Catheter-directed therapy for submassive pulmonary embolism after unsuccessful systemic thrombolysis

Chang Dong¹, Shufen Jiang², Donghua Ji³, Yingqun Ji¹ and Zhonghe Zhang¹

¹Department of Respiratory Medicine, First Affiliated Hospital of Dalian Medical University, Dalian City, Liaoning Province, China; ²Department of Cardiovascular Medicine, First Affiliated Hospital of Dalian Medical University, Dalian City, Liaoning Province, China; ³Department of Intervention Technology, First Affiliated Hospital of Dalian Medical University, Dalian City, Liaoning Province, China

Abstract
Catheter-directed therapy (CDT) has emerged as an important treatment for pulmonary embolism (PE). We present a patient with life-threatening submassive PE with transient hypotension, progressive right ventricular dysfunction, and respiratory failure who failed anticoagulation and had little improvement with systemic thrombolysis, but responded well to catheter-directed therapy.

Keywords
submassive pulmonary embolism, catheter-directed therapy, systemic thrombolysis, anticoagulation

Date received: 27 April 2017; accepted: 14 September 2017
Pulmonary Circulation 2017; 8(1) 1–5
DOI: 10.1177/2045893217736262

Case report
A 53-year-old man was admitted to hospital with complaints of fever for two weeks and chest pain and dyspnea for five days. He had earlier been misdiagnosed as pneumonia because of the high-grade fever (38.4°C) and cough, and had been treated with antibiotics. However, his chest pain and dyspnea worsened and he developed hemoptysis. There was no significant past medical history or family history. However, the man had been a smoker for 40 years. Physical examination was unremarkable except for a few moist rales in the right lung. At admission, his temperature was 37.3°C, heart rate was 90/minute, and blood pressure was normal at 120/85 mmHg. Arterial blood gases on room air indicated mild hypoxemia (pH = 7.44, PaO₂ = 69 mmHg, PaCO₂ = 34 mmHg, and SaO₂ = 94.2%). D-dimer concentration was 2400 µg/L FEU. Serum alanine aminotransferase (ALT) was 66 U/L, but serum aspartate aminotransferase (AST), creatine kinase, creatine kinase-MB, troponin-I (Tn-I), and brain natriuretic peptide (BNP) were all within normal limits. Electrocardiography (ECG) was normal (Fig. 1). There were no clinical signs of deep vein thrombosis. The two-level Wells’ score was 1 (for hemoptysis), indicating low probability of pulmonary embolism (PE).

While in hospital, the patient had an attack of syncope and temporary loss of consciousness after urination. His blood pressure dropped to 86/58 mmHg for approximately 2 min and then recovered to normal range. Investigation results suggested a diagnosis of submassive PE. Arterial blood gases on 5 L/min oxygen indicated acute respiratory failure (pH = 7.35, PaO₂ = 44 mmHg, PaCO₂ = 33 mmHg, and SaO₂ = 78%); cardiac biomarkers were positive (BNP = 628.34 pg/mL and Tn-I = 0.43 µg/L); and ECG showed new incomplete right bundle-branch block and anteroseptal T wave inversion (Fig. 2), indicating myocardial injury and right ventricular dysfunction (RVD). Serum transaminases were elevated (ALT = 1093 U/L, AST = 524 U/L), indicating acute liver injury, likely due to liver congestion as a result of RVD. Computed tomographic pulmonary angiography (CTPA) revealed extensive filling defects throughout the bilateral main pulmonary arteries, with a right ventricular-to-left ventricular (RV/LV) diameter ratio of 1.3 (Fig. 3).

Corresponding author:
Yingqun Ji, No. 222 Zhongshan Road, Dalian City, Liaoning Province, 116011, China.
Email: jiyingqun@163.com
Fig. 1 Electrocardiograph of the patient on admission is normal.

Fig. 2 Electrocardiograph of the patient after his transient shock shows new-onset incomplete right bundle branch block, anteroseptal T-wave inversion, and S1Q3T3.

Fig. 3 CTPA reveals large filling defects in the bilateral main pulmonary arteries and RV/LV diameter ratio of 1.3.
Unfractionated heparin was administered, with a target activated partial thromboplastin time of 50–70 s. However, the patient’s condition deteriorated with worsening of dyspnea and hypoxia (SaO₂ = 84–91% on 10 L/min oxygen); respiratory rate was 25–38/min, heart rate was 88–108/min, and blood pressure was in the range of 95/70–118/83 mmHg. After ruling out any contraindications, we administered systemic thrombolysis, with infusion of urokinase 20,000 IU/kg over 2 h. There was no significant clinical improvement after three days of observation, and the patient continued to have chest pain, dyspnea, and fever. Body temperature was elevated to 39.3°C, with heart rate of 84–92/min, respiratory rate of 28–33/min, and blood pressure in the range of 99/60–121/80 mmHg without inotropic support. Arterial blood gases on room air showed respiratory failure, with respiratory alkalosis due to compensatory hyperventilation (pH = 7.489, PaO₂ = 52 mmHg, PaCO₂ = 28.5 mmHg, and SaO₂ = 84%). The patient could not be weaned off high-flow oxygen through mask.

Finally, we decided to attempt catheter-directed therapy (CDT) without intrapulmonary thrombolysis, using the Rotarex and Aspirex thrombectomy devices (Straub Medical AG, Wangs, Switzerland) that are designed to macerate and aspirate pulmonary artery thrombus (Fig. 4). As measured by right heart catheterization before CDT, the mean pulmonary artery pressure (mPAP) was 39 mmHg, with left mPAP of 38 mmHg and right mPAP of 40 mmHg. These pressures fell to 35 mmHg, 32 mmHg, and 33 mmHg, respectively, after CDT. No procedure-related complications were encountered.

The patient’s symptoms improved dramatically within 24 h of CDT. Respiratory rate dropped from 33/min to 20/min, oxygen requirement decreased (SaO₂ = 97% on 6 L/min oxygen), and arterial blood gas analysis on room air improved (pH = 7.44, PaO₂ = 74 mmHg, and PaCO₂ = 34 mmHg). The patient was discharged from hospital 21 days from the date of admission. He was prescribed warfarin and advised to maintain international normalized ratio (INR) at 2–3.

![Fig. 4](image-url) (a, b) Initial pulmonary angiogram performed through catheterization shows multiple filling defects in both pulmonary arteries; they are especially marked in the right lower lobe pulmonary artery (a) and in the distal part of the left main pulmonary artery (b). (c, d) Pulmonary angiogram after CDT with the Straub Aspirex S 8F 110 cm mechanical thrombectomy devices shows the recanalized right (c) and left (d) pulmonary arteries.
At follow-up three months after discharge, the patient had no complaints of dyspnea or exercise intolerance. Repeat CTPA scan showed almost complete absorption of the thrombus, and normal RV/LV diameter ratio (Fig. 5).

Discussion

The American Heart Association defines submassive PE as acute PE without systemic hypotension (i.e. systolic blood pressure >90 mmHg), but with either RV dysfunction or myocardial necrosis. Our patient had only a transient (2 min) fall in systolic blood pressure, which recovered to normal range without inotropic support; he also had evidence of RV dysfunction (RV dilation on CT, elevation of BNP, ECG changes) and myocardial necrosis (elevation of Tn-I), all of which suggested a diagnosis of submassive PE.

The patient was otherwise healthy, with no relevant medical history or any obvious risk factors: congenital thrombophilia was ruled out and there was no DVT, surgery, trauma, or cancer to explain the PE. Sometimes PE can occur in patients without any of the known risk factors. We considered the possibility of chronic thromboembolic pulmonary hypertension (CTEPH). However, the patient had no history of venous thromboembolism or of exercise intolerance. Moreover, the central filling defect throughout a distended vessel on CTPA suggested acute PE rather than eccentric wall-adherent thrombi, which is the specific sign of CTEPH. The ECG was also normal on admission. In addition, after effective anticoagulation for three months, the patient did not have dyspnea or exercise intolerance, and repeat CTPA showed almost complete absorption of the thrombus and a normal RV/LV diameter ratio. In view of these findings, CTEPH was improbable.

Acute PE remains the third leading cause of mortality among the cardiovascular diseases. In one study, all-cause mortality at three months after acute PE was 17.4% and as high as 58.3% for massive PE. Submassive PE is associated with high mortality and adverse short-term outcomes, and therefore effective and safe treatment must be provided promptly. The management of patients with submassive PE depends on the clinical presentation and risk classification. By the 2014 European Society of Cardiology (ESC) criteria, our patient had intermediate to high risk of PE. For this subgroup, anticoagulation is recommended, along with close monitoring and early rescue reperfusion. Thrombolysis combined with anticoagulation has been found to be significantly better than anticoagulation alone for reducing clinical deterioration in patients with submassive PE, though there is increased risk of bleeding.

Submassive PE patients who have evidence of severe disorder (shock, respiratory failure, or RV strain) and no contradictions to thrombolysis are more likely to benefit from fibrinolysis. Because our patient failed anticoagulation and had worsening respiratory distress and low risk of bleeding, we administered systemic thrombolysis.

Unsuccessful thrombolysis is defined as persistent clinical instability (hypotension, shock, or hypoxemia) and residual echocardiographic findings of RV dysfunction within 36 h of systemic thrombolytic treatment. Unfortunately, the severe respiratory failure of the patient was not reversed after fibrinolysis. The inverse relationship that exists between duration of symptoms and improvement on lung scan reperfusion scores after treatment suggests that thrombolysis should begin as soon as PE is diagnosed. Rescue thrombolysis did not produce significant improvement, probably because our patient had had symptoms for about two weeks.

One study compared rescue surgical embolectomy with repeat thrombolysis after unsuccessful thrombolysis in acute massive PE. Repeat thrombolysis was successful in only 31% of patients. Mortality was higher and recurrent PE more common in the repeat-thrombolysis group than in the surgical embolectomy group; the incidence of major bleeding was similar in both groups. However, surgical treatment causes major trauma and imposes a greater strain on heart and lung function. Considering that PE patients often have life-limiting co-morbidities, surgical embolectomy is unsuitable for most people.

CDT uses low-profile devices (≤10 F) for mechanical fragmentation and/or aspiration of embolus, with or without injection of a thrombolytic drug. Due to the paucity of high-quality studies in support of CDT over thrombolytic therapy, the tenth edition of the Antithrombotic Guidelines...
recommends CDT for patients with acute massive PE when systemic thrombolysis fails or is contraindicated. One study reviewed 12 patients (seven with failed systemic thrombolysis and five with contraindications to medical fibrinolysis) who were treated with CTD with or without catheter thrombolysis and reported an overall success rate of 83%. While, two patients died secondary to cardiac arrest, no major bleeding or procedure-related complications were observed. However, various studies of CDT as the first-line treatment strategy for severe PE have also been reported and discussed. In a meta-analysis of 35 studies, 546 of the 571 massive PE patients (95%) received CDT as primary treatment without trial of systemic thrombolysis; the pooled success rate was 86.5%, with major and minor complications seen in 2.4% and 8% patients, respectively. The PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) study, which involved 28 patients with massive PE and 73 patients with submassive PE, has shown that CDT is a safe and effective intervention, with only 6% in-hospital deaths and no major or intracranial bleeding events.

To sum up, management of patients with submassive PE depends on their clinical presentation and risk classification. CDT is an effective and safe option and can be life-saving when systemic thrombolysis fails or is contraindicated. It is also reasonable to consider CDT as the primary treatment for severe PE instead of thrombolysis in institutions where the expertise and resources are available. Further randomized controlled trials are needed to compare CDT with systemic thrombolysis.

**Conflict of interest**
The author(s) declare that there is no conflict of interest.

**Funding**
Yingqun Ji was funded by a National Key Research and Development Program of China (2016YFC0905600).

**References**
1. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011; 123(16): 1788–1830.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics – 2017 Update: A Report From the American Heart Association. *Circulation* 2017; 135: e146–e603.
3. Goldhaber SZ, Visani L and De Rosa M. Acute pulmonary embolism: clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). *Lancet* 1999; 353(9162): 1386–1389.
4. Sinha SK, Sachan M, Goel A, et al. Efficacy and safety of thrombolytic therapy in acute submassive pulmonary embolism: follow-up study. *J Clin Med Res* 2017; 9(2): 163–169.
5. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35(43): 3033–3069.
6. Meyer G, Vicaud E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014; 370(15): 1402–1411.
7. Meneveau N, Sérode MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest* 2006; 129(4): 1043–1050.
8. Daniels LB, Parker JA and Patel SR. Relation of duration of symptoms with response to thrombolytic therapy in pulmonary embolism. *Am J Cardiol* 1997; 80(2): 184–188.
9. Kearon C, Akles EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149(2): 315–352.
10. Kuo WT, van den Bosch MA, Hofmann LV, et al. Catheter-directed embolectomy, fragmentation, and thrombolysis for the treatment of massive pulmonary embolism after failure of systemic thrombolysis. *Chest* 2008; 134(2): 250–254.
11. Zuin M, Kuo WT, Rigatelli G, et al. Catheter-directed therapy as a first-line treatment strategy in hemodynamically unstable patients with acute pulmonary embolism: Yes or no? *Int J Cardiol* 2016; 225: 14–15.
12. Kuo WT, Gould MK, Louie JD, et al. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol* 2009; 20(11): 1431–1440.
13. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT). *Chest* 2015; 148(3): 667–673.