DOI: 10.7860/JCDR/2017/29173.10801

Original Article

Cardiology Section

Usefulness of B-Type Natriuretic Peptide in Predicting the Involvement of Right Ventricle in Acute Inferior Wall Myocardial Infarction

RAMALINGAM AROUTSELVAN[1], VICTOR ASHOK[2], SETHUMADHAVAN RAGHOTHAMAN[3], HANNAH SUGIRTHABAI RAJILARAJENDRAN[4]

ABSTRACT

Introduction: Cardiovascular Disease (CVD) is the leading cause of deaths globally as the death rate due to CVD has increased from 26% in 1990 to 29.5% in 2010. The Acute Coronary Syndrome (ACS) includes acute Myocardial Infarction (MI) with ST segment elevation, Non-ST Segment Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA). Isolated infarction of the right ventricle is rare and is commonly associated with Inferior Wall MI (IWMI) or Posterior Wall MI (PWMI). B-type Natriuretic Peptide (BNP) is one of the biomarkers which has been evaluated during acute MI.

Aim: In this study, the usefulness of BNP in predicting the involvement of Right Ventricle (RV) in acute ST elevation with IWMI and PWMI was assessed.

Materials and Methods: The study was a prospective observational study, done on 64 patients less than 60 years of age. The study was conducted over a period of four months at Rajiv Gandhi General Hospital, Madras Medical College, Chennai., Tamil Nadu, India. The patients with diagnosis of IWMI, IW with RVMI, IW with PWMI, IW and PW with RVMI were included. BNP levels, Left Ventricular Ejection Fraction (LVEF) and troponin I were measured. Killip class was also observed and patients were classified and compared against different levels of BNP.

Results: When IWMI is associated with RV, PW or RV with PW involvement, BNP level was increased to more than 900 pg/ml, than in isolated IWMI. This increment was statistically significant. There was severe increase in BNP in those having LVEF ≤30%, and majority of patients were in the range of 30-50%. All the patients in Killip class III and IV had severe BNP increase as did those patients with cardiac troponin levels between the range of 2-4 ng/ml.

Conclusion: All the findings are statistically significant and prove that severe BNP increase in acute IWMI is definitely a predictor of associated RV, PW or RV with PW involvement. LVEF has a significant inverse correlation with BNP levels, as the BNP rises, LVEF shows a steady decline. Killip class also shows a poor prognosis with elevated BNP. Troponin I levels are higher with increase in BNP.

Keywords: Cardiovascular disease, Left Ventricular Ejection Fraction, Predictor

INTRODUCTION

Cardiovascular Disease (CVD) has emerged as one of the major fatal diseases, its mortality percentage increasing from 26% in 1990 to 29.5% in 2010 [1]. Acute MI with ST segment elevation, NSTEMI and UA are all parts of ACS. Isolated infarction of the RV is rare and Right Ventricular Myocardial Infarction (RVMI) occurs in about 50% of the cases of IWMI [2,3] or with PWMI. The latest biomarkers include Heart-type Fatty Acid Binding Protein (H-FABP), serum amyloid A, myeloperoxidase, interleukin-6 and ischaemia modified albumin.

BNP is a natriuretic peptide that is mainly released from the cardiac myocytes in the left ventricular wall in reaction to stress and tension of myocardial wall [4]. There is a n-terminal prohormone natriuretic peptide of brain (NT-proBNP) which is an inactive remnant of hormonically active BNP. BNP and NT-proBNP will be secreted into circulation after the cleavage of prohormone pro BNP and BNP. The BNP has a protective mechanism in the body that causes diuresis, sodium excretion and dilation of vessel and the sympathetic nervous system inhibition. Half-life of BNP is nearly 20 minutes but of NT-proBNP is 120 minutes.

In this study, the usefulness of BNP in predicting the involvement of RV in acute ST elevation with IWMI and PWMI was assessed. The LVEF was also assessed and correlated with the different levels of BNP. In this study, BNP levels were compared with cardiac troponin I and Killip class, in predicting the prognosis after acute MI.

MATERIALS AND METHODS

The study was a prospective observational study, done during the period between November 2014 to February 2015. The study population were 64 patients, less than 60 years of age, with acute IW ST elevation MI with no history of cardiac disease. The patients with diagnosis of IWMI, IW with RVMI, IW with PWMI, IW and PW with RVMI were included. The patients aged more than 60 years, with AWMI, NSTEMI/UA, history of MI, valvular heart disease, renal failure, liver cirrhosis, other causes of pulmonary hypertension, anaemia and other infections were excluded. Ethical clearance and informed consent of the patients were obtained.

The study population was divided into three major groups.

Group 1: Mild BNP increase	301-600 pg/mL
Group 2: Moderate BNP increase	601-900 pg/mL
Group 3: Severe BNP increase	more than 900 pg/mL

With ECG & ECHO they were further divided into four sub-groups

Sub-group 1: IWMI	15 patients
Sub-group 2: IW and PWMI	13 patients
Sub-group 3: IW with RVMI	22 patients
Sub-group 4: IW and PWMI with RVMI	14 patients

The LVEF was measured for all 64 patients and tabulated for different BNP levels. Killip class was recorded for all these patients and TIMI scoring for STEMI was also calculated. Detailed ECG assessment was done to localise MI. The BNP levels and troponin I levels were

measured in blood by rapid quantitative test in the first 24 hours, using a Alere Triage cardio three panel. This panel is a single use fluorescence immunoassay device to simultaneously determine the concentration of CK-MB, troponin I and BNP in EDTA anti-coagulated whole blood or plasma concentrations.

STATISTICAL ANALYSIS

Descriptive statistics were done for all data and suitable statistical tests for comparison were used. Continuous variables were analysed with ANOVA and categorical variables were analysed with Chi-square test or Fisher-exact test. Statistical significance was taken as $p<0.05$. Epi Info software (7.1.0.6 version; Center for disease control, USA) was used to analyse the obtained data from the study.

RESULTS

The study was done on 64 patients, hailing from in and around Chennai. All patients less than 60 years of age were included in the study. Most of the patients were from low socioeconomic group and were included in the study irrespective of gender, habits like smoking or drinking and any associated diseases like diabetes and hypertension.

The localisation of MI with ECG along with the number of cases in each category, namely, IWMI - 15, IW/RVMI - 22, IW/PWMI - 13, IW/RV/PWMI - 14 was recorded and labelled as in [Table/Fig-1]. The BNP levels were divided into mild, moderate and severe categories. The LVEF was measured, and the sample division was done as follows: ≤30%, 31-40%, 41-50% and 51-60%. The values for the different categories of BNP were as seen in [Table/Fig-2]. The Killip classification was recorded and the patients were divided into class I, II, III and IV and the number of patients in each BNP category was found to be as in [Table/Fig-3]. The levels of cardiac troponin I was also recorded and tabulated against different BNP levels as in [Table/Fig-4]. Upto a maximum of 4 ng/mL was recorded starting from 0.01 ng/mL, being the lowest. Higher the cardiac troponin level, the BNP severity also increased.

DISCUSSION

The prognosis in MI can be predicted by scoring system like TIMI scoring system and Killip classification. The other enzymes like troponin I and CK-MB are also used for prognostic implications. BNP is one of the most sensitive biomarkers of cardiac muscle strain. This study evaluates its use as a prognostic marker in patients with acute IWMI with RVMI.

In acute IW MI with right ventricular involvement, RV involvement is sometimes a misnomer, as RV infarction leads to temporary RV-dysfunction and indicates viable myocardium which recovers with early reperfusion. LV is a thick walled pressure pump. RV is a thin walled volume pump which ejects into a low resistance pulmonary circulation. Factors responsible for RV systolic pressure and flow include shortening of the RV free walls, contraction towards the septum (APEX to RVOT) and LV septal contraction. Nearly 50% of the patients with IW MI have associated right ventricular involvement. In most of the cases LV systolic function is preserved. Clinical features of RVMI are severe right heart failure, clear lungs and low output hypotension. So RV involvement is associated with increased, mortality and mobility.

BNP has usefulness as a prognostic marker among patients with ACS, including those with STEMI/NSTEMI/UA [5,6]. IW STEMI has raised BNP values; however, anterior wall STEMI has comparatively raised BNP values. IWMI with RV involvement has increased BNP levels compared to isolated IWMI [7]. In OPUS-TIMI 16, the 10 months mortality rate was increased to two to three folds in patients whose BNP was significantly higher [8]. TIMI II and TACTICS-TIMI 18 trials confirmed this [9,10]. The ESI guidelines and AHA guidelines suggest that BNP assays are useful adjunct to clinical assessment. Levels of BNP differentiated whether shortness of breath is due to heart failure or a respiratory cause in a multinational study "Breathing not properly" [11]. In addition BNP cut-off value was 100 pg/mL as normal. The diagnostic accuracy of BNP is 81.2%, compared to 74% for clinical judgments alone. The role of BNP in diagnosing dyspnoea as a cause for heart failure in acute conditions was established in the above study. In these trials BNP value of 100 pg/mL had a negative predictive value. More than 400

ECG-MI/ Localisation	Number of patients with Mild BNP increase	Per-centage	Number of patients with Moderate BNP increase	Per-centage	Number of patients with Severe BNP increase	Per-centage
IWMI	8	80	5	83	2	4
IW/RVMI	2	20	0	0	20	42
IW/PWMI	0	0	0	0	13	27
IW/RV/ PWMI	0	0	1	17	13	27
Total	10	100	6	100	48	100

[Table/Fig-1]: MI localisation and BNP levels.
ECG - Electrocardiogram, MI - Myocardial Infarction, BNP - B-type natriuretic peptide
Chi-square Test
p-value=0.00001

LVEF %	Number of patients with Mild BNP increase	Per-centage	Number of patients with Moderate BNP increase	Per-centage	Number of patients with Severe BNP increase	Per-centage
≤ 30%	0	0	0	0	11	23
31-40%	1	10	1	17	18	37.5
41-50%	4	40	2	33	19	39.5
51-60%	5	50	3	50	0	0
Total	10	100	6	100	48	100

[Table/Fig-2]: LVEF and BNP levels.
LVEF - Left ventricular ejection fraction, BNP - B-type natriuretic peptide
ANOVA
p-value=0.0001

KILLIP Classifi-cation	Number of patients with Mild BNP increase	Per-centage	Number of patients with Moderate BNP increase	Per-centage	Number of patients with Severe BNP increase	Per-centage
Class I	8	80	4	67	8	17
Class II	2	20	2	33	18	37.5
Class III	0	0	0	0	21	43.5
Class IV	0	0	0	0	1	2
Total	10	100	6	100	48	100

[Table/Fig-3]: Killip classification and BNP levels.
BNP - B-type natriuretic peptide
Fisher's Exact Test
p-value=0.002

Cardiac Troponin I	Number of patients with Mild BNP Increase	Per-centage	Number of patients with Moderate BNP Increase	Per-centage	Number of patients with Severe BNP Increase	Per-centage
≤ 1 ng/ml	7	70	4	67	8	17
1.01-2 ng/ml	3	30	2	33	22	46
2.01-3 ng/ml	0	0	0	0	13	27
3.01-4 ng/ml	0	0	0	0	5	10
Total	10	100	6	100	48	100

[Table/Fig-4]: Cardiac troponin I and BNP levels.
BNP - B-type natriuretic peptide
ANOVA*
p-value= 0.004153

pg/mL has a positive predictive value. Values of 100 to 400 pg/mL is grey area.

The infarct size [12,13] and regional wall motion abnormalities correlate well with BNP levels. Patients with AWMI, low cardiac index and heart failure have increased levels of BNP and have the worst prognosis. Patients with increased levels of BNP in the first six hours have increased risk of mortality. Patients with increased levels in the third to fourth week have increased cardiac related complications in the next five to ten years. BNP is an independent marker of myocardial inflammation and necrosis. This was not proved in TACTICS-TIMI-18 [10]. Dynamic risk profile can be done by serial BNP measurements. When BNP levels are very low and troponin levels, normal patients are at very low risk of cardiovascular events.

In our study, patients with IW MI were divided into only IWMI, IW with RV involvement, IW with PW involvement and IW with PW and RV involvement as in [Table/Fig-1]. In simple terms, mild BNP increase is seen in isolated IWMI patients; whereas, severe BNP increase is seen in patients with IWMI associated RV and PWMI. Among the three groups showing severe BNP increase, the patients with IW/RV MI have the highest incidence [Table/Fig-1]. The cut-off value for this significant BNP level is 900 pg/mL. The difference between groups was significant with a p-value of 0.00001 according to Chi-square test. This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance. Hence, severe BNP increase levels correlates with incidence of IW/RV/PWMI and mild BNP increase levels correlate with incidence of IWMI in ECG.

In studies done by Kaya MG et al., it was found that PWMI with RV involvement had higher BNP values than isolated PW infarction. The study was conducted on 49 patients who were admitted with first attack of IWMI, with and without RV involvement. As per the study, plasma BNP levels were higher in IWMI with RVMI compared to isolated IW MI alone [7]. In the present study also, the same was true, though along with this finding, it was found that the higher levels of BNP is found in IWMI associated with PW alone as well as in PW with RV involvement when compared to isolated IWMI. So, we can conclude that BNP levels correlate with higher incidence of RV involvement.

According to Gunes Y et al., the basal BNP level is an indicator of LVEF [14]. It is a prognostic indicator as well. In a study conducted by Kallistratos MS et al., It was found that plasma BNP levels were related to LVEF. In patients with impaired LVEF, it was observed that the exercise capacity was lower [15]. In the present study, by conventional criteria the association between ECHO LVEF% findings and BNP increase was found to be statistically significant ($p<0.05$). In simple terms, the incidence of lowest LVEF ≤ 30% was highest in severe BNP increase group [Table/Fig-2]. The difference between groups was significant with a p-value of 0.0001 according to ANOVA test. The higher mean LVEF levels, being 51.5%, was measured in mild BNP increase group and the lower mean LVEF being 40.04%, was measured in severe BNP increase group. This indicates that there is a true difference among the study groups and the difference is significant and has not occurred by chance. Hence, severe BNP increase is associated with decreased LVEF% levels. There was a reverse correlation between BNP level and LVEF and the p-value was very significant. The increase in BNP levels inversely correlates with LVEF.

After acute MI, BNP has been identified as an important indicator of prognosis. It has been a prognostic indicator for early and delayed complication of MI and also Killip class [16]. In a study conducted by Grabowski M et al., in patients with STEMI, 126 patients were included [17]. With higher Killip class BNP level was severely increased. In this study, the incidence of Killip classification class I is 80% in mild BNP increase group compared to 67% in moderate BNP increase and 17% in severe BNP increase group. Whereas, the incidence of Killip classification class IV was 0% in mild and moderate BNP increase and 2% in severe BNP increase group [Table/Fig-3]. The major part of patients in class II and III, belonged to the severe BNP increase group, indicating a strong link between Killip classification and BNP increase. The difference between groups was significant with a p-value of 0.002 according to Fisher's exact test. This indicates that there is a true difference among the study groups and the difference was significant and has not occurred by chance. We can hence, conclude that severe BNP increase is associated with higher Killip class.

In our study, the cardiac troponin I levels are significantly high. This is statistically significant. In a study it was proved that for each additional biomarker that was positive the mortality rate doubled [18]. In our study significant increase in Troponin I levels were associated with increase in BNP levels. The incidence of cardiac troponin I levels ≤1 ng/mL is 70% in mild BNP Increase group compared to 67% in moderate BNP Increase and 17% in severe BNP increase group. Similarly, the incidence of cardiac troponin I levels 3.01-4 ng/mL range is 0% in mild and moderate BNP increase and 10% in severe BNP Increase group [Table/Fig-4]. The difference between groups is significant with a p-value of 0.004153 according to ANOVA test. The lowest mean cardiac troponin I levels (0.80 ng/mL) is measured in Mild BNP Increase group and the highest mean cardiac troponin I levels (2.00 ng/mL) is measured in severe BNP Increase group.

LIMITATION

Major limitation of the study was lesser number of patients. The use of ECHO and ECG in the first 24 hours can still be difficult in diagnosing RVMI as RV dysfunction and stunning is frequently transient. Effect of type of treatment on BNP levels was not assessed in this study. Newer biomarkers like NT-proBNP could have been used but it was not used because of its higher cost.

CONCLUSION

Plasma BNP levels are significantly higher in IWMI, when right ventricle is involved. In patients with IWMI right ventricular involvement may be suspected when BNP levels are significantly higher. Severe increase in BNP levels correlate with higher incidence of right ventricular involvement as indicated by occurrence of significant increase in BNP levels in IW/RV/PWMI diagnosed by ECG and ECHO. Isolated IWMI is associated with mild BNP increase. We conclude that severe BNP increase is associated with decreased LVEF. Severe BNP elevations in higher KILLIP classification strongly confirmed prognostic value of BNP.

REFERENCES

[1] Mann, Zipes, Libby, Bonow, Braunwald's Heart disease, A Textbook of cardio-vascular medicine, Vol 1, 10th edition, 2015, Elsevier, pg.1
[2] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI): Effectiveness of intravenous thrombolytic treatment in acute myocardiac infarction. Lancet. 1986;1(8478):397-402.
[3] ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet. 1988;2(8607):349-60.
[4] Watanabe I, Tani S, Washio T, Onikura M, Kumabe N, Hirayanagi K, et al. Relationship between the plasma levels of brain natriuretic peptide and left ventricular ejection fraction in asymptomatic patients with previous myocardial infarction. Int Heart J. 2005;46(6):1007–14.
[5] M Mukoyama, K Nakao, K Hosoda, S Suga, Y Saito, Y Ogawa, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest. 1991;87(4):1402–12.
[6] Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation. 1993;87(2):464–69.
[7] Kaya MG, Ozdogru I, Kalay N, Dogan A, Inanac T, Gul I, et al. Plasma B-type natriuretic peptide in diagnosing inferior myocardial infarction with right ventricular involvement. Coron Artery Dis. 2008;19(8):609–13.
[8] Cannon CP, McCabe CH, Wilcox RG, Langer A, Caspi A, Berink P, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation. 2000;102(2):149-56.

[9] Feit F, Mueller HS, Braunwald E, Ross R, Hodges M, Herman MV, et al. Thrombolysis in Myocardial Infarction (TIMI) phase II trial: outcome comparison of a "conservative strategy" in community versus tertiary hospitals. The TIMI Research Group. J Am Coll Cardiol. 1990;16(7):1529-34.
[10] Januzzi JL Jr, Buros J, Cannon CP; Tactics TIMI 18 Investigators. Peripheral arterial disease, acute coronary syndromes, and early invasive management: the TACTICS TIMI 18 trial. Clin Cardiol. 2005 May;28(5):238-42.
[11] Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, et al. Breathing not properly multinational study investigators. Bedside b-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the breathing not properly multinational study. J Am Coll Cardiol. 2003;41(11):2010-17.
[12] Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation. 2002;106(23):2913-18.
[13] Inoue T, Sakuma M, Yaguchi I, Mizoguchi K, Uchida T, Takayanagi K, et al. Early recanalization and plasma brain natriuretic peptide as an indicator of left ventricular function after acute myocardial infarction. Am Heart J. 2002;143(5):790-96.
[14] Güne Y, Okçün B, Kavlak E, Erbas C, Karcier S. Value of brain natriuretic peptide after acute myocardial infarction. Anadolu Kardiyol Derg. 2008;8(3):182–87.
[15] Kallistratos MS, Dritsas A, Laoutaris ID, Cokinos DV. N-terminal prohormone brain natriuretic peptide as a marker for detecting low functional class patients and candidates for cardiac transplantation: linear correlation with exercise tolerance. J Heart Lung Transplant. 2007;26(5):516–21.
[16] Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Global registry of acute coronary events investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345-53.
[17] Grabowski M, Filipiak KJ, Malek LA, Karpinski G, Huczek Z, Stolarz P, et al. Admission B-type natriuretic peptide assessment improves early risk stratification by Killip classes and TIMI risk score in patients with acute ST elevation myocardial infarction treated with primary angioplasty. Int J Cardiol. 2007;115(3):386-90.
[18] Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation. 2002;105(15):1760-63.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Cardiology, Government Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.
2. Associate Professor, Department of Cardiology, Government Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.
3. Assistant Professor, Department of Cardiology, Government Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.
4. Professor, Department of Anatomy, Chettinad Hospital and Research Institute, Kelambakkam, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Victor Ashok,
7D, KG Towers, 100 Feet Bypass Road, Velachery, Chennai-600042, Tamil Nadu, India.
E-mail: drashokcardio@yahoo.co.in

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 09, 2017**
Date of Peer Review: **May 26, 2017**
Date of Acceptance: **Sep 06, 2017**
Date of Publishing: **Nov 01, 2017**