Neurohormonal Prediction of Post-Infarction Ventricular Dysfunction and Coronary Disease

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Little information is available about the potential role of brain (type B) natriuretic peptide in patients with acute myocardial infarction. We therefore analyzed peptide levels, measured at discharge from our coronary care unit, in 56 patients admitted with a diagnosis of acute myocardial infarction. We examined peptide concentrations in the light of different features in our patients, and found a significant association between natriuretic peptide levels and the two most important prognostic factors: left ventricular ejection fraction, and the severity and extent of coronary disease. Type B natriuretic peptide was a good predictor of these features, and we conclude that concentration of type B natriuretic peptide, measured at discharge from the coronary care unit, provides important clinical and prognostic information in patients with acute myocardial infarction.

Key words: *Natriuretic peptides. Myocardial infarction. Ventricular dysfunction.*

Predicción neurohormonal de disfunción ventricular y enfermedad coronaria postinfarto

Existen pocos datos acerca del comportamiento del péptido natriurético cerebral o tipo B en los pacientes con infarto agudo de miocardio. En este estudio evaluamos este aspecto mediante el análisis de los valores de péptido natriurético tipo B al alta de la unidad coronaria en 56 pacientes ingresados con el diagnóstico de infarto. Analizamos dichos valores en función de las características diferenciales de estos pacientes. Encontramos una asociación significativa entre los valores de péptido y los dos factores pronósticos a largo plazo más importantes en estos pacientes: la fracción de eyección del ventrículo izquierdo y la gravedad y extensión de la enfermedad coronaria, de los que el péptido natriurético tipo B es un buen predictor. Concluimos, por tanto, que los valores de péptido natriurético tipo B medidos al alta de la unidad coronaria proporcionan una importante información clínica y pronóstica en los pacientes con infarto agudo de miocardio.

Palabras clave: *Péptidos natriuréticos. Infarto de miocardio. Disfunción ventricular.*

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INTRODUCTION

Brain (or type B) natriuretic peptide (BNP) is a potent neurohormonal regulator with natriuretic and vasodilatory action. It also inhibits the activity of the sympathetic nervous system and the renin-angiotensin axis. The peptide is secreted by cardiac muscle (largely the ventricular muscle), mainly in response to pressure or volume overloads (or both).[1] In chronic heart failure (CHF), BNP can be used as a marker of neurohormonal activity, and its determination is of diagnostic[2,3] and prognostic[4] value. It is also of use in the monitoring of treatment.[5] Studies on the behavior and clinical importance of BNP in acute myocardial infarction (AMI), however, are rare, although high levels have been related to a greater incidence of CHF, systolic dysfunction, ventricular remodeling and, in general, poorer proginosis.[6-9] The aim of the present work was to determine the relationship between BNP levels at discharge from the coronary department and variables of interest in risk stratification before discharge in patients who had suffered AMI.

PATIENTS AND METHODS

The study subjects were 56 consecutive patients aged ≤65 years (53.6±9.4 years) who were discharged from the coronary department with a diagnosis of AMI according to new criteria.[10] At discharge, the plasma BNP level of all patients was recorded using a fluorescence immunoanalyzer (Triage BNP Test®, Biosite). This system brings a reactive strip into

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TABLE 1. **Patient Baseline and Clinical Characteristics***

Clinical characteristics (n=56)	
Age, years	53.6±9.46
Male	49 (87.5%)
Previous AMI	18 (32%)
Previous and/or inferior AMI	32 (57%)
Other site	6 (11%)
ACS with elevated ST segment	44 (78.6%)
ACS without elevated ST segment	12 (21.4%)
CK peak	1.258.4
Thrombolysis	21 (38%)
Primary PTCA	2 (3.6%)
Coronary angiography	44 (78.6%)
LVEF on release	52.5±13.9
Length of stay, days	11.7±6.7
Death	1 (1.8%)
Background	
Smokers	28 (50%)
High blood pressure	25 (44.6%)
Diabetes	13 (23.2%)
Hypercholesterolemia	21 (37.5%)
Ischemic heart disease	11 (19.6%)
Myocardial infarction	9 (16.1%)
Brain natriuretic peptide (BNP)	
Time taken to run tests, h	60.64±17.9
Values, pg/mL	318.2±369.4

*PTCA indicates percutaneous transluminal coronary angioplasty; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; ACS, acute coronary syndrome; CK, creatine kinase.

TABLE 2. **Mean Brain Natriuretic Peptide Levels According to Baseline and Clinical Characteristics***

	Mean BNP in Groups, pg/mL		
Characteristics	**Yes**	**No**	***P***
Diabetes	533.77	253.02	.015
Prior ischemic heart disease	639.8	239.6	.024
Elevated ST in acute phase	330.5	273.17	.64
Maximum Killip class >I	728.8	139.2	<.0001
LVEF on release ≤40%	683.4	196.4	.003
Extent of disease >1 vessel	489.9	171.4	.005

*LVEF indicates left ventricular ejection fraction; BNP, brain natriuretic peptide.

TABLE 3. **Mean Brain Natriuretic Peptide Levels and Killip Class, Left Ventricular Dysfunction and Coronary Disease***

	Cases, %	**BNP, pg/mL**	***P***
Maximum Killip class			
I	39 (69.6)	139.23	<.0001
II	8 (14.3)	546.75	
III	6 (10.7)	783.5	
IV	3 (5.4)	1.104.67	
LVEF on release			
≤40%	14 (25%)	683.43	.003
>40%	42 (75%)	196.45	
Coronary angiography findings			
No significant lesions	7 (16.7%)	58.4	.023
1 vessel diseased	13 (31%)	232.2	
2 vessels diseased	16 (38.1%)	441.5	
3 vessels diseased	6 (14.3%)	619	
ADCA lesion	19 (45%)	586.1	.0003
No ADCA lesion	23 (55%)	133.5	

*ADCA indicates anterior descending coronary artery; BNP: brain natriuretic peptide

contact with a sample of whole blood collected by peripheral venous puncture. The precision, diagnostic exactness and stability of this system have been previously reported.[3] The left ventricular ejection fraction (LVEF) was also determined before release using at least one of the following techniques: two dimensional echocardiography, radioventriculography or contrast ventriculography. Systolic ventricular dysfunction was defined as an LVEF of ≤40%. Forty four patients underwent coronary angiography at the discretion of the attending physician: lesions of ≥70% were considered significant.

Statistical Analysis

Quantitative results are expressed as means±standard deviations, categorical results as absolute frequencies and percentages. The Student *t* test was used to determine the significance of differences between pairs of means; analysis of variance was used to examine differences between several means. Relationships between quantitative variables were analyzed by linear regression. Multiple regression was used for multivariate analysis. Significance was set at *P*=.05. All calculations were made using SPSS v.11 software.

RESULTS

Table 1 shows the patients' baseline characteristics and clinical characteristics at release. Brain natriuretic peptide levels were analyzed with respect to these clinical characteristics (Table 2), and were significantly higher in patients with prior ischemic heart disease, diabetes mellitus (DM), CHF, left ventricular dysfunction, or existing coronary disease.

Brain Natriuretic Peptide, Heart Failure and Left Ventricular Ejection Fraction

Univariate analysis showed significant differences between mean BNP levels at discharge according to the presence and severity of CHF during hospitalization (maximum Killip class reached; *P*<.0001), and between the mean BNP values of patients with and without left ventricular dysfunction (Table 3).

In multivariate analysis, the BNP level was the only variable related to post-AMI LVEF (*P*=.01; Table 4).

TABLE 4. **Association of Clinical Variables With LVEF on Release From Coronary Department***

Clinical Variables	Univariate, *P*	Multivariate, *P*
Age, years	.93	.25
Male	.45	.45
Diabetes	.24	.61
Prior ischemic heart disease	.36	.30
Prior AMI	.26	.66
ACS with elevated ST segment	.17	.15
BNP	<.0001	.01
Killip	.009	.87

*AMI indicates acute myocardial infarction; ACS, acute coronary syndrome; BNP, brain natriuretic peptide.

A model for predicting the LVEF was produced based on the mean BNP level at discharge from the coronary department. After the stepwise regression analysis of all the variables (age, masculine sex, DM, prior ischemic heart disease, anterior AMI, acute coronary syndrome with elevation of the ST segment, BNP, and maximum Killip class attained) that might affect LVEF, BNP at discharge was found to have the greatest predictive power (LVEF=59.26-0.02 BNP [pg/mL]). Introducing the remaining clinical variables into the model led to no significant improvement. Figure 1 shows the linear association between BNP levels and LVEF.

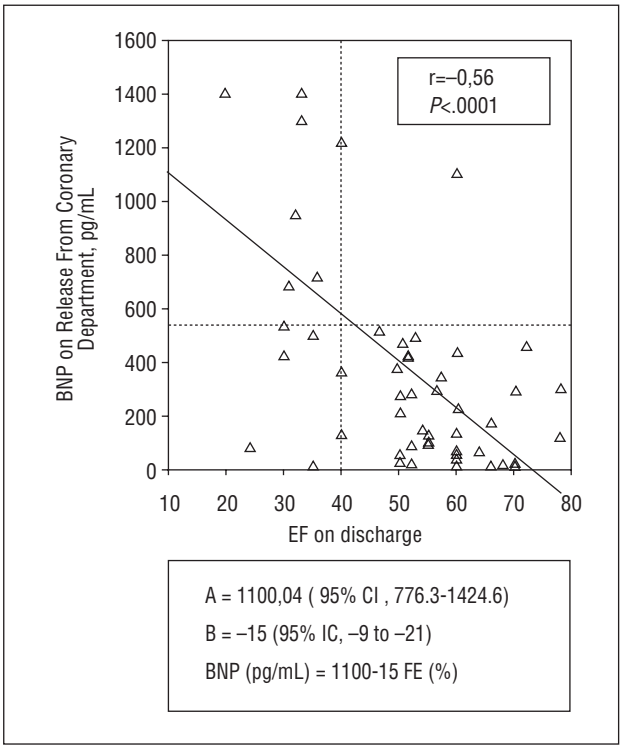
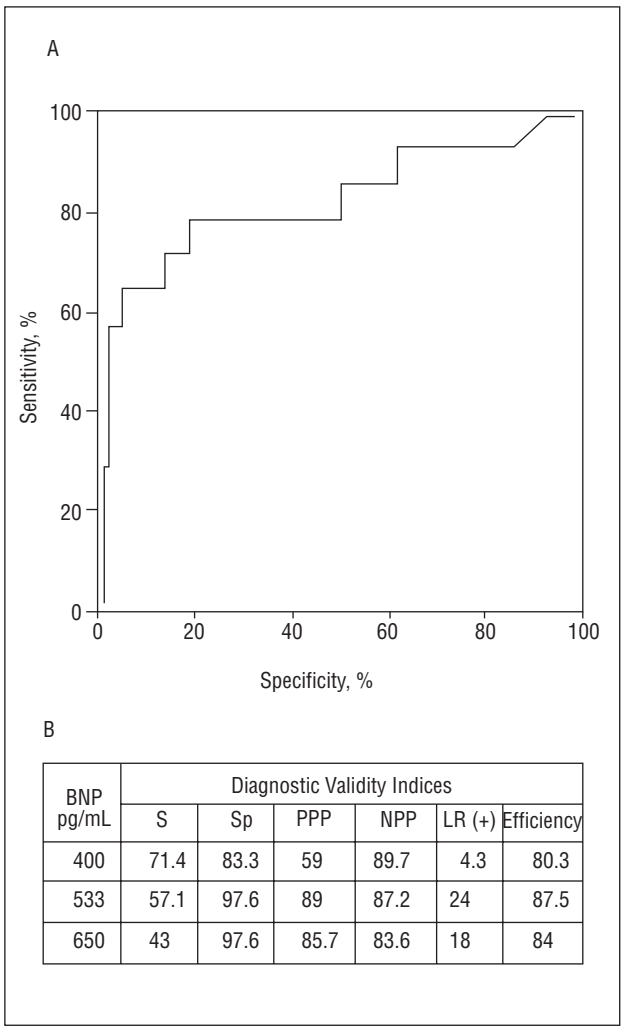


Fig. 1. Regression line for brain natriuretic peptide (BNP) levels and left ventricular ejection fraction (LVEF) on discharge from the coronary department. A and B. regression coefficients



BNP pg/mL	Diagnostic Validity Indices					
	S	Sp	PPP	NPP	LR (+)	Efficiency
400	71.4	83.3	59	89.7	4.3	80.3
533	57.1	97.6	89	87.2	24	87.5
650	43	97.6	85.7	83.6	18	84

Fig. 2. A. ROC curve showing brain natriuretic peptide levels with respect to diagnosis of left ventricular dysfunction (LVEF ≤40%). B. Diagnostic validity indices for different cut-off points. LVEF indicates left ventricular ejection fraction; Sp, specificity; LR(+), positive likelihood ratio; S, sensitivity; NPP, negative predictive power; PPP, positive predictive power.

The diagnostic exactness of BNP levels in the detection of patients with post-AMI left ventricular dysfunction was examined using ROC analysis. The area under the curve was 0.82. The optimum cut-off point was 533 pg/mL. Figure 2 shows the diagnostic validity indices for different cut-off points.

Brain Natriuretic Peptide and Extent of Coronary Disease

Coronary angiography was performed in 44 patients (78.6% of the sample). A clear relationship was seen between BNP levels and the extent of coronary disease, the number of diseased blood vessels, and significant anterior descending coronary artery (ADCA) disease (Table 3). In univariate analysis, the number of vessels with significant lesions was related

only to DM, BNP levels and prior ischemic heart disease. After adjusting for these variables, the BNP level was the only characteristic at discharge that remained independently associated with the number of diseased vessels and significant ADCA disease (*P*=.001 and *P*=.01 respectively).

DISCUSSION

The discovery of the natriuretic peptides confirmed the heart as an endocrine organ capable of regulating hemodynamic status in conjunction with other systems (the central nervous system, baroreceptors, the kidney, etc).[1] Brain natriuretic peptide is a perfect marker of neurohormonal status in patients with CHF. Independent of other variables such as age, LVEF or gender, high BNP levels are indicative of a poor prognosis.[4]

After an AMI, BNP levels increase over the course of the next 24 hours,[6,7] becoming stable in the subacute phase. Advanced age is also a cause of high BNP levels.[11] Several studies conclude that patients with increased BNP levels in the subacute phase of AMI have a worse prognosis, and suffer a greater incidence of left ventricular dysfunction, CHF, ventricular remodeling and death in the mid-long term.[6-9]

In the present study, we determined BNP levels in the subacute phase of AMI in young patients, and thus avoided the early peak in the plasma concentration and the influence of age.

The levels of BNP at release from the coronary department correlated with LVEF. This, plus the demonstrated mid-long term prognostic value of BNP levels, could help select or prioritize patients for an echocardiogram in the coronary department when this cannot be made available to all who present with AMI (of course, the determination of BNP levels can never replace an echocardiogram). Further, since BNP levels seem to be related to the extent and severity of coronary disease (number of diseased vessels or ADCA disease or both) knowing them could help when making decisions on whether to follow invasive or conservative management strategies.

The behavior of BNP in AMI could be influenced by certain treatments (as seen in CHF), by residual ischemia or the size of the AMI etc. This work does not examine these possibilities although it is unlikely that the conclusion would change. Patients with high BNP levels show greater left ventricular dysfunction and extensive coronary disease (or both) and might benefit from invasive management. The determination of BNP levels on discharge from the coronary department (at some moment during the second to the fourth day post-AMI), is a simple technique that provides important information on clinical status (with respect to CHF) as well as prognostic information (LVEF and extent of coronary disease). In addition, it is a marker of great predictive power in the detection of post-AMI ventricular dysfunction, which must be taken into account when taking decisions on patient management.

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