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)01157-8

A Rapid Bedside Test for B-Type Peptide Predicts Treatment Outcomes in Patients Admitted for Decompensated Heart Failure: A Pilot Study

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OBJECTIVES The goal of this study was to determine if B-type natriuretic peptide (BNP) levels predict outcomes of patients admitted with decompensated heart failure.

BACKGROUND Treatment of decompensated congestive heart failure (CHF) has often been based on titration of drugs to relieve patient's symptoms, a case that could be made for attempting to also treat neurohormonal abnormalities. Because BNP reflects both elevated left ventricular pressure as well as neurohormonal modulation, we hypothesized that BNP might be useful in assessing outcomes in patients admitted with decompensated CHF.

METHODS We followed 72 patients admitted with decompensated New York Heart Association class III to IV CHF, measuring daily BNP levels. We then determined the association between initial BNP measurement and the predischarge or premoribund BNP measurement and subsequent adverse outcomes (death and 30-day readmission).

RESULTS Of the 72 patients admitted with decompensated CHF, 22 end points occurred (death: n = 13, readmission: n = 9). In these patients, BNP levels increased during hospitalization (mean increase, 233 pg/ml, $p < 0.001$). In patients without end points, BNP decreased (mean decrease 215 pg/ml). Univariate analysis revealed that the last measured BNP was strongly associated with the combined end point. In patients surviving hospitalization, BNP discharge concentrations were strong predictors of subsequent readmission (area under the receiver operator curve of 0.73).

CONCLUSIONS In patients admitted with decompensated CHF, changes in BNP levels during treatment are strong predictors for mortality and early readmission. The results suggest that BNP levels might be used successfully to guide treatment of patients admitted for decompensated CHF.
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Heart failure is the leading cause of hospital admission among patients over the age of 65 years and accounts for 3% of the total national health care budget, 70% of which comes from hospitalization (1). Despite advances in treatment, patients admitted with decompensated heart failure have significant hospital mortality and early readmission rates (1–4). This stems, in part, from the fact that there are no reliable indicators of the adequacy of treatment (5,6).

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from membrane granules in the cardiac ventricles as a response to ventricular volume expansion and pressure overload (7–9). B-type natriuretic peptide levels have been shown to be elevated in patients with symptomatic left ventricular (LV) dysfunction and correlate to LV filling pressure, New York Heart Association (NYHA) classification and prognosis (10–12). Falling BNP levels reflect beneficial treatment but, until recently, had the same pitfalls of measurement as other neurohormones and cytokines (13–15).

Using a recently developed rapid BNP assay (Biosite Diagnostics, San Diego, California), we asked whether BNP levels might be useful in assessing therapeutic responses in patients admitted with decompensated congestive heart failure (CHF). To test this hypothesis, we observed the relationship between BNP measurements performed during hospitalization and serious adverse outcomes.

METHODS

Patients. Between March 1999 and December 1999, we identified a convenience sample of 72 male Veterans patients between 28 and 102 years old (mean age = 68 ± 1.6 years) who had been admitted for CHF (Table 1). Criteria for inclusion included new-onset CHF confirmed by at least one cardiologist using standard Framingham criteria or exacerbation of previously documented CHF. All patients had to be at least NYHA class III to be included. The initial BNP level had to be drawn within 24 h of admission and within 24 h of discharge or death to be included in the study. Informed consent was obtained from a protocol approved by the UCSD Institutional Review Board. Inability and unwillingness to consent to study participation were the only two criteria for exclusion. During this period,

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Manuscript received April 27, 2000; revised manuscript received September 20, 2000; accepted October 26, 2000.

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CHF = congestive heart failure
LV = left ventricle, left ventricular
NYHA = New York Heart Association
SEM = standard error of the mean

approximately one hundred and ten patients were screened. Failure to enroll patients was due to the inability to consent (refusal or intubation) or that the initial BNP was drawn after the 24 h limit.

Study protocol. Patients were treated in standard fashion with either oral or intravenous diuretics and vasodilators. Blood was also sampled whenever treatment changes were made or the patient's condition changed (typically, on a daily basis throughout hospitalization). In patients who died during hospitalization, the last measured BNP concentration was considered the "discharge" BNP measurement. Physicians treating the patients were blinded to the results of BNP measurements.

Because of the small sample size and the low anticipated rate of adverse events, this study used a (prespecified) combined outcome of either death in hospital or death within 30 days after discharge or readmission to the hospital facility for CHF within 30 days. At 30 days, patient records were checked for readmission or death. Events outside facilities were also tracked by medical records, as patients are always transferred to the VA when stable. One hundred percent of patients received complete follow-up at 30 days.

Measurement of BNP plasma levels. For each BNP measurement, 5 ml of whole blood 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. There is a 15 to 20 min turn around time for the assay. 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 (1 to 2 days), an approach known to produce well-calibrated results with whole blood sample methods.

Table 1. Patient Characteristics in 72 Patients With Decompensated Congestive Heart Failure

Characteristic (% of patients, unless otherwise specified)	Patient Values
Age (mean ± SEM)	68.0 ± 1.6
Admission NYHA class (mean)	3.64 ± 0.07
Ejection fraction	37% ± 2%
Etiology of heart failure	
Ischemic heart failure	71.8%
Idiopathic heart failure	16.9%
Other	11.3%
Associated COPD	26.8%
Associated renal failure	25.4%
Hospital stay (days, mean)	16.1 ± 2.9
Parenteral vasodilator/inotrope (milrinone/dobutamine)	41.8%
Swan-ganz catheter placement	34.1%
End points	30.6%
Deaths	18.1%
Readmission (within 30 days)	12.5%

COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; SEM = standard error of the mean.

Statistics. Comparisons of group means were made using *t* tests for independent samples. In all cases, comparisons were first computed using raw BNP values and then verified with log-transformed BNP values because the BNP distribution was positively skewed. Both procedures yielded identical results.

To evaluate the association between BNP measurements and the combined outcome, we used logistic regression. We also performed a subgroup analysis looking at the association between surviving discharge BNP concentration and readmission to the hospital. In surviving patients, we also computed a receiver-operated curve to assess whether discharge BNP could be used to distinguish patients who would later be readmitted from patients whose CHF was successfully treated.

The number of subjects was not sufficient to permit a true multivariate analysis of the many predictors; thus, the analyses were conducted in a univariate manner. Each logistic regression involved the entry of a single nominal predictor or a continuous covariate and no other predictors.

RESULTS

Patient outcomes and BNP levels. Patients who died or were readmitted tended to have an increase in their BNP concentration during the course of hospitalization (+239 ± 233 pg/ml); patients who had successful treatment tended to have decreases in their BNP concentration during hospitalization (−216 ± 69 pg/ml) ($p < 0.05$).

Figure 1 shows the association between BNP concentration, NYHA classification (at admission and discharge) and patient outcome. Patients who had good outcomes tended to be characterized by decreases in both their NYHA class and BNP levels during hospitalization, with final BNP levels of 690 ± 103 pg/ml (Fig. 2, A1 and B1). Figure 2, A2 and B2, shows admission and last measured BNP levels and NYHA classification in those patients who were readmitted within 30 days of discharge. Even though the NYHA class decreased with treatment in this group, there were only minimal decreases in BNP levels during hospitalization, with a mean discharge BNP of 1,506 ± 452 pg/ml. Finally, subjects who died in the hospital (Fig. 2, A3 and B3) had rising BNP levels and little change in symptoms.

Figure 2 shows a significant association between end points and rising versus falling BNP levels ($p < 0.001$).

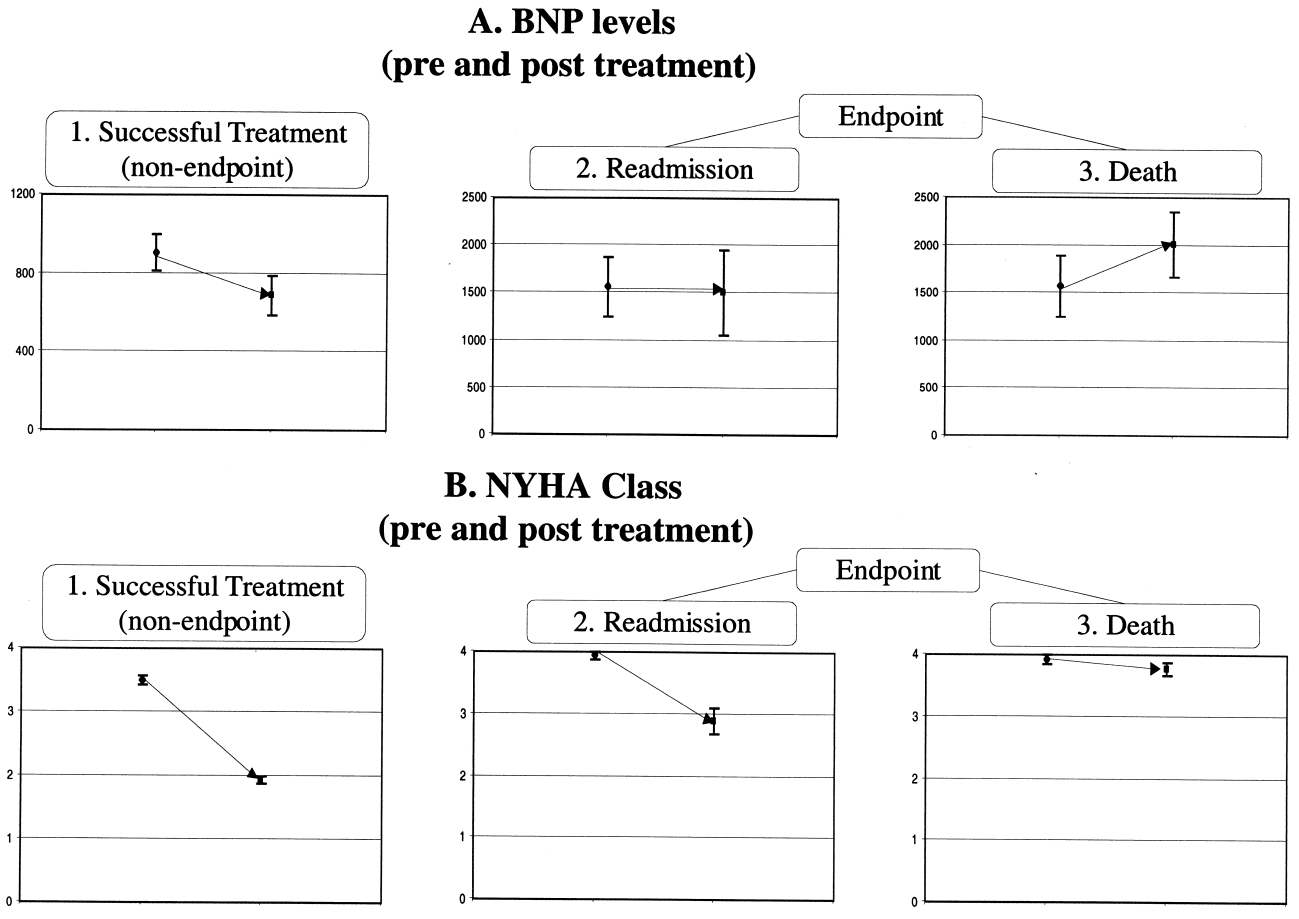


Figure 1. B-type natriuretic peptide levels and NYHA classification before and after treatment in relation to end points or no end points (successful treatment). Each value represents mean ± SEM and is analyzed by analysis of variance. BNP = B-type natriuretic peptide; NYHA = New York Heart Association.

Patients with falling BNP levels during treatment had only a 16% end point rate.

Defining a potential target discharge BNP level. Table 2 shows univariate logistic regression to predict combined end points (death or readmission) or readmission for both discrete and continuous variables. The only historical variable that significantly predicted outcomes was a previous hospitalization of CHF ($p = 0.05$). B-type natriuretic peptide levels and admission NYHA classification were both strong predictors of combined end points, as well as being strong predictors of 30-day readmission subsequent outcome. Although both admission BNP levels and the change in BNP levels over the period of hospitalization were significant predictors of outcome, the last measured BNP level was the single variable that was most strongly associated with patients experiencing one of the prespecified end points. The mean BNP concentration was significantly greater in patients experiencing end points (1,801 ± 273 pg/ml standard error of the mean [SEM] vs. 690 ± 103 pg/ml SEM) than in patients with successful treatment of CHF ($p < 0.001$).

In examining the subgroup of patients surviving to discharge, although NYHA classification was the most significant predictor ($p = 0.0002$) of readmission, discharge BNP was also associated with readmission within 30 days ($p = 0.02$). The receiver operator curve, shown in Figure 3, illustrates the sensitivity and specificity of BNP measurements at discharge in discriminating patients who will require readmission in 30 days from those successfully treated for their CHF. Potential discrete cut points are labeled. The area under the receiver operator curve was 0.72, indicating fair to good discriminatory power. The area under the curve (C-statistic) for all end points (death and readmission) was 0.84.

	Endpoint	
BNP	Yes	No
Increase	15 (52%)	14 (48%)
Decrease	7 (16%)	36 (84%)

Figure 2. The relation between end points and rising versus falling BNP levels during treatment. Values are given as percentages and analyzed by chi-square analysis. BNP = B-type natriuretic peptide ($p < 0.001$).

Table 2. Univariate Predictors of End Points

History	All End Points		30 Day Readmission	
	Likelihood Ratio	p Value	Likelihood ratio	p Value
Age		0.51		0.37
Previous CHF admission (1 yr)	3.85	0.05		0.89
History CHF	3.06	0.08	0.2	0.4
Idiopathic	0.04	0.85	0.18	0.45
Ischemic	0.48	0.49	0.27	0.91
LV size		0.11		0.06
Ejection fraction		0.11		0.21
History of COPD	0.13	0.71	0.13	0.97
History of diabetes	0.35	0.55	2.55	0.09
History of renal disease	0.97	0.32	0.00	0.62
Hospital				
Days in hospital		0.001		0.91
Admission BNP		0.003		0.03
Log admission BNP		0.001		0.01
Discharge BNP		< 0.0001		0.05
Log discharge BNP		< 0.0001		0.02
Delta BNP		0.020		0.7
% change BNP		0.008		0.9
Admission NYHA class		0.0004		0.354
Discharge NYHA class				0.0002
Delta NYHA class				0.204

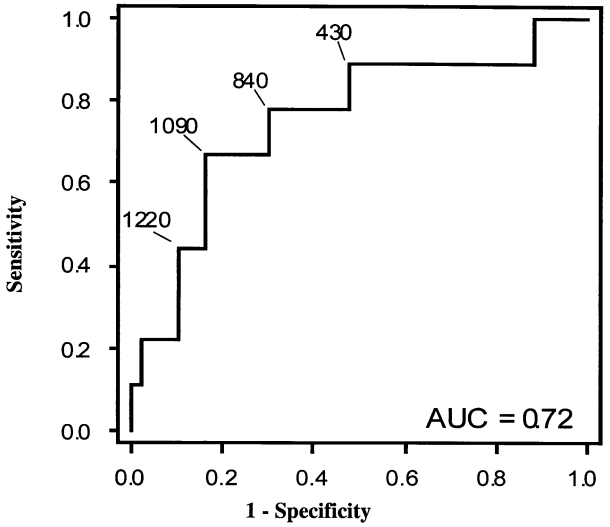
BNP = B-type natriuretic peptide; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; LV = left ventricle; NYHA = New York Heart Association.

DISCUSSION

Congestive heart failure is characterized by complicated cardiorenal, hemodynamic and neurohormonal alterations (16,17). Although patients who are admitted to the hospital with decompensated heart failure often have improvement in symptoms with the various treatment modalities available, there has been no good way to evaluate the long-term effects of the short-term treatment. Indeed, in-hospital mortality and readmission rates for patients with CHF are extremely high (3,4). The conventional tests for cardiac function take time and often do not correlate with symptomatic changes in the patient's conditions. A simple and reliable method to assess therapeutic efficacy ("a digitalis level") in patients being treated for decompensated CHF is lacking (6).

The fact that increased levels of vasoconstrictor neurohumoral factors such as norepinephrine, renin and endothelin-1 have been found to be significant prognostic predictors in CHF suggests an important role of these vasoconstrictors in the pathogenesis of CHF (18–21). Although they are antagonizing, these vasoconstrictors have led to improvements in cardiac function (22,23); the use of these markers as monitors of therapy is impractical, in large part due to difficult assay characteristics, general instability of markers and wide-ranging, often overlapping values (24,25).

The vasodilator neurohumoral natriuretic peptide family may be better candidates for neurohumoral profiling in CHF (26). In particular, BNP has drawn recent interest in



BNP Level (pg/ml)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy (%)
430	89 (48-107)	52 (37-66)	25 (11-44)	96 (80-100)	58
800	78 (35-104)	68 (53-80)	30 (13-54)	94 (81-99)	69
950	67 (24-99)	74 (59-85)	31 (11-58)	92 (79-98)	73
1220	44 (7-55)	90 (78-85)	44 (7-85)	90 (78-90)	83

Figure 3. Receiver operating characteristic curves for patients with decompensated congestive heart failure compares the sensitivity and specificity of BNP measurements to 30-day readmission rates. Discrete cut-points are labeled. The AUC (C-statistic) was 0.72 for readmission. Sensitivity, specificity, positive and negative predictive values and accuracy are recorded for each cut-point of the receiver operating characteristic curve. AUC = area under the curve; BNP = B-type natriuretic peptide.

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its ability to match the decompensated state of circulatory congestion (13,14,27–31).

B-type natriuretic peptide is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides (32,33). The source of plasma BNP is cardiac ventricles, which suggests that it may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides (6,7,34). Tsutamoto et al. (34) found that plasma BNP was more useful than ANP or norepinephrine for assessing the mortality in patients with chronic CHF and that plasma levels of BNP provided prognostic information independent of other variables previously associated with a poor prognosis.

Although extensive guidelines have been published on the outpatient management of patients with CHF or asymptomatic LV dysfunction (35), few guidelines address appropriate management during the period of inpatient hospitalization (the phase of care that contributes highly to morbidity and cost). This is the first study that specifically examines outcomes of patients admitted for decompensated CHF using BNP levels drawn throughout hospitalization. Our data suggest that rapid testing of BNP may someday be used to tailor treatment of patients admitted with decompensated heart failure.

Patients whose discharge BNP level fell below 1,220 pg/ml with treatment in the hospital had a reasonable likelihood of leaving the hospital in good condition and not being readmitted within the following 30 days. A final BNP level ≤430 pg/ml had a strong negative predictive value for readmission. This level is similar to that seen in a group of 200 patients with LV dysfunction on echocardiography with no previous diagnosis of CHF (36). This level also correlates to NYHA classification of approximately class II to III ([37] and personal observation).

Why is plasma BNP a useful predictor of decompensated CHF outcome? B-type natriuretic peptide is a truly ventricular hormone. There is a direct relationship between ventricular wall stress and secretion of BNP (28). B-type natriuretic peptide responds to changes in LV filling pressure (28,29). 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 (38–40). Cheung et al. (41) has suggested that BNP level reflects long-term intravascular volume status rather than momentary volume. Our data agree more with Tsutamoto and others (34,42), whose data suggest that BNP is the emergency hormone that responds immediately to ventricular overload.

Study limitations. This was an observational study conducted using a prospective retrospective design in a convenience sample of male patients. As such, the data must be interpreted with caution. Because of the small sample size, multivariate analysis was not performed. Regression studies present the fit of parameters to observed data rather than the predictive performance.

Point-of-care testing and tailored treatment for decompensated heart failure—is there a future? The correlation between the drop in BNP level and the patient's improvement in symptoms (and subsequent outcome) suggests that BNP guided treatment might make "tailored therapy" more effective and, in some cases, might reduce the need for invasive hemodynamic monitoring in selected patients. Although there has not been sufficient testing of the value of plasma protein measurements for tailoring therapy of CHF once the patient has been discharged (43), several research groups have recently reported data suggesting that BNP measurements may be useful in the adjustment of medications in heart failure (43–46).

In conclusion, the data presented in previously published papers, when combined with the results of this study, suggest that point-of-care testing of BNP may be an effective way to improve the in-hospital management of patients admitted with decompensated CHF. Future studies should examine the feasibility and outcomes of BNP-directed therapy of CHF using point-of-care measurements.

Acknowledgments
The authors would like to thank the physicians and nursing staff working at the VA Medical Center for their cooperation and support.

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