

Q: Does measuring natriuretic peptides have a role in patients with chronic kidney disease?

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A: Yes, measuring the levels of certain natriuretic peptides can help diagnose decompensated heart failure and predict the risk of death and cardiac hospitalization in patients across a wide spectrum of renal function.

However, at this time, it is unclear whether routinely measuring natriuretic peptides will result in any change in the management of patients with chronic kidney disease. Additionally, using these peptides to monitor volume status in dialysis patients has not yet been deemed useful, although it may be complementary to echocardiography in evaluating cardiac risk in patients with end-stage renal disease.

■ A BRIEF REVIEW OF NATRIURETIC PEPTIDES

Natriuretic peptides include atrial natriuretic peptide, brain natriuretic peptide (BNP), C-type natriuretic peptide, and urodilantin.

BNP, which is homologous to atrial natriuretic peptide, is present in the brain and the heart. The circulating concentration of BNP is less than 20% of the atrial natriuretic peptide level in healthy people, but equals or exceeds that of atrial natriuretic peptide in patients with congestive heart failure.

BNP starts as a precursor protein. This is modified within the cell into a prohormone, proBNP, which is secreted from the left ventricle in response to myocardial wall stress.

In the circulation, proBNP is cleaved into a biologically active C-terminal fragment—BNP—and a biologically inactive N-terminal fragment (NT-proBNP).¹ NT-proBNP is primarily cleared by the kidney. BNP is cleared by receptor-mediated binding and removed by neutral endopeptidase, as well as by the kidney.

Both BNP and NT-proBNP have been investigated as diagnostic markers of suspected heart disease.

■ PEPTIDE LEVELS ARE HIGH IN CHRONIC KIDNEY DISEASE AND HEART FAILURE

An estimated 8.3 million people in the United States have stage 3, 4, or 5 chronic kidney disease,² defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m². Approximately 50% of patients with heart failure have chronic kidney disease, and almost 60% of patients with chronic kidney disease have some abnormality in ventricular function.

A few years ago, researchers began investigating the benefits and limitations of using natriuretic peptides to diagnose cardiac dysfunction (left ventricular structural and functional abnormalities) in patients with chronic kidney disease.

One important study³ was conducted in almost 3,000 patients from the Dallas Heart Study who were between the ages of 30 and 65 years—a relatively young, mostly healthy population. The authors found that natriuretic peptide levels did not vary as long as the estimated glomerular filtration rate was within the normal range. However, when the estimated glomerular filtration rate dropped below a threshold of 90 mL/min/1.73 m², the

BNP and NT-proBNP levels can help diagnose decompensated heart failure

doi:10.3949/ccjm.76a.08065

concentrations of both NT-proBNP and BNP increased exponentially. NT-proBNP levels rose more than BNP levels, as NT-proBNP is primarily cleared by the kidney.

More recent studies found that the high levels of NT-proBNP in patients with chronic kidney disease do not simply reflect the reduced clearance of this peptide; they also reflect compromised ventricular function.^{2,4} This relationship was supported by studies of the fractional renal excretion of NT-proBNP and BNP in several populations with and without renal impairment.⁵ Interestingly, fractional excretion of both peptides remained equivalent across a wide spectrum of renal function. Seemingly, cardiac disease drove the increase in values rather than the degree of renal impairment.

■ HIGH PEPTIDE LEVELS PREDICT DEATH, HOSPITALIZATION

Both BNP and NT-proBNP are strong predictors of death and cardiac hospitalization in kidney patients.^{1,4,6}

In patients with end-stage renal disease, the risk of cardiovascular disease and death is significantly higher than that in the general population, and BNP has been found to be a valuable prognostic indicator of cardiac disease.⁷

Multiple studies showed that high levels of natriuretic peptides are associated with a higher risk of death in patients with acute coronary syndrome, independent of traditional cardiovascular risk factors such as electrocardiographic changes and levels of other biomarkers. However, these data were derived from patients with mild renal impairment.²

Apple et al⁸ compared the prognostic value of NT-proBNP with that of cardiac troponin T in hemodialysis patients who had no symptoms and found that NT-proBNP was more strongly associated with left ventricular systolic dysfunction and subsequent cardiovascular death.

■ PEPTIDE LEVELS ARE HIGHER IN ANEMIA

A significant number of patients with congestive heart failure have renal insufficiency and low hemoglobin levels, which may increase natriuretic peptide levels. It is unclear why

anemia is associated with elevated levels of natriuretic peptides, even in the absence of clinical heart failure and independent of other cardiovascular risk factors.⁹ Nevertheless, anemia should be taken into consideration and treated effectively when evaluating patients with renal impairment and possible congestive heart failure.

■ PEPTIDES COMPLEMENT CARDIAC ECHO IN END-STAGE RENAL DISEASE

Numerous studies have found a close association between BNP and NT-proBNP levels and left ventricular mass and systolic function in patients with end-stage renal disease.^{10,11} Data from the Cardiovascular Risk Extended Evaluation in Dialysis Patients study¹² suggest that BNP measurement can be reliably applied in end-stage renal disease to rule out systolic dysfunction and to detect left ventricular hypertrophy, but it has a very low negative predictive value for left ventricular hypertrophy in this patient population: someone with a normal BNP level can still have left ventricular hypertrophy.

In addition, volume status is harder to assess with BNP alone than with echocardiography, and an elevated BNP value is not very specific.¹³

In essence, both BNP and NT-proBNP can be used to complement echocardiography in evaluating cardiac risk in patients with end-stage renal disease. With additional data, it may be possible in the future to use them as substitutes for echocardiography when managing ventricular abnormalities in patients with end-stage renal disease.

■ USING SPECIFIC CUT POINTS IN RENAL DISEASE

When evaluating a patient with acute dyspnea and either chronic kidney disease or end-stage renal disease who is receiving dialysis, both BNP and NT-proBNP are affected similarly and necessitate a higher level of interpretation to diagnose decompensated heart failure. Currently, researchers disagree about specific cut points for natriuretic peptides. However, deFilippi and colleagues⁴ suggested the following cut points for NT-proBNP for diagnosing

Volume status is harder to assess with BNP alone than with echocardiography

heart failure in patients of different ages with or without renal impairment:

- Younger than 50 years—450 ng/L
- Age 50 to 75 years—900 ng/L
- Older than 75 years—1,800 ng/L.

A BNP cutoff point of 225 pg/mL can be used for patients with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m²,

based on data from the Breathing Not Properly multinational study.¹⁴

There is no set cut-point for either BNP or NT-proBNP for predicting death and cardiac hospitalization in renal patients, but abnormally high levels should signal the need to optimize medical management and to monitor more closely. ■

REFERENCES

1. Austin WJ, Bhalla V, Hernandez-Arce I, et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Pathol* 2006; 126:506–512.
2. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol* 2008; 101:82–88.
3. Das SR, Abdullah SM, Leonard D, et al. Association between renal function and circulating levels of natriuretic peptides (from the Dallas Heart Study). *Am J Cardiol* 2008; 102:1394–1398.
4. DeFilippi CR, Seliger SL, Maynard S, Christenson RH. Impact of renal disease on natriuretic peptide testing for diagnosing decompensated heart failure and predicting mortality. *Clin Chem* 2007; 53:1511–1519.
5. Goetze JP, Jensen G, Møller S, Bendtsen F, Rehfeld JF, Henriksen JH. BNP and N-terminal proBNP are both extracted in the normal kidney. *Eur J Clin Invest* 2006; 36:8–15.
6. Zoccali C. Biomarkers in chronic kidney disease: utility and issues towards better understanding. *Curr Opin Nephrol Hypertens* 2005; 14:532–537.
7. Haapio M, Ronco C. BNP and a renal patient: emphasis on the unique characteristics of B-type natriuretic peptide in end-stage kidney disease. *Contrib Nephrol* 2008; 161:68–75.
8. Apple FS, Murakami MM, Pearce LA, Herzog CA. Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. *Clin Chem* 2004; 50:2279–2285.
9. Hogenhuis J, Voors AA, Jaarsma T, et al. Anemia and renal dysfunction are independently associated with BNP and NT-proBNP levels in patients with heart failure. *Eur J Heart Fail* 2007; 9:787–794.
10. Madsen LH, Ladefoged S, Corell P, Schou M, Hildebrandt PR, Atar D. N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease on hemodialysis. *Kidney Int* 2007; 71:548–554.
11. Wang AY, Lai KN. Use of cardiac biomarkers in end-stage renal disease. *J Am Soc Nephrol* 2008; 19:1643–1652.
12. Mallamaci F, Zoccali C, Tripepi G, et al, on behalf of the CREED Investigators. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 2001; 59:1559–1566.
13. Biasioli S, Zamperetti M, Borin D, Guidi G, De Fanti E, Schiavon R. Significance of plasma B-type natriuretic peptide in hemodialysis patients: blood sample timing and comorbidity burden. *ASAIO J* 2007; 53:587–591.
14. McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly multinational study. *Am J Kidney Dis* 2003; 41:571–579.

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