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Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Case Report / Приказ случаја

Dušanka Obradović [1,2,†], Biljana Joveš [1,2], Svetislava Milić[1],
Jovan Matijašević [1,2], Stanislava Sovilj-Gmizić[1]

Deciding on thrombolytic therapy in pulmonary embolism – Is there room for lactate?

Одлука о тромболитичкој терапији код плућне емболије – Да ли има простора за лактат?

[1] Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica,Serbia;
[2] Faculty of Medicine Novi Sad, University of Novi Sad. Serbia

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† **Correspondence to:**
Dušanka OBRADOVIĆ
Put Doktora Goldmana 4, 21204 Sremska Kamenica, Srbija
E-mail: **dudaob@yahoo.com**

Deciding on thrombolytic therapy in pulmonary embolism – Is there room for lactate?

Одлука о тромболитичкој терапији код плућне емболије – Да ли има простора за лактат?

SUMMARY

Introduction Diagnostic and therapeutic algorithms for pulmonary embolism (PE) have been frequently modified; however, the first step has remained determination of clinical probability, which dictates further procedures.

The objective was to illustrate therapeutic dilemma in a patient with intermediate high risk for 30 day mortality.

Case outline The patient was 56-years-old woman who was referred as suspected PE. According to Wells score, the patient was deemed as low-probability for venous thromboembolism, and after further stratification she was placed in a group with intermediate high risk for 30-day mortality. PE was confirmed by computerised tomography pulmonary angiography and she initially received heparin. During the further clinical course she developed haemodynamic instability, and she received thrombolytic therapy, with positive outcome. The patient also had increased lactate at admission - marker of tissue hypoperfusion which is not a part of the routine laboratory work-up in PE patients.

Conclusion Current guidelines state that patients with intermediate high risk for 30 day mortality should be treated with heparin, and then continuously monitored in order to timely recognise potential haemodynamic instability and consequently apply thrombolytics. In the outlined case, thrombolytic therapy was apllied only after the patient developed haemodynamic instability, although she previously had early signs of tissue hypoperfusion.

Keywords: pulmonary embolism; thrombolytic therapy; lactate

САЖЕТАК

Увод Дијагностички и терапијски алгоритам за плућну емболију (ПЕ) се више пута мењао, али је увек први корак у постављању дијагнозе одређивање степена клиничке вероватноће постојања ПЕ, што условљава даље процедуре.

Циљ је био да се илуструје терапијска дилема код болеснице са интермедијерно високим ризиком за 30-дневни морталитет.

Приказ болесника Болесница стара 56 година је упућена са сумњом на ПЕ. Према Велсовом бодовном систему припадала је групи са малом клиничком вероватноћом постојања ПЕ, а применом препоручених критеријума групи са интермедијерним високим ризиком за настанак смртног исхода у наредних 30 дана. ПЕ је потврђена КТ-ангиографијом. Примењена је, према препорукама, иницијално хепаринска терапија, а због настанка хемодинамске нестабилности у даљем току и тромболитичка терапија, са позитивним исходом. Код болеснице је иницијално у биохуморалном статусу био повишен маркер ткивне хипоперфузије – лактат, који се не ради рутински код болесника са ПЕ.

Закључак Код болесника са средње високим ризиком од смртног исхода у року од 30 дана, актуелна је препорука да се лечење започне хепарином, а сталним мониторингом на време препознају знаци хемодинамске нестабилности и ординира тромболитична терапија. У приказаном случају, тромболитичка терапија је ординирана тек по развоју хемодинамске нестабилности, упркос претходно присутним раним знацима ткивне хипоперфузије.

Кључне речи: плућна емболија; тромболитичка терапија; лактат

INTRODUCTION

Pulmonary embolism (PE) is a condition with many non-specific symptoms, which is the reason why even today PE is largely underdiagnosed and the correct diagnosis is unfortunately often made post mortem [1]. Incidence of PE is high – among the cardiovascular diseases, it is in the third place, right after myocardial infarction and cerebrovascular insult [2]. Even with all the current guidelines [3,4] for prevention, diagnostics and therapy PE is a very common cause of death not only in the out-patients, but also in the hospitalized patients. The current guidelines [3,4] state that determining clinical probability of PE is a ”conditio sine qua non” in a diagnostic algorithm. Further diagnostic steps depend on the determined level of clinical probability for PE. Further stratification of patients is used to define early mortality risk within 30 days of diagnosing PE. Criteria used for this

stratification include haemodynamic stability, PESI (Pulmonary Embolism Severity Index) [5] (Table 1), signs of right ventricular (RV) dysfunction and elevated cardiac biomarkers (troponin T or I, NT pro BNP-brain natriuretic peptide) (Table 2) [4]. The main criterion when it comes to the choice between anticoagulant therapy versus thrombolytic therapy is the presence of shock, that is haemodynamic instability [4] This decision is often a big challenge in everyday clinical practice, and that is why we choose this particular case in order to illustrate clinical dilemmas in a difficult decision whether to apply thrombolytic therapy or not.

Table 1. Prognostic index for patients with pulmonary embolism based on clinical presentation severity (Pulmonary Embolism Severity Index-PESI) [5].

PESI index		Simplified PESI	Our patient
Age		1 (if older than 80)	
Sex	10		
Carcinoma	30	1	
Chronic heart failure Chronic lung disease	10 10	1	**1**
Heart frequency	20	1	
Systolic blood pressure < 100mmHg	30	1	
Respiratory rate	20		
Temperature < 36°C	20		
Change of mental status	60		
SaO2 < 90%	20	1	
Risk stratification	Class I-IV	≥ 1 points=10.9% risk for early mortality	+

Table 2. Stratification of patients with pulmonary embolism according to the risk for early mortality [4].

Risk for early mortality		Risk factors and scoring systems Shock or hypotension	PESI class III-IV or s PESI ≥1	RV dysfunction confirmed by imaging methods	Cardiac biomarkers (pro BNP and troponin)
High		+	+	+	+
Intermediate	High	-	+	Both positive	
	Low	-	+	Either one (or none) positive	
Low		-	-	Both negative or n/a	
Our patient-Intermediate high		**-**	**+**	**Both positive**	

CASE REPORT

The patient was a 56- year old female who was referred to the Institute of Pulmonary Diseases of Vojvodina for suspected PE. Her symptoms included pain in her right shoulder and also pain which she localised in the right hypochondrium, along with the loss of apetite followed by weight loss of more than 10 kilos during the previous month. Patient's previous medical history showed that she had been diagnosed with bronchiectasis 5 years earlier, which was the cause of several previous hospitalizations at the Institute. At admission, the patient is afebrile, eupneic, normocardic, normotensive, and endinspiratory cracles were audible over the both lung bases. ECG showed incomplete right bundle branch block, sinus rhythm at 80 bpm. Blood gas analysis showed severe type I respiratory insufficiency with the signs of hyperventilation (PaO2 5.76 kPa, PaCO2 4.12 kPa, pH 7.40, SaO2 78.5%). Chest X ray (Figure 1) showed bilateral patchy infiltrates in lower lung fileds, blunted right FC sinus and enlarged cardiac silhouette. According to the Wells scoring system [6]

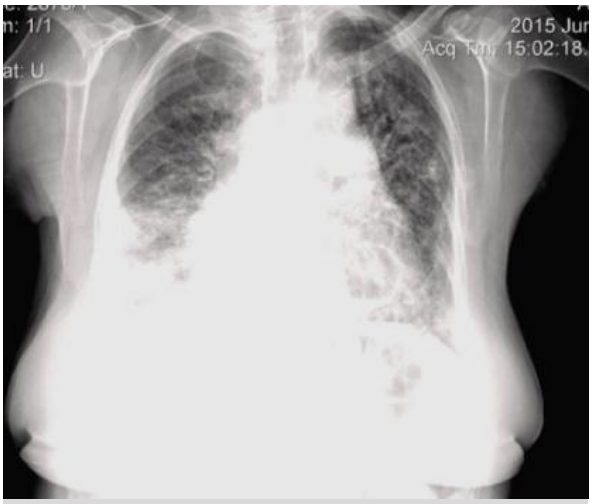


Figure 1. Chest X ray upon admission.

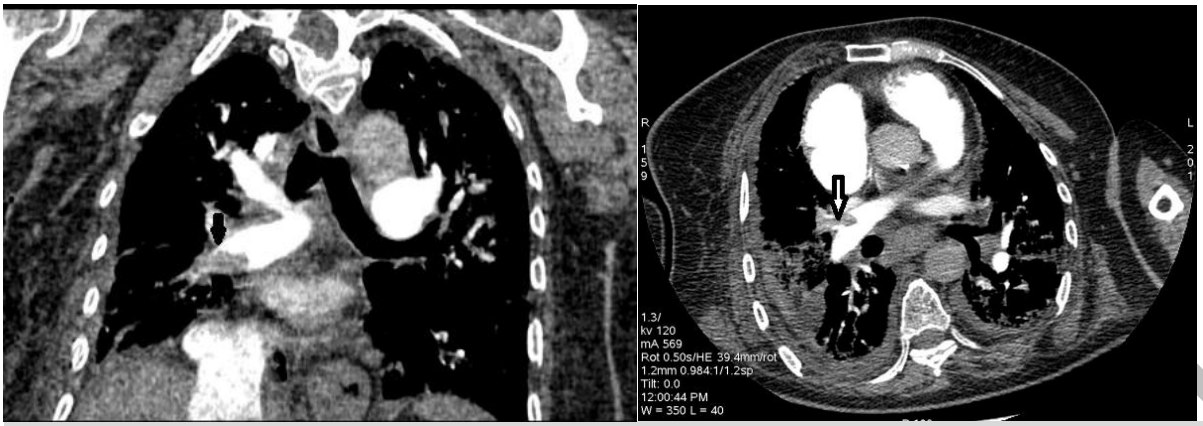
(Table 3), the patient was classified as low clinical probability for PE (Wells 0). American Chest Physicians association recommends [3] that patients with low clinical probability for PE should be tested for PERC criteria (Pulmonary Embolism Rule-out Criteria) [7] (Table 4). Since our patient did not meet PERC criteria (older than 50, and SpO2 lower than 95%), the cited guidelines recomend testing for D dimer, which was in this case extremely elevated (7000 ng/ml). Next and final diagnostic step was computerized tomographic pulmonary angiography (CTPA), which confirmed PE in our patient: there were filling defects in distal part of right pulmonary artery as well as in the middle lobe branch and eight segment branch, along with suspected thrombi in peripheral branches for left lower lobe, and bilateral bronchiectasis (Figures 2a and 2b). Quanadli index of pulmonary obstruction [8] was 19.5%. Laboratory findings included increased WBC count (15×10^9/l), CRP was moderately increased with normal procalcitonin level and elevated serum lactate (2.46 mmol/l). NT pro BNP was also significantly elevated – 15 000 ng/ml. Echocardiography verified signs of chronic pulmonary hypertension with suspected acutisation: enlarged right atrium and ventricle, with the ratio of end-diastolic diameter of right ventricle to left ventricle of > 0.9, free RV wall was hypokynetic, with decreased TAPSE (Tricuspid annular plane systolic excursion) of 8mm, which is an indictor of global RV dysfunction. There was a moderate degree of

Table 3. Wells scoring system for determining clinical probability of pulmonary embolism [6].

Criteria	Points	Our patient
Predisposing factors		
Previous venous thromboembolism	+1,5	**0**
Recent surgery or immobilization	+1,5	**0**
Malignancy	+1,0	**0**
Symptoms		
Hemoptysis	+1	**0**
Clinical signs		
Tachycardia (over 100bpm)	+1,5	**0**
Clinical signs of deep venous thrombosis	+3	**0**
Clinical evaluation		
Alternative diagnosis less likely	+3	**0**
Clinical probability		
Low	0-1	
Intermediate	2-6	**0**
High	>6	
Modified Wells scoring system:		
Low clinical probability of pulmonary embolism	≤4	**≤4**
High clinical probability of pulmonary embolism	>4	

Table 4. Pulmonary embolism rule-out criteria for patients with low pre-test probability.

Clinical characteristics	Meets criterion	Does not meet criterion
Age <50	0	1
Initial heart rate<100bpm	0	1
Initial SaO2<94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 weeks	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1



Figures 2a and 2b. Computerised tomographic pulmonary angiography findings: filling defects in distal part of right pulmonary artery as well as in the middle lobe branch.

pulmonary hypertension (RVSP- RV systolic pressure of 65 mmHg), mainly explained by presence of chronic pulmonary commorbidities (bronchiectasis and chronic respiratory insufficiency). PaccT (Pulmonary artery acceleration time) was 70 msec. Vena cava inferior was dilated and barely collapsible during the inspirium. Ejection fraction of left ventricle was preserved (EF 60%).

Prognostic wise, and calculated according to the simplified PESI index (Simplified Pulmonary Embolism Severity Index-sPESI) [9] (Table 3), this patient had a 10.9% risk for early mortality. Furthermore, since her sPESI index was ≥ 1 and due to the fact that she also had echocardiographic signs of RV dysfuntion along with positive cardiac biomarkers, this patient was classified as high intermediate risk for early mortality, in line with the European Society of Cardiology guidelines. [4] Therapy recommendations for these patients imply anticoagulant therapy, with continuous monitoring of their vital parameters. Thrombolytic therapy within this group is recommended only if haemodynamic instability ensues.

Our patient was diagnosed and treated in accordance with all the cited guidelines – she was admitted to the Institute's High Dependency Unit, where she was continuously non-invasively monitored and received parenteral heparin therapy. However, six hours upon admission, she developed haemodynamic instability and was immediately transferred to Intensive Care Unit (ICU). Her initial APACHE II score was 20 (PDR 35.5, adjusted 32.6). She then received thrombolytic therapy (streptokinase) according to the rapid protocol. After 72 hours there was a recurrent PE, and the intensivists repeated thrombolytic therapy. During the further clinical course she had to be intubated, and due to the necessity for prolonged ventilatory support, percutaneous tracheostomy was performed. After five days in ICU she was stabilized and afterwards transferred to the general ward. Oral anticoagulant therapy was titrated and she was discharged from hospital on day 30.

DISCUSSION

Some conclusions can be drawn from this report; yet, several everyday clinical dilemmas illustrated by this clinical scenario remain.

Firstly, the patient was categorized as having low clinical probability for PE (Wells 0). However, since she met two PERC criteria, PE could not be ruled out without D-dimer. The patient's D-dimer was extremely elevated , which preconditioned final diagnostic step – CTPA. Also, echocardiographic findings were interpreted as chronic pulmonary hypertension with suspected signs of acutisation. Since the patient had a pre-existing lung disease (bronchiectasis, respiratory insufficiency), which probably led to chronic pulmonary hypertension, this was an additional diagnostic dilemma.

Another moot point is appropriate therapy in patients with confirmed PE which are categorized as having intermediate high risk of early mortality, such as our patient. Many patients in this group due well on anticoagulant therapy only; however, there are a few cases were haemodynamic instability develops during parenteral anticoagulant therapy, which then necessitates thrombolytics. This is the reason the patients in this subgroup must be carefully monitored in order to timely recognize clinical deterioration. Research in this field so far has not been conclusive – further studies are needed in order to confirm true predictors of early mortality [10, 11, 12] which would be included in a satisfactory prognostic model. Current research results [11] show that patients with PE who initially had increased lactate levels had significantly higher mortality (17.3% versus 1.6%). Bova et al conducted a research [12] on patients with intermediate mortality risk and showed that the combination of cardiac biomarkers, echocardiographic signs of RV dysfunction, tachycardia and hypotension increased the risk of complications during the initial 30 days as high as seven times. Thromboembolism lactate outcome study (TELOS) [13] in normotensive patients with PE revealed that this group of patients, if they had RV dysfunction, elevated troponin and elevated plasma lactate are considered at intermediate–high risk and this patients had significantly more PE related complications. In recent study [14] which compared the ESC , Bova and TELOS model for more accurately identifying patients with PE and intermediate high risk concluded that adding plasma lactate to the Bova score was significantly powerfull model.

In conclusion, although our patient was initially stable on anticoagulant therapy, there were two episodes of haemodynamic instability during the first 72 hours, which significantly increased her mortality risk. Our dilemma remains: since she had increased lactate levels at the very beginning, indicating poor perfusion despite normal blood pressure, shoud have we given thrombolytic therapy earlier? American College of Chest Physicians suggests that broader criteria for true haemodynamic instability should be considered in these patients, including hypotension, tachycardia, distended jugular veins, clinical signs of poor tissue perfusion and hypoxemia [15], but further studies are warranted.

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