

# Low-dose systemic thrombolysis in patient with recent major abdominal surgery and high-risk pulmonary embolism: Case report and narrative review

Michele Domenico Spampinato, Francesco Frezza,  
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## ABSTRACT

**Introduction:** Systemic thrombolysis is the treatment of choice for hemodynamically unstable patients with acute pulmonary embolism (PE) while for the intermediate-high risk ones the possibility of severe bleeding seems to outweigh the benefits. Surgical or percutaneous therapy is an option in case of contraindication/failure of fibrinolysis but they are not available in every hospital.

**Case Report:** An 85-year-old woman arrived at the Emergency Department for rapid onset dyspnea, thoracic pain with hypotension, tachycardia, and hypoxia. A computed tomography pulmonary angiography revealed acute PE of the main branches of the pulmonary right and left arteries. Due to hemodynamic instability and a history of recent intestinal resection surgery (25 days before), a continuous infusion of low-dose thrombolysis regimen with 50 mg rt-PA in 2 hours was started. After 30 minutes of rt-PA infusion, all vital signs were improved and at the end of rt-PA infusion. Point of care ultrasound (POCUS) revealed a reduced size of right

ventricle with a decrease in right/left ventricle ratio. Hospital stay and a follow-up at two weeks revealed no complication due to the fibrinolytic administration or anticoagulant therapy.

**Conclusion:** Anticoagulation is still the cornerstone therapy for patients with PE, but there's a lack of trials on reperfusion strategy. Moreover, different guidelines give different short-term risk classifications, indication, and dosage of thrombolytic drugs and absolute and relative contraindications to systemic thrombolysis. This case report shows the potential benefit of low-dose rt-PA in patients with relative contraindications to thrombolysis and presenting with vital signs compatible with hemodynamic instability.

**Keywords:** Emergency medicine, Point of care systems, Pulmonary embolism, Systemic thrombolysis

## How to cite this article

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## INTRODUCTION

Venous thromboembolism (VTE) is the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke, clinically presenting as deep venous thrombosis (DVT) or pulmonary

embolism (PE), with an annual incidence equal to 53–162 per 100,000 population for DVT and 39–115 per 100,000 for PE [1]. Moreover, according to the 2019 guidelines on PE published by the European Society of Cardiology (ESC), acute PE causes almost 300,000 deaths per year in the United States, ranking high among the causes of cardiovascular mortality, considering that 30-day mortality is above 3–4% in intermediate-high risk patients and over 11% in high-risk groups. Major trauma, surgery, estrogen-containing oral contraceptive, hormone replacement therapy, infection, blood transfusion, diabetes mellitus, obesity, cigarette smoking, hypercholesterolemia, hypertension, and myocardial infarction/heart failure are the principal risk factors for VTE. The diagnostic pathway of acute PE represents a real challenge since the non-specific clinical signs and symptoms that patients may present, such as dyspnea, chest pain, presyncope/syncope or hemoptysis. There is a decrease in fatality rates in Europe, Asia, and North America due to awareness of the problem, good assessment of clinical pretest probability, better use of diagnostic tests combined and adherence to guidelines [1].

Systemic thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is the mainstay therapy for hemodynamically unstable patients with acute PE (high-risk PE), while for the intermediate-high risk ones the possibility of severe bleeding due to systemic use of rt-PA outweigh the benefits. In case of failure/contraindication of thrombolysis surgical embolectomy or percutaneous catheter-directed treatment is recommended but not every institution is capable of performing these procedures [1]. However, patients not always fit in a precise category: putting together the definition of high risk and intermediate-high risk PE proposed by the ESC and the indicated relative contraindications may pose the patient in a gray zone where finding the right therapy may represent a clinical challenge.

## CASE REPORT

An 85-year-old woman was admitted to the Emergency Department (ED) for rapid onset dyspnea and thoracic pain. Her past medical records revealed a history of hypertension, severe osteoporosis, mixed anxiety-depressive disorder, and a recent (25 days before) intestinal resection for a colonic volvulus. She presented alert but slightly confused, SpO<sub>2</sub> 80%, respiratory rate (RR) 30 bpm, blood pressure (BP) was 100/50, and heart rate (HR) 130 ppm rhythmic. The physical examination revealed normal vesicular murmur, tachycardia with no auscultable murmurs, preserved peripheral pulses and no peripheral improntable edema. Her abdomen was normal. Geneva clinical prediction rule for pulmonary thromboembolism (PTE) [2] was equal to 6, corresponding to an intermediate clinical probability of PTE. A thorax X-ray performed in the emergency room

revealed no abnormalities. Electrocardiogram (ECG) revealed sinus tachycardia conducted with a known Right Bundle Branch Block (RBBB). Arterial blood gas analysis (ABGA) showed pH 7.49, pCO<sub>2</sub> 30 mmHg, pO<sub>2</sub> 50 mmHg, HCO<sub>3</sub><sup>-</sup> 22 mmol/L, normal Base Excess, and lactate levels. Point of care ultrasound (POCUS) showed a preserved lung sliding with A-pattern in all thoracic areas, right ventricle/left ventricle visual ratio (RV/LV) > 1, Tricuspid Annular Plane Systolic Excursion (TAPSE) = 14 mm and Pulmonary Artery Systolic Pressure (PASP) of 48 mmHg, positive McConnell Sign [3], a suspected floating thrombus, 3.4 cm non-collapsing inferior cava vein, and a positive compression ultrasonography (CUS) for right popliteal deep vein thrombosis. A bolus of 5000 IU of unfractionated heparin (UFH) was then administered and a computed tomography pulmonary angiography (CTPA) was performed, confirming the suspicion of PE involving the main branches of the pulmonary right and left arteries. Blood analysis revealed normal white blood count, normal C-reactive protein level, d-dimer 28.3 UI, high sensitivity Troponin I 101 ng/L. Oxygen therapy was provided via High Flow Nasal Cannula (HFNC) with 40% fraction of inspired oxygen, flow 60 L/minute, and a continuous infusion of 50 mg rt-PA in 50 mL saline solution at 25 mL per hour was started, followed by parenteral anticoagulation with UFH. After 30 minutes of rt-PA infusion, all vital signs were improved with a decrease of HR to 85 ppm at the end of infusion and the increase in SBP (up to 130 mmHg) and SpO<sub>2</sub> (up to 97% in room air). At the end of rt-PA infusion, POCUS revealed a reduced size of RV with a decrease in RV/LV ratio, PASP was not measurable due to non-detectable tricuspidal insufficiency and TAPSE increased to 24 mm with a 1.8 cm inferior cava vein collapsing < 50%.

During the in-hospital stay, the patient was asymptomatic and hemodynamically stable with no external signs of hemorrhage, stable hemoglobin levels, and in five days was discharged at home. A follow-up at two weeks revealed no complication due to the fibrinolytic administration or anticoagulant therapy.

## DISCUSSION

Emergency physicians have the task of resuscitating the unstable patient with undifferentiated shock while founding proper differential diagnosis in order to start specific treatment as soon as possible. Clinical history and presentation of our patient were highly suggestive for PE, but a correctly diagnostic workup is fundamental, including all differential diagnosis (septic, hypovolemic, cardiogenic, distributive, and neurogenic causes of shock). A recent abdominal surgery could have led to the development of intra-abdominal septic sources, but normal body temperature, no signs of peritonitis at physical examination and no lactate levels on ABGA, reduced the likelihood of sepsis. Point of care ultrasound had a great role in differential diagnosis workup: a

preserved pleural sliding and lung A-pattern virtually excluded pulmonary parenchymal causes of respiratory distress. Furthermore, the presence of signs of right ventricular overload and a positive CUS has allowed us to consider PE as the most likely diagnosis. Computed tomography pulmonary angiography is 24/24 and 7/7 immediately available in our ED enabling us in rapidly confirming the presence of PE. According to the ESC Guidelines on Pulmonary Embolism 2019 [1], the patient had a Pulmonary Embolism Severity Score (PESI) of 195 (Class V) with evidence of right ventricular dysfunction and elevated Troponin levels. Despite our patients did not fit the ESC definition of hemodynamic instability (Systolic BP < 90 mmHg or vasopressors required to achieve a BP  $\geq$ 90 mmHg despite adequate filling status and end-organ hypoperfusion or systolic BP drop  $\geq$ 40 mmHg, lasting longer than 15 minute and not caused by new-onset arrhythmia, hypovolemia, or sepsis) she had a positive shock index (defined as HR/BP > 1) [4], which is associated with higher inpatient mortality, so we considered her unstable and therefore eligible for primary reperfusion treatment.

European Society of Cardiology guidelines [1] recommend accelerated i.v. administration of rt-PA 100 mg over 2 hours because this therapy, according to literature, reduces total mortality, PE recurrence, and PE-related mortality in hemodynamically unstable patients while the decrease in overall mortality is not significant in the stable ones [5, 6]. However, the proposed protocol is associated with a 9.9% rate of severe bleeding and a 1.7% rate of intracranial hemorrhage [5], hence in patients with high-risk in whom thrombolysis has failed or is contraindicated, surgical embolectomy/percutaneous catheter-directed treatment is recommended [1]. Mechanical reperfusion was not immediately available in our institution and the recent abdominal major surgery was a cause of concern for us, even if it was not an absolute contraindication according to ESC [1].

In 2011, the American Heart Association (AHA) defined “massive pulmonary embolism” only “sustained hypotension (systolic BP <90 mmHg for 15 minutes or requiring inotropic support, pulselessness or sustained heart rate < 40 ppm with signs/symptoms of shock” [7]. According to AHA, fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications and may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications.

According to the 2016 CHEST guidelines on Antithrombotic Therapy for VTE Disease [8] in patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect, if appropriate expertise and resources are available, catheter-assisted thrombus

removal is recommended. While no other therapeutic options are provided in cases of no catheter-assisted thrombus removal available, systemic thrombolysis is recommended only in patients with systolic blood pressure < 90 mmHg and there is no suggestion on thrombolytic drug and dosage. In 2017 [9], the American College of Cardiology published an “expert analysis” on acute management of PE, concluding that despite an interventional approach to massive and submassive PE has great promise, absolute contraindications to anticoagulation are absolute contraindications to any type of endovascular treatment strategy involving thrombolytics. In their opinion, relative contraindications, especially if not correctable, should be carefully reviewed on an individualized basis.

The “Thrombosis and Haemostasis Society of Australia and New Zealand” in 2019 published their guidelines on Diagnosis and Management of Venous Thromboembolism [10], but did not give any recommendation on fibrinolytic therapy.

2020 NICE guidelines on PE [11] recommend against pharmacological systemic thrombolytic therapy in patients with PE and hemodynamic stability with or without right ventricular dysfunction, recommending the fibrinolytic treatment only in patients with hemodynamic instability, which is not further defined. No recommendation in terms of medication and drug dose is provided.

In 1994, two different trials were published in order to test reduced dose bolus rt-PA (0.6 mg/kg in 15 minutes) versus full dose (100 mg/2 h) in the treatment of hemodynamically stable patients with PE. As reported by Goldhaber et al. [12], efficacy was similar in the two groups but there were also no differences in terms of bleeding complications. A Randomized Clinical Trial published by Wang et al. [13] in 2010, compared the efficacy and safety of a 50 mg/2 h rt-PA regimen with a 100 mg/2 h rt-PA regimen for acute PE and either hemodynamic instability or massive pulmonary artery obstruction, demonstrating similar efficacy of the two regimens and less bleeding tendency in the 50 mg/2 h group, especially in patients with a bodyweight < 65 kg (14.8% vs 41.2%,  $P = 0.049$ ). In 2013, Sharifi et al. [14] published the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial that evaluated the role of half-dose (0.5 mg/kg, maximal dose 50 mg) thrombolysis with rt-PA plus anticoagulation versus standard anticoagulation alone for patients with moderate PE, demonstrating a statistically significant reduction in mortality plus recurrent pulmonary embolism, hospital stay, development of pulmonary hypertension in the treatment group compared with the control group with no difference in mortality or bleeding. In 2014, Zhang et al. [15] published a meta-analysis of five trials (440 patients) on low-dose rt-PA for acute PE. Five studies (440 patients) were included, three of which compared low dose rt-PA (0.6 mg/kg, maximum 50 mg over 2 hours) with standard dose (100 mg over 2 hours). There were more major bleeding events in the standard

dose rt-PA group than in low dose group [odds ratio (OR) 0.33, 95% confidence interval (CI) 0.12–0.91], while there were no statistical differences in recurrent PE or all-cause mortality between these two groups. Two studies compared low dose rt-PA (0.6 mg/kg, maximum 50 mg/2 min bolus or 10 mg bolus,  $\leq$  40 mg/2 h) with heparin. There was no significant difference in major bleeding events (OR 0.73, 95% CI 0.14–3.98), recurrent PE or all-cause mortality. According to the author's conclusion, low dose rt-PA was as effective as the standard dose but safer. In addition, compared with heparin, low dose rt-PA showed the same risk of major bleeding. In 2018, Zhang et al. published the results of a similar trial [16] conducted in order to investigate the efficacy and safety of thrombolysis with low-dose rt-PA defined as 30 mg over 2 hours plus Low Molecular Weight Heparin (LMWH) compared with LMWH therapy alone in patients with acute intermediate-risk PE. Although full-dose systemic rt-PA is not recommended in intermediate-risk PE due to safety concerns, they demonstrated a significant reduction in PASP, RV/LV ratio and symptom severity in the low-dose group with no hemodynamic decompensation, recurrent PE, deaths and no major bleeding in the low-dose rt-PA group while there were three episodes of hemodynamic decompensation and two of recurrent VTE in the LMWH alone group. Although important, it is unclear if these outcomes have long-term morbidity or mortality benefit. In 2019, Rothschild et al. [17] presented a case series of 45 patients administered low-dose alteplase for submassive PE with high-risk characteristics. In their report, 97.8% of patients survived discharge and at 30-day, with all-cause mortality of 4.4%. Despite no patients having a HAS-BLED score  $>$  2, bleeding which needs blood transfusion was observed in 5 cases.

In 2019, the Pulmonary Embolism Response Team (PERT) Consortium published a consensus practice guidelines on diagnosis, treatment, and follow-up of pulmonary embolism [18] in which recommended to consider the low-dose systemic thrombolysis both in high-risk PE with relative contraindications to thrombolysis (i.e., major surgery in the past one month) and in selected intermediate-risk PE with evidence or risk for clinical deterioration and presence of low bleeding risk.

The role of low-dose thrombolysis in the management of postoperative patients has also been reported in different case reports. In 2009, Bulpa et al. [19] published a case series of two patients, one with recent surgery and the second with fresh hemorrhagic duodenal ulcer, afflicted by PE and treated with low-dose urokinase. In both patients low-dose was effective without hemorrhagic complications. In 2014 Bayram et al. [20] reported a case of 63-year-old man with a history of intracranial surgery due to glioblastoma multiforme 20 days prior to being admitted to the ED for cardiac arrest due to PTE. 50 mg of rt-PA was administered during cardiopulmonary resuscitation with return of spontaneous circulation and no complication due to fibrinolytic therapy. A similar case report is described by Lampert et al. [21]

in 2017. A patient with massive PE who underwent neurosurgery for a glioblastoma 30 days prior treated with systemic thrombolysis: the patient recovered from cardiogenic shock and even if developed an Intracranial Hemorrhage (ICH) into the resection cavity had no symptoms and no new neurological deficits. Moreover, three prior case reports [22–24] showed successful systemic thrombolysis for massive PE without ICH in patients with major contraindications due to intracranial pathology. In 2014, Condliffe et al. published an article called “Management dilemmas in acute pulmonary embolism” [25]. They identified 25 reports including 64 patients treated with thrombolysis following major recent surgery. Major bleeding occurred in  $>$ 50% of patients receiving thrombolysis within 1 week of surgery and in 20% of patients treated with thrombolysis 1–2 weeks postoperatively. They concluded assessing that within 1–2 weeks following surgery thrombolysis may be an acceptable risk depending on the nature of the surgery; besides, in their opinion, if thrombolysis is indicated but there is a high risk of hemorrhage a half-dose regimen is a considerable strategy. Top of that even full dose rt-PA has been used in acute PE after surgery, as reported by Zhang et al. [26] in 2013 in a case series of 21 postoperative patients who received thrombolysis within three weeks from surgery: five patients (29%) had no complications, while mild hematuria was observed in seven patients (41%) due to urethral lesions caused by the introduction of the urinary catheter. Five (including one who died within 24 hour) had mild hemorrhaging at the surgical site and hematuria; no patients experienced severe bleeding and no blood transfusions were required.

In 2016, Shen et al. [27] described the successful use of low-dose thrombolysis with 25 mg of Alteplase in a high-risk patient who had a cardiac arrest soon after lung resection surgery complicated by a mediastinal hematoma that required surgical drainage and blood transfusions. In the same year, Burrage et al. [28] described a case of submassive PE and right heart thrombus following cardiac surgery successfully treated half-dose thrombolysis with alteplase (10 mg IV bolus, then 40 mg over 1 hour), and subsequent heparin infusion. Abrupt clinical improvement post-thrombolysis was manifested by improved hemodynamics, oxygenation, and resolution of RBBB and completely recovered without hemorrhagic complication and discharged on day 5.

As underlined by the great heterogeneity of the guidelines on the management of pulmonary embolism, the optimum management continues to be a clinical challenge, especially for intermediate-risk PE [29]. One reason, it could be that the high-risk and intermediate-risk acute PE categories are heterogeneous: there are “mild” and “severe” ends of the spectrum for each group and clinical trials have never differentiated patients within these classifications [30]. The available data for low-dose systemic thrombolysis are intriguing and may be applicable in some clinical settings, particularly when patients have relative contraindications to thrombolysis

or are elderly or frail. However, even if low-dose systemic thrombolysis may be an excellent alternative to full dose systemic thrombolysis, it carries inextricable bleeding risk.

## CONCLUSION

Patients deserve the best treatment based on the best evidence. Although anticoagulation continues to be the mainstay of treatment, there are no head-to-head trials of reperfusion strategy nor systematic revision establishing the correct dose of fibrinolytic in patients with relative contraindications to thrombolysis. Moreover, there is currently insufficient evidence to definitively guide diagnosis and treatment of PE in the perioperative and post-operative setting, and no known decision support tool to serve as a cognitive aid in this unique setting. Over time, AHA, CHEST, ESC, NICE and other guidelines changed the definition of high-risk and intermediate-high risk PE, indication and dosage of fibrinolytic drugs and absolute and relative contraindications to systemic thrombolysis. As emerged from this short narrative review of literature, thrombolytic treatment with low-dose rt-PA seems to be effective and safe in high-risk patients with relative contraindications to fibrinolysis. Waiting for further data, given current knowledge and differences between international guidelines, after a careful evaluation between risks and benefits the clinician is in the best position to judge the relative merits of thrombolysis on a case-by-case basis, giving the right treatment to the right patient, in the right moment.

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Michele Domenico Spampinato – Conception of the work, Design of the work, Drafting the work, Final approval of

the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Francesco Frezza – Conception of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Stefano Geniere Nigra – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

### Guarantor of Submission

The corresponding author is the guarantor of submission.

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### Consent Statement

Written informed consent was obtained from the patient for publication of this article.

### Conflict of Interest

Authors declare no conflict of interest.

### Data Availability

All relevant data are within the paper and its Supporting Information files.

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