Utility of a Rapid B-Natriuretic Peptide Assay in Differentiating Congestive Heart Failure from Lung Disease in Patients Presenting With Dyspnea

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OBJECTIVES
Since B-type natriuretic peptide (BNP) is secreted by the left ventricle (LV) in response to volume elevated LV pressure, we sought to assess whether a rapid assay for BNP levels could differentiate cardiac from pulmonary causes of dyspnea.

BACKGROUND
Differentiating congestive heart failure (CHF) from pulmonary causes of dyspnea is very important for patients presenting to the emergency department (ED) with acute dyspnea.

METHODS
B-natriuretic peptide levels were obtained in 321 patients presenting to the ED with acute dyspnea. Physicians were blinded to BNP levels and asked to give their probability of the patient having CHF and their final diagnosis. Two independent cardiologists were blinded to BNP levels and asked to review the data and evaluate which patients presented with heart failure. Patients with right heart failure from cor pulmonale were classified as having CHF.

RESULTS
Patients with CHF (n = 134) had BNP levels of 758.5 ± 798 pg/ml, significantly higher than the group of patients with a final diagnosis of pulmonary disease (n = 85) whose BNP was 61 ± 10 pg/ml. The area under the receiver operating curve, which plots sensitivity versus specificity for BNP levels in separating cardiac from pulmonary disease, was 0.96 (p < 0.001). A breakdown of patients with pulmonary disease revealed: chronic obstructive pulmonary disease (COPD): 54 ± 71 pg/ml (n = 42); asthma: 27 ± 40 pg/ml (n = 11); acute bronchitis: 44 ± 112 pg/ml (n = 14); pneumonia: 55 ± 76 pg/ml (n = 8); tuberculosis: 93 ± 54 pg/ml (n = 2); lung cancer: 120 ± 120 pg/ml (n = 4); and acute pulmonary embolism: 207 ± 272 pg/ml (n = 3). In patients with a history of lung disease but whose current complaint of dyspnea was seen as due to CHF, BNP levels were 731 ± 764 pg/ml (n = 54). The group with a history of CHF but with a current COPD diagnosis had a BNP of 47 ± 23 pg/ml (n = 11).

CONCLUSIONS
Rapid testing of BNP in the ED should help differentiate pulmonary from cardiac etiologies of dyspnea. (J Am Coll Cardiol 2002;39:202–9) © 2002 by the American College of Cardiology

Rapidly and accurately determining the etiology of shortness of breath in patients presenting with acute dyspnea is extremely important. The two chief causes of dyspnea, congestive heart failure (CHF) and lung disease, are often difficult to differentiate. Physical exam findings, lab tests and chest X-rays are often nonspecific (1,2). A blood test that could easily, rapidly and accurately help in diagnosing CHF would be of great use, especially in the emergency department (ED).

B-type natriuretic peptide (BNP) is a neurohormone secreted mainly in the cardiac ventricles in response to volume expansion and pressure overload (3–6). B-type natriuretic peptide levels are elevated in patients with left ventricular (LV) dysfunction and correlated to the severity as well as prognosis (7–11). In a recent pilot trial, BNP levels obtained by a rapid assay were able to accurately detect CHF in patients presenting with dyspnea (12). The purpose of the present study was to determine if BNP levels could accurately differentiate CHF from dyspnea of pulmonary etiologies.

METHODS
This study was approved by the University of California Institutional Review Board. A convenience sample of 321 patients presenting to urgent care with dyspnea was recruited June 1999 through June 2000 at the San Diego Veteran’s Health Care System. To be eligible for the study, the patient had to have shortness of breath—either at rest, with exertion or upon lying down—as a prominent complaint. Other associated symptoms could be edema, weight gain, cough or wheezing. Patients whose dyspnea was clearly not secondary to CHF (knife wounds, trauma and cardiac tamponade) were excluded. Patients with unstable angina or acute myocardial infarction were excluded unless their predominant presentation was dyspnea. To identify potential patients, a physician or a trained research assistant reviewed nurse descriptions of patients’ principal complaints. Patients fitting the above criteria were queried regarding participation in the study. The rate of refusal of...
Abbreviations and Acronyms

- BNP = B-type natriuretic peptide
- CHF = congestive heart failure
- COPD = chronic obstructive pulmonary disease
- CV = coefficient of variation
- ED = emergency department
- EDTA = ethylene diamine tetra acetic acid
- LV = left ventricle or left ventricular
- PEF = peak expiratory flow
- ROC = receiver-operating characteristic

patients approached for entry was <5%. When a patient was identified as possibly having CHF, consent was obtained and a blood sample was collected for purposes of measuring the patient's BNP. The research assistant collected other data, including elements from the present and past history, the physical exam and the patients' medications. Patients with right heart failure from cor pulmonale were classified as having CHF.

Confirmation of the diagnosis.

1. **CHF**: The diagnosis of CHF was based on independent confirmation of two cardiologists and was based on generally accepted Framingham criteria (9) with corroborative information including hospital course (response to diuretics, vasodilators, inotropes or hemodynamic monitoring) and results of further cardiac testing, including echocardiography, nuclear medicine ejection fractions or left ventriculography done at cardiac catheterization.

2. **Baseline LV dysfunction with no acute CHF**: based on the known past history (confirmed by ventricular function studies) whose final cause of acute dyspnea was not CHF.

3. **Pulmonary disease**: the following diagnostic tools were utilized to classify a patient as having pulmonary disease and to subdivide them as type of pulmonary disease: 1) a chest X-ray without signs of heart enlargement or pulmonary venous hypertension or a chest X-ray with signs of chronic obstructive lung disease, pneumonia or lung cancer; 2) normal heart function as seen by echocardiography, nuclear medicine, ejection fractions or left ventriculography; 3) abnormal pulmonary function tests or follow-up results in pulmonary clinic; 4) a positive response to treatment with steroids, nebulizers or antibiotics in the ED or hospital; and 5) no admissions for CHF over the next 30 days. Chest X-rays that were performed within 30 days of presentation to the ED were used in reporting and analysis of the data. Either high-probability ventilation perfusion scan or pulmonary angiography confirmed pulmonary embolism.

4. **Cardiac problems other than CHF**: this included patients whose primary complaints turned out to be secondary to angina pectoris or atypical chest pain.

5. **Other problems that were not considered to be of cardiac or pulmonary etiology**: patients that were placed into the other category were diagnosed with such problems as, but not limited to, anxiety or psychological stress, gastrosophageal reflux disease, allergic reaction or cirrhosis. There were some patients whose dyspnea was not due to a CHF exacerbation, yet they were noted to have an underlying type of LV dysfunction. This was an additional categorization above and beyond one of the diagnostic four they were placed into.

Measurement of BNP plasma levels. All samples were collected by venipuncture into ethylene diamine tetra acetic acid (EDTA) tubes. The blood samples were kept at room temperature and analyzed within 4 h of the draw time. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate with the Triage BNP assay. In some cases, the sample was centrifuged and plasma was removed, aliquoted and frozen at −70°C before analysis. The BNP assay is a sandwich immunoassay that consists of a disposable device to which 250 μl of EDTA-anticoagulated whole blood or plasma is added. The Triage Meter is used to measure the BNP concentration by detecting a fluorescent signal that reflects the amount of BNP in the sample.

Once 250 μl of whole blood or plasma was added to the device, the cells were separated from the plasma by a filter and the plasma containing BNP entered a reaction chamber that contained fluorescent-tagged BNP antibodies to form a reaction mixture. The reaction mixture was incubated for about 2 min and then migrated through the diagnostic lane by capillary action to a zone of immobilized antibody that binds the desired BNP-fluorescent antibody complex. The excess sample fluid washed the unbound fluorescent antibodies away. After about 15 min, the device was placed into the Triage Meter, which measures the fluorescence intensity of the BNP assay zone. The Triage Meter then correlated the fluorescence measurement to the BNP concentration by using an internal calibration curve. The assay was completed in approximately 15 min.

**PRECISION.** The coefficient of variation (CV) for intra-assay precision is 9.5% for 28.8 ng/l, 12.0% for 584 ng/l and 13.9% for 1,180 ng/l. The CV for interassay variation is 10% for 28.8 ng/l, 12.4% for 584 ng/l and 13.9% for 1,180 ng/l. The measurable range of the BNP assay is 5.0 ng/l to 1,300 ng/l.

**ANALYTICAL SENSITIVITY AND DETECTION LIMIT.** The analytical sensitivity, the lowest concentration distinguishable from zero, is <5.0 ng/l (95% confidence interval: 0.2 ng/l to 4.8 ng/l). The measurable range of the BNP assay is 5.0 ng/l to 1,300 ng/l.

**INTERFERENCES.** Naturally occurring analytes, such as hemoglobin, triglycerides, cholesterol and bilirubin, do not interfere with the assay. Several proteins structurally related to BNP and commonly used therapeutic agents are also analyzed for possible interference with the BNP assay. None
of these compounds produce any interference or significant assay cross-reactivity.

**BNP STABILITY.** B-type natriuretic peptide stability varies between room temperature and 4°C. Concentration differences are considered significant when there was >15% difference between the time point and the initial value. Using these criteria, 100% of the samples are stable up to 8 h at 4°C. At room temperature, however, three samples are stable for 8 h, and three samples are stable for 4 h. Therefore, the minimum stability of BNP at room temperature is determined to be 4 h.

**Statistics.** Group comparisons of BNP values were made using t tests for independent samples and analyses of variance with post-hoc Tukey tests where indicated. In all cases, these were computed with raw BNP values and repeated with log-transformed BNP values since the BNP distribution was positively skewed. Both versions yielded the same conclusions. Results are expressed as mean ± SD for the raw values. The diagnostic utility of BNP in separating CHF from other diseases was determined using receiver-operating characteristic (ROC) curves. The results are expressed in terms of the area under the curve and the 95% confidence interval for this area. Sensitivity, specificity and accuracy were computed for BNP using a selection of possible cut-points. To evaluate the utility of BNP measurements in the diagnosis of CHF, we compared the sensitivity, specificity and accuracy of BNP measurements to individual findings, to a multivariate model of clinical findings and to clinical judgment. For each of the different clinical and X-ray findings identified by ED physicians and different threshold BNP concentrations, we computed sensitivity, specificity and accuracy. Then, to determine if BNP measurements added independent diagnostic information to commonly collected clinical variables, we applied multivariate step-wise logistic regression. We developed the best predictive model based on historical, clinical and X-ray findings using a p value of ≥0.1 for entry into the model. After a stable model was obtained, we added BNP measurements to the predictive model and assessed improvement in the degree of fit.

**RESULTS**

Table 1 shows the characteristics of the 321 study patients. A total of 42% had a history of CHF, while 40% had a history of pulmonary disease. About one-half were on cardiac drugs and one-half were on pulmonary drugs. Three-fourths of all patients had dyspnea at rest. Jugular venous pressure elevation was present in 20% of patients and wheezing in 29% of patients. Gallops were rare (6%). The BNP levels were higher in the 139 patients who were admitted (546 ± 787 pg/ml) than they were in the 181 patients who were not admitted (209 ± 419 pg/ml).

The final diagnosis along with BNP levels of patients is illustrated in Figure 1. A total of 42% of patients had CHF as a final diagnosis for their dyspnea. This group had much higher BNP levels than the 85 patients with a final diagnosis of pulmonary disease (759 ± 799 pg/ml vs. 61 ± 92 pg/ml, p < 0.001). In patients with baseline LV dysfunction but whose cause of dyspnea was other than CHF, BNP levels averaged 149 ± 84 pg/ml. Patients with other types of cardiac disease or noncardiac, nonpulmonary disease had BNP levels within the range of normal. Twenty-eight patients with CHF had a history of chronic obstructive pulmonary disease (COPD) plus elevated jugular venous pressure and/or edema. Their mean BNP level was 669 ± 715 pg/ml.

The ability of BNP to differentiate CHF from pulmonary disease was assessed with ROC curve analysis (Fig. 2). The area under the ROC curve using BNP to differentiate CHF from pulmonary disease was 0.99 (0.96 to 0.99, p < 0.001). A BNP value of 94 pg/ml had a sensitivity of 86%, specificity of 98% and an accuracy of 91% for differentiating CHF from pulmonary disease.

**Types of pulmonary disease.** Figure 3 breaks down the BNP levels in each classification of pulmonary disease. The average BNP levels for the majority of the lung categories are well below those of the CHF group. It is noted that the BNP levels of the small groups of patients with pulmonary embolism, lung cancer and tuberculosis were higher than the rest of the diseases in the pulmonary group. Figure 4 shows BNP levels in patients with a past history of pulmonary disease but a final diagnosis of acute CHF as well as patients with a past history of CHF but a final diagnosis of acute pulmonary disease. Those patients with a history of CHF but whose dyspnea was due to a current COPD exacerbation (n = 11) had an average BNP of 47 ± 23 pg/ml. Those with a history of COPD with a current...
CHF exacerbation (n = 54) had an average BNP level of 731 ± 764 pg/ml.

Association between BNP levels and final diagnosis. Univariate analysis was performed for all variables pertinent to a diagnosis of CHF or lung disease, along with BNP concentrations at 80, 100, 120, 140 and 200 pg/ml. The sensitivity, specificity and accuracy for each variable is reported in Table 2. The best clinical predictor was a past history of CHF (79% accuracy) followed by heart size and pulmonary venous hypertension on chest X-ray (73% and 70% accuracy) and elevated jugular venous pressure (70% accuracy). B-type natriuretic peptide was an accurate predictor of patient diagnosis. The negative predictive value of 80 pg/ml was 99%.

In multivariate analyses, we evaluated the combined explanatory power of history, symptoms, signs, radiological studies and lab findings (Table 3). The addition of BNP levels to the regression substantially increased the explanatory power of the model, suggesting that BNP measurements provided meaningful diagnostic information not available from other clinical variables.

DISCUSSION

Because patients with LV dysfunction have improved survival and increased well-being on medications such as angiotensin-converting enzyme inhibitors and beta-blockers (13), it is imperative to make the correct diagnosis as accurately and as early in the course of the disease as possible. For the acutely ill patient presenting to the ED, a misdiagnosis could place the patient at risk for both morbidity and mortality (14). Therefore, the ED diagnosis of CHF needs to be rapid and accurate.

Dyspnea, the chief symptom in patients with CHF, is reported to be relevant in 2.7% of ED visits and 15% to 25% of all hospital admissions (1,2,15,16). To be able to differentiate cardiac from pulmonary causes of dyspnea is a difficult yet critical aspect of the physician’s job. Yet despite the tools available to physicians, the differentiation can still be difficult. A reliable history cannot always be ascertained in an acutely ill patient, and dyspnea, a key symptom of CHF, may be a nonspecific finding in the elderly or obese patient in whom comorbidity with respiratory disease and physical deconditioning are common (14,17). Physical exam findings, routine lab values, electrocardiograms and chest X-rays are also not accurate enough to always make the appropriate diagnosis (15–19). Echocardiography has limited availability in acute care settings and may not be helpful in delineating diastolic dysfunction. Finding a blood test that would aid in the diagnosis and management of patients with CHF would clearly have a favorable impact on the staggering costs associated with the disease (20).

B-type natriuretic peptide is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides (3,4). Release of BNP appears to be directly proportional to ventricular volume expansion and pressure overload (3,6,21) and, hence, has been found to be useful for evaluating patients with dyspnea or with LV dysfunction (9–12,22–24). The recent availability of a rapid assay for BNP has already proven valuable in evaluating the effectiveness of BNP in point-of-care settings (9–12,23–26). This includes rapidly differentiating CHF from other causes of dyspnea in
patients presenting to the ED (12), screening patients for LV dysfunction (24) and monitoring hemodynamically guided treatment of CHF (26).

In the present study BNP was able to distinguish CHF from pulmonary and other clinical presentations with a high specificity, sensitivity and accuracy. Even in those patients with comorbid conditions of CHF and COPD, BNP was useful in distinguishing the reason for the visit to the ED. In the 65 patients with both conditions, those with a current COPD exacerbation had an average BNP of 47 pg/ml, whereas those with current CHF had an average BNP of 731 pg/ml.

Multivariate analysis showed that assessing BNP levels added to the diagnosis above and beyond these clinical tests or physical findings such as chest X-ray findings, rales and edema. When BNP was added to the data available, it still was significant in improving the diagnosis of CHF, which is seen as significance of $p > 0.001$, 87% sensitivity, 95% specificity and a 91% accuracy.

Other tests used to differentiate CHF from pulmonary disease. While use of echocardiography and Swan–Ganz catheterization may help differentiate CHF from pulmonary dyspnea in specific settings, other tests have not fared so well. These include peak expiratory flow (PEF) and dyspnea differentiation index, which is the product of the PEF and the partial pressure of arterial blood/1,000 (27). While some positive results have been found, there is a large overlap in values as well as failure to predict comorbidity states (27). Peak expiratory flow rate has also been proposed as a way to distinguish CHF from lung disease. However, values tend to decrease with more severe forms of heart failure, limiting its usefulness in this setting (28,29). Finally, end tidal CO$_2$ measurements as well as breath sound auscultations have also been proposed as a means to differentiate pulmonary from cardiac dyspnea. Neither test has been able to perform accurately enough to be of practical value (28,30).

Rational use of BNP in the urgent care setting. Several confounding issues should be addressed if the rapid BNP
In some cases, patients have both cardiac and pulmonary diseases occurring concurrently, such as when pneumonia triggers CHF. In these settings, both a high BNP level and consolidation on chest X-ray would be likely. This underscores that BNP is not a stand-alone test and that clinical judgment always should be taken in the highest regard.

Patients who present with a COPD exacerbation, which has triggered worsening cor pulmonale, may present with dyspnea and signs of right ventricular volume overload (including edema and ascites). In these patients BNP levels are likely to be high (300 pg/ml to 600 pg/ml), though usually not as high as cardiac dyspnea from elevated LV end-diastolic pressure. Nagaya et al. (31) recently measured hemodynamics and BNP levels in 44 patients with right ventricular overload from pulmonary hypertension. The mean BNP level in this group was 294 pg/ml and correlated with indexes of pulmonary artery and right ventricular

Figure 3. Mean ± SD for B-type natriuretic peptide (BNP) values in patients with various types of pulmonary disease. COPD = chronic obstructive pulmonary disease; TB = tuberculosis.

Figure 4. B-type natriuretic peptide (BNP) levels in patients with a past history of pulmonary disease but a final diagnosis of acute congestive heart failure (CHF), as well as patients with a past history of CHF but a final diagnosis of acute pulmonary disease. Data are expressed as mean ± SE for BNP values. COPD = chronic obstructive pulmonary disease.
end-diastolic pressures, as well as with long-term changes in hemodynamics. Thus, the positive predictive value of BNP might decrease at values between 80 pg/ml to 300 pg/ml in patients with possible right ventricular involvement. We also had three patients with large pulmonary embolism whose BNP levels were elevated into the 200 pg/ml to 300 pg/ml range, probably from acute right ventricular pressure overload.

While the positive predictive value of BNP might be mitigated in the above settings, the importance of a negative predictive value of BNP in settings of acute dyspnea cannot be overstated. For instance, an extremely ill patient who has cardiogenic pulmonary edema on chest X-ray with a normal BNP level likely has adult respiratory distress syndrome. A patient with large cardiac silhouette on chest X-ray but who has a normal BNP level could quite possibly have cardiac tamponade.

Finally, there are several circumstances in which BNP may be elevated for other reasons. Since patients who have end-stage renal failure or who are on dialysis have elevated BNP levels (32), diagnosing CHF in this population should rely on more standard criteria. Also, in some patients dyspnea may be the clinical manifestation of acute myocardial infarction. B-type natriuretic peptide is also a marker of necrosis and may be elevated in these patients (23). Thus, if other features suggest myocardial infarction (e.g., changes, chest pressure, etc.) cardiac markers should be measured.

**Study limitations.** The study population was drawn from the Veterans Affairs Medical Center and was 95% male. Thus, these results need to be confirmed in a non-Veterans Affairs population and with women. The patients studied were those who came to the ED with symptoms, and results may not be easily generalized to the outpatient setting.

### Table 2. Univariate Analysis

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### Table 3. Multivariate Analysis

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CHF = congestive heart failure.
Conclusions. The rapid measurement of the BNP concentration in the blood appears to be a sensitive and specific test for differentiating patients with CHF from primary pulmonary causes of dyspnea in acute care settings. If further studies validate our exploratory investigation, it is possible that BNP may prove to be a cost-effective addition to the diagnostic armamentarium of acute care physicians.

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