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Natriuretic peptide testing: A window into the diagnosis and prognosis of heart failure

ABSTRACT

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels can indicate a variety of heart problems, as well as general critical illness. BNP and NT-proBNP assays are useful for evaluating patients with acute dyspnea, as a low level of natriuretic peptide can help rule out congestive heart failure (CHF) and reduce reliance on echocardiography. Conversely, these assays can be particularly useful in recognizing CHF in a patient with acute dyspnea and a history of chronic obstructive pulmonary disease. However, clinical judgment must always be part of the evaluation of BNP or NT-proBNP assay results.

KEY POINTS

Assays for BNP or NT-proBNP are powerful tools, but they are not meant to be used in isolation and are no substitute for a physical examination and other diagnostic tools.

High natriuretic peptide levels also occur in mitral regurgitation, right heart conditions, and diastolic dysfunction.

Routine use of natriuretic peptide assays may more rapidly identify patients with heart failure, expedite their management, and exclude patients with a very low probability of having CHF, thereby potentially saving a great deal of money.

*The author has indicated that he has served as a consultant and a speaker for the Ortho and Roche corportations.

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BIOMARKER ASSAYS for the B-type natriuretic peptides BNP and N-terminal pro-BNP (NT-proBNP) are currently approved by the US Food and Drug Administration for evaluating suspected congestive heart failure (CHF). In the few years that they have been available, they have become widely used for acute patient evaluation; other uses are to estimate prognosis and, possibly, to monitor and guide CHF therapy. But they should not be the only criterion: physicians should consider the entire clinical picture, not just the peptide level.

I will explore here the role of natriuretic peptide assays in evaluating patients with acute dyspnea, as well as in assessing prognosis and monitoring and guiding therapy.

THE CHALLENGE OF DIAGNOSING CHF

CHF is not a single entity, but the end stage of a number of diseases that may differ considerably in pathophysiology, symptoms, and management. Diagnosing CHF can be challenging, especially if a patient is aware only of fatigue and if the physical signs are subtle.

Echocardiography is the gold standard for assessing CHF. Unfortunately, it is expensive and takes advanced training to perform and interpret. In addition, patients with very different ejection fractions can present with the same clinical picture. The classic picture of systolic heart failure—low ejection fraction, dilated left ventricle, and incomplete mitral closure—is seen in only about half of patients with CHF.

TWO TYPES OF BNP-RELATED MARKERS

The BNP markers arise from myocardium. BNP release depends on wall stress, which

could arise from CHF, ischemic heart disease, or pulmonary thromboembolism. Wall stress triggers a rapid sequence of events that up-regulate the BNP gene. The 108-amino acid precursor peptide proBNP is cleaved into two parts:

- **BNP,** a 32-amino acid peptide that has a number of natriuretic vasodilatory effects on the heart and vascular system. It is a very active hormone that is quickly cleared by several mechanisms: through natriuretic peptide receptors, neural endopeptidase degradation in the circulation, and probably passive renal excretion. BNP has a half-life of only about 20 minutes.
- **NT-proBNP,** a 76-amino acid peptide that is believed to be biologically inert with no neural hormonal effects. It is now thought that about 20% of NT-proBNP in humans is cleared by passive renal excretion, and the rest is slowly and passively removed by other ways, such as clearance via the reticular endothelial system. It has a half-life of 1 to 2 hours.

Although both these peptides are released in response to the same signal and are secreted in a 1:1 ratio from a common precursor, the concentration of NT-proBNP can be many times higher in the same patient because of its longer half-life.

BNP and NT-proBNP have often been regarded as "ventricular markers," but this is true only in the sense that the ventricles account for most of the myocardium. The natriuretic peptides are also secreted from the atria. BNP and NT-proBNP are released from myocytes and probably to some extent directly by fibroblasts in the perimyocardial regions.

BNP is one of a large family of natriuretic peptides that have many effects on the kidneys and blood vessels. Scientists have been interested in natriuretic peptides for 25 years, but clinical trials have been performed only in the past 5 to 10 years. Nesiritide (Natrecor), a bioengineered form of BNP, is now used to treat acute decompensated CHF.

BNP assays are no substitute for a physical examination and other diagnostic tools

THREE LARGE STUDIES

Three large trials have recently examined the role of measuring BNP or NT-proBNP in evaluating patients with suspected heart failure. The studies had similar entry criteria (undifferentiated acute dyspnea, whether or not heart failure was evident). The evaluating physicians were blinded to BNP or NT-proBNP levels.

PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department)[1] measured NT-proBNP in 600 patients who presented to the emergency department with dyspnea, comparing the results with the clinical assessment of the managing physicians for identifying acute CHF. The study found that patients with acute heart failure had a median value of NT-proBNP of more than 4,000 pg/mL vs 130 pg/mL in patients without acute heart failure. Of patients who did not have acute heart failure (eg, those suffering an allergic reaction or anxiety attack), patients with a history of CHF had higher levels than patients with no history of CHF, although the levels were not nearly as high as those with acute CHF.[1]

BNP (Breathing Not Properly),[2] a multinational study, measured BNP levels in more than 1,500 patients who presented with acute dyspnea. The levels were evaluated as a tool to discriminate between patients with and without CHF, and for patients with CHF, between those with and without systolic heart failure. The findings of this study showed the value of BNP testing in circumstances of diagnostic uncertainty.

REDHOT (the Rapid Emergency Department Heart Failure Outpatient Trial)[3] evaluated BNP levels in more than 450 patients at multiple centers who presented to the emergency department with acute dyspnea. Events were counted over the following 90 days, and rates compared with initial BNP levels.

Both the PRIDE and REDHOT trials showed that more severe heart failure is associated with higher levels of natriuretic peptides, and in these trials the severity of heart failure was often underestimated.

IS IT HEART FAILURE OR COPD?

BNP assays are powerful tools, but they are not meant to be used in isolation and are no substitute for a physical examination and other diagnostic tools. The combination of clinical judgment and natriuretic peptide testing pro-

vides the optimal balance of sensitivity and specificity.

Knudsen et al[4] found that information from BNP assays is additive to chest radiography in correctly diagnosing CHF.

However, in some subgroups in REDHOT and PRIDE, the BNP or NT-proBNP assays clearly outperformed clinical acumen. The cause of dyspnea is especially difficult to discern in a patient with a history of both CHF and chronic obstructive pulmonary disease (COPD), and it is difficult to recognize the new onset of CHF in a patient with a history of COPD.[5] In the 22 patients in the PRIDE study with a history of COPD who developed new-onset CHF, not a single one was correctly diagnosed on the basis of clinical factors; however, 73% of them had an elevated NT-proBNP level. COPD and CHF are managed very differently, and missing the diagnosis can be dangerous, especially if a patient with CHF due to an arrhythmia is mistakenly treated with cardiotonic agents such as nebulizers.

OTHER SYNDROMES WITH HIGH NATRIURETIC PEPTIDE LEVELS

What does a high natriuretic peptide level reveal about a patient's underlying condition? Most obviously, the level is inversely associated with ejection fraction.[6] However, factors independent of systolic function should also be considered.

Mitral regurgitation. Troughton et al showed that despite preserved left ventricular function, patients have higher natriuretic peptide levels with more severe mitral regurgitation, even before symptoms worsen or atrial arrhythmias develop.[7]

Right heart syndromes, including cor pulmonale, pulmonary hypertension, and pulmonary thromboembolism, also have elevated natriuretic peptide levels, although the levels are not as high as with acute left heart failure.[6]

Diastolic dysfunction. Abnormal diastolic function in the absence of left ventricular systolic dysfunction can also cause high natriuretic peptide concentrations, reflecting a number of different characteristics. Levels of BNP and NT-proBNP increase with the severity of diastolic dysfunction. Levels decrease with diuresis as the patient improves from a restrictive to an impaired relaxation pattern (Alan Maisel, personal communication).

However, because patients with preserved left ventricular function tend to have lower concentrations of natriuretic peptides, even those presenting with CHF tend to have lower values than patients with impaired left ventricular systolic function.[8] Because a relatively low BNP value can occur with poor right ventricular function, it is important to integrate clinical factors with laboratory values.

BNP TESTS CAN SAVE MONEY

Considering the high cost of health care to society, it is important to use new tests in a way to both improve care and reduce costs, if possible. Hospital and nursing home costs account for an estimated $18.3 billion of the $27.9 billion that will have been spent on heart failure in 2005.[9]

At the Massachusetts General Hospital, patients with heart failure stay in the hospital an average of 7 days. Much of this time can be attributed to delayed recognition of heart failure or waiting for tests such as echocardiography to help determine the diagnosis. Routine use of BNP or NT-proBNP assays may help to more rapidly identify patients with heart failure, expedite their management, and exclude patients with a very low probability of having CHF, thereby saving money on unnecessary echocardiograms. The cost of a BNP or NT-proBNP assay depends on the measurement method used, but averages around $20.

It is difficult to recognize new-onset CHF in a patient with COPD

In a study by Mueller et al,[10] patients who presented to an emergency department with dyspnea were randomized to a diagnostic strategy using a BNP assay or to standard assessment. Patients who were managed with BNP measurement were diagnosed faster, were admitted less frequently to the hospital and the intensive care department, were discharged faster, and incurred fewer costs than the standard assessment group. The 30-day death rates were the same in the two groups.

The PRIDE study used an algorithm to guide clinical decision-making. For example, an NT-proBNP level less than 300 pg/mL ruled out CHF without further testing. The study found that conventional management

of heart failure incurred an average of $3,800 vs nearly $500 less for patients whose NT-proBNP level was routinely measured at presentation.[11] Patients who had NT-proBNP testing also had fewer major adverse events and a small but significant reduction in later mortality, which I believe is attributable to earlier diagnosis and to avoiding missing the diagnosis of CHF in some patients in the emergency department and erroneously sending them home.

BNP'S ROLE IN THE EMERGENCY DEPARTMENT

We should use natriuretic protein assays as tools and not as absolute thresholds for making decisions. Elevated levels can indicate a variety of conditions other than CHF[12]: acute coronary syndromes, preexisting structural heart disease, right ventricular strain, critical illness, or end-stage renal failure.

Acute coronary syndromes are especially important to consider. Ischemia can cause increased wall stress, probably from diastolic abnormalities.

BNP may be low in obese patients with heart failure

Sabatine et al[13] measured BNP levels before and after patients underwent exercise tolerance testing and found that BNP levels rose in proportion to the severity of myocardial ischemia.

BNP assays can help to stratify risk, eg, to determine which patients with preexisting left ventricular dysfunction are at the highest clinical risk. De Lemos et al[14] found that BNP is even better than serum troponin concentration for predicting mortality.

Jernberg et al[15] also found that in patients with acute coronary syndromes with non-ST-segment elevation, a high NT-proBNP level was a better indicator of mortality risk than troponin T. Patients with both high NT-proBNP and high troponin had an aggregate risk of death of nearly 60%.

The combination of high levels of these two markers, one indicating wall stress and the other indicating ischemia and a high likelihood of subsequent ischemic events, identifies a subgroup of patients that benefit most from urgent triage to early revascularization.

Previous structural heart damage. Some experts argue against using the BNP or NT-proBNP level as a diagnostic marker because these levels remain elevated after structural heart disease is established, but I believe this is rather a strength of these assays: BNP and NT-proBNP deviations are a signal that we should manage patients aggressively even if their underlying damage may not be otherwise apparent.

Right ventricular strain. Patients with pulmonary embolism have elevated natriuretic peptides due to right ventricular strain, and natriuretic peptide assays can be useful in determining the diagnosis.[16]

BNP and NT-proBNP can also help stratify risk and guide treatment decisions. Kucher et al[17] found that patients with high levels of natriuretic peptides are more likely to have right heart dilatation as seen by echocardiography, which is sometimes the deciding factor for whether or not to use thrombolytic therapy.

Critical illness. We hoped that BNP might serve as a marker for heart failure in critically ill patients and substitute in some circumstances for invasive Swan-Ganz catheterization procedures. However, Tung et al[18] investigated the role of BNP in evaluating shock due to different causes (eg, cardiogenic, septic, and posttraumatic) and found that a high BNP level was not related to filling pressures in many patients, but was associated with an increased risk of death. The association of severity of critical illness and high BNP levels may be due to generalized end-organ damage, including damage to the heart, during severe illness.

FALSE-NEGATIVE BNP VALUES

Fortunately, the BNP assays are very sensitive, and false-negative results are unusual. However, they do occur, making clinical judgment crucial. Situations in which BNP or NT-proBNP may be low during heart failure include:

Right heart failure. Patients with pure right heart failure often have much lower values for BNP than patients with left heart failure.

Mild CHF. Tang et al[19] found that 21% of patients with mild heart failure (New York Heart Association class 2) have plasma BNP

levels in the normal diagnostic range (< 100 pg/mL).

Diastolic heart failure. Up to 10% of the time with NT-proBNP, and up to 20% of the time with BNP, we may observe false-negative values in the presence of heart failure with preserved left ventricular function.[8]

Obesity. For unknown reasons, BNP values decrease with increasing body mass index, even in patients with heart failure.[20] For people with a body mass index of 35, the risk of a false-negative BNP value is about 20%, and the risk of a false-negative NT-proBNP is about 15%.

The association of low BNP values and obesity was once thought to be due to natriuretic peptide receptors on adipose tissue or because adipose cells secrete neural endopeptidases, increasing BNP clearance. One would then expect NT-proBNP levels to not be affected; however, both BNP and NT-proBNP fall in parallel with increasing body mass index.

USING A DECISION ALGORITHM

At Massachusetts General Hospital we use a flow diagram to guide our usage of natriuretic peptide assays in evaluating patients who present with dyspnea (**FIGURE 1**). Although the diagram has many decision points, it incorporates the reality of different clinical situations, and its use strengthens the positive predictive value of the assays.

THE NATRIURETIC PEPTIDE ASSAY AS A PROGNOSTIC TOOL

BNP and NT-proBNP assays are useful not only for the evaluation of the acute patient, but also for assessing prognosis. For patients with heart failure, ejection fraction and the New York Heart Association classification are not always sufficient.

The International Collaborative of NT-proBNP (ICON) study is a multinational study of nearly 1,300 patients that found that NT-proBNP was the strongest predictor of death within 60 days of developing acute CHF.[21]

Logeart et al[22] found that the predischarge BNP level is a strong, independent marker of death or re-admission 6 months following decompensated CHF and is more relevant than common clinical and echocardiographic parameters.

The PRIDE study found similar results at 1-year follow-up and that NT-proBNP measurements were even more predictive of death in patients presenting with dyspnea who did not have acute CHF. These results highlight that natriuretic peptides are not just a marker of CHF, but also can be regarded as a final common pathway for myocardial wall stress.[23]

MONITORING AND GUIDING THERAPY

Therapies that reduce BNP and NT-proBNP levels include diuresis, exercise, biventricular pacing, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and spironolactone. Beta-blockers may either reduce or increase BNP and NT-proBNP levels, and treatment with the therapeutic form of BNP (nesiritide) increases BNP levels but decreases NT-proBNP.

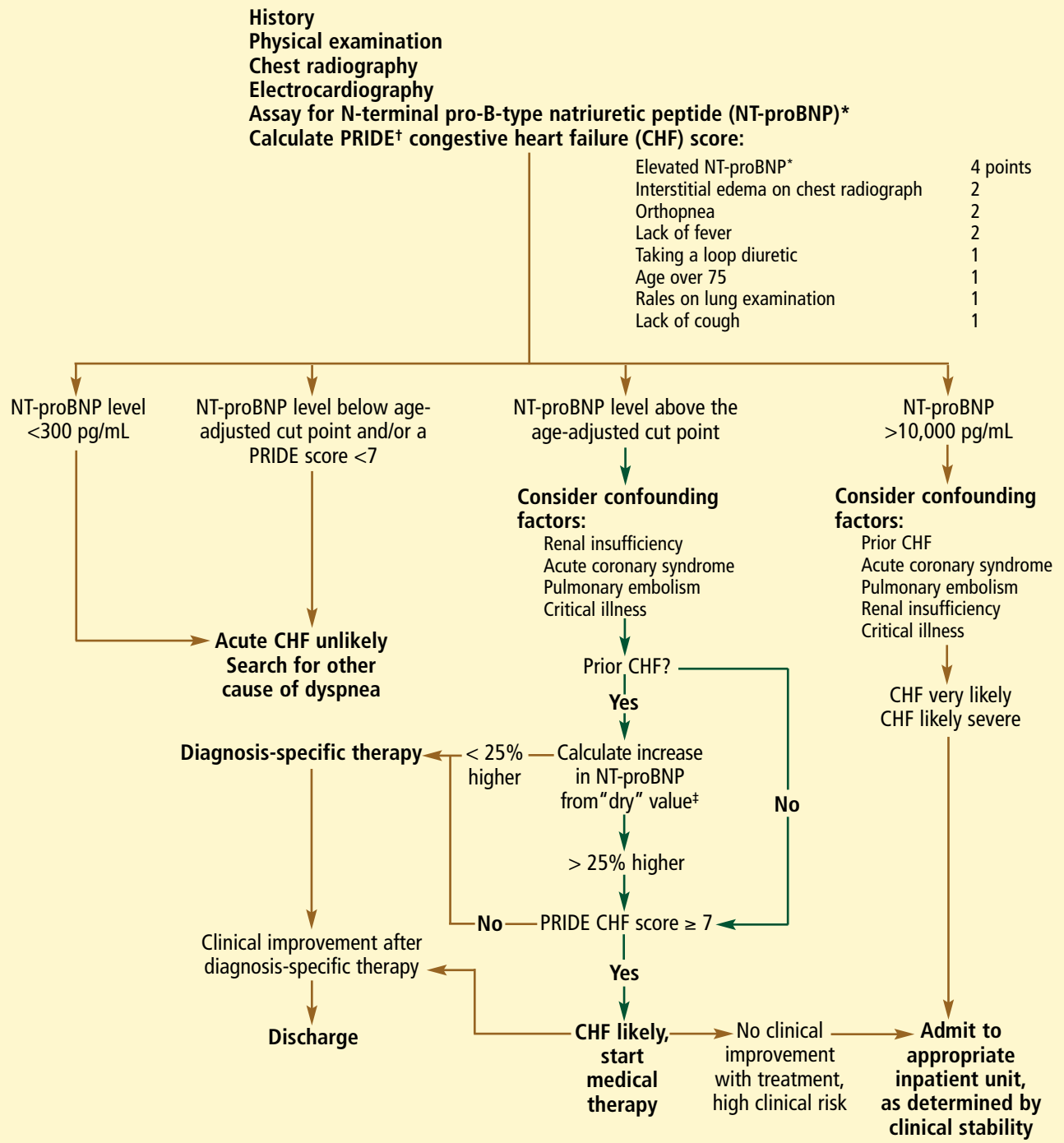
B-type natriuretic peptides correlate to some extent with high filling pressures, and successful heart failure therapy tends to lower BNP and NT-proBNP levels.

BNP may be lower in diastolic than in systolic heart failure

Bettencourt et al[24] found that patients whose NT-proBNP levels fell at least 30% between admission for CHF and discharge had higher rates of hospitalization-free survival compared with patients whose NT-proBNP levels decreased less or increased, which raises the question of whether we should be aiming for lower absolute values of BNP or NT-proBNP as a target for therapeutic intervention for our patients.

Based on evidence of the association of prognosis with both absolute BNP or NT-proBNP levels and the change in BNP or NT-proBNP levels during hospitalization, it is possible that aggressive treatment aimed at lowering levels of these markers would lead to more favorable outcomes. Troughton et al[25] randomized 80 patients with mild to severe CHF to have their therapy managed based on either NT-proBNP levels or standard clinical assessment. Patients whose treatment was based on NT-proBNP levels had fewer cardiovascular events, heart failure, and deaths over

Use of natriuretic peptide testing in the evaluation of a patient with dyspnea



*The cut points for NT-proBNP elevation are: >450 pg/mL under age 50; >900 pg/mL ages 50-75; >1,800 pg/mL over age 75
†PRIDE = ProBNP Invesigation of Dyspnea in the Emergency Department
‡Dry value = a prior baseline NT-proBNP level when the patient was euvolemic and hemodynamically stable, if available

FIGURE 1

the 6 months of the study. Several clinical trials are under way to evaluate whether therapeutically reducing levels of these markers is helpful to patients with CHF.

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