# NT-proBNP levels, as predictor of left ventricular systolic and diastolic dysfunction in patients with chronic heart failure

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## Abstract

**Background**: Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Diastolic and systolic heart failure are the two clinical subsets of the syndrome of heart failure (HF), Regardless of ejection fraction (EF) the severity of HF and its prognosis and degree of exercise intolerance are closely related to the degree of diastolic filling abnormalities. Echocardiography parameters and the amino-terminal pro-B-type natriuretic peptides ( NT-proBNPs) provide powerful incremental assessment of  left ventricular (LV) diastolic and systolic functions.

**Aim:** The objective was to assess the correlation between echocardiographic parameters and plasma N-terminal pro brain natriuretic peptide (NT- proBNP) level in patient with systolic or diastolic dysfunction.

**Method:** The study included 109 heart failure patients. They underwent conventional and tissue Doppler imaging (TDI) echocardiography and NT-proBNP level was measured at the same time.

**Results:** Significant correlations were found between NT-proBNP level and late diastolic mitral annulus velocity $A_m$ (r=-0.72, P=0.0001), systolic mitral annulus velocity $S_m$ (r=-0.72, p=0.0001), early diastolic mitral annulus velocity $E_m$ (r =- 0.51, p=0.0001), early transmitral to $E_m$ velocity ratio (r=0.51, p= 0,0001), LV ejection fraction (r=-0.83, p=0.0001).
In multiple regression, log NT-proBNP levels were independently related to age, LV ejection fraction, $A_m$ velocity and $E_m$ velocity ($R^2$=0.78, P=0.0001), the relation to ejection fraction was the strongest (β= -0.56).

**Conclusions:** NT-proBNP levels correlate with echocardiographic parameters, and are simple, accurate markers of systolic and diastolic heart failure.

**Keywords:** Chronic Heart Failure; Conventional Echocardiography; Tissue Doppler Imaging; NT-pro BNP.

## Introduction

The syndrome of HF is a common manifestation of the later stages of various cardiovascular diseases, including coronary artery disease, hypertension, valvular disease, and primary myocardial disease. Heart failure (HF) has traditionally been divided into HF with a reduced ejection fraction (EF; systolic HF) and HF with a normal EF (diastolic HF). Despite the substantial differences in the EF, Both groups have reductions in exercise tolerance, neurohumoral activation, and abnormal left ventricular (LV) filling dynamics and impaired relaxation and have similar clinical symptoms and signs. Furthermore, both groups have substantial neuroendocrine activation [1, 2]
Differentiating the two types of HF is important, as their long-term drug treatments are not the same. Chronic heart failure (CHF) is currently recognized as a clinical syndrome occurring not only as a result of rnechanical dysfunction of the ventricles, but also due to complex molecular, endocrine, neuroendocrine, and inflammatory changes [3] Neurohormonal activation plays a fundamental role in the onset and progression of heart failure and the use of biochemical markers as prognostic indicators in heart failure have expanded in the last decade.

Numerous studies have indicated that B-type natriuretic peptides (BNP) can be used for patient diagnosis, prognosis and therapy monitoring. Levels of BNP have been shown to be elevated in patients with cardiac dysfunction [4, 5]. Plasma BNP levels provide clinically useful information concerning the diagnosis and management of left ventricular dysfunction and heart failure, which complements other diagnostic testing procedures (e.g., electrocardiograms, chest x-rays, and echocardiograms) [ 6,7 ]. BNP levels can be used to assess the severity of heart failure, as demonstrated by the correlation with New York Heart Association classifications [8]. Plasma BNP levels also increase with decreasing physiological functional capacities, as measured by left ventricular ejection fraction (LVEF) or exercise-based evaluations [9].
Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) has a longer half-life than BNP and has more stability and apparently less intra patient variability [10]. It appears, however, to be more affected by renal function than BNP. The median day-to-day coefficient of variation for BNP is about 25%, compared to 20% for NT-pro BNP [10, 11]. NT-proBNP levels also rise more gradually for a given level of cardiac dysfunction.

Echocardiography is now the most commonly used noninvasive tool for the assessment of cardiac anatomy and function. Conventional echocardiography predictors of poor outcome, such

as left ventricular (LV) ejection fraction (EF) and restrictive filling pattern have recently been supplemented by tissue Doppler imaging (TDI). In patients with heart failure (HF) symptoms, echocardiography often reveals a low left ventricular ejection fraction (LVEF). Up to 50% of symptomatic patients have a preserved LVEF, and abnormal diastolic function is assumed if no valvular lesions are identified [12]; in this regard, echocardiography may be useful in confirming diastolic dysfunction [13].          NT-pro BNP has been studied as a biomarker of severity and prognosis of CHF in small studies [14-17] and shown to be very reliable. In HF patients, plasma levels of NT-proBNP and BNP are elevated and correlate strongly with NYHA functional status [18, 19].          NT-proBNP appears to be a more discerning marker of early cardiac dysfunction than BNP [20-21].

The level of NT-proBNP remained predictive of death and of the combined endpoint of death and HF hospitalization. BNP correlates with echocardiographic indices of diastolic function and systolic function [22-23] but the relationships between NT-proBNP and echocardiographic findings have not been established.

The present study was performed in order to clarify the integrative value of NT-proBNP testing with respect to the information gained from echocardiography in patients with systolic and diastolic heart failure and to compare the utility of NT-proBNP level and echocardiography parameters.

## Patients and Methods

The study enrolled 150 patients with systolic and diastolic heart failure, presenting to the Cardiology Department of the University Kebangsaan Malaysia (UKM) Medical Center, have signs and symptoms according to European society of cardiology for heart failure (ESC clinical classification for HF).

 Patients with severe renal failure (serum creatinine >5mg/dl), no sinus rhythm, MI within 3 months, HF caused by cor pulmonale, congenital heart disease, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, ventricular thrombus were excluded. All patients gave their written informed consent to take part in the study. Among the 150 patients initially enrolled in the study, 6 patients passed away, 28 patients withdrew their consents and 7 patients did not answer at the time of examination, leaving 109 patients eligible for analysis. The study was approved by the local ethics committee of University Kebangsaan Malaysia.

**NT-proBNP measurment**

At the time of echocardiographic examination, a blood sample was collected into tubes containing- separating gel, processed, and frozen at – 80 Ċ for later measurement of NT-proBNP using a commercially available automated immunoassay (Cobas e 411 analyzers, Roche Diagnostics).

**Echocardiography**

Recordings were made with a (GE/ VIVID I) using a 3S transthoracic transducer with the patient in the supine left lateral position during quiet respiration. Two-dimensional echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography [24]. The following variables were measured: The LVEF was calculated from apical four chamber view using the modified Simpson's method. Patients with LVEF $\geq$ 50% were defined as having diastolic heart failure. Diastolic indices included: early and late transmitral diastolic velocities (E and A); early deceleration time (DT); systolic velocity ($S_m$), early and late diastolic tissue Doppler velocities at the septal mitral annulus ($E_m$ and $A_m$).

**Statistical analysis**

Data were analyzed using the statistical software (IBM SPSS Statistics version 19). Continuous data are expressed as mean $\pm$ standard deviation (S.D). Categorical data are expressed as numbers (%). Log- transformation was used for NT- proBNP levels to achieve normality in distribution, spearman's correlation coefficient as a statistical method, used to correlate echocardiographic parameters with NT- proBNP levels.

P value of $< 0.01$ level was considered significant and multiple linear regression analysis was used to determine correlations between variables.

## Results

For the 109 patients included in the study, mean age was $59 \pm 10$ years (range 35 - 83 years), there were 21 female (19%) and 88 male (81%).
Patients with LVEF $\geq$50% were 24 (22%) and patients with LVEF $< 50\%$ were 85 (78%)

**NT-proBNP level**

The median NT-proBNP level among the 109 patients in this study was 707.50 pg/mL (range 5– 17100 pg/ml; inter-quartile range (IQR) = 193–2108 pg/mL).
Baseline clinical and echocardiographic data of the patients were included in table 1.

**Echocardiographic findings and NT-proBNP level**

Univariable correlations between log NT-proBNP levels and echocardiographic parameters are shown in Table 2. Several parameters of diastolic function and systolic function correlated with log NT-proBNP levels.

A strong and highly significant correlation between $S_m$ velocity and log NT-proBNP level (r = - 0.72, P=0.0001) and between $A_m$ velocity and log NT-proBNP level
(r = - 0.72, P= 0.0001) was found in all patients (Fig. $1_{A,B..}$). The correlation between Em velocity and log NT-proBNP level was weaker than Am, but still highly statistically significant (r = - 0.52, P=0.0001). Additionally, log NT-proBNP levels correlated significantly with E/Em ratio (r= 0, 51, P=0.0001) and with LVEF (r = - 0.83, P=0.0001) (Fig.$1_{C,D.}$ ) and moderate correlation with DT (r= - 0.419, P =0.0001), but weak correlation with E, A and E/A. Analysis with a multiple linear regression model revealed log NT-proBNP levels to be independently related to age and echocardiographic parameters: LVEF, $A_m$ velocity and $E_m$ velocity,($R^2$=0.78,P=0.0001) and the ejection fraction was the strongest predictor of NT-proBNP level (β= - 0.56)

## Discussion

NT-proBNP and BNP levels are increasingly used in the evaluation of dyspnoeic patients with suspected HF. [25,26] .Natriuretic peptide levels can reflect LV systolic [27,28] and diastolic function [23,29,30] . Cardiovascular guidelines recommend considering both peptides [31].

In this cohort, the correlation was studied between log NT-proBNP and echocardiographic variables, The result of the present study show that in patients with HF there are a weak correlation between Doppler mitral flow E , A , E/A and NTproBNP, and negative moderate correlation between DT and NT- pro BNP. Significant negative correlations  were found between

NT-proBNP levels and TDI-derived mitral annulus velocities, the correlation is being strong for $A_m$ velocity, $S_m$ velocity and $E/E_m$ ratio, which is known to be an echocardiographic marker of LV filling pressure and NT-pro BNP levels. $E_m$ is weaker than $A_m$ but still significant correlation with NT-pro BNP levels, there was negative strong correlation between LVEF and NT-pro BNP level.

On the other hand, the results confirmed a strong correlation between $S_m$ velocity and LVEF, assessed by 2D echocardiography using Simpson's method. Patients were studied with isolated diastolic LV dysfunction who had a preserved LVEF (>50%) and high $S_m$ velocities.

Similar study was performed by M.Tretjak et al.[32] but the results are different, that examined the relationship between NT- BNP levels and TDI-derived mitral annulus velocities in patients with HF, the correlation is being the strongest for $E_m$ velocity,and weaker for $E/E_m$ ratio and no correlation between DT and NT-proBNP

Another study by Mottram et al. [33] examined the relationship between BNP levels and echocardiographic indices of systolic and diastolic function in a highly selected group of patients, their results showed a moderate correlation between BNP and $A_m$ velocity, which is comparable with the result of the present study, but no relationship between BNP and $E_m$ velocity.

On the other hand, Troughton et al. [23] examined the relation of BNP to echocardiographic diastolic indeces in patients with systolic heart failure. They found a significant relationship between BNP levels and $E_m$ velocity and stronger correlation for DT and $E/E_m$ ratio. The results are comparable with the results of the present study.

Dokainish et al. [34] explained partially in the published study that $E_m$ velocity correlates better with NT-proBNP levels than $E/E_m$.

Changes in NT-proBNP levels can be used to evaluate the success of treatment in patients with left ventricular dysfunction. Some authors suggest that echocardiographic findings may be important in determining the individual target level [23]. The findings of the present study showed the mitral annular velocities from TDI in all patients were lower than in previously published studies of normal subjects [35], and suggest that the monitoring of HF treatment using serial $A_m$, $S_m$, $E/E_m$ and $E_m$ measurements would be very simple and highly reproducible along with NT-pro BNP. Since $A_m$, $E_m$ velocities are relatively preload-independent, reducing preload with diuretics would have no significant impact on and an increase would actually indicate improvement in LV systolic and diastolic function. Further studies are needed to clarify the possibility of TDI guided therapy of HF.

The implication of the present study; a widely availability and more cost-effectiveness of NT-proBNP may help streamline the selection of patients for echocardiography and routine NT-proBNP testing may thus be useful in places in where echocardiography machine is not available to evaluate the LV function.

Echocardiography takes time, is expensive, requires specialized training to perform and interpret, and thus may not be optimal for regular use in some settings, such as the emergency department.

## Limitations of the study

The limitation of the present study was, the patients were receiving diuretics, beta-blockers, ACE inhibitors spironolactone therapy, with different dosages and we did not take the medication and obesity into account, some patients have low levels of NT- pro BNP, the suggested explanation

could be that they respond to the optimal therapy; another explanation is that patients with end stage HF may have low natriuretic peptides (NP) levels because the ability of their ventricles to release NP may have become exhausted. In the interpretation of plasma NP levels several factors such as age, renal function, cardiac rhythm, obesity, and drug therapy should be taken into account, which may have had some influence on the NT-proBNP levels. In the present study patients with severe renal failure were excluded.

## Conclusion

This study emphasized that echocardiography and the amino-terminal pro-B-type natriuretic peptides (NT-proBNP) provide powerful incremental assessment of
LV function.
Elevated NT-proBNP levels correlated with several important echocardiographic indices of systolic and diastolic heart failure mainly late diastolic mitral annulus velocity $A_m$, systolic velocity $S_m$, $E/E_m$ ratio , early diastolic mitral annulus velocity $E_m$ ejection fraction EF and should therefore be incorporated into echocardiographic evaluation of LV function of patients with HF. The complex evaluation joining NT-proBNP and imaging test seems to be a rational approach.

## Acknowledgements

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**Table I**
Basic clinical and echocardiographic data

| | |
|---|---|
| All patients (n) | 109 |
| Male (n) | 88 (81%) |
| Female (n) | 21 (19%) |
| Age (years) | $59 \pm 10$ |
| Patients with diastolic heart failure | 24 (22%) |
| Patients with systolic heart failure | 85 (78%) |
| Median NT-pro BNP | 707.50 |
| IQR | (193-2108) |
| LV systolic function | |
| EF<50% | $33 \pm 9$ |
| LV diastolic function | |
| EF $\geq$50% | $57 \pm 6$ |
| Transmitral flow | |
| E (m/s) | $0.78 \pm 0.22$ |
| A (m/s) | $0.64 \pm 0.26$ |
| E/A | $1.58 \pm 1.13$ |
| DT (ms) | $167 \pm 58$ |
| | |
| Tissue Doppler velocity | |
| $S_m$ | $0.043 \pm 0.014$ |
| $E_m$ (m/s) | $0.047 \pm 0.016$ |
| $A_m$ (m/s) | $0.059 \pm 0.027$ |
| $E/E_m$ | $18.63 \pm 8.12$ |

 Results are presented as mean $\pm$ standard deviation
LVEF=left ventricular ejection fraction; E=transmitral early diastolic velocity;
 DT=deceleration time; $E_m$=TDI derived mitral annular early diastolic velocity; $S_m$=TDI derived mitral annular systolic velocity. ; $A_m$=TDI derived mitral annular late diastolic velocity; $E/E_m$= ratio of early transmitral to early mitral annular velocity.

**Table II**
Univariable correlations of echocardiographic indice with log NT-proBNP levels

|  | Spearman's Correlation | P-value |
|---|---|---|
| Age | 0.013 | 0.895 |
| LVEF | - 0.834 | 0.000 |
| EF<50% | - 0.759 | 0.000 |
| EF $\geq$50% | 0.049 | 0.822 |
| E | 0.103 | 0.285 |
| A | - 0.298 | 0.002 |
| E/A | 0.257 | 0.007 |
| DT | - 0.419 | 0.000 |
| $S_m$ | - 0.727 | 0.000 |
| $E_m$ | - 0.516 | 0.000 |
| $A_m$ | - 0.725 | 0.000 |
| $E/E_m$ | 0.511 | 0.000 |

 Correlation is significant at the 0.01 level (2-tailed).
 LVEF=left ventricular ejection fraction; E=transmitral early diastolic velocity;
 DT=deceleration time; $E_m$=TDI derived mitral annular early diastolic velocity; $S_m$=TDI derived mitral annular systolic velocity. ; $A_m$=TDI derived mitral annular late diastolic velocity; $E/E_m$= ratio of early transmitral to early mitral annular velocity.

**Table III**
 Multivariable correlations of clinical and echocardiographic parameter with log NT pro BNP levels

|  | Standardized β Regression coefficient | P-value |
|---|---|---|
| Age | 0.229 | 0.000 |
| LVEF | - 0.563 | 0.000 |
| E | 0.202 | 0.042 |
| A | - 0.175 | 0.070 |
| E/A | -0.118 | 0.283 |
| DT | -0.094 | 0.079 |
| $S_m$ | -0.127 | 0.105 |
| $E_m$ | -0.29 | 0.032 |
| $A_m$ | -0.222 | 0.005 |
| $E/E_m$ | - 0.195 | 0.091 |

  Correlation is significant at the 0.01 level (2-tailed).
 LVEF=left ventricular ejection fraction; E=transmitral early diastolic velocity;
 DT=deceleration time; $E_m$=TDI derived mitral annular early diastolic velocity; $S_m$=TDI derived mitral annular systolic velocity. ; $A_m$=TDI derived mitral annular late diastolic velocity; $E/E_m$= ratio of early transmitral to early mitral annular velocity.

FIG.1. Scatter plots showing the correlation between log NT-proBNP level and (A) systolic mitral annular velocity ($S_m$);); (B) late diastolic mitral annular velocity ($A_m$);(C) ratio of early transmitral to early mitral annular velocity ($E/E_m$); (D) ejection fraction (EF)
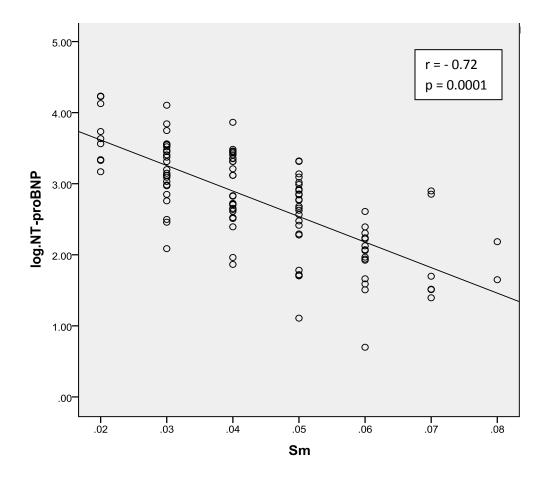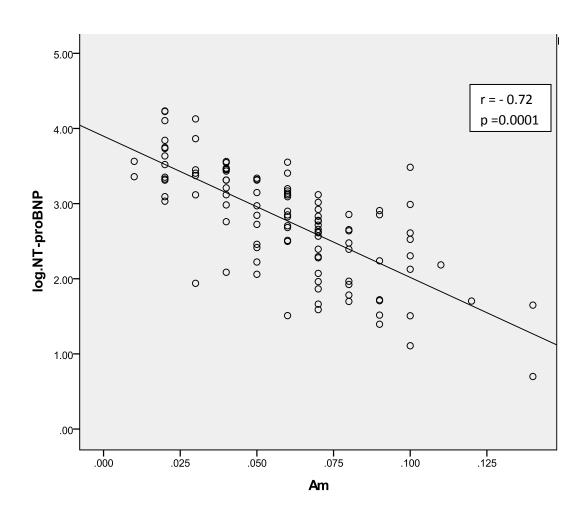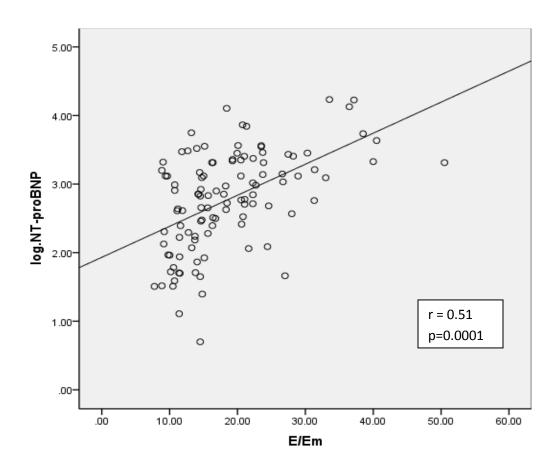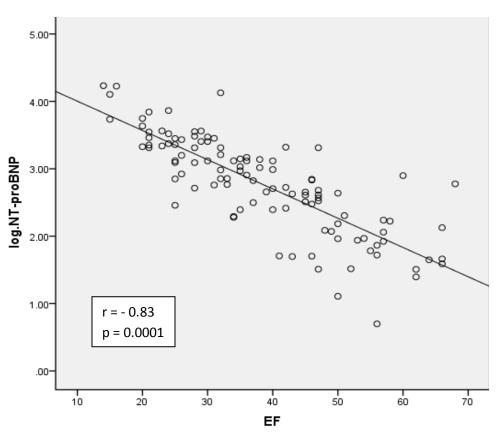


FIG.1. (A)

FIG.1. (B)

FIG.1. (C)

FIG.1. (D)