EDUCATIONAL COMMENTARY – UPDATE ON BNP AND NT-proBNP

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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- Discuss factors that affect the interpretation of B-type natriuretic peptide (BNP) and N terminal (NT)-proBNP results.
- List conditions/diseases in which BNP and NT-proBNP levels are increased.
- Interpret BNP and NT-proBNP levels for patients with congestive heart failure.

B-type natriuretic peptide (BNP), 1 of 4 natriuretic hormones, is synthesized as a prohormone in ventricular myocytes. Myocardial ventricular wall stress stimulates release and cleavage of proBNP into BNP and the biologically inactive fragment NT-proBNP. BNP helps to decrease blood pressure and is an antagonist to the renin-angiotensin-aldosterone system. BNP, with a half-life of approximately 20 minutes, is cleared from plasma by receptor binding and proteolysis. NT-proBNP, with a half-life of approximately 70 to 120 minutes, is cleared by renal excretion.

Testing

In November 2000 the first assay for BNP in blood was introduced in the United States, and since then several automated and point-of-care assays for BNP and NT-proBNP have become available. Numerous clinical trials worldwide have confirmed the value of BNP or NT-proBNP measurements for the initial diagnosis of congestive heart failure (see “B-type Natriuretic Peptide (BNP)”, API Chemistry Educational Commentary, 2002 3rd Test Event, for a detailed discussion), staging of severity, and subsequent assessment of the prognosis of patients with this condition. Although reference ranges are method-dependent and it is recommended that method-dependent cutoff values be established, some general cutoff values have been utilized for interpretative purposes. Using a value of <100 pg/mL for BNP level, heart failure is highly unlikely. When values >500 pg/mL occur, heart failure is highly likely. For NT-proBNP, age-specific cutoffs of >450 pg/mL for patients under 50 years and >900 pg/mL for patients 50 years and older are sensitive and specific for heart failure, whereas heart failure is highly unlikely when NT-proBNP values are <300 pg/mL.

Use of these cutoffs, in conjunction with other clinical information, has resulted in decreased unnecessary hospitalization and improved treatment time, and hence decreased healthcare costs. BNP and NT-proBNP are extremely efficient and effective in the emergency department to help rule out heart failure in patients presenting with shortness of breath. Concerning their use as prognostic indicators, studies have shown that patients with higher values of BNP or NT-proBNP on admission and/or discharge...
generally do worse. Investigators who performed a systematic review of the literature concluded that for patients with heart failure the relative risk of death increases by about 35% for each 100-pg/mL increase in BNP. The potential use of these biomarkers for several other purposes has been investigated and will be discussed later.

Factors Affecting Results
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 results, and particularly when making comparisons with results of published clinical trials. For the most part, BNP and NT-proBNP have been shown to give equivalent results even though they are molecules with different biological functions and properties. A clear advantage to measuring one rather than the other has not been established. There is general agreement, however, that measuring both is unnecessary. There is no conversion factor to allow direct comparison of BNP and NT-proBNP values. Intraindividual biological variation for both BNP and NT-proBNP can be up to 100%, suggesting that in order for successive values in a patient to be clinically meaningful, the values have to either double or half.

Biological factors affecting BNP and NT-proBNP results include age, gender, renal function, and specific conditions/diseases. Concentrations generally increase with age and are consistently higher in women than men. Levels are elevated in newborns for the first few days of life and decrease in the following days to stabilize at adult values. Infants with diabetic mothers have higher cord blood levels of the peptides, and evidence suggests that the levels are even higher when the mother’s glucose control is suboptimal. Impaired renal function causes increased levels of both analytes, although this increase is more accentuated for NT-proBNP. Other conditions in which increased levels of the peptides occur include pulmonary disease, systemic hypertension, hyperthyroidism, Cushing syndrome, Conn syndrome, hepatic cirrhosis with ascites, paraneoplastic syndrome, subarachnoid hemorrhage, glucocorticoid use, Duchenne muscular dystrophy, Chagas disease, Kawasaki disease, conditions such as infections and inflammation causing myocardial damage, and procedures resulting in myocardial cytotoxicity such as chemotherapy. Cardioactive drugs including diuretics, vasodilators, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and spironolactone lead to decreased BNP concentrations.

Validation Issues
Another consideration for laboratorians is that no two assays for either BNP or NT-proBNP give exactly the same results, even assays from different manufacturers using the same antibodies and calibration materials. Both analytes have some generally accepted reference ranges and cutoff values; however, several studies demonstrate that these are method dependent. Sample stability also appears to be
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method dependent, probably due to the different stabilities of the immunoreactive forms of the peptides present in blood. EDTA plasma is the proper specimen for BNP in order to maintain stability for at least 24 hours, whereas NT-proBNP is stable for at least 72 hours at room temperature in serum. Both BNP and NT-proBNP seem to be stable during freeze-and-thaw cycles, although at least one study demonstrated an approximate 10% decrease following one freeze-and-thaw cycle. Specimen stability including the effect of time and temperature, and the influence of different anticoagulants and gel separator tubes should be verified by each laboratory for the assay it uses. Each laboratory should also establish reference ranges and cutoff values for its patient population when validating a BNP or NT-proBNP assay.

Other Uses
The primary use of BNP and NT-proBNP is in the diagnosis, stratification, and prognosis of heart failure. Several other uses of these peptides have been and are continuing to be investigated. BNP and NT-proBNP measurements may be clinically useful for determining optimal treatment for patients with heart failure and for monitoring treatment. The inclusion of BNP and NT-proBNP with other cardiac biomarkers for risk stratification of patients with acute coronary syndrome is another promising potential future use. Any condition involving myocardial stress is a potential candidate for use of BNP and NT-proBNP for diagnostic, stratification, or prognostic purposes. Multiple uses of BNP and NT-proBNP levels with corresponding method-dependent threshold values determined for each use is a future possibility.

Suggested Reading


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