

Review Article

Endovenous Treatment for Acute Massive Pulmonary Thromboembolism

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Treatment for venous thromboembolic conditions differs significantly depending on whether the condition is acute or chronic. Endovenous treatment is now available for treating the most severe cases of acute massive pulmonary thromboembolism, and the goal is rapid central clot removal to relieve life-threatening pulmonary circulation. Endovenous catheter interventions include catheter-directed thrombolysis and catheter-assisted thrombus removal. The latter is divided into aspiration thrombectomy, fragmentation, and rheolytic thrombectomy. Data from cohort studies indicate that the clinical outcome and safety after open surgical treatment and endovenous treatment may be comparable. This paper reviews the current approaches to endovenous treatment for acute massive pulmonary thromboembolism, and presents our study of hybrid treatment using a combination of local fibrinolysis, mechanical fragmentation, and clot aspiration.

Keywords: catheter-directed thrombolysis, catheter-assisted thrombus removal, fragmentation, aspiration

Introduction

Although the etiology and pathology of pulmonary thromboembolism (PTE) are yet to be completely determined, it is known that deep vein thrombosis (DVT)

plays an important role in the development of PTE. Thus, PTE may be considered a complication of DVT, and these conditions are regarded as a single disease entity that is termed venous thromboembolism (VTE).¹⁾

The diagnosis and treatment for PTE differ significantly depending on whether the condition is acute or chronic. The immediate mortality rate of acute PTE is approximately 10%. Among the survivors, a confirmatory diagnosis cannot be made in 70% of patients, and the mortality rate of this group may approach 30%.²⁾ Death in patients with acute massive PTE is caused by sudden circulatory collapse as a consequence of obstructed pulmonary blood flow. Initial therapy must therefore be directed toward rapidly restoring pulmonary circulation.³⁾ Conventional therapeutic options are anticoagulation therapy, systemic thrombolysis, and surgical thrombectomy. Recently, endovenous treatments, including catheter-directed thrombolysis (CDT) and catheter-assisted thrombus removal (CATR) have been introduced for this condition.⁴⁾

The aim of these procedures is to prevent death due to right-sided heart failure through prompt peripheral dispersal of the central thrombus, resulting in reduced pulmonary vascular resistance and increased pulmonary flow.⁵⁾

This review describes the principles, current techniques, results, and complications of endovenous treatment for managing patients with life-threatening PTE.

Indications

Endovenous catheter intervention is indicated for patients with acute massive PTE with unstable hemodynamics despite other appropriate treatment. The indications for this treatment are as follows:

1. Arterial hypotension (<90 mmHg systolic);
2. Circulatory collapse with need for cardiopulmonary resuscitation (shock index: heart rate/systolic blood pressure > 1);
3. Right ventricular afterload stress and/or pulmonary hypertension (mean pulmonary arterial pressure > 25 mmHg);
4. Angiographic findings: Miller score > 20/34 (Fig. 1)⁵⁾ or

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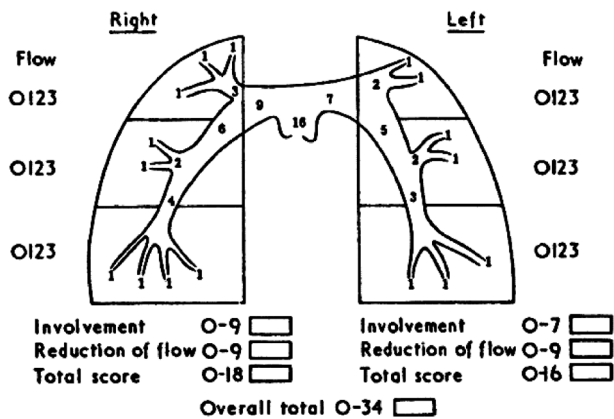


Fig. 1 Miller score.⁵⁾ The right and left main pulmonary arteries are considered to have nine and seven major branches, respectively, and an embolus in any of these branches gives a score of one point. Each lung is considered to have an upper, middle and lower zone, and in each of these three zones, the absence of pulmonary artery flow confers a score of three points, severely reduced flow gives two points, mildly reduced flow one point, and normal flow scores 0 points. The Miller score can thus range from 0 to 34.

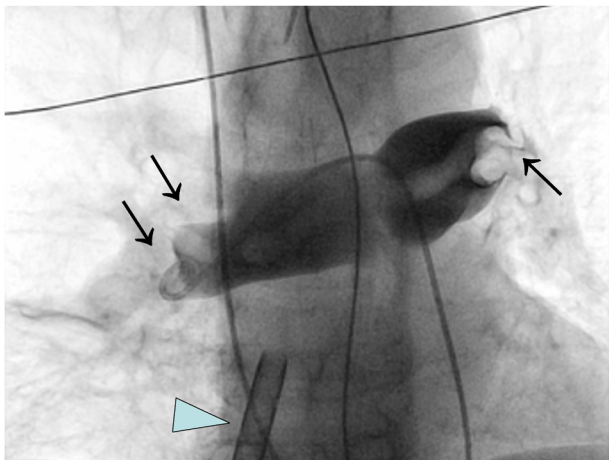


Fig. 2 Patient with cardiopulmonary arrest on arrival. A septuagenarian female was in state of shock on admission. After introducing extracorporeal life support (arrowhead), spontaneous circulation was restored. Right-side heart overload was visible on ultrasound and emergency angiography was performed, revealing massive thrombo-emboli in the pulmonary trunk (arrows). No peripheral pulmonary vascular trees were seen. Advanced medical treatment was not applied because ROSP (return of spontaneous circulation) took 100 min.

angiography severity index $> 9/18$.⁵⁾

Cardiopulmonary arrest on arrival is also a current indication for this therapy, and such patients are occasionally rescued (Figs. 2 and 3).

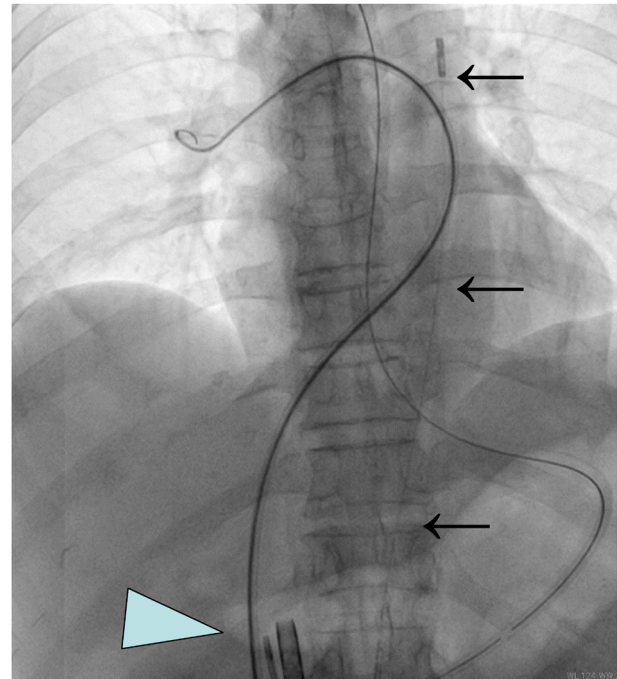


Fig. 3 Patient with cardiopulmonary arrest on arrival. A female in her sixties was admitted with cardiopulmonary arrest and return of spontaneous circulation after 10 min. Extracorporeal life support was introduced at 30 min (arrowhead), and an intra-aortic balloon pump at 90 min (arrows). She received catheter intervention at 95 min, and was transferred to a long-term care hospital three months later.

Definition of Techniques

Endovenous catheter interventions include CDT and CATR.⁴⁾ The latter is divided into aspiration thrombectomy, fragmentation, and rheolytic thrombectomy.

Catheter-directed thrombolysis (CDT)

CDT with intrapulmonary infusion of thrombolytic drugs aims to accelerate clot lysis and achieve rapid reperfusion of the pulmonary circulation. In 1988 Verstraete et al. published a prospective, randomized, multicenter comparative study of intravenous versus intrapulmonary treatment with 100 mg of recombinant human-tissue plasminogen activator (rt-PA) over seven hours, which showed that intrapulmonary infusion offered no significant benefit over intravenous administration.⁶⁾ Therefore, the use of catheters to inject thrombolytics in the pulmonary arteries is not currently supported.⁴⁾ Appropriate methods of injection such as the super-selective or pulse-spray technique should be used to ensure the efficacy of treatment^{1,5)} (Fig. 4). Proposed intrapulmonary CDT regimens are as follows:

- Urokinase: An infusion of 250,000 IU/h mixed with 2,000 IU of heparin over 2 h, followed by an infusion of 100,000 IU/h of urokinase for 12–24 h.

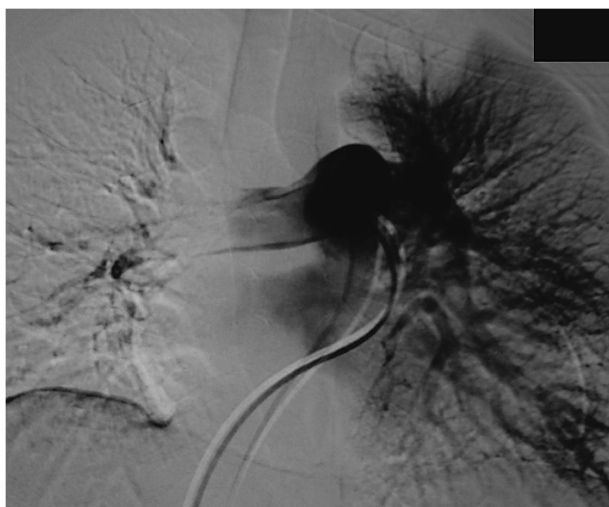


Fig. 4 Concept of catheter-directed thrombolysis. The emergency angiogram shows massive thrombi in the right main pulmonary artery (PA). Thrombolysis from the main PA was not effective, and selective thrombolysis from the catheter embedded in the right main PA is needed.

- rt-PA: A bolus of 10 mg followed by 20 mg/h over 2 h, or 100 mg over 7 h. Mutant human-tissue plasminogen activator (Mt-PA) is only available in Japan. These regimens are applied approximately 5–10 times.

Residual right-heart disturbance may play an important role in the prognosis of acute PTE. Overnight CDT with 10 mg of rt-PA and ultrasound-accelerated thrombolysis are receiving a lot of attention, because they show improvement of the sub-annular right/left-ventricular dimension ratio and no increase in bleeding complications.^{7,8)} The ultrasound-accelerated thrombolysis device is not yet permitted in Japan.

Catheter-assisted thrombus removal (CATR)

Catheter interventions other than CDT therapy include aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy. These techniques are followed by thrombolytic therapy in most cases. It has been suggested that the clinical results of these techniques are comparable to those of surgical thrombectomy.⁹⁾ Efficacy evaluation should be based on improvements of the hemodynamics and oxygenation, and not on the angiographic findings.¹⁰⁾

Aspiration thrombectomy

The Greenfield embolectomy device was first introduced for the aspiration of acute PTE, but it is no longer popular because of poor operability. Aspiration thrombectomy using guiding catheters with a large lumen has attracted attention because of its simplicity and excellent clinical results.¹¹⁾ By contrast, catheters designed to remove thrombi from the coronary arteries percutaneously are not useful in the treatment of acute PTE because of their low suction power.

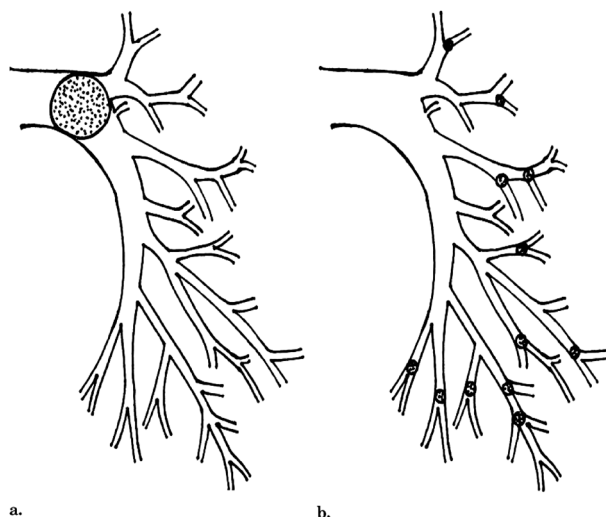


Fig. 5 Concept of clot fragmentation.²⁾ A central thrombus in the pulmonary artery is broken down and redistributed to the periphery, improving perfusion.

Thrombus fragmentation

Thrombus fragmentation is performed to directly break the thrombotic mass in a proximal pulmonary artery and redistribute microemboli into the peripheral vessels²⁾ (Fig. 5). Considering that the cross-sectional area of the distal arterioles is more than four times that of the central circulation, and that the volume of the peripheral circulatory bed is approximately twice that of the pulmonary arteries, the redistribution of large central clots as smaller clots in the peripheral pulmonary arteries may acutely improve cardiopulmonary hemodynamics, with significant increases in total pulmonary blood flow and right-ventricular function.⁵⁾ Although the thrombi are not recovered, small fragments of a thrombotic mass respond better to thrombolytic therapy because the total surface area exposed to thrombolytics is increased significantly. Currently used methods of fragmentation include cutting a thrombotic mass by rotating a modified pigtail catheter¹²⁾ and crushing the mass with a balloon catheter.

Rheolytic thrombectomy

Rheolytic thrombectomy is a theoretically safe method because the thrombi are removed, but it can be ineffective in many cases when used alone to treat acute PTE. Angio Jet (Boston Scientific, Marlborough MA, USA) is now withdrawn from the market because the US Food and Drug Administration has issued a black-box warning on the device label.¹³⁾

Hybrid Treatment

In very severe cases of PTE, the total volume of thromboemboli in the pulmonary vascular trees is extremely large,

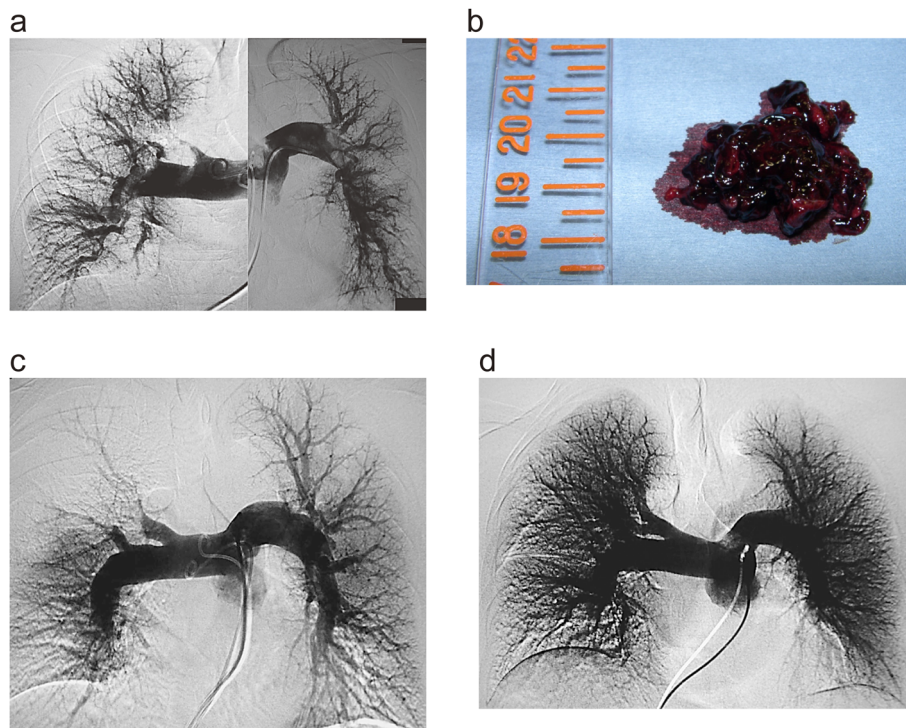


Fig. 6 Case presentation. (a) A 70-year-old male was on long-term bed rest due to olivopontocerebellar atrophy. He underwent sudden-onset respiratory failure. Emergency contrast-enhanced computed tomography revealed acute pulmonary thromboembolism. A pulmonary angiogram shows massive thrombi in both pulmonary arteries (PA). PA pressure (PAP) was 48/20 (30) mmHg. (b) Massive fresh red thrombi were aspirated by emergency thrombectomy. (c) Improvement of vascular flow in PA is confirmed after the catheter intervention. PA pressure was 33/15 (23) mmHg and the procedure time, 116 min. (d) Angiogram obtained at five days after treatment. The postoperative course was uneventful.

and mono-therapy with thrombolysis, thrombectomy, and aspiration is not effective. We have developed a combined approach to thrombolysis using mechanical fragmentation, localized fibrinolysis and clot aspiration and have achieved good results³⁾ (Fig. 6).

Procedures

A 6-Fr conventional curved pigtail catheter for pulmonary angiography was used in the fragmentation catheter system. A long guidewire was placed in the pulmonary artery (PA) at a peripheral site, and the proximal tip of the guidewire was inserted into the most proximal hole of the curved pigtail catheter (Fig. 7). The catheter was then inserted over the guidewire and through the 8-Fr PA sheath. The emboli were fragmented by mechanical action of the rotating pigtail catheter. The catheter was manually rotated around the axis of the stationary guidewire, and advanced or withdrawn over the guidewire as required. After fragmentation, all patients received an intrapulmonary injection of mt-PA (640×10^4 IU, equivalent to 12.8 mg over 64 min), followed by manual clot aspiration using a large-lumen guide catheter. Strong manual aspi-

ration was performed by drawing back the plunger of a regular Luer-Lok 20-mL syringe while slowly withdrawing the catheter through the introducer sheath. During thrombolysis, all patients received heparin sodium (initial dose: 5,000 IU, maintenance dose: sufficient to maintain an activated partial thromboplastin time ratio of 2). After this treatment, additional systemic urokinase was infused on the intensive care unit to remove residual thrombi, depending on the patient's condition. The original dosing regimen was $24-48 \times 10^4$ IU/day for three days.

Eid-Lidt et al. evaluated another type of hybrid treatment, combining clot fragmentation with a conventional pigtail catheter and aspiration with Aspirex (Straub Medical, Wangs, Switzerland),¹⁴⁾ and reported promising results¹⁵⁾ (Fig. 8).

Results

A meta-analysis of 594 patients from 35 studies revealed that the pooled clinical success rate of CDT was 86.5%, and the pooled risks of minor and major procedural complications were 7.9% (95% confidence interval [CI]:

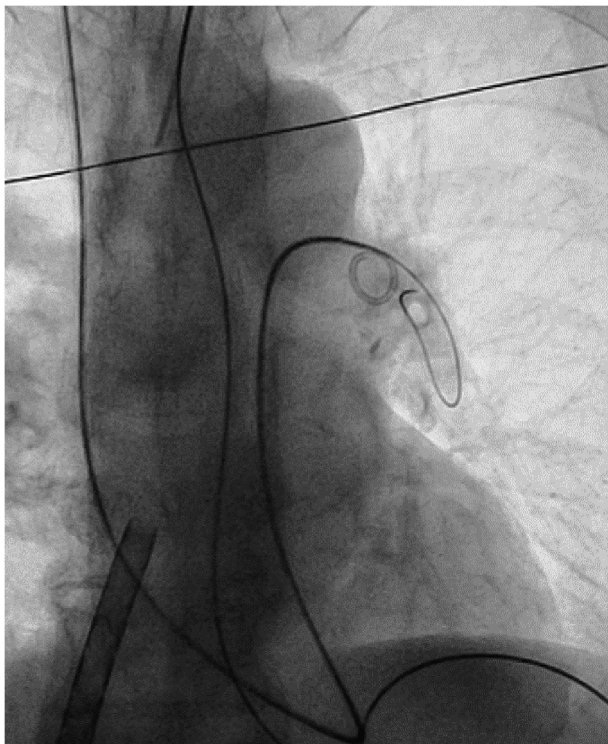


Fig. 7 Modified pigtail catheter. The radiograph shows a modified rotating pigtail catheter inserted for the fragmentation of emboli. A guidewire is inserted into the most proximal hole of the curved pigtail catheter.

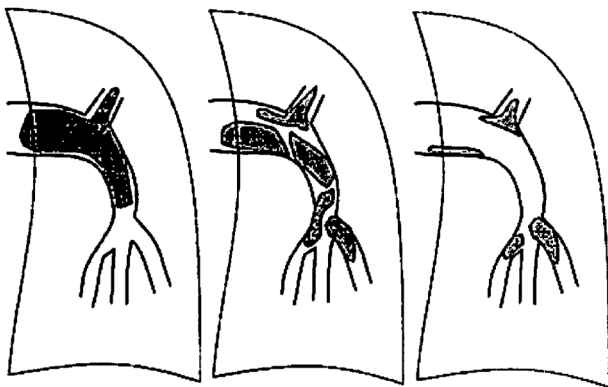


Fig. 8 Concept of combination of clot fragmentation and aspiration.¹⁵⁾

5.0–11.3%) and 2.4% (95%CI: 1.9–4.3%), respectively.¹⁶⁾ No randomized comparative studies on medical and surgical treatment have been reported. The long-term outcomes of surgical embolectomy are generally good with acceptable survival rates,¹⁷⁾ but the late mortality rates associated with catheter intervention have not yet been reported. Data from cohort studies indicate that the clinical outcome and safety of open surgical treatment and endovenous treatment may be comparable.¹⁰⁾ The initial results from a prospective multicenter registry evaluating

the safety and effectiveness of CDT for acute massive and sub-massive PTE have recently been reported, but no consensus has been reached.^{13,18)} Data of treatment outcomes for very severe cases requiring extracorporeal life support treated with catheter-based intervention are limited; we showed that the 30-day mortality rate was 30%.¹⁹⁾

Complications

Minor bleeding at the insertion site occurred in 29 of the 348 patients (8%) with and without thrombolytic agents, and major bleeding at the insertion site occurred in 8 of the 348 patients (2%).⁹⁾ One patient experienced perforation of the right ventricle with the Greenfield catheter.⁹⁾ In a systemic review and meta-analysis,¹⁶⁾ among 594 patients, the pooled risk of minor and major procedural complications was 7.9%, and 2.4%, respectively. Major procedural complications, including groin hematomas (n=11: requiring transfusion), non-cerebral hemorrhages (n=5: sites unspecified, requiring transfusion), massive hemoptysis requiring transfusion (n=2), renal failure requiring hemodialysis (n=1), cardiac tamponade (n=1), and death (n=5) occurred in 25 patients: five procedure-related deaths were all associated with the Angio Jet device.

Guidelines

There is a subtle difference in evaluation among the Japanese Circulation Society (JCS), the American College of Chest Physicians (ACCP), and the European Society of Cardiology (ESC)^{1,4,20,21)} (Fig. 9). In the guidelines of the JCS, CDT and catheter fragmentation/aspiration thrombectomy are evaluated as Class IIb.¹⁾ In the guidelines of ACCP 2016, in patients with acute PE associated with hypotension and who have (i) a high risk of bleeding, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect, if appropriate expertise and resources are available, catheter-assisted thrombus removal is suggested rather than no such intervention (Grade 2C).⁴⁾ In ACCP 2016, surgical embolectomy was not mentioned, whereas in the 2012 guidelines,²¹⁾ in patients with acute PE associated with hypotension, surgical pulmonary embolectomy is suggested rather than no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect, provided surgical expertise and resources are available (Grade 2C). In the 2014 guidelines of ESC, in high-risk groups percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic throm-

Japanese Circulation Society 2009

- Catheter intervention: Class II b
- Surgical embolectomy: with collapse : Class I
without shock: Class II a

ACCP 2012/2016

- Catheter-Based Thrombus Removal: Grade II c
- Surgical embolectomy: Grade II c

ESC 2014

High risk group

- Catheter-directed treatment: Class II a, Level C
- Surgical embolectomy: Class I, Level C

Intermediate or low risk group

- Catheter-directed treatment: Class II b, Level B
- Surgical embolectomy: Class II b, Level C

Fig. 9 Summary of guidelines.

bolysis is contraindicated or has failed, whereas surgical embolectomy or percutaneous catheter-directed treatment may be considered in intermediate-high-risk patient if the anticipated risk of bleeding under thrombolytic treatment is high.²⁰⁾

Summary

The management of patients with massive PTE requires a team approach, including referring physicians, surgeons, and interventional radiologists. This review stresses the improvement of hemodynamics immediately after hybrid interventional treatment for acute PTE. Expeditious use of the catheter technique for embolectomy or fragmentation immediately after angiography provides the patient with the best chance of surviving the initial impact of this life-threatening condition.

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Author Contributions

Study conception: HT, KN
Data collection: HT, TK, NT
Analysis: HT, TI, SI

Investigation: HT, SM, SO, KN

Writing: HT

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Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work: all authors

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