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Head-to-head comparison of the prohormone proBNP$_{1-108}$ with BNP and Nt-proBNP in patients admitted to emergency department

Damien Gruson [a,b,*], Jean-Marie Ketelslegers [b], Franck Verschuren [c], Frédéric Thys [c]

[a] Pôle de recherche en Endocrinologie, Diabète et Nutrition, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium
[b] Department of Laboratory Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium
[c] Department of Acute Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium

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ABSTRACT

Objectives: B-type natriuretic peptide (BNP) and amino-terminal proBNP (Nt-proBNP) are derived from a common precursor, the proBNP$_{1-108}$ (proBNP), synthesized by cardiomyocytes. We determined proBNP concentrations in patients admitted to ED and suspected of CHF.

Design and methods: One hundred fifty six consecutive patients admitted to ED were included. ProBNP, BNP and Nt-proBNP levels were determined at admission.

Results: In this ED population, assays for proBNP, BNP and Nt-proBNP were positively and significantly correlated. Circulating levels of proBNP were higher in patients admitted to ED for CHF than in patients admitted to ED other reasons. Applying receiver operating characteristic curve (ROC) analysis for the diagnosis of CHF, the area under the curve (AUC) was 0.92 for proBNP.

Conclusions: Our study demonstrated that proBNP testing, the precursor of BNP and Nt-proBNP, appears as a relevant tool to assist the diagnosis of CHF in patients admitted to ED.

Introduction

B-type natriuretic peptide (BNP) and amino-terminal proBNP (Nt-proBNP) are recognized as specific markers in patients suspected to have congestive heart failure (CHF), especially in emergency department (ED) [6,10–12,18]. The biologically active BNP and the inactive amino acid Nt-proBNP are derived from a biologically inactive prohormone proBNP$_{1-108}$ (proBNP) [3]. Recent data have demonstrated that proBNP is the major BNP-immunoreactive form in human blood [15] and clear evidence that this proBNP is circulating in patients with severe HF [4]. Giuliani et al. were the first to propose a commercial assay for proBNP testing which was based on a specific monoclonal antibody that recognizes the cleavage site of proBNP [2]. Their study, including 50 healthy volunteers and 170 patients with HF, has also demonstrated that this assay was able to differentiate healthy individuals from HF patients and that plasma proBNP levels were related to the NYHA. The ability of proBNP testing for the triage, management and risk stratification in CHF patients have thus been suggested [16].

The evidence of circulating proBNP has also raised some concerns related to the specificity of the assays for measurement of natriuretic peptides. Thus, a majority of the available commercial BNP and Nt-proBNP assays are cross-reacting with the precursor proBNP which may impact on their clinical value [7]. Therefore, assays with dedicated epitopes to proBNP may also improve the specificity of the method.

The aim of the present study was therefore to evaluate the diagnostic accuracy of circulating levels of proBNP in patients admitted to ED with dyspnea and/or thoracic pain. Moreover, we compared the performances of proBNP assay to two commercial assays for BNP and Nt-proBNP.

Methods

Study population

Study population consisted of 156 consecutive patients admitted to ED with dyspnea and/or chest pain. Patients were classified in 5 major diagnoses groups by clinicians unaware of natriuretic peptides testing results, according to the final medical chart following the ED stay or the hospitalization: CHF, coronary artery disease (CAD), pulmonary embolism (PE), pulmonary diseases (PD) and patients without cardiopulmonary disorders (NCP). CHF was diagnosed on the basis of clinical signs (pulmonary congestion, jugular venous distension, S3, and peripheral oedema), chest radiography, echocardiography and/or radionuclide angiography. All CHF patients had an ejection fraction less than 40%. CAD was defined by a well documented ECG (ST-segment elevation and/or depression $\geq$1 mm); significant coronary stenosis confirmed by angiography and progressive increase in blood cTnI concentrations occurring within 24 h after admission. Final PE diagnosis

* Corresponding author at: Pôle de recherche en Endocrinologie, Diabète et Nutrition, Université catholique de Louvain, Tour Claude Bernard, 54 Avenue Hippocrate, B-1200 Brussels, Belgium. Fax: +32 2 7645418.
E-mail address: damien.gruson@uclouvain.be (D. Gruson).

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Table 1
Patients' characteristics and circulating concentrations of proBNP, BNP and Nt-proBNP at admission to emergency department.

	NCP (n = 41)	PD (n = 20)	PE (n = 24)	CAD (n = 26)	CHF (n = 46)
Male/female	17/24	12/8	13/11	16/10	29/17
Age (years)	67 ± 17	67 ± 18	66 ± 15	65 ± 11	68 ± 9
HTA	17	10	7	15	20
Diabetes	9	3	3	7	8
Atrial fibrillation	0	1	1	5	4
History of myocardial infarction	5	4	0	3	8
History of heart failure	2	1	0	5	5
Chest pain	13	8	10	14	12
Dyspnoea	23	14	12	11	23
Creatinin (μmol/L)	82 ± 24	83 ± 19	81 ± 12	99 ± 42	118 ± 33
proBNP (ng/L)	16 [1–105]	20 [1–138]	240 [8–3757]	105 [4–1459]	1050 [79–6006]
BNP (ng/L)	23 [7–70]	31 [7–86]	141 [15–3095]	77 [14–765]	481 [66–2365]
Nt-proBNP (ng/L)	55 [5–422]	110 [7–330]	811 [25–25,825]	324 [11–2585]	4036 [250–35,000]

was established by lung scintigraphy and/or spiral CT scan according to current recommendations [13]. PD consisted in chronic obstructive pulmonary disease (mean forced expiration volume/vital capacity 66% or less of the predicted value) and/or pneumonia (diagnosed from chest X-ray). Patients without overt cardiopulmonary disorders were classified as dyspnea due to anxiety, psychological stress, gastroesophageal reflux disease and allergy reaction.

Laboratory investigations

Blood was collected in dry tubes (serum) and on EDTA tubes (Sarstedt, Nümbrecht, Germany) at admission to the emergency department. After centrifugation (1500 g, 10 min, 4 °C) within 1 h, EDTA plasma and serum were carefully separated and stored at −80 °C until assayed. $ProBNP_{1-108}$ (proBNP) plasma concentrations were determined on EDTA plasma with the specific BioPlex 2200™ assay (Bio-Rad, Hercules, California). The total imprecision of this assay was previously evaluated for concentration of 229, 673 and 1338 ng/L and were 8.7%, 7.5% and 6.5%, respectively [19]. The lower limit of quantification of the assay was <5 ng/L [19]. The cross-reactivity of the BioPlex 2200™ proBNP assay was <0.05% with BNP and Nt-proBNP [19]. BNP was determined on EDTA plasma with Access 2® BNP immunoassay based on chemiluminescence detection (Beckman Coulter, Fullerton, CA, USA; Biosite reagents). Nt-proBNP was measured on serum samples with a Roche Diagnostics® electrochemiluminescence immunoassay performed with Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). All automated assays were performed according to manufacturer's specifications. The study protocol was approved by the institutional review board and all patients gave informed consent.

Statistical analysis

Statistical analysis, were performed using the Medcalc 7.2.1.0 package (Medcalc Software, Belgium) [14] after log transformation of the variables. The effects of the disease on proBNP circulating levels were tested using one way analysis of variance (ANOVA). Student–Newman–Keuls was used for pairwise comparison between groups. Correlations coefficients determined by the Pearson's test. The McNemar test was used to test the difference between paired proportions. Receiver Operator Characteristics (ROC) curve was constructed to assess clinical performance of the studied assays. A level of p value <0.05 was considered as statistically significant.

Results

Study population characteristics

The study included 156 patients (85 males, 71 females, mean age: 67 years). Final diagnoses included 46 patients with CHF (mean age: 68 ± 9 years; mean creatininemia: 118 ± 33 μmol/L), 26 patients with CAD (mean age: 65 ± 11 years; mean creatininemia: 99 ± 42 μmol/L), 24 with PE (mean age: 66 ± 15 years; mean creatininemia: 81 ± 12 μmol/L), 20 with PD (mean age: 67 ± 18 years; mean creatininemia: 83 ± 19 μmol/L) and 41 patients without cardiopulmonary disorders (mean age: 67 ± 17 years; mean creatininemia: 82 ± 24 μmol/L). The patients Characteristics are described in the Table 1.

Circulating levels of proBNP in ED patients

ProBNP levels were significantly influenced by diagnostic subgroups (ANOVA: p<0.001; Fig. 1) and pairwise comparisons showed that CHF patients had the highest proBNP circulating levels in comparison to all other groups (p<0.05). Some patients with CAD and PE demonstrated increased circulating concentrations of proBNP (Fig. 1). Patients without cardiopulmonary diseases had the lowest values in comparison to the other subgroups (p<0.05). The same results are observed for BNP and Nt-proBNP. However, the absolute values of proBNP were higher than those determined for BNP and lower than those measured for Nt-proBNP. The Table 1 summarizes the circulating concentrations of proBNP, BNP and Nt-proBNP in the different diagnosis subgroups. Interestingly, the concentrations of the three biomarkers were markedly increased in 13 patients with massive PE and altered cardiac function.

Accuracy of proBNP testing for the diagnosis of heart failure

For CHF diagnosis in the cohort of 156 patients, the area under the ROC curve (AUC) of proBNP was 0.92 (95% Confidence interval: 0.87–0.96) and was equivalent to BNP and Nt-proBNP (BNP AUC: 0.91, 95% CI: 0.86 to 0.95 and Nt-proBNP AUC: 0.92, 95% CI: 0.86 to 0.96;

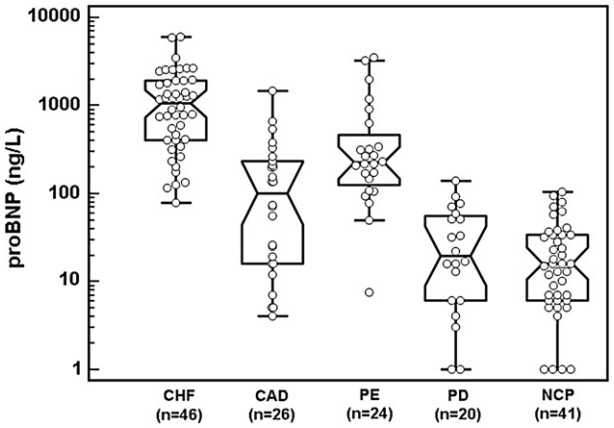

Fig. 1. ProBNP levels according to the diagnosis subgroups (CHF: congestive heart failure, CAD: coronary artery disease, PE: pulmonary embolism, PD: pulmonary diseases, and NCP: no cardiopulmonary disorders).