# Heart Failure: Discrepancy Between NYHA Functional Classification, Serum NT-pro Brain Natriuretic Peptide and Ejection Fraction

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## ABSTRACT

*This study aimed to look for the discrepancy between the laboratory investigation (determination of serum NT-proBNP), electro-physiological assessment (echocardiogram and Doppler study) and clinical assessment of known cases of congestive heart failure. This study conducted in the college teaching hospital from January to October 2011. This study is a cross-sectional in a cohort of patients with heart failure. Known cases of congestive heart failure and healthy subjects served as control group were enrolled in this study. Patients were assessed clinically according to the New York Heart Association (NYHA) functional classification, echo-cardiography by ejection fraction and laboratory by determination of NT-proBNP).Student's "t" test (one paired, two tailed) and simple correlation test were used in data analysis. The results of 169 patients enrolled in this study showed that serum levels of NT-proBNP did not match the NYHA functional classification of heart failure. Serum NT-proBNP was significantly inversed-correlated (r = -0.339, p < 0.001) with the serum ejection fraction and inconsistently related to the E/A ratio assessed by Doppler study. It concludes that serum NT-proBNP level is well correlated with ejection fraction and not well matched the functional disabilities of longstanding heart failure.*

*Key words: NT-proBNP, Heart failure, ejection fraction*

## Kalp yetmezliği: NYHA Fonksiyonel Sınıflandırma, Serum NT-probrain Natriüretik Peptid ve Ejeksiyon Fraksiyonu Arasındaki tutarsızlık

### ÖZET

*Bu çalışma konjestif kalp yetmezliği bilinen olgularda laboratuar inceleme (serum NT-pro BNP değerlendirmesi), elektrofizyolojik değerlendirme (ekokardiyografi ve Doppler çalışması) ve klinik değerlendirme arasındaki tutarsızlığı araştırmayı amaçlamıştır. Bu çalışma Ocak-Ekim 2011 tarihleri arasında üniversite araştırma hastanesinde yapılmıştır. Bu, kalp yetmezliği olan hastalardan oluşan bir kohortta kesitsel bir çalışmadır. Konjestif kalp yetmezliği bilinen vakalar ve sağlıklı bireyler bu çalışmaya kontrol grubu olarak katılmışlardır. Hastalar, klinik olarak New York Kalp birliğinin (NYHA) fonksiyonel sınıflaması, ekokardiyografik olarak ejeksiyon fraksiyonu ve laboratuar inceleme olarak NT-pro BNP değerine göre değerlendirilmişlerdir.  Veri analizi Student's t testi (bir çift, iki uçlu) ve basit korelasyon testi kullanılarak yapılmıştır. Çalışmaya alınan 169 hastanın sonuçları göstermiştir ki serum NT- pro BNP düzeyleri kalp yetmezliğinin NYHA fonksiyonel sınıflaması ile uyumlu değildir. Serum NT-pro BNP düzeyleri anlamlı şekilde ejeksiyon fraksiyonu ile ters orantılıdır (r = -0.339, p < 0.001) ve Doppler çalışması ile değerlendirilen E/A oranı ile tutarsız şekilde ilişkilidir.  Sonuç olarak serum NT-pro BNP düzeyleri ejeksiyon fraksiyonu ile iyi koreledir ve uzun süren kalp yetmezliğinin fonksiyonel kısıtlamaları ile iyi uyum göstermemektedir.*

*Anahtar kelimeler: NT-pro BNP, kalp yetmezliği, ejeksiyon fraksiyonu*

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## INTRODUCTION

Brain natriuretic peptide (BNP) released from cardiac ventricular myocytes in response to volume or pressure overload. Rapid measurement of plasma BNP or NT-proBNP improved the diagnostic accuracy of heart failure (HF) exacerbations (1). Large amounts of proBNP can be detected in plasma of healthy subjects and in particular of patients with heart failure. Plasma concentrations of BNP and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) are more closely related to measurements of cardiac structure, function and to cardiovascular prognosis than ANP or other circulating neurohumoral markers of cardiac disease (2). Natriuretic peptides were known to decrease following medical therapy of HF, suggesting the role of their measurement in monitoring inpatient disease progression and outpatient medical programs (3). Atrial fibrillation was associated with high BNP level in patients with reserved left ventricular ejection fraction, therefore the measurement of BNP concentration in patients with atrial fibrillation allowed to diagnose HF at early stages (4). In hypertension, the Left atrial enlargement, rather than left ventricular hypertrophy was correlated with elevated plasma BNP that produced by increased left ventricular after load (5). Determination of BNP is a useful laboratory test in identifying left ventricular systolic dysfunction in patients suffered from exacerbation of chronic obstructive pulmonary disease (6). Prastaro et al (7) demonstrated NT-pro-BNP cut-off of 1480 pg/ml indicated left atrium dysfunction with 89% specificity and 54% sensitivity, in congestive heart failure patients with severely impaired systolic function, NT-pro-BNP levels reflect left atrium and ventricle dysfunction. Preoperative assessment of NT-proBNP level in coronary artery bypassing grafting (CABG) patients could be a valuable diagnostic method for predicting several postoperative complications, especially pulmonary outcomes and requirement for hemodynamic support. The NT-proBNP level was a predictor of postoperative prolonged mechanical ventilation, respiratory failure, atrial fibrillation, intra-aortic balloon pump counterpulsation use, inotropic support and postoperative platelet transfusions (8). BNP level is not affected by the criteria of metabolic syndrome while diabetes mellitus causes an increase BNP level (9).

The aim of this study was to explore the discrepancy between the laboratory investigation (determination of NT-proBNP), electrophysiological assessment (echocardiogram and Doppler study) and clinical assessments of known cases of congestive heart failure.

## MATERIALS AND METHODS

This study was done in the college teaching hospital from January to October 2011. This study was approved by an institutional review committee and informed consent was obtained from each patient prior to enroll in the study. This study designed as a cross sectional in cohort patients with heart failure and healthy subjects (served as control group). The criteria of inclusion of patients group were; known cases treated-heart failure, ≥ 3 months duration, evidence of risk factors including ischemic heart disease, hypertension, cardiomyopathy valvular heart disease and diabetes mellitus. The criteria of exclusion are: acute left ventricular failure, chronic obstructive lung history, history of cardiac surgery or pacing (because the level of NT-proBNP may be increased), renal failure, terminal illnesses. The patients were allocated randomly using randomized tables from heart failure patients who attended the college teaching hospital for follow up. The sample size of patients was determined using the following formula (10):

$$n = \{\mu \surd([\pi(1-\pi)]) + v\surd([\pi_\circ(1-\pi_\circ)])\}2 / (\pi-\pi_\circ)2$$

Where

n = required minimum sample size

π = proportion of interest which proposed in this study 0.7

$\pi_\circ$ = null hypothesis proportion which equal to 0.5

μ = one side percentage point of normal distribution corresponding to 100% - the significant power. In this study the power 85%, (100%-85%) =15% and μ=1.036

v = percentage of the normal distribution corresponding to the required (two-sided) significant level. In this study the significant level of 5% was considered, v=1.96

Therefore the estimated sample size should be more than 53 patients

The control group included an apparent healthy subjects with normal limits electrocardiographic, echocardiographic , chest X-ray and laboratory investigations (complete blood picture, erythrocyte sedimentation rate, fasting serum glucose, serum creatinine and lipid profile). Each patient was examined, assessed and categorized according to the New York Heart Association Functional Classification (NYHA) into four classes: I (no symptoms), II (mild symptoms), III (marked limitation) and IV (severe limitations). The anthropometric mea-
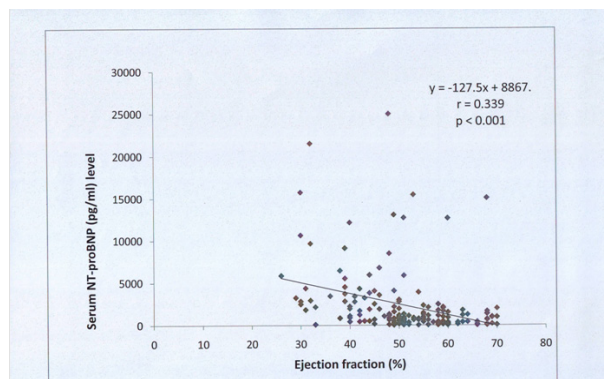
**Figure 1**. *Relationship between ejection fraction (%) and serum level of NT-proBNP(pg/ml) in patients with heart failure.*
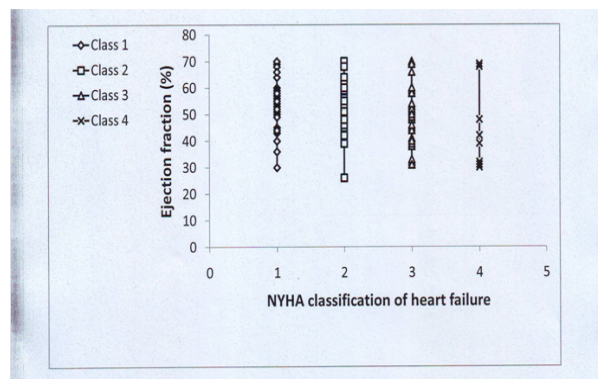


**Figure 2**. *Distribution of cases according to the NYHA classification of heart failure and their corresponding ejection fraction.*

surements including weight (kg), height (m) and the calculated body mass index (kg/m$^2$), electrocardiogram, echocardiography (for the diagnostic and prognostic purposes) and Doppler study (determination the E/A ratio) were obtained. Peripheral venous blood was drawn immediately after admission into tubes until clot formation, then the samples were centrifuged at 2500 rpm for 10 min, and the sera were frozen and stored at -70°C until analyzed for determination of NT-proBNP. The serum level of proBNP (a biomarker of heart failure) was determined in the laboratories of Specialized Center for Cardiac Surgery using the technique of Enzyme Linked Fluorescent Assay (VIDAS NT-proBNP automated test for use on the VIDAS instrument, Biomerieux, France). The principle of this assay is a one step immunoassay sandwich method with a final fluorescent detection (ELFA) and the range of measurement is 20-25000 pg/ml). Levels below 100 pg/ml indicate no heart failure, 100-300 pg/ml suggest heart failure is present, >300 indicate mild heart failure, > 600 ml indicate moderate heart failure and >900 pg/ml indicate severe heart failure.

*Statistical analysis*

The results expressed as absolute number, percent, mean ± SD. The data analyzed using Student's "t" test (one paired, two tailed) and simple correlation test taking the p ≤ 0.05 as lowest limit of significance.

## RESULTS

One hundred and sixty nine (70 male and 99 female) known cases of congestive heart failure and 22 healthy subjects (11 male and 13 female) serve as control group were admitted in this study. The characteristics of the study presented in Table 1. Hypertension (67.5%) and diabetes mellitus (33.7%) are the most common associated illnesses followed by myocardial infarction (26%). No identified cause or associated illnesses were observed in 35 out of 169 (20.7%) patients. Table 2 shows the discrepancy in the level of NT-proBNP taking in considerations the NYHA classification of heart failure and the cut-off level of NT-proBNP for the severity of heart failure. Fifty seven cases (33.7%) were clinically assessed as class 1(mild) heart failure and 18 cases out of this number (31.5%) have serum NT-proBNP level less than 100 pg/ml. In class 2 (mild) heart failure 5 out of 27 (18.5%) cases have serum NT-proBNP level less than 100pg/ml. On the other hand, patients classified clinically as class 3 (moderate) heart failure have serum NT-proBNP level exceeded the level 900 pg/ml in 29 out of 33 (87.9%) patients. In healthy subjects, 2 out of 24 subjects have serum level of NT-proBNP more than 300 pg/ml (8.4%). Further analysis revealed that serum levels of NT-proBNP did not match the NYHA classification of heart failure if the cut-off level of NT-proBNP is taken in consideration according to the manufacturer (Table 3). Figure 1 shows that whatever the NYHA class of heart failure, the ejection fraction is significantly correlated (r = -0.339, p < 0.001) with the serum NT-proBNP level. The mean value of ejection fraction of class 4 is significantly less than

**Table 1**. *Characteristics of the study*

| Number | 169 |
|---|---|
| Gender (M:F) | 70:99 |
| Age (year) | 61.4±11.9 |
| Smokers | 41 (24.3%) |
| Family history | 1 (0.6%) |
| BMI | 21.94±3.358 |
| History of : | |
| Hypertension | 114 (67.5%) |
| Diabetes mellitus | 57 (33.7%) |
| Hyperlipidemia | 18 (10.7%) |
| Atrial fibrillation | 6 (3.6%) |
| History of: | |
| Stable angina | 26 (15.4%) |
| Unstable angina | 4 (2.4%) |
| Myocardial infarction | 44 (26%) |
| Arrhythmias | 3 (1.8%) |

corresponding values of class 3, 2 and 1. Moreover the distribution of cases according to the NYHA classification showed overlap in the values of ejection fraction in each class (Figure 2). Doppler study revealed that E/A ratio was more than 1.5 in three patients with serum NT-proBNP level 300-600 pg/ml and less than 1.0 in seven patients; three of them with serum NT-proBNP 300-600 pg/ml and the other four patients with serum level of NT-proBNP of 600-900 pg/ml.

**DISCUSSION**

The results of this study show that the serum levels of NT-proBNP are not well match the classes of NYHA functional classification of heart failure but significantly correlated with reduced ejection fraction. The primary outcome measures of this study showed that the overall mean level of serum NT-proBNP is progressively increased with NYHA functional classification of heart failure and significantly increased with reduced ejection fraction (%). On the other hand, the secondary outcome measures revealed that the cut-off level of serum NT-proBNP that pointed the presence of heart failure or the severity of heart failure did not well matched. It is well known that serum level of inactive N-terminal proBNP (NT-proBNP) provides primarily information regarding the filling pressures in the heart and its determination to diagnose heart failure at an early stage cannot be recommended because their specificity is too low; the serum level of NT-proBNP is affected by age, gender, body mass index, renal function, and pulmonary capacity (11). Most patients who involved in this study had history and presented with components of metabolic syndrome e.g. high blood pressure, diabetes mellitus and obesity which may altered the serum level of NT-proBNP. Recently, there is evidence that low level of NT-proBNP may be attributed to the metabolic syndrome components (12) and a relationship between metabolic components and lower plasma NT-proBNP concentration was also reported (13). Studies indicate a dual use for NT-proBNP, both to exclude acute heart failure (where NT-proBNP concentrations < 300 ng/L have a 98% negative predictive value), as well as to identify the diagnosis of heart failure (14). The results of this study show significant high serum level of NT-proBNP reported in class III and IV indicating that this test is limited to the severe longstanding heart failure. Previous study reported that NT-proBNP was significantly higher in complicated heart failure patients than in heart failure patients (15). It was significantly higher in heart failure grade III patients complicated with cerebral infarction. In this study neither the severity of heart failure as assessed by NYHA nor the E/A ratio assessed by Doppler study are related to the level of NT-proBNP. Al Bannay and Husain (16) found that the tissue Doppler imaging (TDI)

**Table 2**. *Distribution of cases according to the NYHA classification and the serum level of NT-proBNP according to the instruction of the NT-proBNP manufacturer*

| | Normal (≤100 pg/ml) (n:23) | Suspected (100-300 pg/ml) (n:17) | Mild (300-600 pg/ml) (n:22) | Moderate (600-900 pg/ml) (n:19) | Severe (>900 pg/ml) (n:88) |
|---|---|---|---|---|---|
| NYHA classification | | | | | |
| Class 1 (mild) | 18 | 08 | 09 | 04 | 18 |
| Class 2 (mild) | 05 | 09 | 10 | 14 | 27 |
| Class 3 (moderate) | 0 | 0 | 03 | 01 | 29 |
| Class 4 (severe) | 0 | 0 | 0 | 0 | 14 |
| Serum BNP(pg/ml) | 48.04±27.93 | 177.0±53.72 | 407.5±63.9 | 720.9±90.1 | 4116.3±4685.2 |

**Table 3**. *Distribution of cases according to the NYHA classification and their corresponding serum level of NT-proBNP*

| NYHA classification | Serum NT-proBNP (pg/ml) | Ejection fraction (%) |
|---|---|---|
| Healthy subjects (n=24) | 76.3 ±99.0 | |
| Class 1 (mild)(n=57) | 878.1±1090.1* | 55.43±8.48 |
| Class 2 (mild)(n=65) | 1418.2±3197.7* | 52.88±8.03 |
| Class 3 (moderate)(n=33) | 3969.5±4168.8* | 48.22±10.22†‡ |
| Class 4 (severe)(n=14) | 8270.2±6116.9*†‡+ | 43.42±14.58†† |

The results are expressed as mean±SD, *p < 0.001 compared with healthy subject, †p <0.001, ††p< 0.01 compared with class 1, ‡p < 0.001, ‡‡ p < 0.05 compared with class 2, +p< 0.05 compared with class 3

maintained a steady positive correlation with both NYHA functional class and the Pro-BNP titer in hypertensive patients presented with dyspnea. Significant correlation between ejection fraction and NT-proBNP is observed in this study. ProBNP tended to be decreased in heart failure with preserved ejection fraction and increased with reduced ejection fraction (17). Even in absence of heart failure, proBNP level is strongly correlated with the decrease of ejection fraction in patients with left ventricular systolic dysfunction (18). Limitations of this study include the associated risk factors, variable etio-pathological factors of heart failure and anti-heart failure medications. Nevertheless, the results of this study pointed out that using cut-off level of serum NT-proBNP in longstanding heart failure is not sufficient to assess the patient and clinical examinations as well as the echocardiographic study are required for assessment. This is the first report that highlights the discrepancy between laboratory findings, echocardiographyic study and clinical assessment of known treated cases of heart failure. Most studies were carried on acute or emergency heart failure or looking for the conditions that associated with high serum or plasma level of NT-proBNP. Further study is recommended to assess serum NTproBNP level in chronic heart failure in absence of confounding (risk) factors. It concludes that single determination of serum NT-proBNP provides a useful tool in severe longstanding heart failure patients with reduced ejection fraction.

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