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N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism

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ABSTRACT: Plasma brain natriuretic peptide (BNP), released from myocytes of ventricles upon stretch, has been reported to differentiate pulmonary from cardiac dyspnoea. Limited data have shown elevated plasma BNP levels in acute pulmonary embolism (APE), frequently accompanied by dyspnoea and right ventricular (RV) dysfunction. The aim of this study was to assess plasma N-terminal proBNP (NT-proBNP) in APE, and to establish whether it reflects the severity of RV overload and if it can be used to predict adverse clinical outcome.

On admission, NT-proBNP and echocardiography for RV overload were performed in 79 APE patients (29 males), aged 63±16 yrs.

Plasma NT-proBNP was elevated in 66 patients (83.5%) and was higher in patients with (median 4,650 pg·mL^{-1} (range 61–60,958)) than without RV strain (363 pg·mL^{-1} (16–16,329)). RV-to-left ventricular ratio and inferior vena cava dimension correlated with NT-proBNP. All 15 in-hospital deaths and 24 serious adverse events occurred in the group with elevated NT-proBNP, while all 13 (16.5%) patients with normal values had an uncomplicated clinical course. Plasma NT-proBNP predicted in-hospital mortality.

Plasma N-terminal pro-brain natriuretic peptide is elevated in the majority of cases of pulmonary embolism resulting in right ventricular overload. Plasma levels reflect the degree of right ventricular overload and may help to predict short-term outcome. Acute pulmonary embolism should be considered in the differential diagnosis of patients with dyspnoea and abnormal levels of brain natriuretic peptide.

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Elevated plasma levels of brain natriuretic peptide (BNP) released from myocytes of ventricles upon stretch have been found in patients with congestive heart failure and even in those with asymptomatic left ventricular (LV) systolic dysfunction [1, 2]. Moreover, elevated plasma BNP was found in patients with primary pulmonary hypertension and chronic thromboembolic pulmonary hypertension [3, 4]. Interestingly, elevated plasma BNP was reported to help differentiate pulmonary from cardiac aetiologies of acute dyspnoea [5]. Plasma N-terminal proBNP (NT-proBNP) is also increased in congestive heart failure patients [6] and it may help to stratify their prognosis [7, 8]. However, limited data suggest that plasma BNP may be elevated in patients with acute pulmonary embolism (APE), frequently accompanied by acute dyspnoea and right ventricular (RV) dysfunction [9–11]. Therefore, the aim of this study was to assess plasma levels of NT-proBNP in patients with APE, and to establish whether the levels reflect the severity of RV overload and whether they can be used to predict adverse clinical outcome.

Materials and methods

Clinical data

The study analysed consecutive patients with symptomatic APE. APE was confirmed by contrast-enhanced spiral computed tomography or by high-probability lung scintigraphy according to PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) criteria [12]. On admission, systemic blood pressure (BP) and cardiac frequency (*f*C) were measured, 12-lead electrocardiogram (ECG) and transcutaneous pulsoximetry (Sp,O_2) were also recorded.

Echocardiographic data

In order to assess the degree of RV overload on admission, transthoracic echocardiography (TTE) was performed with Hewlett Packard SONOS 4500 (Hewlett Packard, Andover, MA, USA) or Acuson Sequoia systems (Acuson, Mountain View, CA, USA). The data were stored and off-line calculations were carried out for the assessment of RV pressure overload. Examinations were performed in the left supine position. The end-diastolic transverse dimensions of the RV and LV were measured in the apical four-chamber view at the onset of the R wave of the ECG tracing. Subsequently, the RV:LV end-diastolic ratio was calculated. Quantitatively, the systolic function of RV was assessed, specifically for hypokinesis of the RV free wall, as described previously [13]. After measuring the peak velocity of tricuspid valve regurgitation with continuous Doppler, the tricuspid valve pressure gradient (TVPG) was calculated according to the simplified

Table 1. – Clinical and echocardiographic characteristics of patients with acute pulmonary embolism (APE)

Parameter	APE	Nonmassive APE	Submassive APE	Massive APE
Subjects n	79	18	51	9
Age yrs	63±17	52±20^{+}	67±15*	66±13
Females:males	50:29	6:12	37:14*	6:3
BPs mmHg	123±23	132±21^{+}	126±20	83±11$^{\#,\P}$
fC 1·s^{-1}	101±22	98±24^{+}	98±18	122±29$^{\#,\P}$
Sp,O_2 %	89±7	93±4^{+}	88±7*	85±8$^{\#}$
RV:LV	0.86±0.32	0.63±0.23^{+}	0.90±0.29*	1.21±0.42$^{\#}$
Hypokinesis	23 (29)	0	19 (37)*	4 (44)$^{\#}$
TVPG mmHg	43±13	28±8^{+}	46±13*	38±5$^{\#}$
Deaths	15 (19)	0	10 (19.6)	4 (44.4)$^{\#}$
SAE	24 (30)	0	16 (31)*	7 (78)$^{\#,\P}$

Data are presented as mean±SD or n (%) unless otherwise stated. BPS: systolic blood pressure; fC: cardiac frequency; Sp,O_2: pulsoximetry; RV/LV: right-to-left ventricle diameter ratio; TVPG: tricuspid valve pressure gradient; SAE: at least one in-hospital serious adverse event (death, cardiopulmonary resuscitation, thrombolysis, need for *i.v.* catecholamine infusion). *: $p<0.05$ nonmassive *versus* submassive APE; $^{\#}$: $p<0.05$ nonmassive *versus* massive APE; ¶: $p<0.05$ submassive *versus* massive APE; $^{+}$: $p<0.05$ in analysis of variance (ANOVA) test or Kruskal-Wallis ANOVA test for three groups.

Bernoulli's formula. The acceleration time of pulmonary ejection was measured with pulsed Doppler in the RV outflow tract. Dimensions of inferior vena cava (IVC) were measured during expiration using the subcostal approach.

RV pressure overload was diagnosed when echocardiography showed RV:LV >0.6 with RV hypokinesis and/or elevated TVPG >30 mmHg with shortened acceleration time of pulmonary ejection <80 ms.

Severity of acute pulmonary embolism

According to the systemic systolic BP (BPs) measured on admission and the result of the echocardiographic examination, three subgroups of APE patients were defined: massive APE with BPs $\leqslant$90 mmHg; nonmassive APE with BPs >90 mmHg without echocardiographic signs of RV overload; and submassive APE in whom, despite preserved systemic BPs (>90 mmHg), RV overload was present at TTE.

Biochemical assays

On admission, blood samples were collected from an antecubital vein for routine assays and for plasma NT-proBNP. Samples for determination of NT-proBNP were centrifuged and plasma was frozen until the quantitative assay (electrochemiluminescence method; Roche Diagnostics GmbH, Mannheim, Germany) was performed. Plasma NT-proBNP concentrations greater than age- and sex-specific values were regarded as abnormal (reference values according to the manufacturer: female <50 yrs, <153 pg·mL^{-1}; female $\geqslant$50 yrs, <334 pg·mL^{-1}; males <50 yrs, <88 pg·mL^{-1}; males $\geqslant$50 yrs, <227 pg·mL^{-1}). The protocol of this study was approved by the local Institutional Bioethical Committee. All participating patients gave their informed consent.

Statistical analysis

Data characterised by normal distribution are expressed as mean±SD. Parameters not normally distributed are expressed as median (range). Unpaired, two-sided t-tests or the Mann-Whitney U-test were used for two-group comparisons. Yate's corrected Chi-squared test was used to compare discrete variables. Receiver-operating characteristic (ROC) analysis was performed in order to assess optimal cut-off values for plasma NT-proBNP in the selection of in-hospital deaths and serious adverse events (SAE) during hospitalisation. Odds ratio (OR) analysis was used to assess the influence of NT-proBNP on the in-hospital mortality and on SAE during hospitalisation, which included at least one of the following in-hospital adverse clinical events: death, cardiopulmonary resuscitation, thrombolysis and need for *i.v.* catecholamine infusion. In order to normalise the distribution of NT-proBNP values, their log was used for OR analysis. Multivariate logistic analysis was used to assess factors influencing in-hospital deaths or SAE.

Results

Patients' characteristics and clinical course

The group of 79 APE patients who were investigated included 29 males and 50 females, aged 63±17 yrs (table 1). In nine patients, massive APE was diagnosed. Nonmassive APE was found in 18 patients, while the remaining 51 cases formed the subgroup with submassive APE. TTE was not performed in one normotensive patient. Echocardiography was not performed in three patients with clinically massive APE. However, in the remaining six patients with massive APE, TTE showed significant RV overload. At least one coexisting disease (chronic obstructive pulmonary disease, neoplasm, renal insufficiency, congestive heart failure) was present in 20 (25.3%) of the subjects studied. Initially, all investigated patients with submassive and nonmassive APE were anticoagulated with an *i.v.* infusion of unfractionated heparins, with dose-activated partial thrombin time (APTT) adjusted to reach 1.5–2.0-times control APTT, or received subcutaneous low molecular weight heparins in a body weight-adjusted dose. The decision to start thrombolysis was based on the clinical assessment of each individual patient by the physician in charge. The decrease in systemic BPs <90 mmHg, progressive acceleration of fC or respiratory insufficiency were considered as potential indications for such aggressive treatment. Eventually, five patients with submassive APE received thrombolysis. Three of nine patients with massive APE were thrombolised. The decision to start aggressive therapy was influenced by co-existing conditions increasing the risk of bleeding. Altogether, eight (10%) patients received thrombolysis with 1,500,000 U *i.v.* streptokinase over 2 h. When control APTT decreased down to three-times control, *i.v.* heparin was restarted.

Despite the implemented treatment, 15 of 79 patients died during hospitalisation (in-hospital mortality 18.9%). This included four patients (44%) with massive APE, 10 (19.6%)

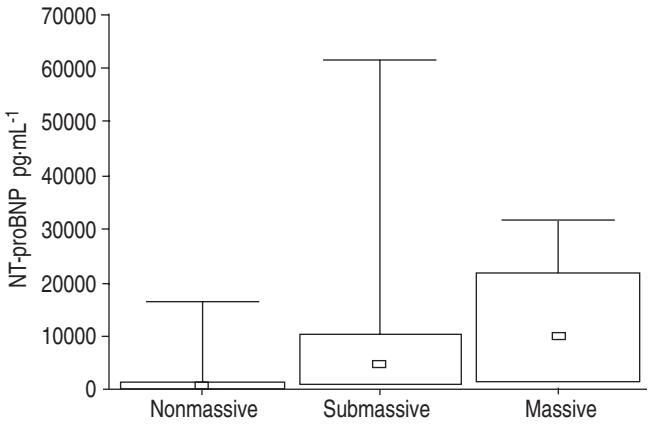

Fig. 1. – Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with acute pulmonary embolism, classified as nonmassive (n=18), submassive (n=51) or massive (n=9). Data are presented as median, 25–75% and min–max. p=0.0002.

with submassive APE and one patient with an initial BP of 160/100 mmHg. The latter patient had subarachnoideal bleeding 2 weeks before the radiologically massive APE and died shortly after admission, probably due to intracranial bleeding during heparin infusion, before echocardiographic examination could be performed. Irreversible RV failure was diagnosed in 11 patients and in three others recurrent fatal APE was clinically suspected. Thrombolysis was used with similar frequency in survivors and nonsurvivors (9 and 13%, respectively). SAE occurred in 24 (30.4%) cases. This group comprised 15 deaths and an additional six patients with thrombolysis, which was accompanied by successful cardiopulmonary resuscitation and *i.v.* use of vasopressor agents in one case. Successful cardiopulmonary resuscitation without thrombolysis was performed in two others.

Plasma N-terminal pro-brain natriuretic peptide

On admission, plasma NT-proBNP levels were above the reference age- and sex-specific values in 66 patients (83.5%). It was elevated in 10 (55.6%) cases with nonmassive APE, while it was significantly more frequent in submassive and massive APE (90.2 and 100%, respectively, p<0.01). Plasma levels in massive APE were significantly higher than in submassive or nonmassive APE: massive 9,865.0 pg·mL^{-1} (414.5–31,168.0), submassive 4,650.5 pg·mL^{-1} (61.0–60,958.0) and nonmassive 363.6 pg·mL^{-1} (16.3–16,329.0) (Kruskal-Wallis analysis of variance, p<0.0002; fig. 1).

Plasma N-terminal pro-brain natriuretic peptide and echocardiographic parameters

Transthroracic echocardiography was performed in 75 patients. Fifty-seven (76%) patients presented with RV overload (RV+), while the remaining 18 (24%) patients showed no alteration in RV morphology or function (RV-). When compared with age- and sex-specific reference values, plasma NT-proBNP levels were abnormal in 52 (91%) patients from the RV+ group and 10 (56%) patients from the RV- group (p<0.002). Moreover, plasma NT-proBNP was significantly lower in RV- than in RV+ (363.6 pg·mL^{-1} (16.3–16,329.0) *versus* 4,650.5 pg·mL^{-1} (61.0–60,958.0), p<0,00001). Interestingly, significant correlations between echocardiographic indices of RV overload and NT-proBNP were found, specifically with the RV:LV ratio (r=0.53, p<0.001) and IVC (r=0.49, p<0.001; table 2). However, plasma NT-proBNP correlated with systemic haemodynamic status to a lesser degree. TTE showed LV systolic dysfunction, defined by its ejection fraction <50%, in three (4.0%) of all investigated patients. However, there were no differences in plasma NT-proBNP between groups with preserved and diminished LV systolic function (16,162.0 pg·mL^{-1} (188.3–2,1494.0) *versus* 2,397.5 pg·mL^{-1} (16.3–60958.0), p=0.39).

Plasma N-terminal pro-brain natriuretic peptide and clinical course

All deaths and SAEs occurred in patients with elevated NT-proBNP levels, while all 13 (16.5%) patients with normal values had an uncomplicated clinical course. Nonelevated plasma NT-proBNP significantly differentiated patients with uncomplicated clinical course form subjects with SAE during hospitalisation (p=0.01) and showed marked trends in distinguishing survivors from nonsurvivors (p=0.06). Thus, normal values of plasma NT-proBNP reached 100% negative predictive value (NPV) for in-hospital mortality or complicated clinical course. However, positive predictive value (PPV) of elevated NT-proBNP for death or SAE was only 22.7 and 36.3%, respectively. Interestingly, plasma NT-proBNP levels were significantly higher in nonsurvivors than in survivors (11,491.0 pg·mL^{-1} (617.9–60,958.0) *versus* median 1,939.0 pg·mL^{-1} (16.3–27,752.0), p=0.0005; fig. 2). Levels were also higher in patients with SAE during hospitalisation than in patients with uncomplicated clinical course (9,678.5 pg·mL^{-1} (414.5–60,958.0) *versus* 1,319.0 pg·mL^{-1} (16.3–27,752.0), p=0.0002; fig. 3). OR analysis revealed that log of plasma NT-proBNP predicted in-hospital mortality (OR 2.15 (95% confidence interval (CI) 1.30–3.56)) and SAE (OR 1.88 (95% CI 1.29–2.74)). A plasma NT-proBNP cut-off value of 600 pg·mL^{-1} for SAE prediction was identified by ROC analysis (fig. 4). Values of plasma NT-proBNP concentration >600 pg·mL^{-1} showed 96% sensitivity and 35% specificity in the prediction of SAE. The same plasma NT-proBNP level in the ROC analysis for fatal in-hospital outcome reached 100% sensitivity and 33% specificity. Multivariate logistic analysis, including clinical and echocardiographic parameters and plasma NT-proBNP levels, showed that in this model, only NT-proBNP and Sp,O_2 predicted in-hospital death and SAE (death: log NT-proBNP OR 1.89 (95% CI 1.12–3.20), Sp,O_2 OR 0.85 (95% CI 0.76–0.94); SAE: log NT-proBNP OR 1.70 (95% CI 1.12–2.58), SO_2 OR 0.84 (95% CI 0.76–0.92)). Other variables, including

Table 2. – Correlations between haemodynamic data and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in 79 patients with acute pulmonary embolism

Parameter	RV:LV		IVC mm		TVPG mmHg		RV mm		*f*C 1·s^{-1}		BPs mmHg		SO_2 %	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Plasma NT-pro BNP	0.53	<0.001	0.49	<0.001	0.40	0.003	0.38	0.003	0.26	0.021	-0.32	0.01	-0.34	0.008

RV:LV: right-to-left ventricle diameter ratio; IVC: inferior vena cava dimension; TVPG: tricuspid valve pressure gradient; *f*C: cardiac frequency; BPS: systolic blood pressure; SO_2: pulsoximetry.

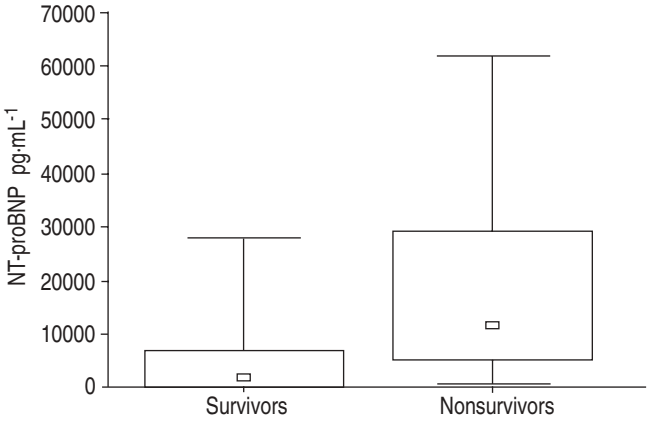

Fig. 2. – Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with acute pulmonary embolism, survivors (n=64) and nonsurvivors (n=15). Data are presented as median, 25–75% and min–max. p=0.0005.

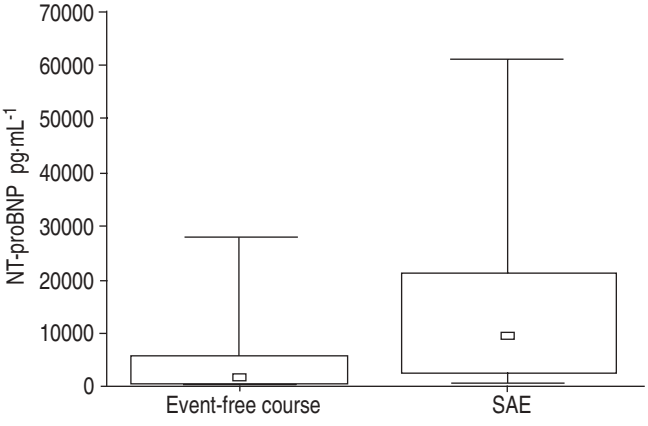

Fig. 3. – Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with acute pulmonary embolism, group with event-free course (n=55) and group with serious adverse events (SAE; n=24). Data are presented as median, 25–75% and min–max. p=0.0002.

age, BPs, RV:LV and TVPG, were nonsignificant in this analysis.

Discussion

Plasma N-terminal pro-brain natriuretic peptide and haemodynamics of patients with acute pulmonary embolism

Elevated plasma levels of BNP were reported to differentiate acute dyspnoea due to congestive heart failure from its other causes [5, 14]. The current data show that 83% of patients with symptomatic APE had elevated plasma NT-proBNP. These findings suggest that APE should be considered in the differential diagnosis of patients with dyspnoea and elevated plasma NT-proBNP. Interestingly, plasma NT-proBNP was increased in almost all cases of clinically massive and submassive APE, which are accompanied by RV overload and dyspnoea, while in patients without echocardiographic signs of RV dysfunction, NT-proBNP elevation was found in only 50% of patients. It may be that NT-proBNP, a biochemical marker of myocardial stretch, is more sensitive in the detection of RV overload than echocardiography.

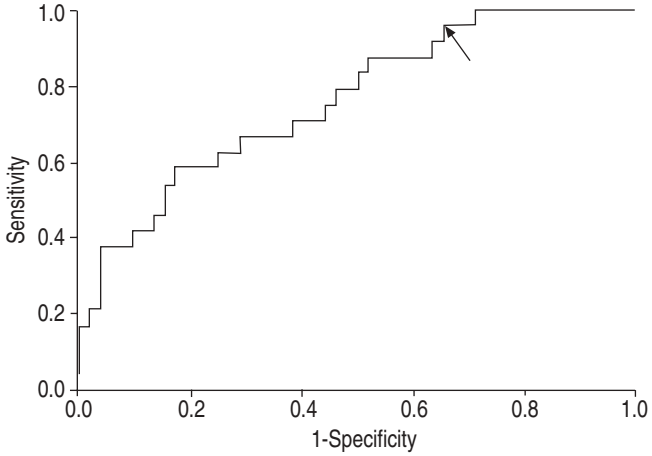

Fig. 4. – Receiver-operating characteristic analysis (ROC curve) for plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) in the selection of serious adverse events during hospitalisation. Arrow: NT-proBNP=600 pg·mL^{-1}. Area under curve=0.76.

However, this cannot be confirmed without direct haemodynamic evaluation, which was not performed on the patients in this study, but significant relationships were observed between RV:LV ratio, IVC and plasma NT-proBNP ($r=0.53$, $p<0.001$; and $r=0.49$, $p<0.001$, respectively). Since BNP is released by myocytes submitted to stretch, elevated plasma NT-proBNP could be expected in patients with distended RV and a higher RV:LV ratio. IVC noncollapsing at inspiration has been shown to indicate elevated right atrial and RV end-diastolic pressures [15]. The current authors also observed a positive correlation between TVPG and plasma NT-proBNP. Interestingly, similar correlations were detected in patients before thombendartherectomy of chronic thromboembolic pulmonary hypertension [3] and also in subjects with atrial septum defect complicated by pulmonary hypertension [16].

Plasma N-terminal pro-brain natriuretic peptide and clinical course of acute pulmonary embolism

Plasma concentration of BNP is related to the severity of congestive heart failure and it is an established independent risk factor of mortality in this population [8]. Recently, elevated levels of BNPs were also reported to affect the prognosis in patients after acute coronary syndromes [17] or primary pulmonary hypertension [4]. In the present study, there were significant differences in plasma NT-proBNP between patients with massive, submassive and nonmassive APE. High mortality rates were observed (in-hospital mortality 18.9%). However, it should be mentioned that most fatalities occurred in patients with massive or submassive APE. In the current authors′ opinion, this high mortality was caused by the coexisting diseases and individually assessed increased risk of bleeding limiting the frequency of thrombolysis. At the time of the study, surgical embolectomy or mechanical fragmentation of proximal clots were not available in participating centres. Moreover, one patient with APE and preserved systemic BP died because of intracranial bleeding. Interestingly, all deaths and SAEs occurred in patients with elevated NT-proBNP, while all 13 (16.5%) patients, including three subjects with RV overload with normal values, had uncomplicated clinical courses. Even more importantly, OR analysis revealed that log of plasma NT-proBNP predicted in-hospital mortality (OR 2.15 (95% CI 1.30–3.56)) and SAE (OR 1.88 (95% CI 1.29–2.74)).

Multivariate analysis, including clinical and echocardiographic variables, showed that only increased plasma NT-proBNP and decreased Sp,O_2 influenced in-hospital deaths and SAE. Lack of haemodynamic and echocardiographic parameters in this analysis, most probably was due to the fact that NT-proBNP reflected the severity of RV overload and haemodynamic compromise. Normal values of plasma NT-proBNP reached 100% NPV for in-hospital mortality or complicated clinical course. ROC analysis of the data revealed that plasma NT-proBNP >600 $pg \cdot mL^{-1}$ showed 96% sensitivity and 35% specificity for the prediction of in-hospital SAE. Interestingly, this cut-off value is very close to the NT-proBNP level of 500 $pg \cdot mL^{-1}$ recently identified by KUCHER *et al.* [11] These authors found, for NT-proBNP concentration >500 $pg \cdot mL^{-1}$, sensitivity of 95% and specificity of 43% in the prediction of complicated clinical outcome. Although plasma NT-proBNP was significantly higher in nonsurvivors than in survivors, and also higher in patients with SAE during hospitalisation than in patients with uncomplicated clinical course, due to low PPV for these events, plasma NT-proBNP cannot be helpful in the selection of high-risk APE patients. However, the current authors do think that normal plasma NT-proBNP may be useful in the identification of low-risk patients. This observation corresponds to findings by KUCHER *et al.* [11] who also showed that low plasma NT-proBNP levels predict benign clinical course in APE patients.

Conclusion

Plasma N-terminal pro-brain natriuretic peptide is elevated in the majority of patients with acute pulmonary embolism resulting in right ventricular overload and reflects the degree of right ventricular overload. Therefore, pulmonary embolism should be considered in the differential diagnosis of patients with dyspnoea and abnormal levels of brain natriuretic peptide. High levels of plasma N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism are associated with serious adverse events and poor prognosis. While normal plasma N-terminal pro-brain natriuretic peptide levels found in a minority of acute pulmonary embolism patients identify subjects with a favourable course of the disease. Therefore, plasma N-terminal pro-brain natriuretic peptide may serve as an indicator of disease severity, which may complement conventional clinical variables.

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