Open Journal of Endocrine and Metabolic Diseases, **2012, 2, 58-62**
http://dx.doi.org/10.4236/ojemd.2012.24009 Published Online November 2012 (http://www.SciRP.org/journal/ojemd)

Prognostic Value of N-Terminal Pro-Brain Natriuretic Peptide in Acute Pulmonary Embolism

Abdelhakem Selem*, Hanan Radwan, Abdelaziz M. Gomaa
Cardiology Department, Ibn Sina Faculty of Medicine, Zagazig University, Zagazig, Egypt
Email: *drhakeem66@yahoo.com

Received August 3, 2012; revised September 5, 2012; accepted October 6, 2012

ABSTRACT

Patients with pulmonary embolism (PE) have a high risk of death and it is important to recognize factors associated with high mortality. N-Terminal pro-Brain Natriuretic Peptide (NT-pro BNP) has recently emerged as a promising biomarker for risk assessment in acute pulmonary embolism (PE). The aim of this study is to detect the in hospital prognostic value of NT-pro BNP in patients with acute (PE). **Methods:** This study included 64 patients diagnosed as (PE) with the mean age of 59.1 ± 16.5 years, 40 patients of them (62.5%) were male. All patients were subjected to 12 leads ECG. X-ray chest, laboratory tests including D-Dimer, troponin I, NT-pro BNP, Doppler ultrasound for the venous system of both lower limbs, Echocardiograhy and 64 multislices CT pulmonary angiography. **Results:** According to the admission level of NT-pro BNP our patients were divided into two groups: group I included 22 patients with normal NT-pro BNP (less than 300 pg/ml), and group II included 42 patients with elevated NT-pro BNP (more than or equal 300 pg/ml). Patients in group II were found to have a significantly higher incidence of heart failure (28.6% vs 4.6%, $p = 0.025$), impaired kidney function (serum creatinine was 1.7 ± 0.6 vs 1.1 ± 0.2, $p = 0.018$), tachypnea (85.7% vs 54.5%, $p = 0.006$) and cardiogenic shock (26.2% vs 0%, $p = 0.014$) but a significantly lower incidence of chest pain (21.4% vs 45.5%, $p = 0.04$) and lower left ventricular ejection fraction (51.3% ± 16.9% vs 67.3% ± 12.8%, $p = 0.043$) compared to group I. There were a significantly higher treatment with thrombolytic therapy (35.7% vs 9.1%, $p = 0.021$) and positive inotropics (35.71% vs 4.55%, $p = 0.006$) in group II compared to group I. Also group II had a higher need for mechanical ventilation (26.12% vs 4.55%, $p = 0.04$) and a longer in hospital stay (19.5 ± 10.3 vs 5.3 ± 4.5, $p = 0.001$) than group I. The in hospital mortality was significantly higher in group II compared to group I (19.05% vs 0.0%, $p = 0.042$). **Conclusion:** Elevated NT-pro BNP levels in patients with (PE) are associated with worse short term prognosis in terms of higher morbidity and mortality and it could be used as a valuable prognostic parameter and good indicator for the need of more aggressive therapy.

Keywords: Pulmonary Embolism; N-Terminal Pro-Brain Natriuretic Peptide

1. Introduction

Pulmonary embolism is a common and serious disease with an incidence rate in hospitalized patients above 5% [1]. It has a high morbidity and mortality both early and late, the overall mortality is 7% to 11% while late mortality is 15% at three months and reaches 50% in patients presenting with cardiogenic shock on admission [2].

Patients with hemodynamic instability at presentation have a high mortality rate [3]. Hemodynamically stable patients with RV dysfunction have high mortality. However; those patients are more difficult to recognize [4].

PE is caused by either inherited or acquired risk factors. Combination of thrombophilia and acquired risk factors often precipitate overt thrombosis. The two most common genetic causes of thrombophilia are factor V Leiden and prothrombin gene mutation while the most common acquired thrombophilia is anti-phospholipid syndrome. The common acquired causes of PE include: advanced age, personal or family history, recent surgery, trauma, or immobility, congestive heart failure, acute infection, pregnancy, oral contraceptive pills and COPD [5].

Dyspnea is the most common symptom of PE. Other symptoms include chest pain, cough, hemoptysis and syncope. Tachycardia is the most frequent sign of PE. Other signs include tachypnea, left parasternal upleft, tricuspid regurgitation murmer, accentuated pulmonary second sound, and evidence of DVT [5].

Right ventricular dysfunction from PE results from a combination of increased wall stress and cardiac ischemia [6]. Myocradial wall stress is a potent stimulus for increased synthesis and secretion of BNP, which gives

*Corresponding author.

the plausibility of elevation of BNP and NT-pro BNP in the setting of acute PE and right ventricular strain [7].

Accurate risk stratification is of paramount importance in selecting the optimal management of pulmonary embolism. BNP and pro BNP has recently emerged as promising parameters for risk stratification of acute pulmonary embolism [8].

The aim of this study is to detect the prognostic value of N terminal pro BNP in patient with acute pulmonary embolism during the hospital stay.

2. Methodology

This study included 64 patients admitted to the hospital during the period from November 2008 to December 2011 with diagnosis of pulmonary embolism with the mean age of 59.1 ± 16.5 years, 40 patients of them (62.5%) were male. The local ethics committee approved the study protocol and written informed consent was obtained from all stable patients and from the first degree relatives of the unstable patients.

Diagnosis of PE in our study depended primarily upon the presence of high clinical suspicion of PE with either: 1) positive CT pulmonary angiography; or 2) the presence of pulmonary hypertension and right ventricular dilatation by echocardiography plus positive Doppler for DVT.

All patients were subjected to full history taking and clinical examination, standard 12 leads ECG, X-ray chest, laboratory tests including D-Dimer, complete blood count, troponin I, NT-pro BNP, kidney and liver function tests. Doppler ultrasound for the venous system of both lower limbs to detect venous thrombosis, echocardiograhy to assess pulmonary artery pressure, right ventricular diameter, right ventricular free wall motion, tricuspid regurgitation, presence of right ventricular or a trial thrombus and left ventricular ejection fraction were done. Also 64 multislices CT pulmonary angiography was done for all patients during the first 24 hours of admission and was considered as the gold standard for diagnosis of pulmonary embolism.

Exclusion criteria included patients with history of preexisting left ventricular dysfunction and chronic renal impairment, acute coronary syndrome, chronic lung disease with cor-pulmonale and patients with negative D-dimer.

According to the admission levels of NT-pro BNP, our patients were divided into two groups: group I included 22 patients with normal NT-pro BNP (less than 300 pg/ml), and group II included 42 patients with elevated NT-pro BNP (≥300 pg/ml). This cutoff value was previously reported by Vuilleumier *et al*., 2007 [9].

Both groups were compared in terms of demographic data, clinical presentation, laboratory data, ECG, echocardiography, CT pulmonary angiography and hospital course including right sided heart failure, hypotension, cardiogenic shock, needs for thrombolytic therapy or positive inotropic support, needs for mechanical ventilation, duration of hospital stay and number of deaths. Statistical analyses were done using SPSS for windows version 17. Continuous variables were expressed as means and standard deviation and compared by student T test while categorical variables were expressed as percentages and compared by chi square test, and results were considered significant if the *p*-value is <0.05.

3. Results

According to the admission level of NT-pro BNP, our patients were divided into two groups: group I included 22 patients with NT-pro BNP less than 300 pg/ml, and group II included 42 patients with elevated NT-pro BNP (≥300 pg/ml).

We found that there were no significant differences regarding the base line characteristics of the studied population including demographic variables, risk factors for cardiovascular diseases and risk factors for venous thromboembolism except the incidence of heart failure which was found to be statistically significantly higher in group II compared to group I (28.6% vs 4.55%, $p = 0.025$) (**Table 1**).

Patients in group II were found to have a significantly higher incidence of impaired kidney function (serum creatinine was 1.7 ± 0.6 vs 1.1 ± 0.2, $p = 0.018$), tachyp-

Table 1. Patients' characteristics.

Variable	Group I 22	Group II 42	*p*-value
Age, years (mean ± SD)	58.7 ± 12	59.3 ± 15	0.87
Sex male *n* (%)	(14) 63.6%	(26) 61.9%	0.89
Body mass index (mean ± SD)	31.6 ± 5	32.3 ± 6	0.64
Diabetes mellitus *n* (%)	5 (22.7%)	10 (23.8%)	0.92
Hypertension *n* (%)	13 (59.1%)	26 (61.9%)	0.82
Dyslipidemia *n* (%)	9 (40.9%)	19 (45.2%)	0.74
Stable coronary artery disease *n* (%)	3 (13.6%)	6 (14.3%)	0.75
Atrial fibrillation *n* (%)	5 (22.7%)	12 (28.6%)	0.61
Heart failure *n* (%)	1 (4.55%)	12 (28.6%)	0.025
Trauma *n* (%)	1 (4.55%)	3 (7.14%)	0.89
Post operative *n* (%)	3 (13.63%)	6 (14.28%)	0.75
Bed ridden *n* (%)	1 (4.55%)	4 (9.52%)	0.83
Oral contraceptives *n* (%)	2 (9.09%)	3 (7.14%)	0.83

nea (85.7% vs 54.5%, $p = 0.006$) and cardiogenic shock (26.2% vs 0%, $p = 0.014$) but a significantly lower incidence of chest pain (21.4% vs 45.5%, $p = 0.04$) and lower left ventricular ejection fraction (51.3% ± 16.9% vs 67.3% ± 12.8%, $p = 0.043$) compared to group I (**Table 2**).

There were no significant difference between the two groups regarding the electrocardiographic signs of pulmonary embolism but there was a significantly higher incidence of dilatation of the right ventricular diameter (more than 30 mm) assessed by echocardiography in group II compared to group I (88.1% vs 45.45%, $p = 0.001$) (**Table 3**).

There were a significantly higher treatment with thrombolytic therapy (35.7% vs 9.1%, $p = 0.021$) and positive inotropics (35.71% vs 4.55%, $p = 0.006$) in group II compared to group I. Also group II had a higher need for mechanical ventilation (26.12% vs 4.55%, $p = 0.04$) and a longer in hospital stay (19.5 ± 10.3 vs 5.3 ± 4.5, $p = 0.001$) than group I. The in hospital mortality was significantly higher in group II compared to group I (19.05% vs 0.0%, $p = 0.042$) (**Table 4**).

Table 2. Clinical and laboratory data of the studied population.

Variable	Group I 22	Group II 42	*p*-value
Dyspea *n* (%)	19 (86.36%)	40 (95.2%)	0.44
Chest pain *n* (%)	10 (45.45%)	9 (21.4%)	0.04
Hemoptysis *n* (%)	3 (13.63%)	5 (11.9%)	0.84
Syncope *n* (%)	2 (9.09%)	7 (16.67%)	0.65
Cough *n* (%)	2 (9.09%)	4 (9.25%)	0.69
DVT *n* (%)	4 (18.18%)	7 (16.6%)	0.84
Tachypnea *n* (%)	12 (54.54%)	36 (85.7%)	0.006
Heart rate (mean ± SD)	99.5 ± 21.4	105.3 ± 35.2	0.36
Systolic blood pressure (mean ± SD)	130 ± 22.5	120.5 ± 32.6	0.19
Cardiogenic shock (Systolic blood pressure <90 mmHg) *n* (%)	0 (0%)	11 (26.2%)	0.014
D-dimer (mean ± SD)	1936.6 ± 415.7	2317.9 ± 678.4	0.06
Troponin I (mean ± SD)	0.31 ± 0.5	1.1 ± 0.9	0.03
NT-pro BNP (mean ± SD)	179 ± 68	1843 ± 538	0.0001
Serum creatinine (mean ± SD)	1.1 ± 0.2	1.7 ± 0.6	0.018

Table 3. ECG, Echocardiography and CT pulmonary angiography data.

Variable	Group I 22	Group II 42	*p*-value
Sinus tachycardia *n* (%)	10 (45.5%)	31 (73.81%)	0.024
Atrial fibrillation *n* (%)	0 (0%)	2 (4.76%)	0.77
Right bundle branch block *n* (%)	2 (9.09%)	7 (16.67%)	0.65
S1Q3T3 *n* (%)	4 (18.18%)	4 (9.52%)	0.55
T wave inversion in V1-4 *n* (%)	7 (31.82%)	13 (30.95%)	0.94
RV >30 mm n (%)	10 (45.45%)	37 (88.1%)	0.001
Pulmonary artery pressure (mmHg) (mean ± SD)	52.1 ± 24	59.3 ± 18.2	0.65
Right ventricular and right atrial thrombus *n* (%)	1 (4.55%)	2 (4.76%)	0.55
Ejection fraction% (mean ± SD)	67.3 ± 12.8%	51.3 ± 16.9%	0.043
CT pulmonary angiography *n* (%)	19 (86.36%)	40 (95.23%)	0.44
Doppler evidence of DVT *n* (%)	14 (62.64%)	24 (57.14%)	0.61

Table 4. Treatment and prognosis.

Variable	Group I 22	Group II 42	*p*-value
Positive inotropics *n* (%)	1 (4.55%)	15 (35.71%)	0.006
Low molecular weight heparin *n* (%)	22 (100%)	42 (100%)	1.0
Pharmacological thrombolysis *n* (%)	2 (9.09%)	15 (35.7%)	0.021
Duration of hospital stay (mean ± SD)	5.3 ± 4.5	19.5 + 10.3	0.001
Mechanical ventilation *n* (%)	1 (4.55%)	11 (26.19%)	0.04
Hospital mortality *n* (%)	0 (0%)	8 (19.05%)	0.042

4. Discussion

Plasma NT-pro BNP elevation in acute pulmonary embolism is probably caused by increased myocardial sheer stress mainly in the right ventricle and depends on the degree and dynamics of embolus events [10].

Patients presented with overt heart failure and hemodynamic instability are known to have high mortality rate in acute phase of the disease [11] and there is consensus that emergency thrombolytics, interventional or surgical therapies is warranted to save their lives [12].

We found that the most common clinical presentation in our study was dyspnea which was 86.4% in group I and 95% in group II, this was comparable to the result of Dores *et al.*, 2011 who found that dyspnea was 83.3% in patients with less than median pro BNP and it was 87.1% among those with more than median pro BNP.

The incidence of chest pain was significantly higher in group I compared to group II (45.5% vs 21.4%) while the incidence of tachypnea was higher in group II than group I (85.7% vs 54.5%) and this was comparable to the result obtained by Dorese *et al*., 2011 [13].

In our study we found elevated NT-pro BNP at admission in patients with pulmonary embolism correlated significantly with worse in-hospital complications including the need for positive inotropics, the need for thrombolysis, the need for mechanical ventilation and duration of hospital stay as well as in-hospital mortality.

The overall mortality rate in our patients was found to be 12.5% (0% within group I and 19.05% in group II, *p*-value 0.042) this result was consistent with keron [2] 2003 who reported that in-hospital mortality was 7% - 11%. Dores *et al*., 2011 [13] reported that the overall three months mortality was 15% while it was 50% for patients presented with cardiogenic shock.

Recent meta analyses of 32 studies including 1172 patients with pulmonary embolism demonstrated the ability of NT-pro BNP to predict adverse effect and also concluded that in patient with higher NT-pro BNP, the concomitant elevation of Troponin I added a prognostic value [14].

N terminal pro BNP or troponin I combined with Echocardiography reliably identify patients with high risk of pulmonary embolism [8].

Agterof *et al*., 2010 [15] suggested that patients with PE who are hemodynamically stable and with low NT-pro BNP levels (less than 500 pg/ml) can be treated as outpatients, with no increase in complication or adverse events which if confirmed would bring considerable benefits in both clinical and economic terms.

Cavallazi *et al.*, 2008 [7] meta-analyzed 16 studies and concluded that BNP and NT-pro BNP are associated with right ventricular dysfunction in patients with acute PE and are significant predictor of all cause in hospital or short term mortality in these patients.

If both troponin I and BNP levels were normal a low risk population free of adverse clinical outcome likely exists and right ventricular function in echocardiography will almost be normal and these patients may be suitable for short hospital stay [16] or even for outpatient management [17].

In contrast patient with elevated cardiac markers may require immediate triage for ICU, urgent thrombolysis [18] and catheter embolectomy [19] or open surgical embolectomy [20].

Kostrubiec *et al*., 2007 [21] found that persistent elevation of NT-pro BNP 24 hours after diagnosis (reduction of less than 50% from initial values) predicts higher mortality at thirty days. Serial measurements of NT-pro BNP may provide additional prognostic information compared to a single measurement at admission as well as being an indicator of therapeutic efficacy.

Despite its proven relevance for prognostic assessment routine NT-pro BNP measurement is not universally accepted strategy for patients with pulmonary embolism [13].

5. Limitations of the Study

1) We studied a small number of patients because we are working in a low capacity general hospital and not a specified big cardiac center; 2) The cutoff value of NT pro BNP which we used in our analysis was relatively low, 300 pg/ml [9]. However, other authors used a higher different cutoff values of 500 pg/ml [10] 600 [21] and 1000 pg/ml [8].

6. Conclusion

Elevated NT-pro BNP levels in patients with pulmonary embolism are associated with worse short term prognosis in terms of higher morbidity and mortality and it could be used as a valuable prognostic parameter and good indicator for the need of more aggressive therapy.

REFERENCES

[1] J. A. Heit, L. J. Melton, C. M. Lohse, T. M. Petterson, M. D. Silverstein, D. N. Mohr and W. M. O'Fallon, "Incidence of Venous Thromboembolism in Hospitalized Patients vs Community Residents," *Mayo Clinic Proceedings*, 2001, pp. 1102-1110. doi:10.4065/76.11.1102

[2] C. Kearon, "Natural History of Venous Thromboembolism," *Circulation*, Vol. 107, No. 23S1, 2003, pp. 22-30. doi:10.1161/01.CIR.0000078464.82671.78

[3] S. Z. Goldhaber, L. Visani and M. De Rosa, "Acute Pulmonary Embolism: Clinical Outcomes in the International Cooperative Pulmonary Embolism Registery," *Lancet*, Vol. 353, No. 9162, 1999, pp. 1386-1389. doi:10.1016/S0140-6736(98)07534-5

[4] S. Konstantinides, "Pulmonary Embolism: Impact of Right Ventricular Dysfunction," *Current Opinion on Cardiology*, Vol. 20, No. 6, 2005, pp. 496-501. doi:10.1097/01.hco.0000179818.65329.bb

[5] S. Z. Glodhabber, "Pulmonary Embolism. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine," 9th Edition, Saunders, 2012.

[6] S. Z. Goldhaber, "Pulmonary Embolism," *Lancet*, Vol. 363, No. 9417, 2004, pp. 1295-1305. doi:10.1016/S0140-6736(04)16004-2

[7] R. Cavallazzi, A. Nair, T. Vasu and P. E. Marik, "Natriuretic Peptides in Acute Pulmonary Embolism: A Systematic Review Published Online," Vol. 34, No. 12, 2008, pp. 2147-2156.

[8] L. Binder, B. Pieske, M. Olschewski, A. Geibel, B. Klostermann, C. Reiner and S. Konstantinides, "N-Terminal Pro-Brain Natriuretic Peptide or Troponin Testing Followed by Echocardiography for Risk Stratification of Acute Pulmonary Embolism," *Circulation*, Vol. 112, No. 11, 2005, pp. 1573-1579. doi:10.1161/CIRCULATIONAHA.105.552216

[9] N. Vuilleumier, M. Righini, A. Perrier, A. Rosset, N. Turck, J. C. Sanchez, H. Bounameaux, G. Le Gal, N. Mensi and D. Hochstrasser, "Correlation between Cardiac Biomarkers and Right Ventricular Enlargement on Chest CT in Non Massive Pulmonary Embolism," *Thombo Research*, Vol. 121, No. 5, 2008, pp. 617-624. doi:10.1016/j.thromres.2007.07.003

[10] N. Kucher, G. Printzen and S. Z. Goldhaber, "Prognostic Role of Brain Natriuretic Peptide in Acute Pulmonary Embolism," *Circulation*, Vol. 107, No. 20, 2003, pp. 2545-2547. doi:10.1161/01.CIR.0000074039.45523.BE

[11] W. Kasper, S. Konstantinides, A. Geibel, M. Olschewski, F. Heinrich, K. D. Grosser, K. Rauber, S. Iversen, M. Redecker and J. Kienast, "Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry," *Journal of American College Cardiology*, Vol. 30, No. 5, 1997, pp. 1165-1171. doi:10.1016/S0735-1097(97)00319-7

[12] "British Thoracic Society Guidelines for the Management of Suspected Acute Pulmonary Embolism," *Thorax*, Vol. 58, No. 6, 2003, pp. 470-483. doi:10.1136/thorax.58.6.470

[13] H. Dores, C. Fonseca, S. Leal, I. Rosário, J. Abecasis, J. Monge, M. J. Correia, L. Bronze, A. Leitão, I. Arroja, A. Aleixo and A. Silva, "NT-pro BNP for Risk Stratification of Pulmonary Embolism," *Portuguese Journal of Cardiology*, Vol. 30, No. 12, 2011, pp. 881-886.

[14] J. C. Lega, Y. Lacasse, L. Lakhal and S. Provencher, "Natriuretic Peptides and Troponins in Pulmonary Embolism: A Meta-Analysis," *Thorax*, Vol. 64, No. 10, 2009, pp. 869-875. doi:10.1136/thx.2008.110965

[15] M. J. Agterof, R. E. Schutgens, R. J. Snijder, G. Epping, H. G. Peltenburg, E. F. Posthuma, J. A. Hardeman, R. van der Griend, T. Koster, M. H. Prins and D. H. Biesma, "Out of Hospital Treatment of Acute Pulmonary Embolism in Patients with a Low NT-pro BNP Level," *Journal of Thromb Haemost*, Vol. 8, No. 6, 2010, pp. 1235-1241. doi:10.1111/j.1538-7836.2010.03831.x

[16] Columbus Investigators, "Low-Molecular-Weight Heparin in the Treatment of Patients with Venous Thromboembolism," *New England Journal of Medicine*, Vol. 337, No. 10, 1997, pp. 657-662. doi:10.1056/NEJM199709043371001

[17] J. H. Beer, M. Burger, S. Gretener, S. Bernard-Bagattini and H. Bounameaux, "Outpatient Treatment of Pulmonary Embolism Is Feasible and Safe in a Substantial Proportion of Patients," *Journal of Thromb Haemost*, Vol. 1, No. 1, 2003, pp. 186-187. doi:10.1046/j.1538-7836.2003.00005.x

[18] S. Konstantinides, A. Geibel, G. Heusel, F. Heinrich and W. Kasper, "Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin Plus Alteplase Compared with Heparin Alone in Patients with Submassive Pulmonary Embolism," *New England Journal of Medicine*, Vol. 347, No. 15, 2002, pp. 1143-1150. doi:10.1056/NEJMoa021274

[19] T. Schmitz-Rode, U. Janssens, S. H. Duda, C. M. Erley and R. W. Günther, "Massive Pulmonary Embolism: Percutaneous Emergency Treatment by Pigtail Rotation Catheter," *Journal of American College Cardiology*, Vol. 36, No. 2, 2000, pp. 375-380. doi:10.1016/S0735-1097(00)00734-8

[20] L. Aklog, C. S. Williams, J. G. Byrne and S. Z. Goldhaber, "Acute Pulmonary Embolectomy: A Contemporary Approach," *Circulation*, 2002, Vol. 105, No. 12, pp. 1416 - 1419. doi:10.1161/01.CIR.0000012526.21603.25

[21] M. Kostrubiec, P. Pruszczyk, A. Kaczynska and N. Kucher, "Persistent NT-pro BNP Elevation in Acute Pulmonary Embolism Predicts Early Death," *Clinica Chimica Acta*, Vol. 382, No. 1-2, 2007, pp. 124-128. doi:10.1016/j.cca.2007.04.010

Abbreviations

PE = pulmonary embolism; DVT = deep venous thrombosis; RV = right ventricle; BNP = brain natriuretic peptide; NT-pro BNP = N terminal pro brain natriuretic peptide.

