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CASE SERIES
Other

Low dose peripheral systemic thrombolysis for treatment of intermediate–high risk acute pulmonary embolism: a case series

Fida Charif [1]*, Houda Khatoun [2], Pierre Nassar[3], Aya Jouni[4], Sadek Jaber[4], Malek Moussa[3], Bilal Choumar[2], and Wassef Karrowni[5]

[1]Pulmonology Division, Beirut Cardiac Institute, Airport road, 1002, Beirut, Lebanon; [2]Radiology Division, Beirut Cardiac Institute, Airport road, 1002, Beirut, Lebanon; [3]Cardiology Division, Beirut Cardiac Institute, Airport road, 1002, Beirut, Lebanon; [4]Faculty of Medical Sciences, Lebanese University, Hadath-Baabda, Beirut, Lebanon; and [5]Department of Cardiovascular Diseases, UnityPoint Health—St. Luke's Hospital, Cedar Rapids, IA 52402, USA

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Background The management of intermediate–high-risk acute pulmonary embolism (PE) is controversial with increasing interest in more aggressive treatment approaches than anticoagulation alone.

Case summary We describe the case series of four consecutive patients who presented to emergency room for acute shortness of breath. They were diagnosed with intermediate–high-risk acute PE based on the computed tomography pulmonary angiography and transthoracic echocardiography (TTE) findings and the elevated simplified PE score index. They received bolus of 5 mg thrombolytics recombinant tissue plasminogen activator (rtPA) administered through peripheral intravenous (i.v.) line followed by continuous infusion at a rate of 2 mg/h along with unfractionated heparin (UFH) at a rate of 500 mg/h for additional ≤10 h. There after the dose of UFH was increased to reach a therapeutic level. Rapid clinical improvement and also improvement in TTE parameters were noted at discharge. Patients were discharged home on oral anticoagulation.

Discussion Intermediate–high-risk acute PE carries increased risk of mortality and morbidities. Catheter-directed thrombolysis uses a low rtPA dose for local thrombolysis and is associated with low bleeding risk; however it is expensive and requires expertise and human resources. Low-dose rtPA through a peripheral i.v. line might be safe and effective in the treatment of patient with intermediate–high-risk acute PE. This therapeutic approach is readily available at most medical centres, can be started in the emergency room (ER), and can be alternative to catheter-directed thrombolysis nowadays during the COVID-19 era and in hospitals at the periphery and with limited resources.

Keywords Intermediate–high-risk pulmonary embolism • Thrombolysis • RV/LV ratio • Case report

ESC Curriculum 2.1 Imaging modalities • 6.7 Right heart dysfunction • 9.5 Pulmonary thromboembolism • 9.6 Pulmonary hypertension

Learning points

- Systemic infusion of low-dose recombinant tissue plasminogen activator (rtPA) through a peripheral intravenous (i.v.) line is safe and an effective in treating intermediate–high-risk pulmonary embolism and can be started rapidly in the emergency room.
- Low-dose rtPA through peripheral i.v. line is less costly than catheter-directed thrombolysis and does not require the use of high level of resources (cath-lab, ICU-bed) and is of increased importance nowadays during the COVID-19 era and also for use in peripheral hospitals or centres with limited resources.

* Corresponding author. Tel: +961 3 719050, Fax: +961 1 456455, Email: mdfcharif@hotmail.com
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Introduction

Acute pulmonary embolism (PE) remains the third most common cause of acute cardiovascular event after myocardial infarction and stroke.[1] The use of thrombolytics is only recommended in high-risk PE; while in intermediate–high-risk PE it is reserved for those who deteriorate on anticoagulation alone.[1] However, due to the higher risk of progression to right ventricular (RV) failure and haemodynamic collapse in the intermediate–high-risk PE patients, as shown in several studies,[2,3] there is growing interest in more aggressive treatment with thrombolysis rather than anticoagulation alone.[3,4] When systemic thrombolysis is chosen, the current treatment protocols are either full dose [100 mg recombinant tissue plasminogen activator (rt-PA)] or half-dose (50 mg rt-PA).[3,4] Catheter-directed thrombolysis (CDT) has gained popularity recently over systemic thrombolysis because of the lower bleeding risk. However, CDT is an invasive procedure with its own risks and requires expertise. Herein we report a case series of four intermediate–high-risk PE patients that were treated successfully with low-dose rt-PA infusion through peripheral intravenous (i.v.) line over 10 h period. We believe this approach is relatively cheap, readily available without the need of high level of expertise, and does not carry the increased bleeding risk with the traditional doses of systemic thrombolysis.

Timeline

	Vital signs	Blood workup	CTPA	RV/LV ratio based on CTPA	TTE findings SPAP (mmHg) TAPSE (mm)	
Patient 1						
On admission	O_2 Sat 94% HR 90 b.p.m. BP 100/70 mmHg RR 24/min	Trop-T 0.104 D-dimer 16 215 BNP NA	Bilateral main lobar and segmental thrombi	1.6	SPAP 58 TAPSE 16	Total of 25 mg tPA through peripheral i.v. over 10 h
On discharge	O_2 Sat 95% HR 65 b.p.m. BP 110/60 mmHg RR 14/min	NA	NA	0.9	SPAP 35 TAPSE 23	
Patient 2						
On admission	O_2 Sat 84% HR 82 b.p.m. BP 110/60 mmHg RR 24/min	Trop-T 0.109 D-dimer 3880 BNP 597	Bilateral main lobar and segmental thrombi	1.3	SPAP 59 TAPSE 15	Total of 25 mg tPA through peripheral i.v. over 10 h
On discharge	O_2 Sat 96% HR 68 b.p.m. BP 110/60 mmHg RR 13/min	NA	NA	1.4	SPAP 52 TAPSE 23	
Patient 3						
On admission	O_2 Sat 85% HR 80 b.p.m. BP 100/66 mmHg RR 23/min	Trop-T 0.101 D-dimer 5928 BNP 57	Right main and bilateral lobar thrombi	1.1	SPAP 50 TAPSE 16	Total of 17 mg tPA through peripheral i.v. over 6 h
On discharge	O_2 Sat 94% HR 69 b.p.m. BP 110/60 mmHg RR 14/min	NA	NA	0.8	SPAP 35 TAPSE 22	
Patient 4						
On admission	O_2 Sat 95% HR 110 b.p.m. BP 119/82 mmHg RR 22/min	Trop-T 0.134 D-dimer 5698 BNP 620	Bilateral lobar and segmental thrombi	1.4	SPAP 57 TAPSE 14	Total of 25 mg tPA through peripheral i.v. over 10 h
On discharge	O_2 Sat 97% HR 78 b.p.m. BP 112/68 mmHg RR 14/min	NA	NA	1	SPAP 48 TAPSE 17	

BP, blood pressure; CTPA, computed tomography pulmonary angiography; HR, heart rate; i.v., intravenous; LV, left ventricle; RR, respiratory rate; RV, right ventricle; SPAP, systolic pulmonary artery pressure; TTE, transthoracic echocardiography

Patient #1

A 70-year-old Asian man with history of chronic obstructive pulmonary disease (COPD) presented to the ER because of sudden onset shortness of breath. His medications included tiotropium, a long acting bronchodilator. Vital signs upon presentation showed: heart rate (HR) 90 b.p.m., pulse oxygen saturation (O_2 saturation) 94% on room air, blood pressure (BP) 100/70 mmHg, and respiratory rate (RR) 24/min. Physical examination revealed distended jugular veins and hepatojugular reflux. Cardiac auscultation was remarkable for fixed split S2 and loud P2 best heard at the second intercostal space. The lung auscultation was remarkable for markedly decreased breath sounds bilaterally.The electrocardiogram (ECG) showed signs of RV strain. Blood workup showed elevated D-dimer (16 215 ng/mL) (cut-off value < 500 ng/mL) and troponin-T (0.104 ng/mL) (cut-off value 0.014 ng/mL) levels (*Table 1*). Transthoracic echocardiography (TTE) showed dilated RV and estimated systolic pulmonary artery pressure (SPAP) of 58 mmHg. Unfractionated heparin (UFH) bolus and infusion were started as per PE protocol. Computed tomography pulmonary angiography showed thrombi in the main pulmonary arteries (PA), the lobar and the segmental arteries bilaterally with an RV/left ventricle (LV) ratio of 1.6. Patient was given a bolus of 5 mg rt-PA administered through peripheral i.v. line, followed by continuous infusion at a rate of 2 mg/h along with UFH at a rate of 500 mg/h for additional 10 h. Thereafter, the dose of UFH was increased to reach a therapeutic level. Improvement of clinical parameters was noticed within a few hours of rt-PA infusion. However, as per our protocol, TTE was repeated at 48 h of completing thrombolysis. Simplified PE score index (sPESI) and laboratory data upon admission as well as SPAP and RV/LV ratio pre and post rt-PA are shown in the table. Computed tomography pulmonary angiography images showing the RV/LV ratio upon admission is presented in *Figure 1A*. Changes of O_2 sat and HR are shown in *Figures 2* and *3*, respectively. Patient was discharged home on direct-acting oral anticoagulant (DOAC) on Day 4. Follow-up at 3 months post-discharge noted the absence of dyspnoea. Repeat TTE 3 months post-discharge showed normal RV diameter with absence of pulmonary hypertension.

Patient #2

A 72-year-old Asian woman, previously healthy, presented to ER with sudden onset dyspnoea. Not taking any home medication. Vital signs upon admission: HR of 82 b.p.m., O_2 saturation 84% on room air, BP 110/60 mmHg, and RR 24/min. Cardiac auscultation was remarkable for loud P2 at the left second intercostal space. The lungs were clear to auscultation. ECG showed non-specific ST segment changes. Blood workup showed elevated D-dimer (3880 ng/mL) and troponin-T (0.109 ng/mL) levels. Transthoracic echocardiography showed dilated RV and SPAP of 59 mmHg. Unfractionated heparin infusion as per PE protocol was started. Computed tomography pulmonary angiography showed thrombi in the main, lobar, and segmental PA bilaterally with markedly enlarged RV and RV/LV ratio of 1.3. An rt-PA 5 mg bolus was given in the ER through a peripheral i.v. line, and then a continuous peripheral i.v. infusion of 2 mg/h of rt-PA along with UFH at a rate of 500 mg/h for additional 10 h. A total of 25 mg of rt-PA was given. Improvement of clinical parameters were noticed within few hours of rt-PA infusion. Transthoracic echocardiography repeated at 48 h after completing thrombolysis. Simplified PE score index and laboratory data upon admission as well as SPAP and RV/LV ratio pre and post rt-PA are shown in the table. Computed tomography pulmonary angiography images showing the RV/LV ratio upon admission is presented in *Figure 1B*. Changes of O_2 sat and HR are shown in *Figures 2* and *3*, respectively. Patient was discharged home on DOAC on Day 4. Follow-up at 3 months post-discharge noted absence of any dyspnoea. The patient refused to get a repeat TTE.

Patient #3

A 79-year-old Asian man with history of COPD and hypertension, presented to ER for new onset dyspnoea and chest tightness of 3 h duration. His home medications included tiotropium and bisoprolol. His physical examination upon admission: HR of 80 b.p.m.; O_2 saturation 85% on room air, BP 100/66 mmHg, and RR 23/min. Heart sounds were audible. Lung auscultation revealed good bilateral air entry with mild bibasilar crackles. ECG showed S1Q3T3 pattern. Blood workup showed elevated D-dimer (5928 ng/mL) and troponin-T (0.101 ng/mL) levels. Bedside TTE showed dilated RV with estimated SPAP of 50 mmHg. Unfractionated heparin as per PE protocol was started. Computed tomography pulmonary angiography confirmed the presence of thrombi involving the main, lobar, and segmental PA and RV/LV ratio of 1.1. A bolus of rtPA 5 mg was given in a peripheral i.v. line; then rtPA intravenously was continued at a rate of 2 mg/h along with UFH at a rate of 500 mg/h for additional 6 h. A total of 17 mg of rtPA was given. Improvement of clinical parameters were noticed within few hours of rt-PA infusion. Transthoracic echocardiography was repeated at 48 h after completing thrombolysis. Computed tomography pulmonary angiography images showing the RV/LV ratio upon admission is presented in *Figure 1C*. Changes of O_2 sat and HR are shown in *Figures 2* and *3*, respectively. Patient was discharged home on DOAC on Day 4. Follow-up at 3 months post-discharge noted the absence of symptoms. Repeat TTE showed normal RV size with the absence of pulmonary hypertension.

Patient #4

A 64-year-old Asian woman with history of COPD and hypertension presented to ER for sudden onset shortness of breath. Her medications included fluticasone/serevent, ramipril, and bisoprolol. Vital signs upon presentation were as follows: HR 110 b.p.m., O_2 saturation 95% on room air, BP 119/82 mmHg, and RR 22/min. Her physical examination revealed distended jugular veins and hepatojugular reflux. Heart sounds were remarkable for loud P2 at pulmonary area. Lung auscultation

Table 1 Shows patients characteristics pre- and post-thrombolysis

Patients	sPESI/original PESI	BNP pg/mL (NL < 100)	D-dimer ng/mL (NL < 500)	Troponin T ng/mL (NL < 0.014)	RV/LV ratio pre/post rt-PA	SPAP mmHg pre/post rt-PA	TAPSE mm pre/post rt-PA
Patient 1	1/90	NA	16 215	0.104	1.6/0.9	58/35	16/23
Patient 2	1/92	597	3880	0.109	1.3/1.1	59/52	15/23
Patient 3	2/109	57	5298	0.101	1.1/0.8	50/35	16/22
Patient 4	2/104	620	5698	0.134	1.4/1	57/48	14/17

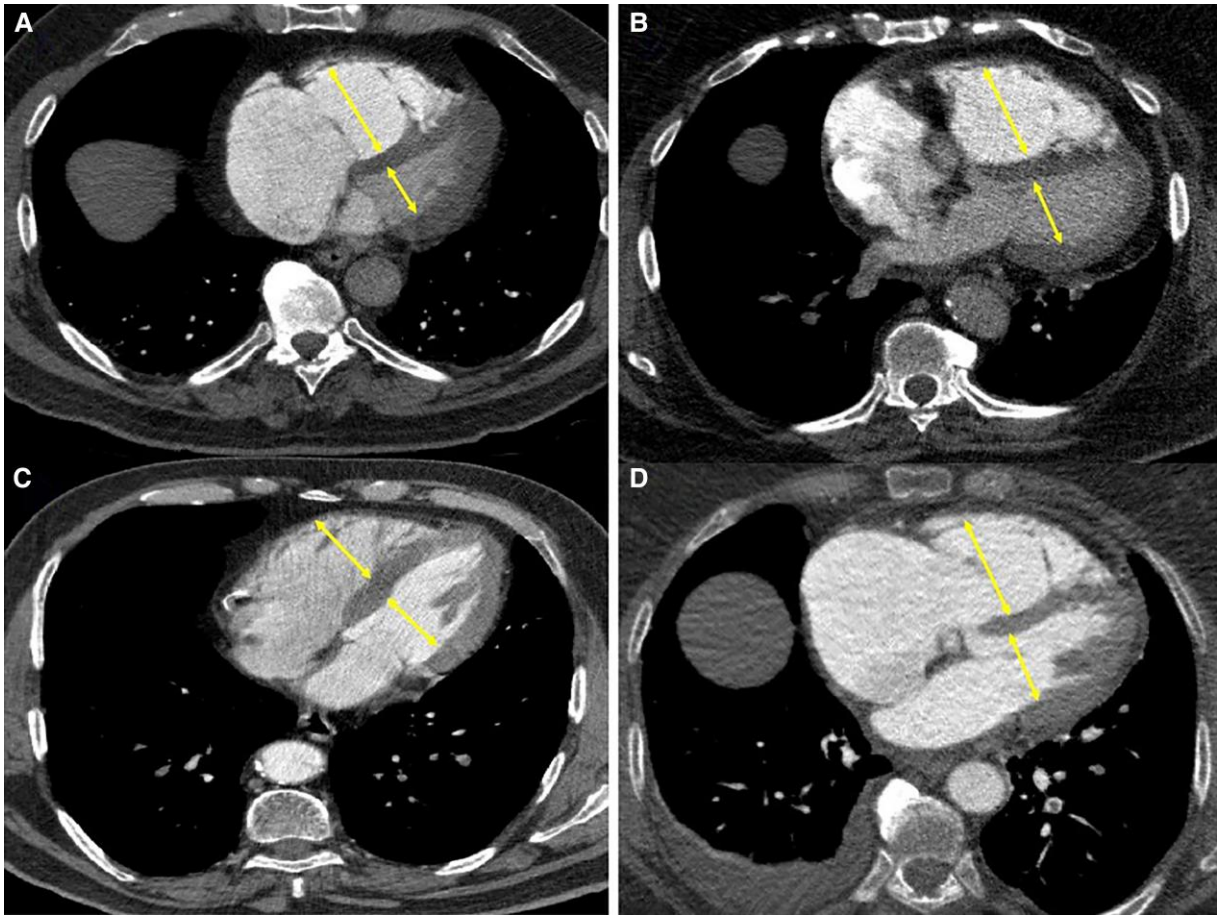

Figure 1 Computed tomography pulmonary angiography axial view shows right to left ventricular diameter ratio (RV/LV ratio): (*A*) Patient 1, RV/LV ratio = 1.6; (*B*) Patient 2, RV/LV ratio = 1.3; (*C*) Patient 3, RV/LV ratio = 1.1; (*D*) Patient 4, RV/LV ratio = 1.4.

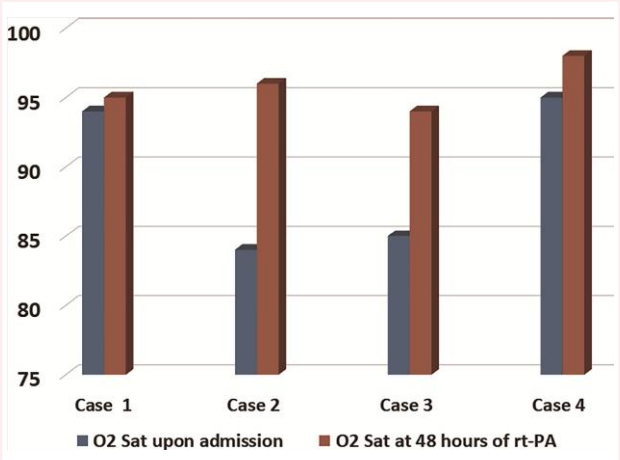

Figure 2 Bar graph shows changes of pulse oxygen saturation (O_2 sat) pre- and post-thrombolysis.

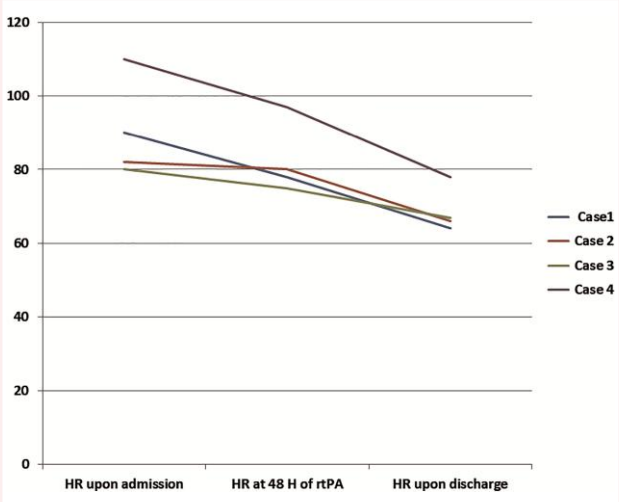

Figure 3 Line chart shows changes of heart rate pre- and post-thrombolysis.

revealed right basal crackles. ECG showed non-specific ST changes. Laboratory test showed elevated D-dimer (5698 ng/mL) and troponin-T (0.134 ng/mL) levels. Bedside TTE showed dilated RV with preserved RV function with RV/LV ratio of 1.4 and SPAP of 57 mmHg. Unfractionated heparin infusion as per PE protocol was started. Computed tomography pulmonary angiography performed urgently showed multiple thrombi in the lobar and segmental PA with an RV/LV ratio of 1.4. Patient received 5 mg rtPA bolus through peripheral i.v. line, followed by 2 mg/h along with UFH at a rate of 500 mg/h for additional 10 h. Improvement of clinical parameters were noticed within few hours of rt-PA infusion. Transthoracic echocardiography was repeated at 48 h of completing thrombolysis. Simplified PE score index and laboratory data upon admission, as well as SPAP and RV/LV ratio pre- and post-rtPA are shown in the table. Computed tomography pulmonary angiography images showing the RV/LV ratio upon admission is presented in *Figure 1C*. Changes of O_2 sat and HR are shown in *Figures 2* and *3*, respectively. Patient was discharged on DOAC on Day 5. Follow-up at 3 months post-discharge noted the absence of dyspnoea. Repeat TTE showed complete normal RV size with mild pulmonary hypertension with estimated SPAP of 42 mmHg.

Discussion

The prevalence of intermediate–high-risk PE is estimated to be at 10% of all normotensive patients with acute PE. It is associated with increased 30-day morbidity (25%) and mortality (7.2%) rates.[5] This PE population necessitates a close monitoring in order to identify patients at risk of haemodynamic deterioration and those who may benefit from early reperfusion therapy.[2,5] Over the recent years, there have been growing interest in treating such patients with catheter-directed infusion of thrombolytics in order to prevent deterioration and at the same time do not significantly increase the risk of bleeding associated with the systemic use of thrombolytics.

We described a case series of four consecutive patients with intermediate–high-risk PE and who are at risk of decompensation. These patients were treated successfully with low-dose rt-PA (total of ≤25 mg) through a peripheral i.v.-line and infused over a period of ≤10 h. We noted rapid clinical and haemodynamic improvement (within few hours of initiation of treatment) and significant improvement in echocardiographic parameters assessed at 48 h of completing thrombolysis. We did not encounter any bleeding events in our group of patients.

Several trials have examined the use of CDT in the treatment of intermediate–high-risk PE patients. The OPTALYSE trial is an ultrasound facilitated CDT trial using a low rt-PA dose infusion in patients with intermediate–high-risk PE;[6] it showed a significant improvement of RV/LV ratio, RV function, and reduction of the clot burden. There was not an increase in the intracranial bleeding risks.[6] In the ULTIMA trial, 59 patients with intermediate–high-risk PE were randomized to receive ultrasound facilitated CDT followed by i.v. heparin or to i.v. heparin alone and resulted in a statistically significantly improved RV/LV ratio, supporting a haemodynamic benefit.[7] However, CDT requires high level of expertise and is not readily available in all centres. In addition, it requires the use of multiple resources (cath-lab, ICU-bed) that are expensive and limited, especially in the COVID-19 era. To our knowledge, our case series is the first to report the use of reduced dose of rt-PA continuous infusion over a period of around 10 h through a systemic peripheral i.v.-line, rather than through CDT in the PA, for intermediate–high-risk PE. This approach needs to be further evaluated by a randomized controlled trial in order to assess its safety and efficacy in the treatment of intermediate–high-risk PE patients.

Conclusions

Low-dose rt-PA continuous infusion through a peripheral i.v. line might be a safe and an effective alternative to CDT in the treatment of patients with intermediate–high-risk acute PE. Our findings shed the light on a potential therapeutic approach that is readily available at most medical centres, relatively inexpensive, and requires less human resources and expertise.

Lead author biography

Fida Charif, MD Pulmonary Specialist, graduated from the Lebanese University, Faculty of Medical Sciences and Université Paris 5, France.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

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