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ИНТЕРВЕНЦИОНАЛНО ЛЕЧЕНИЕ НА БЕЛОДРОБНАТА ЕМБОЛИЯ – КЪДЕ СМЕ В МОМЕНТА?

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INTERVENTIONAL TREATMENT OF PULMONARY EMBOLISM – WHERE DO WE CURRENTLY STAND?

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Резюме. Острата белодробна тромбоемболия е третата най-честа причина за сърдечно-съдова смъртност в света. Внезапното тенсионно обременяване на дясната камера, предизвикано от тромботичните маси в пулмоналната артерия, може бързо да прогресира до клинична картина на тежък кардиогенен шок. Това може да доведе до смъртност над 50%, при пациенти с масивна форма на белодробна тромбоемболия. В такива случаи е мотивирано провеждането на системна фибринолиза, което води до бързо подобрение в деснокамерната функция и стабилизиране на хемодинамиката. Тромболитичният ефект на системната фибринолиза, за съжаление, е съпроводен от петкратно повишен риск от кървене, особено вътречерепно. Следователно в повечето случаи хемодинамично стабилните пациенти биват третирани само с антикоагулантна терапия. Интервенционалното лечение на острата белодробна емболия включва употребата на устройства, използващи ниска доза фибринолитик или такива за перкутанна тромбаспирация. Целта е да се постигне бързо отстраняване на тромботичните маси от пулмоналната артерия, като едновременно се сведе до минимум хеморагичният риск. Този обзор ще се опита да предостави кратък преглед на най-често използваните и налични на пазара устройства, както и клиничните данни, подкрепящи тяхната употреба. Също така, ще бъдат разгледани перспективите в развитието на ендоваскуларното лечение на острата белодробна тромбоемболия.

Ключови думи: остра белодробна емболия, интервенционално лечение, ендоваскуларно лечение

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Abstract. Acute pulmonary embolism is the third most common cause of cardiovascular mortality in the world. The sudden pressure overload of the right ventricle, caused by the thrombotic masses in the pulmonary artery, may quickly progress to profound cardiogenic shock. That results in a mortality rate of more than 50% in patients with a massive form of pulmonary embolism. In such cases, systemic fibrinolysis is warranted, which leads to rapid improvement of the right ventricular function and hemodynamic stabilization. The thrombolytic effect of systemic fibrinolysis is, unfortunately, accompanied by an almost 5 times increased risk of bleeding, especially intracranial one. Therefore, in most cases, for patients with uncompromised hemodynamics, only anticoagulation treatment is offered. Interventional treatment of acute pulmonary embolism consists of the usage of very low-dose fibrinolytic devices or percutaneous thrombus aspiration devices. The goal is to provide rapid removal of the thrombotic masses from the pulmonary artery circulation while keeping the hemorrhagic risk at a minimum. This paper will try to provide a concise review of the most widely used and available devices, together with the latest clinical data, supporting their use. Also, the future perspectives in the field of endovascular treatment of acute pulmonary embolism will be presented.

Key words: acute pulmonary embolism, interventional treatment, endovascular treatment

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Introduction

The global burden of venous thromboembolism (VTE), which consists of pulmonary embolism (PE) and deep vein thrombosis (DVT), occurs at a rate of 10 million cases per year. Of them, around 1 million cases are registered in the United States of America and 700, 000 in Europe [1]. In China, the incidence of PE tripled from 3.9 per 100, 000 in 2000 to 2001 to 11.7 per 100, 000 in 2010 to 2011 [2]. Other studies point out that the incidence of PE in the United States is 600 000 cases annually, with an approximate yearly death rate of around 100 000 cases are contributed to pulmonary embolism, and 5 to 10% of in-hospital death is a direct result of PE [3,4]. Another interesting global trend is that while the incidence of pulmonary embolism increases the mortality decreases. An analysis of the incidence of PE in the United States showed that the rate of PE, from 2004 to 2015, increased from 5.3 per 1000 hospital admissions to 9.7 per 1000 hospital admissions ($p < 0.001$), with the rate of major PE going from 7.9 to 9.7%. In the meantime, the mortality decreased from 8.9% in 2004 to 6.4% in 2015 ($p < 0.001$) [5]. Risk factors, such as thrombophilias, trauma, surgery, malignancy, peripartum state, estrogen therapy, aging (especially over 70 years of age), and obesity are known to be associated with increased incidence of PE [6]. In the era of the COVID-19 pandemic it is worth mentioning this infectious disease and its contribution to thrombosis. COVID-19 infection proved to be a highly prothrombotic state, with its most common vascular complication being VTE. In a study, the weighted mean prevalence (WMP) of VTE was 31.3%, with WMP for PE of 18.9% and WMP for DVT of 19.8% [7]. When patients with COVID-19 infection required treatment in an Intensive Care Unit (ICU) the incidence of VTE went up to 59% and was as high as 27% even in patients who were receiving at least a prophylactic dose of low-molecular heparin (LMH) dose [8,9]. Systemic thrombolysis in PE is associated with a reduction of pulmonary artery pressure (PAP), improvement of right ventricular dysfunction, and lower PE-related mortality [10]. However, these results are offset by an almost 5-times increased risk of bleeding and up to 10-times increased risk of intracranial hemorrhage [10, 11]. Therefore, current treatment guidelines dictate systemic fibrinolysis with the highest class and level of recommendation (IA) for all patients with massive or high-risk PE (hemodynamically unstable patients with instrumental or laboratory signs of right ventricular strain), while patients with submassive or intermediate-risk PE (hemodynamically stable patients with various degree of right ventricular strain) are to be treated with anticoagulation alone unless there is a clinical deterioration [12]. At the moment, percutaneous catheter-directed therapy has a class and level of recommendation IIC, and contemporary PE management guidelines dictate that it should be considered for patients with massive PE in whom systemic fibrinolysis is contraindicated or has failed [12].

There are two mainstreams of available devices for the treatment of acute pulmonary embolism: those that deliver low-dose fibrinolytic directly in the pulmonary vasculature accompanied by some maneuvers for improved penetration of the thrombolytic in the thrombi and those that are used to directly aspirate the thrombotic masses. The rationale is to promptly alleviate the right ventricle from the strain caused by the obstruction of the pulmonary artery and its branches while maintaining a low bleeding risk [13]. This paper will aim to give a succinct review of some of the more important devices and the most valuable clinical trial data so far, and will also try present what is expected in the future regarding the endovascular treatment of pulmonary embolism.

Catheter directed therapy for the treatment of acute pulmonary embolism

The EKOSonic Endovascular System

One of the most widely used devices for low-dosage fibrinolytic therapy is the EKOSonic Endovascular System (Boston Scientific, USA) (Figure 1). It consists of a dual-lumen catheter – one lumen for low-dose thrombolytic delivery, and the other containing a filament that emits high-frequency, low-power, soundwaves. The ultrasound waves help disrupt the fibrin mesh of the thrombus, which facilitates better penetrations of the tissue plasminogen activator (tPA) into the thrombotic masses. The manufacturers of the device named this treatment modality ultrasound-assisted thrombolytic therapy (USAT).

In the ULTIMA trial (ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism) [14]. The efficacy of the device was compared to treatment with unfractionated heparin (UFH) alone for patients with intermediate-risk acute pulmonary embolism. All of the 59 enrolled patients had echographic findings of right ventricle/left ventricle (LV) ratio of > 1.0. Thirty patients were in the USAT group, where up to 20 mg of tPA was applied for a period of 15 hours. The other 29 patients were treated with UFH alone. At 24 hours in the USAT group, there was a significant reduction in the RV/LV ratio (1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 hours, $p < 0.001$). There was no significant reduction in the RV/LV ratio in the heparin-only group. No major bleeding events were registered.

In another investigation, 150 patients were also treated with USAT, 31 of them with massive PE and

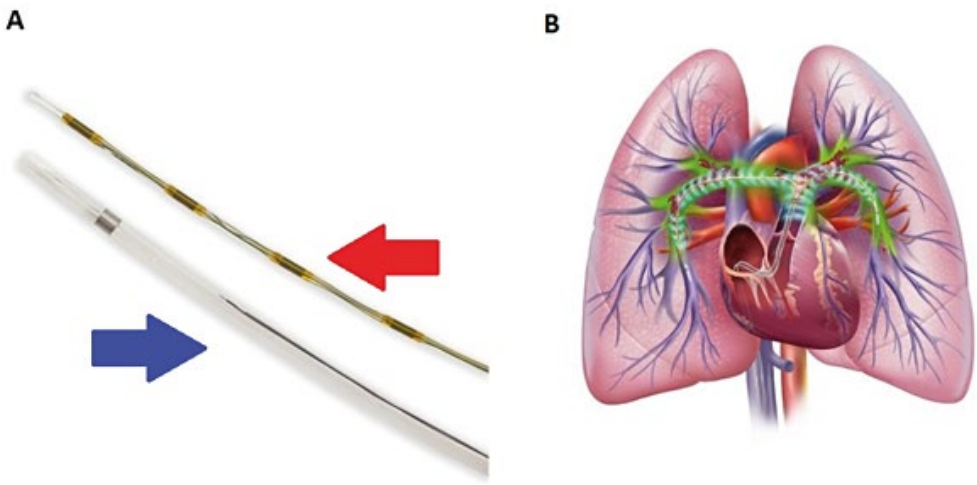

Fig. 1. A. The EKOS Endovascular System Catheter. Red arrow – ultrasonic core, blue arrow – infusion catheter. **B.** Schematic representation of bilateral simultaneous placement of two EKOSonic catheters in the left and right pulmonary arteries

119 with submassive PE. They were part of the multicentre, randomized, prospective SEATTLE II trial (Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy) [15]. All participants had an RV/LV ratio > 1.0, derived from computed tomography (CT) pulmoangiography. The treatment protocol included applying a total dose of 24 mg tPA for a period of 12 to 24 hours. The efficacy of the treatment was evaluated at 48-hours after the procedure. There was a significant reduction in all prespecified parameters for RV strain reduction: the mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure from 1.55 to 1.13, ($p < 0.0001$), mean pulmonary artery systolic pressure (mPAP) decreased from 51.4 mm Hg to 36.9 mm Hg, ($p < 0.0001$), and the registered change in Modified Miller Index (MMI) score was from 22.5 to 15.8 ($p < 0.0001$). There were no intracranial hemorrhages registered in this study, but the authors described 1 GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) severe and 15 GUSTO moderate bleeding events, none of them fatal.

Continuing to evaluate the efficacy of the EKOSonic Endovascular System the investigators of the OPTALYSE PE trial (the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism) used this device for the treatment of 100 patients with intermediate-risk PE [16]. Four different treatment regimens were used, with tPA doses ranging from 4 to 12 mg per lung and different infusion times. A significant reduction of the RV/LV ratio with 23 to 26% ($p < 0.01$) was registered via CT pulmoangiography in all four different arms of the study. However, this was the first study in which ICH was registered while using ultrasound-assisted thrombolysis. Two (2%) of the patients suffered from intracranial bleeding. In one of them, an additional 50 mg of tPA was applied which was thought to be the reason for the accident. The other patient was part of the highest dosing and fastest way of appliance regime (12 mg/per lung for 6 hours). For this patient, the authors concluded, that it is more likely that the cause of the ICH was not the cumulative dose of tPA applied, but more likely the high concentration of the fibrinolytic applied for a short period.

In the prospective multicenter registry PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) 101 patients with acute massive (28 patients) and submassive (73 patients) pulmonary embolism were treated with catheter-directed thrombolysis [17]. In this study both USAT and standard catheter-directed therapy (SCDT), via commercially available catheters, were used. Efficacy endpoints were defined as: stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge. The mean tPA dose used was 28 mg. Clinical success was achieved in 86% of the patients with massive PE and in 93% of the patients with submassive PE. A significant drop of the mPAP with 15.81mmHg (from 51.17 at baseline to 37.2 mmHg after the procedure). It should be mentioned that, while there was no significant difference in the tPA dose for the USAT and SCDT groups there also was no significant difference in the reduction of the mPAP between the two groups – 13.8 mmHg for the USAT and 14.02 mmHg for the SCDT group ($p = 0.9$). No major procedure-related complications, major hemorrhages, or hemorrhagic strokes were observed in this registry.

In the first of its kind study in the field, the investigators of the SUNSET sPE trial compared, head-to-head, USAT vs SCDT for the treatment of submassive PE [18]. Of the 81 patients enrolled 40 were treated via USAT, while the other 41 were managed with SCDT, using either standard Cragg-McNamara (Medtronic, USA) or Uni-Fuse (AngioDynamics, USA) multiple-side-hole catheter. The dose of tPA used was 19 ± 7 mg for the USAT group and 18 ± 7 mg (p = 0.53) for the SCDT group. 48 hours after the procedure a refined Miller index (measured via CT pulmoangiography) was used to evaluate the reduction of thrombotic burden in the pulmonary artery. Although there was a significant reduction in the mean raw pulmonary arterial score in both groups (USAT – 31 ± 4 at baseline to 22 ± 7; SCDT – from 33 ± 4 to 23 ± 7; p < 0.001), there was no statistical difference in the reduction between the two groups (p = 0.76). There were two major bleeding events, both in the USAT group. One was a hemorrhagic stroke, which was managed conservatively and was non-fatal. The other was in a female patient in which both epistaxis and vaginal bleeding were registered.

The BASHIR Endovascular Catheter

A novel device for the interventional treatment of acute pulmonary embolism via pharmaco-mechanical thrombolysis is the BASHIR Endovascular Catheter (BEC) (Thrombolex Inc., USA) (Figure 2). The BEC is placed directly into the thrombotic masses where the expandable infusion basket is opened. The infusion basket itself consists of six mini-infusion catheters each with multiple side holes. Thus, the device facilitates the maceration of the thrombotic masses along with a direct infusion of thrombolytic into the clot. In the first-in-human trial, the BEC was used for the treatment of 9 patients with acute submassive PE [19]. A maximum dose of 14 mg tPA was used and 48 hours after the procedure the RV/LV ratio decreased by 37% (p = 0.0009) and the MMI decreased from 25.4 ± 5.3 to 16.0 ± 4.0 (p = 0.0005). At the 30-day follow-up, there were no device-related complications or deaths. Another ongoing study that will try to evaluate the efficacy and safety of the BEC is the RESCUE trial [20]. This study will aim to enroll at least 100 patients with acute submassive pulmonary embolism. So far the interim results for the first 62 patients were presented [21]. Again, a total dose of 14 mg tPA was used. 48 hours after the infusion the control CT scan showed a reduction of the RV/LV ratio with 32.1% (p < 0.0001) and a reduction in the clot burden with 36.3% (p < 0.0001) by Refined Modified Miller index. No major bleeding events and device-related complications were registered within 72 hours after the procedure.

Fig. 2. The BASHIR Endovascular Catheter – the infusion basket is opened showing the mini-infusion catheters with fibrinolytic being infused from the multiple side holes

The FlowTriever System

The FlowTriever system (InariMedical, Irvine, California) (Figure 3) has European CE Mark approval and FDA 510(k) clearance for the endovascular treatment of PE and clot in transit in the right atrium. The device consists of a suction system and is connected to an up to 24 French (F) flexible, aspiration catheter. Additionally, the catheter has three self-expandable nitinol discs that are used to engage the clots in the pulmonary artery and retrieve them in the aspirational catheter. This device was used in the FLARE study (A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism) for the treatment of 106 patients with intermediate-risk acute PE [22]. An average reduction of the RV/LV ratio with 0.38 or 25.1% (p < 0.0001) was registered 48 hours after the procedure, via CT scan. One major bleeding (non-fatal) was registered and no hemorrhagic strokes were observed. There were no major vascular complications or device-related cardiac or pulmonary injuries.

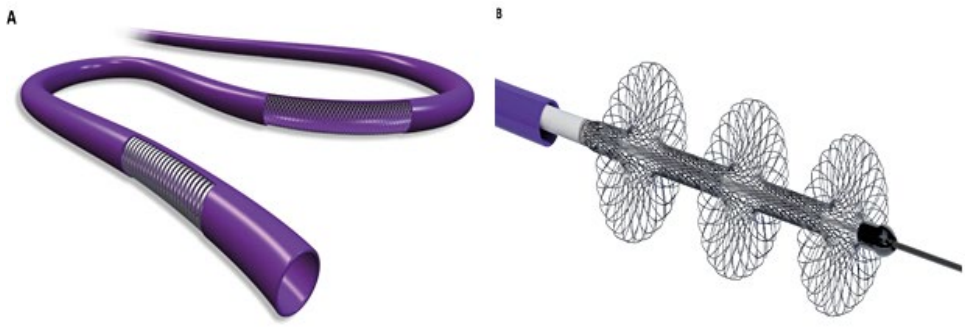

Fig. 3. The FLowTriever Catheter **A.** The 20F flexible FlowTriever catheter **B.** The three self-expandable nitinol discs used for the engagement and retrieval of thrombotic masses

The Indigo Aspiration System

Another percutaneous thrombectomy device is the Indigo Aspiration System (Penumbra Inc., USA) (Figure 4). It is comprised of an aspiration engine that uses catheters up to 12 F (CAT8 and CAT12 catheters) for the evacuation of clots. Another important asset of this system is the Lightning Aspiration Tubing which is an intelligent aspiration system that has a sensor that allows the system to differentiate when it is aspirating thrombotic masses and when blood only. This allows reducing the periprocedural blood loss. In the EXTRACT – PE trial (Evaluating the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism) 119 patients with acute submassive PE were treated with the Indigo System [23]. The efficacy of the procedure was evaluated 48 hours after its end and the mean RV/LV ratio reduction was 0.43 or 27.3% ($p < 0.0001$). Two patients (1.7%) experienced three major adverse events: both of them had major bleeding and one (0.8%) of them died due to device-related death.

Fig. 4. The Indigo Aspiration System – the Penumbra ENGINE is shown together with the Lightning Intelligent Aspiration Tubing

The Aspirex S Endovascular System

The Aspirex S (Straub Medical, Switzerland) is a mechanical aspiration thrombectomy system that offers an up to 10F aspiration catheter, which has a rapidly rotating steel propeller in its core, that creates the negative pressure needed for the aspiration of the thrombotic masses. (Figure 5) The system is powered by a motor that spins at speed of 40 000 rounds per minute. This device was successfully used for the treatment of 16 patients with massive pulmonary embolism [24]. In 14 (88%) of the patients, there was almost complete thrombus clearance. The systolic pulmonary pressure decreased from 72 ± 13 mmHg to 34 ± 9 mmHg ($p < 0.001$) and the RV/LV ratio changed from 1.32 ± 0.15 to 0.84 ± 0.13 ($p < 0.001$) after the procedure. One patient died due to refractory cardiogenic shock.

Fig. 5. Aspirex percutaneous thrombectomy catheter (Straub Medical, Switzerland)

What is to come?

Several exciting clinical trials are expected in the near future that might change the concepts for the treatment of acute pulmonary embolism.

The HI-PEITHO (Ultrasound-facilitated, Catheter-directed, Thrombolysis in Intermediate-high Risk Pulmonary Embolism) is a prospective, multicenter randomized controlled trial (RCT) that will aim to enroll 544 patients with intermediate-high risk pulmonary embolism (hemodynamically stable patients with instrumental and laboratory signs of RV strain) [25]. Patients will be randomized in a 1:1 fashion – one of the groups will be treated with USAT via the EKOS Endovascular System plus anticoagulant, while the other will be treated with anticoagulant only. The primary endpoint will be the composite of PE-related mortality, cardiorespiratory decompensation or collapse, and/or nonfatal PE recurrence within 7 days of initial USAT treatment. Additional follow-up will be at 30-days, 6 months, and 1 year after the procedure. This study will try to shed light on the topic, of whether treatment with anticoagulant alone is still the preferable option for this cohort of patients with PE.

The results from three trials using the percutaneous thrombectomy device FlowTriever will be much expected.

FLASH (FlowTriever All-Comer Registry for Patient Safety and Hemodynamics) is a prospective, multicenter, single-arm registry [26] This study will try to provide real-world data for the treatment of 500 patients with intermediate-high and high-risk PE. Patients will be evaluated 48 hours after the procedure for a composite endpoint of device-related death, major bleeding, or device or procedure-related adverse events.

FLAME (FLowTriever for Acute Massive Pulmonary Embolism) is a prospective, multicenter, parallel-group observational study [27]. 250 high-risk PE patients will be treated in this trial using the FlowTriever device and the primary endpoint will be the composite incidence of all-cause mortality, clinical deterioration, bailout, and major bleeding. The endpoint will be evaluated either through hospital discharge or at 45 days. These two studies, upon finishing, will have the highest numbers of high-risk PE patients treated with catheter-directed therapy so far. Un-

fortunately, there are still no randomized controlled trials comparing endovascular therapy vs systemic fibrinolysis for the treatment of patients with high-risk PE.

In the first-of-its-kind study, the investigators of the prospective, multicenter, randomized controlled trial PEERLESS will compare two fundamentally different endovascular techniques [28]. 550 patients with intermediate-high risk PE will be randomized into two groups. In one of the groups percutaneous mechanical thrombectomy, using the FlowTriever device will be performed, while the patients from the other group will be treated with standard catheter-directed therapy (with any commercially available devices) and low-dose fibrinolytic. A control group of additional 150 patients with absolute contraindications for fibrinolysis will also be enrolled. The primary endpoint, measured at discharge or on day 7 after the procedure, whichever comes first, will be a composite of all-cause mortality, ICH, major bleeding, clinical deterioration, and ICU admission.

Conclusion

Robust but fragmented data is supporting the efficacy and safety of the endovascular treatment of acute pulmonary embolism. We expect additional data from ongoing and upcoming clinical trials. Rapid technological advancement in the field is continuously improving the results of endovascular treatment of PE. Probably, in the near future, based on the awaited new data, interventional management of PE will become the treatment method of choice for patients with acute massive and submassive pulmonary embolism.

No conflict of interest was declared

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