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Interventional therapy of acute pulmonary embolism: where are we and where are we heading towards?

Terapia intervencionista da embolia pulmonar aguda: onde estamos e para onde vamos?

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ABSTRACT - This life-threatening condition, known as pulmonary embolism, is prevalent throughout the world, affecting a large percentage of population and representing one of the leading causes of cardiovascular death. To reduce mortality and morbidity and improve outcomes, early risk stratification is critical. There is a wide range in the severity of a pulmonary embolism, from mild to life-threatening. When a patient has a high-risk pulmonary embolism and is in shock or cardiac arrest, emergency systemic thrombolysis or embolectomy is reasonable, but anticoagulation alone has great results in low-risk pulmonary embolism. Multiple strategies exist to capture the benefits of thrombolysis while minimizing its risks, but clinical experience with such novel intervention strategies is limited. The pulmonary embolism response team comprises interventional cardiologist, interventional radiologist, cardiac surgeon, cardiac radiologist, and critical care specialist, can help determine the type of intervention in a given patient. This article provides an outline of current endovascular interventional therapies and their context.

Keywords: Pulmonary embolism; Thrombolytic therapy; Risk assessment; Anticoagulants; Morbidity; Tissue plasminogen activator

RESUMO - A embolia pulmonar, uma doença com risco de vida, é prevalente em todo o mundo, afetando grande porcentagem da população e representando uma das principais causas de morte cardiovascular. Para reduzir sua mortalidade e morbidade e melhorar os desfechos, é fundamental uma estratificação precoce do risco. Há uma ampla variação na gravidade de uma embolia pulmonar, desde leve até com risco de vida. Quando um paciente tem uma embolia pulmonar de alto risco e está em choque ou parada cardíaca, é razoável realizar trombólise sistêmica ou embolectomia de emergência, mas a anticoagulação isolada tem ótimos resultados na embolia pulmonar de baixo risco. Há várias estratégias para aproveitar os benefícios da trombólise e minimizar seus riscos, mas a experiência clínica com essas novas estratégias de intervenção é limitada. A equipe de resposta à embolia pulmonar, composta de cardiologista intervencionista, radiologista intervencionista, cirurgião cardíaco, radiologista especializado em imagem cardíaca e intensivista, pode ajudar a determinar o tipo de intervenção em um determinado paciente. Este artigo traz um esboço das terapias intervencionistas endovasculares atuais e seu contexto.

Descritores: Embolia pulmonar; Terapia trombolítica; Medição de risco; Anticoagulantes; Morbidade; Ativador de plasminogênio tecidual

INTRODUCTION

Acute pulmonary embolism (PE) is not infrequent, and sometimes it is a fatal condition. To avoid recurrence of thromboembolism and mortality, prompt treatment is essential.[1-5] There is little information on the treatment of PE across the wide spectrum of disease presentations, even though there are ongoing efforts to build evidence-based strategies for stroke and myocardial infarction prevention and intervention. While anticoagulation remains the mainstay of treatment for most cases of acute PE, given the elevated risk of mortality in those manifesting with right ventricular (RV) dysfunction, there may be an opportunity to incorporate more aggressive therapies to improve outcomes in a carefully selected subset of acute PE patients.[6,7] As a result, acute PE care is witnessing a resurgence of interest and a shift in the landscape, par-

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ticularly among patients with severe disease. With precise early risk stratification and appropriate patient selection, via multidisciplinary approaches to management with the advent of PE response teams, various endovascular technologies may have the potential to decrease morbidity and mortality. This review highlights the current state of endovascular interventional therapy for acute PE, and defines which patients are most likely to benefit from their use in various clinical settings.

RISK STRATIFICATION

There are many clinical manifestations of acute PE, ranging from asymptomatic status to severe hemodynamic collapse and death. The risk stratification at initial presentation, which is based on its acute hemodynamic effects and short-term prognosis, is of paramount importance, given the broad spectrum of presentation (Table 1).[8-12] Those with a low risk of problems can benefit from anticoagulation.[13] Anticoagulation alone should also be used to treat most individuals with RV dysfunction, according to current data.[14-16] However, patients who present as survivors of cardiac arrest, or with shock or hypotension, classified as high-risk (or massive) PE, require prompt debulking and reperfusion therapy to attain favorable impact on the mortality and morbidity.

According to the American Heart Association (AHA), [14] acute PE was classified into three categories: massive, submassive, and low risk. The European Society of Cardiology (ESC)[15] classified PE into three risk categories: high risk, intermediate risk, and low risk.

Massive (AHA) or high-risk (ESC) PE is defined as emboli that lead to hypotension, defined as a systolic blood pressure <90 mmHg, a drop of >40mmHg for at least 15 minutes, or need for vasopressor. This cohort comprises around 5% of all PE patients and has a 30% mortality rate, on average, within one month.[4,17-19]

Submassive (AHA) or intermediate-risk (ESC) PE encompasses patients with RV strain without hypotension. Right ventricular strain includes RV dysfunction on computed tomography pulmonary angiography or echocardiography (RV/left ventricular – LV – ratio >0.9),[8,9] or RV injury and pressure overload detected by an increase in cardiac biomarkers, such as troponins or brain natriuretic peptide. The ESC classification also denotes intermediate risk in the absence of RV dysfunction in patients with a simplified Pulmonary Embolism Severity Index (PESI) score >1, which aids in risk stratification of those with prior concurrent comorbid disease. Age over 80 years, cancer, chronic respiratory illness, and heart disease are all included in the simplified PESI, as are heart rate >110bpm, systolic blood pressure <100mmHg, or oxygen saturation level <90%.

The ESC further divides intermediate-risk patients into two subgroups, according to whether patients have both RV dysfunction and RV injury (high intermediate risk) or only one or neither of these findings (low intermediate risk). Approximately 30% of patients with PE are in this group.[20] The patients that do not meet the criteria for submassive or intermediate risk are included in low risk (AHA and ESC). This cohort represents approximately 65% of patients with PE, with 30-day mortality of approximately 1%.[20] The ultimate goal of risk stratification is to stratify patients at high risk of mortality and to identify potential candidates for more invasive and aggressive options for PE treatment.

Interventional therapies for pulmonary embolism

Most patients with pulmonary embolism have been managed with anticoagulation. At the time of presentation, anticoagulation should be started right away. A mortality benefit is more with immediate treatment compared to those patients. With prompt therapy, mortality is lower than in those where time to therapeutic anticoagulation was delayed.[21] Many physicians are contemplating treatment escalation by systemic thrombolysis (ST), catheter-directed therapy, or surgical embolectomy due to adverse outcomes in patients with high-risk and intermediate-risk PE despite anticoagulation. These techniques may be employed in patients with evidence of hemodynamic compromise, in conjunction with invasive hemodynamic support devices, such as extracorporeal membranous oxygenation or isolated percutaneous RV support.[22]

The limitations with anticoagulation for intermediate-risk patients and the hazards of ST and surgical embolectomy have spurred interest in catheter-directed the-

Table 1. Devices for endovascular treatment of pulmonary embolism

Thrombectomy and thrombolysis	Catheter directed thrombolysis (non- ultrasound)	Aspiration	Rheolytic	Catheter directed thrombolysis (ultrasound)	Fragmentation
Devices	Cragg-Mc Namara™ Unifuse™	Indigo® Penumbra FlowTreiver	AngioJet™	EkoSonic™	Pig-tail Catheter Peripheral balloon catheter
Mechanism	Thrombolytic treatment used intrathrombically to treat a larger portion of the clot's surface area	Mechanical aspiration	Negative pressure from the high-flow saline jet allows for aspiration of thrombi	Ultrasound emitting catheter generating an acoustic field creating a more lytic dispersion of the drug infused	Fragmentation of the thrombus by balloon sweeps or manual rotation of pig-tail

Source: the authors.

rapies. In contrast to ST, there is substantially less data supporting the efficacy and safety of these treatments.[23,24] Thrombus load can be reduced rapidly using pharmacomechanical means offered by these devices. They fall into two categories: catheter-directed thrombolysis (CDL) and catheter-directed embolectomy.

SYSTEMIC THROMBOLYSIS

Systemic thrombolysis results in rapid recanalization of the pulmonary artery, with corresponding improvements in pulmonary pressures, RV function, ventilation/perfusion mismatches, and clinical hemodynamic condition, and symptoms.[14,15] This benefit is offset by an increased risk of major bleeding, particularly intracranial hemorrhage (ICH) compared to anticoagulation.[25] Systemic thrombolysis has long been the treatment of choice for high-risk PE patients, because of acute nature of these presentations and risk for further rapid deterioration.[14,15]

The PEITHO (Pulmonary Embolism International Thrombolysis Trial) is the largest randomized controlled trial comparing anticoagulation plus ST with tenecteplase *versus* anticoagulation alone on all-cause mortality, or hemodynamic collapse within 7 days of randomization.[26] ST impacted the primary outcome (2.6% *versus* 5.6%; p=0.015), with the majority of the benefit driven by a lower incidence of hemodynamic collapse. However, these benefits of ST were countered by increased major bleeding. Furthermore, it failed to show a significant influence on mortality at 7 days. Subsequent meta-analysis demonstrated modest mortality rate reduction with ST use in intermediate-risk PE in comparison with anticoagulant therapy, at the expense of increased rates of major bleeding and ICH.[23] ST usage in intermediate-risk PE has demonstrated modest mortality reduction compared to anticoagulant therapy, albeit at the cost of higher risks of severe bleeding and ICH, according to a subsequent meta-analysis.[23] Persistent concern over the risk of ICH, which approaches 2% in clinical trials,[26] and 3% to 5% outside of clinical trials,[4,27] has resulted in lack of enthusiasm for full-dose ST, and has motivated for the development of alternative systemic thrombolytic strategies with reduced bleeding risk.

One alternative strategy has focused on alteplase 50mg intravenous, over 2 hours, compared with the regimen of 100mg intravenous, over 2 hours. This strategy was investigated in two randomized trials comparing its safety and effectiveness with anticoagulation alone and full-dose thrombolysis, but failed to provide definitive evidence of the improved safety profile. However, both studies demonstrated significant improvements in surrogate endpoints of RV performance.[28,29]

Current evidence fails to support the routine use of ST in unselected intermediate-risk patients with PE. Given concerns over treatment efficacy with anticoagulation alone, studies evaluating CDL for intermediate-risk PE have emerged in recent years.

CATHETER-DIRECTED THROMBOLYSIS

Catheter-directed thrombolysis involves the direct injection of pharmacologic thrombolytic agents into the pulmonary artery vasculature, with the goals to achieve similar or improved effectiveness compared to ST, and to reduce the rate of ICH. A multisided hole infusion catheter is used to deliver a significantly reduced dose of thrombolytic drug straight into the thrombus.[22] Thrombolytic doses of approximately one-fourth of those typically administered systemically have been reported in the majority of publications[15,30] on CDL, although the optimal dosing strategy is being actively investigated.[31] In addition, CDL aims to circumvent a limitation of ST, in which blood may be shunted toward unobstructed pulmonary artery segments rather than those with thrombus.[32]

Two commonly used non-ultrasound-assisted CDL catheters are UniFuse™ (AngioDynamics Inc, Latham, New York, United States) and Cragg-McNamara™ (ev3 Inc, Plymouth, Minnesota, United States) catheters. Typically, 4 or 5F catheters, with infusion lengths of 5 to 10cm, are advanced to a position within pulmonary thrombus.[22]

A specialized dual lumen ultrasound-assisted EKOSonic™ endovascular system (EKOS Corp, Bothell, WA) may be used instead of these simple infusion catheters. One lumen emits high-frequency, low-energy ultrasound, whereas the other allows local thrombolysis through multiple ports along its length. Low-energy ultrasound permits more effective thrombolysis at lower doses by facilitating the dissociation of fibrin strands, ultrastructure to thrombolytic binding.[32] These catheters may be placed in one or both PAs. This system allows a gradual targeted infusion of thrombolytic typically over 12 hours. However, newer evidence suggests that a shorter timescale of 2 to 4 hours may be equally beneficial.[33] Ultrasound-aided thrombolysis theoretically has the potential to be more successful in penetrating the thrombolytic agent than standard CDL.

Catheter-directed thrombolysis is not routinely used in PE with intermediate-risk because of insufficient evidence. Nonetheless, there may be a minority of individuals with intermediate risk of PE who might benefit from CDL treatment.

CATHETER-DIRECTED EMBOLECTOMY

Catheter-directed embolectomy is based on mechanical thrombus disruption and removal to decrease thrombotic burden. It should be considered in those with persistent hemodynamic compromise despite thrombolytic therapy, or in those who have contraindications to thrombolytics.[14] Extracorporeal membrane oxygenation or percutaneous RV support are two options for mechanical circulatory support that may be beneficial to these patients.[34]

Mechanical circulatory support can be instituted to serve as a bridge to more definitive treatment, such as CDL, catheter-directed embolectomy, surgical embolectomy, or as

a bailout hemodynamic deterioration during procedure. Thrombi in the central, lobar, or interlobar arteries should be the targets of embolectomy, and anything more distal is unlikely to benefit due to difficulty in catheter navigation into smaller vessels. Due to a dearth of evidence and the lack of a standard approach to catheter-directed embolectomy, a multidisciplinary team may be effective in selecting patients for this therapy.[35] There have been a number of catheter-based embolectomy devices tested for the restoration of pulmonary perfusion in acute PE.

Catheter directed thrombus maceration

A pigtail catheter with a guidewire extending from a side hole of the pigtail loop is rotated to break down fresh thrombus into tiny fragments, so that they can be embolized downstream and allow forward flow. The same purpose could be achieved with peripheral balloons as well. Thrombus maceration may be useful in PE with hemodynamic compromise and totally occluded proximal branches, to allow forward flow and partially decompress the right ventricle until further treatment, such as local thrombolysis ensues.[36] Fragmentation has not been shown to be beneficial on its own, since most documented cases were done in conjunction with thrombolytic therapy.[36]

Rheolytic thrombectomy

This technology utilizes a vacuum and thrombus maceration effects, created by high-speed saline jets that travel backward, from the tip of the catheter. It can also provide pulse delivery of thrombolytic agents when embedded in the thrombus. In view of high incidence of procedure-related complications (hemoptysis from presumed pulmonary hemorrhage, major hemorrhage at access and non-access site locations) this device should be avoided.[37]

FlowTriever

The FlowTriever system (Inari Medical, Irvine, California, United States) makes use of large bore femoral venous access (20 to 24 F), with an aspiration guiding catheter positioned near the thrombus. Using the aspiration guiding catheter, a negative suction is created to remove the clot. If the clot is larger or more chronic, several aspirations may be necessary. This device also has the additional benefit of combining aspiration clot removal with a mechanical mechanism. A catheter consisting of three nitinol disks can be passed through the aspiration guiding catheter and deployed within or distal to the clot. Retraction of the disks combined with aspiration allows for removal of more organized or distal clot. Intermediate-risk patients with proximal PE and RV/LV ratio of 0.9 or higher were incorporated in the prospective, single-arm, multicenter FLARE (FlowTriever Pulmonary Embolectomy Clinical Study). The mean RV/LV ratio fell from a baseline value of 1.53 to 1.15 at 48 hours post-procedure ($p<0.0001$). Median intensive care unit length of stay was 1 day, and overall median length of hospital stay was 3 days. The rate of the safety endpoint, major adverse events at 30 days, was 3.8%.[38]

AngioVac

AngioVac (Angiodynamics, Inc., Latham, New York, United States) is an extracorporeal veno-venous bypass system, designed with a filter for *en-block* suction thrombectomy.[39,40] The design includes extracorporeal filtration of intravascular debris utilizing a funnel shaped inflow tip to engage intravascular thrombi, and a reinfusion catheter to mitigate blood loss. The major disadvantages of this device are its bulk, rigidity, and dependence on a perfusion team. Data on its utilization in the field of PE is limited.

Indigo® thrombectomy system

The Indigo® System (Penumbra, Inc., Alameda, California, United States) is a flexible 8-F small-bore aspiration catheter, which is connected to a continuous suction vacuum system. A wire separator is slid back and forth at the catheter tip to clear clot and aid in aspiration of thrombus. The small size and convenience with which the Indigo® system can be delivered to the pulmonary arteries are two advantages. However, the aspiration can result in substantial blood loss, and that the catheter caliber may not be large enough to effectively perform embolectomy on larger, central thrombi. To limit blood loss, the catheter is usually placed more distally, closer to the clot, and aspiration is performed by slowly pulling back while visualizing the amount of blood flowing into the canister. Indigo® aspiration system was associated with a significant reduction in the RV/LV ratio, and a low major adverse event rate in submassive PE patients, in the EXTRACT-PE trial.[41]

CONCLUSION

Acute pulmonary embolism has traditionally been managed with systemic thrombolysis and anticoagulation. Even though anticoagulation is still the first line of treatment for pulmonary embolism, catheter-based treatments are quickly emerging to meet an unmet clinical need. Risk of bleeding outweighs the advantages of systemic thrombolysis in many instances. Catheter-directed thrombolysis may have a lower risk of bleeding despite similar efficacy, but the data remains scarce. Catheter-directed embolectomy may be appropriate for patients with absolute contraindications to thrombolytic therapy, or those who require rapid thrombus removal. In the future, catheter-directed pulmonary embolism reperfusion therapy may be preferable for both high and intermediate-high risk PE treatment.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: DD; data collection: DD, RM, YPM, MK and BM; data interpretation: DD, RM, YPM, MK and BM; text writing: DD; approval of the final version to be published: DD, RM and NA.

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