

Message from the Medical Editor

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For this second edition of the *Laboratory Report* quarterly newsletter, we want to focus on the provincial-wide rollout of assays for the natriuretic peptide (NP) hormones, the brain or B-type (BNP) and the amino-terminal fragment of the prohormone (NT-proBNP). Although the biochemistry of BNP and NT-proBNP and their use in distinguishing between cardiac and pulmonary causes of dyspnea have been well documented for over a decade, the availability of these assays has been and will continue to be limited in Alberta.¹ Some areas have had access to these relatively expensive analyses for several years but now all hospitals and cardiac clinics will have access to them as well.

With these thoughts in mind, specific recommendations for their use were developed by the AHS Chemistry Laboratory Integration Network in conjunction with a group of cardiologists, internists and emergency physicians. We have included administrative information on current acceptable indications in Alberta as well as a flow diagram adapted from a recent presentation by Dr. Debra Isaac in Calgary.² Because of the wide variety in practice conditions in Alberta, it is likely that not all situations have been addressed, so it may be necessary to contact the pathologist or clinical chemist at your local laboratory for more information.

Again, if you have comments on this issue or ideas for future articles, please contact us.

References

1. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert LA et al. Utility of B-natriuretic peptide (BNP) in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;37:379-85.
2. Isaac D. "Biomarkers for diagnosis and management of Heart Failure." University of Calgary. Calgary, AB. Jan 24, 2012.

Biomarkers for Heart Failure, BNP and NT-proBNP, Coming to Town

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Key Points

1. BNP and NT-proBNP can be measured to help confirm or rule out a diagnosis of heart failure (HF) in acute care settings in patients for whom the clinical diagnosis is in doubt.¹
2. Assays for both BNP and NT-proBNP are Health Canada approved and are equally acceptable tests for determining the likelihood of HF as the cause of a patient's dyspnea.
3. Measurement of BNP and NT-proBNP levels may be considered in patients with an established diagnosis of HF for prognostic stratification.¹
4. In screening for HF, BNP and NT-proBNP levels are neither consistently sensitive nor specific when used in isolation. The test is most useful when used in conjunction with history, physical exam and chest x-ray in patients in whom HF is expected.²

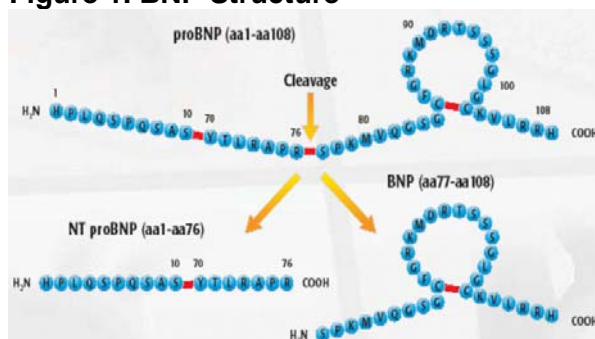
Introduction

Over the next few months, B-Type Natriuretic Peptide (BNP) or Amino-terminal proBNP (NT-proBNP) analysis will be made available throughout Alberta. The purpose of this article is to present an overview of these molecules with information on the interpretation and utility of their measurement.

Biochemistry and Physiology of BNP

BNP is a cardiac neurohormone that helps regulate vasodilation, natriuresis, diuresis and fibrosis. When the cardiac ventricles 'sense' volume or pressure overload, ventricular myocytes synthesize a 134 amino acid (AA), pre-proBNP. A 26 AA "signal peptide" is cleaved intracellularly to yield the 108 AA proBNP. After release from the myocyte, proBNP is cleaved intravascularly to the 32 AA biologically active BNP and the 76 AA inactive NT-proBNP. (see Figure 1.) Binding to specific receptors, BNP increases sodium and water excretion by increasing glomerular filtration rate and decreasing sodium reabsorption and renin and aldosterone secretion.^{3,4}

Figure 1. BNP Structure



NT-proBNP has a longer biological half-life ($t_{1/2}$) (1-2 hrs) than BNP (15 minutes) and therefore the levels fluctuate less but change more dramatically with age. BNP levels may change less with age and non-cardiac conditions.³ NT-proBNP in serum and plasma has a longer *in vitro* $t_{1/2}$ and is stable longer than BNP (~72 hours vs 24 hours) making it the preferred molecule to measure when delays in analysis are necessary.

In general the blood levels of BNP and NT-proBNP, hereafter designated collectively as NP, correlate with both the severity of the symptoms (higher with worsening New York Heart Association (NYHA) class) and patient prognosis (higher with worse prognosis). NP levels are also sensitive to other biological factors such as age, gender, renal function and diastolic dysfunction.

Utility of NP Measurement

BNP and NT-proBNP have proven to be useful in a variety of clinical situations. These are outlined in this and other educational materials and references previously provided by AHS Laboratory Services. Given the finite supply of financial resources available, it is not possible to sanction utilization for all such clinical situations by all physicians. Nevertheless, utilization being introduced at this time represents a significant step forward in comparison to current availability and indications for testing.

Measurement of NP in emergency situations supports the evaluation and treatment of patients with acute dyspnea, reducing time of treatment and discharge and with intelligent utilization, potentially reducing the overall cost of treatment. A randomized controlled trial done in Canada supports the utility of NP measurement to improve the accuracy of diagnosis, reduce the length of stay in the emergency department and reduce overall healthcare costs.⁵ In patients with HF, NP levels provide prognostic information as well and almost certainly will find other uses in the future.^{3,4,6}

Small elevations in NP levels can be non-diagnostic in patients with previous heart failure, chronic left ventricular dysfunction, patients of advanced age with impaired renal function, acute coronary syndrome, pulmonary embolism and high cardiac output states such as sepsis, cirrhosis and hyperthyroidism. NP levels may also appear at lower than expected values in the markedly obese patient and in flash pulmonary edema.³

Current Indications for NP Measurement^{4,7-9}:

- In conjunction with clinical signs and symptoms suspicious for HF to confirm or rule out the diagnosis.
- To determine if current symptoms are primarily due to HF or respiratory disorders, even in the presence of left ventricular dysfunction.
- If there is an intermediate probability (between 20% and 80% likelihood) of HF (**current best use**).

Measurement is not indicated for:

- Low (<20% likelihood) or high suspicion (>80% likelihood) of HF as the cause for symptoms.
- Screening of asymptomatic patients.
- History of HF with other non-cardiac diagnosis and no HF signs or symptoms, e.g. acute appendicitis, hip fracture.
- Other cardiac diagnosis where NP level will not add to clinical management, e.g. cardiogenic shock, peri-operative bypass surgery, acute myocardial infarction.

Current Ordering Guidelines in Alberta

A level at admission and/or discharge is considered to be clinically appropriate. A single pre-discharge NP level can be indicative of future outcomes regardless of initial NP level.³ For these reasons, patients should not normally have more than 2 tests in any 21 day period. Rare exceptions to this can be made upon approval by the pathologist or biochemist on call. A summary of the current availability of NP assays is provided in Table 1.

Table 1. Availability of NP Assays in Alberta

| Ordering Location | Physician Type | Reason |
|-----------------------------------|---|---|
| Community (Heart function clinic) | Cardiologist or internist | a. Known HF patient assessment and management - following / assessing efficacy of therapy. b. Otherwise not available since NP is not an effective screening test in non-acute settings. |
| Emergency Department | ED physician - includes specialists and family physicians | Differential diagnosis of HF from other causes of dyspnea only when the diagnosis is uncertain, i.e., an intermediate pre-test probability. |
| Inpatients | Attending physician, consulting cardiologist or internist | a. Differential diagnosis of HF from other causes of dyspnea only when the diagnosis is uncertain in patients previously admitted for some other reason. b. Differentiate worsening HF from other causes of SOB in a patient with known cardiac dysfunction and other co-morbidities. c. Pre-discharge testing for risk stratification to determine adequacy of therapy prior to discharge and to determine a management plan post-discharge. |

Interpretation of Results

Although there are certain differences between the two biomarkers, both deliver valuable clinical and economic benefits in the diagnosis and management of patients with HF. (See Table 2.) However, the results obtained from the respective markers cannot be compared or interchanged.¹

Table 2. Interpretation of BNP and NT-proBNP

| | Patient Age | Acute HF Unlikely | Acute HF Less Likely | Acute HF Likely |
|------------------|---------------|-------------------|----------------------|-----------------|
| BNP | All ages | <100 ng/L | 100 – 500 ng/L | > 500 ng/L |
| NT-proBNP | <50 years | < 300 ng/L | 300 – 450 ng/L | > 450 ng/L |
| | 50 – 75 years | < 300 ng/L | 300 – 900 ng/L | > 900 ng/L |
| | >75 years | < 300 ng/L | 300 – 1800 ng/L | > 1800 ng/L |

Cost

The overall cost to report a BNP or NT-proBNP is estimated to be \$40 to \$50 per reportable result but will be strongly influenced at each site by method chosen and total volume at that site. Utilization will be monitored against the projected utilization and finite financial resources.

Conclusion

The natriuretic peptides, BNP and NT-proBNP, serve as diagnostic and prognostic tools to enable the physician to significantly improve the treatment of heart failure. Like other tools, these should be used carefully because the proper use and setting will determine their utility. They will be available throughout Alberta in the very near future. The specific assay information may be obtained from the clinical chemist or pathologist at your local laboratory.

References

1. Arnold JMO, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation and use of biomarkers. *Can J Cardiol.* 2007; 23(1); 21-45. Link to online article: http://www.ccs.ca/download/consensus_conference/consensus_conference_archives/2007_HFCC_update.pdf
2. Wang TJ, Levy D, Benjamin EJ, Vasani RS. The epidemiology of "asymptomatic" left ventricular systolic dysfunction: Implications for screening. *Ann Intern Med* 2003; 138; 907-16.
3. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol.* 2007; 50(25); 2357-68.
4. Thygesen K, Mair J, Mueller C, Huber K, Weber M. Recommendations for the use of natriuretic peptides in acute cardiac care. *Eur Heart J* published online Feb 2, 2011. doi:10.1093/eurheartj/ehq509.
5. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type Natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation* 2007; 115; 3103-10.
6. Richards AM, Troughton RW. Use of Natriuretic Peptides to Guide and Monitor Heart Failure Therapy. *Clin Chem* 2012;58:63-71.
7. Maisel A, Hollander JE, Guss D, McCullough P, Novak R, Green G, Saltzberg M, Ellison SR, Bhalla MA, Bhalla V, Clopton P, Jesse R. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type Natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol.* 2004; 44; 1328-33.
8. Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, Nagueh SF. Incremental predictive power of B-type Natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol.* 2005; 19; 1223-6.
9. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type Natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002; 347; 161-7.
10. Isaac D. "Biomarkers for diagnosis and management of Heart Failure." University of Calgary, AB. Jan 24, 2012.

Appendix A. Flow Diagram for use of NP (BNP/NT-proBNP) as adjunct to Clinical Assessment for Diagnosis of Heart Failure¹⁰

