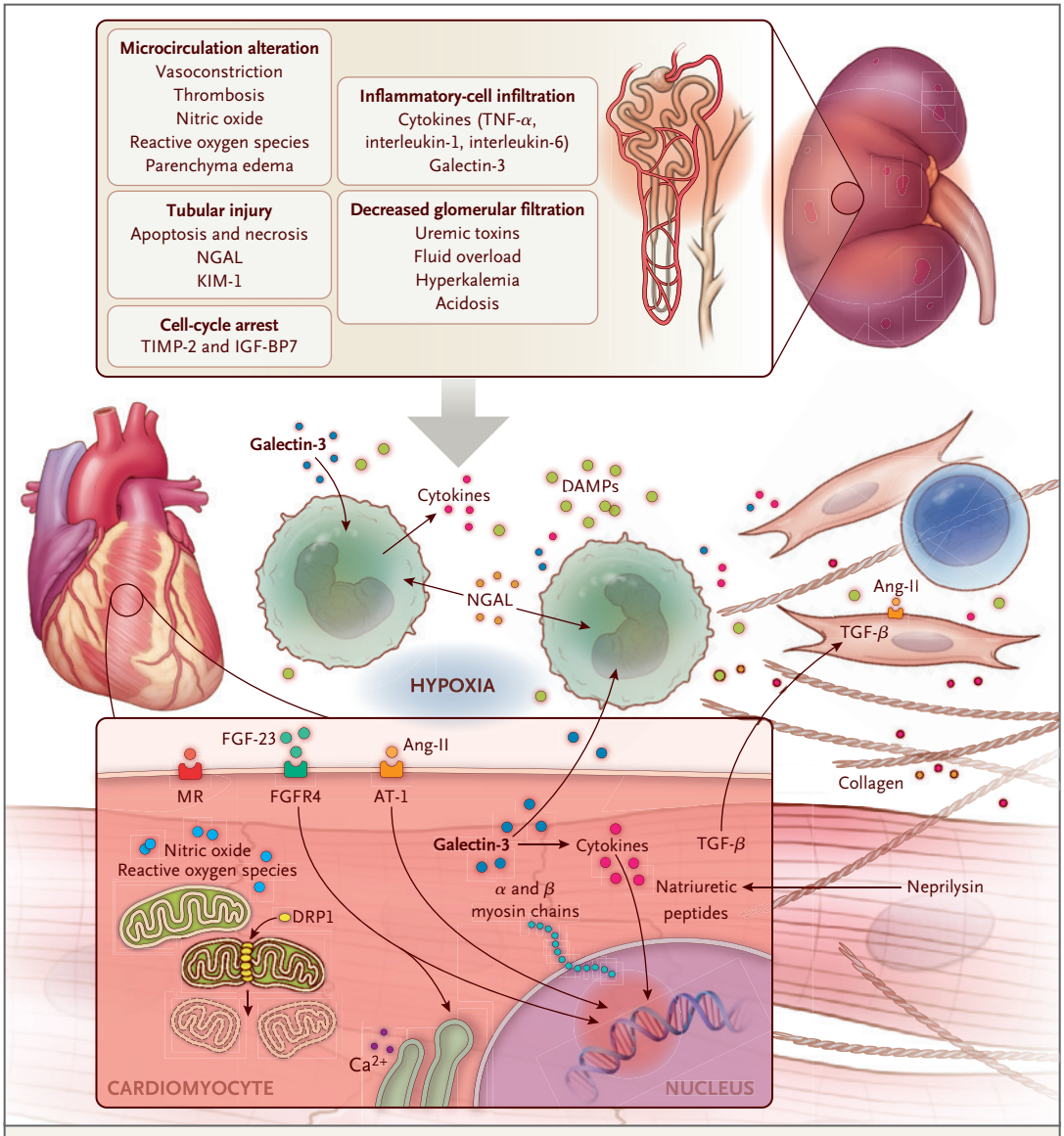

Figure 3. Cellular Mechanisms of Cardiac Damage after Acute Kidney Injury.

Potential cellular mechanisms of cardiac injury after acute kidney injury involve local inflammation and immune response, cellular energy regulation through altered mitochondrial function, and the development of local fibrosis. Ang-II denotes angiotensin II, AT-1 angiotensin II receptor type 1, DAMPs damage-associated molecular pattern molecules, DRP1 dynamin-related protein 1, FGF-23 fibroblast growth factor 23, FGFR4 fibroblast growth factor receptor type 4, IGF-BP7 insulin-like growth factor–binding protein 7, KIM-1 kidney injury molecule 1, MR mineralocorticoid receptor, NGAL neutrophil gelatinase–associated lipocalin, TGF-β transforming growth factor β, TIMP-2 tissue inhibitor of matrix metalloproteinase type 2, and TNF-α tumor necrosis factor α.

tein galectin-3,[45-47] as shown in studies of mice with acute kidney injury in which galectin-3 induced cardiac inflammation, cardiac fibrosis,[48] and cardiac failure. Furthermore, increased expression of galectin-3 has been associated with cardiac damage after acute kidney injury in critically ill patients (Fig. S3).[49] In a community-based cohort study, alteration of kidney function has been reported to be associated with increased galectin-3 levels, whereas the degree of longitudinal rise in galectin-3 levels predicts future heart failure.[50]

In other studies, fibroblast growth factor 23 (FGF-23), a predominantly bone-derived hormone

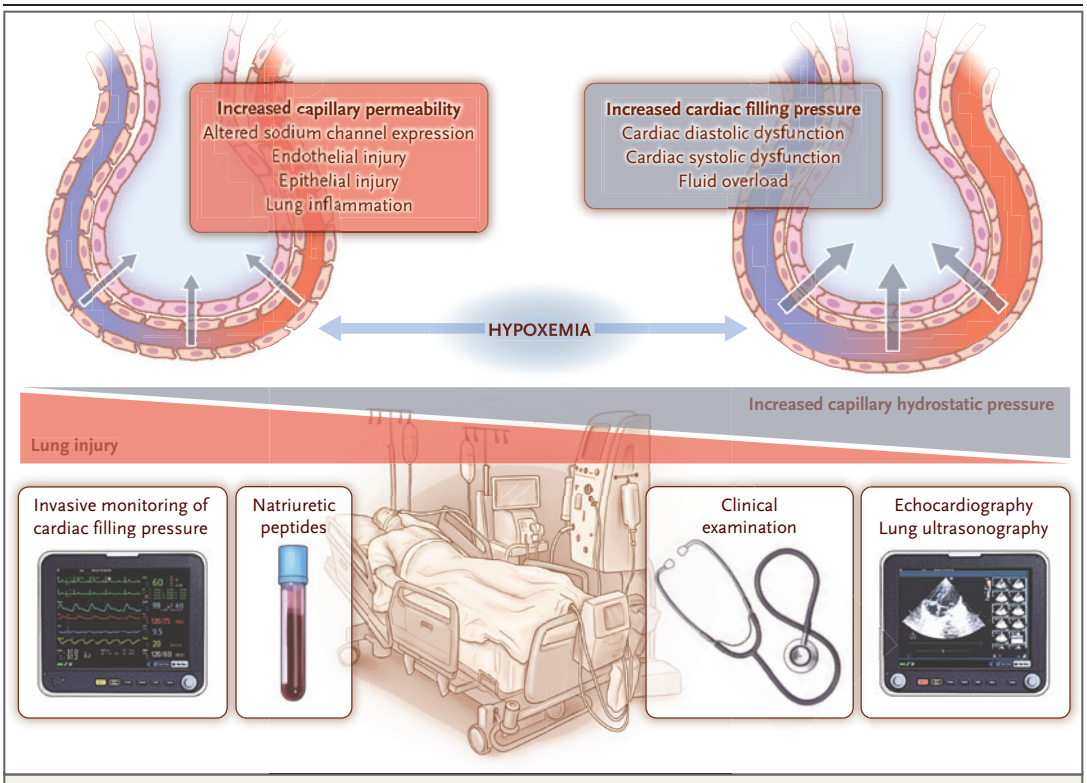

Figure 4. Pulmonary Edema after Acute Kidney Injury.

Mechanisms of pulmonary edema after acute kidney injury involve direct lung injury with increased lung capillary permeability and increased capillary hydrostatic pressure due to increased cardiac filling pressure. Fluid overload in patients with oliguria can contribute to the pathogenesis of pulmonary edema. A combination of clinical examination, measurement of plasma biomarkers such as natriuretic peptides, echocardiography, lung ultrasonography, and in challenging cases, invasive cardiac catheterization may be needed to identify the mechanisms of pulmonary edema in patients who have had an episode of acute kidney injury.

involved in phosphate homeostasis, has been described as a likely mediator of cardiovascular disease associated with chronic kidney disease. FGF-23 was observed to be rapidly up-regulated after an episode of acute kidney injury in a murine model.[51] In addition, reduced expression of klotho, a coreceptor of FGF-23, has been linked to secondary cardiac damage after acute kidney injury (as reviewed by Christov et al.).[52]

Electrolyte disturbances and metabolic acidosis are also thought to contribute to cardiac manifestations after acute kidney injury. Hyperkalemia can induce electrophysiological disturbances that alter cardiac conduction and potentially lead to cardiac arrest.[53] In rats, acute kidney injury increases the risk of ventricular arrhythmia after myocardial infarction because of distorted intracellular calcium homeostasis due to changes in the dihydropyridine receptor on the L-type calcium channel.[31] Profound metabolic acidosis alters myocyte contraction and excitability in vitro.[54]

DIAGNOSTIC FEATURES

Patients with, or recovering from, acute kidney injury often present with clinical signs and symptoms of heart failure, but the diagnosis can be challenging in such patients, since the symptoms are often nonspecific. Biomarkers and imaging techniques are frequently used for diagnostic purposes and to guide treatment decisions and monitor the response to therapy (Fig. 4). Capillary pulmonary pressure measured with a pulmonary-artery catheter can provide useful information regarding possible lung injury or cardiogenic pulmonary edema. Echocardiography, which has become the standard of care for

evaluating cardiac function and left ventricular filling pressures, can be used to detect an altered ejection fraction and cardiac diastolic dysfunction.

Brain natriuretic peptide (BNP) and, more often, N-terminal pro–B-type natriuretic peptide (NT-proBNP), are commonly used as biomarkers of heart failure.[55,56] However, there is no consensus on cutoff values to define heart failure in patients with acute kidney injury, and both false positive and false negative results indicating high cardiac filling pressures have been reported.[55] In patients with kidney disease independent of heart failure, elevated plasma levels of these peptides are often found as a result of reduced renal clearance. The renal clearance of natriuretic peptides ranges from 15 to 60%.[56,57] The effect of a reduced glomerular filtration rate on plasma levels of natriuretic peptides, however, appears to be greatest in patients with severely impaired renal function or in patients receiving dialysis.[58] Therefore, elevated natriuretic peptide levels (both absolute values and variation in plasma levels over time) most likely reflect a contribution of increased cardiac filling pressure in patients with mild altered renal function rather than a decrease in glomerular filtration.[58] Levels of cardiac troponin, a biomarker for myocardial injury, are frequently elevated in patients with renal dysfunction — specifically, in 30 to 75% of patients receiving hemodialysis.[59] Since plasma troponin levels can be affected by both cardiac injury and decreased renal clearance, a single measurement may be insufficient to diagnose acute cardiac ischemia. In our view, the clinical presentation, electrocardiographic findings, and kinetics of troponin are all important to consider in the diagnosis of an acute coronary syndrome in patients with acute kidney injury.

DIAGNOSTIC AND THERAPEUTIC APPROACHES TO CARDIORENAL OUTCOMES

An early and rapid diagnostic test to detect acute kidney injury is important to maximize the effect of mitigating strategies that are likely to improve cardiorenal outcomes. Despite the established clinical importance of acute kidney injury, it has eluded diagnosis in up to 25% of cases in developed countries and in up to 75% of cases in developing countries,[15,60] with a correspondingly high burden of cardiovascular sequelae. Although prevention of the occurrence or progression of acute kidney injury is a critical goal, many cases are diagnosed only in the late stages. Earlier identification with the use of artificial intelligence algorithms[61] or measurement of sensitive biomarkers, such as combined measurement of the tissue inhibitor of matrix metalloproteinase 2 and IGF-BP7 or measurement of NGAL or proenkephalin, has been reported to facilitate the detection of acute kidney injury.[62,63] Early recognition of acute kidney injury could improve the chances of a successful outcome through early implementation of care strategies (e.g., facilitation of focused evaluation, avoidance of nephrotoxins, and hemodynamic optimization).[64] Biomarker levels that suggest acute kidney injury in survivors of ICU stays have been reported to be associated with an increased 1-year risk of death[65]; thus, it has been suggested that the use of biomarkers to identify patients likely to benefit from renal preventive strategies would be important.[64] To this end, obtaining a nephrology or intensive care consultation has been suggested for patients with a diagnosis of acute kidney injury.[66]

THERAPEUTIC PERSPECTIVES ON ONGOING AND POSTACUTE KIDNEY INJURY

Fluid overload is common in patients with acute kidney injury and is associated with poor outcomes.[67] Both reduced cardiac function and fluid overload can contribute to increased pulmonary capillary hydrostatic pressure. The risk of pulmonary edema after acute kidney injury can be further enhanced by increased pulmonary capillary permeability (Fig. 4),[68] which may be mediated by pulmonary inflammation, endothelial injury, altered sodium-channel expression, or oxidative stress.[69] Acute kidney injury can be associated with hypoxemia, which leads to increased and prolonged use of mechanical ventilation in patients admitted to the ICU.[70] Diuretics or ultrafiltration techniques have been shown to be helpful in controlling fluid balance in patients who have acute kidney injury with fluid overload.[71] Such approaches should ideally be guided by measurement or estimation of vascular and cardiac filling pressures with the use of the diagnostic methods described above. Invasive moni-

toring of central venous or right atrial pressure can also be used to guide treatment in the most severely affected patients. However, improved monitoring strategies during treatment of acute kidney injury remain to be prospectively assessed in trials with definitive renal and cardiovascular end points.

Recognized indications for renal replacement therapy are complications of severe acute kidney injury, such as severe fluid overload that is not controlled with diuretics or severe hyperkalemia. But early use of renal replacement therapy has failed to improve outcomes among critically ill patients with acute kidney injury,[72,73] and only a minority of such patients receive renal replacement therapy (5% in a population-based study of residents in Canada).[74] Hemodialysis-induced circulatory stress and reduced renal perfusion have been shown to be associated with repeated episodes of myocardial ischemia and stunning.[75] For patients receiving renal replacement therapy, the use of higher dialysate sodium levels, lower temperature, and individualized ultrafiltration rates have been proposed to improve hemodynamic tolerance of hemodialysis, but with minimal evidence to date.[76,77]

The use of renin–angiotensin–aldosterone system inhibitors is associated with improved outcomes in patients recovering from acute kidney injury,[78] and strategies to prevent cardiovascular damage by reducing activation of the renin–angiotensin–aldosterone system are likely to improve long-term outcomes. In an observational study of the association between renin–angiotensin–aldosterone system inhibition and mortality among 1551 critically ill patients, prescription of an angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) at the time of discharge was associated with a reduced risk of all-cause mortality at 1 year (hazard ratio, 0.47; 95% CI, 0.27 to 0.82), after adjustment for other prognostic factors.[78] Similar findings were observed in a cohort study involving 46,253 patients who had an episode of acute kidney injury during hospitalization: use of a renin–angiotensin system inhibitor after discharge was associated with improved survival (hazard ratio for death, 0.85; 95% CI, 0.81 to 0.89), although there was an increased risk of hospitalization for renal causes among treated patients.[79] Since this was an observational study, confounding by indication is a possibility. Temporary discontinuation of ACE inhibitors and ARBs has been advocated for patients undergoing surgery.[64] Yet it remains largely unknown whether withholding or continuing these treatments before major surgery influences the outcome, and the effects are currently being investigated.[80]

Follow-up by a nephrologist after an episode of acute kidney injury has been associated with reduced all-cause mortality (hazard ratio, 0.76; 95% CI, 0.62 to 0.93).[81] Strikingly, however, only a minority of at-risk survivors of acute kidney injury are referred to a nephrologist for ongoing care.[82] The relatively small number of nephrologists has been proposed as a reason for the low rate of referral. Enlisting primary care providers to screen patients for persistent renal dysfunction and subclinical cardiovascular and renal damage, with selective referral to a nephrologist, cardiologist, or both, may be a more pragmatic approach. This may allow the simultaneous management of cardiac and renal triggers and the consequences of chronic cardiorenal syndrome. Such an approach would include the management or prevention of associated cardiovascular risk factors (e.g., treatment of hypertension and management of obesity or dyslipidemia), interventions to address malnutrition or electrolyte disturbances, avoidance of nephrotoxicity, and individualized adjustment of medications shown to improve clinical outcomes across the cardiovascular and renal continuum in patients with stable chronic kidney disease (e.g., renin–angiotensin–aldosterone system inhibitors and sodium–glucose cotransporter 2 inhibitors) (Table S2).[44]

SUMMARY

Acute kidney injury is recognized as a potential risk factor for future cardiovascular events, especially heart failure. Preclinical models and biomarkers have identified several likely pathophysiological mechanisms, apparently involving mitochondrial injury, inflammation, cellular death, and profibrotic pathways. The therapeutic use of blockers of the renin–angiotensin–aldosterone system may be associated with improved outcomes in patients recovering from acute kidney injury, but interventional trials are needed to refine strategies for treating patients after an acute episode. We believe that it is important for health care professionals to be aware of acute

kidney injury and its effect on the cardiovascular system, if patients are to receive needed, potentially lifesaving treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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