B-Type Natriuretic Peptide (BNP)/NT-proBNP and Renal Function:
Is the Controversy Over?

Christopher R. deFilippi†* and Robert H. Christenson‡

A decade ago, controversy surrounded the observation of increased cardiac troponin concentrations in asymptomatic renal disease patients, with one assay claiming better specificity and another better prognostic potential. This controversy is largely resolved now, with availability of more outcome data, improved low-end sensitivity of the assays, and a general recognition that renal disease was only one cause, albeit an important one, of myocardial injury in the absence of an acute coronary syndrome (1). It should come as little surprise, then, that soon after the introduction of commercial assays for B-type natriuretic peptide (BNP)3 and amino-terminal pro-BNP (NT-proBNP) and the publication of seminal studies for their diagnostic application in patients presenting with dyspnea of uncertain etiology, there has been much debate over the interpretation and significance of these tests in patients with impaired renal function (2, 3).

Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², is a common condition with multiple etiologies that affects an estimated 8.3 million Americans and is found in 33% to 56% of patients with heart failure (4). The use of either BNP or NT-proBNP to diagnose decompensated heart failure in dyspnea patients with concomitant moderate renal disease (eGFR 30–59 mL/min/1.73 m²) is generally accepted clinically. When comparing the diagnostic accuracy of these tests in individuals with and without impaired renal function, only mildly diminished accuracy is observed in renal disease, as long as a modestly increased optimal cutoff is used for BNP or age-specific cutoffs for NT-proBNP (5, 6). The caveat is that concentrations of BNP and NT-proBNP are typically increased to a much greater extent (NT-proBNP more so than BNP) in both asymptomatic and symptomatic patients with CKD than in those with normal renal function. There is controversy regarding to what extent these increases are due to decreased clearance vs increased production. This remains a critical distinction, for although acute decompensated heart failure can result in a perturbation and release of natriuretic peptides (NPs) in sufficient quantities to dwarf the importance of decreased clearance for immediate diagnostic purposes, more subtle uses of NPs, such as for guiding chronic outpatient therapy of heart failure or for prognostication, may no longer be as applicable in patients with CKD.

Two studies published this year, including the one by Niizuma et al. in this issue of Clinical Chemistry (7), provide mechanistic insight into resolving this dilemma (7, 8).

DECREASED RENAL CLEARANCE?

Multiple studies have shown an inverse moderate, but significant, correlation between eGFR and BNP or NT-proBNP concentrations (4). 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 heart failure. Although discrepancies between the two tests are seen when comparing studies looking at only a single marker, studies that test both markers have shown the correlations to be close. Most recently, van Kimmenade et al. (8) showed NT-proBNP and BNP had nearly identical correlations to eGFR (r = −0.30 and r = −0.35, respectively; P < 0.001 for both) in 165 hypertensive subjects. These investigators went a step further by measuring renal fractional extraction (FE) [(renal artery concentration − renal vein concentration)/renal artery concentration] of these NPs and found that, across a range of eGFRs as low as 9 mL·min⁻¹·(1.73 m²)⁻¹, 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, these investigators found in a multivariate regression analysis that cardiac-related factors such as blood pressure, left ventricular mass, and eGFR, but not FE, were significantly associated with BNP and NT-proBNP concentrations, suggesting that...
cardiovascular disease could be playing a dominant role in determining concentrations in CKD patients.

INCREASED CARDIOVASCULAR PATHOLOGY

Patients with CKD have more cardiovascular disease in the form of both atherosclerotic disease and left ventricular hypertrophy and are more likely to die of cardiovascular disease than those without impaired renal function (9). Increased BNP and NT-proBNP concentrations, independent of eGFR and traditional cardiovascular risk factors, are associated with both forms of cardiac pathology in ambulatory CKD patients (10, 11). Prognostic data are more limited in the CKD population. There has been one large outcomes study evaluating 994 African-American hypertensive patients with CKD who were followed for a median of 4.3 years (12). Increased NT-proBNP concentrations were associated with a variety of adverse cardiovascular outcomes, including heart failure and cardiovascular death. In another study of patients with renal disease presenting with dyspnea to the emergency department, both BNP and NT-proBNP remained independent predictors of 1-year mortality after adjustment for risk factors and eGFR (13). However, prior hemodynamic assessments have tempered the enthusiasm to conclude that cardiac pathology is the primary etiology of NP increases. For example, Forfia et al. (14) studied the hemodynamics of 40 intensive care patients with pulmonary artery catheters in place. Despite approximately 4-fold higher BNP and NT-proBNP concentrations in patients with eGFR <60 mL·min⁻¹·(1.73 m²)⁻¹ compared to those with more normal renal function, they found no differences in the pulmonary capillary wedge pressure, cardiac index (cardiac output corrected for body surface area), or left ventricular ejection fraction (14). Even factors that could account for severity of illness, such as use of vasopressors, mechanical ventilation, and extent of hypoxia, were not found to influence the NP concentrations in their study.

Myocardial stretch is one of the most important stimuli of BNP and NT-proBNP release. Pulmonary capillary wedge pressure, cardiac index, and left ventricular ejection fraction can be poor surrogates for myocardial stretch (preload). Preload represents the wall stress at the end of diastole (EDWS) and therefore at the maximal resting length of the sarcomere (the fundamental contractile unit of the myocyte). Wall stress can be thought of according to the Laplace law (an oversimplification given the true complexity of the left ventricular geometry): wall stress = pressure × radius/(2 × wall thickness). Therefore, by assessing only end-diastolic pressure (pulmonary capillary wedge pressure is an approximation of this measure) or end diastolic left ventricular dimensions, one is accounting for only part of the wall stress equation. This may explain the heterogeneity between either of these measures and BNP or NT-proBNP concentrations. This was nicely demonstrated by Iwanaga et al. (15) in patients with compensated heart failure; an excellent correlation was found between BNP and EDWS ($r^2 = 0.89, P < 0.001$) vs a poorer correlation between BNP and end-diastolic pressure ($r^2 = 0.33, P < 0.001$). In the current issue of Clinical Chemistry, these same investigators have extended their findings to include heart failure patients with both CKD and end-stage renal disease (ESRD) (7). When considering the patients with renal disease, after excluding those with ESRD, they found a correlation between BNP and EDWS similar to that observed in patients with normal renal function. For patients with ESRD, the correlation was only modest, suggesting that in this group, hemodynamic factors play a lesser role in determining the natriuretic peptide concentrations than in those with CKD not on dialysis. As expected, patients with CKD have higher natriuretic peptide concentrations than those with normal renal function, but they also have higher EDWS, which can in large part explain the disparate values despite an absence of significant differences in left ventricular ejection fraction, left ventricular mass, and diastolic volumes, all commonly measured cardiac noninvasive parameters.

In summary, the recent publication by van Kimmenade et al. (8) and the study by Niizuma et al. (7) provide possible mechanisms to explain increased BNP and NT-proBNP concentrations seen in prior association and prognostic studies in patients with moderately impaired renal function (7, 8). Taken together, they indicate that increased BNP and NT-proBNP concentrations are predominantly related to and a result of the presence and extent of cardiac pathology rather than impaired renal clearance. Although some questions remain, such as why NT-proBNP rises disproportionately to BNP at lower eGFRs despite similar decrements in FE, the primary issue facing the interpretation of natriuretic peptide concentrations in this population will no longer be what it means, but what to do about it.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: R.H. Christenson, Siemens Healthcare Diagnostics.

Stock Ownership: None declared.


Research Funding: C.R. deFilippi, Roche Diagnostics and Siemens Healthcare Diagnostics; R.H. Christenson, Radiometer America, Inverness Diagnostics, and Siemens Diagnostics.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References


