Diagnostic value of N-terminal ProB-Type Natriuretic Peptide in Emergency Department: Analysis by subgroups

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Abstract

Objectives. Our aim was to evaluate the diagnostic impact of N-terminal pro B-type natriuretic peptide (NT-proBNP) measurement in patients presenting with acute dyspnea in Emergency Department (ED), taking into account clinical and chest x-ray results routinely obtained.
Methods. This was a prospective observational study. Four hundred eighty-eight consecutive subjects evaluated for dyspnea in a metropolitan 600 beds hospital ED, entered into the final data analysis. According to a clinical and radiological score, the patients enrolled were divided in three groups: low (A-group), intermediate (B-group), and high (C-group) probability of heart failure.
Results. NT-proBNP median value was 2445 ng/L (Inter Quartile Range 631-5847 ng/L), and the area under the receiver-operating characteristic curves (AUC) was 0.854 for NT-proBNP, 0.921 for clinical/radiological score and 0.936 for the two in combination (logistic model). In the B-group (intermediate) NT-proBNP test added correct diagnostic information in 126 subjects with HF and in 53 subjects without a final diagnosis of HF. In A- and C-group NT-proBNP test added correct diagnostic information in 1 patient.
Conclusions. NT-proBNP did not substantially enhance diagnostic accuracy in all patients with shortness of breath in ED. However, in patients with not conclusive clinical and radiological results NT-proBNP determinations improved the percentage of correct diagnosis.

Key words: N-terminal ProB-Type Natriuretic Peptide, dyspnea, heart failure, diagnosis

Introduction

Measurement of circulating natriuretic peptides (NP), i.e. B-type natriuretic peptide (BNP) and its precursor, N-terminal proBNP (NT-proBNP), has been proposed as part of the evaluation of patients presenting to the Emergency Department (ED) with acute dyspnea (1-4). Observational studies have suggested that, when used in conjunction with other clinical information, NP testing may be useful in establishing or ruling out the diagnosis of heart failure (HF) (5-7). The inclusion of NP testing to improve the management of patients presenting to ED with dyspnea was evaluated in countries without Public Health System (8) and in nations with universal Public Health System (9). Nevertheless, some randomized controlled study results allow uncertainty about NP additional value in this clinical subset (10,11), and controversial clinical judgements have been published (12-17). In this context, an issue still unresolved is if NP should be tested in any patients presenting in ED with acute dyspnea. The question concerns both economic aspect (18) and clinical interpretation of NP results obtained on overall dyspnoic patients (19,20).

The purpose of the present non-industry-funded study was to evaluate the diagnostic impact of NT-proBNP measurement in patients presenting in ED with acute dyspnea. The potential additive diagnostic value of NTproBNP measurement was evaluated on patients subgroups corresponding to low, intermediate, and high probability of HF, defined on the basis of clinical and chest x-ray findings obtaining during ED evaluation.

Methods

A prospective observational study was designed. The study was carried out in the ED of a metropolitan 600 beds teaching hospital. All consecutive adult subjects with primary complaint of dyspnea, for a period of 12 months, were considered. According with the purpose of the study, patients with at least one NT-proBNP determination performed within the ED workup process were included into the study. The decision to order serum NT-proBNP testing was taken by the ED Attending Physician (AP) blinded to the ongoing study, according with her/his independent clinical judgment. Exclusion criteria were: a) patients presenting with dyspnea without NT-proBNP determination order by the AP; b) patients with dyspnea from clinically overt origins such as pneumothorax and chest wall trauma.
Overall 498 consecutive subjects were considered eligible for the study. Ten subjects were successively excluded from the

study because their ED chest x-ray was not available in clinical records at the time of analysis. The 488 subjects entered into the final data analysis had a mean age of 76.8±11.5 years; 250 (51.2%) were females and 238 (48.8%) males. NT-proBNP was determined on Elecsys 2010 platform (Roche Diagnostics - CV 4-5%) immediately after the blood collection and centrifugation. In agreement with current international recommendations a clinical decision level of 450 ng/L was adopted (21).

Clinical records of the enrolled patients were evaluated to assess the presence or the absence (dichotomous choice) of four clinical and two radiological findings, such as: 1) history of heart failure; 2) history of ischemic cardiomyopathy; 3) pulmonary rales; 4) leg edema; 5) chest x-ray cardiac enlargement; 6) chest x-ray pulmonary congestion. All data are components of the first routine clinical investigation commonly performed to assess patients with acute dyspnea in ED. For each patient enrolled a *clinical/radiological score* was calculated by assigning a score of 1 for the presence and a score of 0 for the absence of any of the six clinical and radiological findings. Taking into account this *clinical/radiological score* the patients enrolled into the study were divided into three groups, as follows: the A-group defines low probability of diagnosis of heart failure and consists of subjects with the *clinical/radiological score* = 0; the B-group defines intermediate probability of heart failure and consists of subjects within the *clinical/radiological score* range 1-3; the C-group defines high probability of heart failure and consists of subjects within the *clinical/radiological score* range 4-6. In our ED, as in many others, the chest x-ray is performed routinely in few minutes in patients with dyspnea, while the results of NT-proBNP is available for AP within about 1 hour. Approximately two months after the enrolment, two cardiologists, blinded to NT-proBNP assay results, revised all available clinical data, including the hospital course, the discharge summary and the echocardiogram when available, and assigned the final diagnosis of HF or no-HF according to Framingham definition of HF (reference standard). In case of discordance between the two cardiologists a third opinion was requested.

Statistical analysis

Data are presented as mean ± SD in the text and table. Comparisons were carried out using χ^2 tests as appropriate. Sensitivity and specificity were calculated within each patient group. Moreover, likelihood positive (LR+) and negative (LR-) ratio between NT-proBNP values above or below the cut-off and presence or absence of HF were determined. A logistic regression model with as dependent variable the final diagnosis of dyspnea of cardiac origin (yes/no) and as independent variables the NT-proBNP concentrations and the *clinical/radiological score* was performed. Receiver-operating characteristic (ROC) curve analysis were calculated for NT-proBNP and ED *clinical/radiological score*. All analyses were performed with SAS software 9.2 version (SAS Institute Inc. Cary, NC).

Results

In the 488 patients analyzed, the median value and interquartile range (IRQ) of NT-proBNP was 2445 ng/L (631-5847 ng/L), while the mean value was 5600 ± 9371 ng/L. The NT-proBNP concentration was <450 ng/L in 107 patients (21.9%) and between 450 and 900 ng/L in 45 patients (9.2%). HF was the final diagnosis for 304 patients (62.2%).
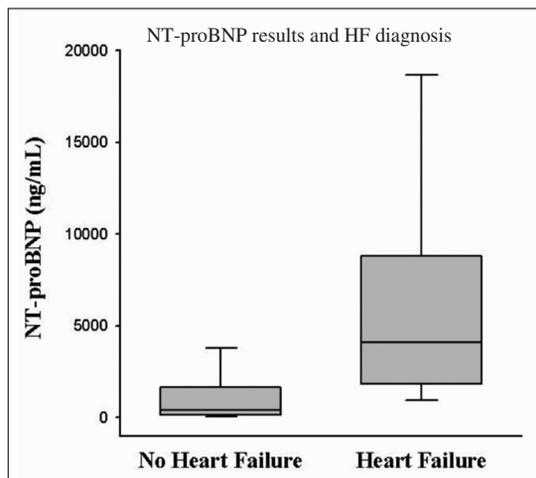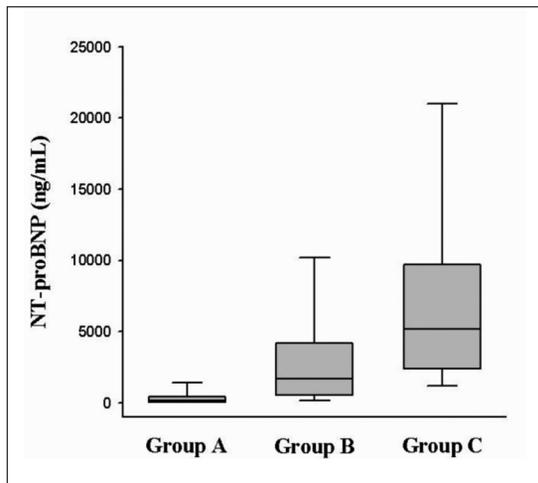

Figure 1. Box Plots showing median levels of NT-proBNP measured in the Emergency Department in two final diagnosis related groups of patients. Boxes show interquartile ranges, I bars represent 10th and 90th percentiles.
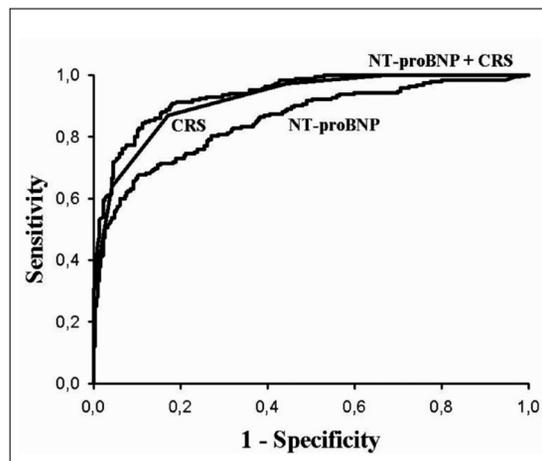
Figure 2. Receiving-Operating-Characteristic Curve (ROC) for NT-proBNP, *clinical/radiological score* (CRS) and the combination of the two in differentiating between HF and no-HF patients.

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Using the 450 ng/L cut-off, NT-proBNP sensitivity was 96.4 %, while specificity was 52.2 %. NT-proBNP distributions in patients who presented to the ED with dyspnea are reported in figure 1, according to the final diagnosis of HF or no-HF. Logistic procedure with as dependent variable the final diagnosis of dyspnea of cardiac origin (yes/no) and as independent variables the *clinical/radiological score* shows a Wald χ^2 value of 8.73 (p=0.0031) for NT-proBNP and a value of 109.97 (p<0.0001) for the *clinical/radiological score*. ROC curves of NT-proBNP, *clinical/radiological score* and the two in combination were calculated (Figure 2). The area under the ROC curves (AUC) was 0.854 for NT-proBNP, 0.921 for *clinical/radiological score*, and 0.936 for the two in combination (logistic model). This latter value was reduced to 0.787 if the chest x-ray results were removed from the model.

Fifty-four subjects, out of the 488 entered into the study, were in the A-group (low clinical/radiological probability of HF), 260 subjects in the B-group (intermediate probability of HF), and 174 in the C-group (high probability of HF). The NT-proBNP results in the three groups are summarized in figure 3.

Figure 3. Box Plots showing median levels of NT-proBNP in the Emergency Department in the three groups of patients, divided according to the *clinical/radiological score* (see Methods). Boxes show interquartile ranges, I bars represent 10th and 90th percentile.

A-group

None of the subjects of the A-group had a final diagnosis of HF and 42/54 subjects of this group had NT-proBNP values below the cut-off. Consequently, in this group, specificity of NT-proBNP was 77.7 % and negative LR was 1.23.

B-group

In the intermediate B-group 135/260 (51.9%) subjects had a final diagnosis of HF, of which 126 subjects had positive and 9 negative NT-proBNP values. Among the remaining 125 patients without a final diagnosis of HF, 72 subjects had positive and 53 had negative NT-proBNP values. In this group sensitivity of NT-proBNP was 93% and specificity 42%. Considering only this group, logistic procedure with as dependent variable the final diagnosis of dyspnea of cardiac origin (yes/no) and as independent variable NT-proBNP values was highly significant (p<0.0007), and the AUC was 0.768. In summary, in this intermediate group, the NT-proBNP test added correct diagnostic information in 126 subjects with HF and in 53 subjects without a final diagnosis of HF. The positive LR was 1.63 and the negative LR was 0.16.

C-group

In the C-group 169/174 (97%) subjects had a final diagnosis of HF, of which 167 subjects had positive NT-proBNP values and 2 subjects had negative; among the remaining 5 patients without a final diagnosis of HF, 4 had positive and 1 had negative NT-proBNP values. The positive LR was 1.22 and negative LR 0.05. In C-group, NT-proBNP test added correct diagnostic information in 1 patient. The results in the 3 groups are summarized in Table 1.

Table 1. Final diagnosis and NT-proBNP in subgroups.

A Group		B Group		C Group
Heart Failure	NT-proBNP +	0	126	167
	NT-proBNP -	0	9	2
No-Heart Failure	NT-proBNP +	12	72	4
	NT-proBNP -	42	53	1

Discussion

Objective of the present study was to evaluate the incremental diagnostic value of NT-proBNP in ED taking into account both clinical and radiological results. The value of NT-proBNP was analyzed dividing patients into subgroups according with their clinical and radiological characteristics. Previous studies demonstrated that inclusion of NT-proBNP improved the management of patients presenting to ED with dyspnea through enhanced diagnosis and reduced costs (6,9,22). The results of these studies greatly increased the NT-proBNP utilization by clinicians in ED. At the state of the art, NT-proBNP use is recommended as a part of the routine evaluation of patients with acute dyspnea (21,23). Nevertheless, in most of previous studies designed to establish the NT-proBNP value, only the clinical judgment of AP, expressed as a percentage of probability of dyspnea of cardiac origin, was considered. In particular, clinical and radiological elements (24) were not considered together for the diagnosis of HF. In the current study a internal score measuring the ED routine clinical and radiological results was used to set probability of being HF the cause of acute dyspnea. Using this score the utility of NT-proBNP in the diagnosis of HF in ED seems limited. In agreement with literature data, NT-proBNP sensitivity was very high. However, NT-proBNP added little diagnostic information to the clinical and radiological score when the whole of patients were considered, as showed by logistic model and AUC of ROC curves (Figure 2). Otherwise, after dividing patients into subgroups according to a clinical/radiological score, different conclusions can be reached. In patients with discordant clinical/radiological results (B-group), NT-proBNP added useful diagnostic information. These patients (intermediate score) seemed those in which NT-proBNP testing can add helpful diagnostic information to clinical and radiological results. The high sensitivity of NT-proBNP testing (95%) makes it particularly useful to exclude HF (rule-out diagnosis). On the other hand, in patients with low or high clinical/radiological probability of cardiac origin of dyspnea (A and C groups) NT-proBNP provided very little additional information. The relative low specificity of NT-proBNP is evident in the patients of A-group (low probability of HF). Moreover, in the patients of C-group (high probability of HF) the adding information of NT-proBNP was very little despite the good sensitivity of the test.

Limitations

The present study was conducted in a single hospital. Nevertheless, our laboratory results of NT-proBNP are in agreement with the prior results available in literature. In particular, the calculated AUC of ROC curve of NT-proBNP was very close to that reported in a larger multicenter trial (9).

Conclusions

Adding NT-proBNP to routine clinical and radiological score had very little utility to confirm or exclude the diagnosis of HF when the clinical and radiological picture was respectively strongly consistent or highly conflicting with this diagnosis. On the other hand, considering only patient with intermediate clinical/radiological results NT-proBNP can add information mainly to rule out the cardiac origin of dyspnea.

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