Chapter 7

Repeated NT-proBNP testing and risk for adverse outcome after acute pulmonary embolism

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Abstract

Introduction

Many studies show that NT-proBNP at diagnosis of pulmonary embolism (PE) can be used to discriminate patients at low risk for adverse outcome after PE. The first aim of this study was to describe the course of NT-proBNP one week after PE. The second aim was to investigate whether adding a NT-proBNP test at day 2 to the test at day 1 would increase the predictive value for adverse events after pulmonary embolism.

Methods

Prospective cohort study with patients admitted for PE. NT-proBNP levels were measured daily. Primary outcome was adverse events during the first week, defined as PE-related mortality or clinical deterioration.

Results

Of 67 patients, nine patients (13%) had adverse events: seven on day 1, two on day 2. The median NT-proBNP level of patients with an event was higher during the first 3 days than of patients without an event. A proBNP cut-off >500 pg/mL on day 1 selected 41% of patients as low risk. A proBNP cut-off >1800 pg/mL on day 2 selected 62% of patients as low risk.

Conclusion

Repeated NT-proBNP testing within 48 hours after presentation with PE can identify 20% extra patients with PE as low risk than when using a single measurement at day 1. These patients could be possible candidates for outpatient treatment. It remains to be seen how these results translate into clinical practice, since all adverse events occurred within 48 hours.

Introduction

NT-proBNP (N-terminal brain natriuretic peptide) has been extensively investigated in the literature as a prognostic factor for an adverse outcome in pulmonary embolism (PE)[1-6]. Patients with an elevated NT-proBNP at the time of diagnosis of PE have a seven times higher risk for an adverse outcome than patients with a low NT-proBNP.

A recently published prospective cohort study has shown that outpatient treatment in patients presenting with acute hemodynamically stable PE and NT-proBNP levels <500 pg/mL is safe with regard to short-term mortality.[7] None of the 152 patients with PE and NT-proBNP levels <500 pg/mL died within 10 days (negative predictive value (NPV) 100%). This high NPV has also been observed in other studies.[2-4] However, when using the cut-off of 500 pg/mL only 43% of PE patients can be treated at home.[7] The first aim of the present study was to describe the course of NT-proBNP levels within one week after the diagnosis of PE. The second aim was to investigate whether adding a NT-proBNP test at day 2 to the test at day 1 would increase the predictive value for adverse events after PE.

Methods

We conducted a cohort study in a large teaching hospital in the Netherlands from April 2006 to June 2008. Patients with objectively proven, acute PE admitted to the hospital were included. Patients who died before the diagnosis of PE was established and patients transferred for treatment to another hospital were excluded. PE was demonstrated by imaging according to the local diagnostic guidelines (high probability ventilation-perfusion scan or abnormal CT-scan). Patients were treated with anticoagulants according to the current international guidelines.[8] NT-proBNP levels were measured every morning using the Elecsys proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Adverse events (defined as PE or major bleeding related mortality, cardiopulmonary resuscitation, mechanical ventilation, use of vasopressors, thrombolytic therapy, thrombosuction, open surgical embolectomy and PE or major bleeding related admission to Intensive Care (IC) unit) were collected during the first week.[3]

For the first aim of the study, to describe the course of NT-proBNP levels after the diagnosis of PE, all patients with acute PE were included. For the second aim of the study patients who had an adverse event during the first day were excluded. In order to find the NT-proBNP cut-off on the second day that would be most predictive for adverse events, we calculated test characteristics (sensitivity and specificity) of various absolute cut-off levels of NT-proBNP on day 2.

Differences in baseline characteristics and course of NT-proBNP levels between groups were examined by Mann-Withney U statistics for continuous variables and χ^2 statistics for

categorical variables. The Fisher's Exact test was used if the count was less than five. SPSS version 17.0 (SPSS Inc., Chigago, IL, USA) was used for all analyses. The study was approved by the local review board and all patients gave informed consent.

Results

In total 67 patients with acute PE were included. The median age was 63 years and 43% were male (Table 1). None of the patients had a history of heart failure.

Nine patients (13%; 95% CI 6.9-25.4%) had adverse events during the first week, seven (78%) on day 1 and two (22%) on day 2. More than 48 hours after presentation with PE no further events happened. Eight patients with an adverse event were treated with thrombolytics, and in one patient surgical embolectomy was performed, because of high bleeding risk. All patients with an adverse event recovered completely.

Patients with adverse events during follow-up had significant lower systolic blood pressure (117 vs. 137 mmHg, p=0.01) and oxygen saturation (84% vs. 95%, p=0.003) at presentation than patients without adverse events. The difference in the course of NT-proBNP in PE patients with and without an adverse event is described in Table 2. The median NT-proBNP level of patients with an event was higher during the first three days than of patients without an event, but after the third day these differences in the median NT-proBNP levels disappeared (Figure 1). The median peak NT-proBNP levels of patients with an adverse event were higher than of patients without an adverse event (3181 vs. 1399 pg/mL, p=0.01). Most of the patients (85%) had reached the highest level of NT-proBNP within 48 hours after the diagnosis of PE.

Of the total of 67 patients, four patients were already hemodynamically unstable or had clinical deterioration before the first measurement of NT-proBNP. When these four patients

Table 1: Baseline characteristics of patients

	All patients N=67		**Events N=9**		**No event N=58**		**P-value**
Age (year)	63	(50-73)	52	(42-62)	65	(51-74)	P=0.081
Male sex n(%)	29	(43)	2	(22)	27	(47)	P=0.280
SBP (mmHg)	134	(125-151)	117	(93-132)	137	(128-153)	P=0.014
Heart Rate (bpm)	88	(74-105)	92	(82-116)	88	(70-105)	P=0.130
Oxygen saturation* (%)	94	(89-97)	84	(79-90)	95	(90-97)	P=0.003
Heart Failure n(%)	0	(0)	0	(0)	0	(0)	-
COPD n(%)	6	(9)	0	(0)	6	(10)	P=0.587
Cancer n(%)	11	(16)	0	(0)	11	(19)	P=0.336

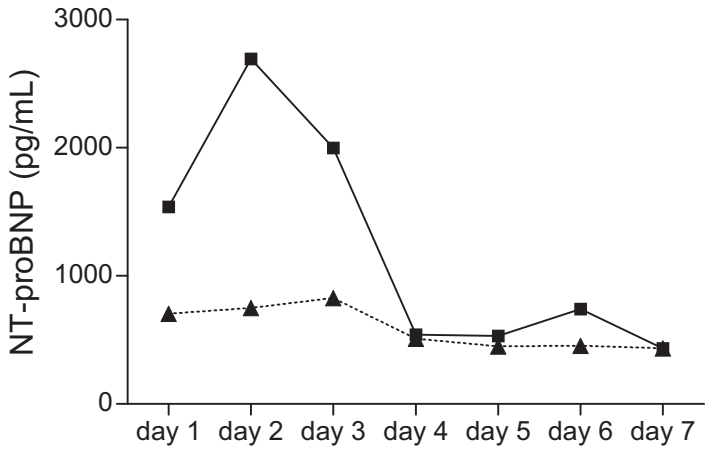
SBP=systolic blood pressure, bpm= beats per minute, n=number. Continuous data are displayed as median (25th percentile-75th percentile). *Patients in whom oxygen saturation was measured while on oxygen suppletion were removed from this analysis (N=10).

Table 2. Course of NT-proBNP

	All patients N=67	Events N=9	No event N=58	P-value
NT proBNP at diagnosis of PE (N=66)	910 (195-2367)	1823 (617-3456)	703 (178-2187)	P=0.153
NT proBNP day 2 (N=63)	1016 (195-3181)	2953 (2301-6600)	749 (160-2215)	P=0.004
NT-proBNP day 3 (N=48)	889 (221-2799)	2632 (1009-3557)	769 (186-2545)	P=0.088
NT-proBNP day 4 (N=40)	508 (243-1121)	512 (264-1574)	508 (177-1121)	P=0.892
NT-proBNP day 5 (N=34)	448 (186-853)	214 (117-1271)	459 (191-819)	P=0.738
NT-proBNP day 6 (N=28)	460 (128-794)	484 (100-867)	460 (177-767)	P=1.000
NT-proBNP day 7 (N=25)	433 (159-768)	101 (60-1437)	478 (237-768)	P=0.231
Peak NT-proBNP	1897 (297-3397)	3181 (2421-5876)	1399 (259-3163)	P=0.011
Proportion patients with peak NT-proBNP < 48 hours	55 (85)	8 (89)	47 (84)	P=1.000
Proportion patients with increase in NT-proBNP from day 1 to day 2	32 (51)	7 (88)	25 (46)	P=0.053
Proportion patients with increase NT-proBNP >50% from day 1 to day 2	18 (29)	5 (63)	13 (24)	P=0.039

NT-proBNP levels are given in pg/mL. Continuous data are displayed as median (25th percentile-75th percentile) and categorical data are displayed as number (percentage).

Figure 1. Course of NT-proBNP



Legend:
■ event ▲ no event

were excluded from the analysis, 63 patients remained, of which five patients (7.9%; 95%CI 3.0-17.6%) had an adverse event. Of the 36 patients with NT-proBNP >500 at day 1 (57%), five patients got adverse events during hospital admission versus none in the patients with NT-proBNP <500 pg/mL (14% vs. 0%; p=0.06).

NT-proBNP cut-off of 1800 pg/mL at day 2 showed the highest sensitivity and specificity for adverse events at day 2 (sensitivity 100% (95% CI 46-100%), specificity 65% (95% CI 51-77%)). When adding the cut-off of 1800 pg/mL at day 2 to the cut-off of 500 pg/mL at day 1, an extra 13 patients (21%) at low risk for adverse events could be added to the 26 (41%) patients already selected as low risk at day 1. When combining two different NT-proBNP cut-off levels at day 1 and 2, 39 of 63 patients (62%; 95% CI 50-73%) could be selected as low risk patients within two days after the diagnosis of PE.

Discussion

In this study the course of NT-proBNP levels within one week after the diagnosis of PE was studied. We investigated whether patients with low proBNP on day 1 or day 2 could be candidates for outpatient treatment. Some hypothesis generating observations could be made: patients with upcoming adverse events have higher NT-proBNP levels during the first three days after PE and have a higher median peak NT-proBNP level than patients with an uneventful clinical course. This study is the first to describe the course of NT-proBNP more than 24 hours after diagnosis of PE. Only one other study has reported on repeated NT-proBNP testing after PE, but only within 24 hours and concluded that persistent elevation in NT-proBNP levels within 24 hours after PE has a high positive predictive value for mortality.[9] Our results show that repeated NT-proBNP testing, as compared to single testing, could play a role in the further selection of low risk patients, who could be candidates for early discharge: when combining two cut-off levels for NT-proBNP on day one and day two, 62% (95% CI 50-73%) of patients could be classified as being low risk for adverse events. This is higher than the average proportions of 42-43% of patients with low risk described in the literature with single testing.[3,7]

The small population is a limitation of this study. Because of this the cut-off on day 2 was based on only two adverse events. In larger populations the cut-off with the highest sensitivity and specificity could be different. The limited availability of NT-proBNP tests in some hospitals may reduce generalisibility of our results.

Our results generated the hypothesis that with an extra NT-proBNP test on day 2, a larger proportion of low-risk PE patients (62%) can be selected as possible candidates for early discharge within 48 hours after the diagnosis of PE. However, since in our study all adverse events in this small population of PE patients happened within 48 hours after the diagnosis of PE, we cannot decide on whether two day-testing is sufficient to exclude adverse outcome

occurring later on. Therefore, the usefulness of repeated NT-proBNP testing for clinical practice has to be proven in a larger cohort of patients.

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