

N-terminal-probrain natriuretic peptide and echocardiography in patients with systolic heart failure

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ABSTRACT

Objective: To compare plasma N-terminal-probrain natriuretic peptide (NT-proBNP) levels with echocardiographic data in patients with systolic heart failure.

Methods: The study included 101 patients with systolic heart failure admitted to Al-Assad and Al-Moussa Hospitals, Damascus, Syria over a 10-month period from February 2004 to January 2005. The findings of the physical examination, electrocardiogram and blood pressure measurement were recorded along with the patient's history, risk factors, and drug treatment. We divided the patients into 4 groups according to the New York Heart Association classifications; class I = 19, class II = 22, class III = 28, class IV = 32 patients. We compared the values with 21 age-matched controls with no heart diseases (age range 49-80 years). During the study period, we carried out the plasma NT-proBNP levels and echocardiography of all patients and controls group. We used electrochemiluminescence immunoassay in measuring plasma NT-proBNP. Authorized physicians evaluated the ejection fraction (EF), systolic pulmonary pressure, and left ventricular

end systolic diameter. Statistical analysis used was T-Distribution, and the difference considered to be significant at $p < 0.05$.

Results: The plasma NT-proBNP levels in patients of asymptomatic heart failure class I (mean 1038 pg/ml) were significantly higher ($p < 0.001$) as compared with the controls (40.9 pg/ml), and it increased directly with the severity of heart failure. Plasma NT-proBNP levels were conversely correlated with the ejection fraction EF ($r = -0.56$, $p < 0.001$) and it increased as the EF declined. There was a significant direct linear correlation between plasma NT-proBNP levels and the left ventricular end systolic diameter ($r = 0.57$) and systolic pulmonary pressure $r = 0.54$.

Conclusion: The left ventricle releases the B-type natriuretic peptide in response to volume or pressure overload, its high level reflects the poor cardiac systolic function, which corresponds with the echocardiographic data.

Saudi Med J 2005; Vol. 26 (11): 1695-1698

Heart failure (HF) is a common and highly morbid disorder, its prevalence increases with age.¹ The diagnosis of heart failure is often difficult especially in the elderly, women, obese people and patients with lung disease.² All cardiac diseases lead to heart failure, which is identified as progressive clinical syndrome, starting by a cardiac functional or structural disorder with no symptoms, then slowly and gradually develops, whereas the

compensatory mechanisms are activated to maintain cardiac function by increasing blood volume, raising cardiac filling pressure, heart rate, and cardiac muscle mass. Eventually, the ability of the heart to contract and relax declines progressively and fails to pump a sufficient amount of blood to meet the metabolic needs. Consequently, the clinical symptoms such as dyspnea, fatigue, and fluid retention all become more obvious.³ However, these

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Received 17th May 2005. Accepted for publication in final form 17th September 2005.

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symptoms are not specific for heart failure; hence, the physical examinations and symptoms alone are not always sufficient to make an accurate diagnosis. The physicians depend on echocardiography (Echo) as a standard diagnostic test to detect the presence of heart failure, but it is expensive and not always easily available in emergency department, when rapid diagnosis and therapy are needed.⁴ The compensatory mechanisms which maintain cardiac function include; increase sympathetic adrenergic stimulation, activation of the renin-angiotensin system, increase vasoconstriction and fluid retention. This compensation lead to increase venous return and ventricular preload, resulting in ventricular hypertrophy and dilatation. Initially, this compensation is useful for a short period, then the hypertrophied-dilatated cells contract and relax more slowly, so the decreased systolic activity leads to a defect in the expulsion of blood (systolic heart failure), which is detected by Echo and characterized with increase in end systolic volume (ESV), and end diastolic pressure (EDP), while ejection fraction (EF) decreases.⁵ The human heart produces peptide hormones called natriuretic peptides, both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are of myocardial cell origin, whereas C-type natriuretic peptide (CNP) is of endothelial cell origin. The heart secretes these hormones in response to increased intracardiac volume or pressure, they play an important role in volume homeostasis and regulation of blood pressure.^{6,7} These hormones share a common structure consisting of a central ring of 17 amino acids with a disulfide bond between cystine bases and variable length N-terminal and C-terminal segments. The left ventricle predominantly produces and secretes the BNP, the name was given because it was first discovered in porcine brain, BNP derives from precursor called pre-proBNP which contains 134 amino acids including a signal peptide of 26 amino acids. Cleavage of the signal peptide produces the proBNP containing 108 amino acids when appropriate signals for hormone release are given. ProBNP is further split into a high molecular weight NT fragment (1-76 amino acids), and the BNP (77-108 amino acid) which is considered to be the biologically active hormone.⁸ Many studies refer to the use of BNP assay as a blood test aids in the diagnosis of heart failure.^{1,2,4} Davis et al⁹ found the first substantial evidence in 1994, which showed that the BNP level was higher in patients with heart failure as compared with patients with lung disease, and the use of the BNP assay was 93% sensitive and 90% specific for the diagnosis of heart failure. However, BNP has a shorter plasma half-life and lower molecular weight compared to the respective NT-proBNP, consequently, it has lower plasma concentrations, therefore the assay of NT-proBNP is

more reliable.¹⁰ The physiological actions of BNP include arterial and venous dilatation, natriuresis, and suppression of renin-angiotensin-aldosterone system as well as the sympathetic nervous system,¹ it may also have autocrine-paracrine effects acting on the heart to inhibit fibrosis and hypertrophy. The aim of this study was to establish a useful correlation between plasma NT-proBNP levels and echocardiographic data in Syrian patients, who presented with systolic heart failure.

Methods. The study included 101 patients with systolic heart failure admitted to Al-Assad and Al-Moussa Hospitals, Damascus, Syria over a 10-month period from February 2004 to January 2005. The associated symptoms were dyspnea, fatigue, and edema. The findings of the physical examination, electrocardiogram and blood pressure measurement were recorded along with patient's history, risk factors, and drug treatment. The patients were divided into 4 groups according to the New York Heart Association classifications. Class I - patients with asymptomatic heart failure (19 patients). Class II - patients with symptomatic heart failure at severe exertion (22 patients). Class III - patients with symptomatic heart failure at slight exertion (28 patients). Class IV - patients with symptomatic heart failure at rest (32 patients). The values were compared to 21 age-matched controls with no heart diseases. Written informed consent was obtained from each subject. We excluded patients with renal failure and diabetes. Authorized physicians carried out Echo for all patients and controls and evaluated the (EF), systolic pulmonary pressure, and left ventricular end systolic diameter. We measured Plasma NT-proBNP level by Electrochemiluminescence immunoassay "ECLIA" (Roche kit) using Elecsys 2010. We collected 2-5 ml of blood in sampling tube containing Ethylenediamine tetra acetic acid (EDTA)/Trasylol as protease inhibitors. The centrifugation was performed within 3 hours of sampling for 10 minutes at 4000 rpm/m and 20°C. The plasma was stored at -80°C until the assay time.

Statistical analysis for comparison of the arithmetic means between studied groups was carried out by T-Distribution, and the difference was considered to be significant at a $p < 0.05$.

Results. The plasma NT-proBNP levels in patients of asymptomatic heart failure class I (Mean 1038 ± 1035 pg/ml) were significantly higher ($p < 0.001$) as compared with the controls (40.9 ± 29.8 pg/ml), and it increased directly with the severity of heart failure. The differences between these groups were statistically important ($p < 0.05$). Plasma NT-proBNP level was reversely correlated to the EF ($r = -0.56$, $p < 0.001$) (**Figure 1**). The level

of NT-proBNP in patients with a left ventricular ejection fraction less than 45% (1324.6 ± 879.4 pg/ml) was significantly higher in comparison with its level in patients with left ventricular ejection fraction more than 45%, $p < 0.001$, and it increases as the EF declines. The EF was evaluated by Echo. The difference was statistically significant $p < 0.001$. There was a significant direct linear correlation between plasma NT-proBNP levels and the left ventricular end systolic diameter (LVESD) ($r = 0.57$) (Figure 2). The plasma NT-proBNP level (3017.08 ± 3034.5 pg/ml) in patients of heart failure with LVESD 4-5 cm raises significantly ($p < 0.001$) as compared with control (40.02 ± 28.5 pg/ml, LVESD up to 3.9 cm). Although there was a slight increase in its levels as the LVESD increases, the differences were not statistically significant $p > 0.05$. Furthermore, similarly to LVESD, there was a direct correlation between plasma NT-proBNP levels and the systolic pulmonary pressure $r = 0.54$ (Figure 3). The difference was statistically significant $p < 0.001$ as plasma NT-proBNP levels compared with the systolic pulmonary pressure in patients of heart failure (2029.7 ± 1602.4 pg/ml at systolic pulmonary pressure of 26-35 mm Hg) and control (39.2 ± 30.3 pg/ml at systolic pulmonary pressure up to 25 mm Hg). Also, there was clear increase in plasma NT-proBNP levels in patients with heart failure as the systolic pulmonary pressure increases, but the differences were not statistically significant $p > 0.05$.

DISCUSSION. Heart failure is a complex clinical syndrome, arising from ventricular dysfunction, where the heart is unable to pump sufficient blood to meet the metabolic requirements at normal filling pressure. Systolic heart failure is characterized by a loss of contractile strength, accompanied by ventricular hypertrophy and dilatation in response to the effects of numerous neuroendocrine systems, that protect blood pressure and contribute to progressive sodium retention, and increase the overload and pressure.¹¹ The myocardium overload stimulates the left ventricle to release a large amount of BNP as a compensatory mechanism which increases sodium elimination, resulting in decrease of fluid volume in the body and its load on the heart, therefore improves cardiac function. Our results indicate a significant difference between plasma NT-proBNP levels in patients of asymptomatic heart failure detected by Echo and control ($p < 0.001$), a substantial period of myocardial dysfunction precedes heart pump failure, when compensatory mechanisms maintain cardiac output. For this reason, in the early stages, the patient may have no symptoms while the plasma BNP concentration raises to a point could be used in the diagnosis. Our data also shows that the correlation of NT-proBNP with the severity of heart

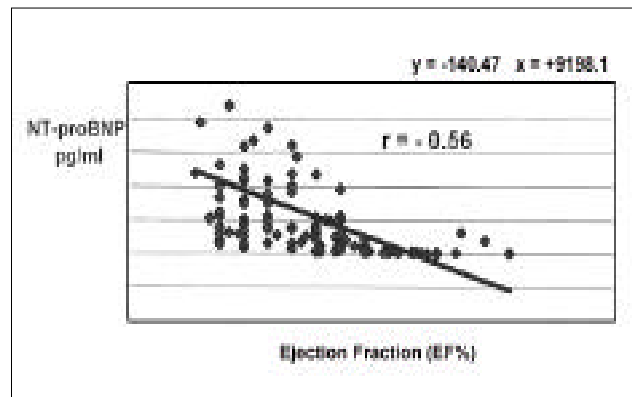


Figure 1 - The correlation between N-terminal-probrain natriuretic peptide (NT-proBNP) levels and the ejection fraction.

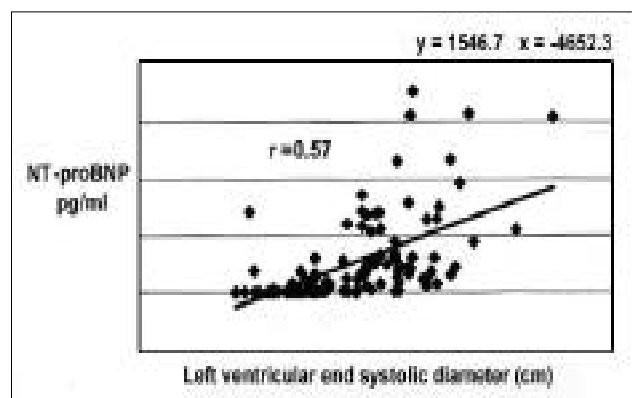


Figure 2 - The correlation between N-terminal-probrain natriuretic peptide (NT-proBNP) levels and the left ventricular end systolic diameter.

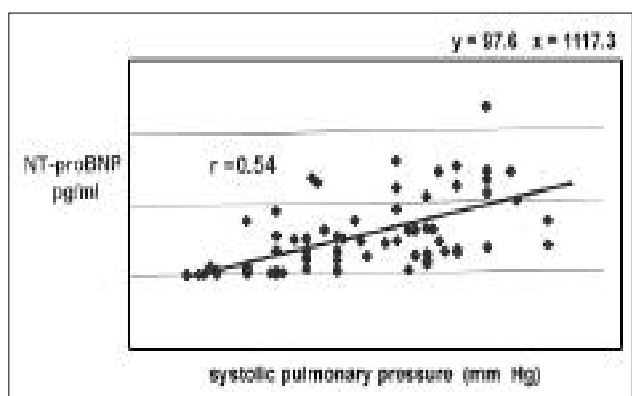


Figure 3 - The correlation between N-terminal-probrain natriuretic peptide (NT-proBNP) levels and the systolic pulmonary pressure.

failure allows the detection the stage of disease, which corresponds to Maisel et al's study.¹² Systolic heart failure which is detected by Echo, identified by the dilated left ventricle with low emptying capacity and EF (< 45%), increased left ventricular end systolic diameter and high systolic pulmonary pressure.¹³ Our result shows reverse relationship between NT-proBNP levels and EF; its level increases significantly as the EF declines, which reflects its utility as a blood test for evaluation of heart function.¹⁴ Whereas our data shows direct correlation between NT-proBNP levels and left ventricular end systolic diameter and systolic pulmonary pressure. The increased load induces myocytes hypertrophy, and the dilation occurs when the hypertrophy fails to normalize the excess load. Consequently, activating an abnormal growth response, resulting in structural changes in LV, causing increase in LVESD and reduced systolic function. Therefore, we observed increased BNP secretion from LV in an attempt to maintain blood pressure and fluid equilibrium,¹⁵ and both its raised level and Echo reflects the poor systolic function.

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