

# N-terminal prohormone of brain natriuretic peptide: a useful tool for the detection of acute pulmonary artery embolism in post-surgical patients

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## Editor's key points

- This study investigated the role of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) for the detection of acute pulmonary embolism (APE).
- NT-proBNP was significantly ( $P < 0.01$ ) higher in patients with APE.
- The sensitivity of the NT-proBNP screening was 93%, specificity 63%.
- In these post-surgical patients, changes in D-dimers and troponin-I levels were not informative.

**Background.** Acute pulmonary embolism (APE) is an important clinical problem in patients after major surgery and often remains a difficult diagnosis because of unspecific clinical symptoms. Therefore, we investigated the role of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) for the detection of APE.

**Methods.** In 44 patients with suspected APE referred to the intensive care unit after major surgery, serum NT-proBNP, troponin-I, and D-dimers were measured according to the standard hospital protocol. To definitively confirm or exclude APE, all patients underwent an angiographic CT scan of the thorax.

**Results.** APE was confirmed in 28 and excluded in 16 patients by CT scan. NT-proBNP was significantly ( $P < 0.01$ ) higher in patients with APE [4425 (SD 8826; range 63–35 000) pg ml<sup>-1</sup>] compared with those without [283 (SD 327; range 13–1133) pg ml<sup>-1</sup>]. The sensitivity of the NT-proBNP screening was 93%, specificity 63%, positive predictive value 81%, and negative predictive value 83%. There were no significant ( $P = 0.96$ ) differences in D-dimers between subjects with and without APE [confirmed APE: 511 (SD 207; range 83–750)  $\mu\text{g litre}^{-1}$ ; excluded APE: 509 (SD 170; range 230–750)  $\mu\text{g litre}^{-1}$ ]. Troponin-I levels were not elevated in 32% of the patients with APE.

**Conclusions.** D-dimer levels are frequently elevated in post-surgical patients and not applicable for confirmation or exclusion of APE. In contrast, NT-proBNP appears to be a useful biomarker for APE diagnosis in the postoperative setting. In the case of NT-proBNP levels below the upper reference limit, haemodynamically relevant APE is unlikely. Troponin-I in contrast is not considered to be helpful.

**Keywords:** acute pulmonary embolism, APE; cardiac biomarker; D-dimer; lung arterial embolism, LAE LE; N-terminal pro-natriuretic peptide, NT-proBNP; pulmonary arterial embolism, PAE

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Acute pulmonary embolism (APE) is a serious and potentially life-threatening event in the perioperative setting. Especially patients undergoing major surgery and being immobilized for a longer period are at risk. In the non-surgical patient, measurement of D-dimers has become a useful and frequently used diagnostic tool for the detection of APE.<sup>1</sup> D-dimer levels are expected to be useful as an exclusion test if results are negative.<sup>2–3</sup> However, there are relevant limitations in the use of D-dimers that make it almost useless in the perioperative setting: elevated levels of D-dimers are common in the post-surgical patient due to an activation of coagulation and fibrinolysis as a result of the surgical trauma<sup>4–5</sup> and in patients with markedly elevated C-reactive protein levels. Consequently, the specificity of D-dimer measurements is far too low to be used for the diagnosis or exclusion of APE in the perioperative setting.

The clinical diagnosis of APE frequently remains difficult due to unspecific symptoms. Thorax CT scans with contrast agent have become the gold standard in the detection of APE but are often unavailable at smaller hospitals due to a lack of devices or staff to run the scans. Furthermore, CT scans are associated with a considerable radiation dose which makes them not desirable in any situation. Echocardiography has become a helpful utility in the diagnosis and risk stratification of APE.<sup>6</sup> Dilatation of the right heart in transthoracic echocardiography and detection of emboli in transoesophageal echocardiography are helpful signs of pulmonary embolism. Especially in cardiac arrest consecutive to APE, echocardiography is a valuable tool.<sup>7</sup> A short theoretical and practical echocardiographic training for non-cardiologists appears to be sufficient for the detection of basic pathologies.<sup>8</sup> Basic echocardiographic training is

frequently performed at intensive care units (ICUs). However, smaller hospitals are not necessarily equipped with ICUs and young registrars frequently had not undergone echocardiographic training yet. Furthermore, the assessment of echocardiography can be limited with difficult anatomic conditions or obesity. For this reason, further non-skill-dependent tests appear to be reasonable, especially when echocardiography is limited by the staff present, for example, at nighttime. Natriuretic peptides have traditionally been used as markers for heart failure.<sup>9</sup> Plasma brain natriuretic peptide (BNP), which is released from ventricular myocytes upon stretching, has been reported to allow differentiating between pulmonary and cardiac disease-related dyspnoea. Additionally, elevated plasma BNP<sup>10 11</sup> and troponin<sup>12 13</sup> levels have also been reported in patients with APE in non-perioperative settings.

Owing to the known limitations of D-dimers in patients who underwent major surgery, we assessed the predictive value of plasma N-terminal (NT)-proBNP and troponin I levels in the detection of post-surgical APE.

## Methods

With approval of the ethical committee of the University of Ulm, Germany, 44 patients [age 62 yr (SD 14); range 30–93 yr] with suspected APE were investigated by laboratory values and CT scan. The study has been registered at clinicaltrials.gov (ID: NCT01633671). All patients underwent major abdominal surgery before their ICU stay. The routine laboratory workup at Ulm University surgical ICU in the case of suspected APE consisted of D-dimers as a traditional marker of PE and also NT-proBNP and troponin-I for cardiac differential diagnosis. The blood samples were obtained within 30–60 min after the onset of clinical symptoms. D-dimer levels were assessed by a Latex-augmented immunoturbidimetric test on a Behring Coagulation System analyser (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) and troponin-I levels by an fluorescence enzyme immunoassay: Tosoh Bioscience AIA21 (Tosoh Bioscience, Tokyo, Japan). NT-proBNP was analysed with an Electro Chemo Luminescence Immuno Assay (ECLIA) using a Roche MODULAR

ANALYTICS E170 (Elecsys Modul) immunoassay device (F. Hoffmann-La Roche AG, Basel, Switzerland).

The consecutive reference values were used: NT-proBNP: Table 1; troponin I: <0.07 µg litre<sup>-1</sup>; D-dimers: <160 µg litre<sup>-1</sup>.

A CT scan of the thorax with contrast agent was performed in all patients for definitive confirmation or exclusion of APE. In the present study at our university hospital, the laboratory assessment of NT-proBNP and troponin I was compared with a CT scan as the CT with contrast agent is expected to be the diagnostic gold-standard in APE.

Echocardiography was not performed as a part of this study to simulate conditions in smaller hospitals which are frequently unable to do so at nighttime due to a lack of staff experienced in this field (e.g. resident/consultant in the theatre, registrar had not undergone echocardiographic training yet).

## Statistics

Laboratory values were tested for normal distribution by the Kolmogorov–Smirnov test. Additionally, the quotient of measured NT-proBNP and upper NT-proBNP reference value was calculated. Differences in laboratory values between patients with proof of APE in the CT scan and those without were assessed by the Mann–Whitney *U*-tests. Furthermore, the sensitivity, specificity, positive predictive value, and negative predictive value of NT-proBNP were calculated. The upper reference value (depending on age and gender) was used as the cut-off value for positive NT-proBNP screening.

## Results

APE was confirmed by CT scan in 28 patients and excluded in 16 patients. D-dimer levels were distributed normally, while NP-proBNP and troponin-I levels were not. The Mann–Whitney *U*-tests were used for further analysis. NT-proBNP levels were significantly higher in subjects with APE compared with those without (Table 2). Furthermore, troponin-I levels were significantly increased. In contrast, there was no significant difference in plasma D-dimer levels between subjects with APE and those without. The four-fold-table of reliability testing is presented in Table 3. The sensitivity of the NT-proBNP screening was 93%, specificity 63%, positive predictive value 81%, and negative predictive value 83%. Troponin-I levels were not increased in nine of 28 patients with APE (32%).

## Discussion

Several previous studies investigated the role of natriuretic peptides in the context of lung embolism, consecutive right heart failure, and mortality in non-surgical patients. These studies revealed increased BNP levels to be an adverse prognostic parameter in pulmonary embolism as well.<sup>14–17</sup> However, the diagnostic value of BNP has not been investigated yet, most likely because there is no need to do so in the non-surgical patient, since D-dimers are valuable.

**Table 1** Normal ranges of NT-proBNP. The gender- and age-dependent reference values for NT-proBNP are given

	Age (yr)	Normal range (pg ml <sup>-1</sup> )
Female	19–44	<130
	45–54	<249
	55–64	<287
	65–74	<301
	>74	<738
Male	19–44	<86
	45–54	<121
	55–64	<210
	65–74	<376
	>74	<486

**Table 2** NT-proBNP, troponin I, and D-dimer levels in patients with and without APE. Data are mean (SD) (range). P-values are obtained from the Mann-Whitney U-test

Laboratory parameter	APE proven in CT scan (n=28)	APE excluded in CT scan (n=16)	P-value
NT-proBNP (pg ml <sup>-1</sup> )	4425 (SD 8826; range 63-35 000)	283 (SD 327; range 13-1133)	<0.01
Quotient: 1.0 ± 0.9 NT-proBNP <sub>measured</sub> /NT-proBNP <sub>upper-reference</sub>	15.8 (SD 32.9; range 0.3-140.6)	1.0 (SD 0.9; range 0.1-3.3)	<0.01
Troponin I (µg litre <sup>-1</sup> )	0.39 (SD 0.67; range 0.02-3.29)	0.04 (SD 0.07; range 0.02-0.30)	<0.01
D-dimers (µg litre <sup>-1</sup> )	511 (SD 207; range 83-750)	509 (SD 170; range 230-750)	0.96

**Table 3** Test reliability of the NT-proBNP screening. The cut-off value for positive NT-proBNP screening is the upper reference value

	CT scan		Sum
	CT-proof of APE	CT-exclusion of APE	
NT-proBNP screening			
NT-proBNP above upper reference	26	6	32
NT-proBNP below upper reference	2	10	12
Sum	28	16	
Sensitivity	93%		
Specificity	63%		
Positive predictive value (PPV)	81%		
Negative predictive value (NPV)	83%		

In our sample of 44 post-surgical patients, APE was proven by CT scan in 28 and excluded in 16 subjects. Serum levels of D-dimers were almost identical in both groups. This confirms the point of view that the measurement of D-dimers is useless in post-surgical patients. NT-proBNP and troponin-I levels were significantly higher in patients with CT-angiographic proof of APE compared with those without. During acute deterioration of pulmonary gas exchange, haemodynamic instability, or both, measuring plasma NT-proBNP concentrations proved to be a valuable tool for diagnosing APE for most of the patients. In the patients with confirmed APE, the mean NT-proBNP level was 4425 (SD 8826) compared with 283 (SD 327) pg ml<sup>-1</sup> in those without APE. The increase in NT-proBNP levels is

most likely caused by an increase in pulmonary vascular resistance due to a partial occlusion of pulmonary vessels and a consecutively increased workload and stretch of the right atrium and ventricle. The NT-proBNP levels observed in patients with APE are similar to those in critically ill patients suffering from acute left heart failure (median 4639 pg ml<sup>-1</sup>).<sup>18</sup> For this reason, the extent of NT-proBNP elevation does not appear to be a proper way to differentiate right- from left-heart-stress, even though the muscle mass of the right ventricle is smaller. The increased cardiac workload and stretch associated with APE appears to result in a damage of myocardial cells resulting in an increase in troponin-I levels. Increased troponin levels have been reported to be associated with a higher mortality in patients with APE.<sup>12-13</sup> Patients with elevated serum troponin I levels are at a higher risk for the development of right ventricular dysfunction and cardiogenic shock consecutive to pulmonary embolism.<sup>19</sup>

In the present study, six patients without CT-angiographic confirmation of APE presented elevated NT-proBNP levels. However, four patients showed high inflammation parameters and two had a pre-existing renal injury according to the RIFLE criteria. This observation confirms previous reports that increased BNP and NT-proBNP levels may also occur in acute ill patients due to systemic inflammatory response syndrome, sepsis or septic shock, acute renal failure, and others.<sup>20-24</sup> In these patients, the specificity of elevated plasma NT-proBNP levels appears to be reduced for this reason which limits the predictive value of NT-proBNP in the detection of APE. Since heart tissue can be damaged by the inflammation process in sepsis, troponin levels can be increased in sepsis.<sup>25</sup> This limits the predictive value of troponins for the detection of APE in septic patients as well.

In the present study, it appears to be more alarming that two patients with proven APE did not show increased levels of NT-proBNP (63 and 333 pg ml<sup>-1</sup>). When taking into account that these two patients were only affected by minor peripheral embolies, it is not surprising that cardiac workload was not increased enough to result in an elevation of NT-proBNP. Consequently, NT-proBNP does only appear to detect clinically relevant APE. Minimal embolism might not be covered by this screening test.

While NT-proBNP was a good indicator of clinically relevant APE, the use of troponin-I on its own cannot be recommended, since troponin-I levels were normal in 32% of the patients with APE.

Since D-dimer concentrations are not valuable in the post-operative setting, measurement of plasma NT-proBNP concentrations may further confirm suspected APE under conditions of otherwise unexplained haemodynamic instability, acute deterioration of pulmonary gas exchange, or both. However neither NT-proBNP nor troponin I levels facilitate the distinction between APE and myocardial infarction since natriuretic peptides are frequently increased in myocardial infarction as well.<sup>26</sup>

In the detection of APE, the assessment of NT-proBNP levels might be particularly helpful in smaller hospitals

without CT scan devices or without staff to run these devices at nighttime. Based on our present results, an NT-proBNP-based screening strategy might help to decide whether to transfer post-surgical patients to larger hospitals. CT scans or echocardiography can be performed at these larger hospitals to confirm or exclude APE. The patients should preferably be transferred to a hospital with a cardiology department and coronary care unit since myocardial infarction remains a potential differential diagnosis of APE. In the case of NT-proBNP and troponin levels below the upper reference value, both, myocardial infarction and haemodynamically relevant APE, are unlikely and problems other than these should be taken into account. Relevant APE is possible if NT-proBNP levels are elevated. However, sepsis or impaired renal function might result in false-positive values. The general value of NT-proBNP in the surgical patient appears to be similar to the value D-dimers in the non-surgical setting; APE is unlikely if laboratory results are negative, but positive results do not necessarily mean that APE is present. Neither NT-proBNP nor D-dimers are able to replace CT scans or echocardiography to obtain definitive results. Studies in larger populations are urgently required to verify the predictive value of NT-proBNP and troponin I for the diagnosis of APE in the surgical patient.

## Declaration of interest

None declared.

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