B-type Natriuretic Peptide (BNP) Assay

Background

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from membrane granules in the cardiac ventricles as a response to ventricular volume expansion and pressure overload.[1] The natriuretic peptide system allows the heart to participate in the regulation of vascular tone and extracellular volume status. The natriuretic peptide system and the renin angiotensin system counteract each other in arterial pressure regulation. Levels of atrial natiuretic peptide (ANP) and BNP are elevated in cardiac disease states associated with increased ventricular stretch.

The main circulating and storage form of BNP is 32 amino acid peptide with a ring structure. Physiological actions of BNP are mediated through a guanylate cyclase-linked receptor, natriuretic peptide receptor A (NPR-A). BNP produces arterial and venous vasodilation. Clearance of BNP is promoted by a NPR-C receptor which removes it from the circulation and BNP is also degraded through enzymatic cleavage by neutral endopeptidase. BNP levels are reflective of left ventricular diastolic filling pressures and thus correlate with pulmonary capillary wedge pressure.

BNP is stable in whole blood and a portable, 15 minute assay has been developed for measuring BNP in whole blood samples (Triage BNP Test, Biosite Diagnostics). BNP levels have been shown to be elevated in patients with symptomatic left ventricular dysfunction and correlate with New York Heart Association (NYHA) classification and prognosis.

Distinguishing congestive heart failure from other causes of dyspnea and/or edema is of great importance in patients presenting for medical attention with signs and/or symptoms that may or may not represent heart failure. A number of studies have demonstrated the limited reliability of the physical examination and Chest X-ray in diagnosing heart failure. Even with the best of clinicians, diagnosing heart failure remains a clinical challenge. BNP measurements have now been demonstrated to be a sensitive and specific test to diagnose CHF in the emergency medicine and urgent-care settings. This assay represents the first clinically available blood test to facilitate the diagnosis of heart failure and to provide risk stratification/prognostic information.

Clinical Studies of the BNP Assay

Clinical studies have indicated that the BNP test facilitates the diagnosis of heart failure, beyond existing clinical information. In a study of 250 patients presenting with dyspnea to an Emergency Medical Center, BNP performance was compared to a gold standard of two cardiologists (blinded to BNP levels) reviewing all clinical, radiographic, and echocardiographic data.[2] Mean BNP concentration in blood in patients with CHF was 1076 $\pm$ 138 pg/ml vs. 38 $\pm$ 4 pg/ml in those without ($p < 0.001$). In patients with lower extremity edema diagnosed with and without heart failure, BNP levels were 1038 $\pm$ 163 vs 63 $\pm$ 16 pg/ml.[2] In patients with dyspnea secondary to COPD or heart failure, BNP levels were 86 $\pm$ 39 with COPD as compared to 1076 $\pm$ 138 with heart failure.

At a blood concentration of greater than 100 pg/ml, BNP was an accurate predictor of the presence of CHF with a sensitivity of 94%, specificity of 94%, and a 96% negative predictive value. BNP was more accurate in diagnosing CHF than history, symptoms, physical exam findings, CXR, and the ECG. In multivariate analysis, BNP added significant, independent diagnostic power compared to other clinical

variables and diagnostic tests. The availability of BNP measurements would have potentially corrected 29 of the 30 diagnoses missed by the physicians evaluating the patient in the emergency medical center. In a community based study of 1,653 subjects, the BNP assay had a 97% negative predictive value for LV systolic dysfunction.[3] In 122 patients suspected of heart failure in a primary care setting who were subsequently referred to a rapid access heart failure clinic, BNP had a sensitivity of 97% and a negative predictive value of 98%.

BNP levels are elevated in both systolic dysfunction and isolated diastolic dysfunction. In a study screening 200 patients scheduled for echocardiography, mean BNP levels were 37 pg/ml in patients where both systolic and diastolic function was normal as compared to 480 pg/ml in patients with abnormal systolic or diastolic function on echocardiography.[4] Patients may have a normal left ventricular ejection fraction but still have heart failure due to abnormal diastolic function, elevated ventricular pressures and as a result, elevated BNP levels. BNP levels are higher in older as compared to younger patients and are 5-10 pg/ml higher in women as compared to men.

In the data set submitted to the FDA, BNP concentration were measured in 1286 patients without CHF with mean levels of 22.6 $\pm$ 27.5 pg/ml.[5] A decision threshold set at 100 pg/ml provided a specificity of > 98%, i.e. less than 2% expected false positives in individuals without CHF. In 804 patients diagnosed with CHF, mean BNP levels were 525.9 $\pm$ 451.9 pg/ml. Sensitivity for the assay at this level was 82.4% though most heart failure patients that had BNP levels below the cut point 100 pg/ml had predominately NYHA class I or II functional status. The sensitivity for Class IV heart failure (symptoms at rest) was 96.3%. Mean levels of BNP by NYHA class were Class I 149 pg/ml, Class II 385 pg/ml, Class III 614 pg/ml, and Class IV 858 pg/ml. Using the 100 pg/ml cutoff, the negative predictive value of the BNP test was $\geq$ 98%.

Based on the available information a BNP < 100 pg/ml, allows clinicians to exclude heart failure as a cause of the patients' symptoms or physical exam signs in most circumstances.

Prognostic Information with BNP

BNP levels have been shown to predict long term mortality in patients with heart failure, independent of other established prognostic variables.[6] In a recent study of 72 patients hospitalized with Class III and IV heart failure, BNP levels were obtained on admission and prior to discharge.[7] In patients without death or rehospitalization within 30 days, BNP levels rose during hospitalization by 233 pg/ml whereas in those without events BNP levels fell by 215 pg/ml. At a level of 400 pg/ml at time of discharge, BNP was 89% sensitive for events and the negative predictive value was 96%. In another study, 69 patients were randomized to have heart failure therapy guided by standard clinical assessment as compared to guided by BNP levels plus clinical assessment.[8] At 6 months, 27% of patients in the BNP group and 53% in the clinical group has an adverse clinical event (p=0.034). In 267 patients with heart failure, BNP levels predicted mortality independent of clinical parameters and LVEF (OR 4.5 95% CI 2.5-9.7, p<0.00001)

Acute Coronary Syndromes

BNP levels have been show to predict mortality in patients presenting with acute myocardial infarction and acute coronary syndromes. In a study of 2525 patients with ACS a BNP level above 40 pg/ml were associated with an independent increased risk of mortality.[9]

Other Conditions

The use of the BNP assay is being investigated in a variety of disease states and clinical scenarios. Some examples include screening for heart transplant rejection, the detection of cardiac dysfunction in patients receiving chemotherapeutic agents, detecting the degree of right heart failure and prognosis in patients with pulmonary hypertension, and detection of left ventricular hypertrophy in patients with ESRD.

Use of the BNP Assay

The BNP assay is recommended in the following clinical circumstances:

CHF Diagnosis

Patients presenting to the Emergency Medical Center or other acute care settings with signs or symptoms that are suggestive of heart failure, but in whom after a careful history and physical examination the diagnosis is not certain are candidates for the BNP assay. This would include patients presenting with dyspnea, lower extremity edema, or other potential heart failure signs or symptoms. The BNP assay should aid in distinguishing heart failure from other causes of dyspnea such as COPD, asthma, pneumonia, or pulmonary embolization.[10] The BNP assay should also assist in distinguishing heart failure from other causes of edema such as nephrotic syndrome or lower extremity venous insufficiency.

A BNP level of < 100 pg/ml makes it highly unlikely that the patients' symptoms are resulting from systolic or diastolic dysfunction heart failure. As such, an echocardiogram would be unlikely to provide additional diagnostic information and is not recommended (unless being done to evaluate for cardiac valvular disease or other abnormalities in the absence of heart failure). Myocardial ischemia/infarction and non-cardiac etiologies for the patient symptoms should be considered and appropriate diagnostic testing ordered as clinically indicated.

A BNP level that is elevated helps to confirm a diagnosis of congestive heart failure. Since patients with acute myocardial infarction accompanied by heart failure, would be expected to have elevated BNP levels a positive BNP result should not be viewed as excluding a diagnosis of AMI. In patients with severe right heart failure due to conditions such as pulmonary hypertension or a large pulmonary embolus, BNP levels may be moderately elevated (200 – 500 pg/ml) above the normal range. Levels above 500 pg/ml, however, would almost always indicate left heart failure. In patients with elevated BNP levels above 500 pg/ml, diagnostic testing for pulmonary embolization (CT angiography or ventilation perfusion scanning) would be recommended only when diagnoses of congestive heart failure and pulmonary embolization are being considered.

EMC or Hospitalized Patients	***Right Heart Failure***	***Renal Insufficiency***
Class I 60-150 pg/ml	Cor Pulmonale 200-500 pg/ml	ESRD 80->3000 pg/ml
Class II 150-300 pg/ml	Pulmonary HTN 200-500 pg/ml	(with LVH or LV
Class III 300-600 pg/ml	Pulmonary embolus 200-500 pg/ml	dysfunction with or
Class IV 600->3000 pg/ml		without high PCW)

BNP < 100 ml/pg	**BNP 100-500 pg/ml**	**BNP > 500 ml/pg**
HF unlikely	HF and other diagnoses	HF likely

Factors that can account for high BNP in the absence heart failure
Advanced Age

Renal failure
Myocardial infarction or acute coronary syndrome
High output states like cirrhosis
Acute, large pulmonary embolism

Factors that can account for low BNP when heart failure is present
Flash pulmonary edema (takes about one hour for BNP to rise).
Cause of heart failure upstream from left ventricle (e.g., mitral stenosis, atrial myxoma)
Marked obesity
Stable NYHA Class I patients on optimal medical therapy

Normal Ranges: 95th Percentile for Plasma BNP (pg/ml) Biosite Assay

	Age 45-54	**Age 55-64**	**Age 65-74**	**Age 75-83**
Women	73	93	120	155
Men	40	52	67	86

Condition	**Effect on BNP Concentration**
Hyperthyroidism	Increased
Cushing's or exogenous glucocorticoids	Increased
Primary aldosteronism	Increased
Addison's	May be increased in treated cases
Hepatic cirrhosis with ascites	Increased
Subarachnoid hemorrhage	Increased

CHF Management

BNP levels objectively reflect severity of disease in patients with heart failure. BNP levels obtained in patients with established heart failure provides prognostic information and monitoring of levels over time may facilitate titration of heart failure medications. BNP stratifies mortality risk independent of other clinical and diagnostic parameters. Investigations are currently taking place to further evaluate the clinical utility of BNP testing for these purposes. In patients being treated for heart failure in whom volume status and the degree of compensation are not clear based on history and physical examination, BNP is likely to provide information that has greater clinical utility than Chest X-Ray testing. As BNP levels correlate with pulmonary capillary wedge pressure, the BNP test could be considered in patients where volume status are uncertain and where right heart catheterization or serial echocardiography may otherwise be performed to assess ventricular filling pressures. In patients with significant renal dysfunction (Cr > 2.5 mg/dl), BNP are elevated in the setting of LVH or LV dysfunction, but may not reflect the patient's current volume status or elevated LV filling pressures. Heart failure patients with persistently elevated BNP levels would be expected to benefit from increased titration of diuretics and further optimization of ACE inhibitor, beta blocker, and spironolactone dosing. In heart failure patients with persistent or worsening symptoms out of proportion to their BNP levels, alternative causes of symptoms should be considered (i.e. hypovolemia or other medical problems such as depression, anemia, or infection).

Caution: The BNP assay, like all laboratory tests, does not provide a definitive diagnosis. The test result should be interpreted by the physician in conjunction with clinical findings and other diagnostic testing. While a negative BNP assay makes the diagnosis of heart failure unlikely it does not exclude the diagnosis of other potentially serious medical conditions such as unstable angina, acute

myocardial infarction, asthma, COPD, or pulmonary embolization. As with the troponin assay, the BNP test result should not be the sole criteria used to determine whether to admit or discharge a patient presenting to the emergency department with dyspnea or other symptoms. Diagnosis, risk assessment, and the decision as to whether inpatient or outpatient management is indicated should be based on the history, physical examination, ECG, and diagnostic tests as indicated.

Assay Characteristics

The Extended Range Triage BNP Test diagnostic level to exclude heart failure is BNP < 100 pg/ml (negative). A level of ≥ 100 pg/ml is considered positive and indicative of heart failure or other condition resulting in LV or RV stretch such as AMI/ACS. An elevated BNP indicates elevated ventricular filling pressure (PCW pressure) as occurs with systolic and diastolic dysfunction heart failure. Elevations can also be seen in acute myocardial infarction or pulmonary embolization severe enough to elevate ventricular pressure. BNP levels are not influenced by hypertension, diabetes, mild renal insufficiency, or COPD. Advanced renal disease and dialysis patients will have elevated BNP levels which while indicating structural heart disease does not necessarily indicate increased ventricular filling pressure. The assay identifies patients with heart failure and correlates with severity of symptoms/NYHA class.

The test measures BNP by immunoassay and utilizes a fluorescence detection system. The assay is linear between 20 and 3000 pg/ml, with a lower limit of detection of 20 pg/ml. Results below and above the detection limits will be reported as <20 pg/ml and >3000 pg/ml, respectively. Samples >3000 pg/ml cannot be re-assayed after dilution. Collect whole blood in a 4 ml lavender top tube-- a minimum of 2 ml of blood is required. Moderately hemolyzed specimens are acceptable. Samples greater than 4 hours old are not acceptable for testing. The rapid BNP test will be available on a STAT basis with a turn-around time of less than 60 minutes or on a routine basis with a turn around time of a few hours. No panic value levels have been set. The cost per reportable for BNP is $26.25 (for comparison, troponin I costs $11.08).

Heart Failure Diagnostic Algorithm

Patient with dyspnea or other signs/symptoms suspicious for heart failure

Hx/PE/ECG	🕓 diagnostic for CHF	🕓 CHF management (quantitate LV function with echocardiology, if not done previously)
	🕓 nondiagnostic	🕓 BNP (whole blood assay sent from ER STAT)
BNP	🕓 >500 pg/ml	🕓 CHF management (quantitate LV function with echocardiology, if not done previously)
	🕓 100-500 pg/ml	🕓 Consider CHF and other acute etiologies (AMI/ACS or pulmonary embolization)
	🕓 <100 pg/ml	🕓 evaluate for other non-heart failure etiologies as cause of patients' signs/symptoms (echo usually not indicated)

In patients in whom both heart failure and an acute coronary syndrome/myocardial infarction are in the differential diagnosis, serial troponins and ECGs should also be obtained. (see UCLA Chest Pain/Unstable Angina Guidelines). In patients with elevated BNP levels above 500 pg/ml, diagnostic testing for pulmonary embolization (CT angiography or ventilation perfusion scanning) would be recommended only when diagnoses of congestive heart failure and pulmonary embolization are being considered. For CHF management please refer to the UCLA Heart Failure Management Guidelines. The UCLA Cardiology Clinical Guidelines may be found at www.med.ucla.edu/champ.

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