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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.

Table 1. Baseline Characteristics of Participants in the Breathing Not Properly Multinational Study

	All		CHF	
	n	%	n	%
Gender				
Male	883	55.7	421	56.7
Female	703	44.3	321	43.3
Race				
White	773	48.7	386	52.0
Black	715	45.1	314	42.3
Other	98	6.2	42	5.7
Age				
Range	18–105		18–105	
Mean	64 (SD = 16.7)		70 (SD = 14.53)	
Presenting symptoms				
Orthopnea	789	49.7	453	61.1
PND	668	42.1	383	51.6
Night cough	636	40.1	301	40.6
Fatigue	1,101	69.4	555	74.8
Weakness	1,067	67.3	537	72.4
History				
CHF	527	33.2	421	56.7
MI	385	24.3	270	36.4
Angina	308	19.4	189	25.5
CABG	176	11.1	127	17.1
AFib	256	16.1	186	25.1
Hypertension	879	55.4	477	64.3
COPD	600	37.8	217	29.2
DM	367	23.1	130	32.0

AFib = atrial fibrillation; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; MI = myocardial infarction; PND = paroxysmal nocturnal dyspnea.

Ethnic makeup included 773 (49%) whites, 715 (45%) blacks, and 98 (6%) classified as other races. Baseline characteristics in patients with CHF who received echos were similar to those who did not receive echos except they were slightly younger, more often black, and had more fatigue.

On examination by ED physicians, 7% of patients had an S-3 gallop, 43% had rales in lower lung fields, 22% had jugular venous distention, and 42% had lower extremity edema. The final diagnosis (made retrospectively by two cardiologists) was CHF in 744 patients (47%), a history of CHF but dyspnea due to non-cardiac causes in 72 patients (4.5%), and no CHF in 770 patients (49%). In 97% of patients with CHF, the final diagnosis of CHF was confirmed by other tests (chest X-ray 79%, echocardiography 77%, radionuclide EF 15%, cardiac catheterization 19%, and response to treatment 86%).

Of the 452 patients with a final diagnosis of CHF who had echos within 30 days, 165 (36.5%) had preserved LV function on echocardiography (NS-CHF), whereas 287 had systolic dysfunction (S-CHF). The mean EF were 28 ± 0.6% and 59 ± 0.6% in systolic and non-systolic dysfunction, respectively ($p < 0.001$). Figure 1 presents box plots showing median levels of BNP measured in the ED in patients with dyspnea not due to heart failure, and those with an adjudicated final diagnosis of heart failure, subdivided by those with S-CHF and those with NS-CHF. The median BNP level in the non-CHF groups was 34 pg/ml, significantly lower than either those with S-CHF or NS-CHF ($p < 0.001$ in both cases). Patients with NS-CHF had significantly lower BNP levels than those with S-CHF (413 pg/ml vs. 821 pg/ml, $p < 0.001$).

The relative proportions of systolic and non-systolic dysfunction differed significantly as a function of severity of CHF as agreed on by both cardiologists ($p < 0.001$). Figure 2 shows a breakdown of each NYHA class in relation to S-CHF and NS-CHF. As the severity of heart failure worsened by NYHA classification, the proportion of

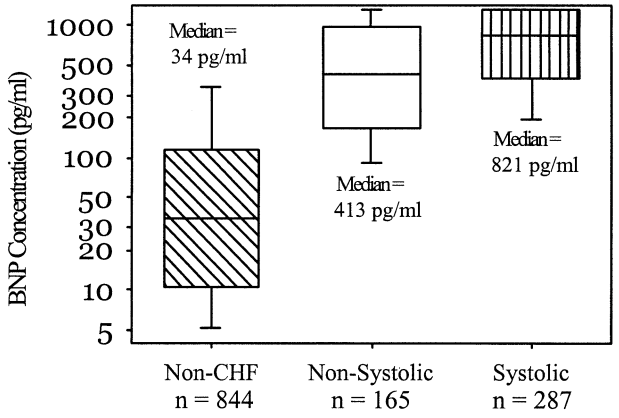


Figure 1. Box plots showing median levels of B-type natriuretic peptide (BNP) measured in the emergency department in patients with dyspnea not due to heart failure, in those with an adjudicated final diagnosis of non-systolic left ventricular dysfunction, and in those with systolic left ventricular dysfunction. CHF = congestive heart failure.

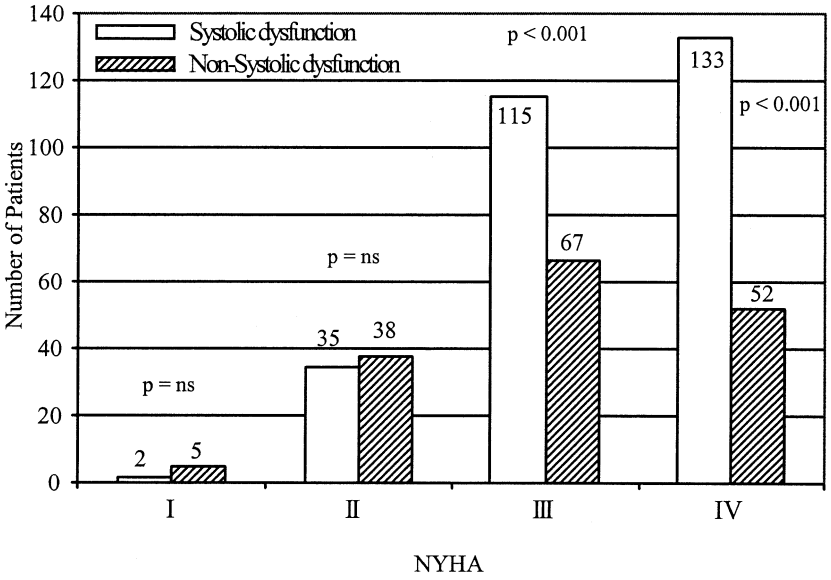


Figure 2. Number of patients in each New York Heart Association (NYHA) functional class with systolic versus non-systolic dysfunction.

S-CHF increased and the proportion of NS-CHF decreased.

Figure 3 presents box plots showing median levels of BNP measured in men and women over 70 years of age with dyspnea not due to heart failure, and those with an adjudicated final diagnosis of heart failure, subdivided by those with S-CHF and those with NS-CHF. The difference between older men and woman with regard to BNP levels in the non-CHF group was not statistically significant. Among males, BNP was higher in both CHF groups than control ($p < 0.001$) but S-CHF and NS-CHF did not differ. Among females, BNP was higher than control in both types of CHF ($p < 0.001$) and women with systolic CHF had higher BNP levels than non-systolic failure patients ($p = 0.03$).

Table 2 shows univariate differences in patients with S-CHF versus NS-CHF on presentation to the emergency room. Patients with NS-CHF less often had a history of heart failure (32% vs. 68%, $p = 0.015$) or myocardial infarction (29% vs. 71%, $p = 0.002$) than those with

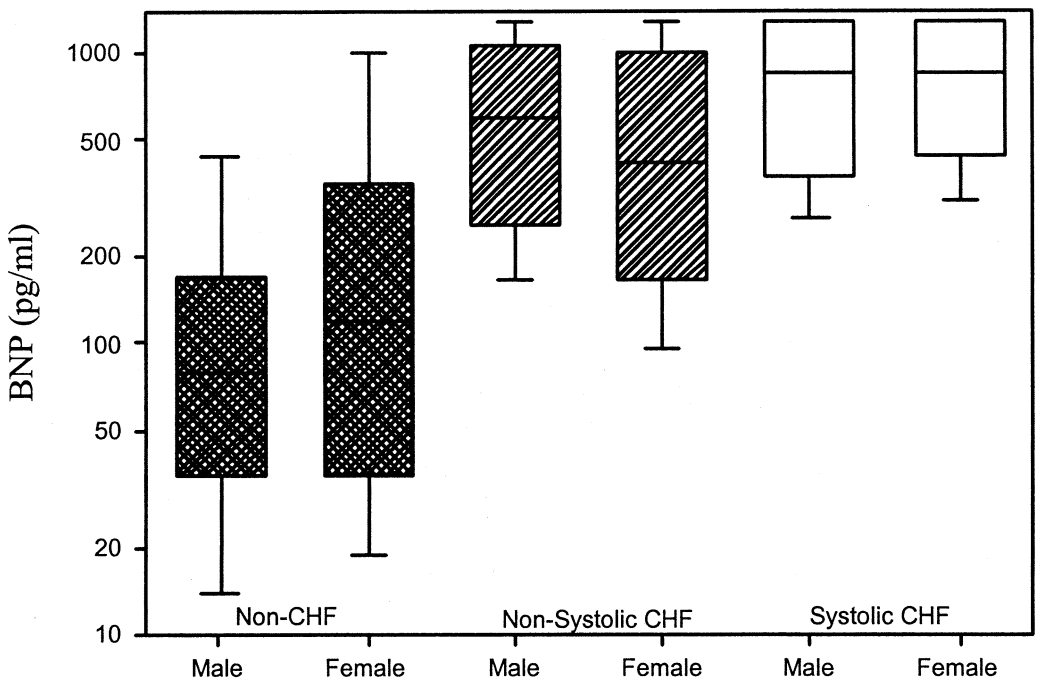


Figure 3. Box plots showing median levels of B-type natriuretic peptide (BNP) measured in men and women over 70 years of age with dyspnea not due to heart failure, and those with an adjudicated final diagnosis of heart failure, subdivided by those with systolic congestive heart failure (CHF) and those with non-systolic CHF.

Table 2. Univariate Predictors of Systolic Versus Non-Systolic Dysfunction

	% Systolic		
Variable	**With Indicator**	**Without Indicator**	**p Value**
Gender (male)	69.4	55.8	0.003
Ethnicity	—	—	NS
White	60.0	66.5	—
Black	65.6	61.5	—
History of CHF	67.7	56.3	0.015
History of MI	70.9	55.9	0.002
History of AFib/AFlutter	61.5	61.7	NS
History of hypertension	60.0	68.4	NS
History of diabetes	56.9	65.2	NS
History of COPD/asthma	61.9	61.7	NS
Orthopnea	65.2	57.9	NS
PND	66.8	51.8	NS
Elevated JVD	65.5	61.2	NS
Rales lower fields	63.3	63.4	NS
Rales upper fields	64.6	62.5	NS
S3 gallop	74.1	60.3	0.045
Murmurs	58.2	65.0	NS
Lower extremity edema	60.2	67.4	NS
Ischemic T-wave inversion	60.9	63.8	NS
Atrial fibrillation or flutter	57.3	64.7	NS
LBBB	79.6	61.5	0.013
Normal chest X-ray	61.3	63.9	NS
Heart size	65.9	60.0	NS
Cephalization of pulmonary vessels	65.0	62.7	NS
Alveolar edema	65.8	63.3	NS
Variable	**Systolic (mean ± SEM)**	**Non-Systolic (mean ± SEM)**	**p Value**
Heart rate (beats/min)	93.4 ± 1.5	88.1 ± 1.9	0.028
Systolic pressure (mm Hg)	136.9 ± 1.8	147.7 ± 2.9	< 0.001
Diastolic pressure (mm Hg)	80.2 ± 1.2	77.3 ± 1.6	0.141
First oxygen saturation (%)	94.2 ± 0.4	91.8 ± 0.7	0.002
Weight (kg)	79.0 ± 1.4	83.7 ± 2.1	0.051
Creatinine (mg/dl)	1.3 ± 0.0	1.2 ± 0.0	0.077
Ejection fraction (%)	27.6 ± 0.6	59.2 ± 0.7	< 0.001

AFlutter = atrial flutter; JVD = jugular venous distension; LBBB = left bundle-branch block; NS = nonsignificant. Other abbreviations as in Table 1.

S-CHF. On physical examination, patients with NS-CHF had slower heart rates (88 vs. 93 beats/min, $p = 0.028$), higher systolic pressures (147 mm Hg vs. 137 mm Hg, $p < 0.001$), and lower mean oxygen saturations (91.8% vs. 94.2%, $p = 0.002$). A third heart sound was present less often in NS-CHF than S-CHF (26% vs. 74%, $p = 0.045$).

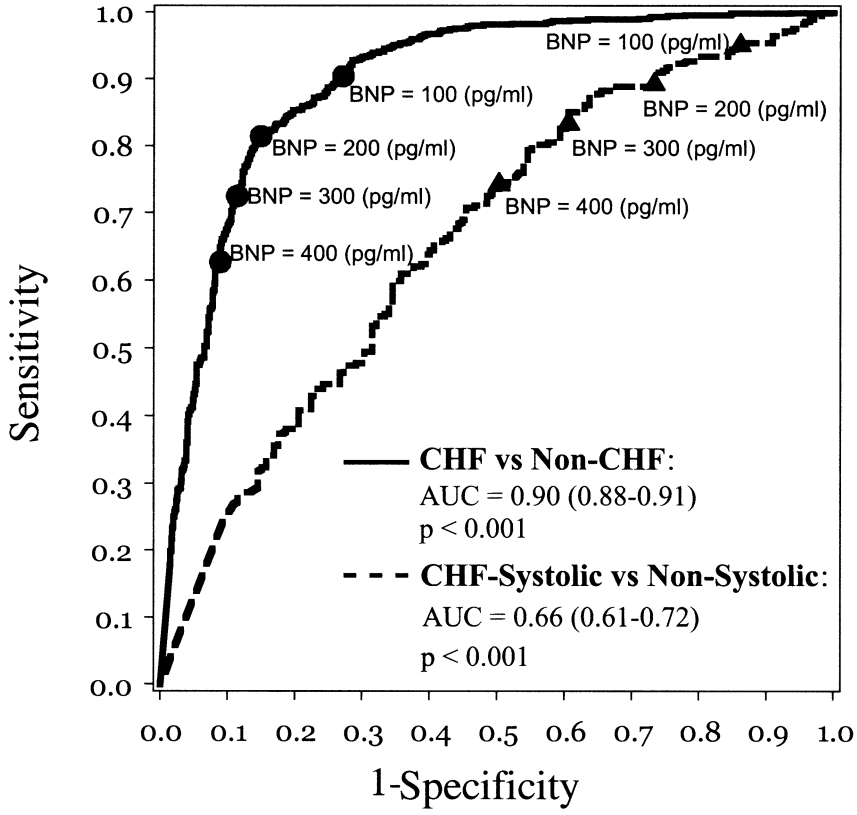
The ability of BNP to detect abnormal heart function was assessed with ROC curve analysis (Fig. 4). B-type natriuretic peptide was accurate in separating all CHF from non-CHF patients (area under the curve [AUC] = 0.90) with 90% sensitivity at the established cutoff of 100 pg/ml. The BNP levels were not very accurate in separating S-CHF from NS-CHF (AUC = 0.66, $p < 0.001$). Although a cut point of 100 pg/ml was 95% sensitive for detecting S-CHF, there was significant overlap between the two groups, with 86% of NS-CHF patients falling above this cutoff.

Logistic regression was used in a multivariate approach for differentiating systolic from non-systolic dysfunction in patients diagnosed with heart failure (Table 3). The BNP level, oxygen saturation, history of myocardial infarction, and heart rate were the variables most closely associated with separating the two entities.

DISCUSSION

As many as 40% to 55% of patients with the diagnosis of heart failure have preserved systolic function (1,2). The prevalence of CHF with preserved systolic function increases with age, with an approximate incidence of 15% to 25% in people less than 60 years old, 35% to 40% between 60 and 70 years, and 50% in people over 70 years of age (18,19).

Few data exist as to the proportion of patients who arrive at the ED with dyspnea as a result of heart failure with non-systolic LV dysfunction. The present study found that slightly over one-third of patients presenting to the ED had non-systolic dysfunction as determined by echocardiogra-



CHF versus Non-CHF

BNP (pg/ml)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
100	90 (88-92)	73 (70-76)	75 (72-77)	90 (87-92)	81
200	81 (78-84)	85 (83-87)	83 (80-85)	84 (81-86)	83
300	73 (69-76)	89 (86-91)	85 (82-88)	79 (76-81)	81
400	63 (59-66)	91 (89-93)	86 (83-89)	74 (71-76)	78

Systolic versus Non-Systolic

BNP (pg/ml)	Sensitivity (%) Detecting Systolic	Specificity (%) Detecting Diastolic	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
100	95 (92-97)	14 (9-20)	66 (61-70)	62 (45-78)	66
200	89 (85-92)	27 (20-34)	68 (63-72)	59 (47-70)	66
300	83 (79-87)	39 (32-47)	71 (65-75)	58 (48-67)	67
400	74 (69-79)	50 (42-57)	72 (67-77)	53 (45-60)	65

Figure 4. Receiver-operating characteristic curve for B-type natriuretic peptide (BNP) for differentiating between congestive heart failure (CHF) and non-CHF cases and between systolic versus non-systolic dysfunction (non-CHF patients excluded). Tables show decision statistics at selected cut points. AUC = area under the curve.

Table 3. Logistic Regression in Attempt to Differentiate Systolic From Diastolic Heart Failure

Step	Predictor Added	Direction in Systolic CHF	Exp. (B)	p Value
1	BNP	Higher	3.64	<0.001
2	O_2 saturation	Higher	1.07	<0.001
3	MI history	Higher	2.11	0.002
4	Heart rate	Higher	1.02	0.006

BNP = B-type natriuretic peptide; CHF = congestive heart failure; Exp. (B) = e^B where B is the slope in logistic regression equation; MI = myocardial infarction.

phy done within 30 days of their index visit. Correctly diagnosing CHF in patients presenting with acute dyspnea will not only allow one to accrue the benefits of improved survival and increased well-being on medications such as angiotensin-converting enzyme inhibitors and beta-blockers (20), but also to avoid a misdiagnosis that could place the patient at risk for both morbidity and mortality (21).

Using a rapid assay for BNP has allowed the prompt differentiation of CHF from non-CHF causes of dyspnea, regardless of the type of heart failure (8,15,16). Additionally, BNP levels are highly prognostic in this setting. Harrison et al. (22) followed 325 patients for six months after an index visit to the ED for dyspnea and found that the relative risk of six-month CHF death in patients with BNP levels more than 230 pg/ml was 24.

It has been previously demonstrated that in the nonemergency setting BNP is elevated in patients with NS-CHF (13,14,20,23–25). Although BNP levels could not by themselves differentiate between S-CHF and NS-CHF, a low BNP level in the setting of normal systolic function by echocardiography was able to rule out clinically significant diastolic abnormalities seen on echo. On the other hand, elevated BNP levels in patients with normal systolic function, especially in older patients with a history of CHF, correlated to ventricular filling abnormalities on Doppler studies (20,24).

In the present study, BNP was elevated in NS-CHF to a median value of 413 pg/ml, higher than that seen in most ambulatory patients with NS-CHF (13,14). Interestingly, Lubien et al. (25) found BNP levels of 408 pg/ml in patients with the restrictive filling pattern, the mitral Doppler pattern most often associated with elevated LV end-diastolic pressures. In patients with normal EF, a high BNP level usually meant diastolic dysfunction. In the ED setting this may be true as well. In the setting of dyspnea in which LV function is normal, a BNP level <100 pg/ml gave a negative predictive value of 96%.

With few exceptions, NS-CHF has not been shown to be distinguishable from S-CHF solely on the basis of history, physical examination, chest X-ray, and electrocardiogram (1–3,26). Recently, Thomas et al. collected data on 225 patients hospitalized with CHF and found that differences in clinical parameters could not predict systolic function in these patients (26); the investigators suggested that specialized tests of ventricular function were needed. The present study supports these data in that of all historical and physical examination variables, only an absent history of myocardial infarction or heart failure, an absent third heart sound, and a high systolic blood pressure and lower heart rate were more predictive of NS-CHF than S-CHF. B-type natriuretic peptide levels are higher in patients with S-CHF than in those with NS-CHF, possibly reflecting an association with greater pathology in patients presenting with S-CHF, as reflected by their higher NYHA classifications. As the BNP level rises, the positive predictive value for S-CHF also increases, so that a BNP level >400 pg/ml offers a 72% likelihood that a patient will have S-CHF. However, the marked overlap in BNP values clearly limits its usefulness in separating the two groups in the clinical setting.

The importance of differentiating patients with NS-CHF from those with S-CHF lies in the underlying etiology and the subsequent treatment of the individual patient. Abnormal NS-CHF can be precipitated by ischemia, abnormally high blood pressure, or atrial fibrillation, all of which would receive different workups and treatment than used for patients with S-CHF, who are more likely to be admitted to the hospital and receive parenteral vasodilator and/or inotropic therapy. The BNP levels clearly cannot substitute for measurements of LV function and should not be considered a surrogate for echocardiography.

In the future, BNP levels may provide a surrogate end point for the evaluation of various treatments of heart failure. Falling BNP levels with treatment is associated with falling wedge pressures, a lower readmission rate to the hospital, and a better prognosis (21,27). Thus, monitoring BNP levels in future treatment protocols for NS-CHF may provide valuable information regarding drug efficacy and patient outcomes.

Study limitations. Echocardiographic recordings form the basis for differentiating between S-CHF and NS-CHF in the current study. Only 710 of the 1,586 patients (45%) enrolled in the Breathing Not Properly multinational study received echocardiograms within 30 days of their ED visit. Numerous previous reports have validated the ability of cardiac ultrasonography to detect abnormalities of contractile function and to quantitate LV volumes and EF (28,29). All patients in this study so designated had clear-cut evidence of LV systolic dysfunction. Although diastolic dysfunction implies an abnormal relationship between LV volume and pressure, echocardiography is capable of assessing only parameters related to volume. As Doppler param-

eters such as transmitral and pulmonary venous flow velocities were not always recorded and provide only indirect measurements of diastolic performance, they were not evaluated in the context of the present study. We also used a cutoff of 30 days for echocardiography, which meant that the study might not have reflected the actual status in the ED (30).

We conclude that BNP is a useful test to distinguish patients with heart failure from those without heart failure. This utility extends to the group with NS-CHF, in whom the diagnosis is more difficult and often incorrectly excluded when the presence of normal LV systolic function is known. However, BNP cannot reliably distinguish S-CHF from NS-CHF. Thus, a measurement of LV function is required to make this distinction and guide therapy accordingly.

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REFERENCES

1. Khandelwal A, McKinnon JE, Shenkman HJ, et al. Epidemiology of systolic and diastolic dysfunction heart failure in 3,471 urban patients (abstr). J Am Coll Cardiol 2002;39:192A.
2. Bonow R, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Ann Intern Med 1992;117:502–10.
3. Cregler LL, Georgiou D, Sosa I. Left ventricular diastolic dysfunction in patients with congestive heart failure. J Natl Med Assoc 1991;83:49–52.
4. Grodecki PV, Klein AL. Pitfalls in the echo-Doppler assessment of diastolic dysfunction. Echocardiography 1993;10:213–34.
5. Cheung BMY, Kumana CR. Natriuretic peptides—relevance in cardiac disease. JAMA 1998;280:1983–4.
6. Maeda K, Takayoshi T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825–32.
7. Clerico A, Iervasi G, Chicca M, et al. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. J Endocr Invest 1998;21:170–9.
8. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide (BNP) in the diagnosis of CHF in an urgent care setting. J Am Coll Cardiol 2001;37:379–85.
9. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin. Circulation 1998;97:1921–9.
10. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509–16.
11. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9–13.
12. Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1347–51.
13. Yamamoto K, Burnett JC, Jr., Jougasaki M, et al. Superiority of brain natriuretic peptide is related to diastolic dysfunction in hypertension. Clin Exp Pharmacol Physiol 1997;24:966–8.
14. Yu CM, Sanderson JE, Shum IOL, et al. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Eur Heart J 1996;17:1694–702.
15. Maisel AM, Krishnaswamy P, Nowak R, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure: primary results from the Breathing Not Properly (BNP) Multinational study. Presented at ACC meeting, Atlanta, March 17–20, 2002.
16. Morrison KL, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel AS. Utility of a rapid B-natriuretic peptide (BNP) assay in differentiating CHF from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002;39:202–9.
17. Mair J, Hammerer-Lercher A, Puschefort B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571–88.
18. Luchi RJ, Snow E, Luchi JM, et al. Left ventricular function in geriatric patients. J Am Geriatric Soc 1982;30:700–5.
19. Wong WF, Gold S, Fukuyama O, Blanchette PL. Diastolic dysfunction in elderly patients with congestive heart failure. Am J Cardiol 1989;63:1526–8.
20. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide (BNP in elucidating left ventricular dysfunction (systolic and diastolic) in patients with and without symptoms of congestive heart failure at a Veterans hospital. Am J Med 2001;111:274–9.
21. Cheng VL, Krishnaswamy P, Kazanegra R, Garcia A, Gardetto N, Maisel AS. A rapid bedside test for B-type natriuretic peptide predicts treatment outcomes in patients admitted with decompensated heart failure. J Am Coll Cardiol 2001;37:386–91.
22. Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide (BNP) predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002;39:131–8.
23. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide (BNP) in elucidating left ventricular dysfunction (systolic and diastolic) in patients with and without symptoms of congestive heart failure at a Veterans hospital. Am J Med 2001;111:274–9.
24. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide (BNP) as a rapid, point-of-care test for screening patients undergoing echocardiography for left ventricular dysfunction. Am Heart J 2001;141:367–74.
25. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002;105:595–601.
26. Thomas JT, Russel JT, Thomas SJ, et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. Am J Med 2002;112:437–45.
27. Sodian R, Loebe M, Schmitt C, et al. Decreased plasma concentration of brain natriuretic peptide as a potential indicator of cardiac recovery in patients supported by mechanical circulatory assist systems. J Am Coll Cardiol 2001;38:1942–9.
28. Remme WJ, Swedberg K. Guidelines for the diagnosis of treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
29. Schiller NB, Acquatella H, Ports TA, et al. Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation 1979;60:547–55.
30. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17–22.

APPENDIX

Breathing Not Properly Multinational Study Investigators: University of California, San Diego, Veterans Affairs Medical Center, San Diego, CA: Study Principal

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