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THE ROLE OF INTERVENTIONAL METHODS IN TREATMENT OF PULMONARY EMBOLISM

Abstract

This review concerns current interventional methods of acute pulmonary embolism treatment. The article provides a rationale for catheter approaches, detailed description of patient selection and risk stratification including an estimation of thromboembolic event massiveness, risk of acute pulmonary embolism, bleeding risk assessment, and individual patient characteristics. The review contains the up-to-date classification of pulmonary embolism on the basis of 30-day mortality assessment and estimation of disease outcome according to the original and simplified Pulmonary Embolism Severity Index. A special attention is paid to interventional methods, in particular, to catheter directed thrombolysis, rheolytic thrombectomy, thrombus fragmentation and aspiration. The results of studies of efficiency and safety of endovascular approaches to pulmonary embolism management are reported. The article emphasizes the importance of further study of various clinical aspects of these methods in order to obtain comprehensive information about the treatment of this severe disease, which is associated with significant disability and mortality.

Key words: *pulmonary embolism, treatment, risk stratification, patient selection, interventional approaches, catheter methods, catheter directed thrombolysis, ultrasound, endovascular treatment*

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tPA — tissue plasminogen activator; ACT — anticoagulant therapy; VTE — venous thromboembolism; CT — computed tomography; CDT — catheter-directed thrombolysis; PA — pulmonary artery; PE — pulmonary embolism; RV — right ventricle; RCT — randomized clinical trials; CO — cardiac output; DVT — deep-vein thrombosis; ECHO-CG — echocardiography

Introduction

Venous thromboembolism (VTE) is a severe and common clinical condition and includes deep-vein thrombosis (DVT), pulmonary embolism (PE), or their combination [1, 2]. The annual incidence of VTE is 100-200 per 100 thousand people [3]. VTE worldwide is estimated at about 10 million cases per year and is associated with significant disability and mortality [4].

The real number of deaths as a result of PE is difficult to determine, as the patient's sudden death is more often attributed to the outcome of a cardiac disease than a thromboembolic event. In USA, up to 600 thousand cases of VTE and approximately 100 thousand deaths due to these conditions are reported annually [5]. In Europe, life-time diagnosis was made only in 7% of cases out of 317 thousand deaths due to PE registered in 2004 [3]. Moreover, in 34% of the total number of tragedies, the disease developed as a sudden PE, and in 59% of cases, death occurred as a result of PE that was not diagnosed during life-time.

Over the past three decades, the general understanding of VTE has improved significantly, but the therapeutic paradigm has undergone only minor changes compared to other common diseases that are associated with high mortality (e.g., cancer

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and cardiovascular diseases, including myocardial infarction and stroke) [6]. The efforts of scientists and practitioners involved in the treatment of PE which has already occurred are aimed at using highly accurate methods to remove a thrombus from the pulmonary circulation system with minimal risk of periprocedural complications, which is usually accompanied by a dramatic improvement in the patient's condition and a decrease in the risk of adverse outcomes [7]. The objective of this review is to discuss interventional approaches in the management of patients with PE, including the use of catheter-directed thrombolysis (CDT), as well as modern methods of fragmentation, aspiration and removal of blood clots from the pulmonary arterial bed using specialized catheter systems.

Interventional Approaches Justification

The adverse effects of systemic thrombolysis, as well as its ineffectiveness, were the basis for studying the possibilities of removing a thrombus with a catheter as an alternative therapeutic option [8, 9]. The use of catheter technology is designed to reduce some of the risk of hemorrhagic complications associated with systemic delivery of thrombolytic agents in various ways [10]. On one hand, the necessary medication that goes directly into the thrombus or even beyond it, may allow to reduce both the fibrinolytic drug dosage and the systemic hemorrhagic effect mediated by it [6]. On the other hand, the use of supplementary methods of thrombectomy reduces the overall duration of treatment, as well as the total dosage of drugs. Among the advantages of invasive methods, the capacity of catheters to directly determine the pressure in the pulmonary artery (PA), cardiac output (CO), and other hemodynamic parameters should be highlighted, which allows the monitoring of the hemodynamic response to the therapy. Finally, thrombectomy based on catheter techniques may sometimes be the only available choice for patients with life-threatening PE who cannot resort to either surgical embolectomy or systemic thrombolysis [11]. The rapidly evolving evidence base forces us to seek a better understanding of when and under what conditions various invasive approaches will prove their benefit in the treatment of serious patients [6].

Treatment based on catheter techniques is aimed at rapidly reducing obstruction and restoring pulmonary blood flow, which leads to an improvement in CO and the change of the patient's hemodynamic status from unstable to stable [2, 7, 11 to 13]. At the same time, the administration of fibrinolytic drugs can be stopped or their dosage can be reduced. There are several approaches based on catheter technology (Table 1) [1, 12]:

- Catheter-directed thrombolysis, including ultrasound exposure;
- Thrombus fragmentation using a pigtail catheter or balloon catheter;
- Rheolytic thrombectomy with a hydrodynamic catheter;
- Aspiration thrombectomy;
- Rotation thrombectomy.

Table 1. *Catheter approaches to acute pulmonary embolism management*

Device	Size, mm (French scale)	Mechanism of action
Pigtail catheter	2-2,67 (F6-8)	Fragmentation
Peripheral balloon	5-10	Fragmentation
Catheter-directed fibrinolysis	1.33-2 (F4-6)	Direct infusion of fibrinolytic agent
Ultrasound-accelerated thrombolysis	2 (F6)	Direct infusion of fibrinolytic agent plus, ultrasound for clot separation#
Guide catheter	2-3.33 (F6-10)	Manual aspiration
Pronto Xl catheter	2-4.67 (F6-14)	Manual aspiration
Penumbra Indigo system	2-2.67 (F6-8)	Suction pump aspiration
Inari FlowTriever	7.33(F22) guidewire	Disruption, retraction, and aspiration of clot
AngioVac	F-26 guidewire and F-18 catheter	Large-volume aspiration with return of filtered blood using a centrifugal pump

Notes: US — ultrasound; # — is currently the only method approved by the Food and Drug Administration (USA)

Over the past two decades, promising endovascular treatment methods have been developed to reduce acute and chronic disability due to VTE [14, 15]. However, careful selection of patients is necessary for the effective use of endovascular therapy, which includes an assessment of the condition severity, the risk of bleeding, the features of the technique used, and the patient's individual characteristics.

Patient Selection and Risk Stratification

Careful selection of patients is a fundamental step in the use of individually tailored endovascular techniques in clinical practice. When addressing the endovascular approach, three key points have to be considered: 1) severity and acuteness of the disease; 2) probability of serious bleeding; and 3) individual patient's characteristics.

Clinical Classification of Pulmonary Embolism Severity

Assessment of the massiveness of PE or the severity of the mortality risk in this event is a crucial step in determining the principles and stages of the treatment strategy [16]. The clinical classification of the severity of a PE episode is based on the calculated risk of early (up to 30 days) mortality due to a thromboembolic event [1]. This distribution (or stratification), which is important in both the diagnostic and therapeutic approaches, is based on an assessment of the patient's clinical status at the time of presentation of the event [17]. High-risk PE is assumed or confirmed in the presence of shock or persistent hypotension, and non-high-risk PE (intermediate or low) — in their absence (Table 2) [1].

Similar to the above classification based on an assessment of the mortality risk, dividing PE into massive, submassive and nonmassive is also used [8, 13]. At the same time, massive PE occurs with hemodynamic disorders (hypotension or the need for inotropic support); submassive — with the right ventricle (RV) dysfunction determined by echocardiography, computed tomography (CT) or elevated cardiac biomarker levels, and non-massive or low-risk PE occurs without evidence of RV dysfunction or hemodynamic insufficiency [12]. Many studies have shown that PE accompanied by hemodynamic disorders is associated with a worse outcome of the disease. The International Cooperative Pulmonary Embolism Registry (ICOPER), which studied the outcomes of 2110 patients with established PE, demonstrated a 90-day mortality rate of 58.3% in patients with massive PE, compared with 15.1% in submassive PE [18].

Comparable findings were obtained in Germany from a study of the MAPPET registry (Management Strategy and Prognosis of the Pulmonary Embolism Registry), consisting of 1,001 patients with acute PE [19]. The intrahospital mortality rate was 8.1% for hemodynamically stable patients compared with 25% for those in whom the disease manifested with cardiogenic shock, and 65% for those requiring cardiopulmonary resuscitation measures.

Terms such as "massive", "submassive" and "nonmassive" embolism, despite their widespread use in specialized literature, are rather vague and variable in interpretation, according to many scientists, resulting in ambiguity (entanglement) in the assessment of the concept itself [8]. On the other hand, although it seems tempting to stratify PE variants based on the absolute frequency of complications, in particular mortality, this approach is difficult due

Table 2. *Classification of patients with acute pulmonary embolism based on early mortality risk*

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V sPESI >I	Imaging Signs of RV dysfunction	Cardiac biomarkers
High		+	(+)	+	(+)
Intermediate-	**high**	–	+	Both positive	
	low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

Note: PESI — Pulmonary embolism severity index; sPESI — ≥ 1 point(s) indicate high 30-day mortality risk; RV — right ventricle

to frequent comorbidities [20]. For example, a non-massive PE can be associated with a high risk of complications in a patient with numerous comorbidities [21], such as obstructive pulmonary disease or congestive heart failure. Massive PE is traditionally defined on the basis of the angiographic extent of an embolic lesion using the Miller score [22], but this definition is limited in routine clinical practice due to insufficient equipment of medical institutions with angiography equipment firstly [8]. From a radiological point of view, massive PE is understood as the reduction of pulmonary perfusion in one lung (>90%) or the total occlusion of the main pulmonary artery, as established by CT pulmonary angiography [13].

In addition to assessing the risk or determining the massiveness of PE after diagnosis, it is extremely important to calculate the prognosis of the disease, in which the PESI (Pulmonary Embolism Severity Index) considers hypotension (systolic blood pressure <100 mmHg) as a predictor of poor prognosis [1].

The PESI score became widely popular in both the original [21] and the simplified version (Table 3) [1, 23].

This method helps to determine the severity of the disease by predicting 30-day mortality and long-term mortality. Patients with a higher index need more aggressive treatment. Traditionally, intravenously administered recombinant tissue plasminogen activator (tPA), alteplase at a dose of 100 mg for 2 hours, is used to treat massive PE [24]. There are opinions in literature that CDT in capable hands can be used as a first line, as an alternative to intravenously administered alteplase, although this approach seems ambiguous so far [25].

According to the guidelines of the American College of Cardiology/American Heart Association, the use of catheter embolectomy is considered for clear cardiopulmonary failure or for submassive PE, when patients have clinical signs of poor prognosis. The European Society of Cardiology recommends a two-stage risk stratification, first using the approved clinical and prognostic assessment of

Table 3. *Original and simplified PESI*

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male	+10	–
History of cancer	+30	1 point
History of chronic heart failure	+10	1 point
History of chronic pulmonary disease	+10	1 point
Heart rate ≥ 110 bpm.	+20	1 point
Systolic blood pressure <100 mm Hg	+30	1 point
Respiratory rate >30 breaths per minute	+20	–
Temperature <36° C	+20	–
Altered mental status	+60	–
Arterial oxygen saturation <90%	+20	1 point
	Risk class*	
	Class I: ≤65 points, very low 30-day mortality risk (0-1.6%) Class II: 66-85 points, low mortality risk (1.7-3.5%)	0 points = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%)
	Class III: 86-105 points, moderate mortality risk (3.2-7.1%) Class IV: 106-125 points, high mortality risk (4.0-11.4%) Class V: >125 points, very high mortality risk (10.0-24.5%)	≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

Note: * — based on the sum of points; bpm. = beats per minute; PESI = Pulmonary embolism severity index; CI = confidence interval

PESI (original or simplified), and then using the visualization methods and determination of biomarkers [21, 23].

In case of a positive clinical and objective risk assessment, catheter-directed therapy may be considered if there are signs of an inevitable deterioration of the functions of the cardiopulmonary system. The lack of large randomized clinical trials (RCTs) in this area leads to discrepancies in recommendations.

Endovascular interventions are not recommended for patients with low risk of PE due to low levels of disability and mortality. The only exceptions are those who have a large saddle embolus without any adverse hemodynamic consequences or RV disorders.

Bleeding Risk Assessment

All patients being considered for endovascular intervention should be evaluated for the risk of bleeding. Active bleeding, recent cerebrovascular or intracranial pathology (stroke, transient ischemic attack, traumatic brain injury, recent neurosurgery) or absolute contraindications to anticoagulant therapy (ACT) are also absolute contraindications to the endovascular treatment including thrombolytics (Table 4). Relative contraindications, especially if not correctable on time, should be carefully reviewed on a case-by-case basis.

Determining Individual Patient Characteristics

Patient preference should be the main criterion in determining which endovascular treatment approach is appropriate for a particular case. It is the responsibility of the physician to determine the risks and benefits and discuss them in the context of each individual patient's life expectancy and functional status. This is especially important when choosing an endovascular method of treating PE/DVT, as it is not performed to prevent death, but with the goal of improving the quality of life in the long run [26]. Careful consideration must be given

Table 4. *Absolute and relative contraindications to catheter-directed thrombolysis*

Absolute	Active bleedingr
	History of recent* CVA or TIA
	History of recent neurosurgery
	History of recent intracranial trauma
	Absolute contraindications to anticoagulation
Relative	History of recent cardiopulmonary resuscitation
	History of recent gastrointestinal bleeding
	History of recent abdominal, ophthalmic or obstetric surgery
	Known severe allergy or adverse reaction to thrombolyic agent or contrast media (with no effect of steroids/antihistamines)
	History of recent trauma (other than intracranial)
	Severe thrombocytopenia
	Known intracranial tumor or vascular abnormality
	Known right-to-left cardiac or pulmonary shunt
	Uncontrolled hypertension: systolic BP >180 mm Hg, diastolic BP >110 mm Hg
	Severe dyspnea or other condition that would preclude ability to tolerate procedure
	Suspected intracardiac thrombus
	Suspected infected venous thrombus
	History of chronic kidney disease
	Severe liver disease
	Pregnancy
	Active infection

Note: *Recent = <3 months; CVA = cerebrovascular accident TIA = transient ischemic attack; BP = blood pressure

to the effect of chronic co-morbidities to the functional status of patients, as well as their ability to tolerate the procedure itself.

Catheter-Directed Thrombolysis

After the publication of the results of some studies that demonstrated low 90-day mortality in patients with submassive PE, who underwent anticoagulant monotherapy (2-3%), and a clearly elevated risk of bleeding was detected when using systemic thrombolytic drugs, many clinicians reluctantly agreed with the use of aggressive treatment methods for this disease [27-29]. CDT remains a rather controversial method, as an alternative to the systemic use of a fibrinolytic drug [7]. Some physicians are concerned that the risks associated with the procedure can be summarized with the appropriate hemorrhagic potential of thrombolytic agents [30]. Others consider CDT as an effective, minimally invasive and safe treatment method to prevent the patient's clinical deterioration and to improve RV function [27, 31].

The primary goal of treatment with CDT is to reduce the RV afterload due to the formation of channels of unobstructed blood flow through the pulmonary arteries, which reduces the pressure in the PA itself, the severity of RV dysfunction and improves the total CO (Figure 1). In patients with massive PE, the goal is to prevent death and at least to transfer patients from the "massive" category to a less threatening condition [25]. In patients with submassive PE, the goal is to prevent long-term disability and mortality due to this event. For successful CDT, the thrombolytic agent must be injected directly into the thrombus that occludes the vessel lumen. Numerous studies have shown that the injection of thrombolytic agent proximal to a blood clot does not provide additional benefits, because the drug will mainly pass in the free, rather than obturated arterial branches [25].

Back in 1988, one small study randomized 34 patients with major (according to angiography data) PE in two groups: patients who received intravenous tPA and those who received infusions of the drug through a catheter at a dose of 50 mg for 2 hours. [32]. The study showed comparable efficacy according to angiographic and hemodynamic results when using both techniques. However, the locally injected dose of fibrinolytic agent in this 30-year-old work was much greater than the dosages used today.

In a later prospective study of 101 patients with massive and submassive PE, in which the catheter technique was used (mainly local fibrinolysis), there was a significant decrease in PA pressure and improvement of RV function without serious complications, major bleeding or strokes [33]. Considering the low risk of major complications, it is reasonable to consider CDT in patients with already stabilized massive PE, having contraindications to

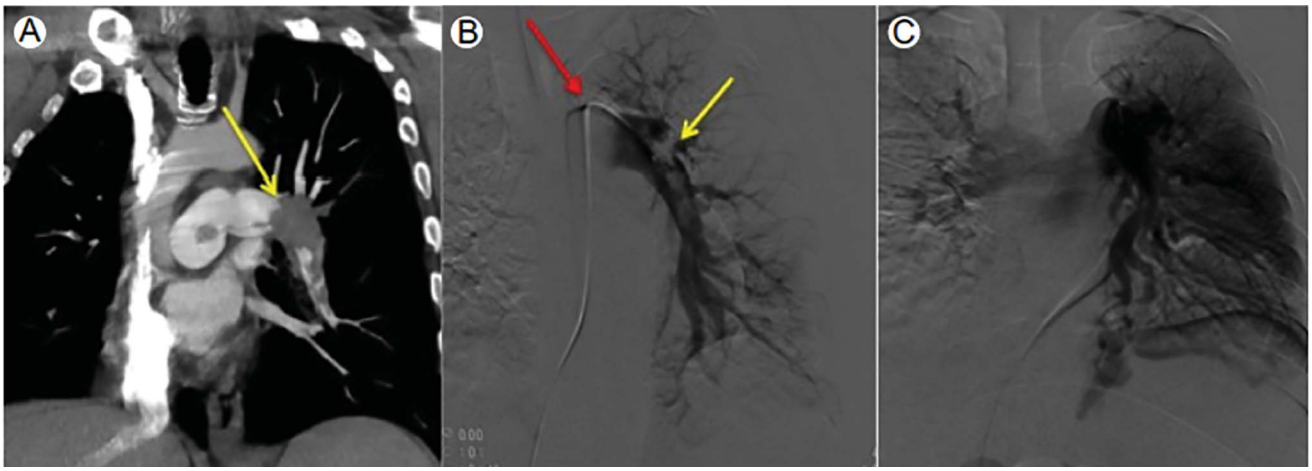


Figure 1. *Catheter-directed thrombolysis in pulmonary embolism treatment*

Notes: A 39-year-old woman with massive pulmonary embolism treated with catheter-directed thrombolysis. Computer tomography and initial pulmonary angiography demonstrate acute thrombus (yellow arrows) within pulmonary arteries (A and B). A standard angled pigtail catheter was used for catheter-directed thrombolysis (red arrow), with the catheter and its side holes embedded within the thrombus. After 14 hours (C), there is a significantly decreased clot burden in the left pulmonary artery. Adopted from A.Bhatt et al. (2017) [25].

systemic thrombolysis, and in patients with intermediate-high risk (presence of RV dysfunction and elevated levels of biomarkers), especially in individuals with an estimated high risk of hemorrhagic complications with use of full doses of systemic fibrinolytic agents [12]. When 52 patients with PE were treated with CDT, a more pronounced favorable hemodynamic effect was observed with duration of symptoms of <14 days compared to the group with longer duration of symptoms [34].

The results of the study (OPTALYSE PE) on the assessment of the dosage and duration of tPA administration in patients with intermediate risk of PE documented by CT angiography were published just recently [35]. One hundred and one patients were divided into 4 groups depending on the treatment regimen: treated with tPA at a dose of 4 mg/one lung for 2 hours; 4 mg/one lung for 4 hours; 6 mg/one lung for 6 hours; and 12 mg/one lung for 6 hours. During administration of a fibrinolytic agent, the dose of heparin was reduced to 300-500 U/hour. In addition, an ultrasonic signal for treatment of the thrombus and a cooling agent were provided through a triple-lumen catheter. Parameters for evaluating the effectiveness of treatment were considered the change in the ratio of the right ventricle to the left ventricle diameters (RV/LV) and the modified Miller score.

According to OPTALYSE PE results, the treatment was accompanied by a statistically significant improvement in the RV/LV diameter ratio (main evaluation criterion) in all groups of patients compared with baseline values. The RV/LV diameter ratio improved in 4 groups by about 25%. The modified Miller score also statistically improved in all groups, although the improvement in this parameter was more pronounced with an increase in the tPA dosage and infusion duration. The following version is considered by the authors as being among the reasons explaining such a difference (almost equal improvement in the RV/LV diameter ratio in all groups regardless of the dosage of the drug, and dose-dependent and time-dependent improvement of the Miller score). Low doses of thrombolytic agents can improve the functional vessel radius enough to improve pulmonary perfusion (Poiseuille's Law) and, therefore, the RV/LV diameter ratio. However, higher doses or longer infusions of thrombolytic drug are required to produce a similar reduction in overall clot burden assessed by the Miller score [35]. The level of major bleeding was 4%, and two cases (2%) occurred in the fourth group, which was the reason for stopping the randomization of patients in the last one.

Percutaneous Thrombectomy

Several percutaneous approaches are used in patients with absolute contraindications to thrombolysis, both separately and in combination. These include thrombus fragmentation with a rotating pigtail catheter, aspiration and rheolytic thrombectomy [13]. Unfortunately removal of a thrombus is not always achieved with simple insertion of a catheter into the PA and aspiration. The aspirated material obtained by catheter extraction or surgical removal usually consists of acute thrombi and older, more organized parts. Removal of the latter through a thin catheter or using aspiration presents considerable challenges. Thus, mechanical catheter-directed thrombectomy is primarily aimed at displacing and changing proximal thrombi, first of all their size, in order to quickly achieve narrowed lobar and segmental arterial branches, increasing the cross-sectional area of arterial tree vessels, and, consequently, reducing the pressure in PA and RV dilatation [6, 13].

Thrombus Fragmentation

Thrombus fragmentation techniques that use balloon angioplasty or pigtail catheter rotation (Fig. 2A and Fig. B) are probably the earliest examples of intervention in the treatment of acute PE [7, 10, 36, 37]. The idea is to use the side holes of the catheter, fully immersed in the thrombus. This allows the thrombolytic agent to contact the maximum surface of the clot [25]. This method is rarely used on its own due to the risk of distal and proximal embolization. New catheters for fragmentation, e. g., the Amplatzer-Helix catheter (EV3, Endovascular, USA), improve clot fragmentation by using microturbines to crush a thrombus, but they do not have the ability to aspirate the fragments formed and cannot move them through the catheter guide.

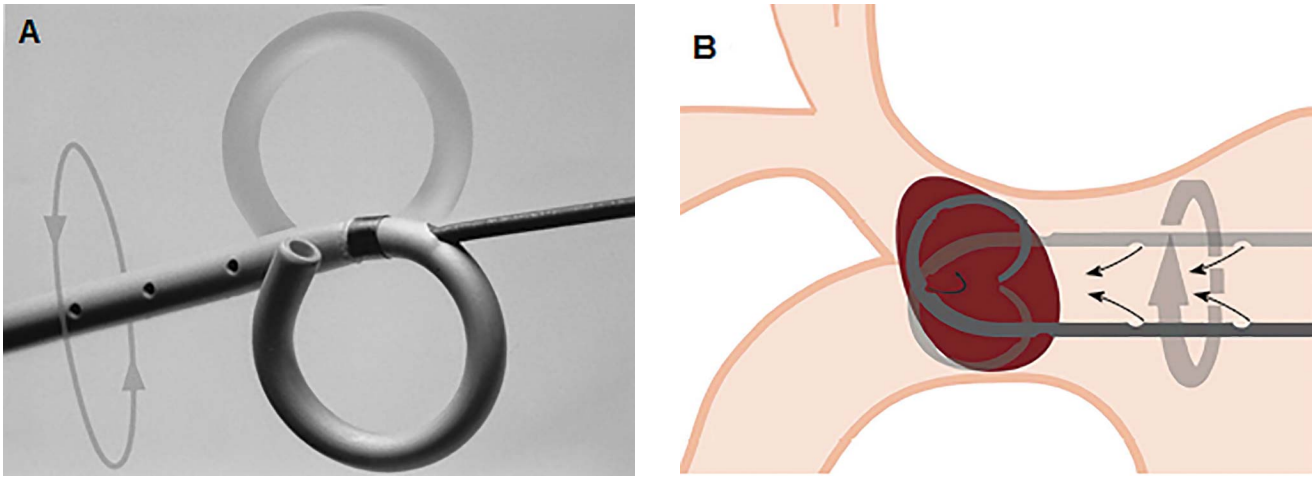


Figure 2. *Pigtail catheters for thrombus fragmentation.*

Notes: Distal ends of pigtail catheters. A — appearance of the catheter with side holes and curved end resembling a tail of a pig; B — schematic representation of mechanical thrombolysis of the thrombus (dark red color) in a pulmonary artery and the infusion of fibrinolytic agents through side holes (marked by little arrows) of the pigtail catheter. Modified from T.Schmitz-Rode et al. (2000) [37] and M.A.DeGregorio et al. (2017) [13].

Ultrasound-Accelerated Catheter-Directed Thrombolysis

CDT efficiency can be increased by using the energy of ultrasonic waves (US-CDT) [6, 27]. The mechanism of action to speed up the fibrinolytic process is associated with the use of ultrasonic energy, which breaks fibrin strands, increasing the surface area of the thrombus and, thus, providing more plasminogen activator receptors for the fibrinolytic action. Thus, low-energy ultrasound disaggregates fibrin fibers in an acutely occurring thrombus, which is used in the EKOS device (EkoSonic, Bothell, USA), combining the radiation of low-energy ultrasound waves and the infusion of a thrombolytic agent through a catheter with several side holes (Fig. 3 and Fig. 4).

Given the available data on US-CDT in the treatment of acute PE, the use of this technique should be applied on a strictly case-by-case basis. N.Kucher et al. (2014) [9] have conducted a multicenter RCT and recommend the following approach to the use of US-CDT based on the results obtained.

Figure 3. *EKOS-catheter with ultrasound transducers embedded within the catheter (marked by blue arrows)*

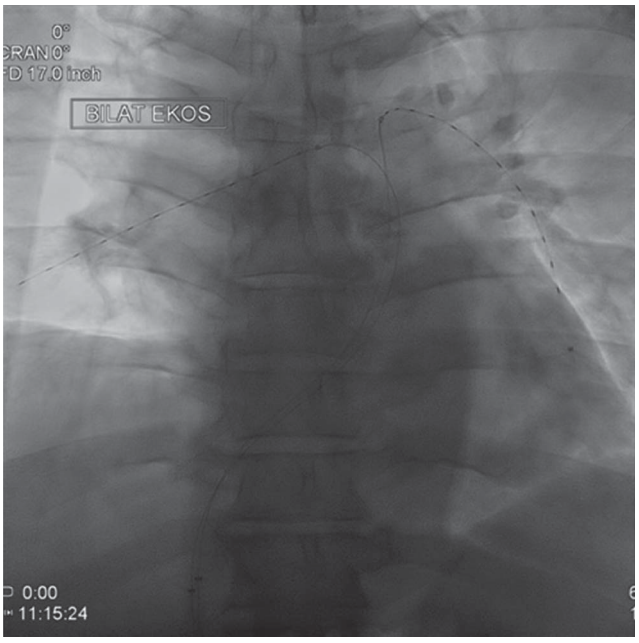


Figure 4. *Bilateral EKOS-catheters placed in the pulmonary arteries via the right common femoral vein approach*

Patients with proven acute PE should be immediately administered an intravenous ACT using first a bolus of 80 units/kg of unfractionated heparin, and then subsequent infusion of the drug. Then an assessment of the function and size of the PV, RV/LV ratio, troponin and brain natriuretic peptide levels is necessary. In addition to the clinical and hemodynamic assessment of the patient's condition, the consent of the patient should be taken into account.

The procedure starts with access through the common femoral vein using a 2 mm single lumen guidewire (F6) for unilateral therapy, two guidewires (2 mm, F6) or one mm dual lumen guidewire with a diameter of 3.33 mm (F10) for bilateral therapy. When performing the procedure, a standard catheterization of the right heart is needed, with simultaneous monitoring of oxygen saturation levels in both systemic circulation and mixed venous blood. To reach the pathological segment, a guidewire with a diameter of 0.89 mm should be used along with a standard diagnostic angiographic catheter. Then the angiographic catheter should be replaced with the selected catheter system. When using an ultrasound system, the guidewire can be removed and the ultrasound transducer system can be attached to the catheter. While the patient is in an intensive care unit, continuous administration of tPA can be initiated at a rate of 1 mg/h into each pulmonary artery. The dose of tPA is divided in half by 5 hours with 0.5 mg/h over the next 10 hours.

The recommended maximum dose of tPA is 20 mg for bilateral catheter placement and 10 mg for unilateral use. tPA infusion and ultrasound exposure should be discontinued after 15 hours. During the active phase of infusion, patients are in the intensive care unit on strict bed rest with continuous monitoring of vital signs, hemoglobin, platelets, fibrinogen levels and activated partial thromboplastin time. After completion of therapy, hemodynamic parameters are re-evaluated. The catheter system and guiding catheter should be removed, followed by manual pressing of the access site until the bleeding stops and stable hemostasis is achieved. In the follow-up period, echocardiography is performed to determine the RV size and function.

According to the data available, US-CDT was superior to the use of heparin alone in reversing RV dilatation at 24 hours without serious hemorrhagic complications or recurrent VTE [9]. In 150 patients in a multi-center study in the USA, US-CDT reduced the mean PA systolic pressure by 30% and the mean RV/LV diameter ratio by 25% [38]. After 90 days, there was a statistically significant difference in the improvement of the RV systolic function due to US-CDT. At the same time there was a tendency to improve the RV/LV diameter ratio, which did not reach statistical significance ($p = 0.07$). No patient experienced intracranial hemorrhage, while one patient had a major bleeding complication. Such an approach offers great promise and is probably preferable for this category of patients, although questions remain as to the safety of the outcome and medium-term and long-term mortality data.

Analysis of subgroups in the PERFECT registry, which compared thrombolysis using ultrasound with a standard CDT, showed an insignificant difference in pressure levels in PA before and after the intervention, despite similar doses of thrombolytic and duration of infusion [33].

In a meta-analysis performed in 2018, which summarized 20 studies with a total of 1,168 patients with high- and intermediate-risk PEs, the pooled estimate for clinical success, 30-day mortality and major bleeding after CDT and US-CDT were analyzed [31]. In the group of patients at high risk, the pooled estimate for clinical success was 81.3% (95% confidence interval (CI), 72.5-89.1), 30-day mortality rate was 8% (95% CI, 3.2-14.0%) and major bleeding was 6.7% (95% CI, 1.0-15.3%). Among patients with intermediate-risk PE, the following results were obtained: 97.5% (95% CI, 95.3-99.1%), 0% (95% CI, 0-0.5%) and 1.4% (95% CI, 0.3-2.8%), respectively. Clinical success in the group of high-risk PE patients who underwent CDT and US-CDT was noted in 70.8% (95% CI, 53.4-85.8%) and 83.1% (95% CI, 68.5-94.5%), respectively. In the group of patients at intermediate risk, the efficacy parameters for both methods differed not so significantly (95% for CDT and 97.5% for US-CDT) [31]. The authors emphasize the clinical success of KDT among high-risk and intermediate-risk PE patients, warning of higher mortality and major hemorrhages in high-risk patients. In addition, the ultrasound assisted CDT showed better values, especially in the group of patients at high risk.

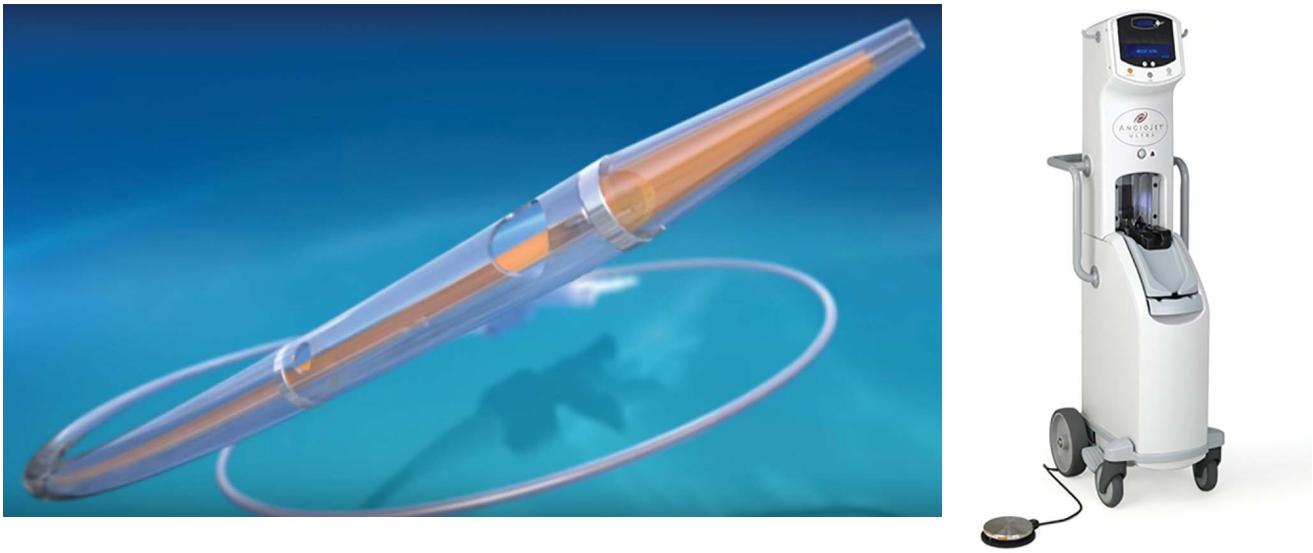


Figure 5. *AngioJet system for rheolytic thrombectomy*

Rheolytic Thrombectomy

Rheolytic thrombectomy is performed using the **AngioJet** device (Boston Scientific, USA), the size of which is selected depending on the target vessel (Fig. 5) [7, 13]. Catheters with a diameter of 2 mm or 2.67 mm (F6-8) are usually advanced in the pulmonary arteries directly to the thrombus using a 0.89 mm guidewire. Fibrinolytic agent (tPA) is delivered through the side holes, and then a high-speed jet is blown through the inner tube to the end of the catheter and back through the wide outer tube. According to the Bernoulli principle, jets that rush under pressure inside the catheter back from the end of the catheter to the pump are used to create zones with relatively low pressure in the region of the large side holes of the catheter. Through these holes, the thrombus or its fragments are captured, destroyed and removed from the body. In addition, these devices can be used for power infusion of a thrombolytic agent, e. g., tPA instead of saline, which is likely to increase the effectiveness of thrombolysis. In the pulmonary vascular system, rheolytic thrombectomy should be used with caution. Caution in the use of AngioJet is associated with relatively frequent complications due to the use of a catheter in the right heart and pulmonary arteries, and includes bradycardia, conduction disorders, hemoglobinuria, renal failure, hemoptysis, and even death [13, 39]. Ensuring proper positioning of the catheter is vital to prevent the risk of catastrophic vascular damage, as well as distal thrombus embolization when using high-pressure injection systems. Therefore, the use of computed tomography is recommended for monitoring when placing any drug delivery system. Despite the precautions, AngioJet (when it is available to use) remains an acceptable choice in the treatment of patients with PE [6, 40].

Aspiration Thrombectomy

A simple vacuum assisted aspiration thrombectomy is a rather easy mechanical option involving the use of an end-hole catheter [25]. An end hole is directed to the thrombus and manual suction is provided by a catheter and a large-volume syringe. Devices for aspiration embolectomy, such as a Greenfield catheter, have advantages over large diameter catheters, as they can remove the thrombus without the adverse effects observed in fragmentation and rheolytic techniques [41]. New devices, such as the Indigo System (Penumbra Inc., USA) and the FlowTriever System (Inari Medical, USA), specially designed for patients with absolute contraindications to thrombolytic therapy, are still at the research stage.

The **Penumbra Indigo** system is a relatively new device that actually automates this process. This mechanical aspiration thrombectomy system is designed to perform continuous drainage [36].

Penumbra Indigo aspiration device consists of 2-2.7 mm (F6-8) straight or curved catheters and a separator pump (Fig. 6AB). The device is approved

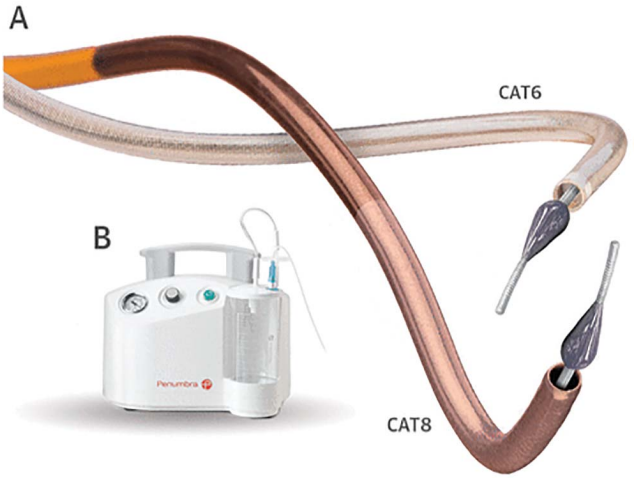
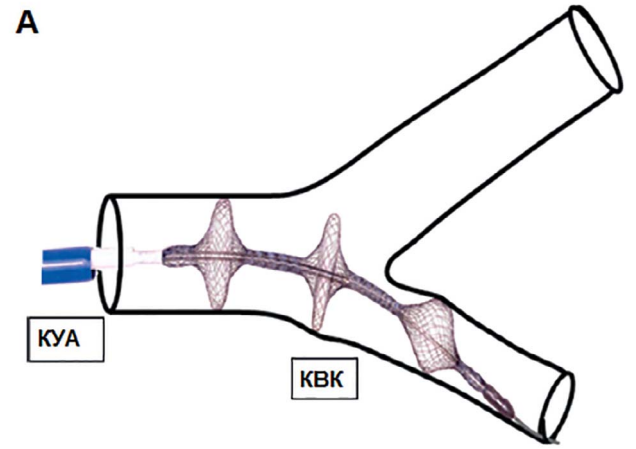


Figure 6. *Penumbra Indigo system with the catheters (A) and the pump-separator (B)*



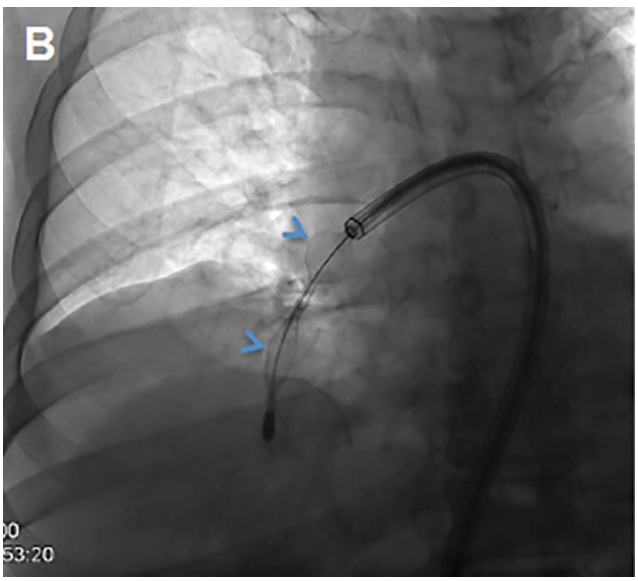


Figure 7. *Schematic illustration of catheter system FlowTriever (A) and radiologic appearance of catheter position in the pulmonary artery being occluded with the thrombus (B)*

Notes: AGC — aspiration guide catheter; FRC — flow restoration catheter. Modified from W.A.Jaber et al. [12].

for removal of thrombi from both the arterial and venous systems [12]. The advantage of the method is that the device requires 2.7 mm (F8) guidewire, which can be placed in the PA system quickly via the catheter delivery system with a guidewire. Once it reaches the thrombus, the thrombectomy catheter moves to the end and the suction mode is activated with a pump. A probe connected to the separator is used to clean the system from thrombotic masses, because the catheter is inside the artery during operation [12].

The **FlowTriever** infusion aspiration system (Inari Medical, USA) consists of three components. First, there is a catheter with a self-expanding nitinol mesh, presented in the form of three closely spaced nitinol discs (Fig. 7A). The discs are equipped with a guiding catheter (the second component) with a diameter of not more than 6.67 mm (F20), inserted immediately to the thrombus over a guidewire [36]. Approaching a thrombus, destroying FlowTriever is advanced straight into the thrombus through the catheter guide into the delivery catheter so that the protected nitinol disks can expand inside the thrombus (Fig. 7B). Then the discs are released using a suction extraction device, which coordinates the mechanical removal of the clot through the FlowTriever and aspiration of the thrombus through the guiding catheter into the device (the third component) [25].

The **AngioVac** system (Angiodynamics, USA) is a circuit with two large diameter catheters connected with a centrifugal pump. A catheter with a diameter of 7.33 mm (F22) with a funnel tip is advanced to the thrombus, and after that, the thrombus is aspirated to the cardiopulmonary pump (Fig. 8). The thrombus is retained inside the pump, and the aspirated blood is returned to the patient through

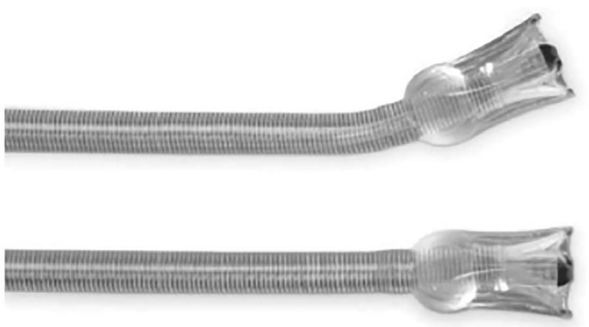


Figure 8. *Aspiration suction cannula AngioVac*

the second venous catheter with a diameter of 5.67 mm (F17) [25, 36]. Due to the scheme presented, a unique requirement for the effective use of the AngioVac system is the presence of a perfusiologist, who should keep the pump working during the thrombus aspiration.

Aspirex S (Straub Medical, Switzerland), a thrombectomy catheter, is also used for aspiration thrombectomy. This device has a single lumen catheter with a diameter of 3.33 mm, which can be advanced through a 0.89 mm hydrophilic guidewire. Aspirex has an L-shaped aspiration port that is advanced to the thrombus. Once inside the thrombus, the internal spiral turbine begins to rotate at high speed, aspirating the thrombus through the port and removing it in a spiral, like a screw. The catheter is connected to an external accumulation system where thrombotic masses are deposited. Although this system is widely used in acute DVT or dialysis access thrombosis, however, there is limited experience in its use in the treatment of high-risk PE patients [42]. The Aspirex catheter system is currently not approved for PE treatment in USA [6, 25].

Provision of Access and Perioperative Management in Endovascular Treatment

The approach suggested in the guidelines of the American Heart Association is recommended to access the vascular bed [8]. An access is made using a 2 mm femoral venous guidewire (F6) and a pigtail-type angular catheter of the same diameter, is advanced into each main PA. The extent of the lesion can be visualized at this stage by the injection of low-osmolar or iso-osmolar contrast agents (30 ml > 2 s). Unfractionated heparin should be used to maintain clotting time > 250 s. A direct thrombin inhibitor, e. g., bivalirudin (0.75 mg/kg IV bolus, then 1.75 mg/kg/h) can be used as an alternative to heparin if there are contraindications to the heparin administration which are not related to bleeding. A 2 mm guiding catheter (F6) is used to reach a thrombus, which after that may be approached by a hydrophilic guidewire, through which, in turn, devices for percutaneous mechanical thrombectomy are advanced. This approach is limited to main and lobar PA branches.

Postprocedural Patient Management

Currently, there are no comparative studies and guidelines regarding the type, dose and duration of use of anticoagulant or antiplatelet drugs after endovascular catheter therapy. Some authors employ an empirical approach to antiplatelet therapy and ACT in these patients. After completion of CDT in acute PE or DVT, ACT is resumed with unfractionated heparin shortly after stopping the bleeding at the puncture point. Then, if necessary, patients are switched to therapy with new oral anticoagulants or vitamin K antagonists. And, finally, in patients with PE/DVT, it is necessary to use compression bandages until acute edema is resolved, and then switch to kneesocks with a pressure of 30-40 mm Hg. After discharge, patients should be followed-up regularly, and during repeated visits, it is necessary to evaluate clinically the possibility of disease recurrence, changes in life quality, as well as to perform continuous analysis of the bleeding risk in those who continue to be on the ACT.

Predictors of Adverse Events

Since endovascular strategies continue to be updated and improved, and specialized catheter systems are widely introduced into modern practice, it is essential to predict the adverse events associated with catheter therapy in both acute DVT and PE. Early studies [9, 43], including the recently completed ATTRACT study [26], did not reveal significant differences in the safety of CDT and anticoagulant therapy alone. In turn, the results of extensive observations in the USA demonstrated that the presence of factors such as age > 75 years, Latin American ethnicity, the presence of shock, cancer, paralysis, renal or congestive heart failure are significant predictors of mortality or intracranial hemorrhage in patients who underwent CDT due to PE [44]. In addition, in patients with cancer and chronic kidney disease, who underwent CDT for PE, there was a higher incidence of acute renal failure and hemorrhagic complications, including intracranial hemorrhages [45, 46]. Before the start of endovascular therapy in acute PE, comorbidities and other risk factors should be considered until

the results of new prospective comparative studies are obtained regarding the safety and efficacy of a particular CDT method.

Special attention should be paid to considering the relationship between the high volume of interventions performed in a medical institution and the level of favorable outcomes of endovascular therapy [2]. The results of a recent national study in the USA showed that institutions with a higher annual volume of procedures (> 5 procedures per year) had rates of mortality and intracranial hemorrhages in the CDT group comparable to the group of patients who received ACT only [47]. In turn, in the centers with a smaller volume of medical procedures (<5 per year), significantly higher levels of mortality and intracranial bleeding were observed in comparison with the group of anticoagulants alone. These data probably reflect heterogeneity in modern practice in the USA and are due to differences in patient selection and monitoring before and after the procedure. It is extremely necessary to standardize endovascular VTE therapy protocols, as this can improve the results of the technique, especially at institutions that perform a low number of interventions [48].

Conclusion

Along with the conventional methods of acute PE treatment (surgical embolectomy, ACT and systemic thrombolysis), in recent times more attention has been paid to the use of catheter treatment approaches that have a number of advantages. The use of the catheter method allows targeted delivery of a fibrinolytic drug, treatment of a PA thrombus with ultrasound and mechanical devices, and also removing thrombus fragments using various rheolytic and aspiration devices. However, at this stage there is no convincing evidence in favor of the routine use of the described techniques in the treatment of submassive or massive PE. In addition, no device is significantly superior to another, based on available literature data. The lack of a strong evidence base regarding the safety of the interventional approach and its effectiveness in comparison with monotherapy with anticoagulant drugs most likely suggests that the endovascular treatment of PE is still in its infancy. Most patients continue to be treated conservatively, and more aggressive methods are reserved only for cases of high-risk or intermediate-high-risk PE in the absence of contraindications. Obviously, it is necessary to conduct larger studies on the comparative analysis of the use of interventional methods of acute PE treatment in regard to their efficacy and safety. In addition, data are needed on the safety and efficacy of indirect oral anticoagulants and vitamin K antagonists after the thrombus is removed by the catheter method in PE, both in terms of therapeutic advantage and in terms of patient preference. It is necessary to use an extremely individualized approach, including patient selection, the type of therapy, the level of experience of both the operating team and the medical institution, in order to maximize the benefits of the intervention strategy and minimize the risk of harm to the patient.

Conflict of interests

The authors declare no conflict of interests.

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