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Original Article

NT-proBNP levels in detecting heart failure in patients with left ventricular systolic dysfunction presenting with Diabetes Mellitus and Hypertension

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ABSTRACT

Purpose: Plasma levels of N-terminal pro b-type natriuretic peptide (NT-proBNP) have gained importance as markers in detecting, diagnosing, and evaluating the severity of heart failure.Patients with diabetes and hypertension are at higher risk of heart failure. The aim of the present investigation was to assess whether NT-proBNP can be used to detect early heart failure in patients with left ventricular systolic dysfunction (LVSD) accompanied with diabetes and hypertension. Materials/Methods: Forty patients with coronary artery disease (CAD) were recruited for this study and were grouped as diabetes mellitus (DM, n= 9), hypertension (HTN, n=8), bothDM and HTN (DM+HTN, n=15) and without DM and HTN (None, n= 8). Echocardiography (ECHO) findings, Fractional Shortening (FS) and Ejection Fraction (EF) were assessed to detect LVSD and NT-proBNP levels were also measured in all patient groups before and after coronary artery bypass graft (CABG). Results: ECHO findings were found to be decreased ($p<0.001$) in patients with DM and HTN before CABG, when compared to CAD patients who neither had DM nor HTN. After CABG, FS and EF was significantly improved in all patient groups.NT-proBNP levels were significantly increased($p<0.001$; $p<0.01$) in all patient groups before CABG and were decreased ($p<0.001$) after CABG. Correlation analysis showed negative correlation between the echo findings and NT-proBNP levels. Conclusions: From the results, it could be speculated that NT-proBNP levels supports echo findings in detecting early heart failure in LVSD patients with DM and HTN.

1. Introduction

Heart failure, a consequence of cardiac disease is clinically recognized by a group of symptoms and signs caused by complex circulatory and neurohormonal responses to cardiac dysfunction [1]. Many investigations have reported the diagnostic value of symptoms and signs of heart failure [2,3]. Increasing evidences have provided information on the evaluation of diastolic and systolic function of the heart by echocardiography (ECHO),Doppler cardiography, nuclear studies or cardiac catheterization; however they fail to determine the presence or absence of heart failure [4]. Similarly, natriuretic peptides are found to be elevated in individuals with left ventricular dysfunction (LVD) [5,6] but their role as diagnostic tools in heart failure remains unclear.

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The types of natriuretic peptides are Atrialnatriuretic peptide (ANP), Brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). B-type or Brain Natriuretic Peptide (BNP), a 32 amino acid peptide is a cardiac neurohormone secreted by cardiac ventricles during ventricular volume expansion, pressure overload and resultant increased wall tension [7,8,9]. BNP is reported to be an independent predictor in detecting LVD in addition to the clinical variables such as pathologic ECHO findings and history of diabetes or coronary artery disease (CAD)[10]. Follow up studies by Cowie et al.[11] in patients with chronic stable heart failure due to left ventricular systolic dysfunction (LVSD) show that higher concentration of plasma BNP was associated with a worse prognosis for patients with heart failure. The role of plasma BNP has been identified not only as an excellent screening tool for left ventricular dysfunction (LVD) precluding the need for expensive echocardiography but also as a potential indicator of recovery of left ventricular hypertrophy and function after heart surgery[12]. The difference between the preoperative and late postoperative plasma BNP levels provides clinically relevant information on the recovery of LV function[13]. Also,

plasma NT-proBNP, a prohormone of BNP has been shown as a useful marker for recovery after a high-risk coronary artery bypass graft (CABG) procedure, with significant correlation with clinical parameters [14]. Reports regarding assessment of NT-proBNP levels in patients with early heart failure with/without DM and/or HTN are limited. The aim of the present study was to assess the impact of NT-proBNP levels in detecting early heart failure in patients with depressed LV function and presenting with DM and/or HTN.

2.Material and Methods

2.1.Subjects

Forty patients with CAD admitted in the Institute of Cardiovascular diseases, Madras Medical Mission, Chennai, India were recruited in this retrospective study. The selected patients had ejection fraction (EF)<40% and were undergoing CABG. Patients with DM with/ without HTN (DM, n = 9; HTN, n = 8; and DM + HTN, n = 15) were considered for inclusion. Age of the selected patients was in the range of 30 – 70 years. Age and sex-matched CADpatients without DM and HTN were also included in the study for comparison of results. Cases were diagnosed by cardiologists. Among the patients with chronic heart disease (CHD), 9 had diabetes, 8 had HTN and 15 had DM & HTN. The data collected included their medical history, physical examination, chest X-ray, and blood tests. All the subjects underwent ECHO evaluation and coronary angiogram. The clinical characteristics of the patients selected are presented in Table 1.

The protocol was approved by the Institutional Ethics Committee and was carried out in accordance with the principle of Declaration of Helsinki. Informed consent was obtained from all the subjects.

2.2.Methods

2.2.1.ECHO findings

The left ventricular EF and fractional shortening (FS) were measured to assess LV systolic function.

2.2.2.Ejection fraction

EF was determined by measuring left ventricular volume (LVV) using Area-length method [15] both in end diastole (LWd) and in end systole (LWs) by the formula, EF = LVVd-LVVs/LVVd. The normal range of EF was taken as 50-60% [16,17]. EF <50% was considered as decreased level.

2.2.3.Fractional shortening

FS was determined by measuring Left ventricular Internal Diameter diastolic (LVIDd) and Left ventricular Internal Diameter systolic (LVIDs). FS was calculated using the formula, FS = (LVIDd-LVIDs)/ LVIDd x 100. The normal range of FS is 27-45% [18]. FS ≤ 25% was considered as an index of LVD [19].

2.2.4.NT-pro BNP measurement

The concentration of NT-pro BNP was measured by competitive EIA method using TRIAGE NT-pro BNP assay Kit[20]. Assay range was 20-1300 pg/ml.

2.2.5.Statistical analysis

Data were analyzed using SPSS for Windows V.13.0. One way analysis of variance (ANOVA) was performed to find out the significance of variations between these groups followed by student's t-test and Spearman's correlation test was conducted for correlation analysis.

3.Results

Based on the clinical characteristics of patients as described in Table 1, the patients were grouped asDM (n = 9), HTN (n = 8), DM/HTN (n = 15) and patients without DM and HTN (n= 8) as controls.Table2 presents the number of patients with diseased vessel. The number of patients with triple vessel disease was high in all the groups when compared to patients with double or single vessel disease.

Table 1. Clinical profile of subjects.

Clinical characteristics	No. of subjects
Total Number	40
Age	30-70 ± 4.7 years
Sex	Male - 38; Female - 2
Angina	15
Dyspnea	18
Orthopnoea	5
Paroxysmal Nocturnal Dyspnoea	3
Diabetes	24
Hypertension	16
Smokers	9
Alcoholic	3
Family history of Coronary Artery Disease	4
Left ventricular dysfunction	
Severe	25
Moderately	7
severeModerate	8

Table 2. Number of patients with diseased vessels.

Diseased vessel	None (n = 8)	DM (n = 9)	HTN (n = 8)	DM + HTN (n = 15)
Triple Vessel Diseas	9	7	3	9
Double Vessel Disease	4	1	1	4
Single Vessel Disease	1	0	0	1

DM Diabetes Mellitus, HTN Hypertension

Table 3. NT-proBNP levels before (pre-NT-proBNP) and after CABG (post-NT-proBNP) in studied population

Parameters	None (n = 8)	DM (n = 9)	HTN (n = 8)	DM + HTN (n = 15)
Pre-NT-pro BNP (fmol/ml)	399.42 ± 42.6	530.08 ± 53.2*	692.06 ± 71.5*^	923.67 ± 95.7*^@
Post-NT-pro BNP (fmol/ml)	280.55 ± 31.4#	445.96 ± 49.3*#	595.37 ± 51.8*$#	722.44 ± 65.9*^@#

DM Diabetes Mellitus, HTN Hypertension

Statistically significant variation is expressed as *p<0.001 when compared with patients who had neither DM nor HTN, ^p<0.001; $p<0.01 when compared with patients who had DM, @p<0.001 when compared with patients who had HTN, #p<0.001 when compared to pre-NT-proBNP

NT-proBNP N-terminal prohormone brain natriuretic peptide, CABG Coronary artery bypass graft, DM Diabetes Mellitus, HTN Hypertension

Table 3 shows the levels of NT-proBNP levels in patients before and after CABG. Results depict that the BNP levels in patients before CABG (pre-NT-proBNP) was found to be significantly high in patients with HTN (p<0.001; p<0.01) and DM + HTN(p<0.001) when compared to patients with DM and patients without DM and HTN. The levels of NT-proBNP were relatively decreased significantly (p<0.001) after CABG which is represented as Post NT-proBNP in all the groups when compared with NT-proBNP levels before CABG. The levels were indeed more significant (p<0.001) in patients presenting with DM and HTN than in patients with HTN or DM.

Table 4 shows the ECHO findings, EF and FS in patients before and after CABG. Before CABG, FS was found to be significantly decreased (p<0.001) <25% in all patient groups, i.e., DM, HTN and DM + HTN. Patients with DM+HTN had significantly decreased (p<0.01) level of FS when compared with DM and HTN patients. Similarly, EF was decreased to <50% in patients with DM + HTN (p<0.01) than in DM and HTN patients Also we observed a significant decrease (p<0.01) in the level of EF in DM and HTN patients when compared to patients without DM and HTN. FS and EF was significantly improved in all patient groups after CABG.

Spearman's correlation analysis was done to correlate LVSD with NT-proBNP levels (Table5). The results showed that there was a negative correlation between FS and NT-proBNP level and also with EF and NT-proBNP levels measured before and after CABG.

Table 4. ECHO findings in studied population

Parameters	None (n = 8)	DM (n = 9)	HTN (n = 8)	DM + HTN (n = 15)
Fractional Shortening (FS)				
Before CABG	40.7 ± 4.6	24.2 ± 3.2*	20.5 ± 3.5$^{*\$}$	16.6 ± 3.1$^{*\$@}$
After CABG	41.5 ± 5.1	27.8 ± 4.1*	23.4 ± 3.7$^{*\$}$	18.7 ± 3.4$^{*\$@}$
Ejection Fraction (EF)				
Before CABG	51.6 ± 6.5	42.3 ± 5.2*	38.9 ± 5.1$^{*\$}$	33.6 ± 4.5$^{*\$@}$
After CABG	57.7 ± 6.8	50.5 ± 6.5$^{\#}$	48.7 ± 6.3$^{\#\$}$	46.9 ± 5.9$^{\#\$@}$

Statistically significant variation is expressed as *p<0.001; #p<0.01 when compared with patients who had neither DM nor HTN, $p<0.01 when compared with patients who had DM, @p<0.01 when compared with patients who had HTN.

DM Diabetes Mellitus, HTN Hypertension, CABG Coronary artery bypass graft

Table 5. Spearman rank correlation coefficient between FS, EF and NT-pro BNP levels.

Variables	rs	P
FS - Pre-NT- proBNP	-0.3027	<0.05
FS - Post- NT-proBNP	-0.4236	<0.05
EF - Pre- NT-proBNP	-0.4512	<0.05
EF - Post- NT-proBNP	-0.3564	<0.05

Based on the critical values of the rank correlation coefficient (Spearman rho, rs) null hypothesis of no correlation is rejected and that the paired values are correlated.

FS - Fractional Shortening; EF Ejection Fraction; NT-proBNP N-terminal prohormone brain natriuretic peptide (Pre-NT-proBNP: before CABG; Post-NT-proBNP: after CABG)

4.Discussion

Heart failure is a public health problem causing substantial morbidity and mortality that increases with age and the most common etiology is CAD. Majority of cases of heart failure within the developed world is due to CHD and HTN. The major risk factors causing heart failure are obesity, hyperlipidemia, hypertension, diabetes, alcohol abuse and smoking[21]. LVSD is one of the causes of heart failure. Detection of echocardiographic abnormalities helps in the characterization of individuals at risk of developing heart failure. Systolic function is usually determined by ECHO measurements such as FS or EF. In this investigation, we measured FS and EF to study the LVSD in patients presenting with DM with/without HTN. A significant decrease in the mean FS and EF was observed in all patient groups. FS and EF was indeed more significantly decreased in patients with DM and HTN before CABG. Simoneet al. suggested that depressed mid wall FS in relation to circumferential end-systolic stress was also associated with other

signs of target organ damage[22]. FS and EF was studied in the same population after they underwent CABG. FS and EF significantly improved in all patients groups. It could be stated that FS and EF are helpful in predicting LVSD.Plasma levels of NT-proBNP were measured in all the patients groups before and after CABG to assess the influence of NT-proBNP in detecting LVSD leading to heart failure in DM and HTN patients. Biochemically, troponin and BNP levels have shown to be very useful predictors of heart failure [23]. BNP has been found to be useful in identifying LVH or LVSD in people with DM, dialysis patients or aortic stenosis [24].

Few studies have reported the relationship of BNP with LV dysfunction parameter such as EF, LV end-diastolic pressure (LVeDP) or pulmonary capillary wedge pressure (PCWP) [25,26]. Elevated BNP levels are reported in patients with diastolic LV dysfunction and CV hypertrophy [27]. Choy et al.[28] and his colleagues have concluded that BNP may be a useful indicator for detecting LVD. Correlation analysis of our results on ECHO findings and BNP levels suggest the relationship between LVD and BNP levels.

Beer et al.[29] and his team have reported that measurement of BNP might serve as an indicator of macro and/or micro vascular disease in patients with type 2 diabetes and concluded by their finding that increased NT-proBNP levels were independently associated with both overt CAD and diabetic nephropathy. Results of our study shows that NT-proBNP levels were high before CABG and were decreased after CABG. This indicates that NT-proBNP levels may serve as an indicator for vascular disease in patients with depressed LV function associated with DM and HTN. Furthermore studies have proved that direct comparison and analysis of BNP and NT-proBNP in patients with acute myocardial infraction adds significant prognostic information to the known risk predictors contributing to mortality and heart failure. Several reports found significantly elevated BNP levels in patients after heart transplantation and the BNP elevation correlated very well in patients with the parameters of right-sided cardiac dysfunction and parameters of diastolic LV dysfunction[30,31].

Recent studies and evidences have shown that BNP and NT-proBNP are both probably very useful for diagnosis of heart failure, especially with dyspnea [32]. There is also strong evidence supporting the information obtained from BNP and NT-proBNP levels when monitoring treatment, however there is certainly no clear evidence for the use of BNP or NT-proBNP in screening asymptomatic patients, even though some studies show that high normal levels of BNP can act as a risk predictor in community populations.

In our investigation, the levels of NT-proBNP before CABG were found to be significantly increased in all patient groups. We could observe a significant increase in plasma NT-proBNP levels in patients with HTN when compared to patients with either DM or HTN. Similarly the levels of NT-proBNP were significantly increased in patients with both DM and HTN than in other patient groups. Retrospective study in the same population after CABG was performed and we found that there was a significant decrease in all patient groups when compared to the values assessed before CABG. The decrease in plasma NT-proBNP level was more significant in patients with DM and HTN when compared to patients with no complications. We performed spearman correlation analysis to evaluate the relationship between echo findings and plasma NT-proBNP level in the study population. We found that there is a negative correlation between NT-proBNP, FS and EF which indicates that NT-proBNP may be used as an indicator of LVD to assess early heart failure in patients with DM and HTNcomplications.

6.References

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