Usefulness of NTproBNP in the Emergency Management of Patients With Severe Dyspnea and an Uncertain Heart Failure Diagnosis

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Introduction and objectives. Measurement of N-terminal pro-B-type natriuretic peptide (NTproBNP) helps in diagnosing heart failure (HF). The test's usefulness may be greatest in patients with severe dyspnea of uncertain origin. However, NTproBNP has not been evaluated specifically in this setting.

Patients and method. This prospective emergency department study included 70 patients with shortness of breath at rest as their chief complaint. In the attending physician's opinion, both HF and a non-cardiac cause were equally probable. Blinded NTproBNP measurement was carried out in blood samples collected on admission. Patients were monitored and their final diagnoses were based on clinical findings, therapeutic responses, and cardiac and noncardiac tests performed during hospitalization.

Results. The NTproBNP level was higher in the 49 patients (70%) with a final diagnosis of HF (*P*=.006); the area under the ROC curve was 0.72 (0.60-0.82). The optimum diagnostic cut-off value was 900 pg/mL, which had an accuracy of 87%, a sensitivity of 98%, and a negative predictive value of 92%. The NTproBNP level was significantly higher in the 6 patients (9%) who died during hospitalization (*P*=.009); the area under the ROC curve was 0.87 (0.76-0.93) and the optimum cut-off value for predicting death was 5500 pg/mL, which had an accuracy of 77%, a sensitivity of 100%, and a positive likelihood ratio of 4.2.

Conclusions. In patients with severe dyspnea and an uncertain diagnosis of HF, an NTproBNP level <900 pg/mL helps exclude the presence of HF, whereas a NTproBNP level >5500 pg/mL identifies patients at an increased risk of death.

Key words: *Natriuretic peptides. Heart failure. Dyspnea. Diagnosis. Prognosis.*

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Utilidad del NTproBNP en el manejo urgente del paciente con disnea severa y diagnóstico dudoso de insuficiencia cardíaca

Introducción y objetivos. El NTproBNP ayuda a identificar a los pacientes con insuficiencia cardíaca. Su utilidad podría ser máxima en pacientes con disnea severa de origen incierto; sin embargo, esta población no ha sido específicamente evaluada.

Pacientes y método. Estudio prospectivo de 70 pacientes que acudieron a urgencias refiriendo disnea de reposo, cuyo diagnóstico clínico inicial fue establecido como dudoso, con probabilidad intermedia de insuficiencia cardíaca. A la llegada a urgencias se extrajeron las muestras analíticas y se determinó el valor de NTproBNP de forma ciega. Los pacientes fueron controlados y el diagnóstico final se estableció sobre la base de los hallazgos clínicos, la respuesta al tratamiento y las pruebas practicadas durante el curso hospitalario.

Resultados. El NTproBNP fue mayor en los 49 pacientes (70%) con un diagnóstico final de insuficiencia cardíaca (p = 0,006), obteniendo un área bajo la curva ROC de 0,72 (0,60-0,82). El valor de corte diagnóstico óptimo fue 900 pg/ml, con una precisión del 87%, una sensibilidad del 98% y un valor predictivo negativo del 92%. En los 6 pacientes (9%) fallecidos durante la hospitalización, el NTproBNP fue significativamente mayor (p = 0,009), con un área bajo la curva ROC de 0,87 (0,76-0,93) y un valor de corte pronóstico óptimo de 5.500 pg/ml, con una precisión del 77%, una sensibilidad del 100% y una razón de probabilidad positiva de 4,2.

Conclusiones. En una población con disnea severa que acude a urgencias con diagnóstico dudoso de insuficiencia cardíaca, un valor de NTproBNP < 900 pg/ml ayuda a excluir la presencia de esta enfermedad, y un valor > 5.500 pg/ml identifica a los pacientes con un mayor riesgo de muerte hospitalaria.

Palabras clave: *Péptidos natriuréticos. Insuficiencia cardíaca. Disnea. Diagnóstico. Pronóstico.*

ABBREVIATIONS

HF: heart failure.
BNP: B-type natriuretic peptide.
ROC curve: receiver operator characteristic curve.
NTproBNP: N-terminal pro-B-type natriuretic peptide.

INTRODUCTION

The diagnosis of heart failure (HF) as the cause of acute dyspnea is often very difficult in the emergency room setting. In fact, signs, symptoms, and systematic tests such as blood analysis, electrocardiogram [ECG], and chest x-ray, lack of sensitivity and specificity.[1,2] Diagnosing HF is especially difficult in patients with severe dyspnea, in elderly people, in obese patients, and in those with concomitant chronic kidney or lung disease. A rapid, precise diagnostic test that could correctly diagnose HF would therefore allow physicians to begin specific treatment.

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted by the ventricles in response to an increase in volume and pressure overload.[3-6] Levels are high in patients with ventricular dysfunction, and correlate with disease severity and patient prognosis.[7-11] Recent studies have suggested that determining BNP levels using rapid analytical techniques helps in the diagnosis of patients with acute dyspnea—especially for excluding HF.[12-16] B-type natriuretic peptide is an active hormone that originates from the cleavage of proBNP into BNP plus an inactive N-terminal peptide (NTproBNP). In patients with HF, the NTproBNP concentration increases beyond that of BNP, and these molecules have a longer half life, possibly facilitating their use in clinical testing.[17,18] However, the usefulness of the rapid determination of NTproBNP concentrations in the context of acute dyspnea is not well established.[19] The studies performed to date have examined a wide spectrum of patients, including those with high and low probabilities of HF according to initial medical examinations in the emergency room. A priori, this test would seem to be most useful in patients with dyspnea of unknown origin and with an uncertain diagnosis of HF or with an intermediate probability of being thus diagnosed. However, these patients are usually of a more advanced age, are more commonly women, and are frequently obese or have kidney failure; these factors affect natriuretic peptide concentrations, worsening their diagnostic value.[18,20]

The present study assesses the usefulness of the rapid determination of NTproBNP levels in emergency room patients with severe dyspnea of unknown origin and with an uncertain diagnosis of HF.

PATIENTS AND METHODS

Population and Study Design

This prospective study involved consecutive patients who, between 1 January and 30 June 2003, came to the emergency room of a tertiary hospital with the main symptom of dyspnea at rest. The emergency room physicians (internal medicine specialists and family doctors trained in emergency medicine) took initial charge of these patients and attempted to make a diagnosis based on anamnesis, a physical examination, a chest x-ray, an ECG, pulsoximetry, and emergency blood analysis. The patients included in the study were those whose dyspnea was of unclear origin and who had an uncertain diagnosis of HF (i.e., they had two equally likely possible diagnoses, one of which was HF). All clinical findings were recorded prospectively by the attending physician. Patients that met the inclusion criteria were offered the opportunity of taking part in the study and gave their consent to be included.

The final diagnosis of HF was established by independent cardiologists in agreement with the criteria of the European Society of Cardiology,[21] based on clinical findings during the patients' stay in hospital, their response to treatment, and on complementary test results (including echocardiography and lung function tests). After treatment in the emergency room, all patients were monitored; all in-hospital deaths and their main causes were registered.

Measurement of NTproBNP

Blood was extracted upon patient arrival at the emergency room. If the patient met the inclusion criteria, NTproBNP levels were determined blind; the result was not given to the attending physician. Samples were collected in tubes containing a lithium heparin anticoagulant, and centrifuged for 30 min at 4ºC. NTproBNP levels were then immediately determined using the proBNP assay method (Roche Diagnostics, Germany) and an Elecsys 2010 analyzer (Roche Diagnostics, Germany). The reactant consists of polyclonal antibodies that recognize epitopes at the N-terminal (1-76) of the proBNP (1-108) molecule. A 20 µL sample was incubated with a biotinylated polyclonal antibody specific for NTproBNP and another labeled with a ruthenium chelate to form a sandwich complex. After incubation, the bound fraction was separated with microparticles covered in streptavidin and quantified by chemiluminiscence. The assay precision ranged from 1.8% at 800 pmol/L to 2.7% at 20.7 pmol/L. The detection limits were 0.6

and 4.130 pmol/L. The pmol/L—pg/mL conversion ratio was 8.457.

Statistical Analysis

The usefulness of the NTproBNP level was studied using receiver operator characteristic (ROC) curves, the area below them, and the 95% confidence interval (CI). Sensitivity, specificity, positive and negative predictive values, and the positive/negative likelihood ratio (defined as the sum of the concordant cells divided by the sum of all the cells in a 2×2 table) were determined for each cut-off point. The NTproBNP concentrations were not normally distributed; the results are therefore expressed as medians and interquartile ranges, and comparisons between groups were performed using the Mann-Whitney U test. Significance was set at $P<.05$. All calculations were performed using SPSS 11.0 and MedCalc software.

RESULTS

Study Population

In the 6 month study period a total of 1267 consultations were made with patients whose main symptom was dyspnea (3.34% of all consultations). Of these, 70 patients presented with severe dyspnea at rest of unknown origin and with an intermediate likelihood of suffering HF (5.52% of the patients with dyspnea). Table 1 shows the baseline clinical characteristics of these patients. Patients were most commonly over 70 years of age (64%), women (57%) and obese (54% with a body mass index of >30), and more commonly had a background of concomitant lung or heart disease (51%). The emergency room physician made a differential diagnosis of HF or the exacerbation of chronic obstructive pulmonary disease (49%), acute bronchitis (20%), pneumonia (11%), asthma (10%), and acute pulmonary thromboembolism (10%). Electrocardiograms performed in the emergency room showed normal sinus rhythm in 53% of patients and were absolutely normal in 26%.

TABLE 1. **Patient Characteristics (n=70)***

Age, years, mean±SD	74±11%
Women	57%
Body mass index, mean±SD	31.1±7%
High blood pressure	66%
Prior heart disease	73%
Prior HF	54%
Prior AMI	20%
Atrial fibrillation	38%
Prior pneumonia	57%
Prior kidney failure	14%
Medications	
ACEI	46%
Beta-blockers	25%
Loop-acting diuretics	60%
Bronchodilators	28%
Symptoms	
Dyspnea at rest	100%
Orthopnea	54%
Nocturnal paroxistic dyspnea	36%
Signs	
Edema	45%
Lung crackles	65%
Jugular ingurgitation	26%
Third noise	6%
Abnormal ECG	74%

*SD indicates standard deviation; ECG, electrocardiogram; AMI, acute myocardial infarction; HF, heart failure; ACEI, angiotensin converting enzyme inhibitors.

Usefulness of NTproBNP

The cause of dyspnea was finally diagnosed as HF in 49 patients (70%), and not HF in 21 (30%). On arrival at the emergency room, the patients with a final diagnosis of HF had a median NTproBNP level of 3391 (5.147) pg/mL compared to 581 (6.464) pg/mL for those who were finally diagnosed not to have HF ($P=.006$). For a final diagnosis of HF, the area under the NTproBNP ROC curve was 0.72 (95% CI, 0.60-0.82) (Figure 1). Table 2 shows the sensitivity, specificity and predictive values for different cut-off concentrations of NTproBNP. The optimum cut-off value was 900 pg/mL; this provided a precision of 87%, a sensitivity of 98% (89%-99%), a negative predictive power of 92% (57%-97%), acceptable specificity (60%; 36%-81%), a positive predictive power of 86% (77%-93%), and a positive likelihood ratio of 2.5 (1.4-5.2).

Except for 2 patients who died within 48 h, all patients (n=68) underwent echocardiography. Twenty nine patients (43%) had a left ventricle ejection fraction (LVEF) of <50%; these patients showed an NT-proBNP level of 4054 (7217) pg/mL compared to 2012 (5079) pg/mL in those with a conserved LVEF ($P=.015$). With respect to the diagnosis of HF, the presence of systolic dysfunction at admission had a precision of only 68%. Twenty one patients with HF had an LVEF of ≥50%, of whom 57% showed atrial fibrillation and 76% showed high blood pressure. For 20 (95%) of the 21 patients in this subgroup, emergency room NTproBNP values were >900 pg/mL. Nine patients with no prior heart disease who were diagnosed with HF had NTproBNP levels of >900 pg/mL, while 6 out of 10 patients (60%) with prior heart disease but no HF had NTproBNP levels of <900 pg/mL. Of the 18 patients (26%) whose ECG was perfectly normal at admission to the emergency room, 11 were finally diagnosed with HF. Therefore, the negative predictive power of a normal ECG in the emergency room was 61%—significantly lower than the

TABLE 2. **NTproBNP Cur-off Values for the Diagnosis of HF***

NTproBNP	S	Sp	NPP	PPP	Precision
500 pg/mL	100% (93-100)	45% (23-68)	100% (57-100)	82% (75-88)	83%
900 pg/mL	98% (89-99)	60% (36-81)	92% (57-97)	86% (77-93)	87%
1100 pg/mL	96% (86-99)	65% (41-84)	87% (55-97)	87% (78-94)	87%
1500 pg/mL	88% (75-95)	65% (41-84)	68% (40-87)	86% (76-93)	81%

*Sp indicates specificity; S, sensitivity; NPP, negative predictive power; PPP, positive predictive power.

92% for a NTproBNP level of <900 pg/mL. The prevalence of a normal ECG was greater among patients without HF (11 out of 21 [52%] compared to 7 out of 49 [14%] with HF; *P*<.001). The overall precision of ECG testing was 76%.

Six patients (9%) died during their stay in the hospital, 4 because of HF and 2 due to non-cardiac causes (pulmonary thromboembolism and sepsis due to pneumonia). Among those who died, the median NTproBNP level was 10 071 (14 278) pg/mL compared to 2563 (4221) pg/mL in those who survived (*P*=.009). For the prediction of death, the NTproBNP level obtained an area under the curve of 0.87 (95% CI, 0.76-0.93) (Figure 2). The optimum cut-off value was 5500 pg/mL; this allowed the identification of patients who died with a precision of 77%, a sensitivity of 100% (54%-100%), a specificity of 76% (64%-86%), a negative predictive power of 100% (94%-100%), a positive predictive power of 29% (13%-40%), and a positive likelihood ratio of 4.2 (1.5-7.1).

Figure 3 shows the NTproBNP values on a logarithmic scale according to the final diagnosis of HF and in-hospital death. NTproBNP values of <900 pgl/mL were associated with a non-cardiac cause of dyspnea, whereas those >900 pg/mL were associated with HF. Values of >5500 pg/mL identified a subgroup at significant risk of death.

DISCUSSION

This study shows that NTproBNP levels may be of diagnostic and prognostic value when dealing with patients presenting at the emergency room with severe dyspnea and an uncertain diagnosis of HF.

Several studies have reported the diagnostic usefulness of BNP levels in the emergency room, but these were performed with non-selected patients.[12-16] Davis et al[12] studied 52 patients and obtained a sensitivity of 93% and a specificity of 90% for the diagnosis of HF. More recently, when BNP levels were measured in 250 non-selected patients using the Triage BNP test (Biosite Inc, San Diego, California), the area under the ROC curve for HF was 0.97—an exceptionally high figure that clearly indicates almost perfect sensitivity

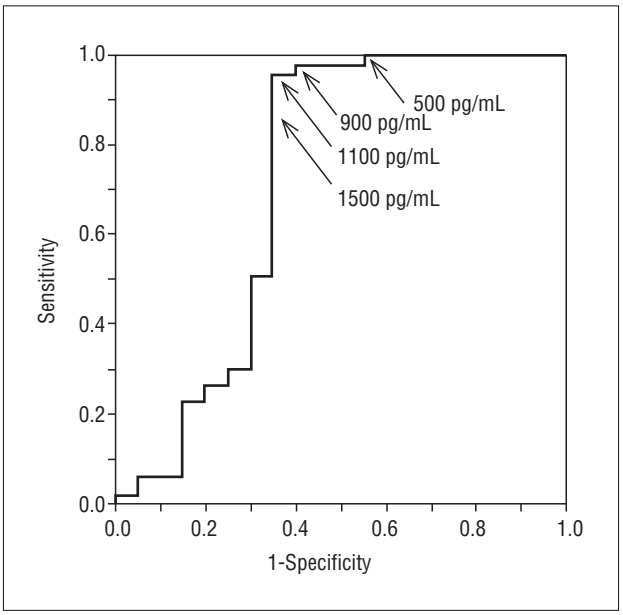

Figure. 1. NTproBNP ROC curve for the diagnosis of heart failure (area under the curve 0.72 [95% CI, 0.60-0.82]).

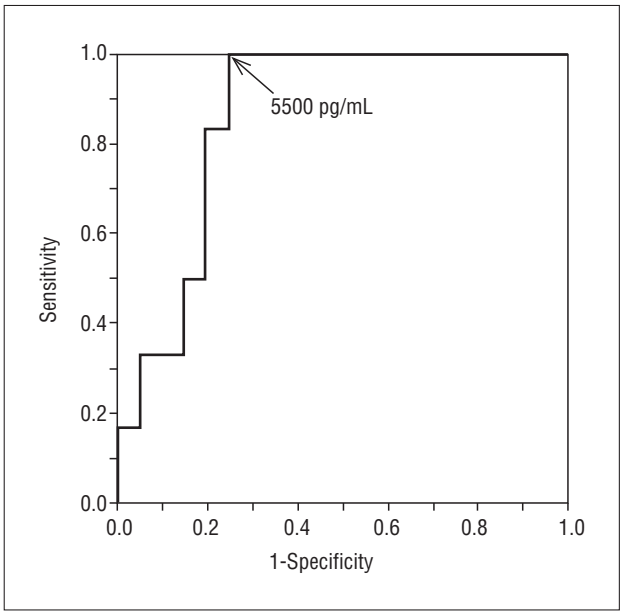

Figure. 2. NTproBNP ROC curve for in-hospital death (area under the curve 0.87 [95% CI, 0.76-0.93]).

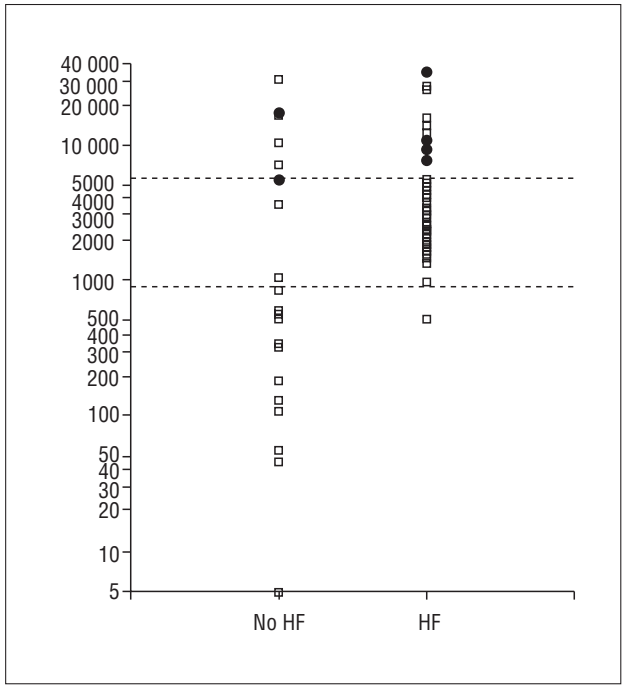

Figure. 3. NTproBNP on a logarithmic scale (y axis) with respect to the final diagnosis of heart failure (x axis) and in-hospital death (·). The discontinuous lines represent the cut-off (900 pg/mL) and prognostic values (5500 pg/mL).

and specificity.[13] However, in the latter study, nearly all the patients were relatively young men (mean age 64 years). The Breathing Not Properly Multinational Study was a multicenter, prospective study involving 1586 non-selected patients that presented at the emergency room with dyspnea. In this study, the precision of clinical diagnosis and BNP levels were similar, the latter being more sensitive but less specific than clinical judgment. A Bayesian subanalysis showed that the BNP level was a useful indicator especially when the probability of HF (as determined by the emergency room physician) was intermediate. The authors indicated that, like other diagnostic tests used in clinical practice, knowing the BNP level was most useful when HF was suspected as the cause of the dyspnea but when a diagnosis remained uncertain.

The present study is the first to prospectively assess the usefulness of a rapid test for NTproBNP in a population made up entirely of patients with dyspnea of uncertain origin and with intermediate probability of HF (as determined by attending emergency room physicians). The availability of a rapid, easily accessible diagnostic test that is easy to interpret is of particular importance for such patients in times of emergency given the difficulty in deciding how to proceed.

The diagnostic capacity of a test that can distinguish between the presence of a particular disease is determined using ROC curves.[22] These show the true positives (sensitivity) with respect to the false positives (1-specificity) for the different cut-off points of the test in question (in this case the different NT-proBNP levels). The area under the curve summarizes the information contained by all the cut-off points: the bigger the area the greater the diagnostic capacity of the test. In the present population, the area under the ROC curve was 0.7, somewhat less than that reported for other populations (0.89-0.98).[12-16] The patient baseline characteristics reflect the differences between the present and earlier studies. All the present patients suffered dyspnea at rest, the average age was higher, and the percentage of women patients higher. Since NTproBNP concentrations correlate directly with these variables[18,20] some diagnostic specificity might be lost.

The best cut-off point for the diagnosis of HF was 900 pg/mL. This provided a high negative predictive power (92%) and an acceptable positive predictive power (86%); above all this therefore helps in the exclusion of HF. This cut-off value was significantly higher than the reported for the same test when used in a primary care setting and with outpatients (300 pg/mL).[23-26] Bayés-Genís et al studied a population with dyspnea in the emergency room, but only 14 (16%) had an uncertain diagnosis of HF.[27] A similar cut-off value (957 pg/mL), however, provided a negative predictive power of just 67% compared to the 92% obtained in the present work. These differences show that the a priori characteristics of the population for which NTproBNP levels are tested determine the best cut-off value; knowing this point is vital for using this test and interpreting its results correctly.

The prognostic value of BNP levels in chronic HF has been well established by a number of studies. High BNP concentrations are associated with increased mortality and morbidity independent of other classic risk factors.[9-11] In patients with HF in the emergency room, traditional risk factors are of no prognostic value.[28] In this context, the prognostic value of BNP could be of great importance in optimizing therapeutic management. Harrison et al[29] reported that the BNP levels of patients who presented at the emergency room are highly predictive of cardiac-associated death at six months. In the present work, NTproBNP level at admission to the emergency room was found to be a predictor of all-cause death during hospitalization. A NTproBNP value of >5500 pg/mL is associated with a significant increase in the risk of death and, therefore, with a lack of response to treatment. Other authors have shown that monitoring the response of BNP levels to treatment is of additional prognostic value at the time of patient discharge.[30] In the present study, a single determination of the NTproBNP level was sufficient to identify patients with a poorer prognosis, for whom a more aggressive approach to treatment is required from the outset. The main cause of death in 2 of

the 6 patients who died was non-cardiac, although these patients also had high NTproBNP levels at the time of admission. Previous papers have reported an association between high BNP levels and a poorer prognosis in patients with pulmonary thromboembolism or septic shock.[31,32] In these critical situations, a high NTproBNP level would reflect the presence of a subclinical heart problem and, as a consequence, indicate a more severe clinical picture and poorer prognosis. In severe, acute respiratory failure, high BNP levels have been reported to reflect pulmonary hypertension and right ventricular overload.[33]

Limitations of the Study

The main limitation of this study is that the results are only applicable to similar populations and hospital situations. Like all diagnostic tests, BNP and NTproBNP tests should be demanded whenever there is doubt about a diagnosis. The present study assesses the diagnosis of HF in a population with an uncertain diagnosis in agreement with systematic clinical practice for the emergency room at our hospital. The positive and negative predictive power of the test depended on the probable pretest diagnosis of HF, which in this study was high (70%). Therefore, its use in other situations or with other populations could give rise to a different performance. As always, an attempt to come to a diagnosis must first be made by looking at the clinical evidence. However, the identification of a cut-off value for NTproBNP levels should help to improve clinical judgment, aid in the establishment of a more firm diagnosis, and improve the stratification of risk in this kind of population. The impact of this test in systematic clinical practice can only be evaluated by undertaking randomized studies.

CONCLUSION

In patients with severe dyspnea and an uncertain diagnosis of HF who sought help at our emergency room, a NTproBNP level of <900 pg/L helped to exclude the presence of the latter. Values of >5500 pg/mL allowed the identification of patients at greater risk of dying during their hospitalization.

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