Original Article

Association of Levels of N-terminal-Pro-B-Type Natriuretic Peptide with Localisation of Thrombus in Acute Pulmonary Embolism

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ABSTRACT

Background and objectives. Brain-natriuretic peptide (BNP) is a potent natriuretic, diuretic hormone that is released from heart into the circulation. We aimed to investigate whether N-terminal-pro-BNP (pro-BNP) could predict localisation of thrombus in patients with acute pulmonary embolism.

Methods. Emergency patients found to have thrombosis in the pulmonary artery on helical computed tomography were enrolled. The thrombi which were localised in the main/right or left pulmonary artery were classified as central and those at segmentary/sub-segmentary levels as peripheral. The patients were evaluated by an echocardiogram and pro-BNP levels were measured.

Results. Forty-nine patients were enrolled. The thrombus was unilateraly located in 63.3 percent patients and peripherally in 81.6 percent. The difference in pro-BNP levels between those with central and peripheral thrombi was significant ($p<0.05$). Pro-BNP levels of patients with and without evidence of right ventricular overload (pulmonary hypertension, right heart dilatation, interventricular septal hypokinaesia) were also significantly different (respectively, $p<0.001$, $p<0.01$, $p<0.01$). The pro-BNP levels of patients who were followed up in the intensive care unit and needed thrombolytic treatment were significantly higher (respectively $p<0.001$, $p<0.01$).

Conclusions. Higher pro-BNP levels indicate higher probability of more central location of thrombus, resulting in a more adverse clinical course. Further studies are needed to determine the predictive values of pro-BNP levels for localisation of pulomnary embolus. **[Indian J Chest Dis Allied Sci 2012;54:223-226]**

Key words: Computed tomography, Pro-BNP, Pulmonary embolism, Thrombus.

INTRODUCTION

Brain-natriuretic peptide (BNP) is a potent natriuretic and diuretic hormone which has a smooth muscle relaxant effect and is released from heart into the circulation. The levels of BNP are increased in patients with congestive heart failure and acute myocardial infarction. It serves as a marker for right ventricular dysfunction in acute pulmonary embolism.[1] The aim of the study was to investigate whether N-terminal-pro-BNP (pro-BNP) could predict the localisation of thrombus in patients with acute pulmonary embolism, as this is an important consideration in the management.

MATERIAL AND METHODS

The patients who presented to the emergency department with acute onset of dyspnoea, chest pain and/or haemoptysis and who had high levels of D-Dimer (>0.5 pg FEU/mL) were evaluated with helical computed tomography (CT) within 24 hours, for suspected pulmonary embolism. Simplified Revised Geneva, Wells and Miniati clinical scores were calculated. Acquired risk factors for developing venous thromboembolism (VTE) including surgery, malignancy, trauma, immobility, estrogen therapy, previous VTE and any hereditary risk factor were noted. Patients who had thrombus on helical CT were enrolled in the study.

Ejection fraction, functions of right and left ventricule and pulmonary arterial pressure were evaluated by echocardiogram. Pro-BNP levels were evaluated by ROCHE Elecsys-ProBNP assay. The assay uses two polyclonal antibodies, one of which is labeled with ruthenium complex and measures the inactive cleavage product of BNP, NT-pro-BNP. The

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electrochemiluminescent test is performed on the automated Elecsys immunoassay analyser and requires 18 minutes to first result. Two cut-offs are used, one at 125 pg/mL for patients less than 75 years old and a second cut-off at 450 pg/mL for patients more than 75 years of age.[5] Those who had clinical conditions that may cause an increase in pro-BNP levels, such as congestive heart failure (ejection factor <50%), chronic lung diseases that can cause cor-pulmonale (e.g., chronic obstructive lung disease, interstitial lung disease) and renal failure were excluded.

The study had approval of the Ethics Committee of Ufuk University. Informed consents from all patients were taken before inclusion in the study.

The D-Dimer levels were measured with the Tina-quant® D-Dimer Test system that is a particle enhanced immunoturbidimetric assay. All CT studies were analysed on a multi-slice work-station (GE LightSpeed ®[16]). Echocardiogram was performed and pro-BNP levels were measured within 24 hours.

Arterial blood gas analysis was performed in all patients. Thrombi that were localised in the main/ right or left pulmonary artery on helical CT were classified as central while the ones that were present at segmental/sub-segmental levels were classified as peripheral.

The association between pro-BNP levels and localisation of thrombus on helical CT, and echocardiogram findings (right heart dilatation, presence of pulmonary hypertension and/or interventricular septal hypokinaesia) and clinical course (out-patient treatment, hospitalisation, need for intensive care unit, need for thrombolytic treatment) were evaluated. The levels of pro-BNP and the three clinical scorings accross probability cateogries according to simplified Revised Geneva, Wells and Miniati scores were also evaluated.

Statistical Analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) (version 15). Continuous variables are presented as mean±standard deviation or median [min-max] and categorical variables as percentages. Differences between the groups were determined by Mann-Whitney or Kruskal-Wallis test as the variables were not normally distributed. Significance value was considered as $p<0.05$. Pro-BNP levels are expressed as pg/mL.

RESULTS

Forty-nine patients were enrolled in the study. Their mean age was 67.3±13.4 years. Twenty-four (49%) were females. Forty-three of the patients (87.8%) had acquired risk factors. None of the patients had any known hereditary risk factor for VTE. The clinical features of patients are presented in table 1. The thrombi of 31 (63.3%) patients were unilateraly located, while these were bilateral in 18 (36.7%). The thrombi were peripheral in 40 (81.6%) and central in 9 (18.4%).

Table 1. Clinical features of patients

	Female (n=24)	Male (n=25)	Total
Comorbidities			
Malignancy	2	3	**5**
Hypertension	2	1	**3**
Hyperlipidemia	2	2	**4**
Diabetes mellitus	1	3	**4**
Acquired Risk Factor for VTE			
Surgery	8	7	**15**
Previous VTE	2	1	**3**
Trauma	1	3	**4**
Malignancy	2	3	**5**
Immobility	8	4	**12**
Obesity	2	2	**4**
	23	**20**	**43**
No Risk Factor for VTE	1	5	**6**
Total	**24**	**25**	**49**

VTE=Venous thromboembolism

There was no statistically significant difference between pro-BNP levels of the patients who had unilaterally and bilaterally located pulmonary embolus ($p>0.05$). The mean pro-BNP levels in patients who had central thrombi were 2902.2±3899.3 and 821.7±1778.8 in patients who had peripheral thrombi. The difference was significant ($p<0.05$). In patients who had unilateral thrombi, significant differences were found between those with central and peripheral thrombi ($p<0.05$). While the pro-BNP levels in patients with bilateral and central thrombi were higher than bilateral and peripheral thrombi, the differences were not statistically significant ($p>0.05$).

The mean pro-BNP levels in patients who had pulmonary hypertension on echocardiogram were 2264±3193 while in those without pulmonary hypertension, the levels were 408.4±1081.6. The difference between the two groups was statistically significant ($p<0.001$). Similarly, patients who had dilatation of the right atrium and ventricule had significantly higher levels of pro-BNP than those who did not (3118.9±3779 *versus* 512.2±1076, respectively, [$p<0.01$]). The differences between pro-BNP levels in patients with and without hypokinaesia on interventricular septum on echocardiogram was also significant, the levels being 4279±4225 *versus* 603.7±1239, respectively ($p<0.01$). The mean and

median pro-BNP levels according to localisation on helical CT and echocardiogram findings are presented in table 2.

Table 2. Pro-BNP levels according to localisation of thrombus and echocardiogram findings

	Mean	Median (range)	p Value
Localisation of Thrombus			
Unilateral	907.6±2030.4	227 (24-10171)	>0.05
Bilateral	1713.9±2928.2	175 (16.4-9029)	
Central	2902.2±3899.3	1105 (16.46-1-171)	>0.05
Peripheral	821.7±1778.8	158 (18.4-8498)	
Echocardiogram			
Pulmonary hypertension present	2264±3193	797 (62-10171)	<0.001
Pulmonary hypertension absent	408.4±1081.6	135 (16.4-5722)	
Dilatation of right atrium and ventricule present	3118.9±3779	1105 (62-10171)	0.003
Dilatation of right atrium and ventricule absent	512.2±107	146 (16.4-5722)	
Interventricular septal hypokinaesia present	4279±4225	2546 (62-10171)	0.003
Interventricular hypokinaesia absent	603.7±1239	148 (16.4-5722)	

The pro-BNP levels in patients who required treatment in intensive care unit were significantly higher than who were managed in the in-patient clinic ($p<0.001$). The patients who required thrombolytic treatment had higher levels of pro-BNP than those did not ($p<0.01$). When the levels of pro-BNP in patients who had low, intermediate and high probability for pulmonary embolism according to all three clinical scoring systems were compared, those who had high clinical probability according to Simplified Revised Geneva scoring had significantly higher levels of pro-BNP ($p<0.001$) (Table 3). Otherwise, there was no statistically significant difference between different clinical probabilities according to Wells and Miniati scoring systems ($p>0.05$) (Table 3).

Table 3. Pro-BNP levels according to Simplified Revised Geneva, Wells and Miniati scorings

	Mean	Median (range)	p Value
Simplified Revised Geneva			
Unlikely	176.7±206.2	129 (16.4-1038)	<0.001
Likely	2189.8±3070	797 (18.4-10171)	
Wells			
Low	236±186	160 (115-508)	>0.05
Intermediate	994±2070	156 (16.4-10171)	
High	2471±3654	481 (18.4-9029)	
Miniati			
Low	1092±1901	379 (100-5722)	>0.05
Intermediate	1558±2637.5	293 (138-5509)	
High	1189±2528	168 (16.4-10171)	

DISCUSSION

Acute pulmonary embolism shows wide variations in clinical presentation from asymptomatic course to a massive pulmonary embolism that may be fatal. When planning treatment of disease early, risk classification is important. The patients who have high risk of complicated clinical course and death need more agressive treatment and monitoring. Otherwise, those who have low risk can be externed from hospital in a short time or may not ever need hospitalisation.[6,7] The amount of pulmonary vascular bed that is affected determines the clinical course of patient. The increase of this amount proportionally increases stress on the right heart. Bio-markers, like BNP and troponins, have been found to be related to high risk of mortality, serious adverse events and right ventricular dysfunction.[8]

Pulmonary vascular resistance increases during acute pulmonary embolism due to obstruction of a part of the pulmonary vascular bed and also hypoxic vasoconstriction. Increased right ventricular overload can cause right ventricular dilatation resulting in myocardial stretch.[9] Pro-BNP is released as a result of myocardial strain. In this study, patients who had clinical conditions that can cause myocardial stretch like congestive heart failure, cor-pulmonale and renal failure were excluded. The affect of ageing had already been accounted for the assay that was used to measure pro-BNP levels by using second cut-off level for elderly patients. So, in the present study, the increased serum levels of pro-BNP were related to the amount of pulmonary vascular bed that was affected. It is likely that location of thrombus determines the amount of vascular bed that is affected as a result of acute pulmonary embolism.

Pro-BNP levels of patients with centrally located thrombi had higher levels than those with peripheral ones. Earlier Alonso-Martinez *et al*[10] found that centrally located thrombi resulted in higher levels of pro-BNP.

We also evaluated the relationship between clinical probabilities according to three different clinical scoring systems (Simplified Revised Geneva, Wells and Miniati) with pro-BNP levels. Only clinical probabilities of patients according to Simplified Revised Geneva scoring had a significant association with pro-BNP levels. These clinical scorings were developed to estimate clinical probability of pulmonary embolism and these have similar accuracy.[11] Higher pro-BNP levels imply that acute pulmonary embolism is more likely to have adverse clinical outcomes. Therefore, from the results of the present study, the Simplified Revised Geneva clinical scoring appears to be more predictive of adverse clinical course than the other two scoring systems.

Recently, Yetkin *et al*[12] showed that BNP levels in patients with acute pulmonary embolism significantly correlated with pulmonary arterial pressure. In our study, patients who had pulmonary hypertension, dilatation of right heart spaces and interventricular septal hypokinaesia had higher levels of pro-BNP, confirming the above study. Another study[1] showed that high levels of pro-BNP distinguished patients with pulmonary embolism who had a higher risk of a complicated clinical course, were not sufficient to determine more invasive treatment. In the present study, patients who required thrombolytic treatment had higher levels of pro-BNP than those in whom anticoagulant treatment alone was adequate. The cut-offs of pro-BNP levels that mostly help to determine the treatment remain to be determined. It was shown that BNP has also a prognostic role in acute pulmonary embolism, the patients with adverse clinical events having higher levels of BNP.[13] In the present study, adverse events accompanying acute pulmonary embolism were not evaluated, but as an indirect indicator of a complicated clinical course, patients who need thrombolytic treatment and those who needed follow-up in intensive care unit had higher levels of pro-BNP.

The present study have a few limitations. First, the number of patients is limited and does not allow to determination cutt-off levels of pro-BNP for more invasive treatment. Further studies including larger number of patients are necessary to clarify this point. Secondly, following synthesis of precursor of BNP intracellulary as a result of myocardial stretch, it is processed to a pro-hormone and then cleaved into BNP and inactive N-terminal fragments, like pro-BNP.[14,15] Thus, after start of myocardial strech following acute pulmoary embolism, increase of serum pro-BNP levels are delayed several hours. Blood sample collection from patients in the first few hours of pulmonary embolism lead to false negative results. Serial measurements of pro-BNP levels (e.g., on admision, and 6 hours later) may overcome the limitations.

CONCLUSIONS

Higher pro-BNP levels indicate higher probability of a more central location of thrombus in pulmonary embolism, resulting a more adverse clinical course and also leading to right ventricular overload. Further studies with larger number of patients are needed to determine exact cut-off levels of pro-BNP to help in treatment decisions. Simplified Revised Geneva score appears to be more valuable to predict higher pro-BNP levels, and thus, indicates more adverse clinical course in acute pulmonary embolism.

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