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ORIGINAL RESEARCH

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# Acute on chronic heart failure—Which variations on B-type natriuretic peptide levels?

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## Abstract

**Objective:** Natriuretic peptides are useful diagnostic and prognostic markers in patients presenting to the emergency department (ED) with acute shortness of breath. However, B-type natriuretic peptide (BNP) level represents a single snapshot in time, while changes relative to a patient's baseline may be useful in risk stratification. We aimed to define the variation of BNP levels between chronic stable and acute decompensated heart failure (ADHF) that is associated with significant clinical outcomes.

**Methods:** We performed a retrospective cohort chart review study of chronic heart failure (HF) patients followed in an outpatient clinic from 2010 to 2013. Inclusion criteria were available hospital and clinic BNP levels and at least 1 year of follow-up care. ADHF was defined as a hospital admission for acute HF. Dry BNP was defined as its concentration after >3 months of optimal treatment and no variations in New York Heart Association class. Dry BNP was compared to the BNP at a subsequent ED visit that was associated with hospitalization because of ADHF.

**Results:** Overall, 253 patients were included. Their median (interquartile range [IQR]) dry BNP was 191(83–450) pg/mL. There were 67 ADHF admissions, occurring 15 ± 15 months after patient's dry BNP was established. At subsequent ED admission, the median (IQR) BNP was 1505 (72–2620) pg/mL. Patients requiring inpatient admission had a BNP ~250% higher than their stable BNP (404 vs 164 pg/mL, $p < 0.001$).

**Conclusions:** In this group of chronic stable HF patients, a doubling of BNP was observed in patients who required hospitalization for acute decompensated HF. BNP doubling may represent a useful parameter to reflect clinically relevant acute decompensated HF.

KEYWORDS
acute decompensated heart failure, B-type natriuretic peptide, chronic heart failure

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# 1 | INTRODUCTION

## 1.1 | Background

Heart failure (HF) affects an estimated 26 million people and is responsible for 1%–2% of hospitalizations in the United States and Europe.[1] Natriuretic peptides (NPs), including B-type natriuretic peptide (BNP) and its amino-terminal pro-peptide equivalent (NT-proBNP), represent the current gold standard of biomarkers for diagnosis, severity assessment, management, and prognosis of HF.[2] The clinical value of NPs is well recognized and their strong negative predictive value for a HF diagnosis is highlighted in HF guidelines.[3,4] In patients with suspected acute HF, BNP has the potential to allow rapid and accurate exclusion of the diagnosis.[5]

## 1.2 | Importance

BNP is secreted from the heart ventricle, in response to any condition that contributes to volume or pressure overload, mainly reflecting the degree of myocardial stretching and dysfunction.[6] Conversely, it is decreased with concurrent obesity or as a result of effective heart failure therapy. Finally, it may be chronically elevated in stable heart failure or as a result of renal insufficiency.[7] Thus, knowledge of the patient's stable baseline BNP concentration, in comparison to the level at emergency department (ED) presentation, is important to determine if relative changes are clinically significant. Unfortunately, the definition of a clinically relevant BNP change that is associated with hospitalization is poorly described.

## 1.3 | Goals of this investigation

The aims of this study were to determine the variation of BNP levels in a population of chronic stable patients and to identify what levels were associated with future acute decompensated HF (ADHF) hospitalizations.

# 2 | MATERIAL AND METHODS

## 2.1 | Design

We conducted a retrospective chart review of patients with chronic HF followed in a HF clinic of a university tertiary care hospital.[8]

## 2.2 | Selection of patients

Patients with a first appointment between January 2010 and December 2013 and a follow-up of more than 1 year were included. Patients not achieving clinically stability under optimal medical treatment for a 3-month period until end of study period and patients lost to follow-up were excluded. Demographic, clinical, laboratory, and echocardiogram parameters were recorded.

**The Bottom Line**

B-type natriuretic peptide (BNP) levels in chronic heart failure are often a challenge to interpret. In this retrospective study of 253 chronic heart failure patients, 67 patients admitted for acute decompensation had a BNP 2.5 × their baseline, which may represent a clinically relevant parameter.

We defined a patient's dry BNP as the level after 3 months of optimal guideline compliant treatment,[9] in a clinically stable patient (defined as no change in New York Heart Association [NYHA] class), for whom BNP remained unchanged (with a mean fold change of 1.0), for at least 2 consecutive visits. Routine laboratory values were recorded. Plasma creatinine at admission was compared to steady state, as creatinine levels can be associated with increase in BNP levels.[10]

## 2.3 | Outcome

The first 2 hospital admissions for ADHF (diagnosis according to the European Society of Cardiology)[9] after the initial appointment were eligible for registry inclusion. Patients presenting with ADHF because of acute coronary syndrome, and those whose symptoms were ultimately attributed to non-ADHF causes, were excluded. Clinical and laboratory parameters were detailed by chart review. Dry BNP was compared to the first BNP obtained at their ADHF hospitalization. All BNP concentrations were measured in the same core laboratory.

## 2.4 | Data analysis

Patients with and without ADHF admissions were compared in terms of demographic, clinical, laboratory and echocardiogram parameters. Continuous variables of baseline demographic and clinical characteristics are presented as mean (standard deviation) if normally distributed, or median (interquartile range [IQR]) if non-normally distributed. Categorical variables are presented as count (percent). Variable comparisons were done by chi-square testing for categorical variables. Normal and skewed distribution continuous variables were evaluated by either a 2 independent-sample t-test or the Mann–Whitney U test, respectively. All statistical analyses were conducted with SPSS 20.0, and a $p < 0.05$ was considered statistically significant. The study protocol has been approved by the local ethics committee.

# 3 | RESULTS

## 3.1 | Baseline characteristics of the patients

During the study period, 442 patients had a first appointment in our HF clinic. From these, 189 (42%) were excluded, because of a

**TABLE 1** Baseline characteristics of the patients and comparison between patients with and without admissions for ADHF

| | Sample (n = 253) | Admitted for ADHF (n = 50) | Not admitted for ADHF (n = 203) | *p* Value |
|---|---|---|---|---|
| Age (y), median (IQR) | 71 (19) | 76 (13) | 70 (19) | 0.01 |
| Male, n (%) | 176 (70) | 39 (78) | 137 (68) | 0.15 |
| Etiology of HF, n (%) | | | | |
| Ischemic | 111 (44) | 31 (62) | 80 (39) | 0.01 |
| Idiopathic | 62 (25) | 8 (16) | 54 (27) | 0.12 |
| Hypertensive | 25 (10) | 7 (14) | 18 (9) | 0.28 |
| Alcoholic | 19 (8) | 1 (2) | 18 (9) | 0.10 |
| Valvular | 16 (6) | 1(2) | 15 (7) | 0.16 |
| Other | 20 (8%) | 2 (4) | 18 (9) | 0.14 |
| Cardiovascular risk factors/co-morbidities, n (%) | | | | |
| Arterial hypertension | 171 (68) | 34 (68) | 137 (68) | 0.52 |
| Diabetes mellitus | 98 (39) | 31 (62) | 67 (33) | 0.01 |
| Body mass index, kg/m$^2$, median (IQR) | 26 (7) | 26 (6) | 26 (7) | 0.46 |
| CKD ≥3 KDIGO | 72 (29) | 24 (48) | 48 (24) | 0.01 |
| AF | 70 (28) | 22 (44) | 48 (24) | 0.01 |
| NYHA functional class (stable status), n (%) | | | | |
| I | 89 (35) | 7(14) | 82 (40) | 0.01 |
| II | 133 (53) | 31 (62) | 102 (50) | 0.14 |
| III | 30 (12) | 12 (24) | 18 (9) | 0.01 |
| IV | 1 | 0 | 1 | |
| LV ejection fraction, n (%) | | | | |
| Preserved (>50%) | 17 (7) | 6 (12) | 11 (5) | 0.10 |
| Mid-range (40%–49%) | 29 (11) | 5 (10) | 24 (12) | 0.17 |
| Reduced (30%–39%) | 63 (25) | 10(20) | 53 (26) | 0.37 |
| Severely reduced (<30%) | 144 (57) | 29 (58) | 115 (57) | 0.86 |
| Basal BNP (stable status), pg/mL, median (IQR) | 191 (370) | 404 (524) | 164 (247) | 0.01 |
| Pharmacologic treatment | | | | |
| ACEi, n (%) | 205 (89) | 36 (72) | 169 (83) | 0.07 |
| Lisinopril equivalent-dose, mg/d, mean ± SD | 13 ± 9 | 10 ± 7 | 13 ± 7 | |
| ARB, n (%) | 11 (4) | 1 (2) | 10 (5) | |
| BB, n (%) | 234 (92) | 43 (86) | 191 (94) | 0.10 |
| Carvedilol equivalent-dose, mg/d, mean ± SD | 28 ± 16 | 25 ± 15 | 29 ± 16 | |
| Loop diuretics, n (%) | 208 (82) | 49 (98) | 159 (78) | 0.01 |
| Furosemide equivalent-dose, mg/d, mean ± SD | 78 ± 47 | 101 ± 56 | 71 ± 42 | |
| MRA, n (%) | 87 (34) | 16 (32) | 71 (35) | 0.43 |
| Spironolactone equivalent-dose, mg/d, mean ± SD | 19 ± 13 | 21 ± 21 | 18 ± 10 | |
| Ivabradine, n (%) | 23 (9) | 3 (6) | 20 (10) | 0.39 |

Abbreviations: ACEi, angiotensin conversion enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BB, beta-blockers; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; NS, not significant; NYHA, New York Heart Association.

follow-up of <1 year (n = 144 [32.5%]) or for not having a stable BNP (n = 45 [10.1%]). Overall, we included 253 patients (70% men), with a median (IQR) age of 71 (60–78) years. Baseline characteristics of the patients are presented in Table 1.

When stable, most patients were in NYHA class I or II. Left ventricular ejection fraction (LVEF) was reduced (LVEF <40%) in 207 (82%) and severely reduced (<30%) in 144 (57%). Consistent with guideline directed therapy for a population with high rates of systolic

dysfunction, most patients were taking angiotensin conversion enzyme inhibitors (n = 205; 89%) and beta-blockers (n = 234; 92%). Mineralocorticoid receptor antagonists were prescribed in 34%. The median (IQR) dry weight BNP was 191 (83–450) pg/mL.

### 3.2 | Admissions for acute decompensated heart failure

During follow-up (ranging from 12 to 73 months), there were 67 admissions for ADHF, in 50 patients. The major decompensating factors were infection (n = 18; 27%), progression of the disease (n = 10; 15%), poor therapeutic compliance (n = 9; 13%), and dysrhythmia (n = 7; 10%); in 15% of the cases, the decompensating factor was not identified. At admission, 49% of the patients were NYHA Class IV.

ADHF hospitalization occurred an average of 15 ± 15 months after dry BNP was reached. Median (IQR) admission BNP was 1505 (724–2620) pg/mL, corresponding to an increase of 2.5 times the dry weight BNP. Plasma creatinine was also increased in 27 cases, from 1.5 to 5 times higher versus the steady state value.

Hospital length of stay was a mean (±SD) of 7 (±5) days. Although most patients were managed on a regular medical floor, 19 required an intermediate care unit. Of the latter, 7 needed non-invasive mechanical ventilation and 7 required inotropic support. Nine patients (18% of patients admitted) died during hospitalization. There were 23 cases of hospital readmission at 6 months, within a mean of 73 ± 53 days.

### 3.3 | Comparison between groups

When compared to patients not admitted for ADHF (Table 1), patients admitted for ADHF were older, with a higher prevalence of diabetes mellitus, CKD ≥3 Kidney Disease Improving Global Outcomes (KDIGO) (48% vs 24%, $p < 0.001$) and atrial fibrillation. Patients admitted for ADHF also had a higher proportion of a history of ischemic heart disease as the cause of their HF and were more frequently NYHA class III at baseline, despite having received similar pharmacologic treatment. Finally, we found no differences on LVEF between the 2 groups. Dry BNP was significantly higher in patients subsequently admitted for ADHF (404 vs 164 pg/mL, $p < 0.001$).

### 3.4 | Limitations

There are limitations in this study. Being a single-center study, its confirmation by other centers is needed, and the low frequency of HF with preserved ejection fraction in our population may constitute a selection bias. Additionally, only 20% of our patients were admitted for ADHF. Although consistent with a stable population, this supports the predictive capability of an elevated dry BNP. Furthermore, because of limited sample size, we are not able to comment on the clinical significance of BNP increases smaller than a doubling of baseline. It must also be considered that, in the era of angiotensin receptor neprilysin inhibitor therapy for HF with reduced ejection fraction (HFrEF),[3,11,12] its association with an increased BNP may decrease its use as a disease monitoring marker. However, this should be considered in view of real-world eligibility data that suggest only 20%–40% of HFrEF patients are sacubitril/valsartan candidates,[13] such that our data remains applicable for the majority of HF patients. Finally, because of our retrospective chart review methodology, our findings must consider limited to hypothesis generating only, with future prospective evaluations required to identify the precise delta BNP that will predict the necessity for ADHF hospitalization.

## 4 | DISCUSSION

In patients presenting to the ED and subsequently requiring inpatient hospitalization for ADHF, we found that BNP levels were ~250% higher than their dry BNP. This suggest that doubling of baseline BNP represents a threshold of a clinically meaningful increase in BNP.

Although many studies report on BNP in various environments, including its use as a diagnostic tool in the emergency setting[5,14,15] and for risk stratification and prognosis when hospitalized for HF,[16–19] the magnitude of changes of dry BNP levels in patients with chronic stable HF who decompensate and require hospitalization for ADHF has not been previously reported.

It has been demonstrated that BNP increases with age,[20] and it may increase as HF duration increases, even when adjusted for age.[21] The variation of NPs' levels in stable chronic HF patients has already been assessed by our group and others.[22,23] In HF patients, variations of intra-individual BNP concentrations of >30% (ranging from 30% to 50%), with reference change values at the 95% confidence interval ranging from 99% to 130%, have been described.[24] According to these results, only a great variation in BNP levels should be considered significant in an individual patient. Our results expand this knowledge, suggesting that the relevant BNP increase of 2.5 from baseline indicates significant clinical deterioration that required hospitalization.

In chronic HF, a doubling of the dry BNP test result is clinically relevant and is associated with an increased risk of subsequent hospitalization. This knowledge may assist ED physicians' decisions on the management of these patients.

### AUTHOR CONTRIBUTIONS

PB: Design the study, wrote paper. IC: Collected data, added in writing the paper. FS: Collected data, added in writing the paper. PL: Design the study, statistical analysis. FP: Participated in writing, major contribution for remaking the paper before submission.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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