EDUCATIONAL COMMENTARY – BNP AND NT-proBNP UPDATE

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LEARNING OBJECTIVES

On completion of this exercise, the participant should be able to
• discuss the use of testing levels of the B-type natriuretic peptides, B-type natriuretic peptide (BNP) and amino terminal pro B-type natriuretic peptide (NT-proBNP), in patients with heart failure.
• interpret BNP and NT-proBNP levels in patients with heart failure.
• list conditions/diseases in which BNP and NT-proBNP levels are increased.
• discuss factors that affect the interpretation of BNP and NT-proBNP results.

Introduction

Heart failure (HF), also called congestive heart failure (CHF), affects approximately 5.7 million people in the United States, with 550,000 new cases diagnosed each year. Assays for B-type natriuretic peptide (BNP) and amino terminal pro B-type natriuretic peptide (NT-proBNP) were introduced in the United States in 2000; since then, these assays have been used to diagnose and monitor HF. They are also now increasingly used for other purposes.

B-type natriuretic peptide, a neurohormone, is synthesized as a prohormone in the heart and is released from ventricular myocytes in response to increased myocardial wall stress from volume or pressure loading and other factors. The peptide proBNP is cleaved into BNP and the biologically inactive fragment NT-proBNP. BNP helps decrease blood pressure and is an antagonist to the rennin-angiotensin-aldosterone system. With a half-life of approximately 20 minutes, BNP is cleared from plasma faster than NT-proBNP, which has a half-life of approximately 70 to 120 minutes.

Heart Failure Diagnosis

Numerous clinical trials worldwide have confirmed the primary use of BNP or NT-proBNP levels in the initial diagnosis, staging of severity, and subsequent assessment of the prognosis of patients with HF. Clinical studies have demonstrated that assaying either BNP or NT-proBNP gives equivalent results, and either can be used, as long as the values and cut points are not used interchangeably.1 A BNP level below the rule-out value of 100 pg/mL indicates that HF is highly unlikely. Conversely, a level greater than the rule-in value of 500 pg/mL indicates that HF is highly likely in patients without renal failure. For NT-proBNP, an age-independent rule-out value of less than 300 pg/mL had a negative predictive value of
EDUCATIONAL COMMENTARY – BNP AND NT-proBNP UPDATE (cont.)

98% for ruling out HF. Age-specific cutoffs of greater than 450, 900, and 1800 pg/mL for patients younger than 50, 50 to 75, and older than 75 years may be used to rule in HF. In general, levels are decreased in obese patients and increased in patients with renal impairment.

In patients with compromised renal function, different cutoffs are recommended. For patients with a glomerular filtration rate (GFR) less than 60 mL/min/1.73m³, the recommended cutoffs for rule-out are 200 to 225 pg/mL for BNP and 1200 pg/mL for NT-proBNP. Even with these adjustments, detection and/or exclusion of HF in patients with GFR less than 30 mL/min/1.73m³ is less accurate. Obese patients with HF have lower values, although the effect occurs more often with BNP than NT-proBNP. A BNP cutoff of 55 pg/mL is recommended to rule out HF in patients with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 35. Values between the rule-in and rule-out cutoff points are considered to be in a grey zone; it is recommended that echocardiography be used to help determine a diagnosis.

In addition to renal function and obesity, other biological factors that affect BNP and NT-proBNP results include age, sex, and specific conditions/diseases. Concentrations generally increase with age and are consistently higher in women than men. Elevated levels of BNP or NT-proBNP are not necessarily diagnostic for HF. Non-HF cardiac conditions in which these B-type natriuretic peptides are elevated include valvular heart disease, atrial fibrillation, left ventricular hypertrophy, ischemia, and tachyarrhythmias. Noncardiac conditions in which these B-type natriuretic peptides are elevated include diabetes mellitus, renal impairment, cirrhosis, chronic obstructive pulmonary disease, sepsis, pulmonary embolism, anemia, endocrine disorders, and some severe neurological diseases. Conversely, cardioactive drugs including diuretics, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and spironolactone can cause decreased natriuretic peptide concentrations.

In spite of the limitations mentioned, BNP and NT-proBNP have been shown to be extremely efficient and effective markers in the emergency setting to help rule out HF in patients with shortness of breath.

Heart Failure Prognosis, Risk Stratification, and Treatment Guidance

Measurement of BNPs has been shown useful for establishing prognosis or disease severity in chronic and acute HF. In general, there is a direct correlation between increased levels and increased risk, with levels of BNP above 125 pg/mL and NT-proBNP above 1000 pg/mL associated with increased risk in patients with chronic HF. In patients with acute HF, natriuretic peptide levels help determine the severity and predict long- and short-term mortality. In other studies, an NT-proBNP cutoff of 986 pg/mL for 1-year
EDUCATIONAL COMMENTARY – BNP AND NT-proBNP UPDATE (cont.)

mortality demonstrated the best sensitivity and specificity, and admission concentrations greater than 5180 pg/mL were strongly predictive of death within 76 days.2

Levels can be used for risk assessment, with recommendations that at a minimum an admission baseline level and a second discharge level be measured. Patients with discharge BNP levels less than 400 pg/mL have a better prognosis than those with higher levels.5 Reductions of BNP levels by 30% have been associated with improved survival. A discharge level can also be used for comparison if a patient returns with symptoms of possible decompensation. Follow-up testing can be helpful in identifying the potential for readmission. Discharged patients with 30-day BNP levels greater than levels at discharge have a higher risk for decompensation.

The use of natriuretic peptide levels to guide therapy has been studied extensively, and results of several studies are inconclusive. Recent meta-analyses of trials concluded that BNP-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care, especially in patients younger than 75 years.1 In another study, a 50% drop in natriuretic peptide levels was associated with an approximately 50% drop in adverse events.5

Other Uses of B-type Natriuretic Peptide Levels

Although the primary use of BNP and NT-proBNP levels is in the diagnosis, stratification and prognosis, and possible treatment guidance of heart failure, use of these peptides for other purposes continues to increase. Natriuretic peptide levels, either alone or in combination with troponin levels, have demonstrated value for risk stratification of patients with acute coronary syndrome. High-risk patients have been identified by admission values of BNP greater than 80 pg/mL for men and women and NT-proBNP greater than 1170 pg/mL for men and greater than 2150 pg/mL for women.2 Natriuretic peptide levels in conjunction with other biomarkers are potentially useful for diagnosis, risk assessment, and therapy guidance in many disease processes. Maisel and Daniels predict that in the next 5 years, in addition to continued use for diagnosis of HF, the natriuretic peptides will be used increasingly for the following purposes: monitoring of hospitalized and discharged patients with HF, guiding outpatient treatment, outpatient risk profiling, diagnosing for HF with preserved ejection fraction, screening for left ventricular dysfunction, and following up patients with valvular heart disease.5 In the future, it is possible that there will be multiple uses of BNP and NT-proBNP levels, with corresponding method-dependent threshold values for each use.

Laboratory Considerations

Laboratory professionals performing assays for BNP and NT-proBNP must be cognizant of many factors when validating these assays for their institution, establishing reference and cutoff levels, interpreting test
EDUCATIONAL COMMENTARY – BNP AND NT-proBNP UPDATE (cont.)

results, and, particularly, when making comparisons with results of published clinical trials. As previously mentioned, BNP and NT-proBNP assays have been shown to give equivalent results, although they measure molecules with different biological functions and properties. There is no consensus indicating a clear advantage of measuring one or the other, but there is general agreement that it is not necessary to measure both. There is no conversion factor to allow direct comparison of BNP and NT-proBNP values.

Intraindividual biological variation in both BNP and NT-proBNP levels is greater than analytic imprecision, and this must be considered when interpreting serial measurements. Therefore, it has been suggested that changes should be at least 30% or greater to be considered clinically relevant.\(^2\)

Another consideration for laboratorians is that no two assays for BNP or NT-proBNP give identical results, even when considering assays from different manufacturers using the same antibodies and calibration materials. Assays are not standardized or harmonized. Although there are some generally accepted reference ranges and cutoff values for both analytes, several studies demonstrate that these values are method dependent. However, BNP and NT-proBNP assays generally show concordance at concentrations of 100 ng/L and 125 ng/mL, respectively.\(^2\) Sample stability also appears to be method dependent but, in general, NT-proBNP is more stable than BNP. EDTA plasma is the proper specimen for BNP to maintain stability for at least 4 hours at room temperature. Serum and heparin plasma are the preferred specimens for NT-proBNP, which is stable for at least 2 days at room temperature.\(^2\) Finally, each laboratory should establish reference ranges and cutoff values for its patient population when validating a BNP or NT-pro-BNP assay. Recommended characteristics of the reference population study include selection of persons who are symptom free and have normal heart function assessed by imaging, normal renal function, normal hemoglobin, and a normal BMI.\(^2\)

Summary

The primary clinical uses of measurement of the B-type natriuretic peptides BNP and NT-proBNP are diagnosis and prognosis/risk assessment of patients with HF. Other uses of natriuretic peptide levels that have shown clinical utility include guidance and monitoring of therapy for patients with HF and risk stratification of patients with acute coronary syndrome. In the future, other applications of BNP and NT-proBNP levels may become components of routine practice.
EDUCATIONAL COMMENTARY – BNP AND NT-proBNP UPDATE (cont.)

References


5. Maisel AS, Daniels LB. Breathing not properly 10 years later: what we have learned and what we still need to learn. J Am Coll Cardiol. 2012;60(4):277-282. doi: http://dx.doi.org/10.1016/j.jacc.2012.03.057

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