Delta NT-proBNP: Better Marker of Neuroendocrine Pathways Blockade in Decompensated Congestive Heart Failure?

Valentín Del Río-Santiago, MD; Luis F. Rodríguez-Ospina, MD; Robert P. Giugliano, MD; and Sonia Vicenty-Rivera, MD

The American College of Cardiology, the American Heart Association, and the Heart Failure Society of America currently recommend using NT-proBNP only when the diagnosis of heart failure is in doubt. This clinical evaluation of 148 records of patients consecutively discharged from VA Caribbean Healthcare System in San Juan, Puerto Rico, provides compelling evidence that delta NT-proBNP can be a useful tool in the clinical assessment and management of elderly patients hospitalized with decompensated congestive heart failure.

Congestive heart failure (CHF) constitutes a major disorder affecting a large number of patients within the U.S. and its territories. Worldwide, CHF is the leading cause of hospital admissions among patients aged > 65 years.[1] A 2010 update from the American Heart Association (AHA) estimated that there were 5.8 million people with heart failure (HF) in the U.S. in 2006.[1] Furthermore, the use of biomarkers within the cardiology field has increased in popularity.

As part of the ongoing studies of HF, biomarkers belonging to the natriuretic peptide family are now a matter of current research. B-type natriuretic peptide (BNP) is secreted by heart chambers as pre-proBNP and then enzymatically cleaved to the N-terminal-proBNP (NT-proBNP) and BNP in response to excessive stretching of cardiomyocytes.[2-4] Both peptides (BNP and NT-proBNP) have proven useful in the diagnosis of HF patients.[5] The American College of Cardiology (ACC), the AHA, and the Heart Failure Society of America (HFSA) recommended their use for screening and risk stratification of patients in which the diagnosis of HF is uncertain.[2,3] Despite its impact and significance, data have been published about the intraindividual biologic variability of these cardiac biomarkers and need to be considered when interpretation and conclusions about serial NT-proBNP testing is performed.[5] Delta NT-proBNP has been used in patients with acute coronary syndrome, predicting short-term adverse cardiac events and being superior to baseline NT-proBNP.[6] Although the baseline serum NT-proBNP level is a well-recognized tool for diagnosis and prognosis of CHF, it is unclear whether delta NT-proBNP (delta NT-proBNP = NT-proBNP admission − NT-proBNP discharge) is effective in Hispanic patients admitted with decompensated CHF (D-CHF). On the basis of the aforementioned, a record review was performed to assess the potential clinical application of delta NT-proBNP in patients admitted with diagnosis of D-CHF as well as its relationship with patients' outcomes.[7-9]

METHODS

In a retrospective study, data from 148 patient records consecutively discharged from VA Caribbean Healthcare System (VACHS) in San

Dr. Del Río-Santiago is the chief cardiology fellow of the Cardiovascular Diseases Fellowship, **Dr. Rodríguez-Ospina** is the chief cardiologist and program director of the Cardiovascular Diseases Fellowship, and **Dr. Vicenty-Rivera** is staff physician, all in the Cardiology Section at the VA Caribbean Healthcare System in San Juan, Puerto Rico. **Dr. Giugliano** is staff physician at Brigham and Women's Hospital in Boston, Massachusetts.
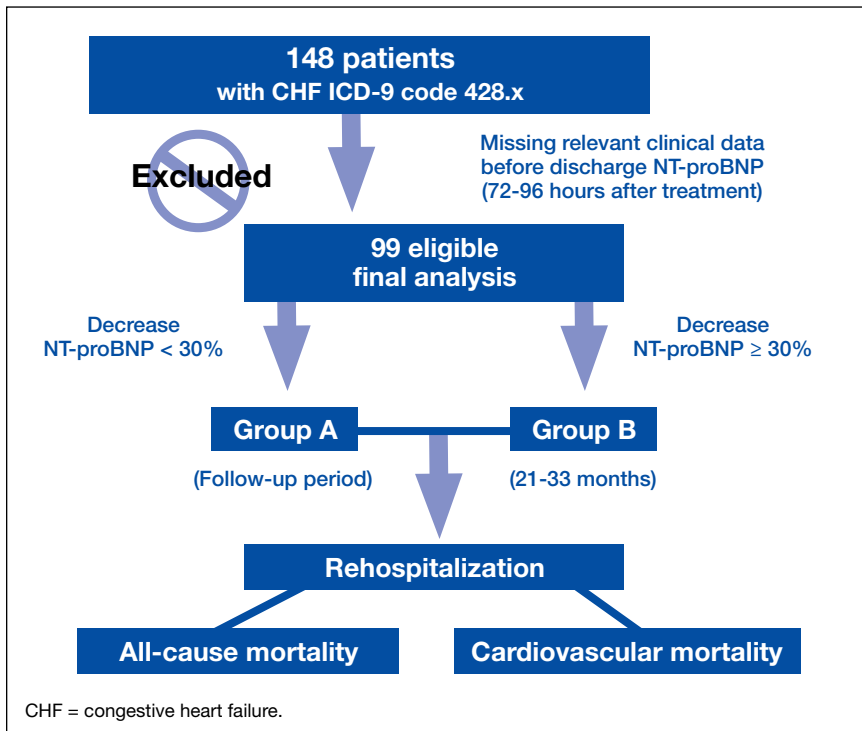
Figure 1. Flow chart of study methodology.

Juan, Puerto Rico, were reviewed between July 1, 2007, and June 30, 2008, in which there was a diagnosis of HF based on the International Classification of Diseases ([ICD]-9 code 428.x). The diagnosis of D-CHF was confirmed by a cardiology fellow, based on the description of typical symptoms and clinical findings supported by an electrocardiogram, chest X-ray, and Doppler echocardiography, as recommended by current guidelines of the ACC/AHA/HFSA.[2,3] Forty-nine patients were excluded because of missing proBNP data at admission before discharge. Subgroup analysis of clinical, demographic, laboratory, and echocardiographic data were assessed from the electronic medical records of 99 subjects that met the study inclusion criteria of both admission (before treatment) and before discharge (72 to 96 hours after treatment) NT-proBNP level data.

Patients were divided into 2 groups (group A and group B).

Group A comprised those patients with a reduction from the admission NT-proBNP to the discharge NT-proBNP level < 30% (delta NT-proBNP < 30%). Group B included those patients that achieved a differential reduction from the admission to the discharge NT-proBNP level > 30% (delta NT-proBNP > 30%). The employed 30% cutoff for the group division was established based on the previous study by O'Brien and colleagues, the mean length of stay for HF hospitalization, and taking into account the significance of the relative change value to demonstrate a difference in brain natriuretic peptide results over time.[2,5] Rehospitalization and survival probability estimates of both groups were determined. Patients were followed from admission date to a minimum of 21 months (Figure 1).

STATISTICAL ANALYSIS

Variables were summarized using the mean for continuous data and frequencies and percentage for categorical data. Differences between subject groups were tested using analysis of variance adjusted for continued variables, *t* test for ordinal variables, and chi-square or Fisher exact test for categorical values. Logistic regression analysis was used to determine which factors were associated with the finding of delta NT-proBNP ≥ 30% in this group of patients with CHF. Results were expressed as odds ratio (OR) and 95% of confidence intervals (CI) of the OR. Significance levels were indicated by a *P* < .05. Cox proportional hazard model in multivariable analysis was used to investigate the ability of delta NT-proBNP ≥ 30% to independently predict all-cause mortality, cardiovascular mortality, and rehospitalization events in the patients' cohort. All analysis was conducted using NCSS Statistical Analysis and Graphics Software (Kaysville, Utah), version 2004.

RESULTS

Population mean age was 76.7 ± 8.8 years; mean New York Heart Association (NYHA) class 3; mean left ventricular ejection fraction (LVEF) was 36.6 ± 16.0%; mean admission NT-proBNP was 12,965.0 ± 10,341.7 pg/mL; and mean discharge NT-proBNP was 10,717.1 ± 10,736.5 pg/mL. Mean hemoglobin (Hgb) and hematocrit (Hct) were 12.3 ± 2.1 g/dL and 36.9 ± 6.2%. Most patients had chronic kidney insufficiency stage 3 with a mean serum creatinine (SCr) of 1.59 ± 0.81 mg/dL and mean glomerular filtration rate (GFR) of 54.7 ± 22.6 mL/min. The baseline clinical and laboratory data of the 99 patients are shown in Table 1. Subjects in the investigation were further

Table 1. Baseline characteristics comparing group A vs group B (n = 99)

	Group A (n = 66)	Group B (n = 33)	P value
Basic data			
Age (years)	76.5 ± 9.4	77.3 ± 7.7	= .65
LVEF (%)	35.6 ± 16.0	38.5 ± 16.0	= .40
NYHA class	3.02 ± 0.8	2.8 ± 0.9	= .23
SBP (prior to discharge [mm Hg])	141.6 ± 15.8	132.4 ± 15.0	= .006
HR (before discharge [bpm])	88.8 ± 17.5	81.2 ± 14.6	= .02
Height (cm)	169.9 ± 6.9	171.7 ± 15.8	= .54
Weight (kg)	79.2 ± 23.3	80.6 ± 18.2	= .75
BMI (kg/m^2)	27.4 ± 7.7	27.6 ± 6.9	= .87
Laboratory data			
Hgb (g/dL)	11.9 ± 1.8	13.1 ± 2.3	= .01
Hct (%)	35.6 ± 5.5	39.3 ± 6.8	= .01
SCr (mg/dL)	1.70 ± 0.9	1.46 ± 0.47	= .17
BUN (mg/dL)	31.1 ± 19.6	29.4 ± 13.4	= .61
GFR (mL/min)	53.3 ± 23.1	57.4 ± 21.6	= .39
Albumin (g/dL)	3.5 ± 0.6	3.4 ± 0.5	= .74
Serum sodium (mEq/L)	139.2 ± 4.1	139.1 ± 4.5	= .91
Admission proBNP	13,156.3 ± 10,322.5	12,582.5 ± 10,529.6	= .80
Discharge proBNP	14,262.1 ± 11,352.2	3,627.1 ± 3,674.0	= .001
Serum glucose (mg/dL)	160.2 ± 83.9	145.4 ± 83.9	= .41
Associated conditions (%)			
Arterial hypertension	93.9	81.8	= .12

divided into group A if they achieved a delta NT-proBNP < 30% (differential reduction from admission to discharge NT-proBNP level < 30%) and group B if delta NT-proBNP ≥ 30%. Both groups were similar in most clinical, demographic, laboratory, and echocardiographic data: patient's age, medication profile, past medical history, smoking status, ethanolism status, NYHA classification, serum sodium, SCr, blood urea nitrogen, GFR, body mass index (BMI), serum albumin level, and LVEF (Table 1).

Although admission level of NT-proBNP was not different between both groups, follow-up NT-proBNP level was significantly higher in group A (14,262.1 ± 11,352.2 pg/mL) compared with group B (3,627.1 ± 3,674.0 pg/mL) (P = .001). Interestingly, the selected cohort demonstrated an association between a delta NT-proBNP < 30% (group A) with a higher baseline systolic blood pressure (SBP) and heart rate (HR) as well as a lower Hgb/Hct level; all of which demonstrated statistical significance (P < .006, P = .02, and P = .01, respectively) compared with group B. A 4-fold increase in the 30-day rehospitalization rate was noticed among patients in group A (P = .04), compared with patients in group B. Also, the data showed that among those with a difference from the admission to discharge NT-proBNP level was < 30% (group A = delta NT-proBNP < 30%), the survival probability estimate for any cause of death at the end of the study period was 0.57 (CI 95%, 0.46-0.66) compared with 0.90 (CI 95%, 0.82-0.95) in the group of patients with delta NT-proBNP ≥ 30% (group B) (Table 2). Survival probability estimate among group A (delta NT-proBNP < 30%) for cardiovascular death was 0.68 (CI 95%, 0.57-0.77); while in group B (delta NT-proBNP ≥ 30%) was 0.95 (CI 95%, 0.88-0.98) (Table 2).

Table 1. (continued)

	Group A (n = 66)	Group B (n = 33)	P value
Diabetes mellitus	60.6	60.6	NS
Dyslipidemia	62.1	57.6	= .75
Cardiovascular disease	25.8	42.4	= .31
Pacemaker	18.2	12.1	= .62
Peripheral vascular disease	22.7	18.1	= .73
Chronic obstructive pulmonary disease	25.8	21.2	= .74
Atrial fibrillation	42.4	33.3	= .54
Carotid disease	7.6	15.2	= .50
Myocardial infarction	47.0	21.2	= .06
Coronary artery bypass grafting	21.2	12.1	= .47
Percutaneous intervention	3.0	9.1	= .46
Smoking	43.9	48.5	= .77
Ethyl alcohol (ethanol)	48.5	45.6	= .84
Medication data			
Aspirin	59.0	73.0	= .35
Warfarin	21.2	18.2	= .82
Clopidogrel	23.4	26.7	= .78
Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers	75.8	78.8	= .80
Hydralazine + nitrates	22.7	18.2	= .73
Beta blockers	95.5	90.9	= .47

BMI = body mass index; BUN = blood urea nitrogen; GFR = glomerular filtration rate; Hct = hematocrit; Hgb = hemoglobin; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCr = serum creatinine; SBP = systolic blood pressure.

DISCUSSION

The development of HF symptoms is related to the activation of several neuroendocrine mechanisms.[10] In the event of a low renal perfusion pressure due to a fall in cardiac output, the renin-angiotensin-aldosterone system (RAAS) is activated, causing vasoconstriction along with sodium and water retention. RAAS activation serves as a renal protective mechanism to overcome vital organ hypoperfusion. However, it promotes the formation of reactive oxygen species (ROS), which is associated with endothelial damage to cardiac cells. Reactive oxygen species production also increases the oxidative states and decreases nitric oxide generation, enhancing activation of proinflammatory cytokines (IL-1, IL-6, CRP, TNF-α), which are linked with atherosclerosis and cardiac remodeling.[11] Sympathetic nervous system (SNS) activation also contributes as a compensatory mechanism. It stimulates renin release, generates ROS, and induces inflammation and myocardial damage (apoptosis, necrosis, and hypertrophy).[11] Even though these compensatory mechanisms provide valuable support for the heart in normal physiologic conditions, they also have a fundamental role in the progression of HF. That the physiologic role of brain natriuretic peptides involves the inhibition of RAAS, endothelin secretion, as well as counteracting the effects of norepinephrine, the authors considered that modification in the use and interpretation of NT-proBNP might change the overall HF management. Considering the potential source of error of plasma natriuretic concentrations depending on the assay used, age, gender, comorbidities (renal dysfunction, pulmonary embolism, etc), and BMI, the study revealed that a decrease in the admission NT-proBNP level of 30% or more is associated
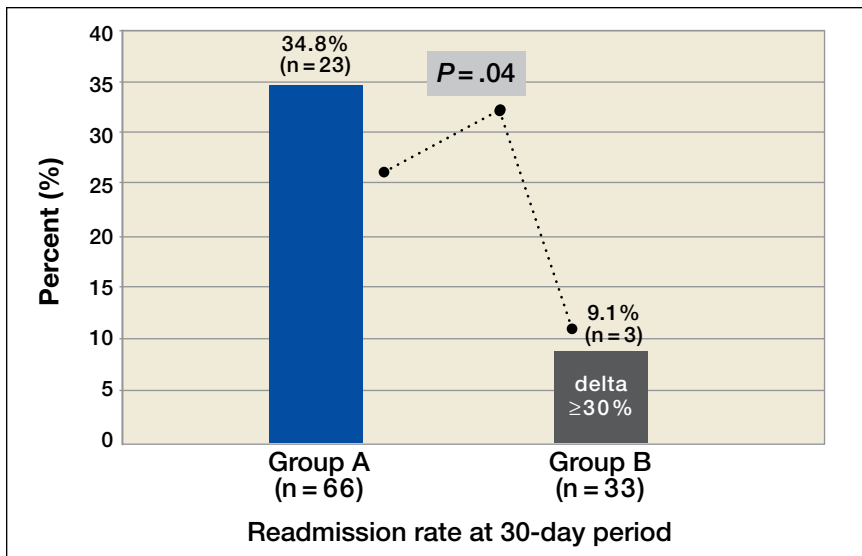
Figure 2. Difference in rehospitalization rate, according to delta proBNP variation.
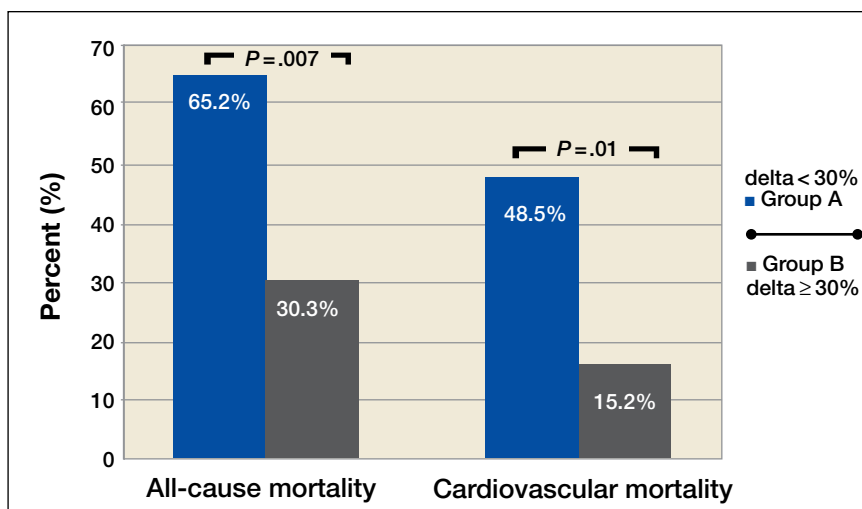

Figure 3. Difference in mortality rate, according to delta proBNP variation.

with a higher survival probability and a lower 30-day readmission rate.[7,12] The rationale for the use of the 30% cutoff was based on previous studies by O'Brien and colleagues and Bettencourt and colleagues.[13,14]

Systolic Blood Pressure and Heart Rate

It was observed that those patients with a delta NT-proBNP < 30% (differential reduction from the admission to discharge NT-proBNP level < 30%) had higher SBP and HR than those patients who attained a delta NT-proBNP ≥ 30%. Higher SBP and HR in group A are indicative of excessive SNS activation, aimed at maintaining cardiac output through increased catecholamine release.

Anemia

A low Hgb level is a frequent and deadly finding in patients with D-CHF.[10,15,16] Anemia etiology has a multifactorial origin (renal insufficiency, hemodilutional, cytokine activation, etc), being usually characterized as an anemia of chronic disease with normal mean corpuscular values.[16] Patients who achieved a delta NT-proBNP ≥ 30% (group B) had normal Hgb/Hct levels (13.1 ± 2.3) as established by the World Health Organization (Hgb < 13 g/dL or Hct < 39% in men and Hgb < 12.0 g/dL or Hct < 36% in women). However, patients in group A (difference from the admission NT-proBNP level to the discharge NT-proBNP level < 30%) had a significantly lower Hgb level (11.9 ± 1.8 g/dL); these values had statistical significance (P = .01). In the setting of HF, increased levels of acute phase reactants C-reactive protein, erythrocyte sedimentation rate, tumor necrosis alpha, and interleukin-6 cause anemia due to cytokine-mediated bone marrow suppression and inhibition of erythropoietin production.[11,17] Also the kidney's perception of inadequate circulating volume causes an excessive activation of neurohormonal compensatory mechanisms that enhances sodium and water retention, contributing to the development of "pseudoanemia" due to a dilutional effect.

Outcome

A few decades ago, research into the treatment of HF focused on the role of neuroendocrine blockade.[7,8,18] Today, no doubts exist about the increment in survival rates associated with the inhibition of the RAAS and adrenergic nervous system. The data revealed a 4-fold increase in the 30-day rehospitalization rate among patients in group A (delta NT-proBNP < 30%), compared with patients in group B (delta NT-proBNP

Table 2. Survival probability estimate comparing nonanemia vs anemia groups (n = 99)

	All-cause mortality		Cardiovascular mortality	
	Odds ratio	Confidence interval (95%)	Odds ratio	Confidence interval (95%)
Group A Delta proBNP < 30%	0.57	0.46-0.66	0.68	0.57-0.77
Group B Delta proBNP ≥ 30%	0.90	0.82-0.95	0.95	0.88-0.98
	P = .007		*P* = .01	

≥ 30%) (*P* = .04) (Figure 2). Moreover, those with a difference from the admission NT-proBNP level to the discharge NT-proBNP level < 30% (delta NT-proBNP < 30%) had a lower survival rate (all-cause and cardiovascular) than those with a change from the admission NT-proBNP to the discharge NT-proBNP level > 30% (delta NT-proBNP ≥ 30%). Compared with group B, patients in group A had 2.2 and 3.2 times the likelihood of all-cause mortality (*P* = .007) and cardiovascular mortality (*P* = .01), respectively (Figure 3). Interestingly, out of the entire study group, only one-third of the patients admitted with D-CHF had a follow-up NT-proBNP measurement.

The findings correlate with those observed by Bettencourt and colleagues and Noveanu and colleagues in terms of the use of serial natriuretic peptide levels to predict the mortality of those patients admitted with D-CHF.[13,19] In contrast, this study demonstrated that the use of delta NT-proBNP may be practical for predicting the chance of readmission at 30 days and may be applied to nonwhite groups, specifically to Hispanics. The latter statement is relevant because Hispanics constitute the largest and fastest growing ethnic group in the U.S., with epidemiologic studies revealing that Hispanics with HF are more likely to be younger and less likely to be insured than their non-Hispanic counterparts.[20-22]

Clinical Relevance
Although guidelines only recommend NT-proBNP use in cases when the diagnosis of HF is uncertain, the authors consider that the follow-up level with the calculation of delta (difference between admission [before treatment] and before discharge [72 to 96 hours after treatment]) NT-proBNP levels may provide valuable information that will permit the fine-tuning of medical therapy with the goal of obtaining the best possible neuroendocrine pathways blockade. The use of delta proBNP adds objective information to the clinical subjective impression of patient improvement. Furthermore, it may assist in the selection of patients who need a more intensive intervention or treatment optimization before discharge home or a closer follow-up as an outpatient.

Limitations
There are 2 limitations that need to be acknowledged and addressed regarding the present study. The first limitation concerns the retrospective nature of this investigation. The second limitation has to do with the extent the study findings can be generalized beyond the cases studied. This study is a subgroup analysis with a small sample. Therefore, a prospective analysis with a larger sample is required.

CONCLUSION
The incidence and prevalence of D-CHF among the elderly population shows an annual crescendo trend. It is well-known that the pathophysiologic basis of D-CHF involves activation and interaction of several neuroendocrine mechanisms (RAAS, oxidative stress, inflammation states, and SNS). Recognizing that D-CHF is a clinical diagnosis, current guidelines for HF management recommend using NT-proBNP only when the diagnosis of HF is in doubt. This study showed that delta NT-proBNP seems to be a simple, useful tool in the clinical assessment and management of elderly patients hospitalized with D-CHF. Delta NT-proBNP < 30% may serve as a marker of augmented neuroendocrine pathways activation and is associated with increased rates of readmissions and death outcomes. The authors believe that these results may be applicable to a large proportion of patients admitted with D-CHF, but first a prospective analysis with a larger sample may be required. ●

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