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Rationale for catheter-based therapies in acute pulmonary embolism

M.A. de Winter[1], G.J. Vlachojannis[2], D. Ruigrok[3], M. Nijkeuter[1], and A.O. Kraaijeveld[2]*

[1]*Department of Internal Medicine, UMC Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands;*
[2]*Department of Cardiology, UMC Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; and*
[3]*Department of Pulmonology, UMC Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands*

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Pulmonary embolism (PE) is a common disease resulting in significant morbidity and mortality. High-risk features of PE are hypotension or shock, and early reperfusion is warranted to unload the strained right ventricle and improve clinical outcomes. Currently, systemic thrombolysis (ST) is the standard of care but is associated with bleeding complications. Catheter-based therapies (CDT) have emerged as a promising alternative having demonstrated to be equally effective while having a lower risk of bleeding. Several CDT are currently available, some combining mechanical properties with low-dose thrombolytics. Recent guidelines suggest that CDT may be considered in patients with high-risk PE who have high bleeding risk, after failed ST, or in patients with rapid haemodynamic deterioration as bail-out before ST can be effective, depending on local availability and expertise. In haemodynamically stable patients with right ventricular (RV) dysfunction (intermediate-risk PE), CDT may be considered if clinical deterioration occurs after starting anticoagulation and relative contraindications for ST due to bleeding risk exist. Decision on treatment modality should follow a risk-benefit analysis on a case by case base, weighing the risk of PE-related complications; i.e. haemodynamic deterioration vs. bleeding. As timely initiation of treatment is warranted to prevent early mortality, bleeding risk factors should be assessed at an early stage in all patients with acute PE and signs of RV dysfunction. To ensure optimal management of complex cases of PE and assess a potential CDT strategy, a multidisciplinary approach is recommended. A dedicated Pulmonary Embolism Response Team may optimize this process.

Introduction

Pulmonary embolism (PE) is frequently diagnosed and has a high morbidity and mortality of up to 65% if left untreated.[1] In Europe, its incidence is estimated at around 0.95 per 1000 persons per year.[2] Moreover, PE is a major factor in healthcare expenditure, irrespective of whether it occurs as a complication of an underlying disease, following surgery, or as an isolated event.

According to current guidelines of the European Society of Cardiology (ESC), PE is classified according to haemodynamic parameters and right ventricular (RV) function indices, including elevated levels of circulating biomarkers.[3] While clot burden does not predict outcome in PE,[4] acute RV failure is the primary pathophysiologic mechanism leading to death in acute PE.[5] Mechanical obstruction of the pulmonary vasculature and concomitant vasoconstriction due to release of vasoactive mediators by the endothelium and platelets lead to an acute pressure overload of the non-preconditioned RV. After initial compensatory mechanisms fail, this strain leads ultimately to increase in

*Corresponding author. Tel: +31 88 7571744, Fax: +31 88 7555427, Email: a.o.kraaijeveld-3@umcutrecht.nl

maladaptive dilatation and a vicious circle towards RV failure.[6] This downward spiral is further aggravated by impairment of RV myocardial contractility due to ischaemia and inflammation caused by decreased coronary perfusion in the setting of increased wall stress in addition to increased oxygen demand.[6,7]

In stable patients without signs of RV failure, classified as low-risk PE according to current ESC guidelines, anticoagulation is the cornerstone of treatment. However, patients with signs of acute RV failure and/or haemodynamic instability, classified as intermediate or high-risk PE, have poor outcomes, and early reperfusion may be needed to unload the RV.

Systemic thrombolysis (ST) is the treatment of choice in haemodynamically unstable patients (high-risk acute PE). However, it comes at the cost of an elevated risk of major bleeding.[3,8] Interestingly, in clinical practice thrombolytic therapies—although effective—are used in a minority of high-risk patients, and it seems that concerns for major bleeding complications might be one of the leading factors implicated in this underuse of ST.[5] In patients presenting with intermediate-risk PE, thrombolytic therapy does not play a role, except in case of haemodynamic decompensation.

Next to surgical embolectomy, catheter-based therapies (CDT) have been introduced as an alternative in those high-risk PE patients with contra-indications to systemic full dose-thrombolysis, or after failed ST, with the inherent advantage of low bleeding complications while documenting efficacy by reducing thrombus load thereby unloading the RV. Furthermore, the role of CDT in the treatment of intermediate-risk PE is being studied with increasing frequency. This review will discuss the rationale for CDT use in the treatment of acute PE in different patient risk categories.

Type of catheter-based therapies

All percutaneous CDT ultimately aim at removal of thrombotic obstruction in the pulmonary arteries. Different techniques and several devices are available for CDT, with the most important summarized in *Table 1*. In principle, CDT can be grouped into mere mechanical, pharmacological, and combined approaches. A further in-depth discussion on the background of these therapies is provided in a separate article in the current *EHJ Supplements* issue (by Dr Romain Chopard and colleagues).

The most simplistic approach is catheter-mediated thrombus fragmentation, which is achieved by either rotating a catheter, most commonly a pigtail, or a J-tipped wire in the thrombotic proximal pulmonary artery, aiming to recanalize the vessel by decreasing thrombotic burden which is pushed into the periphery. A similar mechanical approach is angioplasty of the thrombotic pulmonary artery segments using peripheral balloons (most commonly 5–10 mm diameter balloons).

Other techniques target on the removal of thrombus by suction embolectomy. In this group, the most simplistic approach is manual aspiration of thrombus using the catheter. Another technique is the rotational thrombectomy system with combine over-the-wire rotational mechanical clot fragmentation and active thrombosuction aiming to prevent distal embolization. Rheolytic thrombectomy is based on an over-the-wire device which uses the Venturi effect to create a low pressure within the catheter through a high flow saline jet stream, thereby aspirating thrombus which is then evacuated through the exhaust lumen of the catheter.

Importantly, mechanical approaches can be used in conjunction with local thrombolytic application directly in the thrombotic pulmonary artery, which can also be combined with the application of local ultrasound. These techniques apply lower dosages of the thrombolytic agent compared to ST, thereby potentially decreasing the associated bleeding risk.[10]

Catheter-based therapies in high-risk pulmonary embolism patients

Although surgical pulmonary embolectomy is currently considered as a Class I-C indication in the ESC guidelines,[3] societal guidelines suggest that CDT may be considered as an alternative for three subgroups of patients with high-risk PE: (i) patients at high risk of bleeding, (ii) patients with persistent haemodynamic instability after ST treatment ('failed treatment'), and (iii) patients considered at high risk of death before ST can be effective (Class IIa recommendation, Level C evidence).[3,8,11] It is important to note that, although guidelines recommend the use of CDT for patients with high-risk PE only, most available evidence originates from study populations consisting of patients with intermediate-risk PE. This is not surprising, as conducting studies in high-risk PE patients can be challenging, due to the need of immediate treatment, and informed consent issues. Following, the indications for CDT in different high-risk PE subgroups will be discussed.

High risk of bleeding subgroup

Systemic thrombolysis is associated with a risk of major bleeding of up to 20%, including a 2–3% risk of intracranial bleeding.[12,13] Thus, in patients with risk factors for bleeding ST is considered contraindicated. As CDT are associated with a lower risk of major bleeding of ~7% in high-risk PE patients, it is considered an appropriate alternative in this subgroup.[14] To guide patient selection, evaluating the presence of bleeding risk factors prior to starting treatment is warranted. Deciding on treatment for individual patients should be based on a risk-benefit analysis by weighing risk of PE-related complications and haemodynamic deterioration vs. bleeding risk. As most PE-related deaths occur within the first hours after presentation, rapid initiation of treatment is pivotal.[3,8,11] However, assessing risk of bleeding in an acute setting may be challenging since time as well as available information about the patient may be limited.

Both the American College of Chest Physicians (ACCP) and ESC guidelines provide a list of important absolute and relative contraindications prior to administering ST (*Table 2*).[3,8,11] In addition, few studies aimed to identify risk factors for bleeding during or following thrombolytic

Table 1 Techniques and devices for percutaneous catheter-directed treatment of pulmonary embolism

Technique	Device example
Catheter interventions without thrombolysis	
Thrombus fragmentation	Pigtail catheter
	Balloon angioplasty using peripheral balloons
Rheolytic thrombectomy	AngioJet PE® (Boston Scientific, USA)
Suction embolectomy	Manual aspiration using sheath with detachable haemostatic valve (Argon Medical Devices, Athens, TX, USA)
Rotational thrombectomy	Aspirex® thrombectomy
Combined techniques	Pigtail fragmentation (5F) plus AngioJet PE® (Boston Scientific, USA)
Catheter interventions with thrombolysis	
Catheter-directed thrombolysis	UniFuse® (AngioDynamics, Latham, NY, USA)
Ultrasound-assisted catheter-directed thrombolysis	EkoSonic® (EKOS, Bothell, WA, USA)
Pharmacomechanical thrombolysis	AngioJet PE® Power Pulse™ thrombolysis and thrombectomie (Boston Scientific, USA)
Combined techniques	Pigtail fragmentation (5F) plus AngioJet PE® Power Pulse™ thrombolysis and thrombectomie (Boston Scientific, USA)

Adapted from Engelberger *et al.*/ESC guidelines 2019).[3,8,9]

treatment. In previous studies on predictors of bleeding after thrombolytic therapy, the following predictors were identified: female gender, African-American race, multiple sites of invasive procedures (i.e. multiple venous punctures, invasive devices, presence of intra-aortic balloon pump and femoral venous access), high-risk PE, medical history (including acute pancreatitis, aortic dissection, acute myocardial infarction, dementia, cancer, and diabetes), low body weight, elevated bilirubin (>3 mg/dL), and concomitant use of catecholamines.[15,16] Although several bleeding risk scores have been developed for patients with PE and deep venous thrombosis to guide treatment decisions in an outpatient setting, none of these have been validated for the high-risk PE population in the acute setting. In addition, existing scores are currently not recommended by guidelines as their predictive accuracy is moderate and methodological limitations exist.[17]

Aforementioned contraindications and bleeding risk factors can be used to assess an individual patient's risk of bleeding and to guide treatment decisions. While guidelines mention absolute and relative contraindications, all bleeding risk factors can be considered relative in the context of high-risk PE. The risk-benefit balance should be leading in decisions regarding thrombolysis and/or CDT for high-risk PE. The total population of high-risk PE patients is very heterogeneous, comprising everything between mildly hypotensive to patients in cardiac arrest. While both ends of the spectrum require urgent treatment, the latter reflects a critical situation in which everything must be brought into play. In that case, thrombolytic treatment may still be the best option, even when multiple absolute contraindications are present. This emphasizes the importance of individualized decision-making in acute PE. Decisions regarding rescue reperfusion modalities lie in the hands of the treating team of physicians and should be based on individual risk factors and local availability and expertise. The best treatment modality for individual patients can be decided by balancing the number and severity of contraindications, on the one hand, and the severity and urgency of PE on the other hand.

As risk of bleeding associated with thrombolytic therapy is dose-dependent, CDT using lower doses of thrombolytic agent are considered appropriate for patients with relative contraindications.[18] In case of multiple or important absolute contraindications, one may want to refrain from using any thrombolytic agent. In that case, interventional options without the use of a thrombolytic agent can be considered. As always, this depends on local availability and experience.

Next to bleeding complications in general, it is important to take into account risk of intracranial bleeding in particular. With only a low dose of thrombolytic agent administered locally or no thrombolytic agent at all, intracranial haemorrhage (ICH) is a rare complication of CDT.[19] However, as it results in high rates of functional disability and mortality, it can be considered the most devastating complication of thrombolytic therapy. Therefore, as shown in *Table 2*, many risk factors for intracranial bleeding specifically are listed as absolute contraindications to ST. A large cohort study found that patients with a history of stroke, chronic kidney disease, or aged 75 years or older are at highest risk of intracranial bleeding following CDT.[19] This is further illustrated by our previously published case series of high-risk PE patients, in which ICH following CDT treatment with the EKOS catheter only occurred in two patients, both of whom had absolute contraindications for thrombolytic therapy (i.e. concurrent ischaemic stroke and recent subarachnoid haemorrhage).[20]

Failed systemic thrombolysis subgroup

Generally, ST is effective in improving haemodynamic status in >90% of patients with high-risk PE.[21] Thrombolytic treatment is most efficient when initiated within 48 h after the onset of PE symptoms, but may still show benefit when performed within 14 days.[22] Failed ST is commonly defined as a combination of persistent clinical instability

Table 2 Absolute and relative contraindications to fibrinolysis according to international guidelines[3,8,11]

Contraindications		ACCP	ESC
Absolute	Haemorrhagic stroke or stroke of unknown origin at any time	X	X
	Ischaemic stroke	Within 2 months	Within 6 months
	Central nervous system damage or neoplasms	X	X
	Recent major trauma/surgery/head injury within 3 weeks	Significant head trauma; intracranial or intraspinal surgery within 3 months	X
	Gastrointestinal bleeding within the last month		X
	Known bleeding risk	X	X
	Active internal bleeding	X	
Relative	Transient ischaemic attack in the preceding 6 months		X
	Remote ischaemic stroke in the preceding 3 months	X	
	Oral anticoagulant therapy	X	X
	Pregnancy or within 1 week postpartum	X	X
	Non-compressible puncture site		X
	Cardiopulmonary resuscitation	Prolonged	Traumatic
	Refractory hypertension (systolic blood pressure >180 mmHg)	X	X
	Advanced liver disease		X
	Infective endocarditis		X
	Active peptic ulcer		X
	Age >75 years	X	
	Recent bleeding	X	
	Major surgery within 3 weeks	X	

(hypotension, shock, and hypoxaemia) and echocardiographic RV dysfunction 36–48 h after ST.[21] Unsurprisingly, this situation is associated with a high mortality and treatment decisions can be particularly difficult. Before the widespread introduction of CDT, rescue surgical embolectomy and repeat ST were the only available options. It has been reported that surgical embolectomy is associated with better clinical outcomes compared to repeat ST in terms of treatment success and fatal bleeding.[21] However, this invasive procedure is rather time-consuming and may not be available in all hospitals. Sag *et al.*[23] showed that CDT is an effective alternative in patients with failed ST, leading to improvement of clinical outcomes and echocardiographic parameters at a low complication rate. Results from our registry indicate that high-risk PE patients who underwent both ST and CDT with the EKOS catheter had a higher mortality in general but similar incidence of major and fatal bleeding compared to patients who received CDT only.[20] This suggests that patient's clinical condition is most threatened by haemodynamic instability due to PE rather than bleeding, reflecting the underlying severe disease requiring intensive treatment, such as emergency CDT. As repeat ST is associated with less treatment success and surgical embolectomy may not be available in time, CDT indeed seems an attractive treatment modality after failed ST.

High risk of death before systemic thrombolysis can be effective subgroup

The ACCP guideline recommends the use of CDT over ST in patients considered at high risk of death before ST can be effective. As stated in the recommendation, this depends on local availability of resources and appropriate expertise.[11] However, in our opinion, this is debatable. CDT requires that a patient is stable enough to be transported to the catheterization laboratory, which should be available and prepared for the procedure. From our experience, CDT can seldom be started within 20 min, especially during on-call hours, and these hospital-specific time metrics have to be taken into consideration when deciding on the optimal treatment strategy.

Catheter-based therapies in intermediate-risk pulmonary embolism patients

While the discussion in high-risk PE is focused on the position of CDT in relation to ST, the role of CDT in intermediate risk is still to be elucidated. The primary goal of thrombolysis, whether it is systemic or local, is reduction of clot burden, thereby unloading the RV, with the aim of improving clinical outcome and reducing PE-related mortality. In intermediate-risk acute PE, which is by definition associated with signs of RV dysfunction but without haemodynamic instability, risk of cardiovascular collapse and/or mortality is around 5–6%.[24] The remaining question is whether thrombolysis can improve clinical outcomes. The PEITHO trial showed that ST in intermediate-risk acute PE is associated with a reduction in the composite endpoint of all-cause mortality or haemodynamic decompensation in the first 7 days; this was due to a reduction in haemodynamic collapse and not mortality.[24] However, this came at the expense of an increased risk of bleeding, while long-term benefit in terms of exercise capacity, RV dysfunction or

chronic thromboembolic pulmonary hypertension incidence was absent.[25] This lead to the consensus that ST is not routinely recommended in intermediate-risk PE.[3,8] In this line, CDT has a potential role in intermediate-risk PE by reducing the risk of haemodynamic collapse and/or mortality while not coming at the expense of increased bleeding risk. However, definitive evidence regarding this rationale is not yet available. ULTIMA is the only randomized controlled trial performed so far, including 59 patients with intermediate-risk PE, randomizing them between heparin vs. heparin plus ultrasound-assisted CDT.[10] Primary endpoint was the change in RV/left ventricular (LV) ratio on transthoracic echocardiography after 24 h. The study was positive regarding this primary outcome. However, after 90 days neither RV/LV ratio nor mortality was different between groups. Importantly, the rate of major bleeding was not different between groups.

Two more prospective studies (SEATTLE II and PERFECT) provided evidence on the positive effect of CDT on RV/LV ratio.[26,27] Mortality rates were 2.7% in intermediate-risk acute PE in both studies, which are in the expected range. Since both studies were uncontrolled trials, evidence for a positive effect of CDT on a major clinical outcome such as mortality is lacking so far.

Several retrospective studies have shown similar results. In addition, bleeding risk was in the range of 0–9%, thus acceptable.[28,29]

In conclusion, although CDT seems effective on reducing RV load in the acute phase and the bleeding risk is lower compared with ST, evidence regarding its long-term outcomes and effect on mortality is so far absent.[30] Interestingly, a recent survey on clinical decision-making between either CDT or anticoagulation alone in patients with intermediate-risk PE showed that patients are willing to accept a higher risk of bleeding than physicians if it would improve their long-term exercise capacity.[31] This further underlines the importance of studies including assessment of long-term functional outcomes. The lack of trials on relevant clinical outcomes in intermediate-risk PE patients may, in part, be explained by the relatively low rate of death and/or haemodynamic collapse in intermediate-risk PE. This would require large sample sizes to show survival benefits, and it is questionable whether such a trial will be feasible in the near future. Although trials on the use of CDT in intermediate-risk PE are pending, the question remains whether the benefit of CDT on top of conventional anticoagulation in patients with a relatively low but still increased risk of haemodynamic collapse and/or mortality would outweigh the risks.

Aforementioned results of previous studies have led to the recommendation to consider the use of ST in patients with intermediate–high-risk PE only if clinical deterioration occurs after starting anticoagulation.[3,8,11] According to the ACCP guideline, clinical deterioration does not only comprise hypotension but also progressing symptoms, worsening of vital signs, tissue perfusion, or gas exchange or elevated cardiac biomarkers.[11] Subsequently, as in high-risk PE, CDT is to be considered in aforementioned setting when there is also significant bleeding risk. Similarly, treatment should be decided by weighing risk of further haemodynamic compensation vs. risk of bleeding associated with treatment for individual patients. To detect clinical deterioration, patients with intermediate risk should be monitored intensively in the acute phase. Timely initiation of thrombolytic treatment if haemodynamic instability occurs is of vital importance to prevent morbidity and early mortality. Assessing the presence of bleeding risk factors at presentation may help to proceed to more intensive treatment as soon as possible if needed. In an early stage, risks and benefits of various treatment options for an individual patient should be compared, including different CDT modalities or oral anticoagulation alone. If the clinical situation requires escalation to thrombolytic or CDT treatment, this should be initiated rapidly.

Other specific patient populations

Besides recommendations following PE risk assessment, thrombolytic treatment may be the preferred treatment strategy in other specific patient subgroups. In this line, current international guidelines recommend thrombolytic therapy in patients with intermediate- or high-risk PE with a free thrombus in the right atrium or ventricle, patent foramen ovale, PE-related cardiopulmonary arrest, diffuse perfusion defects, severe hypoxaemia, and severe or worsening RV dysfunction.[3,8,11] Again, the base for treatment decisions in these specific subgroups should be made on a case by case basis, taking both risk of PE-related complications and bleeding into account.

Multidisciplinary evaluation of therapeutic options, the Pulmonary Embolism Response Team

To streamline the multidisciplinary treatment of PE in the acute phase, Pulmonary Embolism Response Teams (PERTs) are being increasingly utilized globally. Pulmonary Embolism Response Teams comprise a multidisciplinary team of physicians, often including cardiologists, pulmonologists, emergency care physicians, intensive care physicians, internists (including haematologists and vascular medicine specialists), (interventional) radiologists, vascular or thoracic surgeons, and pharmacists or a selection of these, depending on hospital logistics.[32] The goal of a PERT is to rapidly consult about various treatment options. Treatment may include medical, surgical, and endovascular therapies. In addition, multidisciplinary follow-up should be provided and data regarding the effectiveness of treatment may be collected. The PERT should be activated as soon as a patient meets criteria for PERT activation. Infrastructure regarding PERT activation varies between hospitals as resources vary. In some cases, all PERT team members are involved at once, whereas in other cases, a core team discusses the case and may ask for opinions of other members if needed. In any case, it is important that PERT activation does not delay treatment, as rapid initiation of treatment is paramount to reduce mortality.

Pulmonary Embolism Response Teams are commonly employed for patients with high-risk PE, intermediate-high-risk PE and in some cases for patients with low-risk PE and contraindications to anticoagulant treatment.[32]

The benefit of a PERT compared to multidisciplinary discussion alone is that the more streamlined approach may facilitate rapid initiation of treatment, including CDT. It is still to be elucidated whether the PERT approach leads to reduced mortality and better outcomes, as no randomized trials exist.[32] The results of cohort studies suggest that the introduction of a PERT leads to an increase in the use of CDT.[33,34] This may be related to more rapid recognition of severe PE, involving interventional specialists in an earlier stage, or a more positive attitude towards CDT after recent publications on CDT in intermediate-risk patients (e.g. the PEITHO trial).[24,32] In these cohort studies, no differences in mortality or bleeding complications were observed.[32,35] Furthermore, after their introduction, PERTs were increasingly activated both during daytime and at night, suggesting that physicians appreciate the value of this approach.[36]

Conclusion

Catheter-based therapies for acute PE may be considered in patients with RV dysfunction who are haemodynamically unstable or show clinical deterioration despite of adequate anticoagulation at high risk of bleeding, after failed ST and at high risk of death before ST can be effective. Early reperfusion modality should be decided based on an individualized risk-benefit analysis, taking into account local availability and expertise, preferably using a multidisciplinary approach or dedicated PERT.

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