Review

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Novel Biomarkers for Cardio-renal Syndrome

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Cardio-renal syndrome (CRS) is a frequent and life-threatening syndrome. It is a disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Acute kidney injury (AKI) is strongly associated with increased morbidity and mortality in patients with CRS. Early detection of renal dysfunction is not possible using the traditional marker, serum creatinine, and therefore efforts to explore possible biomarkers for early detection of AKI are being made. Apart from predicting AKI, several biomarker studies also identified predictors for poor prognosis such as the need for renal replacement therapy (RRT) or death. It is possible that biomarkers can become risk factors in an improvement of clinical outcomes of CRS. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with renal dysfunction and the treatment for this disease can be modified based on cardiac biomarkers. In addition to natriuretic peptides, which are established cardiac markers, several new biomarkers have been identified and may play important roles in CRS. In this review, we will briefly summarize the literature on novel renal and cardiac biomarkers and discuss their potential roles in the clinical outcome of CRS.

Key Words: Cardio-renal syndrome; Biomarker; Acute kidney injury; Heart failure

Introduction

Cardio-renal syndrome (CRS) is a frequently occurring and life-threatening disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Acute kidney injury (AKI) is strongly associated with increased morbidity and mortality in patients with CRS. Although the incidence of CRS is increasing, the tools for early detection of AKI lack sensitivity and have limited specificity. Early detection of renal dysfunction is not possible using the traditional marker, serum creatinine, and so efforts are being made to identify biomarkers that can be used for early detection of AKI. Apart from predicting AKI, several biomarker studies have also demonstrated the possibility of prediction for poor prognosis such as the need for renal replacement therapy (RRT) or death. It is possible that these biomarkers may eventually be considered as risk factors and be used to improve the clinical outcomes of CRS. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with renal dysfunction. Early identification of patients who have renal dysfunction and cardiovascular risk may help to ensure that these patients receive aggressive treatment. The early identification of CVD in patients with renal dysfunction can be possible using cardiac biomarkers. In addition to established cardiac markers such as natriuretic peptides, several new biomarkers have been identified and may play important roles in the diagnosis and treatment selection for CRS.

In this review we will briefly summarize the literature on novel renal and cardiac biomarkers and discuss their potential roles in the clinical outcome of CRS.

New Renal Biomarkers

1. Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2 (LCN-2), is a 25-kDa polypeptide that plays an important role in the innate immune response to bacterial infection[1]. NGAL was first reported as an early biomarker for ischemic renal injury after cardiac surgery in children[2]. Mishra et al. reported that NGAL was an excellent predictor of AKI after cardiac surgery[2]. NGAL seems to be an important marker in the kidney after ischemic or nephrotoxic injury, and can be detected in the blood and urine of humans soon after renal injury[3,4]. Several studies have confirmed these findings in patients with worsening renal function secondary to cardiopulmonary bypass (CPB) surgery, coronary angiography, or acute heart failure[5-8]. NGAL expression is significantly increased in the plasma and/or urine of these patients compared to patients with stable renal function. In a study of 119 patients admitted with acute heart failure, elevated plasma NGAL at time of admission predicted the development of type 1 CRS[6]. Above a cutoff value of 170 ng/mL, NGAL was associated with development of type 1 CRS within 48 to 72 hours with a sensitivity of 100% and a specificity of 86.7%[6]. Renal injury is also common in patients with chronic heart failure. In chronic heart failure patients, both urine and serum NGAL levels were found to correlate with renal function[9]. Furthermore, it was reported that both serum and urine NGAL levels correlated with various markers of renal function, such as serum creatinine, cystatin C, and albuminuria[9,10]. Therefore, it has been speculated that NGAL may be a potential indicator of kidney injury in CRS.

2. Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with an immunoglobulin and mucin domain. The proximal tubule is sensitive to ischemic injury. KIM-1 is markedly induced in response to renal injury and is expressed on the proximal tubule apical membrane. A number of studies have demonstrated KIM-1 to be a marker of AKI occurring after CPB surgery and cardiac catheterization[8,11,12]. Urinary KIM-1 was also associated with increased risk of death or hospitalization, independent of GFR in patients with chronic heart failure[13].

3. Cystatin C

Cystatin C (CysC) has a low molecular weight (13.3 kDa), and it is an endogenous cysteine proteinase inhibitor produced by nucleated cells at a constant rate. It is filtered by glomerular filtration, reabsorbed and catabolyzed by renal tubules, and not secreted in the urine except after tubular injury. If renal function and glomerular filtration rate (GFR) decrease, the blood levels of CysC rise. It has been proposed that serum levels of CysC are a more precise and better early marker of renal function than serum creatinine levels. Several studies of biomarkers in cardiac surgery patients have shown that urine CysC at various time points was able to predict AKI[14]. Plasma CysC levels were significantly higher at various times after CPB surgery among patients who developed AKI compared to those who did not. Furthermore, CysC showed superior diagnostic accuracy for detecting declining GFR compared with serum creatinine in patients after CPB surgery[15]. Changes in CysC levels also have been investigated in recent studies to assess contrast-induced nephropathy[7]. It has been shown that the plasma level of CysC was a strong and independent marker of CRS and mortality in acute heart failure patients[16]. In patients with chronic systolic heart failure, plasma CysC levels were directly correlated with ventricular dysfunction and were suggested as a prognostic factor[17].

4. N-acetyl-β-D-glucosaminidase

The enzyme N-acetyl-β-D-glucosaminidase (NAG) is a

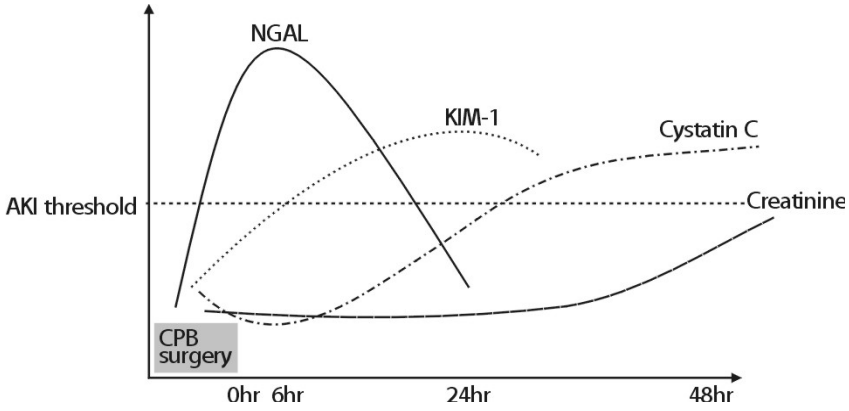

Fig. 1. Representative curves showing changes in biomarker levels for the detection of acute kidney injury (AKI) after cardiopulmonary bypass (CPB) surgery (adapted from a previous study[22]).

lysosomal brush border enzyme found predominantly in proximal tubular cells. It has a large molecular weight (>130 kDa) and is therefore not filtered by glomerular filtration. Urinary NAG has been shown to be a marker of kidney injury, particularly tubular damage, in patients with nephrotoxicity such as that due to radiocontrast media, environmental toxins, and ischemia[18,19]. It was reported that urinary NAG is increased in postoperative AKI patients with cardiac surgery but not in stable renal function[11]. Similar to KIM-1, NAG was also associated with increased risk of death or hospitalization in chronic heart failure[13].

5. Interleukin-18

Interleukin-18 (IL-18) is an 18-kDa pro-inflammatory cytokine originating from proximal tubular cells and is detected in the urine after acute proximal tubular damage. In patients with kidney transplantation, the urine level of IL-18 has been studied as a biomarker for delayed graft function[20]. However, IL-18 has shown inconsistent results in prediction of postoperative AKI in cardiac surgery patients[11,21].

6. Combinations of renal biomarkers

It is possible that a combination of promising biomarkers such as NGAL, KIM-1, and CysC could be applied for the early detection of postoperative AKI in CRS. It was reported that using combined biomarkers (KIM-1, NAG, and NGAL) for early detection of postoperative AKI enhanced the sensitivity compared to using single biomarkers[8]. Fig. 1[22] shows representative curves of the predicted time course in the use of combined biomarkers for the detection of AKI in CRS patients. However, the translational process of how to combine the biomarkers and apply the knowledge gained from them in the clinical field remains an obstacle.

Cardiac Biomarkers

1. Natriuretic peptides

Three different natriuretic peptides (NPs) have been identified: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and N-terminal fragment proBNP (NT-proBNP). The main stimulus for secretion of BNP and NT-proBNP is increased left ventricular (LV) wall stress caused by volume expansion, such as with heart failure.

NPs were found to be increased in patients with renal dysfunction and were correlated with renal function[23]. Despite these findings, a recent study showed that NPs had a high predictive value for volume expansion and

cardiac events in dialysis patients[24,25]. However, the best predictive cut-off values for BNP or NT-proBNP were much higher than those measured in the general population. NT-proBNP levels are more stable than BNP levels because of their longer half-life. No studies have compared the diagnostic accuracy of BNP and NT-proBNP in patients with renal dysfunction, but both BNP and NT-proBNP have been shown to have similar predictive values for LV hypertrophy and coronary disease in predialysis patients with chronic kidney disease (CKD)[26]. In a study of hemodialysis patients, NT-proBNP was significantly predictive of mortality, and this relationship to mortality was higher with NT-pro-BNP than with other biomarkers[27].

NPs also have prognostic potential in CKD patients without clinical signs of heart disease. Carr SJ et al. demonstrated that the plasma BNP level predicted the overall mortality and cardiovascular events in patients with predialysis CKD without clinical signs of heart failure[28]. A recent study also indicated that NT-proBNP was a more powerful predictor for mortality and cardiovascular death in asymptomatic dialysis patients compared with cardiac troponin T (cTnT)[29].

These NPs may provide objective clinical guidance in CKD patients and thus may improve the cardiovascular outcomes of CKD patients. Several studies have suggested that NT- proBNP- or BNP-guided treatment reduced cardiovascular events and heart failure-related deaths in patients with heart failure[30,31].

2. Cardiac troponins

Cardiac troponins (cTn) such as cTnT and troponin I (cTnI) are present in the heart muscle and are released into the circulation upon myocardial injury. cTn is frequently increased in CKD patients despite the absence of myocardial ischemia. This elevation in expression is caused by impaired renal function, which delays clearance, combined with the fact that CKD patients already have the possibility of occult subclinical myocardial injury during uremia. cTnT levels are more frequently increased compared with cTnI in patients with end stage renal disease (ESRD)[32]. Despite this controversy, cTn still plays an important role in the prediction of cardiac event in patients with renal dysfunction. Recent clinical data reported that elevated cTnT was a powerful predictor of poor prognosis regardless of renal function[33]. Elevated cTnT is also linked to LV hypertrophy and systolic dysfunction in ESRD patients[34]. The significance of cTnI levels remains ambiguous, because of the lack of standardization of the assay for this protein. Only limited and inconclusive data has suggested a predictive value of cTnI for mortality in patients with ESRD, whereas it is recommended to use cTnT as a prognostic factor and for mortality stratification in ESRD[35]. Additionally, cTnT had a more powerful value for prognostication of cardiovascular outcome beyond the standard clinical and biochemical markers in ESRD. Furthermore, the predictive value of cTnT for mortality and cardiovascular outcomes was independent of inflammation and renal function.

3. Other cardiac biomarkers

There is also evidence supporting important roles for proinflammatory cytokines in heart failure. The overproduction and release of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha, IL-1, and IL-6, showed potential as a marker of myocardial cell injury. Asymmetric dimethylarginine and myeloperoxidase are also promising markers whose expression levels have been demonstrated to correlate with cardiac outcome in CRS.

Limitations of Biomarkers

Variable biomarkers are useful for detecting CRS and predicting the outcomes of CRS. However, the total number of patients in most of the biomarker studies has remained small. To confirm and generalize these results, validation studies with adequate sample sizes are required. Single biomarkers are unlikely to be sufficient to diagnose, stratify

the severity, and predict the prognosis of CRS. More complicated processes may be required to combine biomarkers to maximize the features of each biomarker. Because of variability in the measurements of biomarkers, careful assessments of biomarker validity are required.

Conclusion

There is accumulating evidence that NGAL, KIM-1, CysC, and NAG are useful serum and/or urinary biomarkers for the prediction and renal risk stratification of CRS patients. Although they do not replace serum creatinine, they may evolve to play important, complementary roles to the use of serum creatinine in evaluating the risk stratification of renal injury in CRS patients. A dynamic change in these biomarkers is also useful in the diagnosis and modification of treatment of kidney injury in CRS patients. In kidney disease, adverse cardiovascular outcomes are associated with plasma levels of specific biomarkers such as NPs and cTn. These biomarkers are used for an early diagnosis of acute cardiovascular events and for prediction of cardiovascular outcomes and mortality in patients with renal dysfunction. The combination of established and new CRS biomarkers can guide the modification of treatment modality and thus decrease the morbidity and mortality in patients with CRS.

Conflicts of Interest

The authors report no potential conflicts of interest relevant to this article.

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