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Bedside B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure With Reduced or Preserved Ejection Fraction

Results From the Breathing Not Properly Multinational Study

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OBJECTIVES This study examines B-type natriuretic peptide (BNP) levels in patients with systolic versus non-systolic dysfunction presenting with shortness of breath.

BACKGROUND Preserved systolic function is increasingly common in patients presenting with symptoms of congestive heart failure (CHF) but is still difficult to diagnose.

METHODS The Breathing Not Properly Multinational Study was a seven-center, prospective study of 1,586 patients who presented with acute dyspnea and had BNP measured upon arrival. A subset of 452 patients with a final adjudicated diagnosis of CHF who underwent echocardiography within 30 days of their visit to the emergency department (ED) were evaluated. An ejection fraction of greater than 45% was defined as non-systolic CHF.

RESULTS Of the 452 patients with a final diagnosis of CHF, 165 (36.5%) had preserved left ventricular function on echocardiography, whereas 287 (63.5%) had systolic dysfunction. Patients with non-systolic heart failure (NS-CHF) had significantly lower BNP levels than those with systolic heart failure (S-CHF) (413 pg/ml vs. 821 pg/ml, $p < 0.001$). As the severity of heart failure worsened by New York Heart Association class, the percentage of S-CHF increased, whereas the percentage of NS-CHF decreased. When patients with NS-CHF were compared with patients without CHF ($n = 770$), a BNP value of 100 pg/ml had a sensitivity of 86%, a negative predictive value of 96%, and an accuracy of 75% for detecting abnormal diastolic dysfunction. Using Logistic regression to differentiate S-CHF from NS-CHF, BNP entered first as the strongest predictor followed by oxygen saturation, history of myocardial infarction, and heart rate.

CONCLUSIONS We conclude that NS-CHF is common in the setting of the ED and that differentiating NS-CHF from S-CHF is difficult in this setting using traditional parameters. Whereas BNP add modest discriminatory value in differentiating NS-CHF from S-CHF, its major role is still the separation of patients with CHF from those without CHF. (J Am Coll Cardiol 2003;41:2010–7i) © 2003 by the American College of Cardiology Foundation

As many as 40% to 55% of patients with signs and symptoms of congestive heart failure (CHF) have preserved systolic function (1,2). Cardiac abnormalities in these patients are determined by a complex sequence of interrelated events that may make diagnosis and the success of treatment

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difficult to assess (3). While Doppler echocardiography has been used to examine left ventricular (LV) filling dynamics in these patients, the limitations of this technique suggest the need for other objective measures in CHF patients with preserved systolic function (4).

B-natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload (5,6). B-type natriuretic peptide levels are known to be elevated in patients with symptomatic LV dysfunction and correlate to New York Heart Association (NYHA) class as well as prognosis (7–12). Recently, it has been shown that in patients with preserved LV function, BNP levels may be reflective of diastolic filling abnormalities on echocardiography (13,14).

This study examines BNP levels in patients presenting to the emergency room with shortness of breath as part of the multinational Breathing Not Properly study (15). To define and differentiate characteristics of those with non-systolic dysfunction from those patients with systolic dysfunction, we utilized that subset of patients who had echocardiographic determination of cardiac function within 30 days of their initial visit.

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Abbreviations and Acronyms

AUC = area under the curve
BNP = B-type natriuretic peptide
CHF = congestive heart failure
ED = emergency department
EF = ejection fraction
LV = left ventricular
NS-CHF = non-systolic congestive heart failure
NYHA = New York Heart Association
ROC = receiver operating characteristic
S-CHF = systolic congestive heart failure

METHODS

Study population. The study was approved by the Institutional Review Boards of participating Breathing Not Properly Multinational Study centers. A total of 1,586 patients from seven sites (five in the U.S., one in France, one in Norway) were enrolled from April 1999 to December 2000. To be eligible for the study, the patient had to have shortness of breath as their chief complaint. Patients under age 18 and whose dyspnea was clearly not secondary to CHF (e.g., trauma victims) were excluded. Patients with acute myocardial infarction, severe renal failure, and unstable angina were excluded.

Once a patient was identified as having dyspnea, written consent was obtained, and a blood sample was collected for purposes of measuring the BNP concentration. Other data were collected, including elements from the present and past history, the physical examination, and reports of other blood tests, interpretations of chest X-rays, or interpretations of other diagnostic tests. Echocardiograms were strongly encouraged, either in the emergency department (ED), as an outpatient, or in the hospital if the patient was admitted.

For each patient enrolled in the study, physicians assigned to the ED who were blinded to the results of BNP measurements made an assessment of the probability of the patient having CHF (0 to 100% clinical certainty) as the cause of his or her symptoms at the time of ED disposition.

Confirmation of the diagnosis. To determine the patient's actual diagnosis, two cardiologists reviewed all medical records pertaining to the patient and made independent initial assessments of the final diagnosis: 1) CHF; 2) history of CHF but acute dyspnea due to non-cardiac cause; or 3) not CHF. The cardiologists were presented the components and summary of the Framingham (two major or one major and two minor criteria) CHF score and the National Health and Nutrition and Examination Survey (score $\geq$3) CHF score, calculated from the case report form. The cardiologists were blinded to the BNP results as well as the ED physicians' diagnosis. They did have access to the ED data sheets and any additional information that became available after the ED visit. This included the following: official reading of the chest X-ray that was done in the ED by a radiologist; past medical history obtained from a medical chart that was not available at the time to the ED physicians; the results of subsequent tests such as echocardiography, radionuclide angiography, or left ventriculography done at the time of cardiac catheterization; and the hospital course for patients admitted to the hospital. For patients with a diagnosis other than CHF, confirmation was attempted using the following variables: normal chest X-ray (lack of heart enlargement and pulmonary venous hypertension); X-ray signs of chronic obstructive lung disease, pneumonia, or lung cancer; normal heart function by echocardiography, nuclear medicine ejection fractions (EF), or left ventriculography done at cardiac catheterization; abnormal pulmonary function tests or follow-up in pulmonary clinic; response to treatment in the ED or hospital with nebulizers, steroids, or antibiotics; and no CHF admissions over the next 30 days. In all cases of CHF, the two cardiologists were asked to agree on the degree of severity of CHF by ranking each patient as NYHA class I to IV.

Non-systolic versus systolic dysfunction. A subset of 452 patients with a final adjudicated diagnosis of CHF underwent echocardiography within 30 days of their visit to the ED. Patients with heart failure were defined as having systolic heart failure (S-CHF) if the ejection was 45% or less. Patients were defined as having non-systolic heart failure (NS-CHF) if EF was >45%.

Measurement of BNP plasma levels. During initial evaluations, a blood sample was collected into tubes containing potassium ethylenediaminetetraacetic acid. The BNP was measured in triplicate using the Triage B-Type Natriuretic Peptide test (Biosite Inc., San Diego, California). The Triage BNP test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. The precision, analytical sensitivity, and stability characteristics of the system have been previously described (16,17). Triplicate BNP values were determined on site using the Triage BNP test with either whole blood or plasma samples.

Statistics. For each of the different clinical and X-ray findings identified by ED physicians, the percentage of CHF cases with systolic dysfunction was computed. Group comparisons of BNP values were made using Mann-Whitney *U* tests. Other group comparisons were made using chi-squared tests and *t* tests for independent samples. Receiver operating characteristic (ROC) curves were used to evaluate the utility of BNP for various diagnostic comparisons. Sensitivity, specificity, and accuracy are reported for cut points of selected BNP concentrations. We also used a stepwise multivariate logistic model combining clinical findings and BNP values to differentiate between S-CHF and NS-CHF. The BNP values were log-transformed in this analysis to normalize the distribution.

RESULTS

The baseline characteristics for the overall study group of 1,586 patients are shown in Table 1. The mean age was 64 years. There were 883 (56%) males and 703 (44%) females.