

Plasma BNP Level as Marker for Early Detection of Heart Failure in Primary Hypertensive Patients

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Heart failure is chiefly the end stage of primary hypertension and a major public health problem in Malaysia. The aim of this work is to investigate the level of BNP that may discriminate between primary hypertension patients without heart failure and primary hypertensive patients with heart failure. This study was conducted on 60 hypertensive patients without any clinical symptoms of heart failure referred for echocardiography to evaluate the ventricular function. Patients with metabolic diseases and terminal diseases were excluded from the study. The BNP levels were assessed using the Triage Meter from Biosite Diagnostics. Results showed that BNP level display a negative correlation with ejection fraction (Pearson correlation test). The significant result (paired t test, $p < 0.05$) proves that both predictors are very important and relates to each other. Low ejection fraction is significantly marked with raised BNP level suggesting that BNP may play potential role as screening tool for early detection of heart failure in primary hypertensive patients.

Keywords: BNP, hypertension, heart failure

INTRODUCTION

Heart failure is mainly the end stage of primary hypertension and a major public health problem in Malaysia ^[1]. Risk of heart failure in persons predisposed by hypertension, diabetes or cardiac conditions varies over a 10-fold range depending on the modifiable risk factors and indicators of deteriorating left ventricular function ^[2]. What worries us is recent research done in Malaysia which indicated that the prevalence of hypertension is high in both Malaysian males and females. It poses a serious problem with low awareness, low treatment and poor control of blood pressure. As the prevalence of hypertension increases, the prevalence of heart failure in Malaysia also increases. It accounts from 3 to 20 per 1000 population, though in persons over the age of 65 years, it could be as high as 100 per 1000 population ^[3]. Furthermore, 10% of all medical admissions are due to heart failure and about 45% of patients with heart failure are readmitted at least once within 12 months for acute decompensation ^[1,5]. As Malaysia is a country in epidemiological transition, it may be facing the daunting prospect of an even higher prevalence in the future if aggressive steps of better management of blood pressure are not taken ^[3].

B-type Natriuretic Peptide (BNP), previously known as brain natriuretic peptide is a 32 amino acid polypeptide secreted by the ventricles of the heart in response to volume expansion and pressure overload ^[5]. It contains a 17 amino acid ring structure that is common to all natriuretic peptides. So BNP shares the general effects of all natriuretic peptides which are natriuretic and vasodilatory effects and suppresses the renin angiotensin system. Observational studies have suggested that when used in conjunction with other clinical information ^[6], BNP levels may be useful in establishing or ruling out the diagnosis of heart failure ^[7]. Enhanced BNP production is a strong predictive measure that indicates electrophysiological abnormalities of the heart because volume overload of the ventricles and increased pressure within them are both stimuli for BNP secretion ^[8]. This is an important measure because blood testing can be used as a screening method at the general practitioners setups, district health clinics, and at emergency departments so that misdiagnosis of heart problems or heart failure can be avoided or minimized ^[9].

Despite all the evidences and the suggestion in the Malaysian Clinical Practice Guidelines in Management of Heart Failure pointing to the value of BNP testing ^[10], this test is still not a routine test in Malaysia. BNP testing is seen as only a biomarker for heart failure and though with or without its value the management for patients which is confirmed with heart failure will be the same ^[11]. Recently the management of heart failure will only start when the patient is suspected of suffering from heart failure due to complaints of symptoms. These groups of patients will then undergo further clinical investigation for confirmation ^[12]. However, there are conditions which the patient doesn't realize the occurrence of the symptoms and the delay of diagnosis will increase in morbidity and mortality ^[13]. In order to include

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the BNP testing as a screening test at health centers, we have yet to develop the prognostic values that can be used and be relevant for our Malaysian population.

The prime goal for this study is to determine the levels of BNP that may discriminate between hypertensive patients without heart failure and primary hypertensive patients that have developed heart failure. Identification of the discriminative value of BNP levels will then bring us towards a cost effective management for this group of patients because we are able to select patients who are in need of echocardiography ^[14].

METHODOLOGY

Patient selection

The study was approved by the ethical committees from the National University of Malaysia and International Medical University, Malaysia.

Subjects were recruited from the hypertension clinic at two different medical centers (Universiti Kebangsaan Malaysia Medical Center and International Medical University cardiology clinic, Seremban) by convenient sampling. Between January 2006 and January 2007 all patients from the three main races in Malaysia (Malay, Chinese, Indian) at the clinics were screened for the study. To be eligible for the study, the patients had to have a history of hypertension for more than two years. Only those without complaints of any clinical symptoms of heart failure were selected for the study. Once the patients were identified as being suitable for the study, written informed consent was obtained. None of the patients had chest trauma, pericardial effusion, angina, and renal dysfunction prior to the study. The exclusion criteria are listed in Table 1. The sample size was set for the study to have 80% power to observe a $p < 0.05$ to be statistically significant.

Table 1. Exclusion criteria for the subjects

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1. Secondary hypertension patients.
 2. Patients previously diagnosed with any heart diseases.
 3. Patients with clinical symptoms / complaints of heart failure.
 4. Patients previously diagnosed with myocardial infarction.
 5. Patients with other metabolic diseases (eg: obesity, diabetes mellitus).
 6. Patients diagnosed with malignancy.
 7. Patients with depressive disorder.
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For each patient enrolled in the study, their medical history was taken, and a thorough physical examination was performed followed by a Doppler echocardiography assessment by a cardiologist who was blinded to the results of the measurement of BNP. Those with ejection fraction less than 50% were considered to have left ventricular dysfunction ^[15].

Measurement of plasma BNP

One ml of venous blood was withdrawn into ethylene diamine tetra acetic (EDTA) tube. Each tube was labeled accordingly with the respective patient's reference number. Patients were not required to fast prior to the blood taking procedure because fasting has no effect on BNP levels.

BNP measurement was done using the TRIAGE Meter (Biosite Inc, USA) as the previously reported method ^[16]. Venous blood samples were kept in EDTA tubes at room temperature and analyzed within two hours of collection. The blood was then analyzed in duplicate with the Triage BNP assay. It is a sandwich immunoassay that consists of a disposable device to which 250µl of EDTA anti-coagulated whole blood was added. The meter was used to measure the BNP concentrations by detecting the fluorescent signals that reflect the amount of BNP in the sample. Once 250µl of whole blood was added to the device, the cells were separated from plasma by a filter. Plasma which contained BNP was put in a reaction chamber containing fluorescent-tagged BNP antibodies which would react to BNP forming antigen-antibody reaction. The reaction mixture was incubated for two minutes. After the incubation was completed,

the samples migrated through the diagnostic lane by capillary action to a zone of immobilized antibody that would bind the desired BNP to form a fluorescent antibody complex. After 15 minutes, the device was placed into the meter and the fluorescent complex intensity was measured. An internal calibration curve was used to correlate Triage meter and fluorescent measurement to BNP concentration. The assay was completed within 15 minutes^[17].

Statistical analysis

Data was analyzed using paired t test to compare means of BNP levels between hypertensive patients with ejection fraction of $\leq 50\%$ and those with ejection fraction of $>50\%$. Pearson correlation test was done to test the correlation of BNP level and ejection fraction. The accuracy of plasma BNP in diagnosing heart failure was assessed by receiver-operator characteristic curve.

RESULTS

We successfully recruited 60 patients from 250 patients attending the clinic within the duration of one year. The limited number of subjects is due to the fact that most hypertensive patients who attended the clinic also had other metabolic diseases or clinical symptoms of heart failure. Table 2 describes the characteristics of all subjects recruited. Patients' left ventricular function was assessed via echocardiography. There were 23 (38%) subjects with LVEF (left ventricular ejection fraction) less than 50% which indicated that they had compromised systolic function. Among them, 9 (39%) subjects had LVEF of 40% which indicated that they had developed heart failure.

Table 2. Profiles of subjects recruited

Characteristic	Units	Subjects' profiles
Mean age	year-old	60 ± 3.53
Range	year-old	50 – 64
BMI	kg/m ²	23.71 ± 2.21
Range	kg/m ²	21.30 - 26.12
Sex		
Male		35
Female		25
Smoking status		
Non –smoker	%	100
Smoker	%	-
Mean SBP	mmHg	144.8 ± 2.3
Mean DBP	mmHg	87 ± 2.5
Heart Rate	beat/min	96 ± 2.5
LVEF	%	61 ± 16.6

BNP displayed a negative correlation with ejection fraction (Pearson correlation test; $R = -0.89$) (Figure 1). There was significant difference between mean of BNP levels in the group of patients with LVEF $\leq 50\%$ and the group with LVEF of $\geq 50\%$. Patients with LVEF $\leq 50\%$ showed a significantly higher mean of BNP (85.2 pg/ml) compared to patients with LVEF $> 50\%$ (28.5 pg/ml) (paired t test, $p < 0.05$). Receiver-operator characteristic (ROC) curve was plotted to determine the level that may show potential value of plasma BNP to detect early cardiovascular complication

(Figure 2). The level of ≥ 80 pg/ml (93% sensitivity and 60% specificity) was identified as the cut-off point to determine the presence of systolic dysfunction (area under the ROC curve 0.95; 95% CI: 0.80 – 0.98).

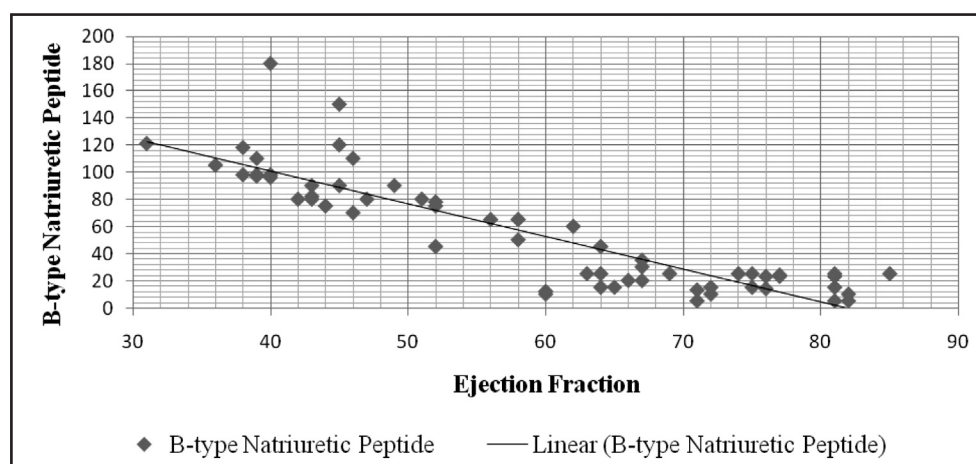


Figure 1. BNP versus ejection fraction scatter plot graph

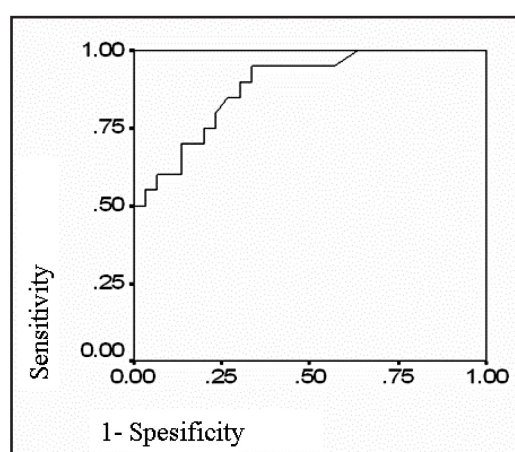


Figure 2. Receiver operating characteristic (ROC) curve plot of sensitivity vs (1-specificity) of BNP level for left ventricular systolic dysfunction

DISCUSSION

Previous data have suggested the value of BNP to be used among heart failure patients, either to predict the prognosis^[18] or as additional information in diagnosing heart failure patients^[19]. Raised BNP levels indicate raised intracardiac pressures, irrespective of whether the raised intracardiac pressure is due to left ventricular hypertrophy, left ventricular systolic dysfunction, valve disease or even fast atrial fibrillation^[20]. Previous studies have proven that BNP was much better used as a prognostic indicator rather than it was as a diagnostic indicator^[21]. Interestingly, we have successfully shown that BNP assay is also to be of value in early screening of heart failure within an increased risk population. Higher levels of BNP are proportional to worsening prognosis in primary hypertensive patients^[22].

Recent data by Verdecchia *et al.* has shown that it was crucial to detect left ventricular hypertrophy (LVH) in primary hypertensive patients because regressing LVH has proven to play an important part in reducing risk of cardiovascular events. Based on their study, blood pressure alone was not a sufficient guide to indicate that LVH had regressed. This pointed to the idea of using BNP serially to ensure that left ventricular hypertrophy is indeed regressing in an individual patient^[23].

Although several studies on assays for BNP found that there was increased BNP level in patients with hypertension^[24], ours is the first data on the performance characteristics of an assay for BNP in a group of chronic hypertensive patients in Malaysia that is not subjected for echocardiography and did not show any clinical symptoms of heart

failure. Our study assessed the value of BNP in the screening of left ventricular systolic dysfunction and heart failure in hypertensive patients. The results showed that BNP, when rapidly tested at bedside, has an excellent sensitivity but a moderate specificity in detecting ventricular systolic dysfunction in these hypertensive patients. Although BNP may only provide additional information in diagnosing heart failure, it is a very useful screening test for systolic dysfunction and heart failure in chronic hypertensive patients.

Study done by Nishikimi *et al.* (1996) had also chosen essential hypertension patients as their study population. However, the major difference was the selection of patients; our study is focused on patients without complaint of any clinical symptoms and they must meet the strict inclusion and exclusion criteria stated prior to being included in the study. Results of BNP levels in their study was much lower than that of our patients' results. The major difference may be due to the difference of parameters chosen for comparison with BNP between both studies. Their study mainly determines the levels of BNP which indicate the occurrence of left ventricular hypertrophy whereby our study was to determine the level which indicates compromised ejection fraction ^[25].

Among the subjects, approximately 38% had compromised systolic function with no clinical symptoms. This may lead towards worse complications and it reflects the inadequacy of hypertension management among the patients. Based on this data, in clinical practice, the assay would have practical uses in; screening patients with chronic hypertension ($\geq 80\text{pg/ml}$ to be ruled out for heart failure); and elevated BNP in patients without clinical symptoms of heart failure should be subjected for echocardiography. These data are sufficiently positive to justify formal trials of the assays in real life strategies for screening those with prolonged hypertension.

Furthermore, BNP assay can be easily set up at any main centers or district hospitals and even at the general practitioners settings ^[26]. Measurement of plasma BNP is simple and relatively inexpensive ^[27]. Baseline plasma BNP may be used as an early predictor of outcome in prolonged primary hypertensive patients and particularly as a guide to a selection of therapies. Early intervention for systolic dysfunction patients promises better prognosis ^[28].

CONCLUSION

This prospective study has shown that plasma BNP increased in hypertensive patients with systolic dysfunction even without any clinical symptoms. Significant result proves that BNP levels and ejection fractions relate to each other. This suggests that BNP is uniquely suited to provide accurate neurohormonal profiling in heart failure, increasing as heart failure progresses. As ejection fraction decreases, the plasma BNP level will relatively increases. A low BNP level has a high negative predictive value for systolic dysfunction or heart failure. The negative correlation between BNP and ejection fraction strongly suggests that BNP may play a potential role as a screening tool for early detection of left ventricular systolic dysfunction in chronic primary hypertensive patients.

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