Srce i krvni sudovi 2021; 40(4): 247-250

Review article

Dilemmas in management of pulmonary embolism

Slonodan Obradovic[1,2], Boris Dzudovic[3], Stavros Konstantinides[4,5]

[1]Clinic of Cardiology, Military Medical Academy, Belgrade, [2]School of Medicine, University of Defense, Belgrade, [3]Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade, [4]Center for Thrombosis and Hemostasis, Johannes Gutenberg University Mainz, Germany, [5]Department of Cardiology, Democritus University of Thrace, Greece

Abstract **Background.** Acute pulmonary embolism (PE) is very heterogeneous disease regarding etiology and clinical presentation. Because of that the treatment of PE need multidisciplinary approach creating locally pulmonary embolism response teams (PERT) to deal with various problems associated with PE management.

Review. We try to review some unresolved issues in the management of PE, through the diagnostic, reperfusion, anticoagulation and subgroups treatments. In spite of the recent advancement in oral anticoagulation therapy for venous thromboembolism, risk stratification and diagnosis of chronic thromboembolic pulmonary hypertension, all build in the 2019 European Society of Cardiology guidelines, many important obstacles in PE treatment remained. Unlike acute coronary syndrome, PE field is lacking randomized clinical trials and many important questions are opened in front of everyday practice.

Conclusion. There are many unmet needs in PE management and we need a lot of randomized trials or data from large registries to resolve some burning problems in the handling of PE patients.

Key words Pulmonary embolism, reperfusion, anticoagulation therapy, biomarkers

Introduction

Acute pulmonary embolism (PE) is the third cause of cardiovascular death, behind the acute myocardial infarction and stroke[1]. The annual incidence of acute PE is approximately 100 per 100.000 inhabitants with significant dependents on age. During the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 pandemic, the incidence of PE is probably doubled, since 5% of COVID-19 PCR positive patients who are examined in emergency departments[2] may have PE. Taking these data into account, approximately 7000 patients would have acute PE in Serbia each year. Intra-hospital case-fatality rate of PE is around 10%, and it can be estimated that 500-700 patients die directly from PE every year in Serbia. Apart of this, acute PE is a leading cause of death in pregnancy and the second cause of death in patients with malignant disease. Many hereditary and phenotypic factors can influence the occurrence of PE and we can call PE as a shadow of various diseases and conditions.

Diagnostic dilemmas

Patients in cardio-respiratory arrest. An algorithm for diagnosis acute PE in patients admitted to the hospital under cardiopulmonary resuscitation (CPR) does not exist. Definitely, acute PE is a differential diagnosis. The data of bystanders could be of great value, because acute dyspnea could precede the cardiac arrest and if there are any data about the potential risk factors for PE (recent surgery, trauma or other illness, hospitalization, previous PE, thrombophilia, long journey, use of certain drugs etc.) we will have strong suspicious for acute PE as a cause of cardiac arrest. The signs of deep vein thrombosis also contribute to this conclusion. Bedside echocardiography is the most useful diagnostic tool under these circumstances, where right ventricle dysfunction could be observed in severe acute PE[3]. However, some other diseases also can provoke acute right ventricle dysfunction, or chronic pulmonary hypertension could also make the diagnosis of acute PE difficult. Additionally, if we find trias, acute dyspnea before loss of consciousness, signs of deep vein thrombosis and right ventricle dysfunction on cardiac ultrasound, the diagnosis of acute PE is very probable and we can proceed to reperfusion therapy if patient is hemodynamically stabilized[4]. Bolus of 50 mg tPA can be repeated twice during CPR[4]. Treatment with thrombolysis during resuscitation has resulted to better survival in case-series[5].

Diagnosis of high-risk PE. Current PE ESC guidelines recommend cardiac ultrasound as the first line diagnostic tool in patient with suspected high-risk PE. However, in patients with suspected high-risk acute PE, with hypotension, echocardiography examination at admission may not be sufficient to make a decision for applying thrombolytic therapy, if the thrombus not seen in right heart chambers, or if patient doesn't have clear signs of deep vein thrombosis[6]. Some patients also can be in a very serious condition, or have very fast tachycardia or poor

Corresponding author: Slobodan Obradovic MD PhD, professor of Cardiology, Clinic of Cardiology, Military Medical Academy, School of Medicine, University of Defense, Belgrade, Serbia, e-mail: sloba.d.obradovic@gmail.com

echocardiography windows, which preclude qualitative ultrasound examination. Computed tomography pulmonary angiography (CTPA) should be performed before the decision for reperfusion therapy whenever is possible.

The role of the lower limb venous compression ultrasound examination (CUS). The significance of CUS of lower limbs veins in PE patients with symptoms suggestive of DVT is controversial. What clinical decision we should make according to this finding? Early hospital discharge is recommended without the necessity for CUS using European Society of Cardiology (ESC) risk model and cardiac ultrasound. Recently published HOT-PE study used HESTIA criteria and cardiac ultrasound, and not CUS for the discrimination of low-risk PE patients planned for the early hospital discharge[7].

Looking for malignancy. How deep we should be looking for malignant disease in patient with acute PE without visible reason for that? During CTPA, it should be wise to examine the abdomen, at least upper abdomen and to carefully explore lungs, mediastinum, liver, kidneys, pancreas, spleen and suprarenal glands. We may also determine also determine some tumor markers if deemed necessary, and perform a gynecological examination, mammography or breast ultrasound, and thyroid examination. Rarely, a malignant process may be found and treated before dissemination, but in most cases cancer is already evident and advanced at diagnosis of acute PE. Therefore, rather limited malignancy survey and follow-up of the patients are needed[8].

Looking for thrombophilia. To look or not to look hereditary thrombophilia? Although it usually does not change the dose or duration of anticoagulant treatment for the patient herself/himself[9] we look for hereditary thrombophilia in patients younger than 50 years especially in females because of the possible complications related to pregnancy[10]. It may also be wise to make an effort to diagnose or exclude antiphospholipid syndrome[11], especially in younger patients without clear risk factors for PE.

Cardiac troponin as a marker of higher PE risk. Use of cardiac troponin for the risk stratification in acute PE has some caveats. Cardiac troponin as a marker of cardiac injury can increase in various reasons such as hypoxemia, coronary disease, tachycardia, anemia etc. Especially high-sensitive troponin can be elevated in healthy elderly patients with concomitant renal dysfunction[12]. Therefore, cardiac troponin may be non-specific for the cause of cardiac injury and for the hemodynamic changes in seen in severe PE. The use of troponin as a marker for high-intermediate PE could make a bias toward older patients with higher risk for bleeding. The cut-off value above the 99-percentiles of the normal laboratory range is too low for the risk stratification in PE. However, only cardiac troponin was used in the large randomized PEITHO trial[13] and recognized as the laboratory marker of choice for risk stratification in the 2019 ESC PE guidelines.

Treatment of high-risk acute PE

Reperfusion. Patients with high-risk PE are hemodynamically compromised or in cardiac arrest. They need prompt reperfusion therapy and resuscitation measures such as mechanical ventilation or extra-corporal-membrane oxygenation (ECMO) and inotrope stimulation with norepinephrine[3]. However, recent data has demonstrated that about only 20% of high-risk PE patients has been treated with reperfusion therapy in USA and Germany[14,15]. The high risk for bleeding and severe comorbidities preclude the wider application of thrombolytic therapy in this group of patients. The clinical benefits of surgical embolectomy and catheter-directed therapy have not been tested in randomized trials and the data of their use are limited to case series and reports with strong possibility of bias through the the selection of patients for certain procedures. It is obvious that many patients with high-risk PE are not eligible for the systemic thrombolysis which is the most available treatment option for reperfusion. All other reperfusion therapies need a high degree of expertise and there is a significant learning curve for the different surgical or catheter based procedures.

Treatment of patient in cardiac arrest. Several systemic thrombolytic protocols are approved by ESC. However, none of them are suitable for patient in cardiac arrest, during resuscitation. Tenecteplase, the bolus thrombolysis, is not recommended because of the high bleeding risk of that drug demonstrated in PEITHO study[13]. Other thrombolytic protocols need time. British Thoracic Society Standards of Care Committie Pulmonary Embolism Guideline Development Group guidelines recommended bolus of 50 mg of tPA (or double dose) in this circumstance and that is the most used protocol of thrombolytic therapy during resuscitation in PE patients in the literature[16,17].

Treatment of intermediate-high risk PE

Mortality rate from PE is discrepant between randomized trials and observational studies. In the randomized PEITHO trial[13], intra-hospital mortality was less than 2% in both the thrombolytic and placebo (only anticoagulation) arm. In contrast, in several other trials, in this group of patients' early mortality rate was 5-15%[18,19]. Many experts agree that this group of patients also needs reperfusion therapy, but standard systemic thrombolytic protocols have an unfavorable net effect, with the benefit in prevention of hemodynamic instability offset by the high risk for major bleeding. Catheter directed thrombolysis or mechanical thrombectomy are promising treatment modalities in this group of patients which use a low dose of tPA[20] or only mechanical fragmentation and aspiration of thrombi without thrombolytic therapy[21]. There is currently a gap between clinical practice and guidelines, with an increasing number of centers performing almost routinely catheter-directed therapy in intermediate-high- and high-risk PE patients without supporting evidence from randomized trials.

There are several studies in which reduced, usually a half of the systemic tPA dose was used with doubtful signs of benefit considering the balance between efficacy and safety[22,23]. There is also (only) one small randomized study that compared systemic half-dose tPA with full dose t-PA in high-risk PE[24]. Additionally, comparison of half-dose tPA with low-molecular heparin in patients with intermedi-

ate-high risk PE was not done in a randomized fashion. The largest observational, retrospective trial[22] did not confirm that half-dose tPA was better than full-dose tPA in reducing mortality or bleeding.

How to estimate anticoagulation failure and to aggravate the therapy? Current guidelines recommend close hemodynamic monitoring in patients with intermediate-high PE for at least 48 hours and the use of rescue thrombolytic therapy, or some other reperfusion therapy in case of hemodynamic decompensation[3]. However, if we wait for shock to develop, it may be too late for successful reperfusion therapy. Earlier, sensitive markers of deterioration should be used, such as increase of heart rate, worsening of hypoxemia, fall of systolic blood pressure, but not below the 90 mmHg, increase of blood lactate concentration, or worsening the RV performance on cardiac ultrasound[21]. Some authors also recommended that an unchanged status after 48 hours of anticoagulation therapy means treatment failure and that we should then proceed to reperfusion modalities[21].

When to start a direct oral anticoagulant in patients with severe PE?
It is obvious that it is not prudent to start direct oral anticoagulants (DOAC) as the first line anticoagulation in patients with intermediate-high and high-risk PE because escalation therapy to systemic or local thrombolysis may become necessary[25]. The combination of DOAC and thrombolysis is unknown zone and it should be avoided if possible. The use of thrombolytic therapy (the authors advise a reduced dose of tPA) in patients on DOAC who develop high-risk PE can be an option if there is no possibility to use catheter-based mechanical thrombectomy. DOACs should be initiated as soon as hemodynamic stabilization is achieved[25].

How to choose DOAC?
Four DOAC have had large published randomized trials in patients with venous thromboembolism which in summary showed that they are non-inferior to vitamin K antagonists for the prevention of recurrent VTE events and safer regarding the occurrence of major or clinically relevant non-major bleeding, in particulare causing significantly less intracranial bleeding than vitamin K antagonists[3]. DOACs are also more convenient for use compared to vitamin K antagonists. All these facts to the recommendation of guidelines by international scientific societies to recommend DOACs in preference to a vitamin K antagonist[3]. Rivaroxaban has a higher initial dose, 15 mg bid for 3 weeks, following by once daily dosing of 20 mg per day. For apixaban, the initial dose is 10 mg bid for 7 days followed by 5 mg bid thereafter. Both rivaroxaban and apixaban have robust data from the randomized trials for the extension therapy after the first the six months following an index VTE event, where the lower dose of rivaroxaban (10 mg per day) and apixaban (2.5 mg bid) were effictive and safe for the prevention of VTE for the long-term anticoagulation. We can choose the higher dose of rivaroxaban or apixaban or the lower doses of these drugs depending on the risk for VTE recurrence and hemorrhagic risk[3]. On the other hand, dabigatran has been tested after at least five days of heparin therapy in higher dose of 150 mg bid. Dabigatran was also non-inferior to a enoxaparin/vitamin K antagonists and similarly safe. Lower doses of dabigatran have not been tested for extended anticoagulation. Dabigatran is contraindicated in patients with glomerular filtration rate (GFR) less than 50 ml/min. Both rivaroxaban and apixaban can be used in this indication without dose reduction in patients with GFR>15 ml/min[3].

Can we safely discharge patient with low-risk PE early?
New anti Xa drugs, rivaroxaban and apixaban can be used from the start as anticoagulant therapy in patients with PE. This enables early discharge from the hospital of patients with low-risk PE. Recent trials successfully tested this using HESTIA criteria and simplified PESI score for the selection of patients with lowest PE risk who could be safely treated at home[7,26]. Patients without any of the HESTIA criteria and those who are PESI 0 can be safely treated at home using rivaroxaban or probably apixaban if they have good social support and easy contact with the physician who treated PE. In this circumstances it is important to exclude serious comorbidities, PE recurrence risk and hemorrhagic risk. Cardiac ultrasound may be necessary for the decision.

How to treat symptomatic patients in sub-acute phase of PE?
A small percentage of patients have persisting symptoms, mostly dyspnea on effort and fatigue, in the subacute phase of PE[27]. These can be accompanied by pulmonary hypertension and RV dysfunction. Cardiac ultrasound, 6-minute walking test, multi-slice detector computed pulmonary angiography, BNP and right heart catheterization is needed before treatment of these patients. Some of them may benefit from sugical pulmonary endarterectomy, percutaneous balloon pulmonary angioplasty or early treatment with drugs for pulmonary hypertension.

Unmet needs in the management of cancer associated thrombosis
There are many unresolved issues in the management of cancer associated thrombosis (CAT). CAT maybe related to tumor and patient characteristics, to surgical, radiation and medicament therapy. VTE associated with *currative* oncology surgery may have very low risk for recurrence and it is very important to manage carefully at follow-up the malignant disease activity after surgery[28]. On the other side, metastatic or advanced local diseases, especially adenocarcinomas may have prolonged thrombotic storm which is resistant to anticoagulant therapy and lead to death. Anti Xa direct oral anticoagulants are at least as (if not more) effective and similarly safe as low molecular weight heparins in patients with active cancer-associated thrombosis[29]. Idiosyncracy on thrombotic reaction to some oncologic drugs is also very often present[30]. Various tumors have very different pathophysiology mechanisms of prothrombotic state. Therefore, we need tumor specific randomized trials for CAT management.

References

1. Belohlavek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp clin cardiol 2013;18(2):129-38.
2. Miro O, Jimenez S, Mebazzaa A, et al. Pulmonary embolism in patients with COVID-19. Eur Heart J 2021;33:3127-42.
3. Konstatinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603.
4. Kurckyian I, Meron G, Sterz F, et al. Pulmonary embolism as cause of cardiac arrest. Arch Intern Med 2000;160:1529-35.
5. Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival: findings from the French national cardiac arrest registry. Chest 2019;156:1167-75.
6. Harjola V-P, Mebazza A, Celutkiene J, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail 2016;18:226-41.
7. Barco S, Schimdtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with oral factor Xa inhibitor rivaroxaban: an international multicenter single-arm clinical trial. Eur Heart J 2020;41:509-18.
8. Van Es N, Le Gal G, Martin-Oten H, et al. Screening for occult cancer in patients with unprovoked venous thromboembolism: a systematic review and meta-analysis of individual patient data. Ann Intern Med 2017;167:410-7.
9. Stern RM, Al-Samkari, Connors JM, Thrombophilia evaluation in pulmonary embolism. Curr Opin Cardiol 2019;34:603-9.
10. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: systematic review. Br J Haemetol 2006;132:171-96.
11. Kelling D, Mackie I, Moore GW, Greer IA, Geaves M. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol 2012;157:47-58.
12. Giannitsis E, Katus HA. Biomarkers for clinical decision-making in the management of pulmonary embolism. Clin Chem 2017; 63(1):91-100.
13. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis in patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370:1402-11.
14. Stein PD, Matta F, Hughes PPG, Hughes JM. Nineteen-year trends in mortality of patien hospitalized in the United States with high-risk pulmonary embolism. Am J Med 2021 (in press).
15. Keller K, Hobhom M, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41:522-9.
16. British Thoracic Society Standards of Care Commitie Pulmonary Embolism Guideline Development GroupThorax 2003;58:470-83.
17. Double bolus alteplase therapy during cardiopulmonary resuscitation for cardiac arrest due to massive pulmonary embolism guided by focused bedside echocardiography. Case Reports in Critical Care 2018; article ID 7986087:1-7.
18. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Resp J 2016;48:780-6.
19. Tong CR, Zhang ZH. Evaluation factors of pulmonary embolism severity and prognosis. Clin Appl Thromb Hemost 2015;21:2773-84.
20. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. JACC Interv 2018;11:1401-10.
21. Pruszczyk P, Federikus A, Kucher N, et al. Percutaneous treatment options for acute pulmonary embolism: a consensus paper of the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and European Association of Percutaneous Cardiovascular Interventions. Eurointervention 2022 (in press).
22. Kiser TH, Burnham EL, Clark B, et al. Half-dose versus full dose algteplase for treatment of pulmonary embolism. Crit care Med 2018;46:1617-25.
23. Brandt K, McGinn K, Quedado J. Low-dose systemic alteplase (tPA) for the treatment of pulmonary embolism. Ann Pharmacother 2015;49:818-24.
24. Wang C, Cheng X, Weng X, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary embolism: a randomized, multicenter, controlled trial. Chest 2010;137:254-62.
25. Leentjens J, Peters M, Kramers C. Initial anticoagulation in patients with pulmonary embolism: thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs? Br J Clin Pharm 2017;83:2356-66.
26. Triaging acute pulmonaryembolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. Eur Heart J 2021;42:3146-57.
27. Fernandes T, Planquette B, Sanchez O, Morris T. From acute to chronic thromboembolic disease. Ann Am Thoracic Soc 2016;13(suppl 3):S207-14.
28. Kim AS, Khorana AA, McCrae KR. Mechanisms and biomarkers of cancer-associated thrombosis. Trans Res 2020;225:33-53.
29. Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res 2019;173:158-163.
30. Steven P. Grover SP, Hisada YM, Kasthuri RS, Reeves BN, Mackman N. Cancer therapy–associated thrombosis. Arterioscler Thromb Vasc Biol 2021;41:1291–305.

Sažetak

Dileme u dijagnostici i lečenju plućne embolije

Slonodan Obradović[1,2], Boris Džudović[3], Stavros Konstantinides[4,5]

[1]Klinika za kardiologiju, Vojno medicinska akademija, Beograd, [2]Medicinski fakultet, Univerzitet odbrane, Beograd, [3]Klinika za urgentnu intrenu medicinu, Vojno medicinska akademija, Beograd, [4]Centar za trombitu I hemostazu, Johannes Gutenberg Univerzitet Mainz, Nemačka, [5]Odeljenje kardiologije, Democritus Univerzitet Trakije, Grčka

Uvod. *Akutna plućna embolija (PE) je veoma heterogeno oboljenje u odnosu na etiologiju i kliničku prezentaciju. Zbog toga tretman PE iziskuje multidisciplinarni pristup i stvaranje lokalnih timova za lečenje PE koji će se uhvatiti u koštac sa raznim problemima u tretmanu PE.*

Pregledni rad. *Pokušali smo da prikažemo problem u današnjem tretmanu PE, kroz dijagnostiku, reperfuziju, antikoagulantnu terapiju i lečenje određenih podgrupa bolesnika. I pored skorašnjeg napretka u lečenju bolesnika sa PE, kao što su uvođenje direktnih oralnih antikoagulantnih lekova, bolje stratifikacije rizika PE i uvrštavanja algoritma za dijagnostiku hronične tromboembolijske bolesti pluća u preporuke za tretman PE iz 2019-te godine, mnogo prepreka u lečenju je ostalo. Suprotno od akutnog koronarnog sindroma, u oblasti PE nedostaju randomizovane studije i mnoga važna pitanja su otvorena u svakodnevnoj praksi.*

Zaključak. *Postoji mnogo važnih, nerešenih pitanja u vezi dijagnostike i lečenja PE, i potrebne su nam brojne randomizovane studije i podaci iz velikih registara da bi bolje lečili PE pacijente.*

Ključne reči: *plućna embolija, reperfuzija, antikoagulantna terapija, biomarkeri*