Original Article

Can NT-proBNP be used as a criterion for heart failure hospitalization in emergency room?

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Abstract

BACKGROUND: Heart failure is a common health problem with poor prognosis. The gold standard for diagnosis is echo-cardiography but it is not always reachable, especially in emergency conditions. NT-pro-brain natriuretic peptide (NT-proBNP) is a novel indicator for the diagnosis of heart failure and is being used in routine tests in emergency rooms. This study was conducted to compare NT-proBNP levels between hospitalized congestive heart failure (CHF) patients and outpatients.

METHODS: This study was designed as a single-centre, prospective, and controlled trial. Blood samples and data were collected from a total of 119 patients with shortness of breath admitted to Department of Emergency, School of Medicine, Marmara University. Patients were primarily diagnosed with decompensated heart failure according to the Framingham criteria and aged above 18 years. A total of 92 patients were included in the study after exclusions. NT-proBNP measurements were made by immune fluorescent method. Available data were compared between hospitalized patients and outpatients.

RESULTS: NT-proBNP levels were significantly higher in hospitalized patients compared to outpatients, and this finding was correlated with the clinical status of the patients. The mean NT-proBNP value of the patients was 9741.9 ± 8973 pg/ml (range: 245-35000) while the mean NT-proBNP value of patients diagnosed with non-decompensated congestive heart failure was 688.9 ± 284.5 pg/ml (range: 115-1450.65).

CONCLUSIONS: NT-proBNP can be used as an easy diagnostic method for congestive heart failure. A certain cut-off value may be determined in further multi-centre controlled trials with larger patient groups.

KEYWORDS: NT-Pro-Brain Natriuretic Peptide, Heart Failure, Emergency.

The incidence of heart failure, as one of the most frequent causes of hospitalization in the general population, is increasing.[1,2] Despite significant advances in the diagnosis and treatment of this disease, prognosis is still poor.[3] This disorder is the final common pathway to death in cardiovascular disease patients.[4] Physiologically, decompensated heart failure is a syndrome characterized with decreased cardiac output and venous return. It is also a pro-gressive worsening of heart associated with molecular abnormalities leading to premature death of myocyte cells. Although contractility disorder and decreased blood pumping function of the heart are responsible for the onset of heart failure as a clinical syndrome, clinical findings are not observed in many patients despite the deteriorations of systolic and diastolic functions. This phenomenon is mainly caused by the compensatory mechanisms which try to

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maintain cardiac output and peripheral perfusion. Therefore, heart failure is not only a heart disease. In fact, it is a combined heart-circulatory disorder.[5]

It is difficult to make differential diagnosis of chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) in patients admitted to emergency departments with acute onset of dyspnoea because of the non-specific symptoms. Symptoms and physical examination findings are not sensitive for the definitive diagnosis of heart failure. Although echocardiography is the gold standard for left ventricular dysfunction,[6] it is not always accessible in emergency conditions. Thus, there had been a need for a reliable, fast and cheap test. Brain natriuretic peptide (BNP) started to be used as a routine approach in emergency rooms for differential diagnosis of shortness of breath in recent years.[7,8]

Heart failure may emerge with the sudden deterioration of heart pump function (e.g. acute myocardial infarction), or can be triggered by an increase in systemic vascular resistance as a result of the rapid decrease of cardiac output in the presence of an underlying cardiac dysfunction. It can also develop in a slow and insidious way with some pathological hemodynamic and neurohormonal reflexes which would start by a myocardial injury or a stress factor. Water and sodium retention in combination with increased systemic vascular resistance can be observed after neurohormonal activation.[9] Although these hemodynamic and neurohormonal mechanisms provide inotropic support, they cause long-term increases in the load and risk. Theoretically, controlling the increased levels of neurohormones would form the basis of the treatment.[10]

Natriuretic peptides constitute the opposite arm of the pathologic neurohormonal activation of the heart failure. These peptides are available in three types, known as ANP (atrial natriuretic peptide), BNP (B-type natriuretic peptide or brain natriuretic peptide) and CNP (C-type natriuretic peptide). ANP is secreted primarily from the atrium, BNP is secreted from cardiac ventricles and CNP is localized in endothelium. BNP was shown to be produced more quickly

in cases of acute loading. This situation causes BNP to be superior to ANP in terms of use in emergency conditions.[11] In case of increased ventricular wall tension, proBNP is produced in both right and left ventricles. It causes inverse effects, such as decreased smooth muscle proliferation of vessels, decreased natriuresis and diuresis, and decreased myocardial fibrosis, on neurohormonal mechanisms. It finally results in vasodilatation and causes decreased norepinephrine, aldosterone, endothelin and renin release. ProBNP is secreted in many cases other than heart failure. Such situations include pulmonary hypertension, cor pulmonale, pulmonary embolism, left ventricular hypertrophy, renal failure, overload situations in circulation, hypertension, acute coronary syndrome, atrial fibrillation, lung cancer, sepsis, and hormone replacement therapy. BNP values are also affected by age, gender, and body weight.[12]

BNP was first isolated from porcine brain tissue as a 32 amino acid protein. Although it is also found in the human brain, it is particularly secreted from the heart ventricles.[13] ProBNP is a 108 amino acid precursor peptide of the BNP which is stored in secretory granules in myocytes. It is divided by a protease into the biologically active form of the 32 amino acid BNP, and the inactive form of the N-terminal-proBNP (NT-proBNP) as a result of increased wall tension in ventricles.[14] NT-proBNP has a longer half-life compared to BNP and is not affected by the administration of exogenous BNP (e.g. nesiritide).[15] NT-proBNP is more dependent on renal elimination and has a half-life estimated to be about 2 hours while the biologically active part (BNP) has a half-life about 22 minutes.[9] Both serum proBNP and NT-proBNP levels are consistent with the clinical severity of the disease according to the heart failure classification of New York Heart Association.[16] Higher values were determined in hospitalized patients and the levels were decreased with aggressive treatment.[17] However, despite sharing a common synthetic pathway, there is no consistent relationship between these molecules. Natriuretic peptide measurement is now included in routine tests for the diagnosis of heart failure in

emergency departments because it is a low cost, easy to use and quick examination in the differential diagnosis of dyspnoea. For the diagnosis of CHF, NT-proBNP has a sensitivity of 99%, a specificity of 85%, a negative predictive value (NPV) of 99%, and a positive predictive value (PPV) of 76%.[9]

The aim of this study was to compare NT-proBNP levels between hospitalized CHF patients and outpatients. The decision of admitting or not admitting a patient to the hospital was applied according to the reference criteria of Agency for Health Care Policy and Research (AHCPR) for CHF hospitalization.[18] These criteria have a historical importance and emergency physicians use them frequently in their routine daily practice. In this context, NT-proBNP levels in patients with shortness of breath admitted to Department of Emergency, School of Medicine, Marmara University were examined.

Methods

Our study was planned as a single-centre, prospective, and controlled trial. Data were collected from a total of 119 patients with shortness of breath admitted to of Emergency, School of Medicine, Marmara University between July 2005 and December 2005. Subjects had a pre-diagnosis of decompensated heart failure according to the Framingham criteria, aged above 18 years and volunteered to participate in the study. It was learned by phone if the patients were hospitalized with the diagnosis of CHF within the last month. Thirteen patients were excluded for being hospitalized during the past month, 4 for being diagnosed with acute coronary syndrome, 6 for having malignancy, and 4 for having serum creatinine levels above 2.5. Remaining 92 patients were included for the analysis. Two separate control groups were constituted. The first group included 45 healthy individuals without a known diagnosis or signs of heart failure. The second control group included 45 patients, who were diagnosed with heart failure in the last year by echocardiography and cardiology outpatient clinic examination but were not clinically decompensated by medical treatment.

The patients in this study were hospitalized in accordance with the criteria of AHCPR for hospitalization in CHF.[18] Treatments were performed based on the latest guidelines. A patient with CHF should be admitted to the hospital if they had respiratory distress (respiratory rate > 40 breaths per minute) or pulmonary oedema (determined by radiograph), hypoxia (oxygen saturation < 90%), anasarca or significant oedema (≥ 2), syncope or hypotension (systolic blood pressure ≤ 80 mmHg), CHF of recent onset (no past history of CHF), evidence of ischemia (chest pain symptoms), inadequate social support for outpatient management, failure of outpatient management, or a concomitant acute medical illness.

Exclusion criteria were having a history of major trauma or surgery within the past 6 months, malignancy, pregnancy, acute coronary syndrome, severe renal insufficiency (creatinine level > 2.5) and being hospitalized with a diagnosis of CHF within 1 month after the initial application.

After informing the patients and their guardians, NT-proBNP levels were measured from blood samples collected for routine biochemical parameters in 3 cc tubes at admission. NT-proBNP measurements were made by immune fluorescent method at the central biochemistry laboratory of the Marmara University Hospital. Patients were asked by telephone 1 month after recommending the outpatient treatment if they were hospitalized with a diagnosis of CHF at Marmara University Hospital or somewhere else.

This study was carried out after obtaining the approval of the Ethics Committee of Marmara University (MAR-YÇ-2005-0157). All subjects gave written informed consents to participate in the study. The investigation conforms to the principles outlined in the Declaration of Helsinki.[19]

All data in the study were compared using Kruskal-Wallis test, Fisher test, and chi-square test where appropriate. Bilateral comparisons were made using Mann-Whitney U test. P values lower than 0.05 were considered as statistically significant. In bilateral comparisons, limit

of significance of p value was calculated with Bonferroni adjustment as p/number of paired comparisons. The data were analyzed using SPSS$_{17.0}$ (SPSS Inc., Chicago, IL, USA). All values are shown as mean ± SE (standard error).

Results

A total of 92 patients were included in this study. The mean age of the whole population was 74.8 ± 10.3 years with 48.9% of the participants (n = 45) being female and 51.1% (n = 47) being male. The mean age of women and men were 75.3 and 74.3 years, respectively. In addition, 60 patients were hospitalized for treatment and 32 patients were discharged after the first treatment at the emergency department observation unit. While 86.8% of inpatients (n = 52) were treated at emergency department observation unit, 6.6% of cases (n = 4) received care in coronary intensive care unit, and 6.6% (n = 4) were treated in the internal medicine ward. There were no significant differences between the mean of ages of the inpatients and outpatients (p = 0.303). Moreover, there were no significant differences in sex distributions between the study groups (p = 0.775).

Demographic properties and the other parameters of the hospitalized patients and the outpatients are shown in Table 1. Age, sex, smoking history, medical history, symptoms, physical examination findings, and laboratory findings were compared between hospitalized patients and outpatients. Statistically significant differences were found only in jugular venous distension (p = 0.001), hepatojugular reflux (p = 0.001), respiratory rate (p = 0.001), and O$_2$ saturation (p < 0.001) among physical examination findings, and pH (p = 0.05) and partial pressure of O$_2$ (pO$_2$) values (p = 0.013) among laboratory findings.

The mean NT-proBNP value of the patients was 9741.9 ± 8973 pg/ml (range: 245-35,000); it was 247.1 ± 276.1 pg/ml (range: 15.36-959.3) and 688.9 ± 284.5 pg/ml (range: 115-1450.65 among healthy individuals and the patients diagnosed with non-decompensated CHF, respectively. A statistically significant difference was observed in NT-proBNP values

between the three groups of patients (p < 0.001).

The mean NT-proBNP value of the outpatients and hospitalized patients were 6835.9 ± 6935.3 pg/ml (range: 245-35000) and 11291.8 ± 9585.5 pg/ml (range: 712-35000), respectively.

Discussion

It is often difficult to make a differential diagnosis in patients admitted to the emergency department with the complaint of shortness of breath. Echocardiography is still the gold standard diagnostic method of heart failure, although its use in emergency departments is limited in terms of both cost and accessibility.[1,6] Therefore, BNP and NT-proBNP have become routine tests in emergency departments in recent years because they are reliable, easy to use and low-cost laboratory tests.[20] American College of Emergency Physicians and European Society of Cardiology recommended the clinical use of natriuretic peptide measurements as an aid in the diagnosis or exclusion of acute heart failure.[9]

Maisel et al. wrote a review about using natriuretic peptide levels in clinical practice and recommended cut points of BNP and NT-proBNP for heart failure diagnosis. Based on their findings, with BNP < 100 pg/ml, heart failure is improbable. Levels between 100-400 pg/ml with clinical suspicion or past history of heart failure indicate probable heart failure. Finally, levels above 400 pg/ml suggest high probability of heart failure. In case of NT-proBNP higher levels were reported. They have also emphasized age dependent variations of NT-proBNP.[17] While a cut point of 300 pg/ml is proposed to rule out the diagnosis of heart failure, for patients younger than 50 years old, between 50-75 and above 75 NT-proBNP levels respectively > 450 pg/ml, > 900 pg/ml, and > 1800 pg/ml have high likelihood of heart failure.[21] Both proBNP and NT-proBNP measurements also give clues about the disease process of heart failure more than excluding the diagnosis. A multi-centre study conducted by Maisel et al. examined 464 patients with CHF who received treatment in the emergency

Table 1. Baseline characteristics of patients

Characteristic	Hospitalized (n = 60)	Outpatient (n = 32)	p
Age (mean)	75.7 ± 9.8	72.9 ±11.0	0.303[*]
Gender (%)			
Woman	50 (30)	46.9 (15)	0.775[**]
Man	50 (30)	53.1 (17)	
Cigarette smoking (%)			
Yes	53.3 (32)	43.8 (14)	0.381[**]
No	46.7 (28)	56.3 (18)	
Past medical history (%)			
Congestive heart failure	73.3 (44)	53.1 (17)	0.051[**]
Hypertension	58.3 (35)	62.5 (20)	0.698[**]
Coronary artery disease	31.7 (19)	37.5 (12)	0.573[**]
Chronic obstructive pulmonary disease	40 (24)	37.5 (12)	0.815[**]
Chronic renal failure (creatinine < 2.5)	13.3 (8)	6.3 (2)	0.485[***]
Peripheric vascular disease	8.3 (5)	6.3 (2)	1[***]
Hiperlipidemia	20 (12)	12.5 (4)	0.366[**]
Diabetes mellitus	45 (27)	18.8 (6)	0.012[**]
Symptoms (%)			
Ortopnea	78.3 (47)	71.9 (23)	0.486[**]
Paroxysmal nocturnal dyspnea	57.6 (34)	53.1 (17)	0.679[**]
Dispnea	90 (54)	93.8 (30)	0.709[***]
Chest pain	35 (21)	34.4 (11)	0.952[**]
Physical examination (%)			
Jugular venous distension	78.3 (47)	43.8 (14)	0.001[**]
Hepatojugular reflux	46.7 (28)	12.5 (4)	0.001[**]
S3	13.3 (8)	3.1 (1)	0.155[***]
Murmur	30 (18)	18.8 (6)	0.242[**]
Crepitation	98.3 (59)	90.6 (29)	0.119[***]
Hepatomegaly	35 (21)	25 (8)	0.325[**]
Oedema	90 (54)	84.4 (27)	0.506[***]
Systolic blood pressure/mmHg	134.3 ± 29.9	134.8 ± 29.5	0.997[*]
Diastolic blood pressure /mmHg	76.8 ± 18.9	79.6 ± 20.3	0.676[*]
Respiratory rate /min	34.2 ± 9.3	28.2 ± 6.7	0.001[*]
Pulse /min	93.8 ± 20.0	89.6 ± 20.6	0.127[*]
Temperature (°C)	36.0 ± 4.8	36.2 ± 1.60	0.670[*]
O_2 Saturation	87 ± 7	95 ± 4	< 0.001[*]
Laboratory Findings			
Arterial blood pH	7.40 ± 0.06	7.43 ± 0.04	0.05[*]
Partial arterial O_2 pressure	61.7 ± 14.0	68.2 ± 12.0	0.013[*]
Partial arterial CO_2 pressure	40.1 ± 10.3	37.3 ± 4.3	0.192[*]
Hemoglobine	11.1 ± 1.8	11.8 ± 2.0	0.205[*]
White blood cell count	8429 ± 3214	8257 ± 2828	0.761[*]
Blood urea nitrogen	32.5 ± 20.5	23.9 ± 7.1	0.095[*]
Creatinine	1.27±0.57	1.07±0.34	0.103[*]

*Mann-Whitney U test (p < 0.05); **Chi-square test (p < 0.05); ***Fisher test (p < 0.05). Values are pesented as number (%) or Mean ± SE (standart error).

department or were hospitalized. Inpatient mortality was shown to be related to admission BNP level in a linear manner.[17] Januzzi et al. studied the cut points of NT-proBNP in the diagnosis of heart failure and the relationship between disease severity and NT-proBNP levels. They found that levels above 1000 pg/ml

were associated with severe heart failure and adverse prognosis.[22]

Natriuretics also give information about future prognosis of heart failure patients. Harrison et al. examined BNP and the prognosis of patients and found that the 6-month mortality and hospital readmission rates of patients were

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40% for those with BNP levels above 480 pg/ml.[23] The same rate was found to be 3% in patients with a BNP limit value of 230 pg/ml. In a 12-month follow-up study, Tsutamoto et al. found that patients with BNP values higher than 73 pg/ml showed significantly increased mortality compared to those with BNP values below this level.[24]

Previous studies all give linear correlations between BNP and NT-proBNP levels and disease severity. However, to our knowledge, the decision of hospitalization for heart failure paitents does not have a known cut point of NT-proBNP. In this study, we aimed to evaluate the general profile of the patients with a preliminary diagnosis of CHF admitted to emergency room with the complaint of shortness of breath. We also compared these properties with NT-proBNP to assess whether it can be used reliably for the decision of hospitalization among these patients.

According to our results, NT-proBNP levels were significantly higher in hospitalized patients compared to outpatients. Additionally, rates of jugular venous distention and hepato-jugular reflux were significantly higher in hospitalized patients. Both of these findings are known to be more specific particularly in the right heart failures. Therefore, it can be concluded that NT-proBNP may be more elevated in the right heart failures.

Our study did not provide a clear answer to the question whether there is any limit value in NT-proBNP for hospitalization. When the data were evaluated, minimum value of NT-proBNP was found to be 712 pg/ml for clinically hospitalized patients and 245 pg/ml, for outpatients. Although these results may seem significant at first glance, when the patients separate evaluation of the patients revealed that the maximum value of 35000 pg/ml for NT-proBNP in hospitalized patients was also reached in outpatients who were not hospitalized at least during the past month. The mean of NT-proBNP in hospitalized patients was 11291 pg/ml and six outpatients had NT-proBNP values higher than this level. Thus, this study has not determined a certain cut-off value of NT-proBNP for hospitalization decision.

This study also had some limitations. The main limitation of was the number of eligible cases. Since Department of Emergency, School of Medicine, Marmara University is a tertiary health facility, it caters to a limited population which may have affected our results.

Moreover, the presence of comorbidities except the exclusion criteria in 8 patients (4 patients with pneumonia, 1 patient with urolithiasis, and 3 patients with exacerbation of COPD) may have influenced the physicians' decision for hospitalization.

Weight and body mass index were not measured in our study. Recent publications show that obesity may interfere with the NT-proBNP levels. This can be the weakest aspect of this study.

All patients in the study group were not evaluated with echocardiography in emergency room conditions. Patients were clinically diagnosed as having CHF. Not using the gold standard diagnostic method for all patients is another important limitation of this study.

Conclusion

NT-proBNP has been shown as an easy diagnostic method among routine emergency service tests in the most recent guidelines on CHF. However, it is not currently included among the classic criteria for hospitalization. A certain cut-off value may be determined in further multi-centre controlled trials conducted with larger patient groups.

As a result, doctors working in emergency departments would have a very practical helper method in terms of approaches to diagnosis and treatment of CHF. Such a method would also prevent unnecessary hospital admissions and high costs of treatment. It would also prevent many secondary problems that may develop in elderly patients with concomitant illnesses due to hospitalizations. However, at present, the main determinant of the follow-up method should be clinical characteristics of the patient.

Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
TCO and EU designed and carried out the research, collected the data, interviewed the patients, coordinated the study, participated in all of the research, and prepared the manuscript. AD provided assistance in designing and conducting the research. OG participated in manuscript preparation and performed the statistical analysis. OO corrected the English manuscript and revised further statistical data. All authors have read and approved the content of the manuscript.

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