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Clinical Biochemistry 38 (2005) 1041 – 1044

CLINICAL BIOCHEMISTRY

NT-proBNP in the differential diagnosis of acute dyspnea in the emergency department

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Received 6 June 2005; received in revised form 14 July 2005; accepted 21 July 2005
Available online 6 September 2005

Abstract

Objectives: The purpose of this study was to verify the usefulness of NT-proBNP in the differential diagnosis of dyspnea in a population of patients presenting in the ER with breathlessness.

Design and methods: In samples from 122 patients presenting in the ER with acute-severe dyspnea and from 25 subjects enrolled as a "comparison group" (NORM), NT-proBNP levels were measured. Patients have been classified on the basis of discharge diagnosis: pulmonary disease (PD, $n = 23$), pulmonary concomitant to cardiac disease (MIXED, $n = 17$), pulmonary embolism (EMB, $n = 8$), cardiac disease (CARD, $n = 56$), acute myocardial infarction (AMI, $n = 11$) and other disease (OTHER, $n = 7$).

Results: A significant difference in NT-proBNP values ($P \leq 0.05$) was found in CARD vs. PD as well as vs. NORM and OTHER groups. 1760 ng/L was the best cut-off value calculated from ROC analysis (AUC ± SE 0.815 ± 0.041). Comparing NT-proBNP values and ER diagnosis, a disagreement in 24 patients was observed. Using the discharge diagnosis as the "gold standard," four cases (17%) were found to be FP and 11 cases (46%) were FN according to ER diagnosis, while 2 patients showed false positive and 7 false negative NT-proBNP values.

Conclusions: NT-proBNP measurement represents a useful biochemical tool helping the ER physician in the rapid and reliable recognition of cardiac involvement in patients presenting in the ER with acute-severe dyspnea.

Keywords: Acute severe dyspnea; Emergency department; Congestive heart failure; N-terminal pro-brain natriuretic peptide; Brain natriuretic peptide

Introduction

The differential diagnosis of dyspnea in patients presenting in the emergency department (ER), or other urgent care setting, with shortness of breath as the main symptom, is challenging mainly when congestive heart failure (CHF) or other cardiac disease is the underlying cause responsible for the symptoms. The signs and symptoms may be not specific or sensitive enough to distinguish between different causes of dyspnea [1]. If findings with electrocardiography (ECG), a tool commonly used in these cases, are normal, left ventricular dysfunction (LVD) may be ruled out [2]. Moreover, echocardiography (ECHO), currently considered the gold standard for detecting LVD, is costly, not always available and sometimes does not reveal an acute condition [3]. In recent decades, new molecules such as cardiac natriuretic hormones (CNH) have emerged as interesting biochemical tools, and their utility in CHF management has been stressed in the last European Society of Cardiology (ESC) guidelines [4].

The purpose of this study was to verify the usefulness of NT-proBNP levels in the differential diagnosis of

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doi:10.1016/j.clinbiochem.2005.07.010

dyspnea in a population of patients presenting in the ER with breathlessness as the main symptom.

Materials and methods

Patients

From March 2002 to February 2003, 122 consecutive patients (58 males; median age 78 years; range 27–93) presenting in the ER of the University Hospital of Padova were enrolled in the study by 4 physicians (cardiologists or internal medicine doctors) working in this department for at least 5 years (mean observed dyspnea cases: about 150/year for each). Selection criteria included acute-severe dyspnea (≥30 acts/min) as the most prominent symptom. Patients with obvious traumatic cause of dyspnea (road traffic or domestic accidents) were excluded, as were those with renal failure (defined by a serum creatinine level more than 250 μmol/L). 25 subjects were recruited in the ER during the study period as part of the comparison group (NORM, 14 males; mean age 70 years; range 37–80) being age-matched with dyspneic patients and unaffected by any form of cardiac or pulmonary disease. Patients fitting the above criteria were questioned regarding participation in the study, and their informed consent was obtained.

Patient discharge diagnosis was made on the basis of clinical and instrumental investigations performed in the admission department according to the adopted clinical guidelines [4–7]. Patients were then assigned to 6 different diagnostic groups (pharmacotherapy before the observation: main medications, % patients):

1. Cardiac disease (CARD, n = 56): congestive heart failure, left ventricular dysfunction, hypertrophic cardiomyopathy, dilatative cardiomyopathy, right heart failure from cor pulmonale, ischemic cardiomyopathy, hypertensive cardiomyopathy, coronary syndrome, atrial fibrillation due to closed calcified aortic stenosis, paroxysmal ventricular tachycardia, ventricular tachycardia and extrasystole due to moderate mitral insufficiency, atrial fibrillation in mitral-aortic insufficiency, atrial flutter (Diuretics, 70%; ACE inhibitors, 55%, Acetylsalicylic acid, 55%);
2. Pulmonary disease (PD, n = 23): pneumonia, bronchial pneumonia, chronic asthmatic bronchitis, chronic obstructive pulmonary disease, calcified fibrothorax after tuberculosis, pulmonary blistered emphysema, chronic tracheobronchitis, pulmonary tumor, chronic respiratory insufficiency (Diuretics, 43%; inhaled bronchodilators, 35%; Nitrates, 26%);
3. Pulmonary and concomitant cardiac diseases (MIXED, n = 17): pulmonary disease and concomitant heart failure or cardiovascular disease (Diuretics, 59%; Nitrates, 35%; ACE inhibitors, 35%);
4. Other disease (OTHER, n = 7): arterial hypertension, syncope, atypical chest pain, transitory ischemic attack, recurrent vertiginous syndrome, peritoneal carcinosis, paroxysmal dyspnea (Diuretics, 43%; Calcium-channel blockers, 43%; ACE inhibitors, 43%);
5. Pulmonary embolism (EMB, n = 8) (Acetylsalicylic acid, 50%; Diuretics, 37%; Nitrates, 37%);
6. Acute myocardial infarction (AMI, n = 11) (Diuretics, 36%; ACE inhibitors, 36%, Acetylsalicylic acid, 27%).

During the study, 7 patients were discharged by the ER (1 CARD, 3 PD, 3 OTHER) whereas 6 died in the ER or during hospitalization (2 AMI, 2 EMB, 2 PD).

Methods

NT-proBNP was measured by a fully automated Electrochemiluminescence Immunoassay (ECLIA, proBNP, Roche Diagnostics). All relevant analytical characteristics of the method used have been described elsewhere [8]. Analysis of variance (ANOVA) on log-transformed values was used to compare NT-proBNP values between groups: a P value ≤ 0.05 was considered statistically significant. The receiver operating characteristic (ROC) curve was calculated to determine NT-proBNP diagnostic accuracy by comparing values observed in CARD groups with those obtained in the other groups studied, excluding NORM and AMI patients. The optimal NT-proBNP concentration (cut-off) for the differential diagnosis of dyspnea (cardiac or not cardiac origin) was determined by selecting the point on the ROC curve that maximizes sensitivity and specificity.

After the definition of the cut-off level, each patient's ER diagnosis was compared with NT-proBNP concentration in order to verify if these two classifications were in agreement in identifying the origin of the dyspnea (cardiac or not) and if NT-proBNP determinations could improve the accuracy of ER diagnosis. The discharge diagnosis was adopted as "gold standard" when the information provided (ER diagnosis vs. NT-proBNP concentration) was contradictory.

Results

The performance of the NT-proBNP assay during the study met the analytical characteristics already described, the total imprecision (CV%) ranging from 2.7 (1981.50 ng/L) to 1.3 (435.00 ng/L). NT-proBNP levels measured in patients studied are summarized in Table 1A. A statistically significant difference ($P \leq 0.05$, Table 1B) was observed comparing NT-proBNP values from the NORM group and from patients with acute dyspnea not attributable to cardiac or pulmonary origin (OTHER) with those from patients with dyspnea of cardiac origin. Furthermore, the peptide levels in patients with pulmonary disease differed significantly ($P \leq 0.05$) from those in patients belonging to the CARD group as well as the MIXED group. In AMI patients, peptide concentrations were

Table 1
(A) NT-proBNP concentrations measured in patients recruited in the ER (emergency department); (B) analysis of variance (ANOVA) performed on NT-proBNP levels (log-transformed) measured in patients studied (NS = not statistically significant)

Groups	NT-proBNP (ng/L)		
	Range	50th percentile	25–75th percentile
(A)			
NORM	33.79–632.90	216.40	65.66–406.02
OTHER	65.69–2744.00	239.20	208.87–543.37
PD	16.09–1760.00	259.70	120.95–418.17
EMB	188.70–5211.00	944.50	308.90–3249.50
MIXED	262.60–27580.00	2006.00	861.70–4937.25
CARD	144.70–36762.00	3509.00	1941.00–9255.00
AMI	1712.00–22455.00	8182.00	5640.25–9095.25

(B)	NORM	OTHER	PD	EMB	MIXED	CARD	AMI
NORM	–	NS	NS	NS	≤0.05	≤0.05	≤0.05
OTHER	NS	–	NS	NS	≤0.05	≤0.05	≤0.05
PD	NS	NS	–	NS	≤0.05	≤0.05	≤0.05
EMB	NS	NS	NS	–	NS	NS	≤0.05
MIXED	≤0.05	≤0.05	≤0.05	NS	–	NS	NS
CARD	≤0.05	≤0.05	≤0.05	NS	NS	–	NS
AMI	≤0.05	≤0.05	≤0.05	≤0.05	NS	NS	–

significantly higher than those observed in all groups studied with the exception of CARD and MIXED groups (P = NS).

In order to identify the peptide concentrations allowing the best differentiation between cardiac and other causes of dyspnea, NT-proBNP values in dyspneic patients were computed in ROC curve analysis (Fig. 1). 1760 ng/L was the NT-proBNP concentration assuring the best combination between sensitivity (0.80, 95% CI 0.71–0.87) and specificity (0.76, 95% CI 0.66–0.84), with a positive predictive value of 0.78, a negative predictive value of 0.79 and a diagnostic accuracy of 0.78 in identifying the cardiac origin of dyspnea (AUC ± SE = 0.815 ± 0.041). At the optimal cut-off level, the calculated likelihood ratio was 3.33 and the post-test probability was 0.74 (95% CI 0.64–0.82), improved in comparison to the pre-test probability (0.46; 95% CI 0.36–0.56). After defining the optimal cut-off

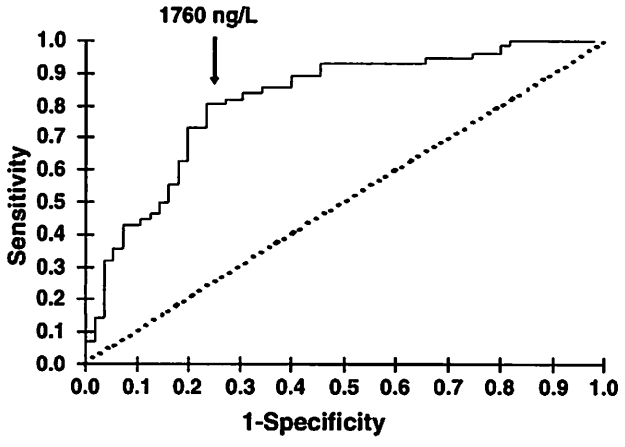

Fig. 1. ROC curve analysis of NT-proBNP values measured in patients studied: cardiac disease (CARD) vs. pulmonary disease (PD) + cardiac concomitant to pulmonary disease (MIXED) + other disease (OTHER) + pulmonary embolism (EMB). AUC ± SE = 0.815 ± 0.041.

(1760 ng/L), we evaluated the agreement between NT-proBNP values and ER diagnosis in identifying the origin of the dyspnea, adopting discharge diagnosis as the "gold standard" when the information provided (ER diagnosis vs. NT-proBNP concentration) was contradictory.

In 98 out of 122 patients (80%), the diagnosis made in the ER was in agreement with the classification carried out on the basis of NT-proBNP values. Considering the 24 discordant cases, the percentage of false positives (FP) and false negatives (FN) was calculated. In particular, in relation to ER diagnosis, four cases (17%) were found to be false positives (actual diagnosis: 3 PD, 1 OTHER) while 11 cases (46%) were false negatives (actual diagnosis: 7 CARD, 4 MIXED). Regarding NT-proBNP data, 2 patients showing a false positive value (2744 and 1760 ng/L, respectively) were found to suffer from chronic obstructive pulmonary disease and from peritoneal carcinosis, respectively. On the other hand, 5 out of 7 patients showing false negative peptide concentrations (range: 144.70–769.60 ng/L) suffered from treated cardiac disease. The NT-proBNP behavior in the MIXED group seems to be of particular value. In fact, 10 out of 17 patients (59%) in this group showed values higher than 1760 ng/L and the concentrations observed were significantly higher than those of patients with pulmonary diseases (Table 1A). Furthermore, in this group, 4 out of 5 discordant cases showed peptide concentrations higher than the cut-off (range: 1976.00–4395.00 ng/L), suggesting that cardiac involvement coexisted with pulmonary dyspnea. The ER physicians did not recognize this concomitant cardiac disease.

Discussion

The results of the present study, which was done in order to verify the accuracy of NT-proBNP measurements in the

differential diagnosis of acute dyspnea in ER, led to some interesting observations. In particular, as reported in previous studies [9,10], the statistically significant difference observed when NT-proBNP levels from patients with acute dyspnea not attributable to cardiac origin were compared with those observed from patients suffering from cardiac diseases (Table 1) supports the ability of the natriuretic peptide assay to provide specific information about the cardiac involvement of acute dyspnea.

Furthermore, as NT-proBNP levels in patients with pulmonary diseases were significantly different from those with cardiac diseases, the peptide assay is of value to clinicians in making differential diagnosis between two clinical conditions which are often hard to differentiate in acute care settings. In our population, 17 out of 40 patients (42%) suffering from pulmonary dyspnea present a concomitant cardiac disease that the NT-proBNP assay allowed us to identify in 10 cases. 4 out of 10 were misdiagnosed in the ER.

The AUC that resulted from our study (0.815) reflects the good test ability that, however, appears less satisfactory than that observed in other studies [9,10]. This difference may be attributable to the high prevalence of co-morbidities in our population as well as to the patient selection criteria used for ROC curve analysis. In fact, we excluded NORM and AMI subjects from this analysis as CNH determinations do not represent the most appropriate biochemical tool useful to ER physicians in this particular clinical setting. However, the clinical specificity of natriuretic peptide increases in patients with acute breathlessness should be further investigated. Increased NT-proBNP levels can, in fact, occur in dyspnea from cardiac diseases, as well as in clinical conditions causing acute ventricular overload (pulmonary embolism, valvular diseases, dilatative cardiomyopathy, atrial or ventricular tachycardia) [11,12]. In patients with acute myocardial infarction, values were higher than in all other evaluated groups, although they were not significantly different in comparison to those in the CARD or MIXED groups. These data support the pathophysiological role of natriuretic peptides, which can be synthesized locally in the ventricles, in response to different stimuli such as ischemia, necrosis and enhanced parietal stress.

In conclusion, even if progress has been made in our understanding of the pathophysiological mechanisms underlying heart failure, this syndrome is still a major public health problem in developed countries. Moreover, the accuracy of current clinical and laboratory criteria used to differentiate between acute dyspnea of cardiac and non-cardiac origin is limited, particularly in the acute care setting. The availability of a sensitive and specific biochemical marker reflecting the hemodynamic changes typically due to heart failure may be of great interest to physicians working in the emergency department.

In the population studied, the significant difference found between NT-proBNP values in CARD vs. PD and OTHER groups, as well as the higher concentrations observed in patients in whom cardiac and pulmonary diseases coexist, seems to be of particular interest. The availability of such a test may therefore help ER physicians in recognizing the cardiac involvement, mainly when it is not clinically straightforward. The rapid information provided by this biomarker may allow an accurate and rapid patient evaluation [13] aiming to improve patient symptoms, prognosis as well as final outcome.

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