Management of Massive Pulmonary Embolism

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A 63-year-old woman was transferred to Brigham and Women's Hospital with massive saddle pulmonary embolism (PE) diagnosed by chest CT scan. She was being treated at a suburban hospital for ulcerative colitis manifested by 10 episodes of bloody diarrhea daily. The diagnosis of PE was suspected when she suffered sudden onset of syncope and hypotension, followed by arterial oxygen desaturation and tachycardia. Echocardiography showed an extremely dilated right ventricle with septal flattening. At Brigham and Women's Hospital, she underwent urgent cardiac catheterization. The mixed venous oxygen saturation percentage was in the 50s. Manual injection of contrast agent into the main pulmonary artery confirmed massive bilateral PE. A Gunther Tulip (Cook, Inc) vena caval filter was placed just below the renal veins, and she was taken to the operating room, where she underwent successful emergency pulmonary embolectomy (Figure 1).

Definition, Clinical Clues, and Imaging Pearls

Massive PE is life-threatening. Some patients may present with abrupt onset of critical illness, and others may suffer stuttering but progressive clinical deterioration despite therapeutic levels of anticoagulation. In the International Cooperative Pulmonary Embolism Registry (ICOPER) of 2454 consecutive patients from 7 countries,[1] 4.2% had massive PE. In the United States, ≈150 000 patients per year are diagnosed with acute PE,[2] resulting in thousands of recognized deaths annually from massive PE. Many additional deaths occur each year in the United States as a result of undiagnosed massive PE that is mistaken for acute myocardial infarction or ventricular arrhythmia.

The principal criteria for categorizing PE as massive are arterial hypotension and cardiogenic shock. Arterial hypotension is defined as a systolic arterial pressure <90 mm Hg or a drop in systolic arterial pressure of at least 40 mm Hg for at least 15 minutes.[3] Shock is manifested by tissue hypoperfusion and hypoxia, including an altered level of consciousness, oliguria, or cool, clammy extremities.[3] Early mortality in patients with massive PE is at least 15%, and the degree of hemodynamic compromise is the most powerful predictor of in-hospital death (Table 1).

Patients with massive PE usually present with profound dyspnea at rest, often accompanied by anxiety, syncope, or lightheadedness. Medical history may include recent surgery or trauma, congestive heart failure, chronic lung disease, prior venous thromboembolism, or cancer. A challenging diagnostic situation arises when massive PE presents in patients who have not previously been ill. They may be mistakenly discharged from the emergency department with the diagnosis of "hyperventilation syndrome." The physical examination is helpful and usually reveals arterial hypotension, tachycardia, tachypnea, or cyanosis. Signs of acute right ventricular dysfunction include distended neck veins, a parasternal heave, an accentuated P2, and a tricuspid regurgitation murmur. The ECG is occasionally normal but more often will have some abnormality such as sinus tachycardia, an S1Q3T3 pattern, T-wave inversions in V_1 to V_4, or a pseudoinfarction pattern (Qr) in V_1.[4]

D-Dimer ELISA testing wastes valuable time in patients suspected of massive PE. Cardiac biomarkers such as troponins or B-type natriuretic peptide are used for risk stratification[5] but are redundant in assessments of these critically ill patients. If available, a bedside transthoracic echocardiogram should be obtained as soon as the diagnosis of massive PE is suspected. The echocardiogram not only is useful for substantiating the diagnosis by confirming right ventricular dysfunc-

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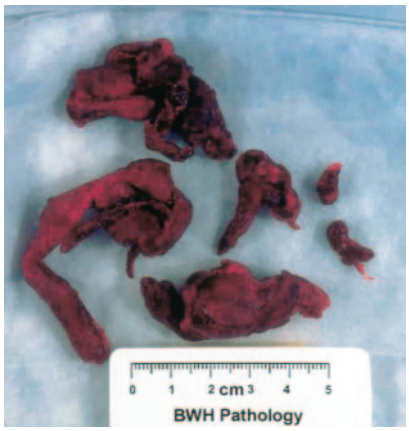

Figure 1. This pulmonary embolectomy specimen measures 11×6×1.5 cm in aggregate.

tion and dilatation but can also exclude diagnoses that may mimic PE such as aortic dissection, pericardial tamponade, or acute myocardial infarction. The echocardiogram can also diagnose complications of PE such as right heart thrombi or even show thrombus protruding into the left atrium via a patent foramen ovale or atrial septal defect.[6] In patients with poor image quality of the right ventricle or in those who undergo cardiopulmonary resuscitation, transesophageal echocardiography may be used.[7] In patients who can be stabilized with fluids, pressors, or mechanical ventilation, a contrast-enhanced chest CT will demonstrate filling defects in the main or lobar pulmonary arteries, as well as right ventricular enlargement on the reconstructed CT 4-chamber view.[8]

Immediate Initial Management

As soon as massive PE is suspected, high-dose unfractionated heparin should be administered in larger-than-usual doses. Most patients should receive at least a 10 000-U bolus of heparin, followed by a continuous intravenous infusion of at least 1250 U/h, with a target activated partial thromboplastin time (aPTT) of at least 80 seconds. The rationale for extremely high heparin doses is the empirical observation that standard doses often do not achieve therapeutic anticoagulation in patients with massive PE and that subtherapeutic dosing of heparin can be fatal. At a minimum, patients with massive PE should initially receive an 80-U/kg bolus of heparin, followed by an 18-U $\cdot$ kg^{-1} $\cdot$ h^{-1} continuous intravenous infusion.

Controversy persists about the proper balance between resuscitation with crystalloid versus with pressors. The most common initial approach is rapid administration of 500 to 1000 mL normal saline. The lower the right ventricular end-diastolic volume is, the more likely this strategy is to succeed and result in an increase in cardiac output.[9]

Fluids should be used with extreme caution. Our experience indicates that excessive fluid administration frequently occurs. In the presence of right ventricular dysfunction, fluid administration exacerbates right ventricular wall stress, intensifies right ventricular ischemia, and causes further interventricular septal shift toward the left ventricle, thereby worsening left ventricular compliance and filling.[10]

Dopamine and dobutamine are first-line inotropic agents for the treatment of PE-related shock. Both agents increase cardiac output but increase pulmonary artery pressure to a lesser extent, thus potentially decreasing pulmonary vascular resistance. Norepinephrine increases both cardiac output and systemic vascular resistance and may be beneficial as monotherapy or in combination with dopamine or dobutamine. In general, there should be a low threshold to initiate pressors. If one pressor is not restoring adequate blood pressure, another should be tried. At times, an α-adrenergic receptor stimulant such as phenylephrine succeeds when other pressors have failed.

TABLE 1. In-Hospital Mortality According to the Degree of Hemodynamic Compromise in 1001 Patients With Acute PE[3]

	n	Mortality, %	95% CI
RV dysfunction, no arterial hypotension	407	8.1	5.8–11.2
Arterial hypotension*	316	15.2	11.6–20.0
Cardiogenic shock†	102	24.5	17.2–33.7
Cardiopulmonary resuscitation	176	64.8	57.5–71.4

RV indicates right ventricular.

*Systolic arterial pressure <90 mm Hg or drop in systolic pressure of at least 40 mm Hg for >15 minutes but no need for catecholamines except for dobutamine ≤5 mg·kg^{-1}·min^{-1}.

†Arterial hypotension plus clinical signs of tissue hypoperfusion and hypoxia, including an altered level of consciousness, a urine output of <30 mL/h, or cold and clammy extremities.

Fibrinolysis

Although systemic fibrinolysis is not worth the risk in all patients with acute PE,[11] it is recommended as standard, first-line treatment in patients with massive PE.[12] In an overview of the 5 randomized controlled trials that included patients with massive PE, fibrinolysis reduced the risk of death or recurrent PE by 55% (Table 2).[11]

In an overview of 11 randomized controlled trials of fibrinolysis versus heparin among 748 unselected PE patients, major bleeding complications occurred in 9.1% of fibrinolysis-treated and in 6.1% of heparin-treated patients (odds ratio [OR], 1.42; 95% CI, 0.81 to 2.46).[11] Major bleeding also occurs more often in patients with massive rather than nonmassive PE, both with fibrinolysis plus heparin and with heparin alone. In an overview of the 5 randomized controlled trials that included patients with massive PE, fibrinolysis doubled the risk of major bleeding: 22% of fibrinolysis versus 12% of heparin patients (OR, 1.98; 95% CI, 1.00 to 3.92).[11]

The preferred fibrinolytic agent is alteplase as a 100-mg continuous 2-hour infusion. Alteplase is the only contemporary fibrinolytic drug approved by the Food and Drug Administration for massive PE. As soon as the decision is made to administer alteplase, heparin should be discontinued. Valuable time may be wasted by obtaining an aPTT before fibrinolysis.

TABLE 2. Death or Recurrent PE of Thrombolysis Versus Heparin Alone in Randomized Controlled Trials With Inclusion of Patients With Massive PE

	Death/Recurrent PE			
Trial	Thrombolysis	Heparin	OR	95% CI
UPET,[25] 1973	10/82	14/78	0.63	0.26–1.53
Tibutt et al,[26] 1974	0/13	1/17	0.41	0.02– 0.83
Ly et al,[27] 1978	1/14	2/11	0.35	0.03–4.42
Dotter et al,[28] 1979	1/15	3/16	0.31	0.03–3.36
Jerjes-Sanchez,[29] 1995	0/4	4/4	0.01	0.00–0.77
Overall[11]	12/128	24/126	0.45	0.22–0.92

UPET indicates Urokinase in Pulmonary Embolism Trial.

At the conclusion of the infusion of alteplase, an aPTT should be obtained. If the aPTT is <80 seconds, intravenous heparin should be restarted as a continuous infusion without a bolus. In the rare instances when the aPTT exceeds 80 seconds after fibrinolysis, heparin should be withheld, and the aPTT should be rechecked in 4 hours. The aPTT is virtually always <80 seconds by this time.

Open Surgical Embolectomy

In the Management Strategies and Prognosis in Patients with Pulmonary Embolism (MAPPET) registry,[3] 193 (40%) of the 478 patients who received fibrinolysis had at least one relative contraindication. Among 304 ICOPER patients who received fibrinolysis, 66 (21.7%) had major bleeding complications, and 9 (3.0%) suffered intracranial bleeding.[1] Thus, fibrinolysis for PE appears to have higher complication rates in "real-world" registries than in the artificial environment of closely monitored clinical trials. These disturbing findings led us to search for alternatives with fewer bleeding risks. We therefore assembled an interdisciplinary team at Brigham and Women's Hospital and successfully undertook open surgical embolectomy. We operated on 29 patients within 24 months and achieved an 89% survival rate.[13] To avoid ischemic injury, the procedure was performed on a warm beating heart, without aortic cross-clamping, cardioplegia, or fibrillatory arrest. Blind instrumentation was avoided, and extraction was limited to visible clot. Patient selection was crucial, with most operations undertaken before the onset of overt cardiovascular collapse.

Catheter Thrombectomy

The only alternative to fibrinolysis or surgical embolectomy for reversing PE-related right ventricular failure and cardiogenic shock is percutaneous catheter thrombectomy.[14] Approximately one third of the patients with massive PE cannot receive systemic fibrinolysis because of absolute contraindications.[3] Few tertiary care centers offer emergency surgical embolectomy with round-the-clock availability. Therefore, catheter thrombectomy may be particularly useful if contraindications to fibrinolysis are present or if surgical embolectomy is not feasible or not available.

An ideal percutaneous PE thrombectomy catheter should be (1) highly maneuverable to allow rapid right heart passage and advancement into major pulmonary arteries; (2) effective in removing obstructing thrombi from major pulmonary arteries to facilitate rapid improvement in hemodynamics, reversing right heart failure and cardiogenic shock; and (3) safe without causing damage to cardiac structures or pulmonary arteries.

The Greenfield suction embolectomy catheter has been available for >3 decades.[15] Thrombus fragmentation without embolectomy using balloon angioplasty or a pigtail rotational catheter has been reported.[16] Several mechanical or rheolytic thrombectomy devices not designed for use in large main pulmonary arteries have been investigated in small PE cohort studies (Table 3).[17–23] The Aspirex device, a highly effective mechanical thrombectomy catheter, has been specifically developed for the treatment of massive PE.[24] The central part of the Aspirex

TABLE 3. Interventional Catheter Devices for Massive PE

Device	Company	Size, F	Guidewire Compatible	Thrombus Fragmentation	Time, s, and Completeness of Thrombus Removal, % complete*
Greenfield suction catheter	Medi-Tech/Boston Scientific, US	10	No	No	...
Pigtail rotational catheter	Cook Europe, the Netherlands	6	Yes	Yes	...
Amplatz thrombectomy device	BARD-Microvena, US	7	No	Yes	83, 66
Angiojet Xpeedior	Possis Medical, US	6	Yes	Yes	118, 67
Hydrolyser	Cordis Europe, the Netherlands	6	Yes	Yes	124, 32
Oasis	Medi-Tech/Boston Scientific, US	6	Yes	Yes	185, 43
Aspirex	Straub Medical, Switzerland	11	Yes	Yes	69, ≈100

*Measurements obtained from flow models with 16.3 to 16.5 g of in vitro–generated thrombus in test tubes with 20-mm internal diameter and 66% stenosis (Amplatz thrombectomy device, Angiojet Xpeedior, Hydrolyser, and Oasis)[30] and in test tubes with 14-mm internal diameter without stenosis (Aspirex).[24]

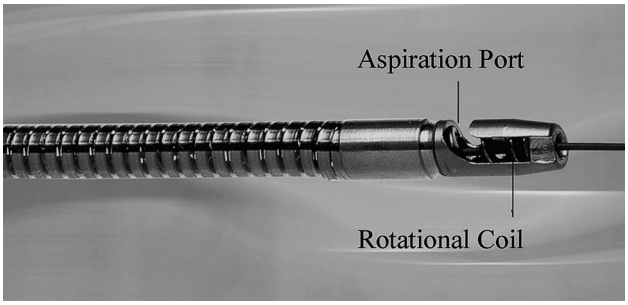

Figure 2. Aspirex PE thrombectomy device is used in combination with 0.035-in hydrophilic guidewire. The 11F Aspirex device removes thrombus through L-shaped aspiration port by high-speed rotation of internal spiral coil. Kindly provided by Straub Medical, Wangs, Switzerland. Reprinted with permission.

device is a protected, high-speed rotational coil that aspirates, macerates, and removes thrombus through an L-shaped aspiration port at the catheter tip (Figure 2).

PE catheter thrombectomy complications include perforation or dissection of cardiovascular structures, pericardial tamponade, pulmonary hemorrhage, and distal thrombus embolization.[14] Other potential complications include blood loss, arrhythmia, contrast-induced nephropathy, anaphylactic reaction to iodine contrast, and vascular access complications such as hematoma, pseudoaneurysm, or AV fistula. To minimize the risk of perforation or dissection, thrombectomy should be performed only in the main and lobar pulmonary arteries, not in the segmental pulmonary arteries. The procedure should be terminated as soon as hemodynamic improvement is achieved, regardless of the angiographic result.

Conclusions and Future Perspectives

We may be asked to manage patients with massive PE because cardiovascular medical specialists are trained to treat hemodynamic derangements with a variety of interventional and pharmacological approaches. A rapid and accurate assessment of risk and a decisive treatment plan should be established. Fortunately, fibrinolysis, catheter intervention, and ongoing collaboration with cardiac surgeons are tools that will assist cardiovascular specialists in maximizing the likelihood of complete recovery for these desperately ill patients.[25–30]

Disclosure

Dr Goldhaber serves on the advisory board of Paion. Dr Kucher serves as a consultant to Straub Medical, Wangs, Switzerland.

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