The Role of Novel Cardiorenal Biomarkers in the Cardiac Catheterization Laboratory for the Detection of Acute Kidney Injury

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Contrast-induced nephropathy related to cardiac and peripheral vascular procedures is a major problem in the United States and abroad. Measures to prevent and treat this complication have been hampered by the lack of clinical tools to detect acute kidney injury following contrast administration. Emerging novel serum and urinary biomarkers may provide sensitive detection of early kidney injury prior to creatinine elevation and allow for more precise risk stratification and management of patients. This article discusses the biologic and clinical data supporting the development and utility of several promising biomarkers in the management of patients undergoing cardiac catheterization and percutaneous coronary intervention.

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KEY WORDS

Contrast-induced acute kidney injury • Cardiac catheterization • Percutaneous coronary intervention • Biomarkers

Contrast administration for coronary and peripheral angiography is a major cause of acute kidney injury (AKI) worldwide. Currently, contrast-induced AKI (CI-AKI) is the third leading cause of hospital-acquired AKI in the United States. Over 50% of these cases are the result of contrast exposure during cardiac catheterization and/or percutaneous coronary interventions (PCI).[1,2] Despite these statistics, effective screening, preventive, and therapeutic strategies for CI-AKI remain areas for improvement.

CI-AKI has been defined by multiple criteria, most often an absolute rise in serum creatinine of $\geq$ 0.5 mg/dL, or increase by at least 25% at 48 hours from pre-contrast levels is considered diagnostic of this complication.[3] Elucidation of the true incidence of CI-AKI has been difficult as the serum creatinine levels may not reflect the underlying renal dysfunction until 72 to 120 hours after the initial insult.[4] Given the progressively decreasing lengths of hospital stays for interventional procedures, detection of CI-AKI in this setting will continue to be challenging. Furthermore, increasing evidence is mounting that serum creatinine lacks the sensitivity to detect occult, but clinically relevant, AKI.[5,6] In addition, serum creatinine levels provide no information as to the etiology or anatomic location of renal injury.[6] For these reasons, discovery and validation of novel biomarkers that reflect early AKI is important.

To provide clinical utility, novel AKI markers will have to fill specific niches. A given marker (or panel of markers) must provide one or more of the following characteristics: (1) pre-contrast AKI risk assessment to aid in primary prevention; (2) early detection of AKI to guide secondary prevention strategies; and/or (3) prognostic information to guide long-term therapy following AKI and predict progression to chronic kidney disease (CKD). To date, most studies in this context have focused on goals 1 and 2, with few addressing goal 3. This article describes the biology and clinical data available for multiple novel biomarkers related to AKI with a particular focus on CI-AKI following cardiac catheterization.

Pathophysiology of CI-AKI

The relevance of specific biomarkers is inextricably linked to the pathophysiology of CI-AKI. Our current understanding of this process suggests that multiple factors play a role in the development of CI-AKI, including medullary hypoxia, direct cellular damage from contrast, and generation of reactive oxygen species.[3] To allow for ion transport, the medulla requires a steep oxygen and blood flow gradient with normally permissive hypoxia in the outer medullary tissue relative to the cortex. The administration of contrast disrupts this fine balance and leads to ischemia and cellular damage. Compounding this process is the production of free radicals and reactive oxygen species during reperfusion. It is this oxidative stress that underlies the rationale to use N-acetylcysteine (NAC) to prevent CI-AKI, albeit with less than uniform clinical success.[7] In addition, the direct cytotoxic impact of contrast has been demonstrated in vitro and may be clinically important, particularly when there is prolonged contact of contrast material with tubular cells.[2] In addition, the osmolarity of the contrast is important when discussing tubular damage. Studies have shown that iso-osmolar contrast induces less cytotoxic damage and vascular stress when compared with high- or low-osmolar agents.[8,9] Ultimately, these pathways converge, leading to loss of normal renal microvasoreactivity and tubular damage. Accordingly, the majority of novel biomarkers that have been studied for the detection of AKI revolve around cellular responses to tubular damage. The relevant biomarkers studied in the context of AKI and their reported anatomic origins is summarized in Figure 1.

To allow for ion transport, the medulla requires a steep oxygen and blood flow gradient with normally permissive hypoxia in the outer medullary tissue relative to the cortex. The administration of contrast disrupts this fine balance and leads to ischemia and cellular damage.

Neutrophil Gelatinase-associated Lipocalin

Biology

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein covalently bound to gelatinase (matrix metallopeptidase 9) in neutrophils. The major ligands for NGAL are small iron-binding proteins known as siderophores.[10] Normally, NGAL is expressed at very low levels in the kidney, colon, stomach, and lungs, and markedly upregulated in response to epithelial damage. In addition, NGAL has been found in atherosclerotic plaques, specifically in plaques that have ruptured and contain active thrombus.[11] In this regard, the source of NGAL has been linked to activated neutrophils. Data have suggested that injury (ischemic or nephrotoxic) throughout the nephron, including of the

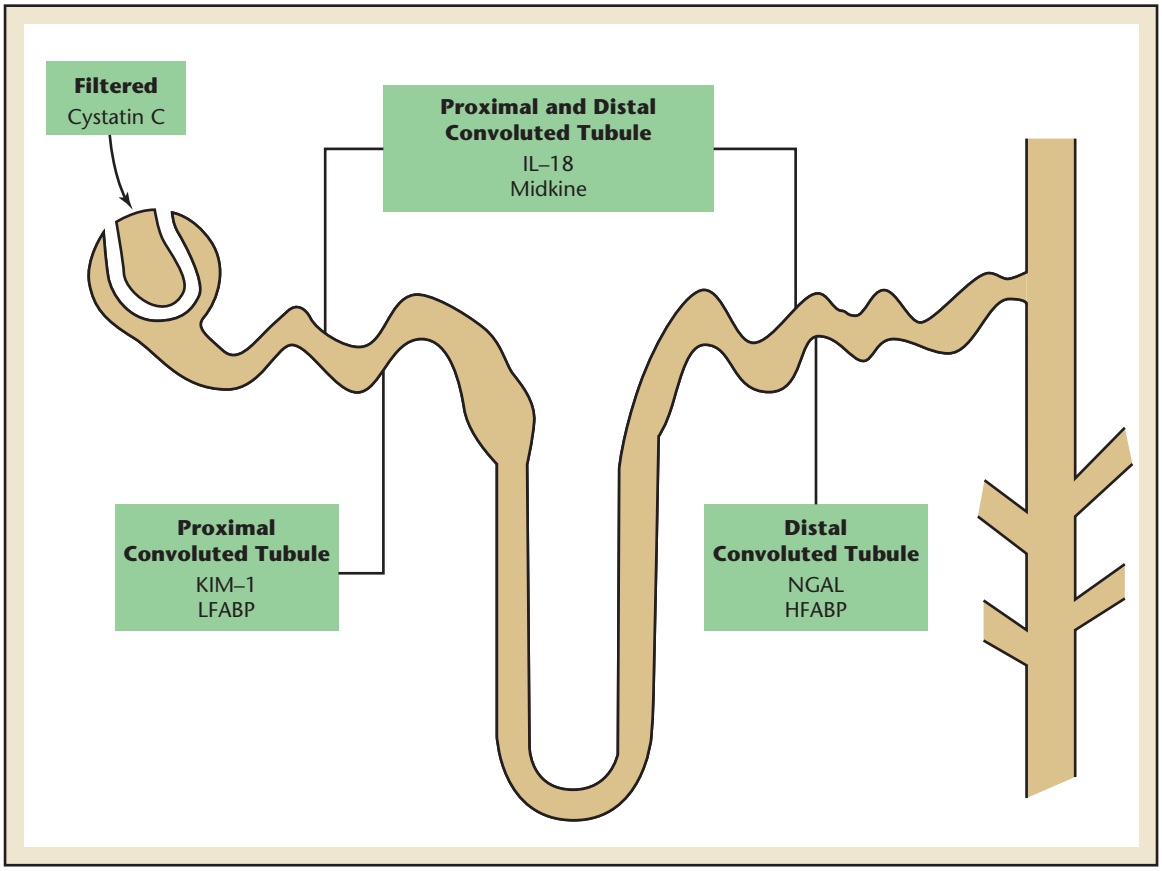

Figure 1. Biomarker action on the renal tubule.

thick ascending limb of the loop of Henle and the collecting ducts, can result in NGAL production.[10] In a mouse model, Paragas and colleagues[12] have demonstrated that, in response to an ischemic insult, NGAL expression occurs in the distal tubular segments of injured nephrons. The plasma levels of NGAL appear related to the acute phase reactant role of this biomarker without necessary dependence on the kidneys for direct production.[11]

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Clinical Background

In different contexts, NGAL production appears related to both vascular wall and renal tubular inflammation and damage. In individuals with normal renal function but stable coronary disease and hypertension, levels of plasma NGAL are higher than control subjects.[11] Systemic NGAL levels are also related to the angiographic extent of coronary artery disease.[13] Furthermore, in patients with ischemic cerebrovascular disease, serum NGAL levels appear related to mortality risk during follow-up.[14,15] In patients without overt atherosclerotic disease or active plaque rupture (eg, intensive care unit, liver transplant, pediatric cardiopulmonary bypass, or kidney transplant patients), early urine and serum NGAL levels appear to be predictive of AKI and elevated levels are related to poor prognosis.[10] Urinary NGAL levels have also been used as a surrogate endpoint for kidney injury in response to therapeutic interventions designed to reduce proteinuria such as angiotensin-converting enzyme inhibition.[16]

Relevance to CI-AKI

Hirsch and colleagues studied 91 pediatric patients with normal baseline renal function undergoing cardiovascular angiography with ioversol (nonionic, low-osmolar) contrast.[1] Urine and plasma samples were drawn at baseline and at 2, 6, and 24 hours after catheterization. A total of 12 patients (11%) developed CI-AKI (defined as $>$ 50% increase in serum creatinine from baseline). At 2 and 6 hours, the urine and plasma NGAL levels were higher in the CI-AKI group versus the non–CI-AKI group. The authors noted that the NGAL level at 2 hours (plasma or urine) was an independent predictor of CI-AKI, irrespective of contrast dosage.

In this study, the subjects were a nonatherosclerotic, nondiabetic, relatively homogenous population; therefore, the rise in NGAL levels was likely a result of contrast-induced renal toxicity rather than extrarenal neutrophil activation.

In contrast to this relatively healthy pediatric population, Malyszko and associates examined multiple AKI biomarkers in 140 adult patients with stable angina (70 with and 70 without diabetes) and normal baseline renal function undergoing coronary angiography (with or without PCI).[17] Most patients received low-osmolar contrast (iopromide; n = 116) rather than iso-osmolar contrast (n = 24). Serum and urine NGAL levels were measured at baseline and 2, 4, 8, 24, and 48 hours after catheterization. At baseline and at each follow-up time point, serum NGAL levels were higher in those with diabetes versus those without diabetes. The serum levels in both groups rose after 2 hours and remained elevated compared with baseline at 24 hours. For urinary NGAL levels, there was less difference between diabetics and nondiabetics (with a small trend for lower levels in diabetics), and the rise in NGAL for both groups occurred at 4 hours, remaining elevated out to 24 hours. In multivariable analysis, estimated glomerular filtration rate (GFR; measured using the Modification of Diet in Renal Disease equation) was the only predictor of serum NGAL levels before catheterization. The authors also found that the small (n = 11) diabetic subgroup receiving low-osmolar contrast had higher urinary NGAL levels compared with diabetic patients who received iso-osmolar contrast (n = 59). Serum NGAL levels were also higher in patients who developed CI-AKI (defined as ≥ 25% rise in serum creatinine at 48 h) versus those who did not, beginning at 2 hours and remaining significantly higher out to 48 hours. Similarly, urinary NGAL levels were higher in the patients who developed CI-AKI beginning at 4 hours and continuing out to 48 hours. The findings of this study, particularly the earlier serum versus urinary rise of NGAL, provide insights into the dual nature of this molecule as both an inflammatory atherosclerotic marker and a marker of kidney injury. For further studies regarding NGAL and its clinical relevance, please refer to Table 1.

Potential Clinical Utility of NGAL

The strongest evidence to date supports the role of NGAL as an early AKI detection tool based on the increased sensitivity of this biomarker for AKI in comparison with serum creatinine. From the data presented by Malyszko and colleagues, NGAL may also have a role in preselecting patients with propensity to develop AKI; therefore, this marker could guide primary prevention strategies.[17] In the context of cardiac catheterization, the role of NGAL as a plaque disruption marker makes it attractive for cardiovascular risk stratification. Small analyses have found associations between the presence of coronary disease and elevated NGAL levels, as well as with elevated blood pressure and NGAL levels.[19,20] NGAL levels may also be elevated in conditions of cardiac injury or strain such as following an acute myocardial infarction or congestive heart failure exacerbation.[21-23] In both conditions, elevated NGAL levels have been linked to adverse outcomes, and, in the case of congestive heart failure, associated with increased risk of death at 2-year follow-up.[24] The specific contributions of vascular inflammation, plaque rupture, and renal tubular damage to the NGAL elevation in the postangiography studies remain unclear.

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Key Points Regarding NGAL

(1) NGAL is both a marker of proximal tubular damage and of atherosclerotic plaque rupture; (2) both urinary and serum NGAL levels appear to rise earlier than serum creatinine in patients who develop CI-AKI; and (3) in patients undergoing PCI, the contribution of plaque disruption versus tubular secretion to NGAL levels may be difficult to separate. Serum rise appears to precede urinary rise of this marker suggesting, in part, a nonrenal origin of NGAL.

Cystatin C

Biology

Cystatin C is a ubiquitous 13 kDa protease inhibitor produced at a constant rate by nearly all nucleated cells. Cystatin C belongs to a family of cysteine protease inhibitors that have a role in a multitude of pathologic conditions, including neurodegeneration, cardiovascular disease, bone remodeling, and cancer.[25] The serum level of cystatin C is closely related to GFR, as this protein is freely filtered in the glomerulus and then reabsorbed completely in the proximal tubule.[26] In addition, cystatin C does not undergo tubular secretion and appears in the urine only by filtration.[27] In contrast to serum creatinine, serum levels of cystatin C

TABLE 1

Studies on Biomarkers in Acute Kidney Injury

Author	Biomarker	AKI Definition	Time Point	Findings	Statistical Model
Hirsch R et al[1]	NGAL	50% increase in Cr	2 and 6 h	Higher NGAL in AKI group	None in study
Malyszko J et al[17]	NGAL	25% rise in Cr	2, 4, 8, 24, and 48 h	Serum NGAL levels high in AKI vs non-AKI group	None in study
Ling W et al[5]	NGAL	25% rise in Cr or increase by 44.2 μmol/L	48-72 h postprocedure	Higher urinary NGAL levels in AKI vs control group	None in study
Tasan-arong A et al[18]	NGAL	50% increase in Cr	3,6,12,18, and 24 h postprocedure	Significant increase in urinary NGAL levels in AKI vs non-AKI group	Sensitivity of 94% and a specificity of 78% for detection of AKI at 6 h after contrast exposure
Malyszko J et al[17]	Cystatin C	25% rise in Cr	2, 4, 8, 24, and 48 h	Levels were higher at 8 and 24 h in CI-AKI vs non-AKI group	None in study
Kato K et al[37]	Cystatin C	25% rise in Cr	Baseline, 1, 2, and 3 d	CI-AKI group had higher levels vs non–CI-AKI group	None in study
Briguori C et al[26]	Cystatin C	0.3 mg/dL increase 48 h after contrast use	24 h before and after contrast administration	Combining cystatin C level rise of $>$10% with creatinine rise, had the highest predictor of a major adverse event	A cystatin C level rise of $\geq$10% had 100% sensitivity and 65.2% specificity in detecting CI-AKI
Yang Y et al[41]	Cystatin C	25% rise in Cr	12-m follow-up	Rise in cystatin C as low as 5% at 24 h was significant in predicting major adverse events	None in study
Kim GS et al[42]	Cystatin C	25% rise in Cr or rise of .5 mg/dL	24 and 48 h poststudy	Higher baseline cystatin C, more likely to develop CI-AKI	None in study
Malyszko J et al[17]	L-FABP	25% rise in Cr	2, 4, 8, 24, and 48 h	24 h, L-FABP levels higher in CI-AKI vs non-AKI patients	None in study
Kato K et al[37]	L-FABP	25% rise in Cr	Baseline, 1, 2, and 3 d	Baseline levels were higher in patients with severe CKD versus mild or moderate disease, and no significant rise in levels following contrast administration	None in study

Author	Biomarker	AKI Definition	Time Point	Findings	Statistical Model
Nakamura T et al[54]	L-FABP	Undefined	Levels before and after contrast	In patients that developed CI-AKI, L-FABP levels were higher as compared with non–CI-AKI group	None in study
Katoh H et al[55]	L-FABP	25% rise in Cr	Prior to procedure, 24 and 48 h postprocedure	L-FABP increased at baseline in patients who developed AKI as opposed to those who didn't	With a cutoff of 19.0 μg/g Cr L-FABP had a 100% sensitivity and an 81.8% specificity for predicting postprocedural AKI
Bulent Gul C et al[63]	IL-18	25% rise in Cr or rise of .5 mg/dL	Baseline, 24, and 72 h	No significant difference between levels in CI-AKI and non–CI-AKI patients	None in study
Malyszko J et al[17]	IL-18	25% rise in Cr	2, 4, 8, 24, and 48 h	IL-18 was significantly higher in patients with CI-AKI than those without at 8 and 24 h postcatheterization	None in study
Ling W et al[5]	IL-18	25% rise in Cr or increase by 44.2 μmol/L	Baseline and 24 h	At 24 h IL-18 was significantly higher in CI-AKI vs non–CI-AKI patients	None in study
Liu Y et al[64]		IL-18	Meta-analysis		Sensitivity (58.2%) and specificity (75.1%) in defining AKI with an AUC ROC of 0.70
Malyszko J et al[17]	Kim-1	25% rise in Cr	2, 4, 8, 24, and 48 h	KIM-1 levels significantly higher at 24-48 h postprocedure	None in study
Torregrosa I et al[70]	Kim-1	50% increase in Cr	Every 12 h	Significant rise in KIM-1 values was found in AKI vs non-AKI group	ROC analysis showing the AUC of KIM-1 as moderately predictive (0.713) of an AKI
Malyszko J et al[17]	Midkine	25% rise in Cr	2, 4, 8, 24, and 48 h	Values significantly increased at 2 h, peak concentration at 4 h	None in study

AKI, acute kidney injury; AUC, area under the curve; CI-AKI, contrast-induced acute kidney injury; Cr, creatinine; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; ROC, receiver operative curve.

are not significantly affected by age, sex, race, or muscle mass.[28]

Clinical Background

Cystatin C has been extensively evaluated as a cardiorenal biomarker. Elevation of this marker predicts incident cardiovascular death, myocardial infarction, and heart failure in patients with and without coronary artery disease, and in individuals with and without CKD.[29-33] The pathophysiology responsible for the association of cystatin C and increased cardiac risk remains unclear. Potential explanations have included the possibility that cystatin C detects occult renal dysfunction, reflects generalized inflammation and propensity to develop atherosclerosis,

or that elevation of cystatin C is an attempt at counterbalancing elastolytic activity associated with the progression and rupture of atherosclerotic plaques.[31,34-36] In reality, these pathways are interrelated, and, as a global cardiovascular risk biomarker, cystatin C likely reflects a contribution of multiple processes. As an AKI biomarker, the kinetics of cystatin C in relation to glomerular filtration and urinary detection make the acute or subacute changes in this marker helpful in tracking dynamic alterations in renal function.

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Relevance to CI-AKI

With regard to CI-AKI, cystatin C remains the most extensively studied biomarker. The earlier rise of this marker versus serum creatinine following contrast exposure lends its use to detect AKI in this setting. In the previously discussed study, Malyszko and colleagues examined serum cystatin C levels 2, 4, 8, 24, and 48 hours, after cardiac catheterization as part of their multimarker approach to postcontrast AKI evaluation.[17] Serum cystatin C levels rose at 8 hours and peaked at 24 hours, and decreased by 48 hours. At 48 hours, cystatin C levels were higher in diabetic versus nondiabetic patients. Furthermore, cystatin C levels were higher at 8 and 24 hours in patients who developed CI-AKI, versus those who did not. Kato and coworkers also examined serum cystatin C levels in 87 patients undergoing elective coronary angiography with or without PCI (with nonionic, low-osmolar contrast).[37] The majority of patients had mild to moderate renal insufficiency (48 patients). Cystatin C levels were assessed at baseline and again at 1, 2, and 3 days after administration of contrast. CI-AKI was defined as an increase of more than 25% from the baseline value of serum creatinine, or an absolute increase of at least 0.5 mg/dL within 48 hours after the administration of contrast medium. In the overall cohort, cystatin C levels did not rise following contrast administration. However, patients with CI-AKI (n = 13) had higher levels versus matched patients without CI-AKI (n = 18); this finding was true across all time points, even at baseline pre-contrast. Cystatin C was the only independent determinant of CI-AKI development. These data suggest that cystatin C may detect baseline renal insufficiency and predict the occurrence of CI-AKI. In one of the largest studies to date, Briguori and associates examined cystatin C levels in 410 consecutive patients with CKD undergoing either coronary and/or peripheral angiography (with or without angioplasty).[26] Cystatin C levels were measured 24 hours before and 24 hours after contrast administration (nonionic, iso-osmolar). Patients were prospectively followed for 1 year with capture of clinical event data. CI-AKI, was defined as an increase in serum creatinine concentration of 0.3 mg/dL from the baseline value at 48 hours after administration of the contrast or the need for dialysis. A significant increase in cystatin C levels was defined as a $\geq$ 10% elevation over baseline values. Using these metrics, 34 (8.2%) patients had a rise in creatinine of $\geq$ 0.3 mg/dL and 87 (21.2%) had a rise of $\geq$ 10% in cystatin C levels. A cystatin C level rise of $\geq$ 10% had 100% sensitivity and 65.2% specificity in detecting CI-AKI. In a multivariable model, the combination of a serum creatinine rise of $\geq$ 0.3 mg/dL and increase in cystatin C level $\geq$ 10% was the highest predictor of major adverse event (cardiac death or dialysis) at follow-up (odds ratio [OR] 4.45, 95% confidence interval [CI], 1.72-11.54; $P = .002$). Notably, the OR for the group without a significant creatinine rise but elevated ($\geq$ 10%) cystatin C levels was still significant (OR 2.52, 95% CI, 1.17-5.41; $P = .02$), suggesting that even subclinical AKI may be relevant and portend adverse outcomes.

The ability of cystatin C to detect subtle changes in GFR has made it an attractive alternative to serum creatinine values as an endpoint of studies designed to test strategies to reduce the incidence of CI-AKI. For example, Kimmel and associates enrolled patients with moderately impaired kidney function undergoing coronary angiography (with low-osmolar, nonionic contrast media) into a randomized study to evaluate two different CI-AKI prevention medications (NAC vs zinc vs placebo).[38] The authors noted that CI-AKI was prevented in all the groups. However, although the creatinine levels did not increase, the cystatin C levels in the placebo and zinc groups rose significantly, whereas levels in the NAC group remained unchanged. Though alternative measurements of renal function were not directly assessed, the authors concluded that cystatin C was able to detect subclinical renal dysfunction in the non–NAC-treated groups. Concordant with these data, Merkle and coworkers studied the impact of NAC on serum cystatin C and serum creatinine at baseline and at 24 hours in 31 patients with CKD undergoing elective coronary angiography with

nonionic, iso-osmolar contrast.[39] There was no rise in serum creatinine or cystatin C levels in these subjects, suggesting a protective benefit of NAC. Kim and coworkers performed a randomized controlled trial to assess the efficacy of NAC on the prevention of CI-AKI using cystatin C as an endpoint of AKI.[40] The authors defined CI-AKI by cystatin C level as an increase in the serum cystatin C concentration of at least 0.5 mg/dL or > 25% within 48 hours of contrast exposure. The authors randomized 166 patients (80 patients in the NAC group and 86 patients in the control group) with normal baseline renal function, undergoing coronary angiography (with low- or iso-osmolar contrast), to NAC or placebo. Serum cystatin C and creatinine concentrations were measured at baseline and again at 24 and 48 hours after contrast exposure. The rate of cystatin C–defined CI-AKI was higher than serum creatinine-defined CI-AKI (10.2% vs 6.0%, respectively). Although the incidence of CI-AKI defined by serum creatinine was lower in the NAC group, this finding did not reach statistical significance. In contrast, cystatin C-defined CI-AKI was significantly lower in the NAC group.

With the increase in endovascular procedures for peripheral arterial disease in the cardiac catheterization laboratory, two studies relevant to CI-AKI warrant mention. Yang and colleagues prospectively measured serum creatinine and cystatin C levels in 350 consecutive patients undergoing peripheral angiography.[41] CI-AKI was defined as a 25% increase of creatinine concentration from baseline. The patients were followed for 12 months for any major adverse events, defined as either death or a decline in renal function necessitating dialysis. Cystatin C was found to correlate poorly with CI-AKI in this study; however, a rise in cystatin C as low as 5% at 24 hours was significant in predicting major adverse events in these patients, whereas having CI-AKI was not significant in predicting major adverse events at 1 year.

The body of literature regarding the role of serum cystatin C to detect early occult AKI demonstrates the ability of this marker to provide more timely detection of CI-AKI and additive prognostic information to serum creatinine assessment. Furthermore, perhaps pointing to its role as a systemic cardiovascular marker, the longitudinal findings of the study by Briguori and colleagues reinforce the concept of cystatin C as a potential predictor of adverse events following CI-AKI.[26] Similarly, in a small population, Ishibashi and colleagues have demonstrated that baseline cystatin C is a modest predictor of short-term mortality and morbidity in patients who develop CI-AKI following coronary angiography.[43] The data presented in this discussion, when taken together, suggest that the true incidence of CI-AKI needs to be readdressed, as defined by the use of more sensitive biomarkers, and that the prospective significance of cystatin C–defined AKI after contrast use will have to be further defined.

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L-type Fatty Acid-binding Protein

Biology

Fatty acid-binding proteins (FABPs) are intracellular proteins that bind and transport free fatty acids to mitochondria or peroxisomes. The family of FABPs contains at least nine distinct types of proteins, which are named for the first tissue in which they were isolated.[44] The primary function of FABP is the facilitation of intracellular long-chain fatty acid transport, but mounting evidence points to the role of these proteins as endogenous antioxidants.[45] Two types of FABPs are found in human renal tubular cells: liver-type FABP (L-FABP) is isolated in proximal tubules, and heart-type FABP (H-FABP) is localized in the distal tubules.[46]

L-FABP is expressed in the human proximal tubules of the kidney and binds fatty acids prior to transport to mitochondria or peroxisomes for oxidation. Experimental studies of animal models of tubulointerstitial damage have revealed that renal L-FABP is upregulated in response to acute injury with increased urinary excretion.[47] Elevated urinary L-FABP levels may also represent a compensatory response to increased filtered albumin-bound fatty acids associated with diabetic proteinuria.[48] Meanwhile, there has yet to be significant research on the use of H-FABP as a marker for kidney damage. For further studies regarding cystatin C and its clinical relevance please refer to Table 1.

Clinical Background

In a series of studies, Kamijo and colleagues have documented that in patients with nondiabetic CKD, urinary excretion of L-FABP increases with worsening of renal function.[49-52] In patients with various renal diseases, urinary L-FABP appears to be more sensitive in predicting progression of CKD than

proteinuria.[50,52] Data suggest that L-FABP levels may be elevated before actual structural tubular damage occurs, in response to cellular oxidative stress.[45] Therefore, L-FABP could be an early sign of tubular stress and its urine excretion may increase before other markers do, making it an attractive molecule for study in the context of early detection of CI-AKI.

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Relevance to CI-AKI

In the previously discussed study, Malyszko and associates also examined urinary L-FABP levels 2, 4, 8, 24, and 48 hours after cardiac catheterization as part of their multimarker approach to postcontrast AKI evaluation.[17] L-FABP levels were first significantly elevated at 24 hours and then decreased at 48 hours, but were still elevated when compared with baseline. At 24 hours, L-FABP levels were higher in patients with CI-AKI versus those without. Bachorzewska-Gajewska and associates studied 25 consecutive nondiabetic patients without CKD undergoing PCI due to unstable angina.[53] Iso-osmolar contrast was used in all subjects. Urinary L-FABP levels rose at 4 hours, peaked at 12 hours, and remained elevated out to 48 hours.

Several lines of data suggest that the degree of renal dysfunction may directly impact the persistence of L-FABP in the urine following contrast exposure. For example, Kato and coworkers studied changes in serum creatinine, serum cystatin C, and urinary L-FABP levels in 87 patients (with variable degrees of renal insufficiency) undergoing elective cardiac catheterization with or without PCI.[37] They found a rise in L-FABP at 24 hours after elective PCI in 41 patients with mild CKD, which decreased by 48 hours. In patients with moderate CKD, levels rose at 24 hours but remained elevated out to 48 hours. Baseline levels were higher in patients with severe CKD compared with patients with mild or moderate disease, and there was no significant rise in levels following contrast administration; however, there were only six patients in this group. In patients undergoing PCI with severe CKD at baseline, further risk stratification currently is challenging. In this regard, Katoh and associates studied urinary L-FABP in 25 patients with severe renal disease (defined as a GFR $<$ 45 mL/min) undergoing PCI with right atrium hemodiafiltration.[55] In the study, patients received hemodiafiltration with blood suction in their right atrium starting 30 minutes before the procedure and lasting until 30 minutes after the procedure. The objective was to remove the contrast from the blood before it reached the kidney. Removing contrast had been previously shown to be effective using an absorbing column placed in the coronary sinus. Right atrium hemodiafiltration was shown to reduce the incidence of AKI in PCI patients compared with control subjects (12% vs 27%; $P = .26$) by filtering the contrast media before it reached the kidney. In addition, the authors measured urinary L-FABP prior to the procedure and at 24 and 48 hours after intervention. They found that urinary L-FABP was significantly increased at baseline in those patients who developed AKI as opposed to those who did not. In addition, they found that urinary L-FABP could be used as an independent predictor of postprocedural AKI, and that when using a cutoff of 19.0 µg/gCr, L-FABP had a 100% sensitivity and an 81.8% specificity for predicting postprocedural AKI. For further studies regarding L-FABP and its clinical relevance please refer to Table 1.

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IL-18

Biology

Interleukin (IL)-18 is a proinflammatory cytokine that has been demonstrated to be an important mediator in the injury response to acute tubular necrosis from either renal ischemia or nephrotoxic agents.[4] This cytokine is elevated in a variety of inflammatory conditions, including acute coronary syndromes, congestive heart failure, and sepsis.[56] Anti–IL-18 interventions have been shown to reduce mortality and disease severity in lung injury, colonic inflammation, and arthritis.[57] Evidence exists to support the role of urinary IL-18 in mediating the inflammatory response to renal ischemic injury.[58-60] Based primarily on mouse models[75] proximal tubular injury appears closely related to increased urinary IL-18 production.

Clinical Background

With respect to AKI, IL-18 has been evaluated in multiple clinical settings, including cardiopulmonary

bypass, allograft rejection, nephrotoxic agents, and critical care. IL-18 appears to provide early detection of AKI, particularly when coupled with NGAL.[61] In addition, early urinary IL-18 levels may predict mortality in cardiac patients and critically ill patients with acute respiratory distress syndrome.[4,56,60] The data for the accuracy of IL-18 to independently predict AKI occurrence and severity are mixed, with several studies suggesting poor receiver operating characteristics in this context.[56,60,62] The total patient sample size for these studies is relatively modest and larger data sets are needed for this specific biomarker.

Relevance to CI-AKI

Similarly, the ability of urinary IL-18 to detect CI-AKI is still unclear. Bulent Gul and associates evaluated the utility of urinary IL-18 levels to detect CI-AKI in a nested case-control cohort of patients (n = 157) undergoing elective PCI for stable angina.[63] Patients had normal renal function at baseline and iopamidol (nonionic, low-osmolar contrast medium) was used in all patients. Urinary IL-18 levels were measured at baseline, 24 hours, and 72 hours; 15 patients (9.5%) met the criteria for creatinine-defined CI-AKI (defined as an absolute rise in serum creatinine > 0.5 mg/dL and/or a rise > 25% from baseline). These 15 patients were compared with a matched group of 36 control patients who did not develop CI-AKI. The authors found no statistically significant differences in IL-18 levels among patients and control subjects or before and after PCI in either the control subjects or the CI-AKI patients. Despite the small sample size, the authors suggested that IL-18 may not be a sensitive marker of early AKI following contrast administration. In the multimarker study by Malyszko and colleagues, the authors also examined urinary IL-18 levels in the study population.[17] In both diabetic and nondiabetic subjects, IL-18 levels rose at 2 hours and remained elevated out to 48 hours, peaking at 24 hours. IL-18 levels were significantly higher in patients with CI-AKI (vs those without CI-AKI) at 8 and 24 hours after cardiac catheterization. Ling and associates also examined urinary IL-18 levels in their study population.[5] At 24 hours after PCI, urinary IL-18 levels were significantly higher in the CI-AKI group as compared with baseline, and significantly higher in the CI-AKI group as compared with the non–CI-AKI group. Levels were no different in the non–CI-AKI group at 24 hours versus baseline. The time of AKI onset determined by IL-18 level was 24 hours earlier than that determined by serum creatinine level. Potentially highlighting the role of this cytokine in atherosclerosis and cardiac disease, urinary IL-18 levels had the highest OR for cardiac events at follow-up when compared with urine NGAL and serum creatinine levels. For further studies regarding IL-18 and its clinical relevance, please refer to Table 1.

Current evidence suggests that KIM-1 may be a signaling molecule that mediates renal injury and repair.

… urinary IL-18 levels had the highest OR for cardiac events at follow-up when compared with urine NGAL and serum creatinine levels.

Kidney Injury Molecule-1

Biology

Kidney injury molecule-1 (KIM-1) is a type-I membrane protein that is markedly upregulated in the proximal tubule epithelial cell after ischemia.[65,66] Although the chemical structure of KIM-1 has been well described, the function of this transmembrane protein remains unclear. Current evidence suggests that KIM-1 may be a signaling molecule that mediates renal injury and repair.[67] KIM-1 protein and gene expression is absent in the normal kidney. In response to ischemic injury, there is rapid transcription and collection of KIM-1 protein in the proximal tubule without expression in the glomerulus. Increased KIM-1 expression has been demonstrated in a variety of animal models. Sohotnik and associates studied KIM-1 in a uninephric rat model of renal ischemia.[68] Following clamp-induced impairment of renal blood flow, urinary KIM-1 levels (as well as NGAL) were measured over time during reperfusion. Both biomarkers rose rapidly in response to renal injury in a control arm treated with a standard renal artery clamp. The study featured a treatment arm that received pretreatment tadalafil (a phosphodiesterase-5 inhibitor); in this group, there was a blunting of biomarker release, suggesting attenuation of kidney injury. Perhaps more relevant to cardiac catheterization, Jost and colleagues examined KIM-1 protein transcription levels in rats after administration of nonionic, low-osmolar, low-visous contrast (iopromide) and nonionic, iso-ismolar, high-viscous contrast (iodixanol).[69] Iodixanol contrast was associated with greater retention of contrast

material in the kidney and significantly higher in KIM-1 mRNA levels as compared with iopromide. The data point to a potential relationship between contrast as a nephrotoxin and increased KIM-1 expression.

Clinical Background

Human data on KIM-1 have supported the concept that this marker is related to clinical ischemic renal injury. Han and colleagues examined KIM-1 levels in patients with AKI, normal control subjects, CKD patients, and individuals with urinary tract infections.[66] The AKI patients consisted of a small but diverse group: 12 individuals with sepsis, 9 patients with cardiac arrest or cardiogenic shock, 2 with hypovolemia (bleeding), 1 due to rhabdomyolysis, 1 due to nephrotoxin administration, and 4 due to CI-AKI.[66] Urinary KIM-1 levels were significantly higher in the AKI group versus the healthy control subjects, CKD patients, or the group with urinary tract infection. In the same article, the authors also examined the time course and rise of KIM-1 in 40 children undergoing cardiopulmonary bypass and noted that KIM-1 levels demonstrated a rise at 6 hours after cardiopulmonary bypass and remained elevated out to 48 hours. The rise in KIM-1 levels preceded a rise in creatinine concentration. A level of KIM-1 of > 2.0 ng/mg $U_{creatinine}$ at 12 hours after cardiopulmonary bypass provided 74% sensitivity and 90% specificity (positive likelihood ratio of 7.37) to diagnose AKI.

Relevance to CI-AKI

Malyszko and colleagues examined KIM-1 levels as part of their multimarker analysis at 2, 4, 8, 24, and 48 hours after cardiac catheterization.[17] In diabetic and nondiabetic subjects, KIM-1 levels remained stable until 24 hours postprocedure, and at 24 and 48 hours, the levels were significantly elevated as compared with baseline. There was a trend toward higher KIM-1 levels in patients with CI-AKI (vs those without CI-AKI), but this finding did not reach statistical significance. Torregrosa and coworkers studied KIM-1 levels in 193 patients after PCI.[70] They measured KIM-1 and serum creatinine values every 12 hours and defined an AKI as a 50% increase in creatinine from baseline. A significant rise in KIM-1 values was found in the AKI group compared with the non-AKI group. In addition, they performed a receiver operating characteristic (ROC) analysis showing the area under the curve of KIM-1 as moderately predictive (.713) of an AKI.[70] The data for KIM-1 in relevance to CI-AKI remain preliminary and there is a paucity of data available; however, the biologic characteristics of this molecule are intriguing and warrant further study.

Midkine

Biology

Midkine is 13kDa cytokine composed of 143 amino acids that signal along the protein-tyrosine phosphatase pathway. It is a heparin-bound growth factor that is highly expressed during the midgestational period of embryogenesis, but is found in very small levels in normal healthy adult tissue.[71] Small residual levels of midkine expression have been found in adult lung, gastrointestinal, kidney, spleen, and thyroid tissue. However, midkine is rapidly upregulated during most inflammatory processes.[72] Midkine is a heparin-bound growth factor expressed in the proximal tubular cells as well as the distal tubular cells in the kidney. It has been shown to regulate kidney tissue cell growth, survival, and migration, and has been shown to have some antiapoptotic activity.

Clinical Background

In addition, midkine is involved in the inflammatory pathway and has been shown to be increased in many kidney inflammatory states, including ischemic renal injury and diabetic nephropathy. Sato and colleagues studied the role of midkine in inflammation in an ischemic injury model.[76] In this study, the kidney of both midkine knockout and wild-type mice was clamped for 90 minutes to induce an ischemic response with reperfusion injury. They found that the tubulointerstitial damage was less in the knockout mice compared with the wild-type mice. In addition, inflammatory chemokine expression, along with neutrophil and macrophage recruitment, was lower in the knockout mice. The human data for midkine have mainly been focused on its proangiogenic effects in inflammatory states. Weckbach and colleagues showed that midkine is increased in human polymorphonuclear leukocytes, as well as vascular endothelial tissue during ischemia-induced injury.[77] In addition, they showed that exogenous midkine induced angiogenesis in test tissues compared with control.

Midkine is a heparin-bound growth factor expressed in the proximal tubular cells as well as the distal tubular cells in the kidney.

Relevance to CI-AKI

As midkine has been shown to be an ischemic cytokine, its role in CI-AKI is now being studied. Malyszko and colleagues examined the relevance of midkine

TABLE 2

Key Points on Novel Biomarkers

	NGAL	Cystatin C	L-FABP	IL-18	KIM-1	Midkine
Key points	A marker of proximal tubular damage and of atherosclerotic plaque rupture; urinary and serum NGAL levels rise earlier than serum creatinine in CI-AKI; the contribution of plaque disruption versus tubular secretion to NGAL levels may be difficult to separate; serum rise appears to precede urinary rise of this marker suggesting a nonrenal origin of NGAL	Serum levels of cystatin C correlate closely with GFR; cystatin C is a global atherosclerotic cardiovascular risk factor and a marker of acute or subacute changes in GFR; serum cystatin C levels provide earlier detection of AKI and more prognostic information in CI-AKI compared with serum creatinine	L-FABP belongs to a family of FABPs that are involved in fatty acid transport and metabolism; increased expression of L-FABP may represent an endogenous antioxidant response to cellular damage; L-FABP appears to detect CI-AKI earlier than serum creatinine; the degree of preexisting renal insufficiency may relate to persistence of L-FABP in the urine following AKI	IL-18 is an inflammatory cytokine that is upregulated in a variety of acute disease states; some, but not all studies, have suggested that this marker has utility in detecting early CI-AKI; the precise role of IL-18 in CI-AKI and in predicting cardiovascular events will require further data	KIM-1 is a type-I membrane protein that is markedly upregulated in the proximal tubule epithelial cell after ischemia; the data in support of KIM-1 as an ischemic marker for AKI remain preliminary and are drawn from relatively small studies; KIM-1 may have a role in detecting early CI-AKI but further examination is needed	Midkine is a cytokine belonging to the protein-tyrosine phosphatase family that is expressed in the kidney; midkine is rapidly upregulated in many tissues during inflammatory processes; midkine has been shown to increase in the kidney as early as 2 hours after PCI; further studies are needed to show if midkine is predictive of AKI
Time measured after AKI, h	6	24	Baseline	Baseline	12	2-8
Sensitivity, %	94	100	100	58.2	74	Undetermined
Specificity, %	78	65.2	81.8	75.1	90	Undetermined

AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

levels to CI-AKI after PCI.[17] The authors studied midkine levels in 89 patients with normal renal fuction who were undergoing PCI. Serum midkine concentration was measured, along with serum and urinary NGAL and serum cystatin C, at 2, 4, 8, 24, and 48 hours after PCI. Midkine level was significantly increased as early as 2 hours after PCI, with a peak concentration at 4 hours. The values returned to baseline by 24 hours. Further studies are needed on midkine to determine if it is predictive of AKI.

Other Biomarkers

N-acetyl-β-glucosaminidase (NAG) and β2-microglobulin (β2m) are both promising markers for various kidney injury states that have recently been studied in CI-AKI models. NAG is a 130 kDA lysosomal enzyme that is normally excreted in the urine in small amounts. The urinary excretion of NAG has been shown to be increased in patients who are exposed to agents that are toxic to tubular cells, including contrast media. Ren and coworkers studied NAG in adult patients after PCI or diagnostic angiography who developed CI-AKI.[73] CI-AKI was defined as an increase in creatinine of $>$ 25% from baseline or an overall increase of creatinine $>$ 0.5 mg/dL at 48 hours after exposure to contrast. It was shown that serum NAG levels were significantly increased in the patients with CI-AKI 24 hours after exposure to contrast media.

β2m has also been shown to be an early indicator of renal damage. β2m is a normal component of major histocompatibility complex class 1 molecules that, when cleaved, is filtered through the glomerulus and completely taken up and destroyed by the proximal tubule cells. However, when proximal tubule cells are damaged, as in CI-AKI, β2m leaks into the urine, making it a sensitive marker in AKI. Rouse and colleagues studied β2m in a CI-AKI rat model.[74] In one model, they defined contrast-induced nephropathy as any histopathology change after administration of contrast media. Using this model, they found that β2m correlated strongly with the histopathology changes with an ROC of 0.89. However, this has yet to be correlated to the standard value of AKI of a 1.5-fold change in serum creatinine. β2m did not provide a good correspondence on ROC analysis when studied by Rouse and colleagues in their rat models.[74]

Conclusions

Development and validation of biomarkers for AKI in the setting of contrast exposure remains an active field. A summary of key points of novel biomarkers can be found in Table 2. Currently, the majority of data are derived from a handful of studies involving a modest number of patients. In addition, comparison and standardization of various assay methods remains unsettled. Further studies, including a variety of patients with differing levels of baseline renal function and cardiovascular disease, are required in this context. It is likely that no single biomarker will be applicable to all patient subsets—rather, a multimarker panel approach will be needed to provide adequate ROCs characteristics to detect early CI-AKI. ■

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MAIN POINTS

- Contrast administration for coronary and peripheral angiography is a major cause of acute kidney injury (AKI), worldwide. Currently, contrast-induced AKI (CI-AKI) is the third leading cause of hospital-acquired AKI in the United States; more than 50% of these cases are the result of contrast exposure during cardiac catheterization and/or percutaneous coronary intervention (PCI).
- Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein covalently bound to gelatinase (matrix metallopeptidase 9) in neutrophils. The strongest evidence to date supports the role of NGAL as an early AKI detection tool based on the increased sensitivity of this biomarker for AKI in comparison with serum creatinine. NGAL may also have a role in preselecting patients with propensity to develop AKI; therefore, this marker could guide primary prevention strategies.
- Cystatin C has been extensively evaluated as a cardiorenal biomarker. In this regard, elevation of this marker predicts incident cardiovascular death, myocardial infarction, and heart failure in patients with and without coronary artery disease, and in individuals with and without chronic kidney disease.
- Interleukin-18 is a proinflammatory cytokine that has been demonstrated to be an important mediator in the injury response to acute tubular necrosis from either renal ischemia or nephrotoxic agents.
- Kidney injury molecule-1 (KIM-1) is a type-I membrane protein that is markedly upregulated in the proximal tubule epithelial cell after ischemia. Current evidence suggests that KIM-1 may be a signaling molecule that mediates renal injury and repair. KIM-1 protein and gene expression is absent in the normal kidney.

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