Novel Biomarkers for Cardio-renal Syndrome

Sul Ra Lee, M.D., Kyung Hwan Jeong, M.D.
Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea

Received: December 12, 2012
Accepted: December 21, 2012
Corresponding Author: Kyung Hwan Jeong, M.D.
Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul 130-701, Korea
Tel: +82-2-958-8200, Fax: +82-2-968-1848
E-mail: khjeong@khu.ac.kr
*This material was not published previously, and will not be submitted for publication elsewhere.

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. NGAL was first reported as an early biomarker for ischemic renal injury after cardiac surgery in children. Mishra et al. reported that NGAL was an excellent predictor of AKI after cardiac surgery. 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. Several studies have confirmed these findings in patients with worsening renal function secondary to cardiopulmonary bypass (CPB) surgery, coronary angiography, or acute heart failure. 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. 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%. 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. 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. 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. Urinary KIM-1 was also associated with increased risk of death or hospitalization, independent of GFR in patients with chronic heart failure.

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 catabolized 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. 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. Changes in CysC levels also have been investigated in recent studies to assess contrast-induced nephropathy. 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. In patients with chronic systolic heart failure, plasma CysC levels were directly correlated with ventricular dysfunction and were suggested as a prognostic factor.

4. N-acetyl-β-D-glucosaminidase

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