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Variability in Measurement of BNP in Routine Evaluation of Heart Failure (VAMPIRE)

Pam R.Taub[1,2], Kevin Shah[2], Kevin Jiang[2], Paul Clopton[2], Mitchell Saltzberg[3], Alan S. Maisel[1,2] and Robert L. Fitzgerald[2,4]*

[1]*University of California San Diego, Division of Cardiology, San Diego, CA, USA*
[2]*Veterans Affairs Medical Center, La Jolla, CA, USA*
[3]*Midwest Heart Specialists, in Downers Grove, IL, USA*
[4]*University of California San Diego, Pathology Department, San Diego, CA, USA*

Abstract

Background: B-type natriuretic peptide (BNP) is an established biomarker for diagnosis of acute heart failure (HF). However, criteria for interpreting BNP changes over time prior to clinical decompensation have not been well established.

Methods: BNP concentrations were followed in 192 patients with HF who had at least 5 BNP measurements over 6 month to 2 year period. Decompensation was defined as a hospitalization for HF. For patients (N = 30) who had a recent (within 2 weeks) BNP measured prior to decompensation, BNP concentrations were examined to determine if there was a significant rise prior to decompensation.

Results: For patients who had a BNP concentration measured within 2 weeks of decompensation, there was a significant increase in BNP concentration prior to decompensation. When patients with a baseline BNP < 200 pg/mL decompensated, their BNP changed by a mean of 560% while when patients with a high baseline BNP (> 200 pg/mL) decompensated, their concentrations changed by 62% (p<.0001).

Conclusion: Patients with low baseline BNP have significantly larger percent changes in BNP concentrations prior to decompensation than those with higher baseline BNP levels. In conclusion, serial sampling demonstrated that there is potential window prior to hospitalization for HF where a rise in BNP concentrations signals decompensation.

Keywords: Serial monitoring; Natriuretic peptides; Prognosis; Point of care

Introduction

Heart failure (HF) is a rising epidemic in the United States. There are more than 3 million HF related admissions annually and approximately 35% of these admitted patients subsequently have HF related deaths or readmissions within 60 days [1]. The estimated direct and indirect cost of HF in the United States for 2009 is $37.2 billion [2]. Prevention of HF admissions will alleviate a significant burden on our health care system.

Subclinical congestion occurs before any physical exam signs manifest and represents an important target in prevention of HF hospitalizations. The clinical diagnosis of HF can be challenging and congestion may be unrecognized until patients are decompensated [3] B-type natriuretic peptide (BNP) has emerged as important biomarker to detect subclinical congestion as levels correlate with pulmonary capillary wedge pressure[4]. BNP levels provide important information for triaging and treating HF patients; however, in the outpatient setting, criteria are lacking for interpreting serial changes in BNP.

The intra-individual variability of BNP measurement depends both on how the measurement is made (e.g. point-of-care vs central laboratory) as well as the time frame of study. Wu showed that the relative change value, percentage change in BNP to suggest clinical improvement was 25% within day but was 71% week to week [5]. Wu also showed that these relative change values would need to be doubled to suggest clinical progression of disease. A key question that needs to be addressed when monitoring serial changes in BNP is the frequency with which to monitor these changes. Two studies have monitored serial samples at three month intervals over a two year period [6,7] while other studies have monitored changes from baseline at 4 and 12 months [8]. Since the biological half-life of BNP is measured in minutes, sampling on a monthly time frame may miss important biological indications of disease progression. While clearly prognostic, the optimal time frame for serial sampling of BNP in stable outpatients requires further study.

In the Variability in Measurement of BNP in Routine Evaluation of HF (VAMPIRE) study, we monitored outpatient BNP concentrations to determine whether changes in BNP are predictive of clinical decompensation. We were interested in providing some guidelines for interpreting percent change of BNP in patients with low and high baseline BNP measurements as well as determining if serial measurements of BNP would provide an indication of decompensation prior to when patients were hospitalized for acute HF. Based on current understanding of BNP cutpoints [9], we hypothesized that patients with a low baseline BNP (< 200 pg/mL) would have a significantly higher percentage change in BNP upon decompensation as compared with patients with a high baseline BNP (≥ 200 pg/mL). This hypothesis is in part based on the ability of BNP to correlate with end-diastolic pressure and subsequent presenting symptoms to the hospital. We also hypothesized that HF patients who were being routinely monitored

***Corresponding author:** Robert L. Fitzgerald, PhD, Center for Advanced Laboratory Medicine, 10300 Campus Point Drive, Suite 150, San Diego, CA 92121, Tel: (858) 657-5733; Fax: (858) 657-5807; E-mail: rfitzgerald@ucsd.edu

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would have a detectable increase in BNP concentration prior to clinical decompensation.

Methods

VAMPIRE included two clinical sites in the United States (Midwestern Heart Chicago, IL and the Veterans Affairs San Diego Healthcare System in San Diego, CA). A total of 200 patients were recruited from heart failure clinics from January 2001 to April 2006. The inclusion criteria were that subjects be at least 18 years of age, were followed in a cardiology clinic, and have at least 5 BNP measurements over a 6 month to two year period. Patients were excluded if they did not have 5 BNP measurements, and if they were treated with Natrecor which could cofound BNP measurements. The study was approved by the Institutional Review Board of both sites and all patients provided informed consent.

This was a purely observational retrospective study, all of the patient clinic visits were part of their routine healthcare. Over 2000 clinical visits were retrospectively reviewed. Of the 200 patients recruited, 192 met the study criteria. BNP measurements were obtained as part of the patient's routine medical care by their cardiologists and physicians were not blinded to the results. Patients were treated according to standard HF guidelines [1]. BNP was measured using the Biosite Triage (San Diego, Ca) instrument. Baseline disease specific variables, demographic characteristics, and echocardiographic measurements were obtained from review of medical records.

The primary endpoint was a clinical decompensation, defined as a hospital admission for HF exacerbation based on review of the medical record by a cardiologist blinded to BNP levels. Baseline BNP was defined as the first BNP value upon study enrollment not corresponding to hospitalization. The percent change in BNP from baseline to decompensation in patients with a high baseline BNP (BNP > 200 pg/mL) was compared with the percentage change in the low baseline BNP group (BNP < 200 pg/mL). Previous studies such as the Breathing Not Properly trial [9] have demonstrated 100 pg/mL as an optimal diagnostic cut point. However, in the VAMPIRE trial we sought to use a more specific cut point of 200 pg/mL to capture a population with more severe HF. In patients with BNP values obtained within two weeks prior to decompensation, trends in BNP were assessed to determine if there was any rise in BNP heralding decompensation. For patients with multiple hospitalizations, only the first hospitalization was included for analysis.

Statistical Methods

Values are expressed as frequencies and percentages for nominal data and as means and standard deviations or medians and inter-quartile ranges for continuous data as appropriate. Groups are compared with chi-square tests, independent samples t-tests, and Mann-Whitney U tests as appropriate to the variable distributions. Paired tests are made with the Wilcoxon matched-pairs signed ranks test without adjustment for multiple comparisons. A p-value less than 0.05 was required for statistical significance.

Results

Table 1 shows the patient demographics separated into subjects who were hospitalized for HF exacerbations and those who were stable and not hospitalized. There was no significant difference in the echocardiographic parameters of ejection fraction, left ventricular end diastolic dimension and left ventricular end systolic dimension between these two groups. Interestingly, patients who were not hospitalized had higher average BNP concentrations (average of all BNP levels obtained during study period) compared to patients who had HF hospitalizations. Other HF risk factors (such as prior history of myocardial infarction, history of coronary artery bypass graft surgery, hypertension, pulmonary hypertension, arrhythmia, chronic renal insufficiency and hyperlipidemia) were higher in the hospitalized group. A total of 74 patients in this cohort had HF hospitalizations. Pulmonary artery hypertension was defined by a mean pulmonary artery pressure >25 mm Hg at rest. Chronic renal insufficiency was defined as a glomerular filtration rate (GFR) of 15 to 59 mL/min per 1.73 m^2. Arrhythmia was defined as documented arrhythmia, specifically atrial fibrillation, supraventricular tachycardia, or ventricular tachycardia.

The low baseline BNP group had significantly larger changes in BNP concentrations prior to decompensation than those with higher baseline BNP concentrations. As shown in Figure 1, the percent change in BNP from baseline to decompensation was 564 +/- 174% in patients with a low baseline BNP (BNP < 200 pg/mL, N=16) as compared with a 63 +/- 16% (mean +/- standard error) change in the high baseline BNP group (BNP ≥ 200, N= 58). This difference was statistically significant (p=0.012).

Figure 2 depicts stable BNP concentrations in patients who did not decompensate. When analyzing these patients whom did not decompensate, those with four data points were plotted with the x-axis depicting mean number of days after enrollment in the study. Figure 3 demonstrates the subgroup of chronic HF patients whom did decompensate. In this figure, the x-axis once again depicts time, specifically mean number of days prior to decompensation. As patients were selected retrospectively if they had a decompensation, their days between clinic visits are not standardized and mean values are represented on the x-axis. This figure demonstrates the trend towards increasing BNP levels prior to decompensation in the group of subjects who had a BNP measured within 2 weeks of decompensation. Patient with HF hospitalizations had a significant increase in their BNP level detected as early as 52 days prior to decompensation. Interestingly, in the 5 days prior to decompensation BNP levels were not significantly different from BNP at the time of hospital admission.

	Hospitalized (N=74)	Not Hospitalized (N=118)	p value
Age (years)	69 +/- 12	68 +/- 12	0.6
Sex (% female)	7 %	32 %	**< 0.001**
Weight (kg)	89.8	88.4	0.694
Ejection Fraction†	37 +/- 15	39 +/- 17	0.653
Left Ventricular End Diastolic Dimension (cm) †	6.0	5.7	0.180
Left Ventricular End Systolic Dimension (cm) †	4.6	4.5	0.524
Average BNP Value (pg/mL)*	611 (360-916)	748 (294-1910)	**0.04**
History of prior MI	61 %	31 %	**< 0.001**
History of CABG	47 %	32 %	**< 0.04**
Hypertension	85 %	54 %	**< 0.001**
Pulmonary Hypertension	50 %	28 %	**0.002**
Arrhythmia	58 %	41 %	**0.021**
Chronic Renal Insufficiency	43 %	26 %	**0.015**
Hyperlipidemia	33 %	10 %	**< 0.001**

*Median (interquartile range)
†Echocardiographic Measurements were available in 69 hospitalized patients and 74 non hospitalized patients

Table 1: Patient demographics.

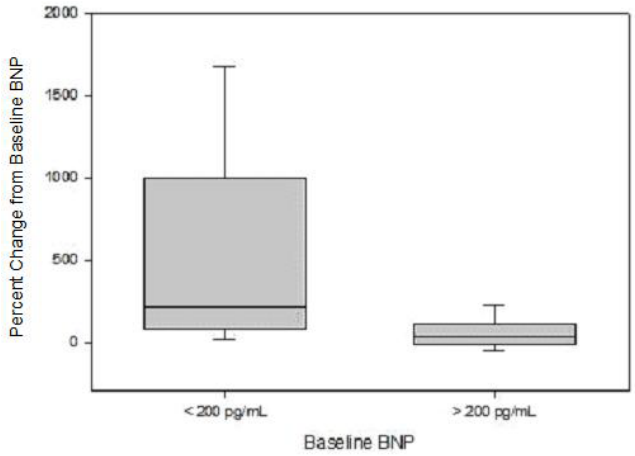

Figure 1: Percent change from baseline BNP in all patients, separated by high vs low BNP groups. Patients with low baseline BNP group (< 200 pg/mL, N=16) had 560 % increase in BNP (SEM 174.5) while those in the high baseline BNP group (> 200 pg/mL, N=59) had a 63 % increase in BNP (SEM 16) prior to hospitalization for decompensated HF (p = 0.012).

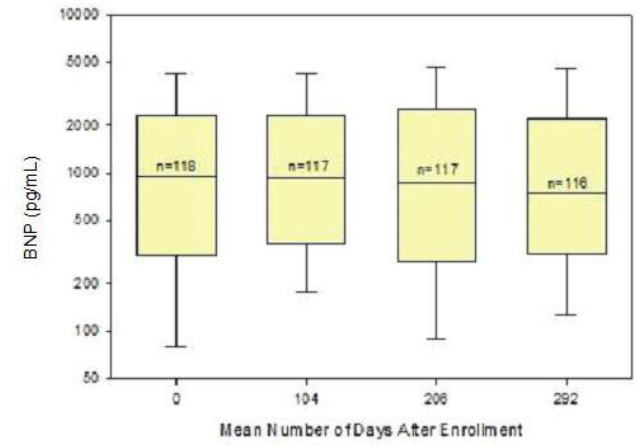

Figure 2: BNP levels over time in patients who did not have decompensation. Patients with at least 4 data points who did not get hospitalized for decompensated heart failure showing no significant differences in BNP concentrations over time. The x-axis on this figure represents the average number of days between the initial and subsequent HF clinic visits for these subjects.

Discussion

Several studies have established that BNP is an important prognostic indicator in outpatients with stable heart failure [7-11]. Koglin et al. showed that a single BNP measurement had prognostic value equivalent to a multivariate heart failure score [8]. When BNP was monitored every 3 months over a 2 year period, an elevated BNP had prognostic value: however once elevated, further changes in BNP (increase or decrease) were not meaningful [10]. In a larger cohort of over 4000 stable symptomatic HF patients from the Valsartan heart failure trial (Val-HeFT) patients with the greatest percent increase in BNP from baseline to 4 and 12 months had the highest mortality and morbidity [11]. These studies demonstrate that elevations in BNP are predictive of adverse events, but leave unanswered questions with regards to the ability of using BNP as a serial marker for long term monitoring of HF patients. Multiple trials have looked at using BNP levels to titrate therapy in the outpatient setting with varying results. The Systolic Heart Failure Treatment Supported by BNP (STARS BNP) trial, Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting (STARBRIGHT), the BNP-Assisted Treatment to Lessen Serial Cardiac Admissions and Death (BATTLESCARRED) trial and the TIME-CHF study have all been conducted and results have been mixed as to the utility of using BNP to titrate outpatient therapy [12-14]. The most recent study used NTproBNP to guide successful therapy [15].

In our cohort of outpatients with heart failure we show that there is a differing pattern of BNP elevations prior to decompensation based on baseline BNP levels. Patients having low baseline BNP demonstrate significantly larger changes in BNP levels prior to decompensation than those with higher baseline BNP levels. This suggests small changes in patients with high baseline BNP levels should be taken more seriously in clinical decision making (Figure 1). For patients with a BNP < 200 pg/mL (N=16), the mean change of 560 % clearly exceeds the minimal change values suggested by Wu [5]. However, when the larger group of patients, those with baseline BNP concentrations ≥ 200 pg/mL (N=59) were analyzed, the mean change was only 60% which would not meet the minimum change criteria. These observations are likely due to patients with low baseline BNP levels having less severe HF and thus more hemodynamic stress is required, as reflected by a large change in BNP, when they decompensate. In contrast, patients with high baseline levels have more advanced HF and are often on a tenuous portion of the pressure-volume curve. In these patients small increases in hemodynamic stress could initiate decompensation.

Interestingly, patients that were never hospitalized had higher average BNP levels (748 pg/mL with interquartile range of 294 to 1910) compared to the hospitalized group (611pg/mL with interquartile range of 360-916). This emphasizes the importance of examining trends and dynamic changes in BNP levels to predict clinical outcome. The lower average BNP in the hospitalized group could also reflect more intensive treatment.

BNP concentration changes prior to decompensation are gradual and detectable long before the acute event (Figure 3). This suggests that more frequent monitoring of these patients may allow clinicians to monitor HF status and optimize treatment prior to decompensation.

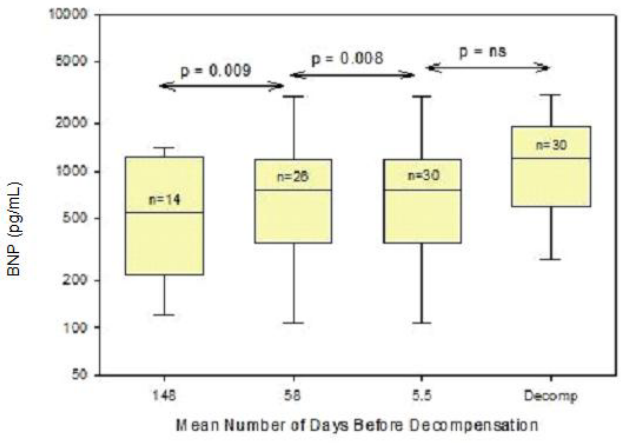

Figure 3: BNP levels over time in patients who were admitted for decompensated heart failure. Patients who were hospitalized and had a BNP measurement within 2 weeks of decompensation.The x-axis represents the average time between clinic visits for these patients prior to decompensation.

Our data is consistent with small trials in which intrathoracic impedance monitors in implanted defibrillators detected subclinical congestion weeks before HF decompensation [16,17]. In these trials, the early detection of congestion resulted in fewer hospitalizations. BNP may emerge as a synergistic tool along with measurements of intrathoracic impedance to prevent HF exacerbations.

When and how a BNP concentration is measured will have important implications for monitoring changes over time. It should be noted that we were using the Triage point-of-care device in this study, which has larger coefficient of variation than commonly used laboratory based assays, yet the results were still positive. It is unlikely that patients would be willing to come to the hospital for a blood draw on a weekly basis, but our results suggest that some type of home monitoring, as is done with blood glucose, could provide interpretable information provided the point-of-care assay was sufficiently precise. Future studies, including the Heart failure Assessment with B-type natriuretic peptide In The home (HABIT) trial, aim to further elucidate the utility in monitoring HF patients for early warning signs of decompensation in advance of acute presentations. Our study aimed to augment the belief that serial natriuretic peptide monitoring in the outpatient setting has some utility to reduce HF hospitalizations, thus lowering the burden on the healthcare system. Home BNP testing may possibly emerge as a modality to monitor a patient's level of congestion and help to titrate the medication regimen in the outpatient setting. In the future, natriuretic peptide home testing may emerge as a modality to monitor a patient's level of congestion and to help titrate medication regimen in the outpatient setting.

Limitations

This was a retrospective study using patients who were being treated chronically for HF, consequently the time points in which BNP concentration were measured where not at standard intervals and collections were infrequent. This infrequent sampling makes it difficult to determine the optimal sampling frequency needed to detect a change in BNP that predicts decompensation. BNP concentrations change rapidly in vivo and the variability of these levels changes greatly over a time period of years. We chose to group patients with a BNP value within two weeks of their decompensation event as we know that BNP concentrations change rapidly and were interested in changes just prior to decompensation. A two week period also provides a realistic time frame for intervention and is realistic for obtaining serial measurements. Although more data is needed, our results suggest that monitoring patients on a weekly basis, as could be accomplished with a home monitoring type of assay, would provide data that could be evaluated on a serial basis to determine if patients were trending towards decompensation. While the BNP time points we collected reflects current routine clinical practice, it made it difficult to compare the group of patients who had a BNP measured within 14 days of their decompensation event (Figure 3) with a control group. In order to provide a useful comparison, we took BNP concentrations from the first four clinic visits of patients who did not decompensate (Figure 2) to provide information on this stable cohort. We also did not account for all the variables that could confound BNP values such as renal function and obesity.

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