



# Akutna plućna tromboembolija – primjena fibrinolitičke terapije u liječenju hemodinamski nestabilnog bolesnika u doba pandemije bolesti COVID-19: prikaz slučaja

## Acute Pulmonary Thromboembolism – Use of Fibrinolysis to Treat a Hemodynamically Unstable Patient in the Era of the COVID-19 Pandemic: A Case Report

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**SAŽETAK:** Plućna embolija (PE) često je i potencijalno smrtonosno stanje. Usprkos napretku u dijagnostičkim postupcima, takvo se stanje često otkriva kasno ili se uopće ne otkriva. Opetovane embolije i smrt u bolesnika s PE-om mogu se spriječiti brзом dijagnozom i primjerenim liječenjem. S obzirom na to da PE ima nespecifičnu kliničku sliku i simptomatologiju, oko trećine bolesnika nije niti dijagnosticirano niti liječeno. Znamo da postoji velika razlika u ishodima između liječenih i neliječenih bolesnika s PE-om (25 – 30 % smrtnosti u neliječenih i 2 – 8 % u liječenih bolesnika). Prikazujemo slučaj PE-a u odraslog bolesnika s akutno nastalom zaduhom, povraćanjem, presinkopom, boli u prsima i šokom u doba pandemije bolesti COVID-19.

**SUMMARY:** Pulmonary embolism (PE) is a common and potentially fatal condition. Despite advances in diagnostic procedures, late detection and non-detection of this condition is also not uncommon. In patients with PE, recurrent embolisms and death can be prevented with prompt diagnosis and adequate treatment. Due to presentation with a non-specific clinical picture and symptomatology, unfortunately almost one third of the patients remain undiagnosed and untreated. We know that there is a large difference in outcome between treated and untreated patients with PE (25-30% mortality in untreated and 2-8% in treated patients). We present a case of PE in the era of the COVID-19 pandemic in an adult patient with acute dyspnea, vomiting, presyncope, chest pain, and shock.

**KLJUČNE RIJEČI:** plućna embolija, COVID-19, šok, fibrinolitička terapija

**KEYWORDS:** pulmonary embolism, COVID-19, shock, fibrinolytic therapy.

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### Uvod

Akutna plućna tromboembolija česta je bolest u centrima za hitan prijam te je dijagnostički izazov za svakodnevnu kliničku praksu. Plućna embolija (PE) i dalje je značajan uzrok pobola i smrtnosti koji zahtijeva brzu dijagnozu i liječenje. Riječ je o poremećaju plućne cirkulacije zbog stvaranja tromba. Tromb može nastati kao posljedica hiperkoagulabilnosti, stagnacije krvi ili oštećenja endotela u krvnim žilama, što je skup promjena koji se naziva Virchowljeva trijada. Predisponirajući čimbenici mogu biti duboka venska tromboza, pretilost, imobiliziranost, intervencij-

### Introduction

Acute pulmonary thromboembolism is a common disease in emergency centers that is a diagnostic challenge for clinicians. Pulmonary embolism (PE) remains a significant cause of morbidity and mortality that requires prompt diagnosis and treatment. PE is a disorder of pulmonary circulation as a result of thrombus formation. Thrombus formation may be due to hypercoagulability, blood stasis, or damage to the endothelium of blood vessels, a set of changes known as the Virchow's triad. Predisposing factors may be: deep vein thrombosis, excessive

ski postupci, starija životna dob, uporaba kontracepcijskih ili nekih drugih skupina lijekova (hormoni, glukokortikoidi itd.). Najčešći su klinički simptomi sinkopa, dispneja, bol u prsnoj koži, hemoptiza i iznenadna srčana smrt. Klinički tijek može biti: fulminantan (sinkopalna PE), akutan (masivna PE), subakutan (submasivna PE) i kroničan (kronično plućno srce). Liječenje je prije svega fibrinolitičko i antikoagulacijsko, uz primjenu rotablačijske fragmentacije i određenih drugih kirurških postupaka koji uključuju embolektomiju, trombendarrektomiju, implantaciju venskih filtara i drugo.<sup>1-8</sup>

## Prikaz bolesnika

Bolesnik u dobi od 79 godina javio se na hitni prijam zbog znojenja, povraćanja, boli u prsima i otežanog disanja. Simptomi su počeli znojenjem i povraćanjem dan prije primitka u bolnicu, dok su se bol u prsima i otežano disanje pojavili nekoliko sati prije primitka. U anamnezi se saznaje o arterijskoj hipertenziji unatrag nekoliko godina, koja je bila dobro kontrolirana, te o koronarnoj bolesti srca koja je liječena implantacijom stenta u cirkumfleksnu arteriju prije 10 godina. Usto, bolesnik navodi uzimanje kortikosteroida koji mu je prije šest mjeseci pripisao dermatolog zbog dijagnoze pemfigusa. U bolesnika nema prisutne ovisnosti ili alergije na lijekove, hranu itd. Obiteljska je anamneza bila negativna što se tiče relevantnih bolesti. Nakon pregleda u hitnoj službi te lošega općega stanja sa znakovima kardiogenog šoka (arterijski tlak 90/50 mmHg, saturacija kisika 55 %, EKG nakon primitka: sinusni ritam s frekvencijom od 118/min, s morfoloijom karakterističnom za blok desne grane; **slika 1**), bolesnik je primljen u jedinicu za intenzivnu koronarnu njegu na daljnje pretrage i liječenje.

Učinjena je analiza D-dimera zbog sumnje na PE s obzirom na kliničku sliku. Bolesnik je liječen putem maske za kisik, a saturacija kisikom povećana je na 80 %. Uključena je bolus doza od 5000 IU intravenskog heparina. Obavljen je hitan ehokardiografski pregled koji je doveo do ovih zaključaka:

- opterećenje desne klijetke
- povećane dimenzije desne klijetke do 50 mm na razini baze
- desna pretklijetka 55 mm. Smanjena vrijednost TAPSE-a na 10 mm, STDI 7, FAC smanjen za oko 30 %.
- smanjena pokretljivost slobodne stijenke desne pretklijetke

obesity, immobilization, intervention procedures, advanced age, use of contraceptives, use of some drugs (such as hormone, glucocorticoid therapy, etc.). The most common clinical symptoms are syncope, dyspnea, anginal pain, hemoptysis, and sudden cardiac death. The clinical course can be: fulminant (syncopal), acute (massive), subacute (submassive), and chronic (chronic pulmonary heart). The therapy is mainly fibrinolytic and anticoagulant, with rotablation fragmentation as well as certain surgical procedures including embolectomy, thrombendarrectomy, implantation of venous filters, etc.<sup>1-8</sup>

## Case report

A 79-year-old patient came to the emergency room because of sweating, vomiting, chest pain, and shortness of breath. Symptoms began with sweating and vomiting the day before admission, while chest pain and shortness of breath began a few hours before admission. The patient reported a history of hypertension several years ago, which was well controlled, and a condition after stenting the circumflex artery 10 years ago. Additionally, the patient reported taking a corticosteroid prescribed by a dermatologist for the last 6 months due to a diagnosis of pemphigus. The patient denied any addictions and allergies to drugs, food, etc. Family history was negative for any relevant diseases. After the initial examination in the emergency room and due to the general severe condition with signs of cardiogenic shock: blood pressure 90/50 mmHg, oxygen saturation 55%, ECG on admission, sinus rhythm with a frequency of 118 / min, with right bundle branch block morphology (**Figure 1**); the patient was admitted to the Intensive and Coronary Care Unit for further examination and treatment.

Samples were taken at admission and D-dimers were examined because there was a suspicion of PE according to the clinical picture of the patient. Oxygen support was included via an oxygen mask, and the oxygen saturation was increased by up to 80%. Intravenous heparin 5000 IU intravenous was given. An emergency echocardiogram was performed with the following observation:

- Echocardiographic finding in addition to the right ventricular load.
- Increased dimensions of the right ventricle up to 50 mm at the level of the base.

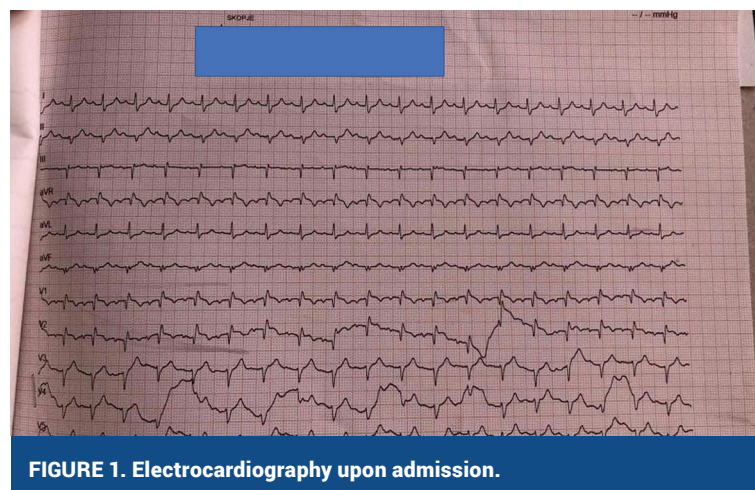


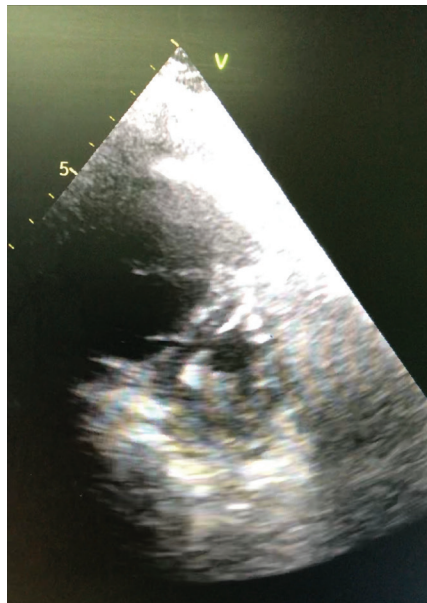
FIGURE 1. Electrocardiography upon admission.

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- prisutan je težak stupanj trikuspidne regurgitacije s maksimalnim gradijentom od oko 40 do 50 mmHg
- granična dimenzija donje šuplje vene koja ne kolabira.
- prisutna je plućna arterijska hipertenzija, oko 70 mmHg. U plućnoj arteriji vidljiva je hiperehogena sjena koja je pomična i veličine 13 × 14 mm te izgleda kao tromb, a plućna arterija otprilike na razini aorte (parasternalna kortikalna os) ima malu ehogenu tvorbu uz tromb.
- na parasternalnoj kratkoj osi na razini lijeve klijetke prisutan je pomak iz desne klijetke – tzv. fenomen „D-oblika“ (**slika 2**)
- lijeva klijetka ima uredne dimenzije te funkciju i kinetiku.

U međuvremenu su pristigli rezultati D-dimera, koji su bili povišeni – 8600 ng/mL. Zbog pogoršanja stanja i prema novim Smjernicama Europskoga kardiološkog društva iz 2019. za plućnu tromboemboliju<sup>9</sup>, započeli smo s primjenom fibrinolitike terapije bez prethodne potvrde dijagnoze s pomoću CT-a.<sup>1,6</sup> Primijenjeno je 100 mg alteplaze tijekom razdoblja od 2

- Right atrium 55 mm. Reduced value of TAPSE 10 mm, STDI 7, FAC reduced by about 30%.
- Reduced free wall kinetics of the right ventricle are noted.
- Severe tricuspid regurgitation present with a maximum gradient of about 40 to 50 mmHg.
- Boundary dimension of the inferior vena cava, non-collapsible.
- Pulmonary arterial hypertension present, approximately 70 mmHg. In the pulmonary artery on the hand, a hyperechoic shadow is visible, mobile with a size of 13×14 mm looking like a thrombus and the pulmonary artery somewhere at the level of the aorta (parasternal cortical axis) presents a small echogenic shape in addition to the thrombus.
- On the parasternal short axis at the level of the left ventricle, there is a push from the right ventricle – a D-shape phenomenon (**Figure 2**).
- The left ventricle has regular dimensions, function, and kinetics.



**FIGURE 2.** There is a push from the right ventricle on the parasternal short axis at the level of the left ventricle – a D-shape phenomenon.

sata, u skladu s protokolom za plućnu tromboemboliju. Nastavili smo primjenjivati fibrinolitiku terapiju tijekom iduća 24 sata uz primjenu još jednoga antikoagulantnog lijeka (fiziološka otopina 500 mL + heparin 25 000 IU intravenski/24 sata) te gastroprotektivnu terapiju. Zbog nejasne kliničke slike i situacije uzrokovane pandemijom bolesti COVID-19, izveden je brzi test za COVID-19, koji je bio negativan. U nalazima laboratorijskih pretraga registrirani su eritrociti  $5,83 \cdot 10^{12}/L$ , hemoglobin 150 g/L, leukociti  $15,2 \cdot 10^9/L$ , trombociti  $193 \cdot 10^9/L$ , troponin I (s) 152,28 ng/L, CRP 6,0 mg/L, kalij 4,8 mmol/L, natrij 140 mmol/L, serumski kreatinin 80  $\mu\text{mol/L}$  i serumski ureja 6,8 mmol/L. Zbog leukocitoze je dodana antibiotska terapija. Sljedećeg smo dana nakon poboljšanja stanja obavili CT an-

In the meantime, we got the results of the D-dimers, with were increased – 8600 ngr/mL. Due to the deterioration of the patient's condition and according to the new recommendations for pulmonary thromboembolism from the European Society of Cardiology from 2019<sup>9</sup>, we started applying fibrinolysis without prior confirmation of the diagnosis with CT.<sup>1,6</sup> Alteplase 100 mg was immediately given to the patient for a period of 2 hours, according to the protocol for pulmonary thromboembolism. Fibrinolytic therapy was continued for another 24 hours with application of another anticoagulant (saline 500 mL + heparin 25000 IU intravenous / 24h) and gastroprotective therapy. Due to the unclear clinical picture and the situation with the COVID-19 pandemic, a rapid test was performed for COVID-19 which was negative. In the meantime,

giografiju prema protokolu za PE, koja je potvrdila dijagnozu PE-a. Nalazi CT-a bili se kako slijedi:

- na račvanju plućnoga stabla ustanovljen je defekt punjenja bez opstrukcije tijekom kroz lumen.
- primijećen je tromb u desnoj lobarnoj arteriji s djelomičnim zahvaćanjem vršnog i srednjeg segmenta desnog režnja, također bez znatne opstrukcije lumena.

Zbog nejasne etiologije PE-a, proveli smo dodatne testove kako bismo isključili ili potvrdili moguće uzroke bolesti. CT abdomena i CT prsnog koša nisu pokazali nikakve patološke nalaze. Doplerska sonografija donjih ekstremiteta pokazala je pravilnu arterijsku cirkulaciju u njima te isključila zastoj (stazu) u dubokim venama, a nisu pronađene ni nove trombotske mase u lumenu vena donjih udova.

Prije no što je bolesnik bio otpušten kući kontrolirani su D-dimeri, koji su tada bili smanjeni na 1462 ng/mL. Provedena je i kontrolna ehokardiografija sa sljedećim nalazima: hiperehogeno okrugla formacija koja nalikuje na stariji tromb. Druga prethodno opisana sjena nije primijećena tijekom ovoga pregleda, a izgled perikarda bio je uredan.

Nakon liječenja antikoagulantnom terapijom, u bolesnika je nastavljena primjena peroralne terapije koja se sastojala od apixabana 5 mg 2 × 2 tijekom 7 dana i 2 × 1 na dan nakon toga. Zbog poboljšanja stanja nakon 6 dana hospitalizacije otpušten je kući iz bolnice sa saturacijom kisika od 98 %, arterijskim tlakom 120/80 mmHg, u EKG-u sa sinusnim ritmom frekvencije od 79/min, devijacijom lijeve osi, rS formi u odvodima D1, D2, D3, aVF i V1-V3 te urednim ST-segmentom i T-valom, uz preporučenu terapiju te uz dogovoren kontrolni pregled za 3 mjeseca.

## Rasprava

Plućna tromboembolija vrlo je čest poremećaj plućne cirkulacije koji se očituje nespecifičnim simptomima i kliničkim znakovima.<sup>7</sup> To je također hitno medicinsko stanje koje, ako se ne dijagnosticira i ne liječi navrijeme, može imati smrtonosan ishod. Na temelju Smjernica Europskoga kardiološkog društva iz 2019. godine, procjena prije početka liječenja u bolesnika s PE-om provodi se na temelju hemodinamskoga stanja nakon primitka u bolnicu, tj. na temelju podjele bolesnika na hemodinamski stabilne ili nestabilne. Bolesnik opisan u ovom prikazu slučaja, koji je bio u kardiogenom šoku, ubrajao se među one s visokim rizikom od zastoja srca, prema našoj procjeni na temelju najnovijih preporuka<sup>9</sup>. Budući da CT plućna angiografija nije mogla biti provedena zbog kliničkoga stanja, uveli smo bolus dozu antikoagulacijske terapije heparinom te proveli hitnu ehokardiografiju koja je pokazala da je lijeva klijetka pritisnuta desnom klijetkom – slučaj fenomena „D-oblika“ s očito povećanim razmjerima desne klijetke i jasnim znakovima opterećenja desne klijetke. Iako nismo imali jasne dokaze da je to uzrok PE-a te zbog nejasne etiologije i nemogućnosti provođenja CT-a plućne angiografije, zbog kliničke nestabilnosti bolesnika odlučili smo se za fibrinolitičku terapiju, uzimajući u obzir sve moguće kontraindikacije. Nakon poboljšanja stanja detaljnije smo raspravili o njegovoj anamnezi, pa smo nakon ovoga, drugog razgovora i dodatnih pretraga provedenih kako bismo potvrdili etiologiju PE-a (test na COVID-19, CT prsnog koša i abdomena, doplerska sonografija krvnih žila donjih udova) došli do krajnjeg zaključka da je etiologija PE-a u ovom slučaju bila terapija kortikosteroidima

the results of the blood tests arrived: RBC 5.83 10<sup>12</sup>/L, Hgb 150 g/L, WBC 15.2 10<sup>9</sup>/L, PLT 193 10<sup>9</sup>/L, Troponin I (s) 152.28 ng/L, CRP 6.0 mg/L, potassium 4.8 mmol/L, natrium 140 mmol/L, serum creatinine 80 μmol/L, and serum urea 6.8 mmol/L. Due to leukocytosis, antibiotic therapy was included. The next day, after the patient's condition improved, we performed a CT angiography according to the protocol for PE, which confirmed the diagnosis of PE. The findings of the CT were as follows:

- At the bifurcation of pulmonary trunk there was a filling defect without obstruction of the flow through the lumen.
- A thrombus was detected in the right lobar artery with a partial involvement of the apical and the medial segments of the right lobe, also without significant obstruction of the lumen.

Due to the unclear etiology of PE, other tests were performed to rule out or confirm possible causes of the disease. CT scans of the abdomen and chest CT scans were performed, with no pathological findings. Doppler sonography of the lower extremities was also performed, with a finding of proper arterial circulation of the lower extremities, exclusion of deep venous stasis, and no fresh thrombotic masses in the lumen of the veins of the lower extremities.

Before discharging the patient to his home, we examined him again for D-dimer, which was now reduced to 1462 ngr/mL. Control echocardiography was performed with the following finding: a hyperechoic round formation resembling an older date thrombus. The other shadow previously described at the time of examination was not visualized.

After treatment with anticoagulant therapy, the patient was transferred to oral therapy comprising apixaban 5 mg 2×2 for 7 days and 2×1 after that. Due to improvement of the patient's condition after 6 days of hospitalization, he was discharged to his home with O<sub>2</sub> saturation 98%, blood pressure 120/80 mmHg, ECG sinus rhythm with a frequency of 79 / min, left axis deviation, rS form in II, III, AVF, V1-V3 leads, regular ST-segment and T wave, with a recommendation for regular therapy and a scheduled next visit in our clinic in 3 months.

## Discussion

Pulmonary thromboembolism is a very common disorder of pulmonary circulation, often presenting with nonspecific symptoms and signs.<sup>7</sup> It is an urgent medical pathology which, if not diagnosed and treated in time, can have a fatal outcome. Based on to the latest recommendations from the European Society of Cardiology from 2019, the assessment for starting treatment in patients with PE is made on the basis of the hemodynamic condition of patients at admission, i.e. the division of patients into hemodynamically stable or unstable. The patient described herein, who was in cardiogenic shock, belonged to patients at high risk of developing cardiac arrest, according to our estimates based on the latest recommendations<sup>9</sup>. Since CT pulmonary angiography could not be performed due to the clinical condition, we administered a bolus anticoagulant therapy of heparin, and we administered an emergency echocardiography which showed that the left ventricle was suppressed by the right ventricle – a D-shape phenomenon with clearly enlarged right ventricular dimensions and clear signs of right ventricular loading. Although we did not have clear evidence that it was caused PE and because of the unclear etiology and inability to organize CT an-

(prednizolon), koju je propisao dermatolog za liječenje pemfigusa te koju je bolesnik redovito i bez prekida uzimao prema terapijskoj shemi tijekom prethodnih 6 mjeseci.

## Zaključak

Plućna tromboembolija je za život opasno stanje koje je povezano sa znatnim pobolom i smrtnosti. Danas postoje mnogi dijagnostički postupci koji maksimiraju vjerojatnost pravodobne dijagnoze ove patologije kako bi se postiglo brže liječenje i bolja prognoza. Uzimajući sve to u obzir, metoda liječenja ipak je najvažniji čimbenik, a ona se temelji na hemodinamskoj kliničkoj slici u bolesnika. Pokazali smo da pravodobno liječenje fibrinolitičkom terapijom može biti spasonosno za život u bolesnika s PE-om koji su hemodinamski nestabilni, uzimajući u obzir sve moguće kontraindikacije. Također treba biti oprezan kod primjene kortikosteroidne terapije u bolesnika koji će je primati dulje vrijeme, a potrebni su i češći pregledi kako bi se pravodobno otkrile moguće komplikacije.

giography of the lungs, we decided on therapy with fibrinolysis, taking into account all possible contraindications, due to the clinical instability of the patient. After improving the patient's condition, we discussed his medical history in more detail, and after this second conversation and the examinations we performed to confirm the etiology of PE (COVID-19 test, CT of the chest and abdomen, Doppler sonography of the blood vessels of the lower extremities), we came to the final conclusion that as the etiology of PE in this case was the corticosteroid therapy (prednisolone) that the patient had regularly taken according to the treatment scheme for the last 6 months without interruption, which was prescribed by a dermatologist for the treatment of pemphigus.

## Conclusion

Pulmonary thromboembolism is a life-threatening condition that is associated with significant morbidity and mortality. Today there are many different diagnostic procedures that maximize the chance of timely diagnosis of this pathology for faster treatment and better prognosis. Taking all these things into consideration, however, the most important factor is the method of treatment, which is based on the hemodynamic clinical picture of the patient. We have shown that timely treatment with fibrinolytic therapy can be lifesaving in patients with PE who are hemodynamically unstable, taking into account all possible contraindications. Care should also be taken with corticosteroid therapy in patients who will be receiving it for a long-time, and more frequent check-ups are required to promptly diagnose possible complications.

**Conflict of interest:** None declared.

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