Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2006; 9 (1-4), 31-36

Determinants of Changes in B-Type Natriuretic Peptide Levels in Hospitalized Patients

Monahan K, Zhou C, Rose J, Adler D

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

J Clin Basic Cardiol 2006; 9 (online): 31

Determinants of Changes in B-Type Natriuretic Peptide Levels in Hospitalized Patients

K. Monahan[1, 3], C. Zhou[2], J. Rose[1], D. Adler[1]

Background: BNP trends in outpatients reflect use of cardiac medications and correlate with morbidity and mortality. However, their role in the inpatient setting is unclear. We hypothesized that (1) BNP measurements are more available and reliable than standard measures of volume status and (2) inpatient BNP trends are influenced by volume and neurohormonal status.

Methods: We conducted a retrospective study of patients with multiple BNP measurements during their hospitalization. The comparative availability of weights and laboratory tests was assessed by examining the frequency of recorded weights and the frequency of recorded phlebotomy results. To evaluate a surrogate for weights, we examined the correlation between changes in weight and concomitant fluid balance. Contributors to BNP trends were determined by multivariate regression analysis.

Results: The cohort consisted of 60 non-critically ill patients. BNP measurements were taken 54 ± 57 hours apart (initial: 939 ± 925 pg/ml; follow-up: 711 ± 726 pg/ml; $p = 0.003$). Laboratory tests were more often recorded than weights (94 ± 11 % vs. 50 ± 33 % of hospital-days; $p < 0.0001$). The correlation between changes in weight and fluid balance was poor. Time between measurements and inter-measurement doses of diuretic and beta-blocker were associated with a change in BNP of at least 24 % and 200 pg/ml.

Conclusions: Inpatient BNP trends may reflect response to diuretics and neurohormonal agents, thus offering information beyond standard indicators of volume status, which are relatively unavailable and unreliable. ***J Clin Basic Cardiol 2006; 9 (online): 31–6.***

Key words: *BNP, heart failure, beta-blocker*

As the role of neurohormones in the pathophysiology of heart failure has become defined, the measurement of B-type natriuretic peptide (BNP) has been shown to be useful in assisting with the diagnosis [1–3], treatment [4], and prognosis in those with [5–6] and without [7] established disease.

Building on prior investigations of norepinephrine and plasma renin activity [8–9], studies of serial BNP measurements over months to years have demonstrated that BNP levels respond to treatment with neurohormonally active agents [10–11] and that, in heart failure patients, changes in BNP correlate with changes in morbidity and mortality [11–12].

There is comparatively little data regarding the role of serial BNP measurements in the inpatient setting. Several studies have shown that an elevated BNP at discharge is a strong predictor of death or readmission [13–15], but those studies drew disparate conclusions regarding the utility of following BNP trends over the hospital course. In the design and interpretation of prospective studies that would address this question more directly, knowledge of several parameters would be useful; these include the optimal interval between measurements, the extent of the information captured by changes in BNP, and whether or not serial BNP measurements would complement standard non-invasive methods of assessing clinical status. As a step toward addressing these issues, we aimed to study, in hospitalized patients, the relationship between trends in BNP and other clinical and laboratory variables. Specifically, we hypothesized that changes in BNP would be influenced by other factors in addition to volume status and that BNP levels could be more readily available than standard measures of weights and fluid balance.

Methods

Design and Data Collection

We conducted a retrospective study of all inpatients at our institution not requiring intensive care who had multiple BNP measurements during a single hospitalization between August 2003 and January 2004. General information such as demographics, length of stay, medical history, and pre-admission medications were gathered from patient charts.

The ADVIA Centaur assay (Bayer Diagnostics; Tarrytown, NY) was used to determine BNP levels during the study period; this assay has a range of 0–5000 pg/ml and a coefficient of variation of 2–4 %, depending on the absolute value of BNP [16].

The precise timing and level of BNP measurements were obtained through queries of our electronic laboratory database. Daily weight and fluid balance data were obtained from the bedside flowsheets. When necessary, input and output totals for a given shift were divided by the number of hours in that shift to provide an hourly estimate. A computerized record of medication charting over each patient's hospital course, logged by the hour, was used to estimate when cardiac medications were administered. Doses were converted to equivalent amounts of representative medications for each class of interest (enalapril for ACE inhibitors, metoprolol succinate for beta-blockers, oral furosemide for loop diuretics) [17–20]. No patient received nesiritide during their hospitalization.

The duration of telemetry monitoring was determined based on how many hours the patient spent on floors with telemetry capability; in our hospital, certain wards are designated for patients requiring monitoring and all patients located on those wards are monitored unless there is a specific order to the contrary. Details regarding the timing of monitoring orders as well as transfers to and from those wards were obtained via review of a computerized order database and the transfer notes in the paper chart.

Renal function was determined by the „Modification of Diet in Renal Disease"- (MDRD-) formula for estimated glomerular filtration rate (GFR); the admission serum creatinine value and admission weight were used in those calculations. Echocardiographic data were obtained from studies performed during the hospitalization under review (83 % of

Received: September 28th, 2006; accepted: November 28th, 2006.

From the [1]Division of Cardiology, Department of Medicine, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH, USA, the [2]Department of Biostatistics, and the [3]Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

Correspondence to: Ken Monahan, MD, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, 383 PRB/2220 Pierce Avenue, Nashville, TN, USA; e-mail: ken.monahan@vanderbilt.edu

patients) or from the most recent study available prior to the current hospitalization (15 % of patients).

Comprehensive chart review revealed that all patients had orders for daily weights, for regular recording of fluid balance, and for daily phlebotomy. Data regarding the presence or absence of a Foley catheter were not uniformly available. The protocol was approved by the institutional review board of Case Western Reserve University and University Hospitals of Cleveland.

Statistical Analysis

Patient baseline characteristics were summarized by means, medians, and standard deviations. These baseline characteristics were compared across three groups categorized by initial BNP level; similar classification schemes have been used previously [2]. Comparisons of continuous variables across these groups were made using the Kruskal-Wallis rank sum test. Differences in categorical variables were assessed using Fisher's exact test. The comparative availability of weights and laboratory tests was assessed by examining, on a patient-by-patient basis, the frequency of recorded weights (on the bedside flowsheet) and the frequency of recorded phlebotomy results (in the laboratory database). Comparisons were made using unpaired t-tests. To evaluate fluid balance as a surrogate for weights, we examined the correlation between changes in weight and concomitant fluid balance using standard linear regression.

To determine the clinical predictors of significant changes in BNP, several predictors of interest were identified *a priori*; these predictors included standard demographic variables (age, gender), but focused on inter-measurement events (time between measurements, administration of diuretics, ACEI, beta-blockers, and change in renal function). The threshold of what constituted a "significant" change in BNP was determined based on previously published data, which incorporate the concept of biologic variation [14, 21–24]. Based on these reports, we defined a change in BNP as significant if it represented at least a 24 % relative difference and a 200 pg/ml absolute difference between measurements. Additional thresholds were not tested due to the possibility of obtaining spurious results through multiple comparisons. We studied how the predictors influenced the change in BNP levels using multivariable logistic regression models. All statistical analyses were conducted using the R statistical package [25].

Results

Cohort Characteristics and Basic BNP Data

Cohort characteristics are shown in Table 1; these data are presented for the entire cohort and stratified by initial BNP level as well. The population was elderly (mean age 71.2 ± 13.7 years), demographically diverse (53 % female, 48 % African-American), and had a high prevalence of diabetes mellitus (37 %) and heart failure (43 %). Although not all comparisons reached statistical significance, compared to those with lower initial BNP values, those with the highest initial levels were generally older, had increased length of stay, were

Table 1. Cohort characteristics stratified by initial BNP level

	Entire cohort	Low BNP < 100 pg/ml	Intermediate BNP 100–400 pg/ml	High BNP > 400 pg/ml	p-value
Number of patients	60	8	15	37	–
Demographics					
Age (years)	71.2 ± 13.7	59.3 ± 16.3	72.7 ± 11.2	73.2 ± 13.1	0.06
Gender (% female)	53	75	60	46	0.31
Ethnicity (% AA)	48	63	60	43	0.64
Admission weight (kg)*	84.3 ± 27.6	87.5 ± 32.0	95.9 ± 21.5	79.3 ± 27.9	0.12
Hospitalization data					
Hospital days	6.4 ± 4.2	4.2 ± 2.6	6.5 ± 5.0	6.9 ± 4.1	0.18
Time monitored (fraction)	0.70 ± 0.41	0.57 ± 0.46	0.64 ± 0.43	0.75 ± 0.39	0.43
Admission diagnosis of heart failure (%)	52	13	47	62	**0.035**
Medical history (%)					
Heart failure	43	25	47	46	0.60
Hypertension	68	63	73	68	0.85
CAD	40	0	47	46	**0.039**
Diabetes	37	25	52	32	0.37
Smoker**	28	38	53	43	1
COPD	32	50	27	30	0.53
Pre-hospital medications (%)					
Loop diuretic	52	63	47	51	0.87
ACEI	37	13	20	49	0.06
Beta-blocker	43	13	33	54	0.06
Cardio-renal data					
LVEF (%)	45 ± 21	48 ± 10	56 ± 20	40 ± 21	**0.029**
LAD (mm)	44 ± 10	36 ± 10	40 ± 13	47 ± 8	**0.011**
RVSP or PASP (mmHg)	48 ± 15	32 ± 8	57 ± 16	47 ± 14	**0.034**
Estimated GFR (ml/min/1.73 m^2)	59 ± 31	88 ± 46	47 ± 30	58 ± 24	**0.028**

*No available weight for 3 patients in the intermediate group and 4 patients in the high group; **Smoking status unknown in 1 patient in the low group and 5 patients in the high group; continuous values are mean ± standard deviation; AA = African American; ACEI = angiotensin converting enzyme inhibitor; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; RVSP = right ventricular systolic pressure

Table 2. Serial BNP data stratified by initial level

	Entire cohort	Low BNP < 100 pg/ml	Intermediate BNP 100–400 pg/ml	High BNP > 400 pg/ml	p-value
Number of patients	60	8	15	37	–
BNP levels					
Initial (pg/ml)	939 ± 925 (603)	41 ± 24 (47)	241 ± 99 (242)	1420 ± 885 (1230)	**< 0.0001**
Follow-up (pg/ml)	711 ± 726 (461)	52 ± 61 (32)	430 ± 576 (267)	968 ± 733 (706)	**< 0.0001**
Absolute difference (pg/ml)	–227 ± 752 (–41)	11 ± 49 (–0.5)	189 ± 568 (9)	–448 ± 816 (–243)	**0.0007**
Relative difference (%)	11 ± 130 (–15)	35 ± 114 (–0.5)	84 ± 225 (3)	–24 ± 45 (–27)	**0.016**
Measurement timing					
Fractional time – initial	0.13 ± 0.19 (0.06)	0.002 ± 0.16 (–0.01)	0.19 ± 0.16 (0.10)	0.13 ± 0.20 (0.05)	**0.016**
Fractional time – follow-up	0.51 ± 0.29 (0.55)	0.36 ± 0.22 (0.32)	0.45 ± 0.25 (0.43)	0.57 ± 0.31 (0.64)	0.11
Inter-measurement interval (hrs)	54 ± 57 (38)	36 ± 45 (20)	33 ± 30 (21)	67 ± 65 (49)	0.051
Inter-measurement events					
Fluid balance (ml)	–1310 ± 3067 (–1070)	–609 ± 903 (–250)	–558 ± 1680 (–514)	–1760 ± 3668 (–1350)	0.10
Diuretic dose (mg of oral furosemide)	249 ± 500 (80)	100 ± 77 (80)	85 ± 105 (40)	347 ± 615 (160)	**0.02**
ACEI dose (mg of enalapril)	35 ± 92 (0)	12 ± 32 (0)	4 ± 11 (0)	53 ± 114 (6)	**0.023**
Beta-blocker dose (mg of metoprolol succinate)	94 ± 153 (25)	45 ± 104 (0)	32 ± 53 (0)	129 ± 178 (50)	**0.04**
Change in BUN (mg/dl)	2 ± 11 (2)	6 ± 5 (6)	–1 ± 11 (0)	3 ± 12 (2)	0.15
Change in SCr (mg/dl)	0 ± 0.4 (0)	0.1 ± 0.2 (0.1)	–0.1 ± 0.7 (0)	0 ± 0.3 (0)	0.30

Values are mean ± standard deviation (median); ACEI = angiotensin converting enzyme inhibitor; BUN = blood urea nitrogen; SCr = serum creatinine

more likely to have been admitted for heart failure, and were more often on standard cardiac medications. Additionally, those with higher initial BNP levels had statistically significant ($p < 0.05$) decreased left ventricular systolic function, larger left atrial dimensions, higher right-sided pressures, and lower estimated GFR than those with lower initial values.

Serial BNP Measurements – Effects of Time Between Measurements and Medications

The details of the absolute and relative changes in BNP levels as well as data regarding measurement timing, inter-measurement fluid balance, and medication administration are presented in Table 2. These data are stratified by initial BNP level. Overall, the average initial level was 939 ± 925 pg/ml and the follow-up level, taken an average of 54 ± 57 hours later, was 711 ± 726 pg/ml ($p = 0.003$ for comparison between initial and follow-up levels). Most of the patients (62 %) had high initial BNP levels with fewer having intermediate (25 %) and low (13 %) initial levels. Both the absolute and relative differences in serial measurements varied significantly based on initial BNP level. Those patients with high initial levels had a net decrease in BNP, while those with intermediate and low initial levels had a net increase in BNP, although the median differences in the latter two groups were very small. The relative difference followed a similar pattern. The initial BNP measurement occurred earlier in those with low BNP levels than in the other two groups. The follow-up measurements occurred progressively later among patients with higher initial BNP in a trend that was monotonic, but not statistically significant. The inter-measurement interval shows a trend towards being greater in those with initially high BNP levels. Those with higher initial levels received more diuretic, ACEI, and beta-blocker between measurements than those with lower initial BNP levels. There were no significant changes in renal function between BNP measurements, regardless of initial BNP level. Figure 1A shows a summary box-plot of the distributions of the initial and follow-up BNP measurements; the individual patient trends of serial BNP measurements as functions of absolute hospital time are shown in Figure 1B.

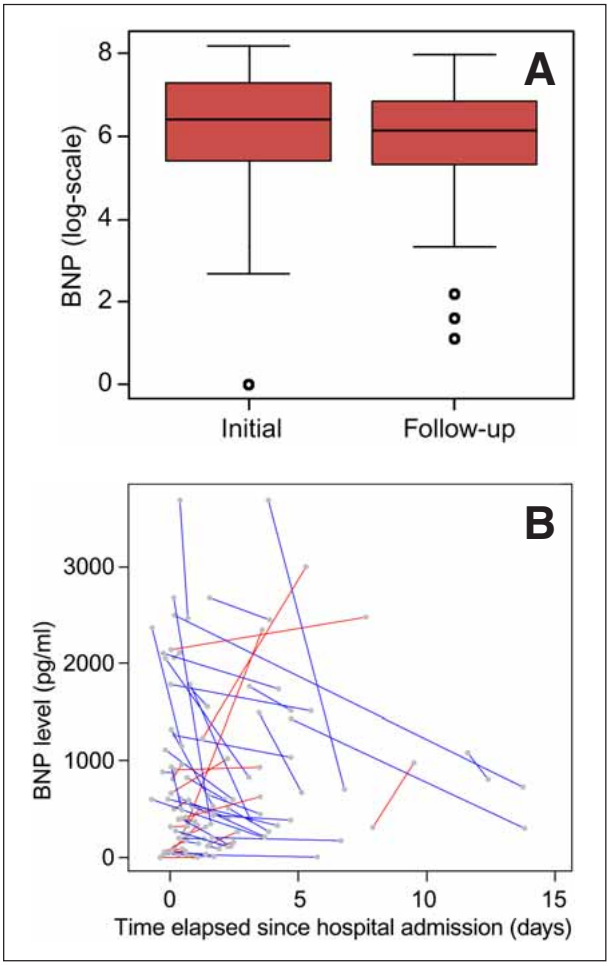

Figure 1. Trends in serial BNP measurements. Panel **A** displays a box-plot of the initial and follow-up BNP levels on a natural log scale. Open circles represent extreme values. Panel **B** shows individual patient trends. Negative values on the horizontal axis denote lab values obtained just prior to the patient being admitted.

Table 3. Analysis of pre-specified predictors of changes in BNP

Predictor	Univariate p value	Multivariate p value
Age	0.09	0.43
Gender	0.61	0.85
Inter-measurement interval	**0.025**	0.07
Inter-measurement fluid balance	0.43	0.99
Inter-measurement diuretic dose	**0.012**	0.95
Inter-measurement ACEI dose	0.72	0.10
Inter-measurement beta-blocker dose	**0.014**	0.19
Inter-measurement change in SCr	0.94	0.75

ACEI = angiotensin converting enzyme inhibitor; SCr = serum creatinine

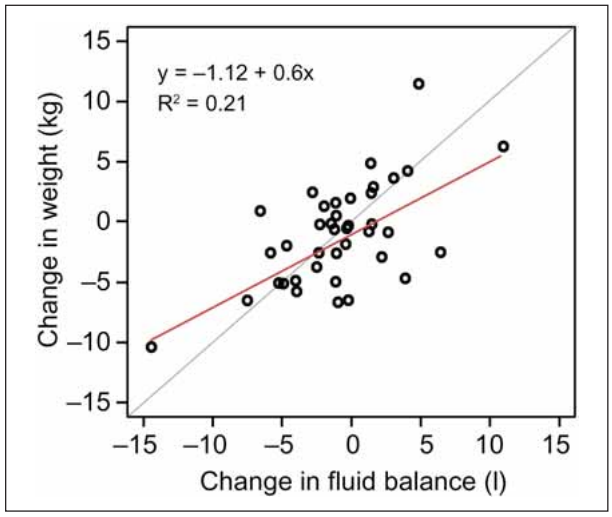

Figure 2. Relationship between changes in weight and fluid balance. The correlation between the two parameters does not allow fluid balance to be used as a surrogate for changes in weight.

Determinants of Change in BNP

Analysis of pre-specified predictors of significant changes in BNP, using our criteria, are shown in Table 3. Of the 60 patients, 24 (40 %) met our definition of a significant change; 19 of those patients (79 %) experienced a decrease in BNP between measurements. Longer times between measurements and higher doses of beta-blocker and diuretic between measurements were associated with degrees of change in BNP that met our definition of significance. These associations were not present in limited sub-group analyses that focused on those patients with a history of heart failure (n = 26; 43 % of cohort) and those admitted for exacerbations of heart failure (n = 31; 52 % of cohort). No parameter remained a significant predictor of change in BNP in multivariate analysis that included all pre-specified variables, possibly due to co-linearity between several model parameters.

Time between BNP measurements was correlated with several other predictors used in the multivariate model. These include inter-measurement ACEI dose ($r = 0.68$; $p < 0.001$), inter-measurement beta-blocker dose ($r = 0.56$; $p < 0.001$), and inter-measurement diuretic dose ($r = 0.56$; $p < 0.001$). Furthermore, inter-measurement beta-blocker dose was significantly correlated with inter-measurement diuretic dose ($r = 0.65$; $p < 0.001$) and inter-measurement ACEI dose ($r = 0.43$; $p < 0.001$).

Availability and Comparison of Daily Weights and Fluid Balance

The availability of daily weights relative to laboratory data as well as comparisons between changes in weight and concurrent fluid balance are shown in Table 4. Laboratory tests were more often recorded than weights (94 ± 11 % vs. 50 ± 33 % of hospital days; $p < 0.0001$); this finding persisted regardless of the duration of telemetry monitoring, hospital length of stay, or initial BNP level. Despite orders for daily weights on all patients, only 15 % of patients had a weight recorded on each day of their hospital course. Given the low availability of weights, fluid balance was evaluated as a surrogate measure of day-to-day volume status. As seen in Figure 2, a linear model explains a relatively small portion of the variability in these parameters ($r^2 = 0.21$). Even for those patients whose weight did not change much over the hospital course, there is large variation in recorded fluid balance and *vice versa*. As explained in Table 4, only two-thirds of the cohort had enough available data to make a comparison; the points shown in Figure 2 represent data collected over an average of two-thirds of those patients' hospital courses.

Discussion

Modeling Predictors of Changes in BNP

In this cohort of elderly inpatients with multiple co-morbid conditions, several pre-specified parameters (time between

Table 4. Availability and reliability of weights and fluid balance over the hospital course

	Labs drawn (% of hospital days)*	Weight recorded (% of hospital days)*	Fluid balance (ml)**	Weight change (kg)**	LOS represented (%)**
Overall	94 ± 11	50 ± 33	–780 ± 4000	–1.7 ± 5.3	66 ± 33
Telemetry monitoring (% LOS)					
< 33	95 ± 9	36 ± 23	1320 ± 2750	–2.2 ± 9.3	46 ± 35
33–66	87 ± 19	42 ± 28	–2380 ± 2420	–1.6 ± 2.7	64 ± 33
> 66	94 ± 10	58 ± 37	–1280 ± 4550	–1.5 ± 3.9	74 ± 31
LOS (days)					
< 3	97 ± 10	51 ± 38	–1660 ± 2440	–3.1 ± 2.4	71 ± 34
3–7	93 ± 11	57 ± 32	–2325 ± 4400	–2.5 ± 3.3	66 ± 36
> 7	91 ± 13	46 ± 32	1200 ± 4000	–0.1 ± 7.3	63 ± 32
Initial BNP (pg/ml)					
< 100	100 ± 0	67 ± 26	143 ± 1680	–0.4 ± 1.0	70 ± 34
100–400	89 ± 14	40 ± 28	750 ± 2300	–1.7 ± 9.4	50 ± 32
> 400	94 ± 11	52 ± 36	–1600 ± 4890	–2.0 ± 4.0	71 ± 33

Values are mean ± standard deviation; *$p < 0.0001$ for all comparisons between availability of weights and labs; **only 40 of 60 patients had sufficient data for a comparison between net fluid balance and change in weight; LOS = length of stay.

measurements, inter-measurement diuretic dose, inter-measurement beta-blocker dose) were associated with our definition of a significant change in serial BNP measurements. Each of these predictors can be linked with a change in BNP by a physiologically plausible mechanism. Assuming some degree of efficacy, diuretics administered between BNP measurements can be expected to cause a decrease in cardiac preload; BNP levels have been shown to correlate with changes in pulmonary capillary wedge pressure, a widely used surrogate for preload [26]. The effect of beta-blockade on serial BNP measurements taken over weeks to months has been studied previously in small groups of patients with chronic heart failure. In patients receiving concurrent ACEI [10] and in those with preserved ejection fraction [27], treatment with beta-blockers for one year resulted in a significant decrease in BNP levels. Several studies of patients with impaired left ventricular function treated for up to 12 months with beta-blockers have shown results ranging from no change in BNP concentrations [28] to sustained decrease in BNP levels [29]. Our results suggest that beta-blocker therapy may affect neurohormonal status, as reflected by changes in BNP, within hours to days of treatment, which is consistent with the relatively short half-lives of commonly used agents. In the present study, longer inter-measurement intervals were also associated with significant BNP changes. This finding is consistent with prior work [22] that suggested the utility of serial testing increases with inter-measurement interval, reaching a maximum at approximately one week.

It is not surprising that inter-measurement interval and inter-measurement doses of diuretics and neurohormonal antagonists are correlated with each other. A longer interval between measurements allows a greater cumulative dose of these standard heart failure medications to be administered. In this capacity, inter-measurement interval may contribute to the change in BNP's ability to serve as a marker of the net effect of efforts expended towards treatment of heart failure in a given patient. Similarly, since diuretics, ACEI, and beta-blockers are often given concurrently in the setting of heart failure treatment, the fact that there are correlations between the inter-measurement doses of some of these agents is not surprising.

Determination of the Threshold for a Significant Change in BNP

There are no uniform established guidelines to adjudicate what constitutes a meaningful change in BNP over any given period of time. Using the concept of biologic variation, prior work has suggested that, based on clinical status, changes in BNP levels are significant if they demonstrate a change of 77 % or 129 % of the initial value [21, 23]. However, those figures are based on small studies in healthy subjects or non-hospitalized patients with stable heart failure, characteristics not shared by the present cohort. In a small group of stable heart failure patients, the intra-individual variation in BNP levels over 24 hours was found to be 24 % [23]. We chose to incorporate this latter figure into our criteria for significance as changes below this level were unlikely to be indicative of the effects of therapy on BNP levels. Recognizing that small changes in low levels might be interpreted as significant if this criterion was used alone, we also included in our definition of significance a component of absolute change in BNP. Using the mean initial level from our cohort, the value of 200 pg/ml was arrived at; this value represents an intermediate between the previously used thresholds of three coefficients of variation of the assay used at our institution (~ 12 %) [16, 24] and the 30 % difference used to stratify levels of change in a recent study whose population closely resembles our own [15]. The clinical relevance of a change in BNP likely depends on both its relative and absolute value; similar combinations of parameters have been used in pulmonary medicine to define meaningful changes in FEV_1 measurements before and after bronchodilator challenge [30].

Role of Laboratory Testing in the Inpatient Assessment of Volume Status

In the absence of invasive hemodynamic monitoring, clinicians rely on weights, fluid balance, and physical examination to assess volume status. While the latter has shown to have prognostic value in heart failure patients [31], its overall reliability may be limited [32]. Our data suggest that weights are difficult to obtain in hospitalized patients and that fluid balance, as measured in the hospital, is an inaccurate substitute for daily weights. Conversely, our study showed that daily lab tests in the hospital setting are readily available and, in the case of BNP, could potentially offer an increased level of precision over standard measures of volume status.

Study Limitations

There are several limitations to the current study. Its small size and retrospective nature limit the generalizability of the findings, although the cohort is representative of a typical general medical inpatient population. The decisions to repeat BNP measurements are not accounted for, thereby potentially subjecting the cohort to selection bias. However, in this setting, a systematic rationale that would have non-uniformly included or excluded subsets of patients from getting repeat BNP measurements seems unlikely. The number of potential predictors and models tested was kept to a minimum due to limitations in power and in order to avoid the effects of multiple comparisons. Therefore, there may be other important predictors of serial BNP changes that were not identified. For example, the cumulative inter-measurement effect of all neurohormonally active medications may be a more useful predictor of change in BNP levels than the effects of individual agents, which were tested in the current study. In addition, we did not assess the impact of baseline heart rhythm or inter-measurement changes in heart rhythm. Although there have been conflicting reports regarding the effect of atrial fibrillation on single BNP measurements [33, 34], BNP levels can change rapidly after electrical cardioversion to sinus rhythm [35]. The definition of a significant BNP change used in the current study has not been validated elsewhere. In addition to incorporating criteria for relative and absolute changes, the most informative definition of a significant change in BNP may also depend on the initial BNP level. The accuracy of the primary data collection for daily weights and fluid balance may not have been optimal and, as such, may underestimate the correlation between the two. However, those data reflect standard practice in a large tertiary care center, which is perhaps a more realistic approximation of a "real world" setting than a rigorously controlled trial. Finally, we did not assess the impact of changes in BNP or the determinants of such changes on hospital readmission rates or post-discharge outcomes.

In summary, the current study suggests that serial BNP levels measured in hospitalized patients may report on preload response to diuretics and neurohormonal response to beta-blocker therapy. Additionally, the lack of availability and the inaccuracy of standard non-invasive measures of volume status limit their utility in the inpatient setting. Further investigation is warranted to identify the optimal inter-measurement interval and optimal criteria for a clinically significant change in BNP levels for hospitalized patients.

References:

1. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natiuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347: 161–7.
2. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004; 350: 647–54.
3. Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med 2004; 164: 1978–84.
4. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355: 1126–30.
5. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stenek B, Pacher R. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002; 105: 2392–7.
6. Hartmann F, Packer M, Coats AJS, Fowler MB, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Anker SD, Amann-Zalan I, Hoersch S, Katus HA. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure. Circulation 2004; 110: 178–6.
7. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004; 350: 655–63.
8. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. Circulation 1993; 87 (Suppl 6): V140–V148.
9. Benedict CR, Francis GS, Shelton B, Johnstone DE, Kubo SH, Kirlin P, Nicklas J, Liang CS, Konstam MA, Greenberg B, Yusuf S. Effect of long-term enalapril therapy on neurohormones in patients with left ventricular dysfunction. Am J Cardiol 1995; 75: 1151–7.
10. Fung JW, Yu CM, Yip G, Cahn S, Yandle TG, Richards AM, Nicholls M, Sanderson JE. Effect of beta blockade (carvedilol or metoprolol) on activation of the renin-angiotensin-aldosterone system and natriuretic peptides in chronic heart failure. Am J Cardiol 2003; 92: 406–10.
11. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003; 107: 1278–83.
12. Bettencourt P, Frioes F, Azevedo A, Dias P, Pimenta P, Rocha-Goncalves F, Ferreira A. Prognostic information provided by serial measurements of brain natriuretic peptide in heart failure. Int J Cardiol 2004; 93: 45–8.
13. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001; 37: 386–91.
14. Logeart D, Thabut G, Jourdain P, Chavelas C, Peyne P, Beauvais F, Bouvier E, Solal AC. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol 2004; 43: 635–41.
15. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004; 110: 2168–74.
16. Wu AHB, Packer M, Smith A, Bijou R, Fink D, Mair J, Wallentin L, Johnston N, Feldcamp CS, Haverstick DM, Ahnadi CE, Grant A, Despres N, Bluestein B, Ghani F. Analytical and clinical evaluation of the Bayer ADVIA Centaur automated b-type natriuretic peptide assay in patients with heart failure: a multisite study. Clin Chem 2004; 50: 867–73.
17. Clark AL, Coats AJS. Severity of heart failure and dosage of angiotensin converting enzyme inhibitors. Br Med J 1995; 310: 973–4.
18. Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. Eur Heart J 2004; 25: 1454–70.
19. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004; 25: 1341–62.
20. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004; 147: 331–8.
21. Wu AHB, Smith A. Biologic variation of the natriuretic peptides and their role in monitoring patients with heart failure. Eur J Heart Fail 2004; 6: 355–8.
22. Wu AHB, Smith A, Apple FS. Optimum blood collection intervals for B-type natriuretic peptide testing in patients with heart failure. Am J Cardiol 2004; 93: 1562–3.
23. Wu AHB, Smith A, Wieczorek W, Mather JF, Duncan B, White CM, McGill C, Katten D, Heller G. Biologic variation for N-terminal pro and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am J Cardiol 2003; 92: 628–31.
24. Miller WL, Hartman KA, Burritt MF, Borgeson DD, Burnett JC, Jaffe AS. Biomarker responses during and after treatment with nesiritide infusion in patients with decompensated chronic heart failure. Clinical Chemistry 2005; 51: 569–77.
25. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2005; Vienna, Austria. http://www.R-project.org.
26. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001; 7: 21–9.
27. Takeda Y, Fukutomi T, Suzuki S, Yamamoto K, Ogata M, Kondo H, Sugiura M, Shigeyama J, Itoh M. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. Am J Cardiol 2004; 94: 448–53.
28. Yoshizawa A, Yoshikawa T, Nakamura I, Satoh T, Moritani K, Suzuki M, Baba A, Iwanaga S, Mitamura H, Ogawa S. Brain natriuretic peptide response is heterogeneous during beta blocker therapy for congestive heart failure. J Card Fail 2004; 10: 310–5.
29. Frantz RP, Olson LJ, Grill D, Moualla SK, Nelson SM, Nobrega TP, Hanna RD, Backes RJ, Mookadam F, Heublein D, Bailey KR, Burnett JC. Carvedilol therapy is associated with a sustained decline in brain natriuretic peptide levels in patients with congestive heart failure. Am Heart J 2005; 149: 541–7.
30. National Asthma Education Program. Expert panel report II: Guidelines for the diagnosis and management of asthma. Publication No 97-4051. National Institute of Health, Bethesda, MD, 1997.
31. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 2001; 345: 574–81.
32. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. J Am Med Assoc 1989; 261: 884–8.
33. Rossi A, Enriquez-Sarano M, Burnett JC, Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. J Am Coll Cardiol 2000; 35: 1256–62.
34. Silvet H, Young-Xu Y, Walleigh D, Ravid S. Brain natriuretic peptide is elevated in outpatients with atrial fibrillation. Am J Cardiol 2003; 92: 1124–7.
35. Vinch CS, Rashkin J, Logsetty G, Tighe DA, Hill JC, Meyer TE, Rosenthal LS, Aurigemma GP. Brain natriuretic peptide levels fall rapidly after cardioversion of atrial fibrillation to sinus rhythm. Cardiology 2004; 102: 188–93.