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NT-proBNP levels on admission predict pulmonary hypertension persistence in patients with acute pulmonary embolism

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ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, but due to its unfavorable prognosis feared complication of thromboembolic disease. We assessed the incidence and risk factors for pulmonary hypertension (PH) in a cohort of consecutive patients admitted with pulmonary embolism to the tertiary University Hospital.
Methods: In our cohort of 120 consecutive patients with proved pulmonary embolism (PE) we studied the course of biochemical and echocardiographic parameters with regards to risk factors predicting pulmonary hypertension at the end of hospitalization.
Results: Echocardiographic signs of pulmonary hypertension were present at the time of discharge in more than one half (50.8%) of patients admitted with pulmonary embolism. Predictors of persisting pulmonary hypertension were initial pulmonary hypertension, high initial NT-proBNP levels and age.
Conclusion: Residual pulmonary hypertension at discharge was present in 50.8% cases, at this time there was a strong relationship between PH and elevated NT-proBNP on admission. The patients will be followed--up and possible development of CTPEH will be evaluated at 6, 12 and 24 month period.

Klíčová slova:
Chronická tromboembolická plicní hypertenze
Plicní embolie
Rizikové faktory

SOUHRN

Kontext: Chronická tromboembolická plicní hypertenze (CTEPH) je málo častou, ale pro svou prognostickou závažnost obávanou komplikací tromboembolické nemoci. Zaměřili jsme se na stanovení incidence a rizikových faktorů plicní hypertenze (PH) v populaci konsekutivních pacientů přijatých pro akutní plicní embolii na kardiologickou kliniku univerzitní nemocnice.
Metody: V našem souboru 120 konsekutivních pacientů s prokázanou plicní embolizací jsme sledovali vývoj biochemických a echokardiografických parametrů s ohledem na možnosti predikce perzistence plicní hypertenze v době propuštění.

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Výsledky: Echokardiografické známky plicní hypertenze v době propuštění byly přítomny u více než poloviny (50,8 %) pacientů přijatých pro plicní embolii. Prediktorem perzistence PH byly kromě vstupní plicní hypertenze také zvýšené NT-proBNP při přijetí a věk.
Závěr: V době propuštění má přetrvávající plicní hypertenzi 50,8 % nemocných. Nalezli jsme silnou korelaci mezi tímto nálezem a zvýšenými hodnotami NT-proBNP při přijetí. Nemocní budou sledováni s ohledem na možný rozvoj chronické tromboembolické plicní hypertenze v intervalu 6, 12 a 24 měsíců od akutního stavu.

Introduction

Data on the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism are inconsistent. Relevant studies of patients surviving symptomatic pulmonary embolism showed CTEPH incidence in the range of 0,1–8,8 % [1–6]. In our paper we give our first results from mid-term study, which was designed to evaluate possibilities of CTEPH prediction in a population of consecutive patients with pulmonary embolism, admitted to tertiary cardiological department.

Population and methods

Altogether 163 patients older than 18 years with proved diagnosis of pulmonary embolism were hospitalized in our department from July 2007 to March 2010. All of them were admitted without undue delay through Emergency Department of our hospital, or directly from the field. Diagnosis was based on multidetector computer tomography angiogram (CTA) using Siemens Somatom Emotion 6 (except one case diagnosed on perfusion scintigraphy in patient with iodine allergy and one case, where diagnosis was based on history, clinical presentation, positive duplex ultrasonography of lower limbs and echocardiography). On admission blood samples were assessed to determine troponin-T (TnT) and N-terminal fragments of brain natriuretic peptide precursor (NT-proBNP) levels (electrochemoluminiscent method on Elexis device [Roche company]) a D-dimer (imunoturbidimetric method on device Compact a STA-R [Stago company]). Within first 24 hours echocardiography was carried out (on PHILIPS SONOS 5500 or GE Vivid 7) by the standard way, especially focused to right ventricle (RV) diameter in parasternal long axis, signs of RV systolic dysfunction (systolic excursion of lateral part of tricuspid annulus [TAPSE], peak velocity of this movement [Sa_{Tri}], RV free wall hypokinesis, RV dilatation) and pulmonary artery systolic pressure estimation based on peak tricuspid regurgitation jet velocity and right atrium pressure according to respiratory variations of vena cava inferior.

Follow-up was offered to all patients, involving, in conformity with study design, re-assessing TnT and NT-proBNP before discharge (usually 7–10 days since admission), if they were initially elevated, and echocardiography in the same interval. Next echocardiographic examination is planned in 6, 12 and 24 months since acute stage, and 6-month visit included also pulmonary CTA. This will be subject of our next report. Agreement with such a dispensarisation was confirmed by signing of Informed consent, endorsed by the Local Ethical Committee.

From the total 163 patients – 2 died early (on the 2nd and 4th hospitalization day, respectively). Out of remaining 161 we included 120 patients into our study (60 males, 60 females, age 19–85, mean 57,9 ± 16,2 years). Reasons for exclusion were patient's refusal to long-term follow-up (7 patients), missing data (insufficient echocardiographical imaging, diagnosis made in another medical facility, early transfer to regional hospital) (8 patients), combined pulmonary hypertension aethiology (8 patients), apparent follow-up noncompliance or terminal stage of associated disease (7 patients). Eleven patients had recurrence of thromboembolism (5 males, 6 females), this group of patients was also excluded from our analysis.

Obtained data were tested for distribution normality, for statistical analysis paired t-test or Wilcoxon's test were used. Correlation between variables was assessed by Pearson's and Spearman's analysis.

Results

The demographic characteristics of our study group are given in Table 1. The following symptoms were present on admission: dyspnea in 111 patients (92.5%), chest pain in 62 patients (51.7%), lower limb swelling in 52 patients (43.3%), cough in 46 patients (38.3%), syncope or presyncope in 33 patients (27.5%) and hemoptysis in 4 patients (3.3%). ECG signs of pulmonary embolism was found in 44 cases (36.7%) (Table 2). A remarkable fact is the D-dimer test negativity in 2 patients (1.7%).

According to pulmonary CTA the radiologist described an extensive pulmonary embolism in 43 patients (35.8%). But criteria of clinically massive (based on guidelines of Czech Society of Cardiology) [7] or high-risk (based on guidelines of European Society of Cardiology) [8] pulmonary embolism met only 5 (4.2%) patients. Acute small pulmonary embolism, i.e. low-risk PE had 19 (15.8%) patients. Remaining 96 (80.0%) cases were classified as a submassive, i.e. intermediate-risk pulmonary embolism because of either RV dilatation, or RV dysfunction (based on echocardiography and/or elevated NT-proBNP), or RV damage (in case of TnT positivity) or their combination (Table 3).

Altogether 107 patients (81.2%) were treated with unfractionated heparin or low-molecular weight heparin, followed by vitamin K antagonist (warfarin) until therapeutic and stable levels of international normalized

Table 1 – Study population characteristics.

Number of patients	120
Age (years)	57.9 ± 16.2
Female (n [%])	60 (50)
BMI (kg/m^2)	29.2 ± 5.48
Systolic blood pressure (mmHg)	135 ± 23.7
Diastolic blood pressure (mmHg)	80.6 ± 14.1
Smoker (n [%])	21 (17.5)
Steroid hormones user (n [%])	24 (20)
History of trauma/surgery/ immobilisation (n [%])	13 (10.8)/13 (10.8)/15 (12.5)
Oncological disease (n [%])	17 (14.2)
Thrombophilia (known or newly detected) (n [%])	15 (12.5)
NT-proBNP (pmol/l)	246 ± 490
Troponin T (μg/l)	0.031 ± 0.0462
Echocardiography on admission	
RV diameter (mm)	31.4 ± 4.51
PAsP (mmHg)	50.8 ± 17.7
TAPSE (mm)	20.5 ± 4.64
Sa_{Tri} (cm/s)	12.3 ± 2.65
Echocardiography at discharge	
RV diameter (mm)	29.6 ± 3.93
PAsP (mmHg)	37.8 ± 11.5
TAPSE (mm)	23.1 ± 4.02
Sa_{Tri} (cm/s)	13.0 ± 2.21

Table 2 – Clinical presentation of pulmonary embolism in patients.

Dyspnea	94.1%
Chest pain	48.5%
Lower limb swelling	44.1%
Cough	37.5%
Syncope, presyncope	30.1%
Hemoptysis	3.7%
ECG signs of PE	39.7%

Table 3 – Risk stratification of study population.

Massive PE	Submassive PE	Acute small PE
3.7%	81.6%	14.7%

Table 4 – Patients with transient and permanent risk factors (RF) and with idiopathic thromboembolism.

Transient RF	Permanent RF	Idiopathic cases
58 (38.3%)	31 (25.8%)	46 (38.3%)

ratio (INR) were achieved. In 13 cases (10.8%) thrombolysis (alteplase) was administrated with concomitant parenteral administration of unfractionated heparin, followed by above mentioned anticoagulant treatment. All patients were discharged with therapeutic doses of anticoagulation therapy.

Risk factors present in our patient cohort are shown in Table 4. Trauma, travelling, immobilization, previous surgery, steroid hormone therapy were considered as a transient risk factors. As a permanent risk factors are listed known thrombophilia and a known oncological disease. Coincidence of permanent and transient risk factors in our study group was noted in 15 cases.

At the time of admission there was RV dysfunction in 83 (69.2%), interventricular septum applanation (D-shaped left ventricle) in 48 (40%), echocardiographic signs of pulmonary hypertension in 95 (79.2%) patients.

Echocardiography at the time of discharge (mean 8 days) revealed lasting RV dysfunction in 60 (50%) patients and residual pulmonary hypertension was detected in 61 (50.8 %) (Table 5).

During the hospitalization there was a statistically significant (p = 0.0014) decrease of RV diameter, estimated pulmonary artery systolic pressure, improvement of RV function parameters and significant decrease of NT-proBNP levels.

Pulmonary hypertension persistence in time of discharge correlated with some variables on admission. A strong correlation was found between discharge PAsP and initial PAsP (Figure 1). Also a positive correlation with initial NT-proBNP (Figure 2), and age was found. Considering all variables obtained at the time before discharge, there was a correlation between elevated pulmonary artery systolic pressure and persisting elevation of NT-proBNP and RV dilatation. Despite the relationship between discharge PH and elevated NT-proBNP as a marker of RV dysfunction, there was surprisingly no correlation with either echocardiographic signs of RV dysfunction, or reduction rate of RV diameter or PAsP during hospitalization, as shown in Table 6.

Table 5 – Means and standard deviations (± values) of RV diameter, pulmonary artery systolic pressure (PAsP), TAPSE, Sa_{Tri} and NT-proBNP on admission and at the discharge time.

	On dimission	At the discharge time
PK	31.72 (± 4.86)	29.8 (± 4.03)
PAsP	53.0 (± 18.9)	39.2 (± 12.0)
TAPSE	20.2 (± 4.59)	22.6 (± 3.98)
Sa	12.2 (± 2.58)	13.1 (± 2.21)
NT-proBNP	297 (± 552)	69.3 (± 205)

Table 6 – Correlation of echocardiographic signs of discharge pulmonary hypertension with particular variables.

	Correlation coefficient	Level of significance
Initial PAsP	0.701	< 0.0000005
Initial NT-proBNP	0.443	< 0.0000005
Age	0.46	< 0.0000005
Discharge NT-proBNP	0.42	< 0.0000005
Discharge RV diameter	0.42	< 0.000001
Initial TAPSE	–0.033	< 0.05
Initial Sa_{Tri}	0.103	< 0.05
RV diameter difference	0.083	< 0.05
PaSP difference	0.071	< 0.05

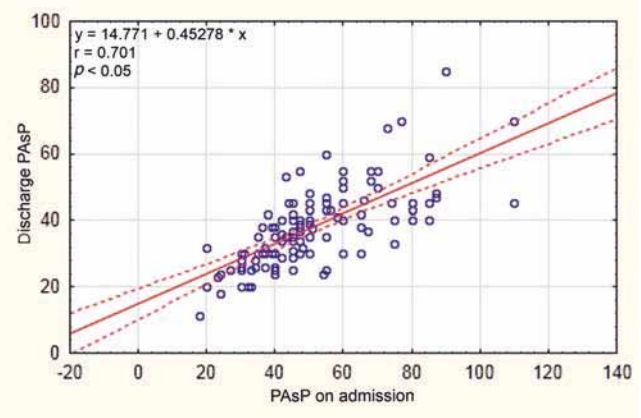

Fig. 1 – The relationship between admission and discharge pulmonary artery systolic pressure.

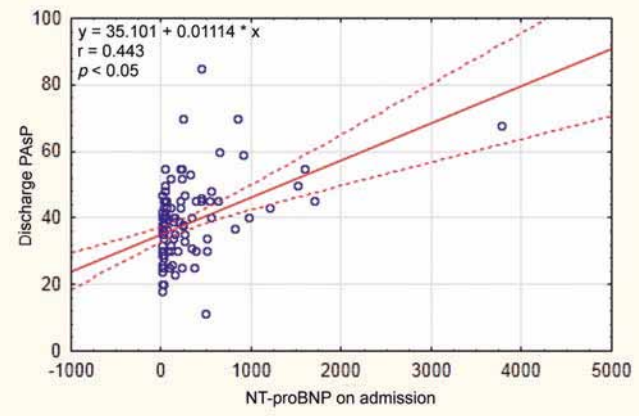

Fig. 2 – The relationship between NT-proBNP levels on admission and pulmonary artery systolic pressure at the time of discharge.

Discussion

During last few years we can see an increasing attention to pulmonary circulation diseases. New specific treatment modalities are coming hand in hand with this interest and as they become more accessible, the result is a better prognosis and quality of life of those patients, who are indicated for such a therapy, especially if they are indicated early.

With the exception of patients, in whom pulmonary embolism is a complication of another underlying disease with unfavorable prognosis, the major adverse prognostic factor after an acute pulmonary embolism is a development of chronic thromboembolic pulmonary hypertension. The aim of our mid- and long-term prospective follow-up of consecutive patients surviving pulmonary embolism is focus on CTEPH risk factors and incidence. We are using routinely obtainable variables (anamnestic, clinical, laboratory and morphologic [echocardiography and pulmonary CTA] data). In this paper we present discharge characteristics of our cohort and some initial implications.

Up to now, the incidence of CTEPH in survivors of pulmonary embolism is not well defined. More accurate prediction is complicated due to several reasons. One of them is the fact, that one half of patients with angiographically documented CTEPH has no history of venous thromboembolism [9,10], which corresponds to the finding, that only one half of patients with PE is properly diagnosed and treated. In addition two thirds of patients with deep venous thrombosis have perfusion lung scintigraphy defects without any PE symptoms [11].

Thromboembolic material in pulmonary vascular bed is in almost all cases early (in experiment within 4–6 weeks) [12–14] resolved by fibrinolytic system. In clinical trials there is a slow resolution of perfusion defects at pulmonary perfusion scintigraphy and so called stable phase is reached in about 2 months in 90% of patients [5]. Perfusion defects persistence after 3 months of anticoagulant therapy is described in two thirds of patients [15].

CTEPH rises from incomplete dissolution and organization of thromboembolic masses, which lead to persistent pulmonary vascular bed obstruction. But pulmonary embolism is believed to be a trigger of subsequent functional and morphological changes in pulmonary arteries wall, which are exposed to increased wall shear stress, but even in those it is situated distally, beyond the obstruction [16,17]. The changes include vascular smooth muscle hypertrophy, intimal thickening and fibrotisation and plexiform lesions formation. Plexiform lesions are organized and recanalised aneurysmatic spots of small pulmonary artery branches proximally and even distally to obstructed areas as a reaction to increased wall shear stress and endothelial proliferation [18]. These changes are identical with pattern which can be seen in patients with pulmonary arterial hypertension. Thus, they represent nonspecific small pulmonary arterial wall reaction to chronically in-

Table 7 – CTEPH incidence data.

	CTEPH incidence
Fedullo PF (2001) [1]	0.1–0.5%
Becattini C (2006) [2]	0.8% (1.5% idiopathic PE) (n = 259)
Miniati M (2006) [3]	1% (n = 320)
Pengo V (2004) [4]	3.8% (n = 223)
Ribeiro (1999) [5]	5.1% (n = 78)
Dentali F (2009) [6]	8.8% (n = 91)

Table 8 – CTEPH risk factors (based on [19,20]).

History of thromboembolic event, especially recurrent idiopathic PE
History of oncological disease
Extensive lung perfusion defects, massive PE
Pulmonary hypertension persistence 5 weeks since acute PE
Atrio-ventricular shunts
Central venous catheter or intracardiac pacemaker electrodes
History of splenectomy
Antiphospholipid syndrome, increased factor VIII
Hypothyreosis and thyreoidal substitution therapy
Chronic inflammatory diseases (e. g. nonspecific bowel inflammations, osteomyelitis)
Blood group different from 0
Increased levels of plasmatic lipoprotein (a)

creased pulmonary artery pressure, which ultimately contributes to further hemodynamic worsening. Additional mechanism of increased pulmonary vascular resistance is an in-situ thrombosis, and/or pulmonary embolus extension to unobstructed areas. Another possibility is also embolisation of partially organized emboli, which could not be dissolved by endogenic or pharmacologic fibrinolysis.

RV is chronically exposed to inappropriate pressure overload. It becomes hypertrophic, and afterwards dilates. Secondary insufficiency of tricuspid valve contributes to further deterioration by RV volume overload. When compensation mechanisms are exhausted, right ventricular failure evolves.

From so far existing CTEPH incidence data (Table 7), the most convincing and accepted is Swedish study, in which CTEPH incidence during 2 years of follow-up in PE survivors was 3.8% [4]. Known CTEPH risk factors are summarized in Table 8.

If there is not any other comorbidity with adverse prognosis, the outcome is determined mainly by the degree of pulmonary hypertension. Values above 30 mmHg are prognostically unfavorable, especially with concomitant right ventricular failure. On the other hand, prognostically nonsignificant is the number of PE recurrences, their extent and localization [21].

The incidence of CTEPH in the survivors of pulmonary embolism is not clear. It is difficult to obtain more accurate data due to several factors. Almost one half of patients with CTEPH have no history of venous thromboembolism and in 30% of patients with CTEPH there is no history of pulmonary embolism [22].

In our own cohort of patients with PE echocardiographic, signs of pulmonary hypertension at discharge time were present in more than one half of patients. Respecting recent guidelines those patients should be dispensarised with focus to possible CTEPH development. According to our results pulmonary hypertension persistence at the time of discharge can be predicted also from high initial NT-proBNP levels and echocardiographic signs of pulmonary hypertension on admission, especially in the elderly patients. Residual pulmonary hypertension at discharge was present in 50.8% cases in our study population, at this time there was strong relationship between PH and elevated NT-proBNP. The development of CTEPH cannot be estimated in such a short time after acute PE, patients will be followed-up and possible development of CTPEH will be evaluated at 6, 12 and 24 month period.

Possible limitation of our study is that our cohort is relatively small due to monocentricity and therefore further evaluation on multicenter basis may be warranted.

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