Prognostic value of brain natriuretic peptide and troponin I in moderate and high risk pulmonary embolism

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ABSTRACT

Background
Brain natriuretic peptide (BNP) and troponins are useful markers for risk stratification in pulmonary embolism (PE). However, it is not clear which of the two biomarkers has better association with the clinical severity of this condition.

Objective
The aim of this study was to assess both biomarkers in moderate and high risk populations.

Methods
A prospective study was undertaken to analyze all patients diagnosed with PE who had positive troponin I (TI) or BNP levels. An echocardiogram within the first 24 hours and clinical follow up during hospitalization were performed on these patients. A composite endpoint of death, recurrent PE, shock, hypotension, mechanical respiratory assistance and thrombolytic therapy was established. The association of both serum markers with the described events was assessed.

Results
Seventy one consecutive patients were included in this study. Patients with moderate or severe right ventricular dysfunction had higher BNP levels (661 pg/ml (420-1113) vs. 316 pg/ml (129-570) p=0.002) without significant difference in TI levels (0.115 ng/ml (0.015-0.345) vs. 0.24 ng/ml (0.076-0.58) p=0.0788). BNP levels were higher in patients with composite endpoint [604 pg/ml (370-934) vs. 316 pg/ml (148-900) p=0.042], whereas no similar association was found for TI [0.12 ng/ml (0.037-0.48) vs. 0.13 ng/ml (0.07-0.41) p=0.46].

Conclusions
BNP showed higher values in patients with right ventricular dysfunction and composite endpoint, indicating its greater sensitivity to identify patients with more severe clinical involvement.

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Key words > Pulmonary Embolism - Brain Natriuretic Peptide - Troponin – Risk stratification

Abbreviations >

BNP	Brain natriuretic peptide	**NT-proBNP**	N-terminal pro-brain natriuretic peptide
RVD	Right ventricular dysfunction	**PE**	Pulmonary embolism
ACE	Adverse clinical events	**TI**	Troponn I

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BACKGROUND

The incidence of venous thromboembolism is 2.1 cases per 1000 subjects/year and close to 1% annually in elderly subjects over 70 years. (1, 2) Thromboembolism is one of the leading causes of death in hospitalized patients and an important cause of morbidity and mortality, especially in elderly subjects and among those with malignant neoplasias. (3)

Pulmonary embolism (PE) is the most relevant clinical presentation of venous thromboembolism, and the treatment of choice is influenced by the severity of the clinical presentation. (4)

In the past decade, different researches were performed with the aim of achieving risk stratification in PE patients. One of the first findings was the correlation among different biomarkers of stress or myocardial injury [brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-Pro BNP) and troponins] and right ventricular dilatation or dysfunction evidenced by echocardiography or computed tomography. (5-9) Right ventricle involvement has relevant prognostic implications, since it has been associated with higher morbimortality. Similarly, BNP serum levels and troponins have been associated with shorter survival and a higher rate of complications in subjects with PE. (10-15)

However, current studies have not compared both biomarkers jointly in patients with clinically relevant (moderate or high risk) PE.

The aims of this study were: 1) to describe clinical, diagnostic, prognostic and therapeutic characteristics in a moderate to high risk PE population, 2) to determine the association between troponin I (TI) and BNP with right ventricular dysfunction (RVD) estimated by echocardiography, 3) to establish the association between TI and BNP serum levels with adverse clinical events (ACE) or the need of a more complex treatment according to the severity of the medical condition.

METHODS

Sample selection

A prospective registry of a consecutive population sample diagnosed with PE between October 2007 and January 2011 was obtained from the Coronary Care Unit of the Hospital Italiano of Buenos Aires.

Inclusion criteria were patients admitted to the Coronary Care Unit with PE diagnosis and at least one positive serum marker (BNP > 90 pg/ml or TI > 0.04 ng/ml). Included patients had to have confirmed PE diagnosis by thoracic angiotomography, pulmonary angiography, conclusive pulmonary scintigraphy, or indirect PE diagnosis (echocardiography suggestive of PE ± venous echo Doppler of the lower limbs showing deep vein thrombosis) for patients with high clinical probability and who were in no condition of being transferred for study by a specific diagnostic method.

Serum markers

BNP serum level was determined by chemoluminiscence (Beckman), with the following normal values provided by the manufacturer: < 45 years, mean 12 pg/ml (95th percentile: 33 pg/ml), 45-74 years, 22 pg/ml (95th percentile: 73 pg/ml), > 74 years, mean 61 pg/ml (95th percentile: 176 pg/ml). Inter-assay and intra-assay BNP coefficient of variation was 2.69% (100 pg/ml level).

TI serum level was determined by chemoluminiscence (Beckman), with a 99th percentile cut-off value of 0.04 ng/ml for the healthy population and a coefficient of variation of 4.61% (0.49 ng/ml level) provided by the manufacturer.

The blood sample was collected and processed upon patient admission to the emergency department or the coronary care unit if the patient was already hospitalized in another hospital section. BNP and TI values were expressed in pg/ml and ng/ml, respectively.

Echocardiogram

A transthoracic color Doppler echocardiography was performed within the first 24 hours of admission to the coronary care unit. It was done without transferring the patient and in charge of an operator blinded to lab results. A qualitative report was made and the following variables of interest were considered: right ventricular systolic function (classified as normal, mild, moderate or severe dysfunction), dilatation of the right heart chambers, tricuspid insufficiency, pulmonary hypertension, interventricular septal thinning and thrombus in transit. Moderate and severe RVD were considered relevant.

Clinical variables

Clinical variables were acquired during the physical exam, chest X-ray, electrocardiogram and routine lab tests, at admission and throughout in-hospital follow-up. Points of interest, such as intra-hospital hypotension (persistent systolic blood pressure < 90 mm Hg for 15 minutes, in absence of any other justifiable cause), signs of shock, mechanical respiratory assistance, mortality and PE recurrence, were specified. Moreover, the adopted treatment and incidence of major bleeding (>10 points hematocrit decrease, in a noncompressible, intracranial site, requiring two or more red blood cell units or surgery) were analyzed.

Therapeutic conduct

Treatment was conducted by the coronary care unit medical teams who were independent from the registry. In all cases, medical conduct was guided by the collection of clinical signs indicative of PE severity, bleeding risk and in some occasions by echocardiographic findings, without considering serum marker levels for decision making.

Clinical events

A composite endpoint of ACE: hypotension, signs of shock, mechanical respiratory assistance, thrombolytic therapy, PE recurrence or intrahospital mortality for any cause was established.

Statistical analysis

Continuous data between two groups were analyzed with the t test for normal variables or with the Mann-Whitney-Wilcoxon test when the distribution was not normal. Logistic regression models were built to establish the association between BNP and TI with relevant RVD and ACE, adjusted for age, gender, heart rate, systolic pressure and electrocardiographic signs of PE, expressing the results as odds ratio (OR). BNP and TI were expressed as median ± interquartile range. The rest of the continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. Statistical significance was considered for $p < 0.05$.

The study was performed following the recommendations for medical research suggested by the Helsinki Declaration, the Guidelines of Good Clinical Practice and the local Ethics Committee regulations.

RESULTS

Descriptive population analysis

Seventy one patients were included in the study, 69% were women and mean age was 72 ± 12 years. Five of the included patients were admitted with hypotension, 2 with respiratory failure and the rest were hemodynamically stable. Basal population characteristics are detailed in Table 1.

Sixty nine percent of the patients presented at least one clinical risk factor for thromboembolic disease. The main symptom was dyspnea (91%) and diagnostic thoracic angiotomography was performed in 84% of the cases. Jugular ingurgitation as a clinical sign of severity was found in 52% of the patients and the "S1Q3T3" pattern in the electrocardiogram was detected in 51% of the cases. Intrahospital mortality was 9.8%. Thrombolytic therapy was administered in 21 patients (20.6%), mainly because of clear signs of shock or sustained hypotension (52% of the cases). Major bleeding was present in 5 patients (7%), one of whom was treated with heparin and the other 4 with thrombolytic therapy; in all of them the indication was for shock or hypotension. Nineteen patients (26.7%) had absolute or relative contraindication for the administration of thrombolytic therapy (recent surgery, polytrauma or active bleeding).

There was no age difference between patients with or without the composite endpoint (71 ± 13 years vs. 77 ± 11 years, respectively; p = 0.23). The analysis of the different endpoint components showed that there was a greater tendency for use of thrombolytic therapy in the low-age group of elderly patients (71 ± 13 years vs. 77 ± 11 years; p = 0.059), without differences in the rest of the analyzed events.

TI and BNP levels were 0.124 ng/ml (0.05-0.42) and 492 pg/ml (223-900), respectively. The echocardiogram showed a certain degree of RVD in 90 % of the cases. The dysfunction was moderate or severe in 52% of the patients (relevant RVD). Clinical characteristics and intrahospital outcome are shown in Table 2.

Two of the 5 patients admitted with hypotension received systematic thrombolytic therapy and survived. On the other hand, of the 2 patients admitted with respiratory failure one was treated with fragmentation and endovascular thromboaspiration and surviced.

Association between BNP and TI levels with RVD and ACE

Patients with relevant RVD showed a significantly higher BNP level [661 pg/ml (420-1.113)] than those with normal or slightly compromised right ventricular function [316 pg/ml (129-570); p = 0.002].

No significant differences were found in TI levels in patients with or without relevant RVD (0.115 ng/ml vs. 0.24 ng/ml; p = 0.08).

Table 1. Basal population characteristics

	n = 71
Continuous Variables, mean ± SD	
Age, years	72 ± 12
Categorical Variables, n (%)	
Women	49 (69)
Risk factors	
Surgery in the last month	16 (23)
Orthopedic or neurological	8 (11)
Other	8 (11)
Previous DVT-PE	8 (11)
Long journey	4 (5,6)
Known neoplasia	13 (18)
Previous fracture or trauma	6 (8,4)
Obesity	16 (23)
Oral contraconceptives	2 (2,8)
Prothrombotic disorder	1 (1,4)
Pregnancy	1 (1,4)
Previous hospitalization	1 (1,4)

SD: Standard deviation. PE: Pulmonary thromboembolism. DVT: Deep vein thrombosis.

Moreover, in the analysis of patients with and without ACE, BNP levels were higher in patients presenting the composite endpoint [604 pg/ml (370-934) vs. 316 pg/ml (148-900); p = 0.042], while serum TI values did not show differences when both groups were compared [0.12 ng/ml (0.037-0.48) vs. 0.13 ng/ml (0.07-0.41); p = 0.46]. The analysis of the different components of the composite endpoint showed that use of thrombolytic therapy was the only variable with significant differences in BNP levels [716 pg/ml (425-1.133) vs. 412 pg/ml (153-853); p = 0.035].

After all patients with initial hypotension and respiratory failure were excluded from the analysis, BNP levels continued to be higher in those patients with relevant RVD and ACE [697 pg/ml (429-1.051) vs. 314 pg/ml (110-541); p = 0.0017; and 697 pg/ml (412-1051) vs. 316 pg/ml (148-900); p = 0.03, respectively].

Regardless gender, age, heart rate, initial blood pressure and the electrocardiographic signs at admission, there was a significant association between BNP and relevant RVD (OR 1.003, 95% CI 1.001-1.004; p = 0.008) or ACE (OR 1.001, 95% CI 1.0001-1.002; p = 0.023). The association between BNP levels expressed in quintiles and relevant RVD or ACE is shown in Tables 3 and 4 and Figure 1. Conversely, no independent association was observed between TI and RVD (OR 6.45, 95% CI 0.9-46; p = 0.07) or ACE (OR 1.37, 95% CI 0.54-3.51, p = 0.51).

DISCUSSION

PE is a highly prevalent pathology with great risk variation according to its presentation, close to 0% in low risk cases, and about 25-58% in high risk cases. (6, 16-19) On the other hand, more than 50% of PE

Table 2. Clinical characteristics and outcome

Physical exam	
SBP mm Hg (± SD)	121 (21)
HR (± SD)	101 (20)
RR (± SD)	24 (6)
Signs of right-sided heart failure, n (%)	37 (52,0)
Electrocardiogram, n (%)	
S1Q3T3 pattern	35 (51,4)
Inverted T wave V1-V4	30 (43,4)
Right bundle branch block	10 (14,7)
AF/AFL	5 (7,2)
Diagnosis, n (%)	
Angiography	2 (2,8)
Pulmonary scintigraphy	4 (5,6)
Thoracic angiotomography	60 (84,5)
Indiret diagnosis	5 (7,0)
Serum markers, median (RIC)	
Troponin I (ng/ml)	0,124 (0,05-0,42)
BNP (pg/ml)	492 (223-900)
Ultrasound, n (%)	
Right ventricular dilatationa	57 (90,4)
Moderate-severe RVDb	31 (52,5)
IVS thinningc	27 (47,4)
Pulmonary hypertensiond	50 (86,2)
Thrombus in right heart chambersa	1 (1,6)
Deep vein thrombosise	28 (62,2)
Clinical outcome, n (%)	
Adverse clinical outcome	28 (39,4)
Death	7 (9,8)
Shock	15 (21,1)
Hypotension	15 (21,1)
Inotropic therapy	16 (22,5)
Assisted mechanical respiration	11 (15,5)
Thrombolytic therapy	21 (29,6)
Recurrent PE	2 (2,8)
Major bleeding	5 (7,0)

AFL: Atrial flutter. BNP: Brain natriuretic peptide. SD: Standard deviation. RVD: Right ventricular dysfunction. AF: Atrial fibrillation. HR: Heart rate. RR: Respiratory rate. IQR: Interquartile range. IVS: Interventricular septum. SBP: Systolic blood pressure.
a The total number of evaluated patients was 63.
b The total number of evaluated patients was 59.
c The total number of evaluated patients was 57.
d The total number of evaluated patients was 58.
e The total number of evaluated patients was 45.

cases correspond to low risk levels both in registries as well as in the majority of studies performed with prognostic biomarkers. (6, 8, 9, 11, 13, 18) To date, several studies performed with serum biomarkers in PE patients show that they can discriminate between patients with or without relevant RVD and with similar endpoints to our composite ACE.

As a result of these findings, diagnostic algorithms have been generated for PE management, suggesting the use of BNP or TI as a first step in risk stratification. (20) Considering that the physiopathology of hemodynamic deterioration is mainly based on RVD, it is reasonable to think that serum biomarkers related to the latter are associated to ACE.

So far, PE risk stratification studies have been set up in a scenario in which two clearly distinct populations coexist: group I, without RVD (approximately 50% of all patients) with an extremely low intrinsic risk of ACE and where serum biomarkers (BNP and troponins) will be negative in the majority of cases, (21, 22) and group II, with RVD, moderate or high intrinsic risk of ACE and where serum biomarkers will be frequently positive. (6, 11) Therefore, it is easy to establish a strong association between both biomarkers and the clinical events similar to the ones described as ACE in this work. The results of different studies set up in this scenario have strongly positioned both BNP and troponins as detection methods to rule out RVD and ACE when they are negative.

However, so far, these biomarkers are not very useful to define a better approach to risk evaluation, turning essential right ventricular assessment by an imaging method. (22)

The purpose of this study was to evaluate the association of both biomarkers with RVD and clinical outcome in a group of more compromised patients, approximately 90% of which had moderate to high risk. BNP was significantly associated with relevant RVD and ACE, even adjusting by gender, age, systolic pressure, heart rate and electrocardiographic changes. Dividing the population in BNP quintiles adjusted

Table 3. Incidence of cardiovascular events in patients with positive and negative cold pressor test

BNP quintiles (maximum-minimum) (pg-ml)*	OR	95% CI
Q1 (30-153)	1	
Q2 (160-320)	0,88	0,087-8,84
Q3 (370-622)	6,8	0,83-55,84
Q4 (644-1.021)	3,86	0,52-28,58
Q5 (1.037-4.000)	10,71	1,25-91,73

* Adjusted for age, gender, heart rate, systolic blood pressure and initial electrocardiographic signs.
BNP: Brain natriuretic peptide. CI: Confidence interval. OR: Odds ratio.

Table 4. Brain natriuretic peptide quintiles and relevant right ventricular dysfunction

BNP quintiles (maximum-minimum) (pg-ml)*	OR	95% CI
Q1 (30-153)	1	
Q2 (160-320)	6,1	0,5-73,74
Q3 (370-622)	11,4	1,02-127,09
Q4 (644-1.021)	24,43	1,64-229,49
Q5 (1.037-4.000)	34,56	1,88-355,33

* Adjusted for age, gender, heart rate, systolic blood pressure and initial electrocardiographic signs.
BNP: Brain natriuretic peptide. CI: Confidence interval. OR: Odds ratio.

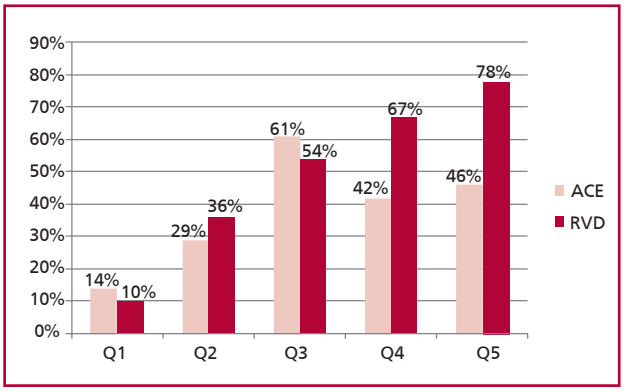

Fig. 1. Relationship between brain natriuretic peptide levels expressed in quintiles and right ventricular dysfunction (RVD) or adverse clinical events (ACE).

by the same variables, a progressive association with relevant RVD was observed, while there was only increased ACE incidence in the last quintile. The individual analysis of the different variables identifying ACE only revealed a significant association with thrombolytic therapy.

In this group of patients, a similar association was not observed with TI, whose levels were not different between patients with or without relevant RVD and ACE. These findings contradict results obtained by other authors, describing a gradual correlation between TI levels and clinical events. (13) The inclusion of a large proportion of low risk patients in previous studies may partly explain published findings. The difference between biomarkers might be attributed to the variations in BNP levels which are apparently more dynamic and could reflect more accurately the patient's hemodynamic-clinical condition. The strong correlation between BNP and intracavitary pressure added to the myocardial injury produced by right ventricular overload might explain the observed association. The fact that no progressive relationship was found between BNP quintiles and ACE, as in the case of relevant RVD, might correspond to factors unrelated to the patient´s hemodynamic-clinical condition, such as hemorrhagic risk, considering that use of thrombolytic therapy was the ACE most strongly associated factor.

Limitations

The registry obtained 71 patients with moderate to high PE risk. Although this is a large number for only one center, it is small to analyze the behavior of serum biomarkers as a function of the proposed composite endpoint and does not allow obtaining a BNP cut-off value for predicting events.

The most important feature of the complex treatment is thrombolysis, and is influenced by clinical judgment that estimates not only intrinsic PE risk but also bleeding probability. The analysis of a potential variable as "thrombolysis intention", probably including seriously-ill patients and high bleeding risk (old age, recent surgery, etc.) has not been considered in our study.

The echocardiogram was not recorded with predetermined measurements, but left to the operator's discretion.

Finally, given the study design and sample size, the evaluation of the association between serologic biomarkers and clinical evolution is limited, and should be tested in studies with a larger number of patients and adjusting the results with a greater number of variables.

Clinical implications

At present, both biomarkers are used as a first approach to assess risk stratification. Some authors claim that these biomarkers have added prognostic value to the echocardiogram and that they may even endorse therapeutic conduct. (12, 20, 23) Some studies postulate the use of BNP and troponins according to their independent results and not as their comparative analysis. In our study, it is evident that BNP, in addition to selecting low risk patients might also optimize stratification of higher risk subjects. Moreover, the fact that TI does not discriminate subjects with higher probability of developing relevant RVD or ACE might relegate it to the initial detection of low risk patients. In the event of selecting a risk stratification serum marker in clinically relevant PE patients, BNP probably provides more information than TI.

CONCLUSIONS

In this group of patients with moderate to high PE risk, BNP evidenced higher values both in patients with significant RVD and in those with a more complicated clinical outcome. The same results were not found in the analysis of TI plasma levels. This finding could reflect a greater usefulness of BNP with respect to TI to identify patients with greater clinical involvement although it should be confirmed in larger studies.

RESUMEN

Valor pronóstico del péptido natriurético cerebral y la troponina I en la tromboembolia pulmonar de riesgo moderado y alto

Introducción

El péptido natriurético cerebral (BNP) y las troponinas son marcadores útiles para la estratificación de la embolia pulmonar (EP), pero se desconoce cuál tiene mejor asociación con la gravedad del cuadro.

Objetivo

Evaluar ambos marcadores en forma comparativa dentro de una población de riesgo moderado y alto.

Material y métodos

Se elaboró un registro prospectivo de los pacientes con diagnóstico de EP que presentaran troponina I (TI) o BNP

positivos. Se realizó un ecocardiograma en las primeras 24 horas y seguimiento clínico en la internación. Se estableció un punto combinado de muerte, recurrencia de EP, shock, hipotensión arterial, asistencia respiratoria mecánica y uso de trombolíticos. Se buscó la asociación entre ambos marcadores y los eventos descriptos.

Resultados
Se incluyeron 71 pacientes consecutivos. Los pacientes con disfunción moderada o grave del ventrículo derecho presentaron niveles mayores de BNP [661 pg/ml (420-1113) vs. 316 pg/ml (129-570); p = 0,002], sin diferencias en los niveles de TI [0,115 ng/ml (0,015-0,345) vs. 0,24 ng/ml (0,076-0,58); p = 0,0788]. Los niveles de BNP fueron mayores en los que presentaron el punto combinado [604 pg/ml (370-934) vs. 316 pg/ml (148-900); p = 0,042], mientras que con la TI no ocurrió lo mismo [0,12 ng/ml (0,037-0,48) vs. 0,13 ng/ml (0,07-0,41); p = 0,46].

Conclusiones
El BNP tuvo valores más elevados en pacientes con disfunción ventricular significativa y en los que tuvieron el punto combinado. Este hallazgo podría reflejar una mayor utilidad del BNP respecto de la TI para identificar a los pacientes con mayor compromiso clínico.

Palabras clave > Embolia pulmonar - Péptido natriurético encefálico - Troponina - Pronóstico

Conflict of interests
None of the authors of the above article has declared any relationship with any organization with direct or indirect financial interests in the topics, events or materials discussed in the study, which might affect its conduction or report, within three years of study initiation.

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