

Assessment of the clinical course of patients with acute pulmonary embolism and right heart thrombi — a single centre experience

Ocena przebiegu klinicznego u chorych z ostrą zatorowością płucną i skrzeplinami w jamach prawego serca. Doświadczenia jednego ośrodka

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Abstract

Introduction. Assessment of the clinical course of patients with acute pulmonary embolism (PE) and a right heart thrombus (RiHT).

Material and methods. The analysis included 13 consecutive patients with echocardiographically detected RiHT and acute PE who were treated in our department. The endpoints were 30-day all-cause mortality and 30-day acute PE-related mortality. When a clear alternative cause of death was reported, a non-acute PE-related death was diagnosed and this contributed to 30-day all-cause mortality. All other fatalities were classified as related to acute PE.

Results. High risk acute PE was diagnosed in 4 of 13 patients, and intermediate risk acute PE was diagnosed in the remaining 9 patients. Thrombolysis was the first-choice treatment in 4 (31%) patients, 6 (46%) patients were only anticoagulated, and the remaining 3 (23%) patients underwent surgical treatment. The main indication for embolectomy was RiHT entrapped in a patent foramen ovale (PFO). Two patients died during the first 30 days; they were hemodynamically unstable and deaths occurred within 48 hours since the diagnosis. No hemodynamically stable patients died within 30 days since the diagnosis.

Conclusions. Thirty-day mortality in patients with RiHT depended mostly on the patient's clinical condition and was not related to the presence or morphology of the thrombus. Patients with shock or hypotension may possibly benefit more from primary invasive treatment compared to drug therapy.

Key words: pulmonary embolism, right heart thrombus, prognosis

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Introduction

Continuous progress in the diagnosis and treatment of acute pulmonary embolism (PE) allows increasingly efficient and effective patient care. However, lack of reliable clinical evidence still makes treatment decisions challenging in some situations, such as the presence of a right heart thrombus (RiHT). RiHT is diagnosed in about 4% of patients with acute PE [1] but its rate during the first 24 hours since admission in hemodynamically unstable patients may be as high as 18% [2]. Identification of RiHT in patients with clinically suspected acute PE allows the diagnosis and requires treatment to be initiated but the optimal management approach has not been established. As stated in the European guidelines on the diagnosis and management of acute PE, the presence of RiHT is associated with worse outcomes [3]. In the recently reported Italian IPER registry that included 57 patients with RiHT, the latter was not found to be associated with early in-hospital mortality [4]. Some other studies also did not report an increased mortality in patients with acute PE and RiHT [5, 6]. The multicentre Right Heart Thrombi European Registry (RIHTER) included 138 patients with RiHT to evaluate the prognostic importance of the size, mobility, and shape of RiHT in relation to other prognostic factors in patients with acute PE. This registry showed that patient outcomes depend mostly on the hemodynamic consequences of acute PE and not the shape, size, or mobility of the thrombus [7]. In this study, we reported in more details the characteristics and clinical course of patients with PE and RiHT who were investigated and treated in our centre. Some

of these findings has been already covered in the summary of the RIHTER registry results [7].

Material and methods

We studied subsequent 13 patients with echocardiographically detected RiHT and acute PE who were treated in our department. This patient group comprised 2% of 746 patients with confirmed acute PE who were treated in our department during the same period. Parameters that characterized the hemodynamic status on admission included systolic blood pressure (SBP), presence of shock or hypotension, the sPESI (simplified pulmonary embolism severity index) score [8], presence and severity of right ventricular overload by echocardiography, the shock index (SI) defined as the ratio of heart rate to systolic blood pressure, and laboratory markers of myocardial damage, i.e. blood levels of cardiac troponins and N-terminal B-type natriuretic propeptide (NT-proBNP) (Table 1). Two management approaches were identified – aggressive (thrombolysis and/or invasive treatment) and conservative, i.e., anticoagulation only.

In accordance to the ESC guidelines, hypotension was defined as SBP < 90 mm Hg not due to other causes, such as acute arrhythmia, hypovolemia, or sepsis [3]. The sPESI score was calculated as the individual sum of scores for each criterion: age > 80 years, oxygen saturation < 90%, SBP < 100 mm Hg, heart rate > 110 bpm, and the presence of chronic heart failure or chronic lung disease [8]. Patients without these conditions were considered low-risk PE. Right

Table 1. Clinical characteristics of the patients

Parameter	RiHT+ N = 13	Fatalities N = 2*	Survivors N = 11
Age [years]	57.8 ± 25.9	78 and 64 years	55.4 ± 27.5
Gender (F/M)	7/6	2/0	5/6
SaO ₂ [%]	92.3 ± 6.3	96 and 83	93.0 ± 6.0
SBP [mm Hg]	106.1 ± 28.4	70 and 80	111.8 ± 27.1
HR [bpm]	100.3 ± 18.4	115 and 110	98.1 ± 19.2
SI ([bpm]/[mm Hg])	1.0 ± 0.4	1.6 and 1.4	0.9 ± 0.3
sPESI > 0, n [%]	11 (85)	2 (100)	9 (82)
Concomitant diseases, n [%]**	5 (38)	1 (50)	4 (36)
Tn (+)***	7 (54)	2 (100)	5 (45)
NT-proBNP > 500 [pg/mL]	8 (62)	1 (50)	7 (64)
Severity of acute PE: high/moderate/low risk (n)	4/9/0	2/0/0	2/9/0
DVT, n [%]	8 (62)	2 (100)	6 (54)

*Data as absolute values; **Concomitant conditions: malignancy, COPD, heart failure; ***Tn (+): troponin I or T level > 0.1 ng/mL, high-sensitivity troponin T level above the upper limit of the reference range for a given method; RiHT – right heart thrombus; F – female; M – male; SaO₂ – oxygen saturation; SBP – systolic blood pressure; HR – heart rate; SI – shock index; sPESI – simplified pulmonary embolism severity index; NT-proBNP – N-terminal B-type natriuretic propeptide; PE – pulmonary embolism; DVT – deep vein thrombosis; COPD – chronic obstructive pulmonary disease

ventricular overload by echocardiography was defined as the RV/LV dimension ratio in the 4-chamber view > 0.9, presence of the McConnell sign, or interventricular septum flattening and paradoxical motion. Laboratory markers of right ventricular overload included elevated NT-proBNP level (> 500 pg/mL) and troponin T or I level above 0.1 ng/mL, or high-sensitivity troponin T level above the upper limit of the laboratory-specific reference range [9]. Based on the European Working Group on Echocardiography report, three types of thrombus morphology were distinguished – oblong, oval, and mural [10].

The diagnosis of PE was based on multidetector row computed tomography imaging (16-slice GE LightSpeed Pro and 64-slice Toshiba Aquilion). Acute PE was diagnosed when thrombi were identified in at least segmental pulmonary arteries.

The endpoints were 30-day acute PE-related mortality and 30-day all-cause mortality. When a clear alternative cause of death was reported, such as sepsis or massive haemorrhage, a non-PE-related death was diagnosed. All other fatalities were classified as related to PE.

Statistical analysis

Statistical analysis was performed using the STATISTICA 2011 and MedCalc software. Dichotomous variables were compared using the chi-square test. Nonlinear variables were compared using the nonparametric Mann-Whitney U test. Predictors of mortality were determined using logistic regression. Cut-off points with highest sensitivity and specificity were determined using ROC curves. $P < 0.05$ was considered statistically significant. The study protocol was approved by the Bioethics Committee at the Medical University of Warsaw.

Results

Clinical characteristics

Right heart thrombus was identified in 13 patients, including mostly oblong RiHT (69%) and one mural thrombus. Except for one case, most (92%) thrombi were mobile. In two patients, the thrombus was entrapped in a patent foramen ovale (PFO) and protruded to the left atrium. At the diagnosis of RiHT, four patients were hemodynamically unstable (high risk PE), and moderate risk PE was diagnosed in the remaining 9 patients based on the evidence of right ventricular overload and increased cardiac markers.

Clinical course

Management of patients with RiHT

Thrombolysis was the first-choice treatment in 4 (31%) patients (alteplase 100 mg over 2 hours in 3 patients; in the fourth patient, the dose was reduced to 70 mg over 2 hours due to an increased bleeding risk), 3 (13%) pa-

tients underwent surgical treatment, and the remaining 6 (46%) patients were only anticoagulated (Table 2).

High risk PE by the ESC definition was the reason for thrombolytic therapy in 2 patients [3]. In the remaining 2 patients, moderate risk PE was diagnosed and thrombolytic therapy was administered due to no improvement despite intravenous unfractionated heparin infusion for several hours. One death was noted in the group treated with thrombolysis – a 78-year-old woman (patient No. 1) treated due to high risk PE. The cause of death was recurrent pulmonary embolism due to heparin-induced thrombocytopenia (HIT). Due to thrombocytopenia, the patient was not considered a candidate for surgical treatment, and repeated thrombolysis was administered due to shock. The clinical course was also notable in the other unstable patient, a 27-year-old male with multiple endocrine neoplasia type 1 (MEN I) and active pituitary adenoma. Due to morbid obesity and high operative risk, thrombolysis was administered despite the presence of intracranial tumour, with very good treatment outcomes.

The decision to proceed with surgical treatment was made mainly due to the presence of a thrombus entrapped in a patent foramen ovale (PFO) and protruding to the left atrium (in 2 patients – No. 6 and 11). In addition, one patient (No. 7) was treated surgically due to a very large thrombus size and critical condition. This patient had sepsis associated with the presence of indwelling haemodialysis catheter and severe respiratory failure that required ventilatory support. In addition, this patient underwent graftectomy of a transplanted kidney one week before acute PE was diagnosed, which increased the risk of bleeding in case of thrombolytic treatment. Of note, none of surgically treated patients died during 30 days since the diagnosis of RiHT, and one death during further follow-up was not related to acute PE.

The remaining patients received anticoagulation only. This group included 2 patients with high-risk PE in whom more aggressive treatment was contraindicated. One of these patients had disseminated malignancy with multiple metastases, including in the central nervous system. This patient was not a candidate for causal treatment of malignancy at the time of the diagnosis of acute PE and died after 3 days of treatment. The other patient with high risk PE who received anticoagulation only was an 85-year-old critically ill woman, bedridden for 6 months before the diagnosis of acute PE, with severe acute kidney injury at the time of the diagnosis. This patient died in the fourth month of the hospital stay due to worsening uraemia. Due to her poor general condition, she was not considered a candidate for renal replacement therapy.

Predictors of mortality

Two patients (15%) died during the first 30 days; they were hemodynamically unstable, in an advanced age

Table 2. Clinical characteristics and the clinical course in patients with the right heart thrombus (RiHT)

No.	Gender, age [years]	Characteristics	RiHT	Treatment and clinical course
1	F 78	High risk acute PE SBP 70 mm Hg HR 115 bpm SI 1.6	Oblong, highly mobile, 10 × 40 mm	Patient successfully treated with rt-PA 0.6 mg/kg due to high-risk acute PE. HIT diagnosed on the 8 th day of heparin treatment, with recurrent acute PE (fondaparinux was initiated). Acute worsening after 3 days, RiHT was diagnosed, the patient was not considered a candidate for surgical treatment, treated with repeated rt-PA administration, died in 4 th day after the diagnosis of RiHT
2	M 26	High risk acute PE SBP 70 mm Hg HR 115 bpm SI 1.6	In the right atrium and the right ventricle, oblong, highly mobile, 10 × 70 mm, TEE: RiHT without communication with PFO	Morbid obesity BMI 55.6 kg/m ² , MEN I, pituitary adenoma, treated with rt-PA 100 mg/2 h i.v., followed by UFH for 3 days, LMWH and VKA. Follow-up echo at 24 h – no RiHT, discharge home in good clinical condition at 8 th day of treatment
3	F 85	High risk acute PE SBP 80 mm Hg HR 100 bpm SI 1.25	Length approx. 30 mm, oblong, moderately mobile	Acute prerenal kidney injury, eGFR 22 mL/min/1.73 m ² , thrombolytic treatment was not administered due to generally poor condition of the patient (immobilisation, cachexia), treated with UFH for 3 days, followed by LMWH, with clinical improvement, follow-up echo at 72 h – RiHT still present, later without RiHT. The patient died in the 4 th month of hospital stay due to sepsis complicated by multiorgan failure
4	F 64	High risk acute PE SBP 80 mm Hg HR 110 bpm SI 1.375	Length > 50 mm, oblong, highly mobile, protruding through PFO to the left atrium	Disseminated malignancy during palliative chemotherapy, CNS metastases, massive proximal lower limb deep venous thrombosis. Follow-up echo at 2 days of treatment – persisting RiHT. Treated with UFH i.v., died after 3 days of treatment
5	M 37	Moderate risk acute PE SBP 120 mm Hg HR 100 bpm SI 0.8	12 × 67 mm, highly mobile, oblong, in the right atrium and the right ventricle	Celiac disease, chronic hepatitis C. Treated with rt-PA 100 mg/2 h i.v. due to large size and mobility of RiHT, followed by UFH for 3 days, LMWH and VKA, follow-up echo at 48 h – no RiHT, discharged home at 7 th day after thrombolysis
6	F 74	Moderate risk acute PE SBP 150 mm Hg HR 65 bpm SI 0.4	8 × 40 mm, oblong, highly mobile, entrapped in PFO	Hyperthyroidism treated with thiamazole, chronic kidney disease eGFR 54 mL/min/1.73 m ² . Surgical treatment with removal of the thrombus, followed by LMWH, discharged home at 14 th day in a good general condition
7	M 27	Moderate risk acute PE SBP 90 mm Hg HR 120 bpm SI 1.3	10 × 47 mm, oblong, highly mobile in the right ventricle	History of kidney transplantation, graftectomy 2 days before diagnosis of RiHT, renal replacement therapy – haemodialysis, sepsis, acute respiratory failure. Surgical treatment on the 4 th day due to worsening of the clinical conditions and contraindications to thrombolysis, follow-up echo at 7 th day of treatment – no RiHT, died in the 4 th month of intensive care due to worsening respiratory failure secondary to recurrent treatment-resistant sepsis
8	F 79	Moderate risk acute PE SBP 110 mm Hg HR 75 bpm SI 0.7	8 × 16 mm, immobile, mural	Diabetes type 2, rheumatoid arthritis. Treated with LMWH, follow-up echo at 72 h – no RiHT, discharged home at 6 th day in a good general condition
9	M 84	Moderate risk acute PE SBP 100 mm Hg HR 84 bpm SI 0.84	17 × 24 mm, oval, moderately mobile, another thrombus 21 × 17 mm attached to a pacemaker lead, oblong, mobile in the right ventricle	Heart failure NYHA class III, LVEF approx. 25%, diabetes type 2, acute kidney injury, permanent atrial fibrillation. Treated with LMWH, follow-up echo at 72 h – persisting RiHT, discharged home at 14 th day in an improved condition without RiHT (resolution in follow-up echo at 8 th day)

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Table 2 (cont.). Clinical characteristics and the clinical course in patients with the right heart thrombus (RiHT)

No.	Gender, age [years]	Characteristics	RiHT	Treatment and clinical course
10	M 67	Moderate risk acute PE SBP 100 mm Hg HR 110 bpm SI 1.1	Length 14 mm, oval, moderately mobile	Heart failure NYHA class II, LVEF approx. 25%, thrombolysis followed by treatment with LMWH and VKA, follow-up echo at 24 h – no thrombus, discharged home at 6 th day in a good general condition
11	M 21	Moderate risk acute PE SBP 120 mm Hg HR 120 bpm SI 1.0	24 × 9 mm, oblong, highly mobile, protruding through PFO to the left atrium	Urgent surgery due to worsening hemodynamic status and RiHT communication with PFO, followed by LMWH and VKA, follow-up echo at one week after the surgery – no thrombus, discharged home at 24 th day in a good general condition
12	F 26	Moderate risk acute PE SBP 140 mm Hg HR 110 bpm SI 0.8	20 × 20 mm, oval, moderately mobile, TEE: RiHT confirmed, without communication with PFO	Morbid obesity, nephrotic syndrome. UFH for 3 days followed by LMWH, follow-up echo at day 3 and 11 – smaller RiHT, discharged home at 12 th day with RiHT in a good general condition. Follow-up echo after several months – much smaller mass, malignancy was excluded
13	F 83	Moderate risk acute PE SBP 150 mm Hg HR 80 bpm SI 0.5	Oblong, highly mobile, length approx. 30 mm	UFH for 3 days, followed by LMWH, follow-up echo at 3 th day – persisting RiHT, discharged home at 14 th day without RiHT (resolution at day 8), in an improved condition

F – female; PE – pulmonary embolism; SBP – systolic blood pressure; HR – heart rate; SI – stroke index [HR/SBP]; rt-PA – recombinant tissue plasminogen activator; HIT – heparin-induced thrombocytopenia; M – male; TEE – transesophageal echocardiography; PFO – patent foramen ovale; BMI – body mass index; MEN I – multiple endocrine neoplasia type 1; LMWH – low-molecular-weight heparin; UFH – unfractionated heparin; VKA – vitamin K antagonist; eGFR – estimated glomerular filtration rate; CNS – central nervous system; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction

and with significant comorbidities (malignancy, chronic obstructive pulmonary disease [COPD]). No hemodynamically stable patients died within 30 days since the diagnosis of RiHT.

Discussion

Right heart thrombi are present in about 4% of patients with acute PE [1, 3, 4, 6, 11] but this rate increases to about 18% [2] to 22% [12] in patients hospitalized in intensive care units. In our centre, the rate of RiHT in patients with acute PE was about 2% (13 of 746 subsequent patients). The authors of the guidelines on the diagnosis and treatment of acute PE noted that the presence of RiHT is associated with worse treatment outcomes [3]. According to other reports, treatment outcomes in patients with RiHT are comparable to those in the general population of acute PE patients [4–6]. Due to lack of randomized studies, it is difficult to establish the effect of RiHT on prognosis. For the same reason, it is controversial whether RiHT is an independent risk factor of early mortality. The RIHTER registry was an attempt to determine the effect of RiHT on treatment outcomes in patients with acute PE [7]. Data on 138 patients with RiHT were compared

with a control group that included 276 patients with acute PE. The mortality rate in the study group was 19%, significantly higher compared to the control group (8%). In both group, all low risk PE patients survived, and the highest mortality rate was noted among hemodynamically unstable patients.

Of note, most deaths occurred within 48 hours after the diagnosis, which suggests that patients with RiHT should be initially managed in an intensive care unit. Similarly to our study, predictors of early mortality included indicators of hemodynamic instability and clinical parameters (SPESI score, SI, hypotension), while morphology of the thrombus did not affect prognosis. Similar results were obtained in subgroup analyses in the IPER [4] and ICOPER [1] registries.

The choice of appropriate therapy in patients with RiHT is still debatable and differs between centres. As suggested in the ESC guidelines, anticoagulation only may be not sufficient in these patients [3]. This suggestion is supported by the literature data showing the highest mortality in patients treated with anticoagulation only [6, 13, 14]. Of note, similar mortality was observed in patients treated with surgical embolectomy, which was not confirmed by our observations. In our study, mortality did not depend on the type of treatment but mostly on the severity of acute PE, and no deaths

were noted among the patients treated surgically. Previous studies did not report detailed data on the clinical condition of patients treated surgically, so perhaps this treatment was used in critically ill patients, which might explain high mortality associated with surgical treatment. This increase in mortality is also in contrast with the RIHTER registry data which showed a trend towards greater survival in patients treated invasively [7]. Thus, the safety of invasive treatment has not been clearly established but this therapy should be undertaken in patients with RiHT and PFO.

Study limitations

The main study limitation was a low number of patients that made it difficult to perform full statistical analysis and obtain an appropriate control group. Due to a retrospective nature of this analysis, not all echocardiographic parameters and clinical data from the time of the diagnosis were

available in all cases. No recommendations are available to guide treatment in patients with RiHT. Thus, the choice of the treatment method often depends on local expertise and opinions.

Conclusions

Our findings indicate that 30-day mortality in patients with RiHT depends mostly on the patient's clinical condition. It seems that the choice of the treatment method should be primarily dictated by the hemodynamic status of the patient. Due to the fact that mortality in patients with RiHT occurred mostly within 48 hours after the diagnosis, these patients should be initially managed in an intensive care unit.

Conflict of interest(s)

The authors declare no conflicts of interests.

Streszczenie

Wstęp. Ocena przebiegu klinicznego chorych z ostrą zatorowością płucną (PE) i skrzeplinami w jamach prawej części serca (RiHT) diagnozowanych i leczonych w jednym ośrodku.

Materiał i metody. Analizą objęto kolejnych 13 chorych ze stwierdzoną echokardiograficznie RiHT i ostrą PE leczonych w klinice autorów. Punktem końcowym była 30-dniowa śmiertelność całkowita oraz zależna od ostrej PE. Zgony niezwiązane z ostrą PE rozpoznawano, jeżeli występowały inne jednoznaczne przyczyny. W innych sytuacjach zgony zakwalifikowano jako związane z ostrą PE.

Wyniki. U 4 spośród 13 chorych z ostrą PE i RiHT rozpoznano ostrą PE wysokiego ryzyka, u pozostałych 9 osób rozpoznano ostrą PE pośredniego ryzyka. Jako leczenie pierwszego wyboru trombolizę zastosowano u 4 (31%) chorych, wyłączone leczenie przeciwzakrzepowe wybrano u 6 (46%) osób, natomiast zabieg kardiochirurgiczny przeprowadzono u 3 (23%) chorych z RiHT i ostrą PE – wskazaniem do jego wykonania była skrzeplina wklonowana w drożny otwór owalny (PFO). W ciągu 30 dni zmarło 2 chorych (15%) – były to osoby niestabilne hemodynamicznie. W ciągu 30 dni od rozpoznania nie zmarł nikt spośród chorych w stanie stabilnym, a większość zgonów nastąpiła w trakcie pierwszych 48 h hospitalizacji.

Wnioski. Śmiertelność 30-dniowa u chorych z RiHT zależy głównie od stanu klinicznego. Osoby z niedociśnieniem lub wstrząsem mogą odnieść większą korzyść z pierwotnego leczenia inwazyjnego niż z leczenia farmakologicznego.

Słowa kluczowe: zatorowość płucna, skrzeplina w jamach prawego serca, rokowanie

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