Clinical utility of plasma NT-proBNP in ruling out heart failure among Egyptian patients

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Abstract: Natriuretic peptides (BNP and NT-pro-BNP) represent useful biomarkers in heart failure diagnosis. So the aim of the present study was designed to assess the diagnostic and prognostic value of serum concentrations of NT-proBNP relative to cardiac troponin I (cTnI) and creatine kinase isoenzymee. The study was conducted on 83 patients with congestive heart failure (chronic), 20 patients with acute heart failure and 20 healthy subjects served as control group. All the biochemical parameters were determined on admission in patients with either acute heart failure or with chronic heart failure at different clinical stages of severity. The results showed that serum creatine kinase isoenzyme MB (CK-MB), serum cardiac troponin I (cTnI) and plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in acute heart failure (group 1) were increased as compared to the serum levels of control group. The mean levels of CK-MB, cTnI and plasma concentration of NT- proBNP were significantly increased ($p<0.05$) in chronic heart failure group (group 2) as compared to the acute heart failure group (group 1) as well as to the control group. Plasma NT-proBNP levels were related with chronic heart failure severity; they were particularly increased in more advanced New York Heart Association (NYHA) classes (stage II, III, IV), and these increments were matched with the increased serum levels of CK-MB and cTnI with the advance of disease severity. In conclusion in heart failure, measurement of NT-proBNP is among the diagnostic biomarkers of all relevant clinical diagnostic aids and is useful across the whole spectrum of heart failure disease severity. High NT-proBNP levels are related to chronic heart failure stages, their increase is directly related to more advanced NYHA classes and to poor prognosis. So NT-proBNP can facilitate diagnosis and can be used as a guide for heart failure therapy.

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1. Introduction

Heart failure is a clinical syndrome characterized by systemic perfusion inadequate to meet the body's metabolic demands as a result of impaired cardiac pump function. This may be further subdivided into systolic or diastolic heart failure. In systolic heart failure, there is reduced cardiac contractility, whereas in diastolic heart failure there is impaired cardiac relaxation and abnormal ventricular filling. Congestive heart failure is a condition in which your heart can't pump enough oxygen-rich blood to meet your body's needs. When your heart doesn't pump efficiently, blood may back up into your lungs and other tissues. The severity of congestive heart failure depends on how much pumping capacity your heart has lost. As they age, most people lose some pumping capacity. However, in congestive heart failure, your heart has very little pumping capacity. Congestive heart failure often results from damage caused by a heart attack, high blood pressure, diabetes or other conditions (Swedberg *et al.,* 2005).

B-type natriuretic peptide (brain natriuretic peptide [BNP]) is a small, ringed peptide secreted by the heart to regulate blood pressure and fluid balance.(American Heart Association, 2008) This peptide is stored in and secreted predominantly from membrane granules in the heart ventricles in a pro form (Pro BNP). Once released from the heart in response to ventricle volume expansion and/or pressure overload, the N-terminal (NT) piece of 76 amino acids (NT-Pro BNP) is rapidly cleaved by the enzymes corin and/or furin to release the active 32 amino acid peptide (BNP)(Van Kimmenade *et al.,* 2006)

Both BNP and NT-Pro BNP are markers of atrial and ventricular distension due to increased intra-cardiac pressure. The New York Heart Association (NYHA) developed four stages functional classification system for congestive heart failure (CHF) based on the severity of the symptoms. Studies have demonstrated that the measured concentrations of circulating BNP and/or NT-Pro BNP increase with the severity of CHF based on the NYHA classification (Quyen *et al.,* 2001, Swedberg *et al.,* 2005)

NT pro-BNP is the inactive form of B type natriuretic peptide and is founded in circulating

plasma also in physiologic status; during heart disease with increased activation of neuroendocrine systems plasma levels of pro hormone are elevated. We must distinguish between chronic and acute disease, in fact because of slower metabolism respect to the active form (i.e. BNP), the pro-hormone appear less sensitive to recognize reactivation and transitorial status. For these reasons, during congestive heart failure diagnostic and prognostic values of two markers Appears similar (Michele *et al.*, 2007).

There is no agreed-upon first-line test for the diagnosis of heart failure and no simple method of measuring the adequacy of cardiac output in relation to normal levels of activity. Heart failure usually is diagnosed in persons with known heart disease who present with nonspecific symptoms (e.g., breathlessness, ankle swelling) and signs (e.g., basal lung crackles). To confirm clinically suspected heart failure, physicians rely on surrogate measures of cardiac function such as left ventricular ejection fraction. However, it is clear that a large proportion of patients with heart failure, particularly older patients and women, have preserved systolic function (i.e., diastolic heart failure). The best way to diagnose and treat these patients is unclear. BNP increases when cardiac myocytes are strained; therefore, BNP is an effective method for detecting heart failure with or without systolic dysfunction (Doust *et al.*, 2006).

The use of biomarkers is one of the most important strategies for risk stratification among the increasing number of patients admitting to hospitals for acute coronary syndrome. The revolutionary benefit of using cardiac-specific troponins in this setting is the excellent specificity and sensitivity for myocardial injury, and several studies have confirmed the superiority of troponins as compared with creatine kinase-MB (CK-MB) for this purpose. The discovery of troponins as valuable markers for predicting mortality in unstable angina (Morrow *et al.*, 2007) led to 'The Joint European Society of Cardiology/American College of Cardiology Committee Consensus for the redefinition of myocardial infarction' from 2000 which included elevated troponins as an obligatory criterion in the diagnostics of acute myocardial infarction (Alpert *et al.*, 2000).

The cardiac isoform of troponin is a highly specific and sensitive marker of myocardial injury and is useful for risk stratification. However, the sensitivity of cardiac troponin is insufficient for early identification of myocardial injury, particularly within 6 hours following the onset of an acute ischemic event, because the initial rise in troponin in the peripheral blood of patients with myocardial infarction is seen after 3 to 4 hours due to release from the cytosolic pool. Therefore, a single test value on presentation is unsuitable for risk stratification (Masaru *et al.*, 2005).

Neurohormonal activation is a hallmark of heart failure and influences its clinical evolution. various neurohormones have acted as biomarkers in chronic heart failure, but B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the most widely embraced marker, particularly, given the availability of a rapid point-of-care assay (Na Li *et al.*, 2007). So the present study was designed to assess the diagnostic and prognostic value of serum concentrations of NT-proBNP relative to cardiac troponin I (cTnI) and creatine kinase isoenzyme MB (CK-MB) determined on admission in patients with acute heart failure and with chronic heart failure at different clinical stages of severity.

2. Patients and Methods

Eighty-three patients who developed congestive heart failure (CHF) on a top of myocardial infraction were screened for this study. All had dilated cardio-myopathy. The diagnosis of idiopathic dilated cardiomyopathy was made in the presence of a depressed left ventricular ejection fraction (impaired left ventricular systolic function) [L.V ejection fraction <40% on two dimensional echocardiography], and in the absence of significant coronary artery disease and other specific heart muscle disease. The patient had symptomatic heart failure New York Association (NYHA) class II to IV. So the diagnosis of dilated cardiomyopathy was based on history, physical as well as radiological examination and echocardiographic findings.

Also the present study comprised 20 patients who were diagnosed as having acute myocardial infarction, who had chest pain lasting >30 minutes. Persistent ischemic ECG changes : evolution of pathological Q waves ≥0.04 seconds or ≥0.1mv segment deviation in at least contiguous leads (ST-elevation MI) or ≥ 0.1mv ST segment depression or definite T-wave inversion (non-ST elevation MI) or new left bundle branch block (LBBB). Beside 20 healthy subjects served as a control group.

Exclusion criteria

Patients were excluded if they have active myocarditis, pericarditis, severe hepatic or pulmonary disease and renal impairment.

Sampling:

Five ml fasting venous blood samples were collected from all subjects of the study and separated into two parts:

1. Two ml of blood sample was taken into EDTA containing tube, and then centrifuged at 3000 rpm

for 5min. at 4℃ and the separated plasma was rapidly frozen at -80 ℃ for storage until the time of assay of N terminal pro-brain natriuretic peptide (NT pro BNP).

2. Three ml blood sample were collected in dry tube without anticoagulant, allowed to clot at room temperature for 30 min, centrifuged at 3000 rpm for 10 min, and the separated serum was stored at -20 ℃ until the time of assay of troponin I (cTnI), and creatine kinase isoenzyme MB (CK-MB).

Methods:

1- Plasma concentration of N-terminal pro-brain natriuretic peptide (NT- proBNP) was measured using immunoassay method based on sandwich formation with un-extracted EDTA plasma according to Karl *et al.*, 1999.
2- Serum creatine kinase isoenzyme MB (CK-MB) was measured by immunochemi-luminometric assay using kits supplied by Chemilumi ACS, centaur, Bayer medical co Ltd, Tokyo ,Japan as described by Piran *et al.*, 1987.
3- Serum cardiac troponin I (cTnI) was measured by immunometric assay according to Cummins *et al.*, 1987 using kit purchased from Bio-Check, Inc 323 Vintage Park Dr. Foster City,

Statistical analysis

Statistical analysis was performed by SPSS for windows, version 11 software (SPSS Inc, Chicago, Illinois). All data were described as mean ± standard deviation, unless otherwise specified. Baseline characteristics were analyzed by the unpaired t –test. Because NT-proBNP values are not normally distributed, natural logarithmic transformation of data was used for statistical analysis when needed. The significance of changes in NT-proBNP levels was evaluated using the paired Student's t -test. A p-value <0.05 was considered statistically significant.

3. Results

The present study was conducted on 103 subjects, who were classified into two groups:

Group 1: it included 20 patients who were diagnosed as having acute myocardial present infarction of mean age of 55-60±2.114 years who had chest pain lasting >30 minutes, and they were 18 males and 2 females.

Group 2: it included 83 patients who developed congestive heart failure (CHF) on a top of myocardial infarction were screened for this study. All had dilated cardio-myopathy. Heart failure severity was evaluated clinically according to the New York Heart Association (NYHA) classification: 26 were in class II, 25 were in class III, and 32 were in class IV, respectively. The patient had mean ± (SD) age of 48-60 ± (2.645) years and they were 74 males and 9 female

Beside **control group:** it included 20 healthy subjects of the same age range and sex served as a control group and they were 17 males and 3 females.

The demographic data and the clinical data (history of hypertension, diabetes mellitus and hypercholesteremia) and the vital signs (heart rate and blood pressure) in the patients with acute and chronic heart failure were illustrated in table (1).

The serum creatine kinase isoenzyme MB (CK-MB), Serum cardiac troponin I (cTnI) and Plasma concentration of N-terminal pro-brain natriuretic peptide (NT- proBNP) levels in acute heart failure (group 1) were increased with a mean levels of 3 ± 0.2ug/L, 18.84 ± 2.79mg/L, and 73.115 ± 16.33 pmoL/L, respectively and these increments were significant ($p<0.05$) as compared to the serum levels of control group as shown in table (2).

The serum CK-MB, cTnI and plasma concentration of NT- proBNP levels in chronic heart failure (group 2) were increased with a mean levels of 7.66 ± 1.47ug/L, 35.59 ± 7.24mg/L, and 105.678 ± 15.129 pmoL/L, respectively and these increments were significant ($p<0.05$) as compared to the serum levels of control group as shown in table (3).

The mean levels of CK-MB, cTnI and Plasma concentration of NT- proBNP were significantly increased ($p<0.05$) in chronic heart failure group (group 2) as compared to the acute heart failure group (group 1) as shown in table (4).

The mean serum levels of CK-MB in the different stages of chronic heart failure (stages II, III, IV) were 6.5 ± 1.235, 7.236 ±1.5 and 8.875± 0.37 ug/L, respectively, there were statistical significance variations between the three stages as the mean levels were increased with increased the stage of disease. The mean serum levels of cTnI were 30.226 ± 5.06, 33.44 ± 6.3 and 41.61 ± 4.69 mg/L, respectively; there were statistical significance variations between the three stages. The mean Plasma concentrations of NT- proBNP were 90.90 ± 3.48, 101.42 ± 6.49 and 121.0 ± 11.08 pmol/L respectively; there were statistical significance variations between the three stages of chronic heart failure as shown in table (5).

Table (1): Demographic and clinical data of the patient's groups

	Acute HF (Group 1)	Chronic HF (Group 2)
Number	20	83
Age (mean ± SD) years	55-60 ± (2.114)	48-60 ± 2.645
Male/ female	18/2	74/9
History		
Hypertension	7 (35%)	44 (53.2%)
Diabetes mellitus	9 (45%)	35 (42.1%)
Hypercholesterolemia	8 (40%)	37 (44.6%)
Current smoker	10 (50.0%)	21 (25.3%)
Prior myocardial infarction	4 (20%)	23 (27.7%)
Angina	3 (15%)	37 (44.6%)
Stroke	0 (0%)	8 (9.6%)
Initial vital signs (mean ± SD)		
Heart rate, beats/min	95.6 ± 16.7	85.6 ± 22.8
Systolic blood pressure, mmHg	150 ± 30.0	144.3 ± 26.5
Diastolic blood pressure mmHg	89 ± 15	85 ± 12
Onset to presentation < 3 h	18 (90%)	29 (34.9 %)

Table (2): Statistical significance of the studied parameters in acute heart failure group.

	Control group	Group (1) Acute HF	P value
Number	20	20	
Sex **Male/female**	17/3	18/2	
Age Range Mean ± SD	61-54 57.05 ± 2.235479	55-60 57.55 ± 2.1145	0.2359
CK.MB (ug/L) Range Mean ± SD	1.7-3.9 2.6695 ± 0.5666	2.7-3.4 3 ± 0.2127	0.0096*
cTnI (mg/L) Range Mean ± SD	5.7-12.3 8.89±2.33844	10.1- 22.7 18.84 ± 2.7934	4.975E-15*
NT-ProBNP (pmoL/L) Range Mean ± SD	58.1 -25.5 36.32 ± 9.7286	57.5- 99,5 73.115 ± 16.33	8.023E-11*

*P value <0.05 considered significant, (CK-MB): creatine kinase isoenzyme MB (cTnI): cardiac troponin I, (NT-proBNP): N-terminal pro-brain natriuretic peptide

Table (3): Statistical significance of the studied parameters in chronic heart failure group.

	Control group	Group (2) Chronic HF	P value
Number	20	83	
Sex Male/female	17/3	74/9	
Age Range Mean ± SD	54-61 57.05 ± 2.24	48-60 56.3979 ± 2.65	0.1536
CK.MB (ug/L) Range Mean ± SD	1.7-3.9 2.6695± 0.5666	5.1-9.2 7.6641± 1.4748	1.9658E-27*
cTnI (mg/L) Range Mean ± SD	5.7-12.3 8.89 ± 2.34	24.9- 47.5 35.59 ±7.25	3.5739E-30*
NT-ProBNP (pmoL/L) Range Mean ± SD	25.5-58.1 36.32 ± 9.73	88- 145.6 105.68 ± 15.13	2.4393E-36*

*P value <0.05 considered significant

Table (4): Statistical significance between the studied parameters in acute and chronic heart failure.

	Acute HF (Group 1)	Chronic HF (Group 2)	P value
Number	20	83	
Age Range Mean ± SD	55-60 57.55± 2.114486	48-60 56.3979 ± 2.64574	0.07305
CK.MB (ug/L) Range Mean ± SD	2.7-3.4 3 ± 0.2127	5.1-9.2 7.66 ±1.47	7.90402E-26*
cTnI (mg/L) Range Mean ± SD	10.1- 22.7 18.84 ± 2.79	24.9- 47.5 35.59 ±7.25	4.82947E-17*
NT-ProBNP (pmoL/L) Range Mean ± SD	57.5- 99.5 73.115 ±16.33	88- 145.6 105.68 ±15.13	1.69281E-13*

*P value <0.05 considered significant

Table (5): Biochemical markers and their statistical significance in the different stages of chronic heart failure.

	Stage II	Stage III	Stage VI
Numbers	26	25	32
CK.MB (ug/L) Range Mean ±SD **P value** Stage II: Stage III Stage III: Stage IV Stage II: Stage IV	 5.1- 8.5 6.5884 ± 1.2355 0.0493*	 5.1- 9.1 7.236 ± 1.5027 9.55E-08*	 7.9- 9.2 8.875 + 0.3724 2.79E-14*
cTnI (mg/L) Range Mean ±SD **P value** Stage II: Stage III Stage III: Stage IV Stage II: Stage IV	 24.9- 36.2 30.2269 ± 5.0665 0.024835*	 24.9 - 42.5 33.444 ± 6.3045 3.31038E-07*	 25.6 - 47.5 41.6281 ± 4.6992 1.44803E-12*
NT-ProBNP (pmoL/L) Range Mean ±SD **P value** Stage II: Stage III Stage III: Stage IV Stage II: Stage IV	 88.3 - 100.6 90.9038 ± 3.4806 1.3693E-09*	 112.8 - 90.6 101.42± 6.4926 8.00959E-11*	 145.6 - 98.3 121.0062 ± 11.0839 2.77139E-19*

*P value <0.05 considered significant

4. Discussion

BNP measurements have been shown to add important information to clinical judgment in establishing a final diagnosis of CHF (Mohammed and Januzzi, 2009). Thus, our findings indicated that plasma concentrations of NT-proBNP were increased in acute and chronic heart failure groups and the increment in chronic heart failure group was higher than the acute heart failure group. An increase in plasma BNP concentration results in improved myocardial relaxation and has an important regulatory role in response to acute increases in ventricular volume by opposing vasoconstriction, sodium retention, and the antidiuretic effects of activated renin– angiotensin–aldosterone system. However, plasma NP levels are elevated in patients with acute myocardial infarction and LV dysfunction; this increase persists during late phases of cardiac remodeling. (Palazzuoli *et al.*, 2010).

The exact mechanism of natriuretic peptides rise in coronary disease is not completely understood. Ischaemia may constitute an independent stimulus for BNP release towards transient decrease of systolic function and compliance, reflecting not only the impairment in left ventricular function, but also the severity of ischaemic insult Palazzuoli *et al.*, 2010.

The results of this study were in accordance with large-scale studies demonstrating the feasibility of detection of left ventricle abnormalities, the use of NT-proBNP for the acute evaluation of dyspneic patients with possible congestive heart failure (CHF) was then explored in three recent studies. In the first such study, Lainchbury and colleagues demonstrated NT-proBNP to be of value in the evaluation of patients with dyspnea and suspected acute CHF in the emergency department. Subsequently, Bayes-Genis and colleagues found that NT-proBNP levels were significantly higher in patients with decompensated CHF, and also demonstrated the value of the marker for identifying those patients with 'masked' heart failure, defined as those patients with LV dysfunction and concomitant pulmonary disease. Furthermore, Bayes-Genis and others demonstrated as the heart failure was treated, NT-proBNP levels fell in tandem Bayes-Genis *et al.*, 2004 and Bettencourt *et al.*, 2004).

The utility of NT-proBNP testing for diagnosing heart failure in patients presenting to

the Emergency Department (ED) with acute dyspnea has been extensively validated in prospective observational studies, including the single-center PRIDE study (ProBNP Investigation of Dyspnea in the Emergency Department; N=599) (Jannuzzi *et al.,* 2005) and the multi-center, multi-national ICON study (International Collaborative of NT-proBNP; N=1256) These studies assessed a single cut-off value of 300 pg/mL for exclusion and age-stratified cut-off levels for ruling in HF Januzzi *et al.,* 2006. In this multi-centre, international study, NT-proBNP testing was valuable for diagnostic evaluation and short-term prognosis estimation in dyspneic subjects with suspected or confirmed acute HF and should establish broader standards for use of the NT-proBNP in dyspneic patients.

The results of the present study showed that, the plasma levels of NT-proBNP in chronic heart failure increased with the increment of the stage of the disease. There are more definitive data supporting the use of NT-proBNP in the Emergency Department were reported. In a blinded prospective analysis of 600 patients presenting with acute dyspnea, the ProBNP investigation of Dyspnea in the Emergency Department (PRIDE) Study investigators demonstrated NT-proBNP levels to be markedly elevated among patients with decompensated CHF. NT-proBNP was highly sensitive and specific for the diagnosis of acute CHF, and correlated with the severity of CHF symptoms. Among all the factors evaluated, an elevated NT-proBNP proved to be the single strongest independent predictor for the final diagnosis of acute CHF. Lastly, in the PRIDE Study, NT-proBNP was superior to clinical assessment for the identification of acute CHF. However, the combination of NT-proBNP testing plus clinical assessment was the most superior tool for patient evaluation (Januzzi *et al.,* 2004).

Also, Muller and colleagues findings indicate that BNP and NT-proBNP may be equally useful as an aid for the diagnosis of CHF in patients consulting an emergency department with shortness of breath as a chief complaint. Of course, different cut off concentrations have to be considered for the analyses BNP and NT-proBNP. This is a consequence of a slower plasma clearance of NT-proBNP than of the biologically active peptide BNP resulting in higher circulating concentrations of NT-proBNP, although both peptides are released by cardiomyocytes on an equimolar basis. Furthermore, the different mechanisms of plasma clearance (neutral endopeptidase clearance receptors for BNP versus renal clearance for NT-proBNP) result in an only moderate correlation of plasma concentrations of the two analysts McCullough *et al.,* 2003.

In previous studies NT-proBNP showed a higher absolute and relative increase related to heart failure, so it could be a more sensitive marker for left ventricular wall stress, and a diagnostic tool useful in the detection of ischemia-related left ventricular dysfunction during exercise. Baseline NT-proBNP levels and exercise induced increase in NT-proBNP levels are significantly higher in subjects with documented myocardial ischemia (demonstrated by perfusion images) (Staub *et al.,* 2005).

Bay and colleagues published one of the first large studies revealing the utility of NT-proBNP in predicting LV dysfunction. From 3,236 hospitalized patients with symptomatic and asymptomatic congestive heart failure (CHF), NT-proBNP had a sensitivity of 73%, specificity of 82%, and, most impressively, a negative predictive value of 98%.The diagnostic value to predict a left ventricular ejection fraction (LVEF) <40% as represented by the area under the receiver operating characteristic curve (AUC) was 0.85. Overall, the study revealed that NT-proBNP added significantly more diagnostic power to the clinical history. Subsequently, other studies revealed that not only was NT-proBNP elevated in CHF from LV dysfunction, but was also in forms of CHF with normal LV function (diastolic dysfunction), although the levels of NT-proBNP among patients with non-systolic CHF are typically lower than those with systolic dysfunction and CHF Yamamoto *et al.,* 1996.

Importantly, the results of the present study appear to confirm previous findings, plasma NT-proBNP levels were significantly higher in patients with chronic HF than in those with acute heart failure, and showed very good diagnostic precision. Also, the NT-proBNP level increased with the severity of disease, confirming the results of other studies Lainchbury *et al.,* 2003 and Bayes *et al.,* 2004. Interestingly, the NT-proBNP values were similar in patients with CHF and an LVEF of above or below 45%. This indicates that NT-proBNP levels are useful in the diagnosis of CHF with preserved systolic function. Further supporting this is the fact that the patients with an impaired ventricular diastolic pattern had significantly higher NT-proBNP levels than those who had normal diastolic function—something also reported in earlier studies Tschope *et al.,* 2005. Natriuretic peptide (NP) levels are strictly related with HF severity; they are particularly increased in more advanced New York Heart Association (NYHA) classes and in patients with poor

outcome. Therefore elevated NP levels were found to correlate with the severity of left ventricular systolic dysfunction, right ventricular dysfunction and pressures, and left ventricular filling alterations. However, the optimal use of NP determination agrees with patient history, physical examination, and all other diagnostic tools Palazzuoli *et al.*, 2010.

5. Conclusion

It has been demonstrated that NT-proBNP levels can facilitate diagnosis of heart failure (acute and chronic). Measurement of NT-proBNP considered among the diagnostic biomarkers of all relevant clinical diagnostic aids and is useful across the whole spectrum of heart failure disease severity. High NT-proBNP levels were related chronic heart failure stages; their increase was directly related to more advanced NYHA classes and to poor prognosis. So NT-proBNP can facilitate diagnosis and can be used as a guide for heart failure therapy.

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