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.
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.3,4 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.12-18 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 4°C. 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 chemiluminescence. 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 2x2 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%.

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 \( \geq 50\% \), 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

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TABLE 1. Patient Characteristics (n=70)*

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

*SD indicates standard deviation; ECG, electrocardiogram; AMI, acute myocardial infarction; HF, heart failure; ACEI, angiotensin converting enzyme inhibitors.
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) \( (P < .001) \). The overall precision of ECG testing was 76%.

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**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. Davis et al. \( (12, 16) \) 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.
The diagnostic capacity of a test that can distinguish between the presence of a particular disease is important for such patients in times of emergency. A rapid test for NT-proBNP is of particular importance given the difficulty in deciding how to proceed.

In the present study, a single determination of the NT-proBNP 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 30 patients was heart failure. All the present patients suffered dyspnea at rest, the average age was higher, and the percentage of women patients higher. Since NT-proBNP concentrations correlate directly with these variables, some diagnostic specificity might be lost.

The diagnostic capacity of a test that can distinguish between the presence of a particular disease is determined using ROC curves. 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). 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 NT-proBNP concentrations are associated with increased mortality and morbidity independent of other classic risk factors.

In patients with HF in the emergency room, traditional risk factors are of no prognostic value. In this context, the prognostic value of BNP could be of great importance in optimizing therapeutic management. Harrison et al. reported that the BNP level at admission to the emergency room was found to be a predictor of all-cause death during hospitalization. A NT-proBNP 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. In the present study, a single determination of the NT-proBNP 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 30 patients was heart failure. All the present patients suffered dyspnea at rest, the average age was higher, and the percentage of women patients higher. Since NT-proBNP levels are associated with increased mortality and morbidity independent of other classic risk factors, in patients with HF in the emergency room, traditional risk factors are of no prognostic value.

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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. 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.

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.

REFERENCES