Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 2, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01156-6

Utility of B-Type Natriuretic Peptide in the Diagnosis of Congestive Heart Failure in an Urgent-Care Setting

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OBJECTIVES The goal of this study was to evaluate the utility of a rapid "bedside" technique for measurement of B-type natriuretic peptide (BNP) in the diagnosis of congestive heart failure (CHF) in an urgent-care setting.

BACKGROUND B-type natriuretic peptide is a protein secreted from the cardiac ventricles in response to pressure overload. One potential application of measurements of BNP in blood is distinguishing dyspnea due to CHF from other causes.

METHODS B-type natriuretic peptide concentrations were measured in a convenience sample of 250 predominantly male (94%) patients presenting to urgent-care and emergency departments of an academic Veteran's Affairs hospital with dyspnea. Results were withheld from clinicians. Two cardiologists retrospectively reviewed clinical data (blinded to BNP measurements) and reached a consensus opinion on the cause of the patient's symptoms. This gold standard was used to evaluate the diagnostic performance of the BNP test.

RESULTS The mean BNP concentration in the blood of patients with CHF ($n = 97$) was higher than it was in patients without ($1{,}076 \pm 138$ pg/ml vs. 38 ± 4 pg/ml, $p < 0.001$). At a blood concentration of 80 pg/ml, BNP was an accurate predictor of the presence of CHF (95%); measurements less than this had a high negative predictive value (98%). The overall C-statistic was 0.97. In multivariate analysis, BNP measurements added significant, independent explanatory power to other clinical variables in models predicting which patients had CHF. The availability of BNP measurements could have potentially corrected 29 of the 30 diagnoses missed by urgent-care physicians.

CONCLUSIONS B-type natriuretic peptide blood concentration measurement appears to be a sensitive and specific test to diagnose CHF in urgent-care settings. (J Am Coll Cardiol 2001;37:379–85)

Differentiating congestive heart failure (CHF) from other causes of dyspnea is of extreme importance in patients presenting to the emergency department with acute shortness of breath. But symptoms and physical exam findings are not sensitive enough to make an accurate diagnosis (1), and, although echocardiography is considered the gold standard for detecting left ventricular (LV) dysfunction, it is expensive, not easily accessible and may not always reflect an acute condition (2). Currently, no blood test can differentiate a patient with heart failure from a patient without heart failure (3).

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the cardiac ventricles as a response to ventricular volume expansion and pressure overload (4,5). B-type natriuretic peptide levels have been shown to be elevated in patients with LV dysfunction and correlate to New York Heart Association class as well as prognosis (6,7). Although plasma BNP appears to be stable in whole blood and relatively straightforward to assay, until recently its utility as a diagnostic aid in the urgent-care setting has been limited by protracted assay time (8).

Using a rapid (15 min), point-of-care test for BNP (Biosite Diagnostics, San Diego, California), we sought to determine if BNP levels could have an impact on the diagnosis of CHF in the urgent-care setting.

METHODS

Study population. The study was approved by the University of California's Institutional Review Board. A convenience sample of 250 patients presenting to the urgent-care area of the San Diego Veteran's Health Care System with symptoms of dyspnea were recruited in June and October 1999. Eligibility included shortness of breath as a prominent complaint. Associated symptoms could be edema, weight gain, cough or wheezing. Patients whose dyspnea was clearly not secondary to CHF (trauma or cardiac tamponade) were excluded. Patients with acute coronary syndromes were excluded unless their predominant presentation was CHF.

A review of medical billing forms from the recruitment period found that 438 patients with relevant medical diag-

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Manuscript received June 14, 2000; revised manuscript received September 20, 2000, accepted October 26, 2000.

Abbreviations and Acronyms

ANP	= atrial natriuretic peptide
BNP	= B-type natriuretic peptide
CHF	= congestive heart failure
LV	= left ventricle, left ventricular
NPV	= negative predictive value

noses were treated during the study (Internal Classification of Disease Revision 9 codes of 428.09 [CHF], 428.1 [left heart failure], 496 [chronic airway obstruction], 782 [edema], 786.05 [shortness of breath] or 786.09 [dyspnea]). The rate of refusal of patients approached for entry was <5%.

Once consent was obtained, other data was recorded, including elements from the history, physical exam, reports of blood tests and interpretations of chest X-rays or other diagnostic tests. Echocardiograms were strongly encouraged, either in the emergency department, as an outpatient or in the hospital if the patient was admitted.

Physicians assigned to the emergency department (specialists or general medicine internists) were asked to make an assessment of the probability of the patient having CHF (low, medium and high) as the cause of his or her symptoms and were blinded to the results of BNP measurements. If a patient had a history of CHF noted, physicians would classify the patient as having either an acute exacerbation of CHF or low probability CHF, with underlying LV dysfunction (i.e., someone with LV dysfunction but seen for bronchitis).

Confirmation of the diagnosis. To determine patients actual diagnosis, two cardiologists reviewed all medical records pertaining to the patient and made independent initial assessments of the probability of each patient having CHF (high or low or low plus baseline LV dysfunction) and were blinded to the patient's BNP level. While blinded to the emergency department physicians' diagnosis, cardiologists had access to the emergency department data sheets as well as to any additional information that later became available. This might include: official reading of chest X-ray, past history not available at the time for the emergency department physicians, the results of subsequent tests to measure systolic or diastolic function and, finally, the hospital course for patients admitted to the hospital. Confirmation of high-probability CHF 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. 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 or left ventriculography done at cardiac catheterization; abnormal pulmonary function tests or follow-up in pulmonary clinic; response to treatment in the emergency department or hospital with nebulizers, steroids or antibiotics; no CHF admissions over the next 30 days. In the cases where cardiologists disagreed on the diagnosis or severity of CHF, further tests were ordered until a consensus was reached.

Measurement of BNP plasma levels. During initial evaluations, a small sample (5 cc's) was collected into tubes containing potassium EDTA (1 mg/ml blood). B-type natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide test (Biosite Diagnostics Inc., San Diego, California). The Triage BNP Test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. After addition of the blood sample to the sample port of the test device, the red blood cells were separated from the plasma via a filter. A predetermined quantity of plasma moves by capillary action into a reaction chamber to form a reaction mixture. After the incubation period, the reaction mixture flows through the device detection lane. Complexes of BNP and fluorescent antibody conjugates are captured on a discrete zone in the detection lane. Excess plasma sample washes the unbound fluorescent antibody conjugates from the detection lane into a waste reservoir. The concentration of BNP in the specimen is proportional to the fluorescence bound in the detection lane and was quantified by the portable triage meter. When possible, BNP levels were measured in whole blood and processed within 4 h. When this was not possible, samples were spun down, and the plasma was frozen until the sample was analyzed (one to two days later), an approach known to produce well-calibrated results with whole blood sample methods.

Statistics. Group comparisons of BNP values were made using *t* tests for independent samples and analyses of variance. Log-transformed BNP values were used in all analyses to reduce effects from skewness in the distribution of BNP concentrations.

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 emergency department 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 stepwise logistic regression. We developed the best predictive model based on historical, clinical and X-ray findings, using a p value $\geq$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. To determine if BNP measurements could improve the diagnostic performance of emergency department clinicians, we compared receiver curves for various BNP cutoff concentrations with the emergency department clinician's diagnosis.

Table 1. Characteristics of the 250 Patients

Characteristics	Percentage of Total Patients
Age	63 ± 0.86
Gender: male/female	94:6
History	
CHF	30%
CAD	40%
COPD	36%
Symptoms	
Shortness of breath at rest	50%
Dyspnea on exertion	70%
Orthopnea	26%
Paroxysmal nocturnal dyspnea	26%
Edema	46%
Physical exam	
Rales	34%
Wheeze	27%
JVP elevation	19%
Murmurs	20%
Systolic blood pressure >149	28%
S3	8%
S4	5%

CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; JVP = jugular venous pressure.

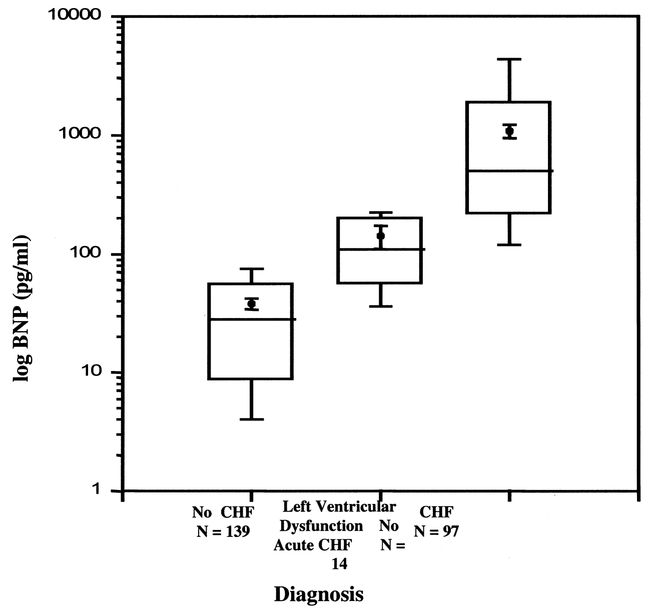

Figure 1. B-type natriuretic peptide levels of patients diagnosed with CHF, baseline left ventricular dysfunction and without CHF. BNP = B-type natriuretic peptide; CHF = congestive heart failure.

RESULTS

The characteristics of the 250 patients are shown in Table 1. Fifty percent of patients had acute shortness of breath at rest as a presenting complaint.

Final cardiology assessment revealed that ninety-seven patients (39%) had acute CHF as a cause of their dyspnea, while fourteen patients (6%) had baseline LV dysfunction with no acute exacerbation of their heart failure. The remaining 139 (55%) had a cause other than CHF for their dyspnea.

Association of BNP levels with diagnosis, severity, physical examination findings and disposition. Figure 1 presents a box plot of log BNP values with means and standard errors for the "no CHF" and the "CHF" groups. The group difference was significant ($p < 0.001$). Patients diagnosed with CHF ($n = 97$) had a mean BNP concentration of 1,076 ± 138 pg/ml while the non-CHF group ($n = 139$) had a mean BNP concentration of 38 ± 4 pg/ml. The group of 14 identified as baseline ventricular dysfunction without an acute exacerbation had a mean concentration of 141 ± 31 pg/ml.

Figure 2 shows BNP values in relation to CHF severity, admission versus no admission from the emergency department, pulmonary disease and pedal edema. Median BNP concentrations increased as the assessed severity of disease increased (Fig. 2A, $p < 0.001$ for differences between groups). B-type natriuretic peptide concentrations were higher for patients admitted to the hospital versus discharged patients (700 ± 116 pg/ml vs. 254 ± 60 pg/ml, $p < 0.001$; Fig. 2B). Patients with a final diagnosis of pulmonary disease without underlying heart dysfunction (Fig. 2C) had lower BNP values (86 ± 39 pg/ml) than those with a final diagnosis of CHF (1,076 ± 138 pg/ml, $p < 0.001$). Finally, mean BNP concentrations were higher for patients with pedal edema secondary to CHF (1,038 ± 163 pg/ml, Fig. 2D) than those with pedal edema due to non-CHF causes (63 ± 16 pg/ml, $p < 0.001$).

Association between BNP levels and final diagnosis. Univariate analysis was performed for all variables pertinent to a diagnosis of CHF, along with BNP concentrations at 80, 100, 115, 120 and 150 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 (81% accuracy) followed by heart size on chest X-ray (75% accuracy). B-type natriuretic peptide was an accurate predictor of patient diagnosis. Accuracy appeared to be optimal at a concentration of 80 pg/ml.

In multivariate analyses, we evaluated the combined explanatory power of history, symptoms, signs, radiological studies and lab findings (Table 3). 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.

A receiver operating characteristic curve, shown in Figure 3, shows the sensitivity and specificity of BNP measurements and compares this to the treating physician's judgment. Although the treating physicians performed well (C-statistic of 0.884), BNP concentration measurements appeared to have better overall performance (C-statistic of 0.979). In the subgroup of patients without a prior history of CHF, BNP again gave a better overall performance than treating physicians (C-statistic of 0.94).

Fifteen patients were diagnosed as having CHF by the

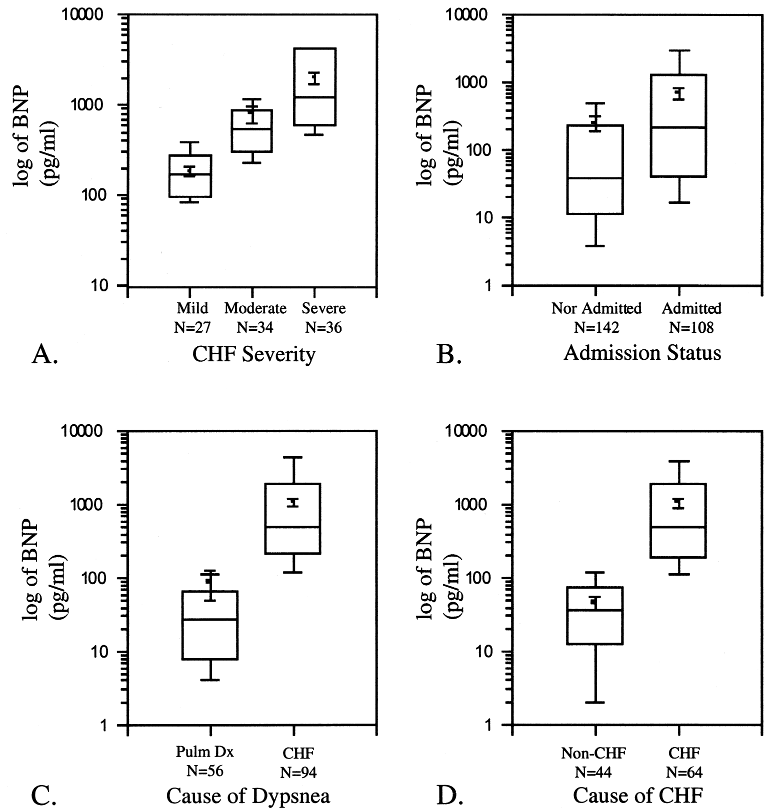

Figure 2. **(A)** BNP concentrations for the degree of CHF severity. **(B)** Hospital admission versus BNP. **(C)** BNP levels in patients with dyspnea secondary to CHF or chronic obstructive lung disease. **(D)** BNP levels in patients with edema diagnosed with CHF or non-CHF. **Boxes** represent mean and interquartile range. **Vertical line without a dot** represents a range from 10% to 90%. A **dot with a line** represents the mean and SEM. Values shown represent the mean (SEM). BNP = B-type natriuretic peptide; CHF = congestive heart failure; Dx = diagnosis.

emergency department physicians when they actually had other causes of their dyspnea. The mean BNP level in this group was 46 ± 13 pg/ml. Fifteen patients with the ultimate diagnosis of CHF were not diagnosed correctly at the time of their visit. In this group, the mean BNP was 742 ± 337 pg/ml. If a cutoff value of 80 pg/ml had been utilized, twenty-nine of thirty misdiagnosed cases would have been corrected.

DISCUSSION

Difficulty in the emergency department diagnosis of heart failure. Because patients with LV dysfunction have improved survival and increased well-being on medications such as angiotensin-converting enzyme inhibitors and beta-adrenergic blocking agents (10), it is imperative to make a correct diagnosis. For the acutely ill patient presenting to the emergency department, a misdiagnosis could place the patient at risk for both morbidity and mortality (11). Therefore, the emergency department diagnosis of CHF needs to be rapid and accurate.

Unfortunately, the signs and symptoms of CHF are nonspecific (1). A helpful history is not often obtainable 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 (2). Routine lab values, electrocardiograms and X-rays are also not accurate enough to always make the appropriate diagnosis (1,12). Thus, it is difficult for clinicians to differentiate patients with CHF from other diseases, such as pulmonary disease, on the basis of routinely available laboratory tests.

Echocardiography, although currently the gold standard in diagnosing LV dysfunction, is costly and has limited availability in urgent-care settings. Dyspneic patients may be unable to hold still long enough for an echocardiographic study, and others may be difficult to image secondary to comorbid factors such as obesity or lung disease. Therefore, even in settings where emergency department echocardiography is available, an accurate, sensitive and specific blood test for heart failure would be a useful addition to the clinical armamentarium.

BNP. B-type natriuretic peptide is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides (13). The source of plasma BNP is cardiac ventricles, which suggests that it may be a more specific indicator of ventricular disorders than other natriuretic peptides (3–5,14). The nucleic acid sequence of the BNP gene contains the destabilizing sequence "tatttat," which suggests that turnover of BNP messenger RNA is high and that BNP is synthesized in bursts (4,15). This release appears to be directly proportional to

Table 2. Univariate Analysis of Variables

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy (%)
History					
CHF	62 (52–71)	94 (88–97)	87 (77–93)	78 (71–84)	80
MI	38 (29–48)	78 (71–85)	55 (43–67)	64 (57–71)	62
HTN	46 (34–59)	55 (47–63)	34 (24–44)	68 (58–76)	52
COPD	34 (25–44)	63 (54–70)	39 (29–50)	58 (49–65)	51
DM	40 (31–51)	81 (74–87)	60 (47–72)	66 (59–73)	64
Symptoms					
Dyspnea	56 (45–66)	53 (45–62)	45 (36–55)	63 (54–72)	54
Dyspnea on exertion	81 (72–88)	37 (29–45)	47 (40–55)	74 (62–83)	55
Orthopnea	47 (37–58)	88 (82–93)	74 (61–84)	71 (63–77)	72
Paroxysmal nocturnal dypsnea	38 (29–48)	81 (74–87)	59 (46–71)	65 (58–72)	64
Cough	42 (33–53)	60 (51–68)	42 (33–53)	60 (51–68)	53
Edema	67 (57–76)	68 (60–76)	60 (50–69)	75 (66–82)	68
Signs					
SB > 149	28 (20–39)	73 (65–80)	42 (30–54)	59 (51–66)	54
SB < 100	6 (3–13)	97 (93–99)	60 (21–93)	60 (53–66)	60
JVP elevated	39 (30–50)	94 (88–97)	81 (67–90)	69 (62–75)	72
Rales	56 (45–66)	80 (72–86)	66 (55–76)	72 (64–79)	70
Wheezing	23 (15–32)	68 (60–76)	33 (23–46)	56 (48–63)	50
Ascites	1 (0–6)	97 (93–99)	20 (19–85)	58 (52–65)	58
S3	20 (13–29)	99 (95–100)	90 (69–100)	64 (57–70)	66
S4	7 (3–14)	96 (92–99)	58 (24–88)	60 (53–66)	60
Murmurs	32 (23–42)	90 (84–94)	69 (53–82)	66 (58–72)	66
Chest x-ray and ECG					
Heart size	88 (75–95)	72 (65–78)	45 (35–56)	96 (91–98)	75
PVH	41 (32–52)	96 (91–98)	87 (74–95)	70 (63–76)	73
ST elevation	6 (3–13)	97 (98–99)	60 (21–93)	60 (53–66)	60
ST depression	12 (7–21)	93 (87–96)	55 (31–76)	60 (53–67)	60
Afib	8 (4–16)	99 (96–100)	89 (48–107)	61 (54–67)	62
BNP levels (pg/ml)					
80	98 (93–100)	92 (86–96)	90 (82–94)	98 (94–100)	95
100	94 (89–97)	94 (89–97)	92 (85–96)	96 (91–98)	94
115	90 (83–95)	96 (91–98)	94 (87–97)	94 (88–97)	94
120	90 (82–95)	96 (92–99)	95 (88–98)	93 (88–96)	94
150	87 (78–92)	97 (93–99)	95 (89–98)	91 (85–95)	93

Afib = atrial fibrillation; BNP = B-type natriuretic peptide; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ECG = electrocardiogram; HTN = hypertension; MI = myocardial infarction; PVH = pulmonary venous hypertension; SB = systolic blood pressure.

ventricular volume expansion and pressure overload (4–7,16). B-type natriuretic peptide is an independent predictor of high LV end-diastolic pressure (6) and correlates to New York Heart Association classification (7).

BNP as a screen of CHF. B-type natriuretic peptide has been used to a limited extent as a screening procedure in primary care settings and in this venue has been shown to be a useful addition in the evaluation of possible CHF (17–20). In a community-based study where 1,653 subjects underwent cardiac screening, the negative predictive value of BNP of 18 pg/ml was 97% for LV systolic dysfunction (19). In a study of 122 consecutive patients with suspected new heart failure referred by general practitioners to a rapid-access heart failure clinic for diagnostic confirmation, a BNP level of 76 pg/ml, chosen for its negative predictive value of 98% for heart failure and similar to the cutoff in the present study, had a sensitivity of 97%, a specificity of 84% and a positive predictive value of 70% (17). Finally, Davis et al. (20) measured the natriuretic hormones atrial natriuretic peptide (ANP) and BNP in 52 patients presenting with acute dyspnea and found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction or concentration of plasma ANP.

Point-of-care testing of BNP in the urgent-care setting. Perhaps the reason BNP has not been used more often is that, until recently, the assay for BNP has been difficult to perform and is time-consuming. The assay used in this study is available in a form that could allow rapid determination of BNP levels at the point of care and, thus, could make a substantial difference in the management of patients presenting to the emergency department with dyspnea.

For diagnostic screening tests to be useful in an urgent-care setting, they should have a high negative predictive value (NPV), allowing clinicians to rapidly rule out serious disorders (21) and facilitate efficient use of valuable resources. In the population studied, a BNP of <80 pg/ml had a NPV of 98%, which would allow clinicians to exclude

Table 3. Multivariate Analysis Using All Significant Variables With BNP Analyzed Last for All 250 Cases and for Cases Where Patients Do Not Present With a History of CHF

Variable	Chi-square	Significance	Sensitivity (%)	Specificity (%)	Accuracy (%)
All 250 cases					
History of CHF	89.01	0	62	93	80
Heart size	31.96	0	77	91	85
Murmurs	19.24	0	77	91	85
Pulmonary venous hypertension	11.9	0.006	78	91	86
ECG—atrial fibrillation	9.06	0.0026	80	91	86
Pedal edema	9.96	0.0016	89	89	89
Orthopnea	6.37	0.0116	80	91	86
ECG—ST depression	4.46	0.0346	82	91	87
History of diabetes mellitus	4.32	0.0377	85	90	88
BNP	95.23	0	96	96	97
Cases without history of CHF					
Pulmonary venous hypertension	32.48	0	41	97	84
Murmurs	26.48	0	76	87	84
Jugular venous distension	11.71	0.006	51	97	87
ECG—atrial fibrillation	12.54	0.0004	49	98	87
ST depression	6.26	0.0124	57	98	89
ECG—T wave inversion	6.09	0.0136	68	97	90
Dyspnea on exertion	5.62	0.0178	81	92	90
History of angina	4.95	0.026	73	97	92
BNP	55.27	0	95	100	98

BNP = B-type natriuretic peptide; CHF = congestive heart failure; ECG = electrocardiogram.

CHF as a cause of symptoms in most circumstances. No single clinical finding had similar sensitivity, specificity and accuracy. And in multivariate analyses, BNP measurements added independent explanatory power when added to models predicting the presence of CHF from the best combination of clinical variables.

Study limitations. This is an observational study performed in a convenience sample of predominantly male patients at a Veteran's Affairs Medical Center. These factors limit generalizability of results observed in this study. As is often true with diagnostic tests, the performance of BNP measurements in other populations may not equal the performance seen in this initial study. A multicenter, international trial is underway (Breathing Not Proper in CHF) in attempt to further elucidate and confirm our findings in broader populations.

Conclusions. The measurement of the BNP concentration in blood appears to be a sensitive and specific test for the

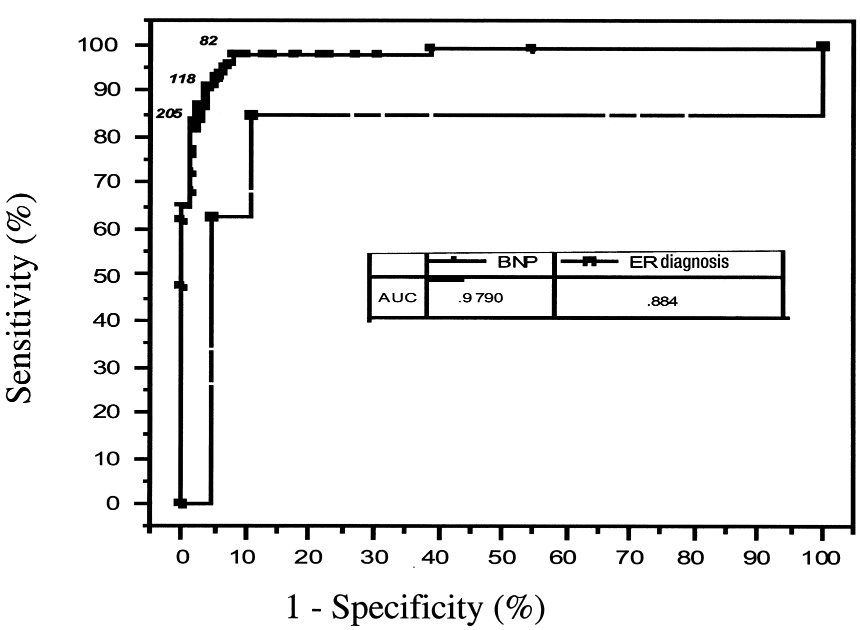

Figure 3. Receiver operating characteristic curves of BNP and emergency department diagnosis using all 250 patients. AUC = area under the curve; BNP = B-type natriuretic peptide; ER = emergency room.

identification of patients with CHF in urgent-care settings. If the results of this study are borne out in subsequent ones, this test may replace chest X-ray (and perhaps even echocardiography) as the test of choice in differential diagnosis of dyspnea in urgent-care settings. At the minimum, it is likely to be a potent, cost-effective addition to the diagnostic armamentarium of urgent-care physicians.

Acknowledgments
The authors would like to thank the physicians and nursing staff working in the emergency department for their cooperation and support.

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