

Laboratories to evaluate amino terminal-proBNP (NT-proBNP), an automated test for diagnosing heart failure

To improve service and lower the cost of laboratory testing in the diagnosis of heart failure versus pulmonary disease, Fairview Laboratories plan to evaluate a new diagnostic method that would allow us to transition from a manual BNP assay to an automated NT-proBNP assay.

The FDA has approved both BNP and NT-proBNP assays as aids in the diagnosis and assessment of heart failure and for risk-stratification of patients with acute coronary syndrome. Fairview Laboratories currently offer BNP assay and plan to switch to an automated NT-proBNP assay this summer.

While both BNP and NT-proBNP will rise with left ventricle dysfunction and both can be measured, they are not interchangeable and the results cannot be directly compared. The FDA-cleared cutoff for ruling out congestive heart failure heart is 100 pg/mL for BNP. For NT-proBNP, there exists a dual, age-related cutoff of 125 pg/mL for patients younger than 75 years old, and 450 pg/mL for patients 75 years and older.

B-Type Natriuretic Peptide (BNP) protein is classed as a cardiac neurohormone and originates from myocytes of the atrium and

ventricles of the heart. It is secreted under conditions of myocardial stretching, volume overload, and increased ventricular filling pressures. ProBNP, the immediate molecular precursor of BNP, is cleaved into BNP and the amino-terminal proBNP (NT-proBNP). Although these peptides are released from the heart simultaneously in a 1:1 ratio, blood concentrations of NT-proBNP are higher because the half-life is one to two hours, compared to 22 minutes for BNP. The diagnostic utility of both BNP and NT-proBNP has been well established in differentiating heart failure from pulmonary disease in patients presenting with symptoms of dyspnea and shortness of breath. Plasma concentrations of BNP and NT-proBNP are increased significantly in heart failure and are normal or increased slightly in patients with pulmonary disease.

*Daniel G. Berntson, M.D.
Michael W. Steffes, M.D., Ph.D.*

References:

1. Wu, A. Heart Failure Diagnosis. *Advance*. 2006;15:34-38.
2. Apple, F. B-Type Natriuretic Peptides. *Clinical Laboratory News*. 2005;12-14.
3. Gantzer, M. Understanding the Natriuretic Peptides. *MLO*. 2005;24-27.

Summary	BNP	NT-proBNP
Description	32-amino acid biologically active hormone cleaved from proBNP	76-amino acid biologically inactive peptide cleaved from proBNP
Testing availability	Manual Triage test currently is performed at all Fairview hospitals	Automated method to be evaluated for possible Summer 2006 implementation at all Fairview hospitals
Half life	20 minutes	1-2 hours
Clearance	By tissue receptors	Unknown; may involve a combination of renal clearance and metabolism by the reticuloendothelial system
FDA Cutoff for Ruling Out Congestive Heart Failure	100 pg/mL	125 pg/mL for less than 75 years 450 pg/mL for 75 years and older
In vitro stability	24 hours	48 hours
Harmonization	Presume all manufacturers will harmonize around the FDA cutoff	A single source of antibodies and calibrators for NT-proBNP (Roche), ensures harmonization of assays
Limitations	Does not allow differentiation of elevated levels due to ventricular dysfunction vs. treatment with synthetic BNP (marketed as Natrecor [®] nesiritide) Biological variability for both BNP and NT-proBNP has been defined as being approximately 100%. In addition, numerous clinical factors, such as renal function, obesity and thyroid function, are known to affect both BNP and NT-proBNP concentrations; therefore, appropriate reference intervals in these populations, without known heart failure, should be established.	Patients with renal impairment may show false elevation

Continued on back

*Automated test evaluation from front***Conditions associated with increased BNP or NT-proBNP:**

- Heart failure
- Left ventricular hypertrophy
- Cardiac inflammation, e.g., myocarditis, cardiac allograft rejection
- Arrhythmogenic right ventricle with decreased ejection fraction
- Kawasaki disease
- Primary pulmonary hypertension
- Renal failure
- Ascitic cirrhosis
- Endocrine disease (primary hyperaldosteronism, Cushing syndrome)
- Geriatric age
- Gender (women have slightly higher levels)

Guidelines for use of BNP or NT-proBNP:

- Exclude the diagnosis of heart failure in cases in which the symptoms would otherwise suggest it.
- Use as a screening tool before echocardiography in patients with suspected left ventricular dysfunction.
- A diagnosis of heart failure should be confirmed with electrocardiography, chest radiography or echocardiography.
- Following an exacerbation of heart failure, a declining BNP portends a favorable outcome.
- An elevated level 48 hours after myocardial infarction strongly predicts heart failure or adverse outcome within the next year.

Collect type and cross samples at least one day prior to elective surgery to avoid delays in blood availability

At University of Minnesota Medical Center, Fairview, we have seen several cases in which blood for type and cross arrived in the blood bank on the same day as the patient's surgery. In some cases, the blood bank sample arrived after surgery had already started. An audit of 100 cases in November 2005 found nine percent of patients had unexpected red cell antibodies, making it difficult to find crossmatch compatible blood.

Of 57 surgical cases at the medical center over a few days in mid-January 2006, blood bank samples for 56 percent of patients were collected on the same day as surgery. In four cases, samples were not available until after surgery had started. In one recent case, a patient developed bleeding and anemia, forcing physicians to stop surgery temporarily until blood became available.

Audits at Fairview Southdale Hospital revealed that type and screen testing is performed the same day on more than 80 percent of elective surgery patients, generally within a few hours before surgery. Procedures for 4 percent to 14 percent of elective surgery patients at Fairview Southdale began before the type and screen tests were completed. Audits revealed that blood bank turn-around was at maximum efficiency, with all tests treated as STAT and completed within 60 minutes.

A problem arises with patients, often previously pregnant or transfused, who have unexpected red cell antibodies with positive tests identified on the day of surgery. Once a patient receives a positive screening test for a red cell alloantibody, testing can take several hours to identify the specific antibody or antibodies, identify crossmatch compatible units and verify that these units lack the corresponding red cell antigens to which the patient has developed antibodies.

No patient should undergo an elective surgical procedure prior to completion of type and screen or type and crossmatch testing. Health care providers should place type and cross orders at least one day prior to surgery. The blood banks can perform blood typing and compatibility testing on a blood sample obtained up to 14 days prior to surgery, provided the patient is not pregnant or transfused within the last three months.

*Ted Eastlund, M.D.
Kathrine Frey, M.D.*

Update

Due to changes in instrumentation and reagents, the following tests have new reference ranges as of April 2006:

Protein S Free Antigen:

Males: 70% – 135% Females: 55% – 125%

Activated Protein C Resistance:

APC Ratio: 2.00 – 3.00

APC Normalized Ratio: 0.83 – 1.12