Catheter-Based Reperfusion Treatment of Pulmonary Embolism

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Case Presentation: A 76-year-old man with a history of hemicolectomy for colon cancer 10 days previously was admitted because of syncope and severe shortness of breath. On physical examination, the patient was hemodynamically unstable, with a systolic arterial pressure of 80 mm Hg, a heart rate of 124 beats per minute, and distended jugular veins. He was agitated and unable to speak full sentences. His respiratory rate was 28 breaths per minute, and oxygen saturation was 80% on room air. Contrast-enhanced computed tomography showed a filling defect of the left main pulmonary artery, complete occlusion of the left lower lobe pulmonary artery, nonobstructive filling defects of the right lower lobe pulmonary artery, and right ventricular enlargement (right-to-left ventricular dimension ratio of 1.4) (Figure 1). The hemodynamic situation remained unchanged after initiation of treatment with oxygen, intravenous unfractionated heparin, and normal saline.

Case Presentation: A 55-year-old woman suddenly developed acute shortness of breath 3 weeks after resection of a meningioma. On physical examination, the patient appeared he-modynamically stable, with a systolic arterial pressure of 100 mm Hg, a heart rate of 96 beats per minute, a respiratory rate of 18 breaths per minute, and an oxygen saturation of 89% while receiving 3 L of oxygen via face mask. A contrast-enhanced computed tomography confirmed subtotal filling defects in both main pulmonary arteries and right ventricular enlargement (right-to-left ventricular dimension ratio on the reconstructed 4-chamber view of 1.1). After administration of unfractionated heparin and fluids, the systemic arterial systolic pressure dropped to 75 mm Hg, and an infusion with norepinephrine was initiated.

How should these 2 cases be further evaluated and treated?

Reperfusion Therapy

Acute pulmonary embolism (PE) is a life-threatening condition with an estimated overall mortality rate of ≈15% at 3 months.[2] Massive (or high-risk) PE is defined as acute PE with sustained systemic arterial hypotension (usually systolic arterial pressure 90 mm Hg), cardiogenic shock, or the need for cardiopulmonary resuscitation; the in-hospital mortality rate may exceed 50%.[3] Submassive (or intermediate-risk)

PE is associated with preserved systemic arterial pressure, but with right ventricular dysfunction on echocardiography or with elevated cardiac biomarkers; the in-hospital mortality ranges between 6% and 8%.[4,5] Patients with low-risk PE are hemodynamically stable and have neither right ventricular dysfunction nor elevated cardiac biomarkers; these patients usually have excellent short-term prognosis once therapeutic levels of anticoagulation are established.[6]

A scientific guideline statement from the American Heart Association[7] provides detailed recommendations on the management of acute PE, including suggestions on the use of reperfusion therapy, ie, systemic thrombolysis, catheter interventions, and surgical embolectomy (Figure 2).

Thrombolysis with a 2-hour continuous intravenous infusion of 100 mg of recombinant tissue plasminogen activator is approved by the Food and Drug Administration for patients with massive PE and may be considered in patients with submassive acute PE judged to have clinical evidence of adverse prognosis. However, a meta-analysis including 13 randomized clinical trials of fibrinolysis versus heparin

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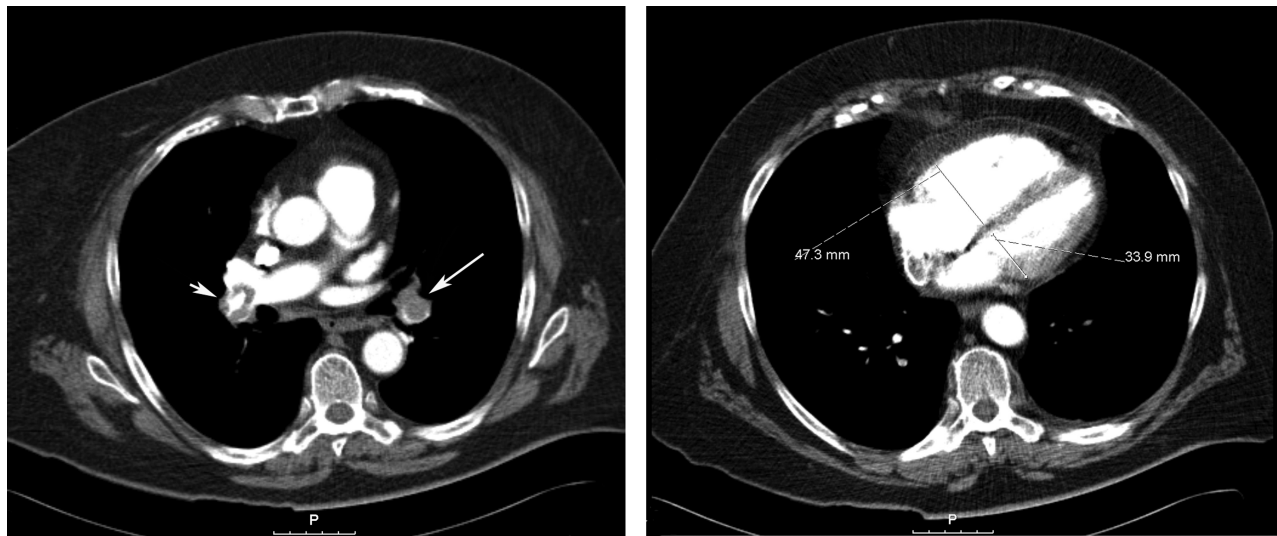
Figure 1. Contrast-enhanced chest computed tomogram from the first case. Left, Complete occlusion of the left lower lobe pulmonary artery (large arrow) and nonobstructive filling defect in the right lower lobe pulmonary artery (small arrow). Right, The subannular right-to-left ventricular dimension ratio was obtained from the reconstructed 4-chamber view.[1] Right (47.3 mm) and left (33.9 mm) ventricular dimensions were measured perpendicular to the interventricular septum and 1 cm above the atrioventricular annulus plane. The right-to-left ventricular dimension ratio was calculated as 1.4.

treatment alone showed no significant reduction in recurrent PE or death.[7] In addition, systemic thrombolysis has absolute and relative contraindications.[7] Absolute contraindications include any prior intracranial hemorrhage, known structural intracranial cerebrovascular disease (eg, arteriovenous malformation), known malignant intracranial neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active bleeding or bleeding diathesis, recent surgery encroaching on the spinal canal or brain, or significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury. Relative contraindications are age >75 years; current use of anticoagulation therapy; pregnancy; puncture of a noncompressible vessel; traumatic or prolonged cardiopulmonary resuscitation (>10 minutes); internal bleeding (within 2–4 weeks); history of chronic, severe, and poorly controlled hypertension or severe uncontrolled hypertension on presentation; dementia; remote (>3 months) ischemic stroke; and major surgery within 3 weeks. It is therefore not surprising that up to two thirds of the patients with massive PE do not receive systemic thrombolysis.[5]

Furthermore, even in selected patients without absolute contraindications to thrombolysis, up to 20% of major hemorrhages and 3% to 5% of intracranial bleeding complications have been reported.[2,8]

Surgical embolectomy requires cardiopulmonary bypass for extracting centrally obstructing pulmonary emboli and is an alternative reperfusion treatment option if absolute contraindications to thrombolysis are present and if performed in an experienced center. According to a meta-analysis on case studies of surgical embolectomy, the pooled mortality rate of 19% from the last decade has substantially improved compared with the pooled mortality rate of 35% before 1990. This observation may likely be attributed to improved surgical techniques and to a change in patient selection.[9]

Indications for Catheter Intervention

Percutaneous catheter-based interventions are appropriate if systemic full-dose thrombolysis is contraindicated or urgent recanalization of PE is warranted, and if performed in an experienced center. The goal of the catheter intervention is the removal of the obstructing thrombi from the main or lower lobe pulmonary arteries, to facilitate right ventricular recovery, and to improve symptoms and survival.[7,10] Since the first description of the Greenfield embolectomy device in 1971,[11] several catheter-based techniques have been introduced.[10]

For patients with absolute contraindications to thrombolysis, contemporary catheter intervention techniques can be separated into 4 categories: (1) thrombus fragmentation, (2) rheolytic thrombectomy, (3) suction thrombectomy, and (4) rotational thrombectomy (Table 1). For patients without absolute contraindications to thrombolysis, 2 approaches are being used: (1) conventional catheter-directed thrombolysis (CDT) and (2) pharmacomechanical thrombolysis (PMT).

Contemporary Catheter Techniques

Thrombus Fragmentation
The aim of this technique is to reduce pulmonary vascular resistance by mechanically disrupting thrombus into smaller fragments. Thrombus fragmentation can be achieved by manual rotation of a pigtail catheter[12] or with peripheral balloon angioplasty catheters.[13] One
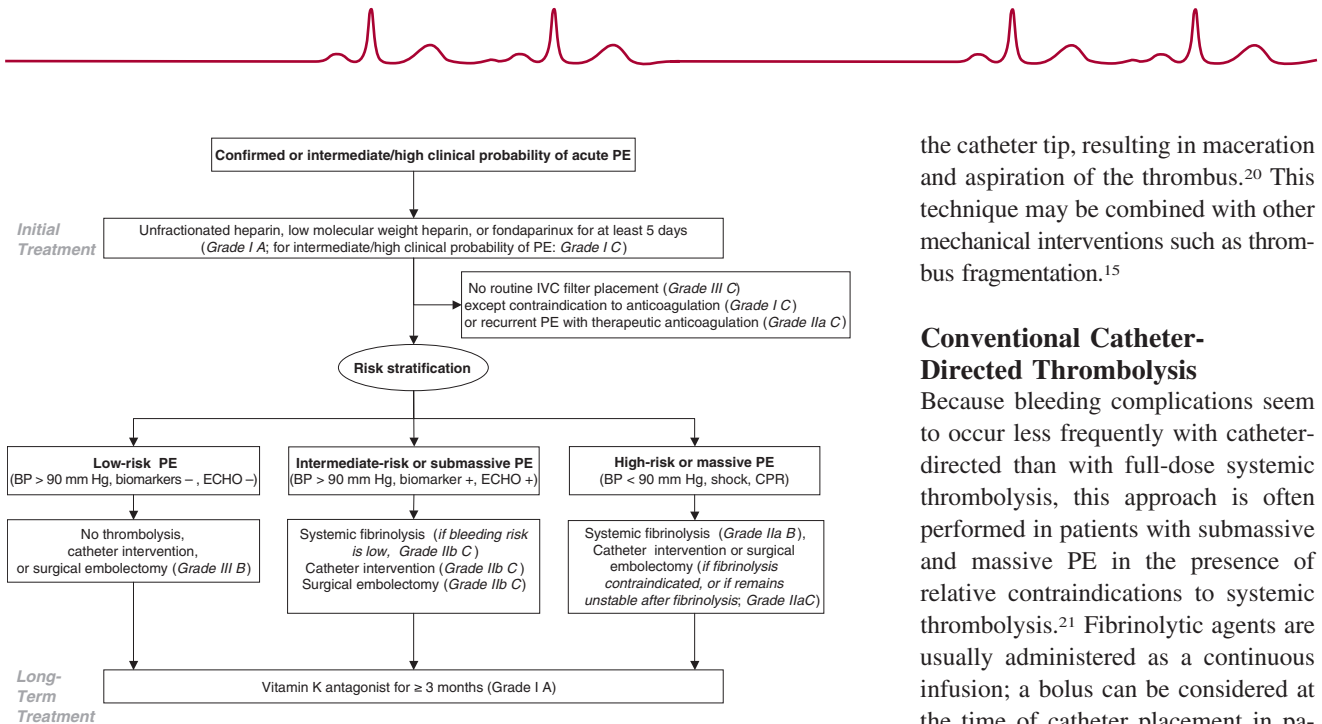
Figure 2. Suggested algorithm for the management of acute pulmonary embolism according to the scientific statement of the American Heart Association with the corresponding levels of evidence.[7] The size of the treatment effect is expressed as Class I to III (I: Benefit ≫ Risk; IIa: Benefit ≫ Risk; IIb: Benefit > Risk; III: Risk ≥ Benefit) and the certainty of the treatment effect as level **A** to **C** (**A**, data derived from multiple randomized clinical trials or meta-analyses; **B**, single randomized trial or nonrandomized studies; **C**, case studies, consensus opinion of experts, or standard of care). Biomarker –, negative test results for troponin or natriuretic peptides; biomarker +, positive test results for troponin or natriuretic peptides; BP, systolic arterial pressure; CPR, cardiopulmonary resuscitation; ECHO –, normal right ventricular function by echocardiography; ECHO +, moderate or severe right ventricular dysfunction by echocardiography; IVC, inferior vena cava; and PE, pulmonary embolism.

disadvantage of this technique is the risk of macroembolization causing hemodynamic deterioration when fragments from a large nonobstructive thrombus embolize.[13] Fragmentation techniques are often combined with other mechanical maneuvers[14,15] or with CDT.[12,16]

Rheolytic Thrombectomy

A high-pressure saline jet within the AngioJet® device generates a pressure gradient by Bernoulli's principle, enabling the removal of thrombus fragments.[17] This device also permits local injection of thrombolytic agents by the Power Pulse spray technique, forcing the drug into the thrombus. Bradycardia is a device-specific side effect and is possibly caused by transient release of bradykinin, adenosine, or potassium secondary to hemolysis. It usually occurs with prolonged thrombectomy runs >20 seconds and may result in heart block or asystole.[18] Hemoglobinuria is also caused by hemolysis and is

usually reversible without clinical sequelae.[19]

Suction Thrombectomy

Suction of thrombus through large-lumen catheters (8–9 F) is achieved by manually applying negative pressure with an aspiration syringe. Conventional vascular access sheaths are not suitable for aspiration of large thrombus because it usually gets trapped within the sheath during suction thrombectomy because of the hemostatic valve. Therefore, this technique requires the use of a dedicated aspiration sheath with a detachable hemostatic valve, permitting percutaneous removal of thrombus without the need for surgical cut down.

Rotational Thrombectomy

The central part of the Aspirex catheter is a protected, high-speed rotational coil that creates negative pressure through an L-shaped aspiration port at

the catheter tip, resulting in maceration and aspiration of the thrombus.[20] This technique may be combined with other mechanical interventions such as thrombus fragmentation.[15]

Conventional Catheter-Directed Thrombolysis

Because bleeding complications seem to occur less frequently with catheter-directed than with full-dose systemic thrombolysis, this approach is often performed in patients with submassive and massive PE in the presence of relative contraindications to systemic thrombolysis.[21] Fibrinolytic agents are usually administered as a continuous infusion; a bolus can be considered at the time of catheter placement in patients who are hemodynamically unstable. Various drug regimens have been used, eg, recombinant tissue plasminogen activator at a dose of 0.5–2.0 mg per hour per catheter for less than 24 hours (bolus dose of 2–5 mg per catheter).

Pharmacomechanical Thrombolysis

PMT is defined as the combination of CDT with a mechanical catheter intervention technique. The combination of thrombus fragmentation or aspiration with CDT may be particularly useful for patients with hemodynamic instability. Another PMT approach is the Power Pulse spray technique for intraclot delivery of low doses of thrombolytic agents, facilitating rheolytic thrombectomy with the AngioJet device. Ultrasound-enhanced thrombolysis may be considered as PMT and is a combination of CDT with a sophisticated catheter system that uses high-frequency, low-power ultrasound. Ultrasound itself cannot dissolve thrombus, but enhances fibrinolysis by causing reversible disaggregation of uncrosslinked fibrin fibers, thereby increasing thrombus permeability for the thrombolytic drug. In addition, ultrasound pressure waves augment the penetration of thrombolytic drug.[22–24]

Table 1.   Catheter Intervention Techniques and Devices

Catheter Interventions Without Thrombolysis		Catheter Interventions With Thrombolysis	
Technique	Device examples	Technique	Device examples
Thrombus fragmentation	Pigtail catheter (5–6F) Peripheral balloon catheters (6–7F, balloon diameter 5–10 mm) Amplatz thrombectomy device 7 F (Bard-Microvena, White Bear Lake, MN)	Catheter-directed thrombolysis (continuous infusion with or without bolus)	UniFuse† 5F, infusion length 10–20 cm (AngioDynamics, Latham, NY) Cragg-McNamara‡ 5F, infusion length 10–20 cm (ev3 Endovascular, Plymouth, MN)
Rheolytic thrombectomy	AngioJet 6F PE catheter (MEDRAD, Minneapolis, MN) Oasis catheter (Boston Scientific, Galway, Ireland) Hydrolyzer (6–7F, Cordis, Miami, FL)	Ultrasound-enhanced, catheter-directed thrombolysis	EkoSonic 6F 12-cm treatment zone device (EKOS, Bothell, WA)
Suction embolectomy	Sheath with detachable hemostatic valve 8–9F (Argon Medical Devices, Athens, TX) plus multipurpose guide catheter (8–9F) plus aspiration syringe (60 mL)	Rheolytic thrombectomy plus catheter-directed thrombolysis	AngioJet 6F PE thrombectomy with Power Pulse thrombolysis (MEDRAD, Minneapolis, MN)
Rotational thrombectomy	Aspirex* 8F, 10F catheter (Straub Medical, Switzerland)	Combined techniques	eg, Pigtail fragmentation (5F) plus AngioJet 6F PE thrombectomy with Power Pulse thrombolysis
Combined techniques	eg, Pigtail fragmentation (5F) plus Aspirex* 8F, 10F thrombectomy		

*Not available in the United States.

†Requires placement of a tip-occluding guide wire.

‡Hemostatic valve at the end of the catheter provides endhole occlusion without the need for placing a tip-occluding guide wire.

Evidence for Catheter Interventions

Catheter interventions have not been compared in a randomized trial with treatment with systemic thrombolysis or with anticoagulation alone, and current evidence is based on single-center case series. An extensive systematic review on mechanical catheter interventions with or without CDT included 6 prospective and 29 retrospective studies with a total of 594 PE patients who underwent a mechanical catheter intervention with currently available low-profile devices (≤10F).[19] The pooled clinical success rate, defined as stabilization of hemodynamic parameters, resolution of hypoxia, and survival of massive PE, was 86%. The effect of the mechanical catheter intervention on the clinical success rate is difficult to assess because 67% of patients received local thrombolysis during the procedure. The success rate was higher in studies in which at least 80% of patients received additional CDT compared with studies with less frequent use of CDT (91% versus 83%). Overall, minor and major procedural complications occurred in 8% and 2%, respectively. A total of 5 procedural-related deaths were reported, 1 from bradyarrhythmia, 1 from widespread distal embolization, 1 associated with cerebrovascular hemorrhage, and 2 with unknown cause.

Another systematic review also included studies of older techniques, such as suction embolectomy with the Greenfield device, and reported an overall clinical success rate of 95% with and 81% without additional use of CDT.[21]

Although a mechanical catheter intervention without thrombolysis is likely not as effective as an intervention with CDT, immediate improvement in hemodynamic measurements has been reported with thrombus fragmentation[25] and with a combination of thrombus fragmentation with rotational thrombectomy.[15] It also remains unclear whether PMT is superior to CDT. In a nonrandomized retrospective study of 33 patients, ultrasound-enhanced thrombolysis resulted in an improved treatment outcome, reduced duration of the thrombolysis infusion, and reduced treatment-related hemorrhagic complications compared with CDT alone.[26] In a retrospective analysis of 24 patients with massive and submassive PE, ultrasound-enhanced thrombolysis rapidly reduced right ventricular enlargement by chest computed tomography.[1] A randomized clinical trial called ULTIMA is currently recruiting patients in Switzerland and Germany with submassive PE to test whether ultrasound-enhanced, low-dose thrombolysis is superior to anticoagulation alone in improving right ventricular enlargement (NCT01166997).

Publication bias likely caused an underreporting of serious complications that may occur with catheter interventions in acute PE; these include periprocedural hemodynamic deterioration, distal embolization, pulmonary artery perforation, systemic bleeding complications, lung hemorrhage, pericardial tamponade, transient heart block or bradycardia, contrast-induced nephropathy, and access-related complications, including hematoma, pseudoaneurysm, or arteriovenous fistula.

Practical Aspects for Catheter Interventions

Patients undergoing invasive pulmonary angiography and catheter intervention

Table 2.   Suggested Step-By-Step Approach for the Catheter Intervention Procedure in Patients With Acute Pulmonary Embolism

1. Prepare the patient for standard cardiac catheterization in the catheterization laboratory.

2. Obtain venous access at the common femoral vein using a standard sheath.

3. Administer a bolus of 80 units per kilogram of intravenous unfractionated heparin. In patients with heparin pretreatment (bolus or infusion), adjust further heparin dosing according to the activated clotting time (target 250–350 s). In patients who received a therapeutic dose of low molecular weight heparin within 12 hours, procedural unfractionated heparin may not be required, particularly not in patients who are candidates for catheter-directed thrombolysis.

4. Perform right heart catheterization and obtain hemodynamic measurements

   Systemic arterial pressure and systemic oxygen saturation by pulse oximetry or if available from an arterial blood sample

   Invasive pressure tracings of (1) the right atrium, (2) right ventricle, and (3) the main pulmonary artery trunk while advancing a diagnostic catheter (pigtail or multipurpose catheter)

   Mixed venous oxygen saturation from the main pulmonary artery trunk for calculation of cardiac output

5. Perform selective conventional cineangiography of the occluded pulmonary artery by injecting a total of 10–15 mL of contrast medium at a rate of 5–8 mL/s using the left anterior oblique view (LAO 20°) for the left pulmonary artery or right anterior oblique view (RAO 20°) for the right pulmonary artery. The tip of the catheter should be placed proximally to the thrombotic occlusion within the right or left main pulmonary artery, to be confirmed by a non-damped pressure tracing.

6. Cross the embolic occlusion using a standard diagnostic catheter and an angle-tipped exchange-length hydrophilic 0.035-inch guide wire (e.g., Terumo Glidewire with torque device). A manual injection of 1 or 2 mL of contrast medium through the diagnostic catheter may be required to confirm successful passage of the embolic occlusion and a safe position of the catheter tip within a large lower lobe segmental branch.

7. Introduce the desired catheter treatment device directly over the 0.035-inch wire into the obstructed pulmonary artery. For the use of specific thrombectomy devices, follow the instructions of the manufacturer.

8. Repeat steps 5–7 if treatment of contralateral pulmonary embolism is required.

9. Repeat step 4 after completion of treatment for assessing the treatment effect on hemodynamic measurements.

require continuous hemodynamic and electrocardiographic monitoring. Duplex ultrasonography of the common femoral vein is useful to rule out suspected concomitant iliofemoral DVT.

In our opinion, it is important to obtain complete right heart hemodynamic measurements before and after completion of the procedure for monitoring the treatment effect (Table 2). The amount of iodine contrast agent should be kept as low as possible and depends mainly on the hemodynamic status and the size of the selected vessel. Despite lower contrast agent requirements with digital subtraction angiography, this technique is not routinely recommended, because most patients with massive PE cannot hold their breath. Nonselective angiography with large (>30 mL) amounts of contrast agent via power injector should be avoided due to the risk of worsening right ventricular failure. To minimize the risk of pulmonary artery perforation, the main and lower lobe pulmonary arteries should be considered for treatment, and segmental branches with a diameter of <6 mm should not be approached.[27]

Cases, Continued

In addition to treatment with dose-adjusted unfractionated heparin, a catheter intervention was selected in both cases. For the first case, bilateral
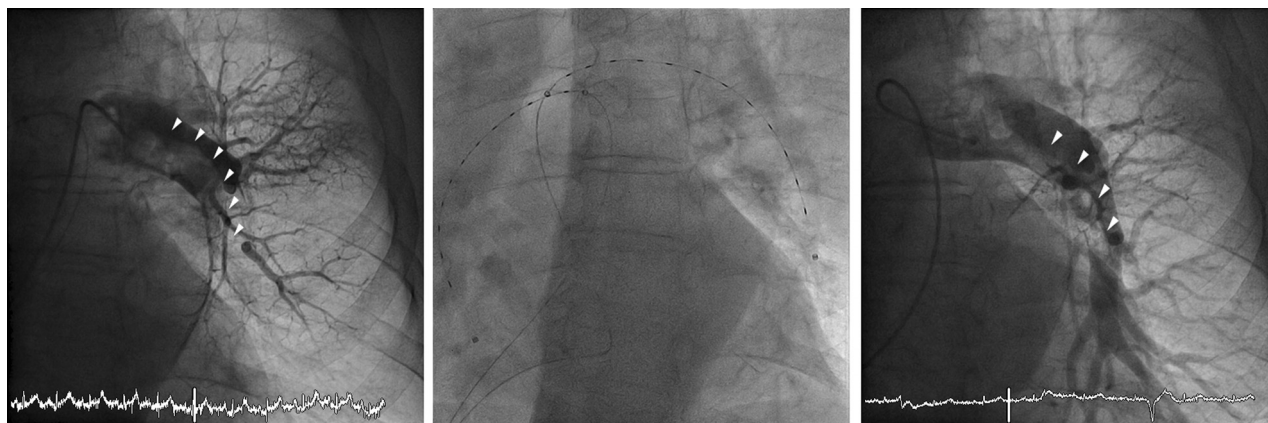

Figure 3. Left, Conventional pulmonary angiogram from the first case showing a subtotal filling defect of the left main pulmonary artery and complete occlusion of the lower lobe pulmonary artery (giant embolus delineated by white arrow heads). Middle, fluoroscopic image of the chest showing placement of two 12-cm treatment zone EkoSonic 6F devices with radio-opaque treatment zone markers and ultrasound elements. Right, Conventional pulmonary angiogram after completion of ultrasound-enhanced fibrinolysis showing residual thrombus (white arrow heads) and a recanalized left lower lobe pulmonary artery.

ultrasound-enhanced thrombolysis was immediately initiated with the administration of 26 mg t-PA over 15 hours (3-mg bolus per device, 10-mg continuous infusion per device over 15 hours) (Figure 3). At completion of the infusion, the patient had improved his hemodynamic measurements: systolic blood pressure 115 mm Hg, heart rate 84 beats per minute, and oxygen saturation 90% on 3 L of supplemental oxygen. Follow-up angiography showed complete reperfusion of the left pulmonary artery and residual nonobstructive thrombus in both pulmonary arteries. The mean pulmonary artery pressure decreased from 39 to 27 mm Hg, and cardiac output increased to from 3.1 to 4.7 L/min. For the second case, it was decided to select a catheter intervention without thrombolysis by using a combined mechanical approach with bilateral pigtail fragmentation and rheolytic thrombectomy. Two thrombectomy runs were performed in both main pulmonary arteries with the AngioJet 6F device. During thrombectomy, the device was advanced at a speed of approximately 5 mm per second. Each thrombectomy run consisted of 2 parts: 1) thrombectomy during 15 seconds from proximal to distal and 2) thrombectomy during 15 seconds from distal to proximal. At completion of the procedure, there was residual thrombus and modest improvement in flow in both pulmonary arteries. The patient remained hypotensive, with a systolic arterial pressure of 85 mm Hg and heart rate of 115 beats per minute. Mean pulmonary artery pressure remained elevated at 35 mm Hg (baseline 37 mm Hg), and cardiac output remained low at 3.2 L/min (baseline 3.0 L/min). Over the next 24 hours, the patient slowly improved, and the norepinephrine infusion was successfully weaned. Both patients were discharged alive on anticoagulant therapy.

Disclosures

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