



Heart Failure, Chronic Kidney Disease, and Biomarkers – An Integrated Viewpoint –

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Chronic kidney disease (CKD) is frequently associated with a progressive decrease in the glomerular filtration rate, which leads to endstage renal disease (ESRD). Heart failure (HF) is a complex syndrome rather than a primary diagnosis, and considered as the endpoint of all cardiovascular disorders. It is the leading cause of death among the cardiovascular diseases in patients with CKD and ESRD. There is some interaction between the heart and kidney (the so-called “cardiorenal syndrome”), and HF patients with the complication of CKD or ESRD show a worse prognosis. Thus, early diagnosis and aggressive management of HF are needed in patients with CKD and ESRD. A number of biomarkers appear to have growing clinical importance and are reported for detection and stratification of HF. Although HF and CKD have a close interrelationship, the utility of the biomarkers has not been adequately studied with regard to the relationship with renal dysfunction. This paper reviews of the current evidence about laboratory biomarkers in patients with HF or CKD, emphasizing the emerging cardiac biomarkers (ie, BNP and cardiac troponins), and the biomarkers of renal injury (ie, cystatin C and neutrophil gelatinase-associated lipocalin). Furthermore, it discusses the potential role of these markers in terms of heart–kidney interactions and their utility in the diagnostic and therapeutic strategies for cardiorenal syndrome. (*Circ J* 2010; **74**: 1274–1282)

Key Words: Biomarkers; Heart failure; Renal failure

Chronic kidney disease (CKD) is frequently associated with a progressive decrease in the glomerular filtration rate (GFR), which leads to endstage renal disease (ESRD). The number of patients with CKD as well as ESRD is dramatically increasing worldwide.¹ Several investigators have documented that patients with CKD are at higher risk of cardiovascular disease than the general population, and show a higher rate of cardiovascular mortality.^{2–4} In particular, ESRD patients have a 500-fold greater rate of cardiovascular mortality than age-matched controls with normal renal function.⁵ Heart failure (HF) is also an increasingly prevalent condition and despite advances in the understanding and treatment, it still has a poor prognosis. It is also the leading cause of death among the cardiovascular diseases in patients with CKD and ESRD.⁶ HF patients with CKD or ESRD show a worse prognosis.⁷ In the Acute Decompensated Heart Failure National Registry (ADHERE), 30% of hospitalized patients with acute HF had a history of chronic renal failure (serum creatinine level >2 mg/dl).⁸ It also showed that admission levels of serum creatinine and blood urea nitrogen were among the strongest independent risk predictors for in-hospital mortality. With regard to chronic HF, Smith et al reviewed 16 studies that focused on the association between renal impairment and mortality in 80,098 HF patients, and reported that 63% of HF patients had at least mild renal dysfunction, and in 20% it was moderate or severe.⁹ There was a consistent risk relationship of a 7% increase in mortality for

every 10 ml/min decrease in estimated GFR. Thus, early diagnosis and aggressive management of HF are needed in patients with CKD and ESRD. Conversely, early recognition and management of CKD are also necessary in patients with HF.

Cardiorenal Syndrome (CRS)

Heart performance and kidney function are closely interconnected, both in health and in disease. CRS is a pathophysiological condition in which combined cardiac and renal dysfunction amplifies the progression of failure of the individual organs and has an extremely bad prognosis. It is more than simultaneous cardiac and renal disease. Although the pathophysiology likely varies according to the specific clinical circumstances, the general processes encompass hemodynamic factors, such as intrarenal hemodynamics, transrenal perfusion pressure, and neurohormonal factors.^{10–12} The latter includes the activation of both the sympathetic nervous system and the renin–angiotensin–aldosterone system, the interplay of various substances such as vasopressin, endothelin, prostaglandins, adenosine and natriuretic peptides, the imbalance between nitric oxide and reactive oxygen species, and systemic inflammation.^{13,14} Atherosclerosis, diabetes mellitus, dyslipidemia, renal vascular disease, anemia, and hypertension are significant precursors and precipitating factors of both HF and renal failure.^{15,16} Heart–kidney interactions include a variety of conditions, either acute or chronic, in

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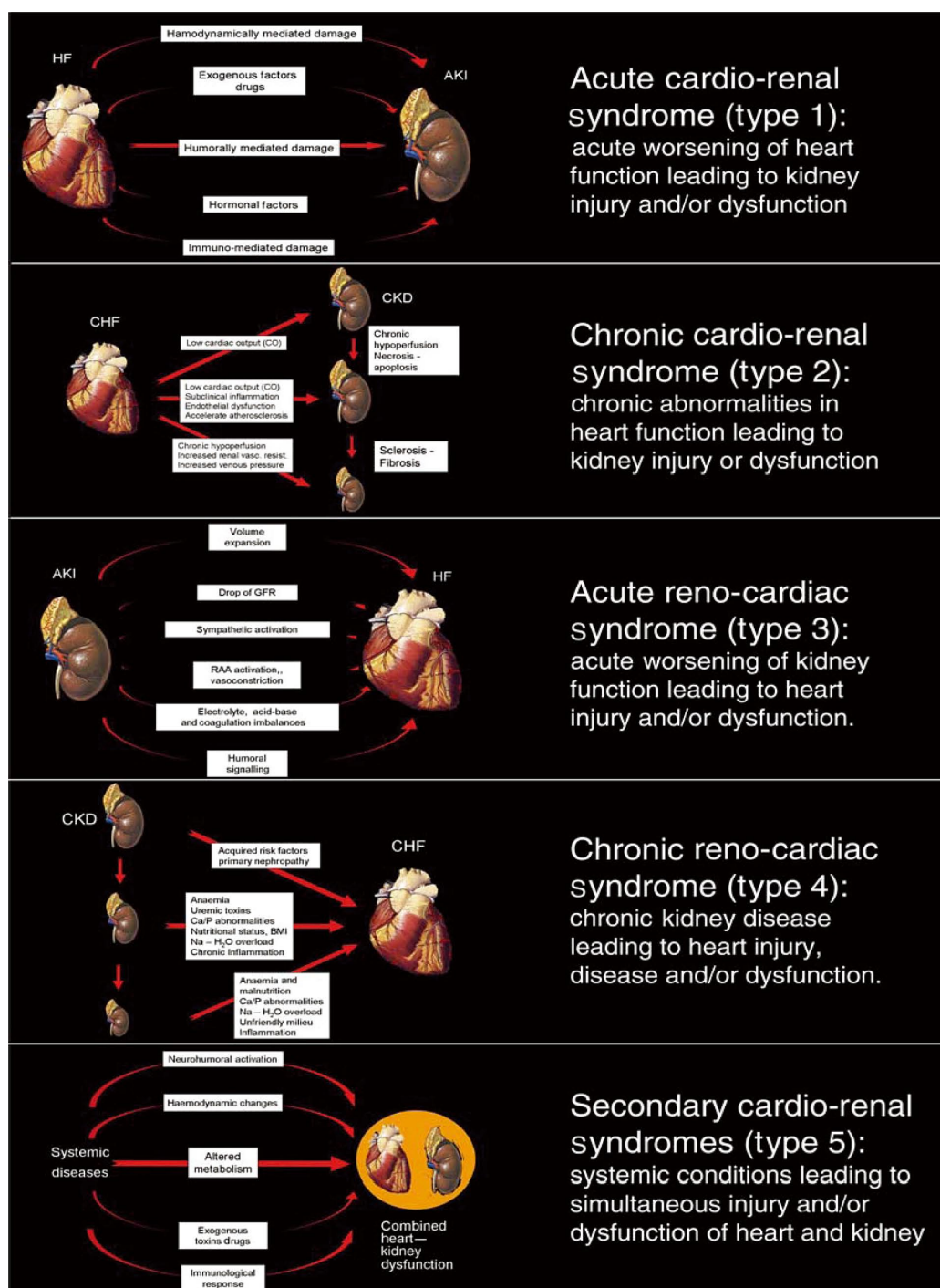


Figure 1. Pathophysiology and definitions of the 5 subtypes of cardiorenal syndrome. (Reprinted from Ronco et al¹⁷ with permission.)

which the primary failing organ can be either the heart or the kidney. Recently, Ronco et al discussed the different heart–kidney interactions and divided the CRS into 5 subtypes: type I, acute CRS; type II, chronic CRS; type III, acute reno-cardiac syndrome; type IV, chronic reno-cardiac syndrome; type V, secondary CRS^{16,17} (Figure 1). The identification of patients and the pathophysiological mechanisms underlying

each syndrome subtype will help physicians to understand the clinical derangements and provide the rationale for management strategies.

Biomarkers

The term “biomarker” (biological marker) was first intro-

Table 1. Laboratory Biomarkers in Heart Failure

Neurohormones
Natriuretic peptides (ANP, BNP, CNP, and related peptides)
Markers of renin-angiotensin-aldosterone system activity
Catecholamines
Endothelins
Arginine vasopressin and copeptin
Adrenomedullin and mid-regional proadrenomedullin
Cardiac injury (apoptosis and necrosis) markers
Cardiac troponins (cTns)
Heart-type fatty acid binding protein (H-FABP)
Fas (APO-1)
Growth differentiation factor-15 (GDF-15)
Oxidative stress markers
Oxidized low-density lipoproteins (oxLDL)
Myeloperoxidase
Isoprostanes
Plasma malondialdehyde
Serum uric acid
Urinary biopyrrins
Matrix remodeling markers
Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs)
Telopeptides and propeptides of collagen type I and type III
Osteopontin
Galectin 3
Inflammatory markers
C-reactive protein (CRP)
Cytokines and related receptors: IL-1, -2, -6, -8, -18, TNF- α , ST2, osteoprotegerin
Pentraxin 3
Hormonal and other markers of cachexia
Triiodothyronine
IGF-1 and GH
Cortisol
Adiponectin
Leptin

duced in 1989 as a Medical Subject Heading (MeSH) term,¹⁸ and the definition was further standardized by the National Institutes of Health working group in 2001 as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or

pharmacologic responses to a therapeutic intervention”.¹⁹ Generally speaking, biomarkers can be divided in 3 groups, according to the technical procedures used. Those variables measured by laboratory tests, such as natriuretic peptides and troponins are defined as “laboratory or molecular biomarkers”, those related to signaling, imaging, and functional tests are defined as “functional biomarkers”, and those related to genetic polymorphisms and other genomic tests are defined as “genetic biomarkers”. Moreover, according to its pathophysiological characteristics and/or clinical use, a cardiac or renal biomarker can be classified into different types: antecedent index (risk factor), screening index, diagnostic index, staging index, prognostic index, and therapeutic monitoring index.¹⁸ A large number of biomarkers have been evaluated in HF and the B-type natriuretic peptides (BNPs) have become established as the most ideal marker so far available²⁰ (Table 1). Measurement of cardiac troponins (cTns) has a pivotal role in acute coronary syndrome (ACS), and there is accumulating evidence of the usefulness of these markers in conditions other than ACS, including HF.²¹ In acute kidney injury (AKI) and CKD, promising biomarkers, both in plasma and in urine, that have become useful for assessment and prognostication, include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, interleukin-18, asymmetric dimethylarginine, and liver-type fatty acid-binding protein.²² In this review we focus on the current evidence about laboratory biomarkers in patients with HF or AKI/CKD, emphasizing the emerging cardiac biomarkers (ie, BNPs and cTns), and the biomarkers of renal injury (ie, cystatin C and NGAL). The roles of these biomarkers are also discussed in relation to each index and the CRS subtype in the setting of CRS.

BNP and NT-proBNP

Overview

The natriuretic peptides are a well-described family of hormones with a major role in sodium and body volume homeostasis. There are 3 major natriuretic peptides (atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide [CNP]), all of which share a common 17-amino-acid ring structure and have actions that are targeted at protecting the cardiovascular system from the effects of volume overload. ANP and BNP are released primarily from the heart, but circulate as hormones that act in various tissues in the body and induce vasodilatation, natriuresis and diuresis. Although ANP is preferentially synthesized and secreted from the atria, BNP

Table 2. BNP vs NT-proBNP

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (kDa)	3.5	8.5
Half-life (min)	20	60–120
Hormonal activity	Yes	No
Clearance	Renal, neutral endopeptidase clearance receptors (NPR-C)	Renal
Correlation with GFR	++	+++
Effect of renal function	++	++++
Removal by hemodialysis	~30%	~10%
Clinical range (pg/ml)	0–5,000	0–35,000
Approved cutoff value for heart failure diagnosis in normal renal function (pg/ml)	100	Age <50 years: 450/ Age ≥50 years: 900

BNP, B-type natriuretic peptide; GFR, glomerular filtration ratio.

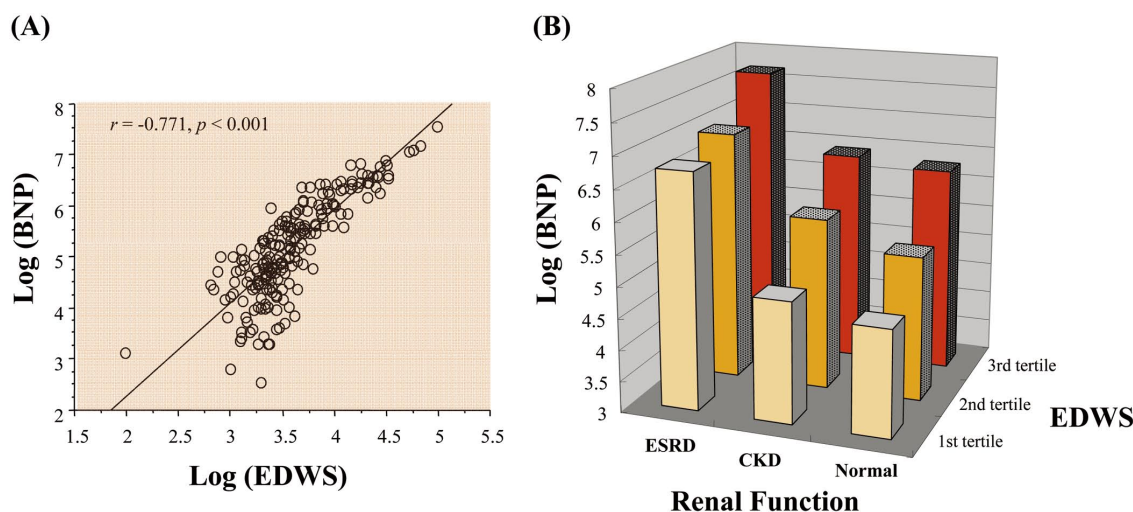


Figure 2. (A) Correlation between log plasma BNP level and log LVEDWS. (Reprinted from Iwanaga et al²³ with permission.) (B) Relationship of renal function (Normal, CKD, ESRD) and LVEDWS with log BNP concentration. Patients were divided into tertiles according to the level of EDWS (1st tertile: <33, 2nd tertile: 33–55, 3rd tertile: >55 kdynes/cm²). BNP, B-type natriuretic peptide; CKD, chronic kidney disease; ESRD, endstage renal disease; LVEDWS, left ventricular end-diastolic wall stress. (Reprinted from Niizuma et al³³ with permission.)

is synthesized in the ventricular myocardium in response to ventricular stretching and wall stress.²³ CNP, derived primarily from endothelial cells, is also synthesized in myocardial tissue. Upon ventricular myocyte stretch, pre-proBNP is enzymatically cleaved to proBNP and released in the form of the active hormone BNP (amino acids 79–108) or an inactive fragment, NT-proBNP (amino acids 1–76, released in a 1:1 ratio). Both BNP and NT-proBNP are widely used as markers for various cardiovascular diseases. However, there are differences between the 2 assays, as detailed in Table 2. NT-proBNP has a longer half-life and thus its levels may be more stable (less sensitive to acute stress). Furthermore, NT-proBNP might be more dependent on renal clearance than BNP.²⁴ Both BNP and NT-proBNP are eliminated only to a small extent during hemodialysis (HD), as detailed by both Wahl et al²⁵ and Madsen et al.²⁶ To date, most studies have demonstrated that both markers are equally useful, even in CKD and HD patients.²⁷ BNP and NT-proBNP, which are associated with the severity of HF and left ventricular (LV) function, are useful markers for diagnosis, management and prognosis in patients with normal renal function. The hemodynamic load (ie, myocardial stretch) is the most important stimulus for BNP and NT-proBNP secretion, based on the results of both basic and clinical studies. Iwanaga et al recently demonstrated an excellent correlation between BNP and LV end-diastolic wall stress (LVEDWS) ($r^2=0.89$, $P<0.001$) in HF patients with normal creatinine levels, and they found that this relationship was more robust than any other parameter previously reported²³ (Figure 2).

NPs in HF and CKD/ESRD

In most previous studies on the diagnostic and prognostic roles of BNP or NT-proBNP in HF, patients with CKD and ESRD have been excluded because of potentially elevated BNP concentrations. Recently, the diagnostic and prognostic potential of plasma BNP levels has been investigated in several studies of CKD, HD, and peritoneal dialysis patients.^{28,29} The

cut point for detecting HF may need to be raised when the estimated GFR (eGFR) is less than 60 ml/min. However, it should be noted that the diagnostic accuracy of plasma BNP and NT-proBNP levels for HF is reduced in this setting, and natriuretic peptide testing for HF should be discouraged in patients on dialysis.³⁰ There is controversy regarding the extent to which these increases are because of decreased clearance vs increased production. In other words, it is unclear whether, in HF patients with CKD and ESRD, increased plasma BNP levels might be more related to hemodynamic stimuli or might result from other factors such as anemia, obesity and cachexia or impaired renal clearance of natriuretic peptides, despite similar hemodynamic stimuli. Multiple studies have shown an inverse moderate, but significant, correlation between eGFR and BNP or NT-proBNP concentrations.³¹ These correlation coefficients typically range from -0.3 to -0.5 and have been studied in both asymptomatic ambulatory patients and emergency department patients with dyspnea or known HF. Most recently, van Kimmenade et al showed that BNP and NT-proBNP had nearly identical correlations to eGFR ($r=-0.35$ and $r=-0.3$, respectively; $P<0.001$ for both) in 165 hypertensive subjects.³² They went a step further by measuring renal fractional extraction (FE) ([renal artery concentration–renal vein concentration]/renal artery concentration) of these natriuretic peptides and found that, across a range of eGFRs as low as $9 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, FEs for BNP and NT-proBNP diminished only modestly and correlated minimally with eGFR ($r=0.20$ – 0.26 ; $P<0.05$ for both). Furthermore, they found in a multivariate regression analysis that cardiorelated factors such as blood pressure, LV mass, and eGFR, but not FE, were significantly associated with the concentrations of natriuretic peptides. Niizuma et al performed a study in a wide spectrum of HF patients with both CKD and ESRD and analyzed the contribution of LVEDWS to the BNP concentration³³ (Figure 2). They showed that LVEDWS was a strong determinant of BNP, even in patients with CKD and ESRD, and that anemia, obe-

sity, and HF type (systolic or diastolic HF) should be also considered in interpreting plasma BNP concentrations in HF patients. Both studies indicate that increased concentrations of natriuretic peptides are predominantly related to, and a result of, the presence and extent of cardiac pathology rather than impaired renal clearance. However, for patients with ESRD (mostly on dialysis) in Niizuma's study, the correlation between LVEDWS and BNP concentration was only modest, suggesting that in this group, hemodynamic factors played a lesser role in determining the concentrations of the natriuretic peptides than in those CKD patients not on dialysis. There might be unknown factors or hidden confounders unique to this population. Currently, the clinical utility of measurements of BNP in HF patients with ESRD seems to be very limited.

BNP-Guided Therapy

What has been contentious recently is "BNP-guided monitoring of therapy" to improve symptoms and ultimately change outcomes. Whether serial BNP measurements to aid in the titration of therapy can improve HF outcomes remains uncertain. The first study to address the question was performed by Troughton et al in 69 patients with HF.³⁴ They reported a significant reduction in HF events, including cardiovascular death and HF hospitalization. Since then, several larger trials have been reported and the largest trial to date is the recently published TIME-CHF study, which compared NT-proBNP-guided therapy with symptom-guided therapy in 499 outpatients with HF.³⁵ That study concluded that the NT-proBNP-guided arm did not improve overall clinical outcomes. However, as with the BATTLESCARRED trial reported by Lainchbury et al,³⁶ it did demonstrate that younger patients (between the ages of 60 and 75 years) had a higher survival free of hospitalization as compared with symptom-guided therapy. The recent meta-analysis by Felker et al suggests that BNP-guided monitoring of therapy was associated with a significant reduction in all-cause mortality in 6 studies randomizing 1,627 patients.³⁷ BNP-guided therapy might be of limited value in older patients because they have increased levels of natriuretic peptides with significant comorbidities, and HF therapy might show less evident benefits and be underutilized for the elderly. Because subanalysis in terms of renal function has not been performed and patients with severe CKD were also excluded from those trials, the impact of renal insufficiency on the treatment effect by BNP guiding remains uncertain.

Cardiac Troponins

Overview

Troponin T, I and C are components of the contractile apparatus of striated muscle. Specific forms of troponins T and I are present in the heart muscle, namely cTnT and cTnI. After myocardial cell damage, cTns are released from the myocytes and their levels are detectable 3–12 h after the injury, with the concentrations in direct proportion to the extent of myocardial injury. Mean time to peak cTnT level is approximately 12–48 h. The concentration returns to the normal range after 5–14 days, which is 4 times longer than for the creatine kinase myocardial band isoenzyme (CK-MB) fraction, probably because of sustained release of structurally-bound protein from disintegrating myofibrils. cTnT is cardiac specific and is not present in the serum following nonmyocardial muscle or other tissue damage.³⁸ For these reasons, the measurement of cTns in ACS has completed the evolution of a modern

clinical test. Recent guidelines endorsed by the European Society of Cardiology and the American College of Cardiology/American Heart Association state that cTns are the preferred biomarkers for detection of myocardial injury and diagnosis of myocardial infarction (MI). More importantly, the test has prognostic value because it identifies ACS patients who are at substantially increased risk of death or recurrent MI.³⁹

cTns in CKD/ESRD

The levels of cTns are frequently elevated in the absence of ACS among patients with renal dysfunction, specifically in 30–75% of ESRD patients.^{40,41} At one time, it was considered that an elevation of the cTns in a setting of decreased creatinine clearance was not of substantial diagnostic or prognostic importance. The GUSTO IV trial, which included 7,033 patients with suspected ACS, indicated that an elevated cTnT level was strongly predictive of poor short-term prognosis, regardless of creatinine clearance.⁴² Although the important limitations in that study were the very small number of patients with severe or ESRD and its confinement to symptomatic patients, cTnT elevation had even greater prognostic importance among patients with a mild to moderate degree of CKD. Moreover, over the past decade, data have emerged to suggest that elevated levels of cTns may predict death among ESRD patients without symptoms of ACS.³⁰ Although the precise mechanism of death is unknown, several studies suggest that the prevalence of increased levels of cTns correlates with increased risk of coronary artery disease (CAD). A current meta-analysis by Khan et al suggests that elevated cTnT (>0.1 ng/ml) identifies a subgroup of ESRD patients who have poor survival and a high risk of cardiac death, despite being asymptomatic.⁴³ Their study concluded that routine measurement of cTnT is prognostically valuable and may help frame therapeutic decisions. However, the pathophysiologic mechanisms causing random increases in cTn concentrations in patients with renal dysfunction or dialysis are still unclear. Even though there are data to suggest an association between renal function and cTns,⁴⁴ elevation of cTn levels in ESRD patients is unlikely to be the result of decreased clearance by the failing kidney.^{45,46} It has been proposed that cTn elevation might reflect cardiac damage in nonischemic cardiomyopathy, or microvascular disease in the setting of LV hypertrophy. Jung et al reported an independent association of cTns with the degree of severity of coronary artery calcification detected by multirow spiral computed tomography in 38 asymptomatic chronic HD patients.⁴⁷ One large study⁴⁸ found that dialysis patients with elevated cTnT levels were more likely to have severe angiographic coronary disease. deFillippi et al found that a high level of cTnT (>median) vs a low level of cTnT remained an independent predictor of multivessel disease (prevalence ratio, 3.7 fold) after adjustment for age and history of clinical CAD in stable patients undergoing long-term HD.⁴⁸ They also suggested the potential complementary role of serum C-reactive protein, which is elevated in more than 70% of HD patients, for predicting all-cause mortality.

cTns in HF

In the failing myocardium, under the influence of various neurohumoral and hemodynamic alterations, there is progressive myocyte loss through both necrotic and apoptotic cell death, and replacement with foci of fibrosis, which could contribute to progressive cardiac dysfunction and LV remodeling. Evidence of myocyte cell death in the human myo-

cardium has been suggested by histologic information from biopsies and more recently by the measurement of markers of myocardial damage in the serum, that is, cTnT and I. These markers may be able to identify subclinical injury to the myocardium. Missov et al first reported the association between troponins and HF in 1997.⁴⁹ La Vecchia et al reported that, in non-ischemic HF, the cTnI level could identify a subgroup of patients with severe HF, and that improvement of HF was associated with disappearance of TnI.⁵⁰ In patients with acute decompensated HF, 6.2% were positive for cTn testing and they showed higher in-hospital mortality (8.0%) than those with a negative cTns test.⁵¹ During routine clinical follow-up of ambulatory patients, elevations in cTnT, particularly if frequent or persistent, were highly associated with an increased risk of events.⁵² In the context of HF, evidence for a role of cTns continues to accumulate, particularly their use in risk stratification. In addition, Sundström et al reported that an elevated serum level of cTnI was an independent contributor to the development of HF in a community-based sample of 1,089 70-year-old men.⁵³ Moreover, Ishii et al⁵⁴ and Taniguchi et al⁵⁵ measured cTnT in combination with BNP measurement in HF patients and analyzed the prognostic value. Both studies suggested that the combination of cTns and BNP measurements might be complementary and highly effective for risk stratification in patients with HF. Also, in the setting of acute HF, Metra et al reported similar results.⁵⁶ Because most studies consist of small numbers of patients and exclude patients with severe CKD, the clinical significance of increased cTn concentrations in patients with HF complicated by CKD is unclear. Recently, Tsutamoto et al reported that decreased clearance via the kidney might contribute to the elevated cTnT levels in HF patients with CKD, information that they obtained by measuring the difference in TnT concentrations between the coronary sinus and aortic root.⁵⁷ It is a controversial issue,^{45,46} and further large studies will be needed to clarify whether renal dysfunction itself or additional myocyte damage affects the clinical outcome of HF patients with CKD. It should be noted that cTn testing does not provide any insight into the mechanism of heart injury and that a broad differential diagnosis, including renal failure and pulmonary embolism, is routinely considered when the cTn concentration is elevated in the absence of ACS.⁵⁸

Highly Sensitive cTn Assay

Until recently, there was some problem regarding the capability of achieving the recommended precision in cTn testing. However, with the development of “highly sensitive” cTn assays, it is now possible to accurately measure troponin concentrations at and below the current 99th percentile of a healthy population.⁵⁹ Recent data obtained using the highly sensitive assays suggest that previously undetectable cTn concentrations are also associated with worse outcomes in patients with ACS and stable CAD.^{60,61} Latini et al tested the prognostic value of the highly sensitive cTnT (hs-TnT) assay in 4,053 patients with chronic HF and showed that cTnT was detectable in 10.4% with the currently available assay compared with 92% using the hs-TnT assay.⁶² Patients with hs-TnT levels above the median had more severe HF and worse outcomes. Also, in the setting of CRS, further evidences for the test's utility are emerging.⁶³

Biomarkers of Renal Injury: Cystatin C and NGAL

Cystatin C in CKD

Cystatin C is a novel endogenous marker of renal function

that may be more sensitive for detecting mild to moderate decrements in GFR. It is a member of the family of cysteine proteinase inhibitors that is produced at a constant rate by all nucleated cells. It is freely filtered across the glomerular membrane and completely catabolized in the proximal tubules. Most studies suggest that it is not affected by age, sex, or muscle mass and has superior diagnostic accuracy compared with serum creatinine for early renal impairment.⁶⁴ However, there is still a paucity of evidence that it actually leverages important clinical decisions more effectively than the use of serum creatinine alone or eGFR. Serum concentrations of cystatin C may be used to detect renal dysfunction in critically ill patients with AKI 24–48h earlier than with creatinine measurements. It is an early marker of impaired glomerular filtration rather than of tubular lesion.⁶⁵ By contrast, the urinary cystatin C to creatinine ratio is a good indicator of renal tubular dysfunction. In AKI, urinary cystatin C levels have been also shown to predict the requirement for renal replacement therapy earlier than those of creatinine.

Cystatin C in HF

High concentrations of circulating cystatin C have been shown to be consistently and strongly associated with cardiovascular outcomes in different clinical scenarios. Moreover, this marker seems to offer more complete prognostic information than other markers of renal function. In acute HF, the prognostic value of the serum cystatin C measurement has been investigated in comparison with other markers of renal function and NT-proBNP by Lassus et al.⁶⁶ They showed that the mortality rate increased significantly with each tertile of cystatin C, and combining the tertiles of NT-proBNP and cystatin C improved risk stratification further. Moreover, in patients with normal plasma creatinine levels, elevated cystatin C was associated with significantly higher mortality at 12 months: 40.4% vs 12.6%. Manzano-Fernandez et al confirmed these results and also included cTnT measurements in their multi-marker risk stratification approach.⁶⁷ They found that each biomarker (cystatin C, NT-proBNP, and cTnT) provided independent and complementary prognostic information. Also, in elderly patients with chronic HF, cystatin C and NT-proBNP levels are reported to be a powerful combination for predicting cardiovascular mortality.⁶⁸

Cystatin C has been shown to be a risk factor for HF and cardiovascular disease mortality in the general population.⁶⁹ Patel et al further tested whether cystatin C could be a marker for subclinical cardiac structural and functional abnormalities in 2,548 participants in the Dallas Heart Study.⁷⁰ They showed that higher levels of cystatin C were associated with increased LV mass and its concentricity, independent of potential confounding variables, including standard measurements of renal function. Of interest, elastolytic proteases and their inhibitors, in particular cystatin C, have been shown to be directly involved in the atherosclerotic process. The increased plasma concentrations of cystatin C may reflect, at least in part, an attempt to counterbalance a potentially damaging increased elastolytic activity.⁷¹ In patients with ACS or stable CAD, several studies have demonstrated that high cystatin C concentrations are associated with an increased risk of death, MI, or HF.^{72,73} Although increased concentrations of cystatin C appear to be indicative of preclinical kidney disease associated with adverse outcomes, there has been no answer to whether pathogenic mechanisms other than renal dysfunction could account for a high cystatin C concentration and explain its predictive value for future cardiovascular risk. Clinical studies involving direct GFR measurements are required to

ascertain both the true role of this promising marker in renal disease and whether atherogenic factors like inflammation can account for increases in cystatin C concentrations, thus explaining its predictive value in cardiovascular disease.⁶⁹

NGAL in AKI/CKD

NGAL, also known as 24p3 and lipocalin-2, is a 25-kDa secretory glycoprotein and a member of lipocalin superfamily of proteins that are originally identified in mouse kidney cells and human neutrophil granules.⁷⁴ NGAL expression has been shown to be induced rapidly in renal tubules in response to acute injury. NGAL seems to be one of the earliest kidney markers of ischemic or nephrotoxic injury in animal models and is detected in the blood and urine of humans soon after AKI.⁷⁵ It has been studied in the setting of post-cardiac surgery, cardiac catheterization, hemolytic uremic syndrome, and kidney transplantation.^{76,77}

NGAL in HF

Aghel et al recently reported that an elevated admission serum NGAL level was associated with heightened risk of subsequent development of worsening renal function in 91 patients admitted with acute HF.⁷⁸ In patients with chronic HF, Damman et al suggested that renal impairment is not only characterized by decreased eGFR and increased urinary albumin excretion, but also by increased urinary NGAL concentration.⁷⁹ Poniatowski et al reported that the predictors of serum NGAL in 150 patients with chronic HF were NYHA class, cystatin C, and eGFR in multiple regression analysis.⁸⁰ NGAL might be investigated as a potential early and sensitive marker of kidney impairment/injury in order to select the appropriate strategy for reducing the risk in the setting of CRS.

However, recent evidence demonstrates a diversity of expression and function of NGAL. It may be stored in specific granules of mature neutrophils and also released by epithelial cells and hepatocytes during inflammation or injury. It has been implicated not only as a marker of renal function, but also of neutrophil activation, as a protective factor against apoptosis and oxidative stress. Increased NGAL expression in atherosclerotic plaques has also been demonstrated.⁸¹ Zografos et al reported that serum NGAL levels were significantly higher in the presence of CAD and correlated with its severity.⁸² Also, in HF, increased myocardial expression of NGAL might be one of the mechanisms for its prognostic value, independent of coexisting renal injury.⁸³ Yndestad et al reported strong immunostaining in cardiomyocytes within the failing myocardium in both experimental and clinical HF.⁸⁴ They also demonstrated that NGAL levels were significantly correlated with total leukocyte count ($r=0.22$, $P=0.006$) and C-reactive protein level ($r=0.43$, $P<0.001$), indicating a relationship with the inflammatory process. Further basic and clinical studies are warranted to elucidate the true pathogenic role of increased NGAL levels and to confirm its use as a biomarker for CRS.

Conclusions

The heart–kidney interaction is far more complex and intricate than that of a simple pump and filter. Of great importance is recognizing the presence of CRS and appreciating the effect it has on treatment options and survival. Reliable biomarkers for early diagnosis and staging of HF or CKD/AKI will lead to more accurate and efficient patient management and the development of strategies for cardiovascular risk stratification

and prevention in this condition. However, it is necessary for clinicians and investigators to consider the pathologic mechanisms linking heart and kidney in their interpretation and utilization of such biomarkers. Furthermore, it is important to look beyond just biomarkers measured at presentation and statistical tests of association to make a compelling argument for the clinical utility of an alternative marker in cardiovascular risk prediction. From such an integrated viewpoint, cardiac and renal biomarkers will facilitate and improve the clinical managements of HF and CKD.

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