Original Article

Management of Pulmonary Thromboembolism Based on Severity and Vulnerability to Thrombolysis

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Background: The incidence of pulmonary thromboembolism has been considered rare in Japan. However, its occurrence has been increasing because of westernized lifestyle and diet, increased diagnostic technique, and recognition of this disease.
Method: Between January 2003 and September 2014, 179 patients were treated for pulmonary thromboembolism. We classified these patients into 3 groups; Massive (n=35), Submassive (n=29) and Nonmassive (n=115) and retrospectively reviewed the treatment options and the outcome.
Results: Percutaneous cardiopulmonary support (PCPS) was applied for patients with hemodynamic instability and IVC filter was inserted if there was proximal DVT. In nonmassive group (n=115), 95.7% of the patient underwent anticoagulant therapy and 47.0% of the patients received IVC filter. In submassive group (n=29), 48.3% of the patient received thrombolytic therapy and 93.1% of the patient underwent IVC filter insertion. Surgical pulmonary embolectomy was performed in 3 patients who had high risk of thrombolytic therapy in submassive group. There was no death in this group. In massive group, 4 patients who had cardiogenic shock died in acute phase. PCPS was applied in 5 patients, pulmonary embolectomy was performed in 13 patients, thrombolytic therapy was performed in 4 patients and 13 patients underwent anticoagulant therapy alone. There were 7 deaths (20.0%) in this group.
Conclusions: In submassive group, treatment should be decided depending on the bleeding risk. In massive group, pulmonary embolectomy was effective. (This is a translation of Jpn J Phlebol 2016; 27: 53–59.)

Background

The incidence of acute pulmonary thromboembolism (PE) in the Japanese population was low in the past. However, the prevalence of PE has been increasing because of the westernized lifestyle and diet, improvement of diagnostic modalities, and recognition of venous thromboembolism (VTE). In 2000, 4,022 PE cases were diagnosed in Japan, and the annual prevalence was 32 patients per 1,000,000 people.[1] Approximately 70% patients with massive PE die of hypoxia or heart failure within the 1st hour after onset.[2] On the other hand, the frequency of reports of peripheral PE is also increasing due to progress made in diagnostic techniques. PE is detected by routine follow-up in patients with cancer and in those undergoing medical checkups. The prognosis after PE depends on the spatial extent of emboli in the pulmonary arteries and the chronological progression of the emboli. Anticoagulant therapy is effective in inhibiting secondary extension of clots and in helping natural fibrinolysis.

The treatment and prognosis of PE depend on the hemodynamic status of the patient. In this study, we investigated the adequacy of treatment based on PE severity.

Materials and Methods

Between January 2003 and September 2014, 300 patients with VTE were treated at our institution. Of these 300 patients, a diagnosis of PE was made in 179 patients via either computed tomography (CT) or autopsy. Hospital records of these 179 patients were retrospectively reviewed for demographic data, hemodynamics, distribution of the embolus in the pulmonary vasculature, treatment, and prognosis. The average age of the patients was 60.5 years (range, 11–91), and 47% were male. The severity of PE was classified according to JCS guidelines.[3]

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Table 1 Indication for surgical pulmonary embolectomy

Patients with Acute massive PE with following conditions;
1. Surgically removable emboli existing in pulmonary trunk or left/right main pulmonary artery, AND
2. Patients who have one or more of the followings;
　　① Shock or cardiac arrest
　　② Insertion of PCPS for cardiac collapse (deep shock or cardiopulmonary arrest)
　　③ Right ventricular load on UCG but has contraindications to thrombolysis or high risk of bleeding for thrombolysis
　　For example:
　　・Acute postoperative state
　　・History of intracranial surgery in the previous 2 weeks
　　・Acute phase of cerebrovascular disease
　　・Gestation
3. Paradoxical embolism with massive/submassive PE
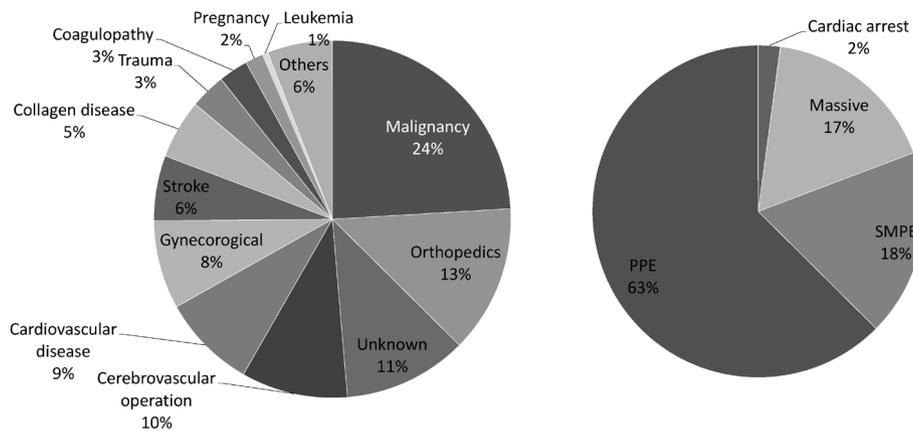

Fig. 1 Predisposing factors and severity of PE in all patients. Left: predisposing factors of pulmonary embolism, Right: severity of pulmonary embolism. SMPE: submassive pulmonary embolism; PPE: nonmassive pulmonary embolism

The patients were classified into three groups: massive PE (n = 35), submassive PE (n = 29), and nonmassive PE (n = 115). Diagnosis of VTE was made based on medical history, symptoms, physical findings, electrocardiogram, chest X-ray, echocardiography, D-dimer test, and CT (with contrast) results. The presence of deep vein thrombosis (DVT) was also evaluated in the pelvis and lower extremities of cases. VTE was diagnosed with verification based on imaging diagnosis of the thrombus. Anticoagulation therapy was used as a standard treatment. Fibrinolytic therapy was used for patients with submassive PE who had right heart failure but a stable hemodynamic condition. Pulmonary embolectomy was selected for hemodynamically unstable patients, e.g., patients with cerebrovascular disease, patients who had undergone a recent craniotomy or another major operation, and patients who were pregnant. Fibrinolytic therapy carries a high risk of bleeding in such hemodynamically unstable patients. Percutaneous cardiopulmonary support (PCPS) was used for hemodynamically unstable patients. Pulmonary embolectomy was considered for patients with massive PE or submassive PE and with a risk of bleeding (**Table 1**). Infe-

rior vena cava (IVC) filter placement was indicated when there was proximal DVT. If anticoagulation therapy was possible, an IVC filter was not placed in PE patients with distal DVT. A retrievable IVC filter was used for patients who had a low risk for bleeding. A permanent IVC filter was used for patients who had a contraindication for anticoagulation therapy. IVC filters were retrieved according to the manufacturer's instructions for use.

Results

Predisposing factors and severity of PE

Figure 1 shows the predisposing factors and severity of PE in all patients in our study. Cancer (24%), orthopedic disease (13%), and cerebrovascular disease (neurosurgery or stroke; 10%) were the most common predisposing factors for PE. Eleven percent of patients were considered to have unprovoked PE, as they did not have underlying disease. Peripheral PE was found in 63% of patients, and 37% of patients had either massive PE or submassive PE.

Outcomes of patients

The outcomes of patients according to their severity of PE were analyzed.

Nonmassive PE

There were 115 nonmassive PE cases (63% of all PE cases) with stable hemodynamics and without right ventricular overload. In most of these patients, the embolus was found in the peripheral pulmonary arteries. More than 50% of patients with nonmassive PE had cancer (**Fig. 2**). Asymptomatic PE, which was incidentally found during follow-up of baseline disease via a CT with contrast accounted for 79% of 115 cases. In many symptomatic nonmassive PE cases, patients exhibited light chest pain and received definitive diagnosis by contrast CT. Among the postoperative patients, nonmassive PE occurred in 24%. A total of 110 patients (95.7%) received anticoagulant therapy with warfarin subsequent to administration of unfractionated heparin. One patient with a large thrombus received fibrinolytic therapy. Anticoagulant therapy was not provided to three patients because they were at high risk for bleeding. An IVC filter was placed in 54 patients (47%) who had proximal DVT. In the nonmassive PE group, there were no deaths due to PE and there was no PE recurrence during long-term follow-up.

We also analyzed 59 nonmassive PE patients who had cancer. Of these patients, 69% (41 cases) were asymptomatic and incidentally diagnosed with PE during the CT follow-up of their baseline disease. Warfarin subsequent to unfractionated heparin was used as a standard therapy protocol. It took 10 ± 6.8 days for the international normalized ratio (INR) to reach a target range of 1.5 to 2.5. In 42% of patients who took warfarin, the INR exce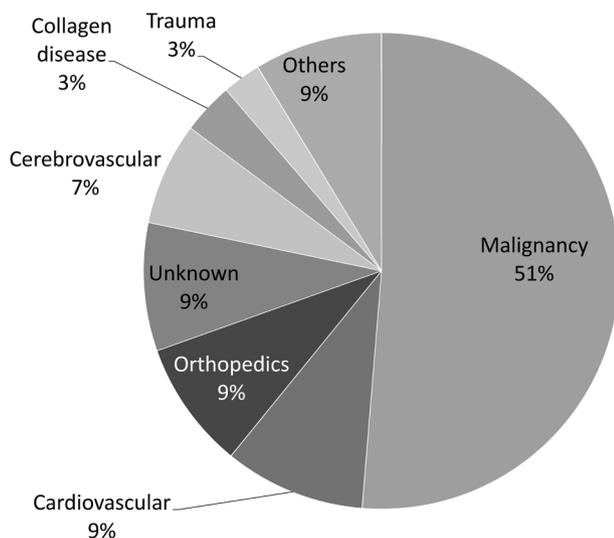eded 2.5 during follow-up. Dose adjustment was necessary, including dose suspension. After insurance industries started to reimburse for factor Xa inhibitors for patients on VTE, 28.5% of patients switched from warfarin to factor Xa inhibitors. Many patients in the nonmassive PE group were repeatedly hospitalized to adjust the INR to within the target range. Therefore, control of warfarin therapy in these patients was unstable. There were no reports of major bleeding.

Submassive PE

Submassive PE, defined as PE with right ventricular enlargement despite stable hemodynamics, was found in 29 patients (16.2% of all PE patients). Right ventricular enlargement was detected by echocardiography or CT. Fourteen (48%) patients underwent fibrinolytic therapy, and 12 patients (42%) underwent just anticoagulant therapy. Surgical pulmonary embolectomy was performed in three patients: one patient in the second week of cerebral hemorrhage, one patient with trauma, and one patient with a free-floating thrombus in the right ventricle. An IVC filter was placed in 27 submassive PE patients (93.1%). There were no reports of either death relevant to PE or major bleeding (e.g., cerebral hemorrhage, gastrointestinal bleeding). Minor wound bleeding was observed in one patient (3.4%) after hip replacement; blood transfusion was not necessary in this patient. A recurrence of PE was observed in one patient (3.4%); however, there was no effect on the patient's hemodynamics. In this patient, treatment of baseline disease was prioritized and the patient's condition improved after increasing the anticoagulant therapy.

Massive PE

Of the 35 patients with massive PE, 4 patients had a cardiac arrest after PE onset and 7 patients required a ventilator plus PCPS. The remaining 24 patients (68.6%) developed cariogenic shock that required administration of inotropic agents to maintain blood pressure. In total, seven patients died (20%); mortality was 100% (4/4) in the patients with cardiac arrest at onset and 12.5% (3/24) in patients who required administration of inotropic agents.

Four patients who exhibited in-hospital cardiac arrest at the onset of PE were contraindicated for or ineligible for anticoagulant therapy; these four individuals had a subarachnoid hemorrhage, multiple traumas, recent spinal surgery, or recent myotomy for cerebral palsy (one patient with each preexisting condition). PCPS was initiated in two of these four patients after cardiopulmonary resuscitation. However, both of those patients died of hypoxic brain damage. The other two patients did not respond to cardiopulmonary resuscitation, and the PE was found at autopsy.

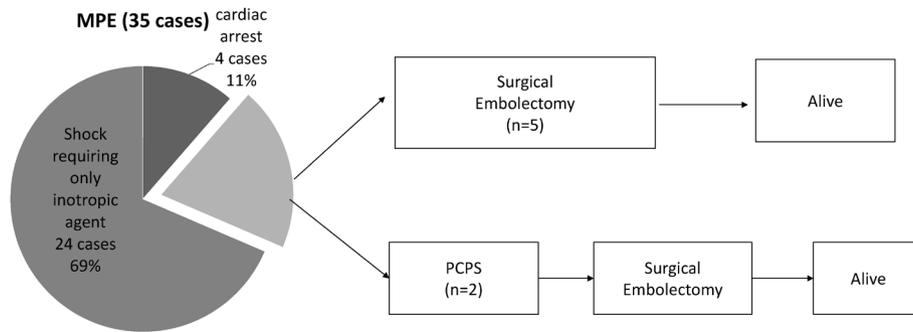Of seven patients who developed deep shock, also

Fig. 2 Predisposing factors of nonmassive pulmonary embolism.

Fig. 3 Outcome of 7 patients with massive pulmonary embolism requiring mechanical cardiopulmonary support. PCPS: percutaneous cardiopulmonary support
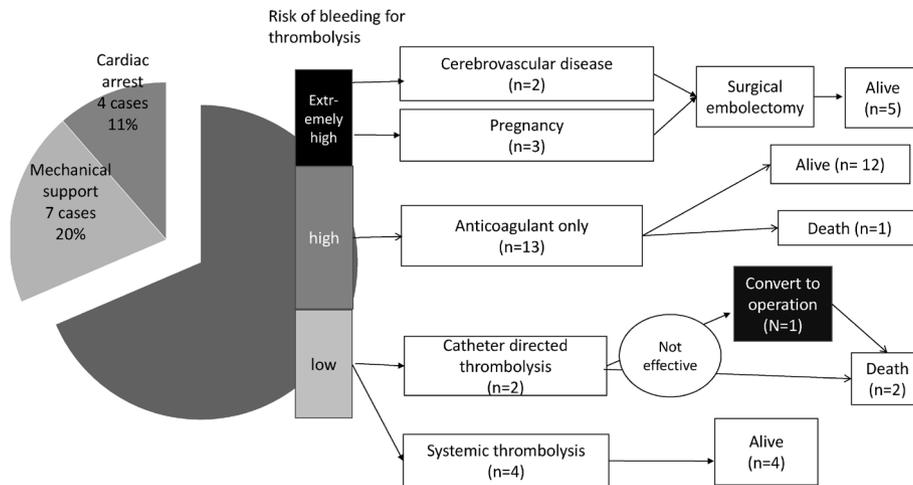

Fig. 4 Outcome of 24 patients with massive pulmonary embolism requiring inotropic agent alone. In this group, management of PE was decided according to risk of bleeding for thrombolysis.

known as circulatory collapse, two patients required mechanical cardiopulmonary support, and surgical embolectomy was performed after PCPS insertion. Five patients underwent immediate surgical embolectomy. All seven of these patients survived (**Fig. 3**). For 24 patients requiring administration of an inotropic agent, management of PE was determined according to the risk of bleeding or fibrinolysis (**Fig. 4**).

Surgical embolectomy was performed in five patients who had contraindications for fibrinolytic therapy, such as a central nervous system disorder or pregnancy, and they all survived. Anticoagulant therapy alone was provided to 13 patients who had a high risk of bleeding (e.g., postoperative condition); however, 1 of these patients died after PE recurrence despite IVC filter insertion. In six patients who had a low risk of bleeding, four received fibrinolytic therapy, and these patients survived. In the earlier years of our study, catheter-directed fibrinolytic therapy was provided to two elderly patients; however, no hemodynamic improvement was obtained. One of these patients died, and the other underwent surgical embolectomy which

resulted in death due to massive bleeding from the respiratory tract. This patient had been hospitalized for a long time before the PE diagnosis, and this was considered an "acute on chronic PE" case.

Treatment for PE based on clinical stage
The mortality rate for PE was 7.7% (1 of 13 patients) in our study. The mortality rate without inclusion of the acute on chronic case was 0%. Average cardiopulmonary bypass time was 59.5 min (17–118 min). Only two patients underwent pulmonary embolectomy with aortic cross-clamp. Aortic cross-clamp times for the two patients were 25 and 33 min. Recurrent nerve palsy was observed in one patient as a complication of surgery. In three patients who were pregnant, pulmonary embolectomy was performed in two of the three patients after cesarean section. Intraaortic balloon pump (IABP) was used during the operation in order to maintain pulsatile flow to the placenta; however, in one case the fetal heartbeat disappeared during the operation. An IVC filter was placed in 11 cases of the 12 (91.7%). Six patients received an IVC filter pre-

Table 2 Summary of treatment for pulmonary embolism based on clinical stage

	Anticoagulant therapy	Fibrinolysis	IVC filter	Pulmonary embolectomy	Catheter directed thrombolysis
Nonmassive PE	110	1	54	0	0
(n=115)	95.7%	0.9%	47.0%		
Submassive PE	28	14	27	3	0
(n=29)	96.6%	48.3%	93.1%	10.3%	
Massive PE	33	4	18	13	2
(n=35)	94.3%	11.4%	51.4%	37.1%	5.7%

Number and percentage of patients on each treatment is shown. There are duplicated count of patients.

operatively, and five received an IVC filter postoperatively.

Two of five (40%) patients who received PCPS died. However, three patients who underwent pulmonary embolectomy after induction of PCPS survived. Fibrinolytic therapy was selected for four patients with a low risk of bleeding, and all four patients survived. With anticoagulant therapy, there was 1 death out of 13 (7.7%). **Table 2** summarizes treatment outcomes after PE based on clinical stage.

Prognosis

No PE recurrence long term, bleeding, or thromboembolic pulmonary hypertension was observed in the 172 patients who survived. An IVC filter was removed from 16 of 126 patients. Currently, IVC filters are placed only in patients who have difficulty continuing anticoagulant therapy.

Discussion

Well-controlled anticoagulant therapy is the standard treatment for VTE. In Japan, unfractionated heparin and warfarin, an inhibitor of vitamin K, had been used for a long time. There were some problems with use of these older drugs: the effectiveness of warfarin differs among individuals, hospitalization is required, it takes time for warfarin to become effective after the switch from heparin, and several foods interact with warfarin. Monitoring of anticoagulant effects is mandatory in these regimens. The recently introduced anticoagulants known as selective factor Xa inhibitors are rapidly effective and have no interactions with foods, and monitoring is not necessary. Management of VTE is about to change with the emergence of these new oral anticoagulants.

PE is a major subgroup of VTE. Peripheral PE, also called nonmassive PE, is often found upon a follow-up CT of baseline disease, and it has an excellent prognosis. Anticoagulant therapy is necessary in treatment of nonmassive PE; however, cancer patients with PE are more likely to develop bleeding and recurrent thromboembolic complications during anticoagulant therapy. Therefore, treatment can be difficult in these patients.[4] The Hokusai VTE study is a randomized, double-blinded, double-dummy trial for the oral Xa factor inhibitor edoxaban. Upon subgroup analysis of patients with cancer, recurrent thromboembolism and bleeding complications were significantly higher in the warfarin-treated group, and the analysis also showed that edoxaban was effective for the treatment of cancer patients with VTE.[5] In early 2016, three types of oral direct factor Xa inhibitor, edoxaban, apixaban, and rivaroxaban, are approved (i.e., reimbursed) for the treatment of VTE. In the American College of Chest Physicians (ACCP) guidelines, these three drugs are recommended for grade IIc VTE and cancer.[6] Warfarin is also recommended for grade IIc VTE. It is expected that an Xa inhibitor will consistently prevent VTE recurrence of nonmassive PE. Length of hospital stay will become shorter with use of these drugs.

Different definitions (at least two) of acute massive PE are found in the literature. One definition is the obstruction of the pulmonary artery tree exceeding 50% of the cross-sectional area, causing acute and severe cardiopulmonary failure from right ventricular overload[7]; the second definition is arterial hypotension (systolic blood pressure of <90 mmHg or a blood pressure drop of at least 40 mmHg for a time period of >15 min, if not due to new-onset arrhythmia, hypovolemia, or sepsis).[8] It is practical to classify cardiogenic shock and cardiac arrest cases as acute massive PE, because it is not always possible to know the anatomical distribution or location of the thrombus. Patients without cardiogenic shock and evidence of right ventricular dysfunction are classified as having submassive PE. Since the risk of hypodynamic deterioration is high in these patients, strict monitoring and anticoagulation together with fibrinolytic therapy have been the indicated treatments. However, the risk of bleeding will increase and that will offset the effect of fibrinolytic therapy. Therefore, many studies have reported that such treatment will not lead to an improvement in prognosis. The most serious complication after fibrinolysis is intracranial hemorrhage. The frequency of intracranial hemorrhage after fibrinolysis occurs in 1.9% of PE patients.[9] As a prognostic factor for submassive PE, Sanchez et al. stated that patients with an elevated cardiac biomarker (e.g., troponin T) should be considered for

aggressive treatment.[10] If patients are over 75 years old, fibrinolysis may be risky and catheter directed thrombolysis (CDT) or surgical embolectomy should be selected.[10] In recent guidelines in Western countries, fibrinolytic therapy is not indicated for patients with submassive PE; instead, anticoagulant therapy is recommended.[11] The role of fibrinolytic therapy for submassive PE should be taken into account in Japan. In our institution, we select a treatment for submassive PE based on the risk of bleeding. Pulmonary embolectomy is considered for patients at high risk of bleeding with fibrinolytic therapy. Pulmonary embolectomy is justified in these patients, because the short-duration exposure to heparin will not increase the risk of bleeding complications.[12] Catheter-directed intervention is less invasive, and it is effective for acute PE. However, these mechanical techniques might cause pulmonary artery injury. If fibrinolysis is incomplete, the risk of developing pulmonary hypertension might increase in the long term. In catheter-directed therapy, the outcome of the treatment depends upon the skills of the operator. Preparation for hemodynamic deterioration during a procedure is also necessary in catheter-directed fibrinolysis and embolectomy.[13]

IVC filters have been used for PE patients with proximal DVT. A filter is used permanently if the expected duration of placement indicated in the manufacturer's instructions will not be exceeded. As a consequence, the IVC retrieval rate has decreased. Recently, we have been using ALN filters, and they are retrieved as soon as they are no longer necessary. In the recent version of ACCP's guidelines, the indications for IVC filter placement are limited, and we no longer use these filters for patients who are able to undergo anticoagulant therapy.[6]

Surgical embolectomy has been reserved for massive PE patients with cardiogenic shock. The mortality reported in the past ranged from 16% to 64%.[14,15] However, the outcome of surgical pulmonary embolectomy is improving, owing to advances in surgical and anesthesia techniques and stricter surgical indications. Pulmonary embolectomy is effective in massive and submassive PE patients with unstable hemodynamics after fibrinolytic therapy.[15] Surgical embolectomy is contraindicated in patients with heparin-induced thrombocytopenia (HIT). It is important to review the individual patient's medical history, because HIT induces arterial and venous thrombosis. When deciding between indications, we struggle to decide surgical indications for acute on chronic PE (chronic PE combined with acute PE). A normal right ventricle without cardiopulmonary disorder cannot generate a mean pulmonary arterial pressure above 40 mmHg.[16] Acute on chronic PE should be suspected when patients present with a mean pulmonary artery pressure greater than 40 mmHg in acute phase. Surgical indications should be decided based on estimated onset and echocardiographic findings for right ventricular hypertrophy (indicating a chronic right ventricular load). In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy should be performed under deep hypothermic circulatory arrest by skilled hands. In our series, postoperative death and postoperative PCPS use occurred in acute on chronic PE cases.

Recently, many authors have reported excellent outcomes after surgical pulmonary embolectomy. Takahashi and colleagues reported a mortality rate of 12.5% (3 of 25 patients), including 16 cases with preoperative PCPS use.[17] In other studies, a mortality rate of 8% (2 of 25) was reported by Kadner et al.[18] and a mortality rate of 6.6% (7 of 105) for patients with massive PE and submassive PE was reported by Neely et al.[19] One risk factor for postoperative death following pulmonary embolectomy is preoperative cardiac arrest. Accurate diagnosis is important, and surgical indications should be decided based on the severity of PE. Stein et al. stated that the mortality of pulmonary embolectomy from 1961 to 2006 was 30% (389 of 1,300) and 20% from 1985 to 2005; the operative mortality rate was 59% in patients with cardiac arrest before pulmonary embolectomy, compared with 29% in patients who did not have preoperative cardiac arrest.[20] Early surgical intervention for severe cases may have life-saving potential.[20] Cardiac surgeons need to be active participants and leaders in multidisciplinary teams in order to improve the outcome of severe PE.[21]

Conclusion

The spectrum of PE severity varies widely. Patients with submassive PE may be asymptomatic, and a significant percentage of cancer patients have submassive PE. Safety of fibrinolysis should be considered in treating submassive PE patients. In massive PE, treatment outcome improves when combined with mechanical support, e.g., PCPS, thrombolectomy, and catheter-directed therapy. The prognosis for patients who have had a cardiac arrest is poor. An interdisciplinary approach, including a cardiovascular surgeon, is important for the treatment of severe PE.

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Disclosure Statement

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