B-Type Natriuretic Peptide Predicts Future Cardiac Events in Patients Presenting to the Emergency Department With Dyspnea

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Study objective: B-Type natriuretic peptide (BNP) is a neurohormone secreted from the cardiac ventricles in response to volume expansion and pressure overload. We have recently demonstrated that BNP can differentiate congestive heart failure (CHF) from other causes of dyspnea in patients presenting to the emergency department. In this study, we assess whether BNP levels drawn in patients presenting with dyspnea to the ED were a predictor of future cardiac events.

Methods: In 325 patients presenting with dyspnea to the ED, BNP levels were determined. Patients were then followed up for 6 months to determine the following end points: death (cardiac and noncardiac), hospital admissions (cardiac), and repeat ED visits for CHF. Receiver operating characteristic (ROC) curves, relative risks (RRs), and Kaplan-Meier plots were used to assess the ability of BNP levels to predict future cardiac events.

Results: The area under the ROC curve using BNP to detect a CHF end point—a CHF death, hospital admission, or repeat ED visit—was 0.870 (95% confidence interval [CI] 0.826 to 0.915). A BNP value of 480 pg/mL had a sensitivity of 68%, specificity of 88%, and an accuracy of 85% for predicting a subsequent CHF end point. The area under the ROC curve using BNP to detect death from CHF was 0.881 (95% CI 0.807 to 0.954) and for any cardiac death was 0.877 (95% CI 0.822 to 0.933). BNP was not associated with death from noncardiac causes. Using Kaplan-Meier plots for all CHF events, rising BNP levels were associated with a progressively worse prognosis. Patients with BNP levels more than 480 pg/mL had a 51% 6-month cumulative probability of a CHF event. Alternatively, patients with BNP levels less than 230 pg/mL had an excellent prognosis with only 2.5% incidence of CHF end points. The RR of 6-month CHF death in patients with BNP levels more than 230 pg/mL was 24.1. The RR of 6-month noncardiac death with BNP levels more than 230 pg/mL was 1.1. BNP levels were also predictive of CHF events in subsets of patients with positive CHF histories and ED diagnoses.

Conclusion: In this study population, BNP levels measured in patients presenting with dyspnea to the ED are highly predictive of cardiac events over the next 6 months.

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INTRODUCTION

Improved and accurate biochemical testing in the urgent care setting can differentiate cardiac from noncardiac causes of chest pain, decreasing the incidence of a missed diagnosis of acute myocardial infarction.[1-4] No similar biochemical test is routinely used to differentiate cardiac from noncardiac causes of dyspnea, despite the morbidity and mortality of a missed diagnosis of congestive heart failure (CHF). This is especially troublesome because the physical examination and laboratory tests are often nonspecific for CHF.[5,6] The ideal biochemical marker for CHF would be rapidly measured, sensitive, and specific for the diagnosis and highly correlated with prognosis, making it valuable for risk stratification in the emergency department.

B-Type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the cardiac ventricles as a response to ventricular volume expansion and pressure overload.[7,8] BNP levels are elevated in patients with left ventricular dysfunction and correlate with New York Heart Association (NYHA) class and prognosis.[9-13] Recently, we found that a rapid BNP assay was both sensitive and specific for identification of patients with CHF in acute care settings.[14] In this study, we tested whether BNP levels drawn in patients presenting with dyspnea to the ED gave prognostic information over a 6-month follow-up period.

MATERIALS AND METHODS

The University of California Institutional Review Board approved the study. A convenience sample of 325 patients presenting with dyspnea to the ED were recruited from June 1999 through March 2000 at the San Diego Veterans Health Care System. To be eligible for the study, the patient had to have shortness of breath either at rest, with exertion, or on lying down as a prominent complaint. Patients whose dyspnea was clearly a result of trauma (eg, knife wounds, cardiac tamponade) were excluded. Patients with unstable angina or acute myocardial infarction (determined by ECG changes and cardiac enzymes) were excluded unless their predominant presentation was that of dyspnea.

To identify potential patients, a physician or a trained research assistant reviewed nurse descriptions of patients' principal complaints. Patients fitting the aforementioned criteria were queried regarding participation in the study. The rate of refusal of patients approached for entry was less than 5%.

When a patient was identified as presenting with the complaint of dyspnea, consent was obtained, and a blood sample was collected for purposes of measuring the patient's BNP level. The research assistant collected other data, including elements from the present and past history, the physical examination, and the patients' medications. A history of CHF was determined by objective criteria (echocardiography) documented in the patient's chart at the Veterans Affairs Medical Center or obtained from other treating institutions. Objective criteria were also required to have a history of chronic obstructive pulmonary disease (COPD) (eg, lung function tests, chest radiograph) and coronary artery disease (CAD) (eg, angiogram). Emergency physicians were asked to code whether they thought the patient had a high or low probability of CHF being the primary cause of the patient's dyspnea. The emergency physician coded his suspected probability after a full workup (chest radiograph, ECG, response to treatment) of the patient, but was blinded to the initial BNP level. The physician also documented his final diagnosis before admission or discharge.

Patients were followed up for 6 months from the time they presented to the ED. Follow-up was either by clinic visit, computerized chart review, or telephone call if no contact had occurred within the 6-month period. All 325 patients received follow-up. End points were defined as death (any cardiac, noncardiac, and CHF), hospital admissions (any cardiac and CHF), and repeat ED visits for CHF. A CHF end point was defined as a CHF death, admission, or repeat ED visit. A cardiac end point was defined as a cardiac (including CHF) death or admission. CHF admissions were determined by a cardiologist (blinded to BNP values), explicit chart review of admission criteria, and hospital course. The same was done for cardiac admissions such as CHF, acute myocardial infarction, arrhythmias, angina, and CAD. The cause of death was determined by autopsy report if present, clinical scenario leading up to death (reviewed by a cardiologist blinded to BNP values), and death certificate if the previous data were not available.

As soon as a patient was determined to be eligible for the study, consent was obtained. Blood was drawn before the administration of any treatment, with the exception of oxygen that may have been administered in cases in which the patient had a low O_2 saturation. All samples were collected

by venipuncture into tubes containing ethylenediaminetetraacetic acid (EDTA). The blood samples were kept at room temperature and analyzed within 4 hours of the draw time. The whole blood was then analyzed in triplicate with the Triage BNP assay (Biosite, Inc., San Diego, CA), and an average was obtained.

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 (Biosite, Inc.) is used to measure the BNP concentration by detecting a fluorescent signal that reflects the amount of BNP in the sample. The assay results are completed within 15 minutes. Information regarding the precise mechanism, sensitivity, precision, interferences, and stability can be found in Wieczorek et al.[15]

All comparisons were calculated using log-transformed BNP concentrations to minimize the skew of the distribution. To evaluate the utility of BNP measurements as a prognostic indicator of future cardiac events, we used receiver operating characteristic (ROC) curves to determine the sensitivity, specificity, and accuracy of these BNP levels and relative risks (RRs) and Kaplan-Meier survival curves to demonstrate risk stratification. The ability of BNP to predict 6-month CHF end points in patients presenting with dyspnea to the ED was assessed with ROC analysis providing area under the curve (AUC) values, sensitivity, specificity, and accuracy. The ability of BNP to predict 6-month mortality was also assessed with ROC analysis comparing the ability of BNP levels to predict CHF, cardiac, and noncardiac deaths. Reverse Kaplan-Meier plots were used to illustrate the 6-month prognosis of the patients stratified by BNP cut points. These cut points were computer generated from the ROC curves at points at which large changes in the sensitivity and/or specificity were seen. RR values were used to compare the prognostic value of several variables (age, medications, medical history, and BNP levels). We were then able to evaluate the prognostic value BNP levels displayed by quantitatively assessing whether or not these values offered additional prognostic information.

RESULTS

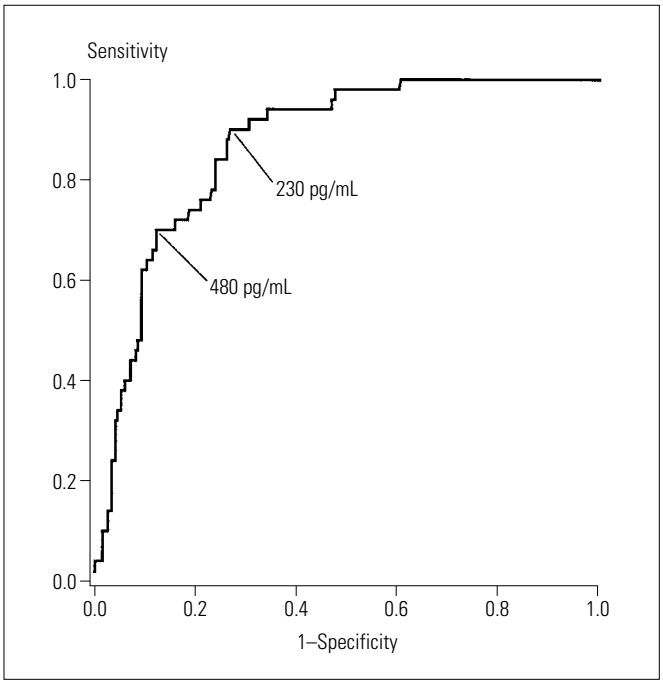
Table 1 shows the demographics of the patient population. Most were men, with an average age of 65 years. Equal numbers of patients had histories of pulmonary disease (40%) and CHF (41%), and 18% of patients had histories of both pulmonary disease and CHF. About half the patients (46%) were taking angiotensin-converting enzyme (ACE) inhibitors and half (53%) were taking bronchodilators.

The ability of BNP to predict a 6-month CHF end point in patients presenting with dyspnea to the ED was assessed with ROC analysis (Figure 1). The area under the ROC curve using BNP to detect a CHF end point was 0.870 (95% confidence interval [CI] 0.826 to 0.915). A BNP value of 480 pg/mL had a sensitivity of 68%, specificity of 88%, and an accuracy of 85% for predicting a subsequent

Table 1.
Patient demographics.

Demographic Characteristic	Value
Men, %	95
Mean age, y (range)	65 (29–93)
History of CHF, %	41
History of COPD, %	40
History of CHF and COPD, %	18
History of CAD, %	54
ACE inhibitors, %	46
Diuretics, %	51
Pulmonary medication, %	53
Admission at initial visit, %	43

Figure 1.
ROC curve for the ability of BNP to predict a 6-month CHF end point (ED visit or hospitalization for CHF or death from CHF) in patients presenting with dyspnea to the ED.



CHF end point. The ability of BNP to predict 6-month mortality was also assessed with ROC analysis (Figure 2). There were 23 cardiac deaths, including 15 CHF deaths, and 13 noncardiac deaths. The area under the ROC curve using BNP to detect death from CHF was 0.881 (95% CI 0.807 to 0.954). The area under the ROC curve using BNP to detect any cardiac death was 0.877 (95% CI 0.822 to 0.933). BNP was not associated with death from noncardiac causes.

Figure 3 shows a reverse Kaplan-Meier plot for all CHF events stratified by BNP levels determined by ROC cut points. These cut points are BNP values that were generated by the computer at points at which large changes in the sensitivity and/or specificity were seen. This shows that increased BNP levels were associated with a progressively worse prognosis. Patients (N=67) who presented to the ED with BNP levels more than 480 pg/mL had a 51% 6-month cumulative probability of a CHF event, and 35% of patients in this group had a CHF death as their event. Alternatively, patients (N=205) who presented to the ED with BNP levels less than 230 pg/mL had an excellent prognosis, with only 2.5% cumulative probability of CHF end points.

Table 2 gives the number of patients, average BNP levels, and the RRs for each end point classification at the cut point of 230 pg/mL. The cut point of 230 pg/mL was used because it avoided many of the false-negatives that the cut point of 480 pg/mL demonstrated. BNP levels more than 230 pg/mL yielded a RR of 37.9 and 24.1 for a cardiac and CHF death within 6 months, respectively. The RR for 6-month noncardiac death with BNP levels more than 230 pg/mL was not statistically significant (1.1).

Table 3 gives the RRs of having a CHF end point within 6 months associated with various background, treatment, diagnostic, and BNP indicators. Increased risks were associated with each of these indicators except for sex, history of COPD, treatment with ACE inhibitors, and treatment with pulmonary medications. The greatest RRs were noted for a cardiologist diagnosis of CHF (33.2), a history of CHF (16.5), and a BNP level of more than 230 pg/mL (15.5).

Figure 2.
ROC curves for the ability of BNP to predict 6-month mortality (from CHF, from any cardiac condition, or from noncardiac conditions) in patients presenting with dyspnea to the ED. There were 23 cardiac deaths, including 15 CHF deaths, and 13 noncardiac deaths.

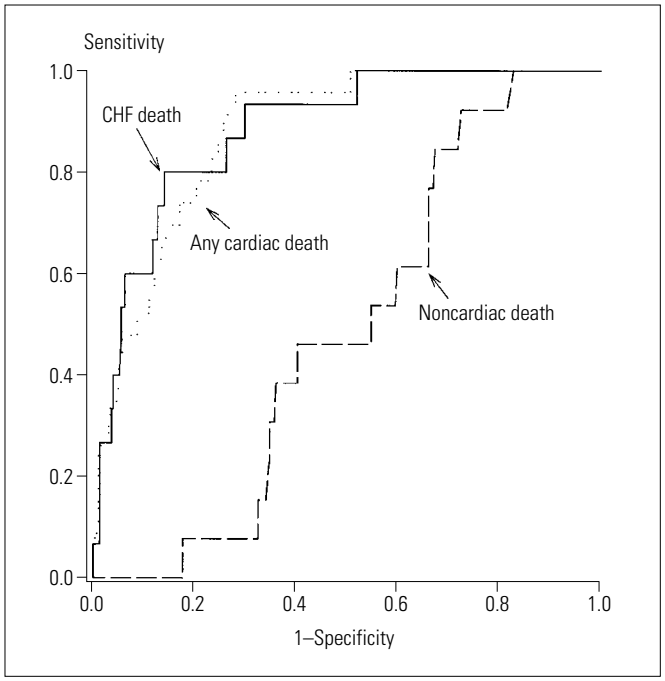
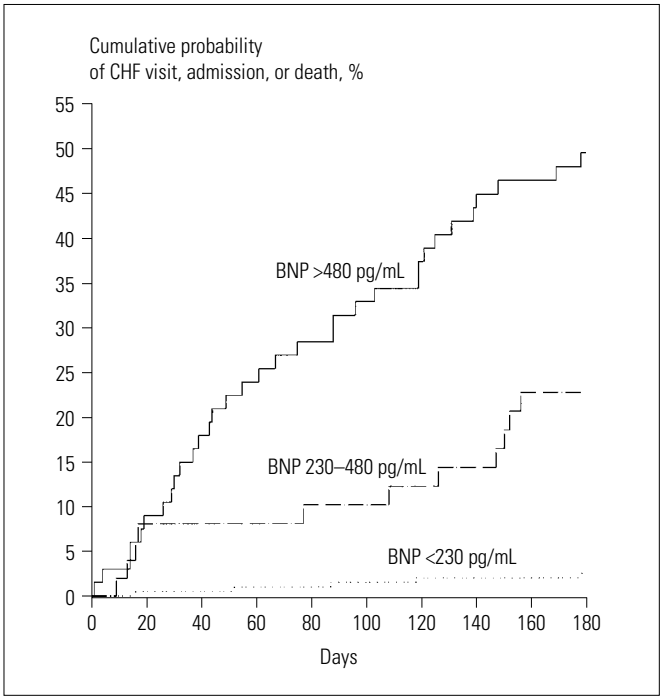


Figure 3.
Reverse Kaplan-Meier plot showing cumulative risk of any CHF event (ED visit/hospitalization for CHF or death from CHF), stratified by BNP levels. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels more than 480 pg/mL had a 6-month cumulative probability of a CHF event of 51%. Patients with BNP levels less than 230 pg/mL had only a 2.5% probability of a CHF event.



The indicators demonstrating a large (RR >3) increased risk of a 6-month CHF event were then analyzed in combination with BNP values to assess whether or not BNP levels provided additional prognostic value over and above these indicators. Both BNP values of 230 (Table 4) and 480 pg/mL (Table 5) did provide additional prognostic information, but again, as a result of fewer false-negative predictions, a BNP cut point of 230 pg/mL proved more accurate. Most interesting from this analysis was the scenario of an ED diagnosis other than CHF and a BNP level of more than 230 pg/mL that showed a RR of a CHF event within 6 months of 11.7. Also, when an emergency physician coded the risk of CHF being the primary cause of dyspnea as low and the BNP level was more than 230 pg/mL, the RR of a CHF event within 6 months was 39.4.

Table 2.
Mean BNP levels for each end point classification and RR of that end point for patients above a BNP cut point of 230 pg/mL.[*]

Group	No. of Patients[†]	Mean BNP (pg/mL)	Standard Error	RR	95% CI
CHF end point[‡]	50	1,033	162	15.5	6.2–43.7
Cardiac end point[§]	86	817	118	4.5	2.9–6.9
CHF death	15	1,547	366	24.1	3.5–491.1
Cardiac death	23	1,413	288	37.9	5.7–755.8
Noncardiac death[‖]	13	156	42	1.1	0.3–3.5
No end point	274	253	35		

[*]The RR for patients with BNP >230 pg/mL compared with those below this cut point. Patients above this cut point had 15.5 times greater risk of a CHF event than patients below this cut point.
[†]Some patients are represented in more than 1 end point category.
[‡]CHF end points include hospitalization or ED visit for CHF and death from CHF.
[§]Cardiac end points include CHF end points plus hospitalization or ED visit or death from ischemia or infarction.
[‖]Noncardiac deaths are deaths from all other causes.

DISCUSSION

Currently, in the United States, there are 4.7 million people with CHF, with an incidence rate of 550,000 new cases diagnosed each year.[16] Associated with substantial morbidity, CHF is the most frequent cause of hospitalization in the elderly, with 900,000 hospitalizations and 250,000 deaths each year.[17] Because of the tremendous total direct costs of care for heart failure, estimated at US$10 to $38 billion, the Health Care Financing Administration has targeted heart failure as the condition most worthy of cost-effective management.[18]

Table 3.
CHF events (hospitalization/ED visit for CHF or death from CHF) as a function of the presence of various clinical indicators.

	With Indicator			Without Indicator				
Indicator	No. of Patients	No. With Events	% With Events	No. of Patients	No. With Events	% With Events	RR	95% CI
Background								
Men	308	49	15.9	16	1	6.3	2.5	0.5–49.5
Age ≥65 y	171	34	19.9	153	16	10.5	1.9	1.1–3.5
CHF history	133	46	34.6	191	4	2.1	16.5	6.0–53.4
COPD history	129	19	14.7	195	31	15.9	0.9	0.5–1.6
Both CHF and COPD history	58	18	31.0	266	32	12.0	2.6	1.5–4.3
CAD history	176	39	22.2	148	11	7.4	3.0	1.5–6.0
Treatment								
ACE inhibitors	149	32	21.5	175	18	10.3	0.6	0.4–1.0
Diuretics	165	41	24.8	159	9	5.7	4.4	2.2–9.5
Pulmonary medication	170	26	15.3	154	24	15.6	1.0	0.6–1.7
Admission at initial visit	139	31	22.3	185	19	10.3	2.2	1.2–3.8
Diagnosis								
ED any cardiac diagnosis	191	42	22.0	133	8	6.0	3.7	1.7–8.3
ED CHF diagnosis	72	36	50.0	252	14	5.6	9.0	5.1–16.4
ED high CHF risk	80	38	47.5	243	12	4.9	9.6	5.2–18.4
Cardiologist CHF diagnosis	136	48	35.3	188	2	1.1	33.2	8.3–196.6
BNP level								
BNP >230 pg/mL	119	45	37.8	205	5	2.4	15.5	6.2–43.7
BNP >480 pg/mL	67	34	50.7	257	16	6.2	8.2	4.7–14.3

Unfortunately, the signs and symptoms of CHF are nonspecific, making the diagnosis of heart failure difficult.[5,6] Dyspnea, the major manifestation of heart failure, is a common complaint of the elderly or obese patient. When a severely ill patient presents to the ED, an accurate history is not always obtainable or reliable, and routine laboratory values, ECGs, and radiographs are often nondiagnostic.[19] It can be difficult for clinicians to differentiate patients with CHF from other diseases such as pulmonary disorders. In addition, in patients with medical histories positive for both CHF and COPD, determining the cause of severe dyspnea can be even more challenging. We showed that, in patients (N=58) with both histories of CHF and COPD, the RR of a CHF end point was decreased to 2.6 from 16.5 if the patient had a history of CHF alone. Compounding the potential diagnosis dilemma is the imperative of rapid and accurate diagnosis because the delayed diagnosis and implementation of proper treatment could place the patient at an increased risk for both morbidity and mortality. Although echocardiography is the current criterion standard in diagnosing left ventricular dysfunction,[16] it has limited availability in EDs. Furthermore, people at high risk for left ventricular dysfunction may have comorbidities, such as obesity and

Table 4.
CHF events (hospitalization/ED visit for CHF or death from CHF) as a function of the presence or absence of various clinical indicators and of BNP levels.

		BNP <230 pg/mL			BNP >230 pg/mL				
Indicator	Indicator Present	No. of Patients	No. With Events	% With Events	No. of Patients	No. With Events	% With Events	RR	95% CI
CHF history	No	160	0	0.0	31	4	12.9		
	Yes	45	5	11.1	88	41	46.6	4.2	1.8–11.6
ED CHF diagnosis	No	192	3	1.6	60	11	18.3	11.7	3.2–52.3
	Yes	13	2	15.4	59	34	57.6	3.7	1.2–21.9
ED cardiac diagnosis	No	112	3	2.7	21	5	23.8	8.9	2.0–45.1
	Yes	93	2	2.2	98	40	40.8	8.6	2.3–50.8
ED high CHF risk	No	190	1	0.5	53	11	20.8	39.4	5.6–816.9
	Yes	15	4	26.7	65	34	52.3	5.0	1.9–15.9
Cardiologist CHF diagnosis	No	176	2	1.1	12	0	0.0		
	Yes	29	3	10.3	107	45	42.1	4.1	1.4–16.0

Table 5.
CHF events (hospitalization/ED visit for CHF or death from CHF) as a function of the presence or absence of various clinical indicators and of BNP levels.

		BNP <480 pg/mL			BNP >480 pg/mL				
Indicator	Indicator Present	No. of Patients	No. With Events	% With Events	No. of Patients	No. With Events	% With Events	RR	95% CI
CHF history	No	183	3	1.6	8	1	12.5	7.6	0.3–73.8
	Yes	74	13	17.6	59	33	55.9	3.2	1.8–5.8
ED CHF diagnosis	No	228	7	3.1	24	7	29.2	9.5	3.2–27.6
	Yes	29	9	31.0	43	27	62.8	2.0	1.1–4.0
ED cardiac diagnosis	No	125	5	4.0	8	3	37.5	9.4	1.9–33.9
	Yes	132	11	8.3	59	31	52.5	6.3	3.4–12.3
ED high CHF risk	No	222	5	2.3	21	7	33.3	14.8	4.5–49.7
	Yes	34	11	32.4	46	27	58.7	1.8	1.1–3.4
Cardiologist CHF diagnosis	No	186	2	1.1	2	0	0.0		
	Yes	71	14	19.7	65	34	52.3	2.7	1.5–4.7

lung disease, that make accurate imaging of the heart more difficult. In addition, the patient with severe dyspnea may be unable to cooperate for a technically adequate echocardiographic study. Thus, even in settings where ED echocardiography is available, an accurate, sensitive, and specific blood test for heart failure would be a useful addition to the clinical armamentarium.[20]

BNP is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides.[8,21] Because the source of plasma BNP is the cardiac ventricles, it may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides.[7,11] 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.[11,22] This release appears to be directly proportional to ventricular volume expansion and pressure overload.[7,8]

Patients presenting with symptomatic left ventricular systolic dysfunction have elevated levels of BNP that also correlate to severity of disease.[8,21] BNP is also an independent, significant predictor of high left ventricular end-diastolic pressure in patients with CHF.[14,23] Finally, BNP levels have been highly predictive of outcomes in patients admitted for decompensated heart failure[13] and may be used to act as triggers or targets of medical therapy.[24]

The results of this study demonstrated that a high BNP level measured in the ED at presentation with dyspnea was predictive of subsequent adverse cardiac outcomes, including recurrent CHF and death by CHF or other cardiac causes. Very low BNP levels had a very high negative predictive value for future events. Our study demonstrated that a BNP level of less than 100 pg/mL is 98% accurate in negatively predicting a CHF event (The BNP cutoff for symptomatic CHF is 100 pg/mL.[*]). At a threshold of 100 pg/mL, BNP sensitivity is 82% and specificity is 95%. In a prior study of 250 patients presenting with dyspnea to the urgent care center, we found that a BNP level of less than 80 pg/mL had a 98% negative predictive value for the subsequent diagnosis of CHF.[14] Presumably, patients presenting with dyspnea and very low BNP levels had better prognosis because CHF was not the cause of their symptoms.

In the present study, patients with BNP levels of more than 480 pg/mL had a dismal prognosis, with a CHF event rate of 51% within 6 months of the initial presentation. When BNP levels were more than 230 pg/mL, the RRs for various cardiac end points ranged from 5 to 38. When assessing RRs, the cut point of 230 pg/mL was better suited because it avoided many of the false-negatives. However, a cut point of 480 pg/mL illustrated the severity of the patient's disease by demonstrating the poor 6-month prognosis seen in the reverse Kaplan-Meier plot (Figure 3). Because BNP levels increase with increasing left ventricular end-diastolic pressure and with progressive deterioration in NYHA class,[10,13,14,23] it is not surprising that the high levels obtained in the ED were associated with a poor prognosis. BNP has proved a predictor of mortality in other settings.[12,25-27]

This is an observational study performed in a convenience sample of predominantly male patients at a Veterans Affairs Medical Center and may not accurately represent the general demographics of patients presenting with dyspnea to other EDs. This limits the generalization of results observed in this study. The performance of BNP measurements in other populations may not equal the performance seen in this initial study.

In summary, delineating the cause of dyspnea can be difficult.[6,19] We have previously shown that BNP levels add substantial information when the diagnosis of CHF is considered.[14] The current findings substantiate that BNP levels are predictive of CHF events over a 6-month follow-up period. Thus, BNP levels are valuable in risk stratification and in diagnosis of CHF in the ED.

Author contributions: AH, PK, QD, and ASM conceived the study, designed the trial, and obtained research funding. AH, PK, QD, ASM, RK, KM, and PH supervised the conduct of the trial and data collection. PC and AH provided statistical advice on study design and analyzed the data; AH and ASM drafted the manuscript and all authors contributed substantially to its revision. ASM takes responsibility for the paper as a whole.

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