Interventional Treatment of Pulmonary Embolism

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Abstract—Pulmonary embolism (PE) is a serious and prevalent cause of vascular disease. Nevertheless, optimal treatment for many phenotypes of PE remains uncertain. Treating PE requires appropriate risk stratification as a first step. For the highest-risk PE, presenting as shock or arrest, emergent systemic thrombolysis or embolectomy is reasonable, while for low-risk PE, anticoagulation alone is often chosen. Normotensive patients with PE but with indicia of right heart dysfunction (by biomarkers or imaging) constitute an intermediate-risk group for whom there is controversy on therapeutic strategy. Some intermediate-risk patients with PE may require urgent stabilization, and ≈10% will decompensate hemodynamically and suffer high mortality, though identifying these specific patients remains challenging. Systemic thrombolysis is a consideration, but its risks of major and intracranial hemorrhages rival overall harms from intermediate PE. Multiple hybrid pharmacomechanical approaches have been devised to capture the benefits of thrombolysis while reducing its risks, but there is limited aggregate clinical experience with such novel interventional strategies. One method to counteract uncertainty and generate a consensus multidisciplinary prognostic and therapeutic plan is through a Pulmonary Embolism Response Team, which combines expertise from interventional cardiology, interventional radiology, cardiac surgery, cardiac imaging, and critical care. Such a team can help determine which intervention—catheter-directed fibrinolysis, ultrasound-assisted thrombolysis, percutaneous mechanical thrombus fragmentation, or percutaneous or surgical embolectomy—is best suited to a particular patient. This article reviews these various modalities and the background for each. **(*Circ Cardiovasc Interv*. 2017;10:e004345. DOI: 10.1161/CIRCINTERVENTIONS.116.004345.)**

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Acute thromboembolic occlusion of a coronary, cerebral, or peripheral artery mandates definitive prompt intervention to open the vessel and restore downstream blood flow. This paradigm evolved over the 1970s to 1990s as endovascular interventional options were developed and proven with thousands of patient-years of outcome data, such that the standard of care, for example, in ST-segment–elevation myocardial infarction advanced from thrombolytic medications to primary percutaneous coronary intervention. In contrast, management paradigms for acute occlusion of the pulmonary artery—pulmonary embolism (PE)—are less agreed on. Confounding this lack of consensus is the evolution of many mechanical and hybrid pharmacomechanical options. PE management, relative to acute coronary syndrome, is beset by a paucity of clinical and outcome data, with treatment guided generally by expert consensus and case series.[1] The goals of this article are to discuss interventional therapies for PE, with reference to how an interventionalist might risk-stratify and select candidate patients, and review emerging data and devices for each type of interventional strategy.

Pulmonary Embolism: Background

PE is the third most common cause of vascular disease in the United States, trailing myocardial infarction and stroke. The intensity and invasiveness of treatments for PE are generally commensurate with the severity of its hemodynamic, cardiac, and respiratory consequences. However, there is no globally accepted risk-stratification scheme for classifying severity of PE. Three professional society statements—from the American Heart Association,[2] American College of Chest Physicians,[3] and European Society of Cardiology[4]—encapsulate contemporary thinking and principles of risk stratification for PE, primarily based on hemodynamic consequences and right ventricular (RV) dysfunction.

Patients with acute PE may present on a spectrum from sudden cardiac arrest or death at one extreme to incidental clots without hemodynamic insult or cardiopulmonary dysfunction (Figure).[2] Some 40% of patients inhabit the latter low-risk category and suffer minimal PE-related mortality or morbidity.[5] Accordingly, conservative management with anticoagulation alone is standard (though surveillance may be considered in subsegmental PE with low risk for clot recurrence and no proximal deep vein leg thrombosis).[3,6] In contrast, 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 positively impact the elevated mortality and morbidity. The exact epidemiology of severe PE is likely unknown because the fraction of out-of-hospital fatalities attributable to PE versus

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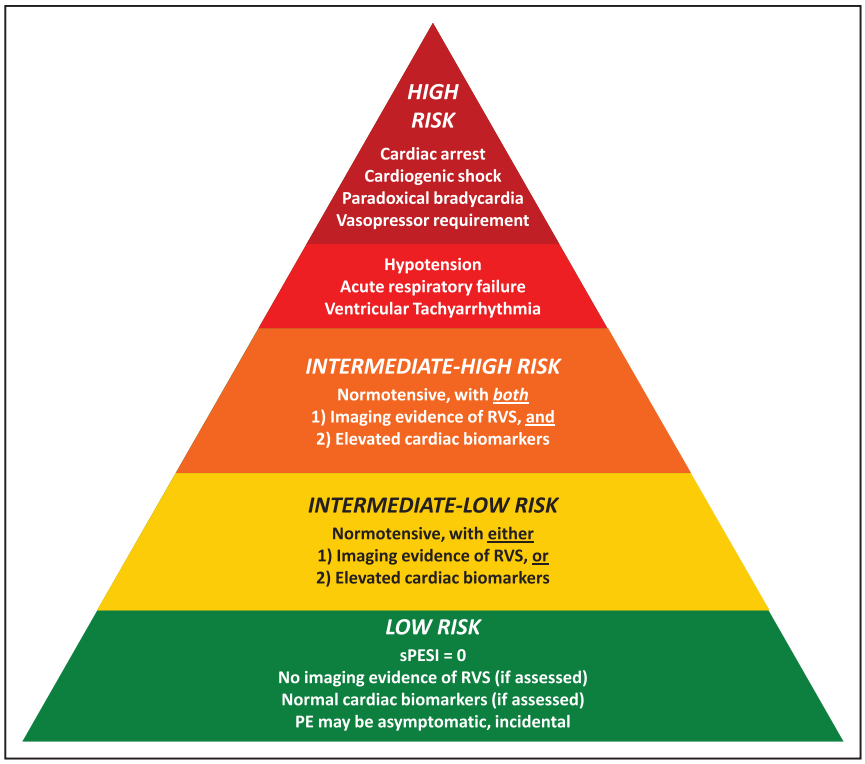

Figure. Risk stratification of PE. Patients with PE are risk stratified based on hemodynamic consequences and indicia, including biomarker and imaging evidence of RVS. The highest-risk patients with PE have acute deterioration because of PE, including cardiac arrest or cardiogenic shock. Other phenotypes that convey higher-risk PEs include paradoxical bradycardia, ventricular tachycardia, and relative hypotension (SBP<90 mm Hg). Normotensive patients with PE may be stratified to an intermediate risk by elevated cardiac biomarkers (troponin and natriuretic peptides) or CT or echocardiographic evidence of RVS (right ventricular dilatation, interventricular septal bowing, and on echocardiography, right ventricular systolic dysfunction). Low risk is defined by absences of hemodynamic sequelae, biomarker elevation, and RVS, and low scores on prognostic indices. CT indicates computed tomography; PE, pulmonary embolism; RVS, right ventricular strain; SBP, systolic blood pressure; and sPESI, simplified pulmonary embolism severity index.

other etiologies (myocardial infarction or acute aortic syndromes) remains difficult to quantify.

The majority of patients with PE fall between these extremes, and various parameters have been devised to assess risk in this normotensive subgroup (Figure).[6,7] Radiographic measures of clot burden by computed tomography (CT) have not correlated with mortality and outcomes.[8,9] Most stratification systems use a composite of factors to assess overall RV strain (RVS).[2,4] Biomarkers provide evidence of myocardial necrosis or RVS by troponin or natriuretic peptides, respectively. Echocardiography assesses RV dilatation, global and local RV systolic dysfunction, tricuspid regurgitation, and interventricular septal bowing.[2,10] CT scanning, commonly performed for diagnosing PE, can provide data on some RVS parameters, particularly RV dilatation and septal geometry.[11] Certain electrocardiographic changes, for example, T wave inversions in early precordial leads, may constitute RVS.[2,12] Patients with PE who are normotensive but manifest at least one factor indicating RVS are considered to have an intermediate-risk PE (submassive in American Heart Association Scientific Statement). After the PEITHO trial (Pulmonary Embolism Thrombolysis),[13] updated European Society of Cardiology guidelines delineated an intermediate–high-risk category: normotensive patients with acute PE with both biomarker and imaging evidence of RVS, distinguished from intermediate–low-risk with either the biomarker or imaging element (Figure). Although guidelines focus on results of biomarker and imaging testing for risk stratification in intermediate PE, because there is not a consensus algorithm, clinicians often integrate additional information, including degree of tachycardia, rest and exertional hypoxemia, and preexisting cardiopulmonary reserve, to judge where on the wide spectrum an intermediate-risk PE patient truly fits.[6,14] Imaging studies for risk stratification moreover may reveal thrombus-in-transit in the right heart, which does not fit clearly within this risk stratification and yet may require prompt intervention.[15] There is a paucity of data on thrombus-in-transit and, therefore, controversy on whether thrombolysis or percutaneous or surgical embolectomy is appropriate therapy.[2,4,15–17]

All-cause mortality in intermediate-risk PE has been reported to be ≈1.9% to 2.9% at 7 days, 4.9% to 6.6% at 30 days, and 14.5% at 90 days.[18,19] In contrast, the PEITHO trial, which randomized >1000 patients with intermediate–high-risk PE, revealed mortality of ≈1.5% at 7 days and ≈2.8% at 30 days.[13] Such mortality estimates directly impact decision-making, in that invasive options may engender periprocedural risks. Overall, positive predictive value of RVS for hemodynamic deterioration or treatment escalation is not sufficient to justify invasive therapy for all submassive PE.[6] However, some patients with submassive PE may need urgent therapy for stabilization, and ≈10% of initially normotensive patients with PE with evidence of RVS precipitously decompensate, with mortality approaching 50%.[20] Unfortunately, predictors to prospectively identify this subgroup at risk of deterioration remain elusive and require further study.[6]

PE Response Teams

Because risk stratification is imperfect, optimal therapy for high-risk and intermediate-risk PE is not defined, experience with novel interventions in PE remains limited, and potential interventional therapies span multiple specialties (cardiology, radiology, and surgery), many hospitals have instituted PE Response Teams (PERT) to generate a consensus diagnostic opinion and treatment plan.[1,15,21,22] Such teams are analogous to evaluations of stroke patients[23] and

combine principles of Rapid Response and Heart Teams.[15,24] PERT functions akin to a Rapid Response team, with a protocol-based plan to activate and convene specialists for the sick patient. Like a Heart Team, PERT mobilizes expertise of diverse disciplines, including interventional cardiologists and vascular specialists, surgeons, echocardiography and radiology, and pulmonary and critical care physicians. PERT melds multiple perspectives together to form the clinical gestalt that informs real-time risk stratification. A PERT model is designed to generate a single collaborative plan for the patient at the important clinical decision point and evaluate specific, even novel, interventional therapies as applied to a patient even in the absence of robust clinical trial data.[1,14,22]

Interventional Therapies for PE

Intervention on an occluded pulmonary artery theoretically promises more complete and earlier recanalization for restoration of distal flow. Ventilated, but not perfused, lung constitutes dead space, so recanalization improves oxygenation by correcting V/Q mismatch. Recanalization reduces effective pulmonary vascular resistance, which decreases hemodynamic burdens on the RV, and allows the RV to provide sufficient preload to the left ventricle to maintain cardiac index. Multiple possible interventions (Table 1) are available for acute PE, and the goal of this article is to review some existing and nascent options available to interventionalists.

Systemic Thrombolysis

Benefits of systemic thrombolysis (ST) accrue from rapid recanalization of the pulmonary artery, with corresponding improvements in pulmonary pressures, RV function, ventilation/perfusion mismatches, and overall hemodynamics.[2,4,25] Although ST achieves these benefits more rapidly when compared with systemic anticoagulation, physiological benefits of anticoagulation (reduced pulmonary pressures and RV dilatation) are similar within days.[2,26,27] Because of this catch-up phenomenon, and higher bleeding risks of thrombolytics compared with anticoagulation, the cardiologist must use risk stratification to identify those patients who may experience clinical deterioration and for whom the potential earlier benefit of thrombolytics justifies higher risk. Additionally, ST has the most benefits if administered within 1 to 2 days of embolism, so that the clot is not impervious to thrombolysis (note, guidelines allow for thrombolysis ≤2 weeks after symptom onset).[4]

Analogously to acute ischemic stroke and myocardial infarction, ST carries numerous contraindications and implies multiple systemic risks, which must be juxtaposed with the risk of the PE. In high-risk PE, ST is generally accepted as first-line therapy because of the gravity and acuity of the PE.[2,4] ST is administered via peripheral intravenous access and can be administered more rapidly in most healthcare settings compared with other specialized invasive procedures that require mobilization of equipment and teams. In the highest-risk scenarios, such as cardiac arrest because of PE, ST can be given as a single bolus: studied regimens have included alteplase 100 mg over 15 minutes and 50 mg over 1 minute.[28,29] These differ from typical administration of alteplase as an infusion of 100 mg over 2 hours.[2]

In intermediate-risk PE, the specific role of ST remains under scrutiny. Several trials have demonstrated improvements in surrogate outcomes, including RV function, pulmonary artery pressures, and clinical decompensation.[25] PEITHO aimed to test the benefit of ST (single bolus weight–based tenecteplase) in a stratum of normotensive yet intermediate–high-risk patients with both laboratory evidence of myocardial necrosis (elevated troponin) and imaging evidence of

Table 1. Comparison of Key Features of Treatment Modalities

Treatment	Administered by	Time to Initiate	Major Benefits	Major Detriments
Systemic anticoagulation	All practitioners	Minutes	Ease, inexpensive	Treatment failure. Time to effect. Limited data on novel oral anticoagulants in intermediate-risk PE
ST	All practitioners	Minutes	Rapid initiation of reperfusion without specialized equipment	Intracranial and other major bleeds
CDF	Interventionalists*	Minutes to hours	Hybrid mechanical and pharmacological approach	Lack of randomized data. Specialized expertise required
USAT	Interventionalists	Minutes to hours	Lower dose of thrombolytic required	Specialized expertise required
Percutaneous thrombectomy	Interventionalists	Minutes to hours	En bloc removal of thrombi	Specialized expertise required, large bore access. May not reach distal thrombi
Surgical pulmonary embolectomy	Cardiothoracic surgeons	Minutes to hours	Comprehensive proximal thrombectomy	Sternotomy. Specialized surgical expertise required
Caval filters	Interventionalists	Minutes to hours	Aim to prevent further thrombus migration, avoid anticoagulation	Multiple late mechanical complications, because of failures to monitor and to retrieve the filter

CDF indicates catheter-directed fibrinolysis; PE, pulmonary embolism; ST, systemic thrombolysis; and USAT, ultrasound-assisted catheter-directed thrombolysis.

*The term interventionalist is chosen so as to encompass physicians of many backgrounds who treat PE, including interventional cardiologists, interventional radiologists, vascular medicine specialists, and vascular surgeons.

RVS (echocardiography or CT).[13] The primary composite outcome of 7-day all-cause mortality or clinical deterioration was significantly reduced by ST (2.6% versus 5.6%, odds ratio 0.44; *P*=0.015), but this outcome was primarily driven by 3-fold reduction in clinical deterioration (1.6% versus 5.0%; *P*=0.002), with statistically similar all-cause 7-day mortality (1.2% versus 1.8%; *P*=0.43). Notably, 4.6% of patients in the placebo arm, compared with 0.8% in the tenecteplase arm, required open-label rescue thrombolysis; this may have underestimated the observed benefit of thrombolysis. A meta-analysis of ST trials, to which PEITHO contributed more than half of patients, demonstrated reduced mortality in intermediate-risk PE (odds ratio, 0.48; 95% confidence interval, 0.25–0.92) but a modest absolute risk reduction (number needed to treat of 65 to prevent 1 fatality).[30]

The benefit of ST in preventing hemodynamic deterioration must be juxtaposed against its major risks of intracranial hemorrhage—≈2% to 3% in PEITHO and other studies[31]—and other major (nonintracranial) hemorrhages. Meta-analysis data identified an overall intracranial hemorrhage rate of 1.46% with ST versus 0.19% with anticoagulation (odds ratio, 4.63; 95% confidence interval, 1.78–12.04), corresponding to a number needed to harm of 79.[30] There is a 3-fold increased risk of major bleeding in patients ≥65 years.[30]

These rates of intracranial and other hemorrhage associated with ST have limited widespread use, even in acute severe PE.[15,19,32,33] American College of Chest Physicians guidelines advise clinicians to use aggressive anticoagulation in intermediate–high-risk PE and withhold thrombolysis unless evidence of clinical deterioration manifests.[3] Other interventional approaches that aim to achieve hemodynamic and pulmonary benefits of thrombolysis, while mediating the risks, are being investigated. Reduced-dose thrombolytic regimens represent 1 idea: a single-center trial of moderate PE (defined by thrombus burden) evaluated half-dose thrombolytic without interrupting concurrent parenteral anticoagulation (as is typically done with full-dose thrombolytic).[34] That study reported similar efficacy as full-dose thrombolytic in terms of pulmonary artery pressure reductions, with similar safety and no increased bleeding despite continuing parenteral anticoagulation.[34] The necessary dose of thrombolytic might also be reduced by local, as opposed to systemic, delivery. Moreover, combining local thrombolytic delivery with a mechanical intervention—pharmacomechanical strategies—may provide synergistic benefits.

Catheter-Directed Fibrinolysis

Local delivery of thrombolytic agents—catheter-directed fibrinolysis (CDF)—has been an area of increasing interest. Navigation of a catheter physically through an obstructive pulmonary artery thrombus creates a channel for drug delivery and increases the surface area of thrombus exposed to thrombolytic agent.[35,36] CDF tries to overcome a limitation of peripherally infused ST, whereby blood is shunted toward the unobstructed pulmonary artery segments rather than those with thrombus; in vitro and in vivo models demonstrate eddy currents in the main pulmonary arteries that shunt blood flow away from thrombotically occluded arteries.[37] The promise of CDF lies in a potential increase in thrombolytic efficacy, coupled with improved safety profile and reduced off-target major and intracranial hemorrhages, because of the local administration and potential for reduced thrombolytic dosing compared with ST. Unfortunately, no controlled studies have been performed comparing CDF to ST in PE, and CDF has been compared with isolated anticoagulation in limited investigations and registries.[38,39]

Two commonly used CDF catheters are Uni-Fuse (Angiodynamics Inc, Latham, NY) and Cragg-McNamara (ev3 Inc, Plymouth, MN) catheters (Table 2). Both are approved by the Food and Drug Administration (FDA) for infusion of thrombolytics into the peripheral vasculature, without specific indication for PE. Operators generally use 4- to 5-French catheters with an infusion length of 5 to 10 cm depending on clot burden as visualized on concurrent pulmonary angiography or preprocedure CT. Minimal clinical outcomes data exist regarding specific utilization of these products for treatment of PE.

Ultrasound-Assisted Catheter-Directed Thrombolysis

Unlike the aforementioned 2 catheters, the EkoSonic endovascular system (EKOS Corporation, Bothell, WA) contains 2 lumens. One houses a filament with multiple ultrasound transducers that emit low-energy ultrasound, whereas the other allows for local thrombolytic delivery through multiple ports along its length. Low-energy ultrasound dissociates fibrin strands, theoretically allowing for more effective thrombolysis at lower doses by opening clot ultrastructure to thrombolytic binding.[40] Catheters may be placed in one or both pulmonary arteries. This platform allows a gradual targeted infusion of thrombolytic over 12 to 24 hours, with an average alteplase dose of 1 mg/h (≈20 mg total). Contrasted to bolus ST, should bleeding complications arise, the infusion can be stopped.

Two prospective evaluations of the ultrasound-assisted catheter-directed thrombolysis (USAT) catheter have been undertaken. ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) randomized 59 patients with intermediate-risk PE to USAT versus heparin anticoagulation.[41] Patients in the USAT arm showed significant improvement in the primary end point of echocardiographic RV/left ventricular (LV) ratio at 24 hours (ΔRV/LV ratio −0.30±0.019 versus −0.03±0.016; *P*<0.001). Significant catch-up was observed in the anticoagulation group, with a marked, albeit more gradual improvement in the RV/LV ratio. The 90-day difference between the 2 arms' RV/LV end point was statistically insignificant (−0.35±0.22 versus −0.24±0.19; *P*=0.07), suggesting an early benefit to USAT, but that heparin-treated patients who did not decompensate early might accrue similar long-term results.[41]

The prospective, single-arm multicenter SEATTLE-II study (A Prospective, Single-Arm, Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) served as primary data supporting FDA 510(k) clearance of the EKOS catheter as a therapeutic device for acute PE.[42] SEATTLE-II enrolled 150 patients with intermediate- or high-risk PE (80% intermediate risk) and demonstrated significant reductions in CT-based RV/LV ratio and pulmonary artery pressures 48

Table 2. Comparison of Available Endovascular Devices for PE

Device	Mechanism	Technical Considerations	Regulatory Status in United States
EkoSonic	USAT	5-French catheter	510(k) clearance for marketing in acute PE
Unifuse	CDF	4- to 5-French catheter	510(k) clearance for treatment of peripheral vasculature
Cragg-McNamara	CDF	4- to 5-French catheter	510(k) clearance for treatment of peripheral vasculature
Angiovac	Veno–veno bypass. Funnel-shaped inflow tip to engage thrombi	26-French access for inflow, 16 to 20-French access for outflow. Requires perfusion team	510(k) clearance for removal of undesirable intravascular material
Flowtriever	Nitinol discs engage and mechanically retrieve clot with simultaneous aspiration	20-French catheter. Must manage blood loss associated with large bore aspiration	510(k) clearance for peripheral thrombectomy. Investigational device exemption study for PE
Indigo System	Mechanical clot engagement with mechanized aspiration	8-French catheter. Large size of some proximal PE renders en bloc aspiration difficult with 8 French device	510(k) clearance for peripheral thrombectomy
AngioJet	Rheolytic thrombectomy with option of thrombolytic vs saline spray	Hypotension and bradycardia	510(k) clearance for peripheral thrombectomy. Black box warning for use in pulmonary arteries

CDF indicates catheter-directed fibrinolysis; PE, pulmonary embolism; and USAT, ultrasound-assisted catheter-directed thrombolysis.

hours after USAT. In the 180 patients treated in these 2 prospective studies, patients suffered a total of 16 bleeding complications (8.9%), notably with zero instances of intracranial hemorrhage; this potential advantage over ST remains to be confirmed with larger, prospective, and randomized data series. Possible reasons for this advantage include the lower overall dose of thrombolytic used with USAT and ability to discontinue the thrombolytic infusion.

Notably, there has been no analysis comparing use of USAT to CDF alone in the pulmonary arteries. However, a trial randomizing patients with acute lower extremity deep venous thrombosis (DVT) to therapy with the USAT catheter with the ultrasound modality activated versus inactivated did not find significant differences in early thrombotic resolution, 3-month primary venous patency, or 3-month symptomatic post-thrombotic syndrome rates.[43] Thus, additive benefits of ultrasound assistance to local delivery of thrombolytics remain speculative.

Percutaneous Mechanical Intervention, Disruption, and Removal of Thrombus

A host of techniques have been used for mechanical disruption or aspiration of PE. Most reports have focused on patients with PE associated with hypotension who were not candidates for ST, either because of concerns about hemorrhagic complications or because of prolonged time necessary for an ST infusion to improve hemodynamics in a critically ill patient.[44,45] Wire disruption, balloon fragmentation, and a rotating pigtail catheter over a wire have all been used to mechanically fragment proximal PE. Sending fragmented thrombus into the distal pulmonary vasculature may still decrease overall pulmonary vascular resistance and RV afterload because of the greater distal cross-sectional area. This process also renders clot fragments more likely to undergo thrombolysis via endogenous pathways or adjunctive pharmacological therapy.

Although these reports confirm the feasibility of such approaches for therapy of high-risk PE, the absence of controlled investigations makes it difficult to draw conclusions regarding comparative efficacy of these techniques to alternative therapeutic measures, including isolated anticoagulation, isolated ST, or surgical embolectomy. Additionally, despite the physiological rationale for mechanical disruption, several reports exist of worsening hemodynamic status.[46,47] All of these procedures require expertise to work within the right heart and proximal pulmonary arterial tree and ability to manage dysrhythmias, cardiogenic shock, and perforations and dissection.

A variety of devices designed for thrombectomy in the peripheral vasculature have been repurposed for use in the pulmonary arteries. The biggest limitation of these devices has been the significantly greater lumen of the pulmonary artery and correspondingly larger clot burden compared with other peripheral vessels. Until recently, few attempts had been made to design percutaneous devices that specifically addressed this issue.

Rheolytic Thrombectomy

The AngioJet (Boston Scientific, Minneapolis, MN) uses high-pressure jets at the tip of a catheter, which creates a lower-pressure zone just behind these jets.[48] As the catheter is advanced, the high-pressure jets disrupt thrombus and allow for its aspiration in the low-pressure zone. Notably, the catheter can be used to spray saline or thromobolytic agents into the clot, allowing local, aggressive thrombolysis of the pulmonary arteries. Published reports of AngioJet for treatment of PE have all been uncontrolled case series, with the largest reporting on 50 patients.[49] Although many series have reported

procedural and clinical success, notable complications of the AngioJet procedure have included bradycardia, hypotension, hypoxia, and hemodynamic collapse.[50] These ill effects are thought to be driven by release of vasoactive agents, such as adenosine and bradykinin, into the pulmonary vasculature as AngioJet runs are performed through acute thrombus.[51,52] Concerns about these complications in the absence of rigorous evidence for this indication led to a black box warning for use of AngioJet in the pulmonary circulation.[44]

Aspiration Thrombectomy

The Aspirex catheter (Straub Medical, Switzerland) is an 11-French device that aspirates thrombus through a flexible catheter tip. The catheter shaft contains a high-speed rotating coil, which creates negative pressure for aspiration and also serves to macerate clot that is brought into the catheter. Two European case series have been reported, with complete thrombus clearance observed in 83% to 88% of patients with intermediate- and high-risk PE.[53,54]

The Indigo Thrombectomy System (Penumbra, Inc, Alameda, CA) is an aspiration catheter designed to engage clot and extract it with a continuous vacuum pump. The catheter comes in multiple sizes, but only the smallest sizes have thus far been tested in any clinical investigations.[55] The larger size (8 French) may be applicable to the pulmonary arteries, though no reports have yet been published of this use.

The Angiovac cannula (Angiodynamics, Inc, Latham, NY) is a veno–veno bypass system designed to remove intravascular material via en bloc suction thrombectomy. This veno–veno bypass circuit is initiated with a filter between the inflow and outflow cannulae to trap unwanted intravascular material. The inflow cannula is a 22-French suction catheter, accessed via femoral or internal jugular veins, featuring a funnel tip to engage intravascular material, including thrombi. The outflow cannula (16- to 20-French size, at the operator's discretion) returns blood to the body via a separate femoral or internal jugular vein. The device has been used in a variety of circumstances, including removal of iliocaval clot, tricuspid valve vegetations, and thrombus-in-transit.[56,57] PE removal has also been reported, though it seems to represent the minority of cases performed with this device (4 of 30 reported cases), in part because of difficulty steering large cannula into pulmonary arteries. The latest generation has design improvements, allowing better navigation of the RV outflow tract by the large bore cannula to attempt to specifically treat PE. Similar to other devices for PE, no comparative effectiveness data exists for use of this device.

Mechanical Thrombectomy

The recently developed Flowtriever (Inari Medical, Irvine, CA) catheter is a large-bore device that mechanically engages thrombus in the pulmonary arteries through deployment of 3 self-expanding nitinol discs. Because the discs are retracted back into the catheter with entrapped thrombus, synchronous aspiration is performed through the catheter with a goal to remove thrombus en bloc from the pulmonary arteries without the use of adjunctive thrombolytics. Currently, a single-arm 150-patient FDA investigational device exemption study is enrolling to assess safety and efficacy of Flowtriever in the pulmonary arteries (FLARE [FlowTriever Pulmonary Embolectomy Clinical Study], http://www.clinicaltrials.gov: NCT02692586).

Other devices used in the past in the pulmonary arteries for mechanical thrombectomy include the Amplatz Thrombectomy Device (ev3 Inc) and the Greenfield device (Boston Scientific). Both fell out of favor because of device bulkiness and rigidity, rendering them challenging to use percutaneously in the pulmonary arteries.

Surgical Pulmonary Embolectomy

Surgical pulmonary embolectomy was once reserved as salvage therapy for patients in extremis, and accordingly outcomes appeared poor because of a selection bias.[21,58] Surgical embolectomy is nevertheless reemerging for treatment of high-risk and certain intermediate–high-risk PE, especially if other methods (thrombolysis) are contraindicated or ineffectual, and the patient has relatively low surgical risks.[4,59,60] Two recent studies suggest in-hospital mortality rates 6.6% to 11.7% based on high- and intermediate-risk PE cohorts,[61,62] with a third reporting overall 4.6% 30-day mortality.[63] Surgical pulmonary embolectomy can be particularly useful for patients with extensive proximal thrombus burden, including thrombus-in-transit and impending paradoxical embolism.[16,17] This technique generally involves median sternotomy access with nonhypothermic cardiopulmonary bypass (though patients could have been supported on antecedent extracorporeal membrane oxygenation [ECMO]) for an approach to extracting thrombi from the bilateral pulmonary arteries under direct visualization.

Vena Cava Filters

Inferior vena cava filters (IVCF), placed in the inferior vena cava (or rarely in the superior vena cava), are nitinol devices that serve to mechanically halt large thrombus from passing through them and into the pulmonary circulation. Although initial iterations of IVCF were designed to remain permanently in the inferior vena cava, nearly all filters placed currently are designed for retrieval when the indication for their use has concluded. There is consensus among guidelines from various professional societies regarding the utility of IVCF in patients with acute venous thromboembolism but who have a contraindication to systemic anticoagulation.[2,3,64] Importantly, these recommendations are based largely on expert consensus, given the paucity of prospective data in this clinical scenario. In practice, IVCF are placed in a much greater array of circumstances,[65,66] which most commonly include patients with venous thromboembolism and impaired cardiopulmonary reserve, as well as PE prophylaxis in scenarios such as severe trauma, neurological injury, burns, or preoperatively.

The proliferation of IVCF use in a variety of clinical conditions raises concerns because these devices are not complication-free. Although acute complications during placement are uncommon, late complications because of failures to monitor and retrieve IVCF are a serious concern. These late complications may include DVT, recurrent PE, post-thrombotic

syndrome, inferior vena cava thrombosis, strut fracture, strut penetration into adjacent anatomic structures, and strut or device migration or embolization.[67–69] The incidence of these complications seems to be related to the IVCF dwell time in observational analyses.[70] Accordingly, FDA issued a statement alerting providers to complications associated with IVCF and encouraging retrieval when the indication for their placement is resolved.[71]

IVCF have been studied in 2 randomized trials. The PREPIC trial (Prevention du Risque D'embolie Pulmonaire par Interruption Cave) randomized 400 patients with proximal DVT to a permanent IVCF plus anticoagulation versus isolated anticoagulation between the years 1991 and 1995.[72] The trial revealed a significant reduction in PE in the IVCF group at 12 days (4.8% versus 1.1%; *P*=0.03), without an associated mortality benefit. At 2 years, patients who received IVCF were more likely to develop symptomatic DVT (20.8% versus 11.6%; *P*=0.02); there was a nonsignificant decrease in clinically evident PE (3.4% versus 6.3%; *P*=0.16) and similar mortality between groups (21.6% versus 20.1%; *P*=0.65). A post hoc analysis including 8 years of follow-up revealed similar results with lower rates of PE but similar mortality and increased DVT rates among patients treated with a permanent IVCF. The PREPIC 2 study included 399 patients with acute PE between 2006 and 2013, randomized to a retrievable IVCF plus anticoagulation, versus isolated anticoagulation.[73] Retrieval was planned for 90 days in the group receiving IVCF, with retrieval ultimately attempted in 82% of patients receiving the device. There were no significant differences in 3-month PE (3.0% versus 1.5%; *P*=0.50) and a variety of 6-month end points, including DVT, major bleeding, or all-cause mortality. No differences were noted in the subgroup of patients with proximal DVT and impaired cardiopulmonary reserve (intermediate-risk PE), though the analysis was underpowered. Overall, existing data and practice supports extremely judicious use of IVCF in acute venous thromboembolism, with careful monitoring and prompt retrieval when they are used.

Mechanical Circulatory Support Options

Emerging data suggest that for PE complicated by cardiogenic shock, ECMO is a useful support: 8 of 17 patients in one single-center series underwent either surgical or percutaneous embolectomy or CDF while on ECMO, with this PE subgroup demonstrating higher rates of survival to hospital discharge than other types of cardiogenic shock patients requiring ECMO.[74] Other types of RV supports, such as Impella-RP (Abiomed, Danvers, MA) and PROTEK-Duo (CardiacAssist, Pittsburgh, PA), face theoretical technical obstacles with placement and operation in acute PE, given these devices require access to the pulmonary artery; PE was an exclusion criteria for the RECOVER-RIGHT Impella-RP trial (The Use of Impella RP Support System in Patients With Right Heart Failure).[75] However, given the novelty of both devices, clinical investigations of their use in PE that verify these concerns have not yet been performed.

ECMO requires significant infrastructure, expert physicians (surgeons, intensivists), and bedside ECMO specialists. ECMO can provide a bridging option after failed ST to stabilize the patient for a short term (days) until the bleeding risks exacerbated by circulating thrombolytic abate. In our experience, PERT discusses whether the patient may require circulatory support at a proximal juncture in the triage and treatment algorithm of high-risk PE (Figure).

Conclusions

Numerous interventional strategies exist for acute PE, but limited trial data are available to guide cardiologists. Risk stratification is the essential first step to tailor PE treatment. For high-risk PE, ST is generally appropriate first-line therapy. When there are prohibitive risks of bleeding or the patient cannot wait for reperfusion from ST to take effect, surgical or percutaneous mechanical thrombectomy may be needed to rapidly stabilize hemodynamics (Figure). Additionally, percutaneous and surgical thrombectomy provide rescue options for failure to improve after ST.

Available data does not support routine use of intervention in intermediate–high-risk PE. ST may be reasonable with lower bleeding risks (eg, aged ≤65 years).[30] The decision to use advanced therapies on a case-by-case basis requires an assessment of latent hemodynamic instability, RV dysfunction, or respiratory compromise[14]; certain patients with an adverse clinical course may merit surgical or percutaneous thrombectomy. For intermediate–high-risk patients who have stabilized but exhibit indicia of marked RVS, USAT and CDF offer theoretical advantages in reducing sequelae of RVS and pulmonary hypertension with lower thrombolytic doses compared with those of ST. At present, EKOS USAT is the only FDA-approved option specifically for percutaneous treatment of PE (Table 2).

PE intervention is an evolving paradigm that may favor more mechanically focused future strategies if high-quality data comparing various modalities substantiates benefits of rapid RV unloading. Until then, PERTs assess competing benefits and risks for individual patients.[21] Future investigations must include cost-effectiveness analyses to juxtapose costs of local expertise and infrastructure versus expected benefit to patients.[6,15]

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