Intervention in Massive Pulmonary Embolus: Catheter Thrombectomy/Thromboaspiration versus Systemic Lysis versus Surgical Thrombectomy

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Abstract

Keywords

- massive pulmonary embolus
- systemic thrombolysis
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- interventional radiology

Massive pulmonary embolus (PE), defined as hemodynamic shock from acute PE, is a life-threatening condition. Deaths from massive PE, especially when unsuspected, occur within minutes to hours of onset and as such prompt intervention can be lifesaving. Acute massive PE patients have traditionally been candidates for treatment with intravenous systemic thrombolysis to improve pulmonary artery pressure, arteriovenous oxygenation, and pulmonary perfusion in an effort to reduce mortality. However, patients with contraindications to systemic thrombolysis or those who have failed thrombolysis may benefit from other techniques including endovascular and surgical embolectomy. This article will review the current medical management as well as catheter-directed therapies and surgical embolectomy in the treatment of patients with massive PE.

Objectives: Upon completion of this article, the reader will be able to differentiate the treatment options for acute massive pulmonary embolus, consisting of systemic thrombolysis, catheter-directed pharmacological and mechanical thrombolysis, and surgical embolectomy, including their technical and clinical considerations.

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Pulmonary embolus (PE) is a morbid and often fatal disease that contributes to 200,000 to 300,000 hospitalizations a year in the United States.¹ The 1-month mortality rate is up to 12% for all patients with PE, which increases to ~31% in those with hemodynamic compromise.^{2,3} One-third of patients with venous thromboembolism (VTE), which has an incidence of ~1 per 1,000 persons each year in the United States, present with manifestations of PE.³ Silent, or asymptomatic, PE may also be present in up to 51% of patients with clinically suspected VTE,⁴ which could rapidly escalate to cardiopulmonary decompensation and sudden death.

Pulmonary Embolus Severity Stratification

PE severity is commonly stratified into three categories based on clinical, biochemical, and radiologic data: low risk, submassive (intermediate risk), and massive (high

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risk). Low-risk PE patients present without any cardiac or hemodynamic compromise and is typically identified with radiologic imaging alone. Submassive PE is defined by imaging (echocardiogram or CT) and/or cardiac biomarker (troponins, B-type natriuretic peptide (BNP)) proven right ventricular (RV) dysfunction, in an otherwise normotensive patient. Massive PE comprises patients with cardiopulmonary failure and/or hemodynamic compromise, which often requires pressor or respiratory support. The preferred initial treatment for all patients is therapeutic anticoagulation, which is usually sufficient for low-risk patients. In the event that there is a contraindication to anticoagulation, low-risk patients may instead be treated with IVC filter placement as a temporizing measure until they are amenable to treatment with anticoagulation or there is no longer a significant risk for PE. Patients with submassive PE have a variety of treatment options available, all of which aim to decrease RV overload to prevent cardiopulmonary decompensation. These include systemic thrombolysis, catheter-directed thrombolysis (CDT), percutaneous mechanical or pharmacomechanical intervention, and surgical embolectomy. Finally, the gold standard treatment for massive PE has traditionally been systemic thrombolysis; however, this is associated with a significant increase in risk of major and intracranial bleeding,⁵ which may make one of the preceding treatment options more preferable in certain scenarios.

Massive Pulmonary Embolus

Massive PE is defined as acute PE in the setting of sustained hypotension (systolic blood pressure < 90 mm Hg for at least 15 minutes or requiring inotropic support), pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with sign or symptoms of shock).⁶ Clinical symptoms that may suggest hypotension include syncope, dizziness, diaphoresis, and anxiety. The patient may also be hypoxic and present with dyspnea, chest pain, or nausea; the latter of which may suggest hepatic congestion secondary to right heart failure. Patients typically present with shock and possibly pulmonary arrest and are either in or on their way to the intensive care unit on vasopressor and/or respiratory support. Despite progress in intensive care management and technical advancements in device therapy, overall mortality rate associated with massive PE remains at ~30%.⁷⁻⁹ Although frequently required for ventilation support, intubation should be deferred if possible, as it may elevate pulmonary artery pressure and exacerbate heart strain.¹⁰ Parenteral systemic thrombolysis is a particularly attractive option for these patients, as it offers a quick and effective solution for resolving acute clot. Alternative options such as surgical or endovascular intervention may not be immediately available or the patient may be too unstable for transport. Prompt thrombolytic administration is optimal, as it maximizes exposure to fresh dissolvable clot. It is also important to treat before increased heart strain leads to cardiac arrest, as poor circulation may limit the effectiveness of intravenous therapy. Regardless of the patient's risk stratification, barring a contraindication to anticoagulation

the patient should immediately be placed on therapeutic unfractionated heparin drip until further intervention can be performed. The American Heart Association (AHA) does not routinely recommend coadministration of heparin with thrombolytics;⁶ however, there have been no randomized trials comparing concurrent anticoagulation and thrombolysis versus holding anticoagulation during thrombolysis. Heparin is normally resumed without bolus after thrombolysis treatment has ended.

Systemic Thrombolysis

Systemic thrombolysis is generally administered as an intravenous 100 mg alteplase infusion over 2 hours.^{11,12} Older agents, including streptokinase and urokinase, are rarely used now due to 12- to 24-hour infusion times. Tenecteplase is frequently used in Europe, and indeed is the agent administered in many notable trials of systemic thrombolytic therapy (e.g., PEITHO¹³); however, it has not been approved for acute PE by the FDA in the United States. Thrombolytics provide the greatest benefit if they are administered within 48 hours of symptom onset.¹² A summary of the key clinical trials of systemic thrombolysis in PE is provided in ► **Table 1**. In a recent meta-analysis which included 16 randomized clinical trials comprising 2,115 patients presenting with PE, the use of systemic thrombolytics was found to be associated with lower all-cause mortality compared with anticoagulants (2.17 vs. 3.89%, respectively); however, there was an increased risk of major bleeding (9.24 vs. 3.42%) and intracranial hemorrhage (1.46 vs. 0.19%).¹⁴ A complete patient history must be reviewed prior to the initiation of therapy. Absolute contraindications include a history of prior hemorrhagic stroke or ischemic stroke within 6 months, central nervous system neoplasm, gastrointestinal bleeding within 1 month or any known active bleeding, or major trauma or surgery within 3 weeks.¹⁵ Low-dose alteplase (50 mg rather than 100 mg) for massive PE may be as effective as the standard dose, with fewer major bleeding events,¹⁶ and could be considered a favorable treatment option in the elderly or frail patient population or those with relative contraindications to thrombolysis. A patient who decompensates into cardiac arrest may no longer have the circulatory support to deliver the thrombolytics to the pulmonary arteries. However, despite the low chance of efficacy, the benefit-to-risk ratio of thrombolysis may still be favorable in these critically unstable patients.¹⁷ In patients with imminent or active cardiac arrest, a bolus infusion of alteplase over 2 minutes showed favorable outcomes compared with the standard 2-hour infusion, without associated increased bleeding risk.¹⁸ In the event of a major bleed, all anticoagulation and thrombolytic agents should be discontinued and consultation to neurology/neurosurgery obtained in the event of an intracranial hemorrhage. Protamine sulfate and cryoprecipitate can be used to counteract the effects of anticoagulation.¹⁹ Intravenous tranexamic acid (TXA; 10 mg/kg three to four times daily²⁰) has been used to decrease hematoma expansion in patients with traumatic intracranial hemorrhage, with fewer deaths in patients who received TXA

Table 1 Key clinical trials of systemic thrombolysis in pulmonary embolus

Trial	Study design	No. of patients	Treatment agent	Control	Inclusion/exclusion criteria ^a	Follow-up, days	Primary end-point	Pertinent findings
PIOPED, 1990 ³⁷	Randomized, double-blind, placebo-controlled	13	Alteplase (40–80 mg)	Heparin	Acute PE ≤ 7 d, not in shock, occlusion of 1 lobar artery or ≥ 2 segmental arteries	7	Pulmonary perfusion (pressure measurements, pulmonary angiogram and V/Q scan)	- Reduction of total pulmonary resistance among patients treated with alteplase compared with heparin alone ($p = 0.03$) - Rate of improvement in pulmonary angiogram not statistically significant in alteplase group compared with control - One major bleed in alteplase group
MAPPET-3, 2002 ³⁸	Randomized, double-blind, placebo-controlled	256	Alteplase (100 mg)	Heparin	Acute PE ≤ 14 d, age < 80 y, RVD or pulmonary HTN or EKG signs of RV strain	30	In-hospital death or clinical deterioration requiring treatment escalation	- Rate of primary endpoint significantly lower with heparin + alteplase vs. heparin alone (11 vs. 25%, respectively; $p = 0.006$) - Recurrent PE rate low in both groups - Bleeding incidence similar in both groups
TIPES, 2010 ³⁹	Randomized, double-blind, placebo-controlled	58	Tenecteplase (30–50 mg)	Heparin	Acute PE ≤ 10 d, age 18–85 y, RVD by echo or CT, normal BP	30	Reduction of RVD by echo at 24 h	- Statistically significant reduction of right-to-left EDD ratio at 24 h in tenecteplase group vs. control (0.31 vs. 0.10, respectively; $p = 0.04$) - Recurrent PE in one in tenecteplase group vs. three in control group - Two major bleeds in tenecteplase group
Fasullo et al 2011 ⁴⁰	Randomized, double-blind, placebo-controlled	72	Alteplase (100 mg)	Heparin	Acute PE ≤ 6 h, RVD by echo or CT, +D-dimer, normal BP, hypoxemia or specified EKG findings	180	Reduction of RVD by echo at follow-up	Thrombolysis group showed a significant early improvement of RV function compared with heparin group, and this improvement was observed also during the follow-up
MOPETT, 2012 ⁴¹	Prospective, randomized	121	Alteplase (50 mg)	Heparin or enoxaparin	Acute PE ≤ 10 d, > 2 lobar or main artery, ≥ 2 new symptoms	840	Pulmonary hypertension and recurrent PE	- No major bleeding in either group - Rate of primary endpoint significantly lower with alteplase + heparin vs. heparin alone (15 vs. 37%, respectively; $p = 0.017$)
PEITHO, 2014 ¹³	Randomized, double-blind,	1,005	Tenecteplase (30–50 mg)	Heparin	Acute PE ≤ 15 d, RVD by echo or CT	7	Death or hemodynamic collapse within 7 d	6 patients in tenecteplase group dies vs. 9 in control (1.2 vs. 1.8%, respectively; $p = 0.42$)

Table 1 (Continued)

Trial	Study design	No. of patients	Treatment agent	Control	Inclusion/exclusion criteria ^a	Follow-up, days	Primary end-point	Pertinent findings
	placebo-controlled							- Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group vs. 6 patients (1.2%) in control group ($p < 0.001$) - Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 vs. 1 patient (0.2%) in control group which was hemorrhagic ($p = 0.003$)
TOPCOAT, 2014 ⁴²	Randomized, double-blind, placebo-controlled	83	Tenecteplase (dose not reported)	Weight-based enoxaparin or dalteparin	Acute PE ≤ 15 d, RVD by echo or CT, myocardial injury by elevated troponin	5	Composite outcome: (1) death, circulatory collapse or major bleeding within 5 d or (2) recurrent PE, poor functional capacity within 90 d	- Trial prematurely terminated - Adverse outcomes occurred significantly less with tenecteplase + heparin vs. placebo + heparin (15 vs. 37%, respectively, $p = 0.017$)

Abbreviations: BP, blood pressure; CT, computed tomography; EDD, end diastole dimension; EKG, electrocardiogram; HTN, hypertension; PE, pulmonary embolus; RV, right ventricle; RVD, right ventricular dysfunction.

^aExclusion criteria: All studies excluded patients with high risk of bleeding (including active bleeding, recent surgery, thrombocytopenia) and severe hypertension (systolic blood pressure > 200 mm Hg).

compared with those receiving placebo.²¹ Although no trials exist of TXA use in alteplase-induced intracranial hemorrhage, there are case reports of its effective use in reducing hematoma expansion.²² Best supportive measures to prevent shock in the event of a major bleed include volume resuscitation, manual pressure, and possibly intervention including embolization or surgery.

Catheter-Directed Pharmacological and Mechanical Thrombolysis

Endovascular techniques to recanalize complete and partial occlusions of the pulmonary arteries are potentially life-saving in selected patients with acute massive PE.^{6,23} The 2011 AHA guidelines⁶ recommend either CDT or surgical embolectomy in patients with massive PE with contraindications to fibrinolysis or patients who remain unstable after receiving fibrinolysis (Class IIa, Level of Evidence C). More recently, the American College of Chest Physicians 2016 guidelines²⁴ recommend the use of CDT in massive PE in patients with (1) a high bleeding risk, (2) failed systemic thrombolysis, or (3) shock that is likely to cause death before systemic thrombolysis can take effect (e.g., within hours), if local expertise is available (Grade 2C). However, there is some debate that CDT can also be used as first-line therapy for massive PE.²⁵ CDT can include infusion of thrombolytics, rheolytic, mechanical, and/or aspiration thrombectomy. Conventionally, CDT is performed with a multi-sidehole infusion catheter that is inserted across the clot to maximize the surface area treated by thrombolytics, to obtain vascular channels through the affected pulmonary arteries. Newer devices utilizing embedded ultrasound transducers in the catheter (EKOS, BTG) purportedly increase diffusion of the thrombolytic into the thrombus.²⁶ Typically, 0.5 to 1 mg/hour alteplase is infused via the catheter for 24 hours with periodic fibrinogen and hemoglobin checks to prevent or rule out hemorrhage. Bilateral pulmonary artery angiography and main pulmonary artery pressure are frequently obtained before and after treatment to evaluate extent and severity of clot burden as well as response to therapy. After 24 hours, the patient may return to the angiography suite and follow-up mechanical or aspiration thrombectomy may be performed on residual thrombus, although several CDT protocols allow for catheter removal in an ICU setting.

Devices for suction thrombectomy include small caliber catheters, such as the Indigo (Penumbra; ►Fig. 1) and larger caliber catheters, such as the AngioVac Aspiration catheter (Angiodynamics; ►Fig. 2). The AngioVac device allows for increased suction capacity and venovenous recirculation, and is of particular importance where massive PE is accompanied by right heart clot in transit. It should be noted, however, that severe complications such as right ventricular free wall perforation²⁷ have been reported.¹³ Rheolytic thrombectomy with the AngioJet (Boston Scientific) device uses the Bernoulli principle to break apart thrombus and has been used in the setting of massive PE;^{25,28} however, procedural-related complications including bradyarrhythmias and deaths^{29,30} have been reported using this device in the pulmonary arteries

Fig. 1 Small caliber suction thrombectomy catheter (black arrow), the Indigo (Penumbra Inc.) within the left pulmonary artery in a patient with acute massive PE.

prompting the FDA to issue a black box warning. Mechanical thrombectomy may also be performed with a variety of other devices that include the Cleaner (Argon Medical Devices), Aspirex (Straub Medical), Helix Clot Buster (ev3), and FlowTriever (Inari Medical; ►Fig. 3), all of which use various techniques to disrupt and/or aspirate thrombus. If the risk for thrombolysis is too high, mechanical and aspiration thrombectomy may be performed alone without prior thrombolytic infusion. There is evidence that this may lead to a significant

Fig. 2 Large caliber suction thrombectomy catheter (white arrow), the AngioVac (Angiodynamics) aspiration cannula, within left pulmonary artery in a patient with acute massive PE with contraindications to systemic thrombolysis.

Fig. 3 (a) Initial pulmonary angiogram in a patient with acute massive PE and contraindications to systemic thrombolysis demonstrating extensive thrombus in the right pulmonary artery (white arrow). (b) Mechanical thrombectomy device (white arrow), the FlowTreiver (Inari Medical), has been deployed across the site of thrombus prior to removal. (c) Postthrombectomy pulmonary angiogram demonstrates marked improved perfusion of the right pulmonary artery (white arrow). Compare with ► Fig. 3a.

reduction in right heart strain without the associated bleeding risk of thrombolysis.³¹ Often the decision of which catheter-directed approach is employed relies on a multitude of factors including local technical capabilities and the clinical picture of the patient.

Surgical Embolectomy

Another option for patients with massive central PE and contraindication or failure to respond to fibrinolysis includes surgical pulmonary embolectomy. Studies have demonstrated improved response to second-line surgical embolectomy rather than repeat systemic or catheter-directed thrombolysis.³² For clot-in-transit within the right heart, the threat of rapid hemodynamic deterioration may necessitate acute surgical intervention particularly when CDT by a

interventionalist is not immediately available, or when an underlying right-to-left shunt is present and can be treated surgically.³³ Cardiopulmonary bypass is often achieved prior to surgical resection; however, the procedure can be performed off bypass, with normothermia, and without aortic cross-clamping or cardioplegic or fibrillatory arrest. Unfortunately, despite the efficacy of the procedure, there is a high rate of PE recurrence postsurgically which contributes to a high mortality risk due to returned strain on an already overloaded right heart. This threat is diminished with preprocedural IVC filter placement.³⁴ Other complications include postoperative bleeding with or without cardiac tamponade and sternal wound infection.³⁵ Recent data support first-line surgical embolectomy for massive PE as an alternative to systemic fibrinolysis; however, this necessitates the availability of an on-call cardiothoracic surgery

team at all times.³⁶ The 2011 AHA guidelines⁶ for surgical embolectomy included patients with massive PE and contraindications to fibrinolysis or patients who remain unstable after receiving fibrinolysis, and states that the decision to proceed with CDT versus surgical embolectomy requires interdisciplinary teamwork, discussion that involves the surgeon and interventionalist, and an assessment of the local expertise.

Conclusion

Massive PE is a life-threatening disease with a high mortality. Prompt treatment is essential to save lives. In the absence of any contraindication, patients with massive PE should be immediately treated with full-dose intravenous systemic thrombolysis. The subset of patients who fail systemic thrombolysis with ongoing hemodynamic compromise or those with contraindications may be candidates for various catheter-directed therapies or surgical embolectomy. The decision algorithm within this subset of patients is complex and may be aided by a multidisciplinary team-based approach and may depend on local expertise.

References

- Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. *Arch Intern Med* 2003;163(14):1711-1717
- Casazza F, Becattini C, Bongarzone A, et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). *Thromb Res* 2012;130(6):847-852
- White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(23, Suppl 1):I4-I8
- Huisman MV, Büller HR, ten Cate JW, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest* 1989;95(03):498-502
- Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353(9162):1386-1389
- Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. 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
- Gulba DC, Schmid C, Borst HG, Lichtlen P, Dietz R, Luft FC. Medical compared with surgical treatment for massive pulmonary embolism. *Lancet* 1994;343(8897):576-577
- Stulz P, Schläpfer R, Feer R, Habicht J, Grädel E. Decision making in the surgical treatment of massive pulmonary embolism. *Eur J Cardiothorac Surg* 1994;8(04):188-193
- Yalamanchili K, Fleisher AG, Lehrman SG, et al. Open pulmonary embolectomy for treatment of major pulmonary embolism. *Ann Thorac Surg* 2004;77(03):819-823, discussion 823
- Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med* 2011;184(10):1114-1124
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2, Suppl):e419S-e496S
- Konstantinides SV, Torbicki A, Agnelli G, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35(43):3033-3069, 3069a-3069k
- Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370(15):1402-1411
- Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311(23):2414-2421
- Torbicki A, Perrier A, Konstantinides S, et al; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29(18):2276-2315
- Piazza G, Hohlfelder B, Jaff MR, et al; SEATTLE II Investigators. a prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II Study. *JACC Cardiovasc Interv* 2015;8(10):1382-1392
- Kürkciyan I, Meron G, Sterz F, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. *Arch Intern Med* 2000;160(10):1529-1535
- Sors H, Pacouret G, Azarian R, Meyer G, Charbonnier B, Simonneau G. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. *Chest* 1994;106(03):712-717
- Goldstein JN, Marrero M, Masrur S, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol* 2010;67(08):965-969
- Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376(9734):23-32
- CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011;343:d3795
- French KF, White J, Hoesch RE. Treatment of intracerebral hemorrhage with tranexamic acid after thrombolysis with tissue plasminogen activator. *Neurocrit Care* 2012;17(01):107-111
- Kucher N. Catheter embolectomy for acute pulmonary embolism. *Chest* 2007;132(02):657-663
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149(02):315-352
- Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. 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
- Lin PH, Annambhotla S, Bechara CF, et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular* 2009;17(Suppl 3):S137-S147
- Al-Hakim R, Park J, Bansal A, Genshaft S, Moriarty JM. Early experience with AngioVac aspiration in the pulmonary arteries. *J Vasc Interv Radiol* 2016;27(05):730-734
- Margheri M, Vittori G, Vecchio S, et al. Early and long-term clinical results of AngioJet rheolytic thrombectomy in patients with acute pulmonary embolism. *Am J Cardiol* 2008;101(02):252-258

- 29 Dwarka D, Schwartz SA, Smyth SH, O'Brien MJ. Bradyarrhythmias during use of the AngioJet system. *J Vasc Interv Radiol* 2006;17(10):1693–1695
- 30 Jeyabalan G, Saba S, Baril DT, Makaroun MS, Chaer RA. Bradyarrhythmias during rheolytic pharmacomechanical thrombectomy for deep vein thrombosis. *J Endovasc Ther* 2010;17(03):416–422
- 31 Reekers JA, Baarslag HJ, Koolen MG, Van Delden O, van Beek EJ. Mechanical thrombectomy for early treatment of massive pulmonary embolism. *Cardiovasc Intervent Radiol* 2003;26(03):246–250
- 32 Meneveau N, Séronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest* 2006;129(04):1043–1050
- 33 Konstantinides S, Geibel A, Kasper W, Olschewski M, Blümel L, Just H. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation* 1998;97(19):1946–1951
- 34 Greelish JP, Leacche M, Solenkova NS, Ahmad RM, Byrne JG. Improved midterm outcomes for type A (central) pulmonary emboli treated surgically. *J Thorac Cardiovasc Surg* 2011;142(06):1423–1429
- 35 Vohra HA, Whistance RN, Mattam K, et al. Early and late clinical outcomes of pulmonary embolectomy for acute massive pulmonary embolism. *Ann Thorac Surg* 2010;90(06):1747–1752
- 36 Aymard T, Kadner A, Widmer A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited? *Eur J Cardiothorac Surg* 2013;43(01):90–94, discussion 94
- 37 Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. *Chest* 1990;97(03):528–533
- 38 Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347(15):1143–1150
- 39 Becattini C, Agnelli G, Salvi A, et al; TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res* 2010;125(03):e82–e86
- 40 Fasullo S, Scalzo S, Maringhini G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. *Am J Med Sci* 2011;341(01):33–39
- 41 Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; “MOPETT” Investigators. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). *Am J Cardiol* 2013;111(02):273–277
- 42 Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost* 2014;12(04):459–468