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REVIEW

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Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review

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Pulmonary embolism remains a common and potentially life-threatening disease. For patients with intermediate- and high-risk pulmonary embolism, catheter-based revascularization therapy has emerged as potential alternative to systemic thrombolysis or surgical embolectomy. Ultrasound-assisted catheter-directed thrombolysis is a contemporary catheter-based technique and is the focus of the present review. Ultrasound-assisted catheter-directed thrombolysis is more effective in reversing right ventricular dysfunction and dilatation in comparison with anticoagulation alone in patients at intermediate risk. However, a direct comparison of ultrasound-assisted thrombolysis with systemic thrombolysis or surgical thrombectomy is not available. Ultrasound-assisted thrombolysis with initial intrapulmonary thrombolytic bolus may also be effective in high-risk patients, but evidence from randomized trials is not available. This review summarizes current data on ultrasound-assisted thrombolysis for acute pulmonary embolism.

Keywords Pulmonary embolism • Catheter-based revascularization • Ultrasound-assisted thrombolysis • Bleeding

Introduction

Pulmonary embolism (PE) spans a broad spectrum of clinical outcomes and remains a life-threatening disease.[1,2] In the International Cooperative Pulmonary Embolism Registry (ICOPER), the mortality rate at 3 months was 17%, with nearly half of deaths directly attributable to PE.[3] Early clinical outcomes mainly depend on initial haemodynamic status and the extent of right ventricular dysfunction. Various prognostic models have been developed to classify patients into risk groups. The simplified Pulmonary Embolism Severity Index (sPESI) stratifies patients by clinical parameters only,[4] while the European Society of Cardiology (ESC) model includes imaging and biomarker test results of right ventricular dysfunction and myocardial injury.[2,5] According to the ESC model, *high-risk* PE is defined as PE with sustained systemic arterial hypotension, cardiogenic shock, or the need for cardiopulmonary resuscitation, and is associated with an in-hospital mortality rate >15%.[6] Haemodynamically stable patients without right ventricular dysfunction and normal cardiac biomarkers are classified as *low-risk* patients with mortality rates <3%. Haemodynamically stable patients with evidence of right ventricular dysfunction or positive biomarkers are classified as *intermediate-risk* patients with mortality rates of 3–15%.[2] The initial stratification of PE patients into different risk groups has an important impact on the various treatment options, in particular for the use of revascularization therapy such as systemic thrombolysis, catheter-based treatment, or surgical embolectomy.[2,7,8]

Revascularization therapy

Several randomized controlled trials have consistently shown that systemic thrombolysis rapidly improves right ventricular function and haemodynamic parameters in patients with acute PE.[9,10] However, the effect of systemic thrombolysis on recurrent thromboembolic events and mortality remains controversial. A meta-analysis by Jaff *et al.*,[7] including 13 randomized controlled trials of systemic thrombolysis ($n = 480$) vs. heparin anticoagulation alone ($n = 464$), showed no reduction in recurrent PE or death. In another meta-analysis by Wan *et al.*, five trials were identified which included high-risk PE patients. A significant decrease of recurrent PE or death from 19% with heparin alone to 9.4% with thrombolysis (odds ratio: 0.45, 95% CI: 0.22 − 0.92) was observed.[11] In the meta-analysis by Jaff, there was a non-significant increase in major bleeding complications with systemic thrombolysis vs. heparin alone (10.1 vs. 7.3%, odds ratio: 1.53, 95% CI: 0.86–2.74), and a significant increase of overall

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bleeding complications (24.1 vs. 13.8%, odds ratio: 2.16, 95% CI: 1.25–3.71).[7] The risk of bleeding complications was confirmed in the Pulmonary Embolism International Thrombolysis (PEITHO) trial comparing a single, weight-adapted i.v. bolus of tenecteplase with standard anticoagulation alone in 1006 patients with intermediate-risk PE.[12] This large trial showed a significant reduction in the combined primary endpoint of all-cause mortality and haemodynamic collapse within 7 days of randomization in favour of tenecteplase. The main driver for the efficacy difference was not mortality but a reduction in haemodynamic collapse in favour of tenecteplase.[13] Unfortunately, the benefits of thrombolysis came at the cost of an increased risk of non-intracranial major bleedings (6.3 vs. 1.5%, $P < 0.001$) and intracranial haemorrhage (2.4% vs. 0.2%, $P < 0.001$).[13] In registries, systemic thrombolysis was associated with major bleeding rates reported as high as 20%, with intracranial haemorrhage in up to 3%.[3,14]

Of note, systemic thrombolysis is nowadays withheld in more than two-thirds of patients with high-risk PE.[15,16] The proportion of unstable PE patients receiving thrombolytic therapy in the USA decreased from 40% in 1999 to 23% in 2008.[17] The reasons for the decrease in systemic thrombolysis over the last years remain unclear and cannot be explained by increased use of catheter-based or surgical revascularization.[17]

Catheter-based therapy and surgical embolectomy are alternative revascularization strategies for patients at increased risk of death, especially if the bleeding risk under systemic thrombolysis is increased.[2,7,8]

Catheter-based revascularization for pulmonary embolism

The aim of catheter-based revascularization treatment is to remove the obstructing thrombi from the main or lobar pulmonary arteries, to facilitate right ventricular recovery, to improve symptoms, and to reduce mortality and long-term complications.[18] Contemporary catheter-based revascularization techniques for PE can broadly be classified as interventions with local thrombolysis and those without thrombolysis. The latter techniques are being used for patients with absolute contraindications to thrombolysis and comprise thrombus fragmentation, rheolytic or rotational thrombectomy, or suction thrombectomy.[7,18] Intraclot administration of thrombolytic drugs might be more efficient than systemic thrombolysis since the systemically administered drug is rapidly washed into non-occluded arteries and may partly not reach obstructive thrombus as shown in an animal flow dynamics model by Schmitz-Rode *et al.*[19] The administration of local thrombolysis can be performed with conventional catheter-directed thrombolysis (CDT) through a multi-sidehole catheter placed into the thrombus, or with pharmacomechanical thrombolysis, defined as the combination of CDT with a mechanical catheter-based technique.

Most evidence for catheter-based interventions is based on single-centre case series.[18] In a systematic review of contemporary catheter-based revascularization techniques including 594 PE patients in 35 studies (6 prospective and 29 retrospective), the pooled clinical success rate, defined as stabilization of haemodynamic parameters, resolution of hypoxia, and survival to discharge, was 86.5%.[20] Clinical success rate was higher in studies in which at least 80% of patients received local thrombolytic therapy during the procedure. However, a direct comparison of techniques with or without local administration of thrombolytic drugs was not possible. Therefore, it remains debatable if catheter interventions without adjunctive thrombolysis are effective. Overall, minor and major periprocedural complications occurred in 7.9 and 2.4%, respectively, and a total of five procedural-related deaths were reported.[20]

What is ultrasound-assisted thrombolysis?

Ultrasound-assisted thrombolysis may be considered as pharmacomechanical thrombolysis and consists of a combination of CDT with a catheter system that employs ultrasound energy.[21] Basic research has demonstrated that ultrasound facilitates the delivery of thrombolytic agents into blood clots.[22–24] Braaten *et al.*[23] showed *in vitro* that ultrasound exposure causes a reversible disaggregation of uncrosslinked fibrin fibres, an effect that may create additional binding sites and facilitate the thrombolysis effect. In addition, ultrasound pressure waves may increase thrombus penetration of thrombolytic drugs by acoustic streaming.[22]

The EkoSonic® Endovascular System (EKOS Corporation; Bothell, WA, USA) is currently the only commercially available catheter system for intravascular ultrasound-assisted thrombolysis. It combines a multi-sidehole drug infusion catheter with a multi-element ultrasound core wire (*Figure 1*). The thrombolytic drug is delivered through the infusion catheter while the ultrasound core delivers high-frequency (2.2 GHz), low energy (0.5 W per transducer) intravascular ultrasound along the entire treatment zone (*Figure 2*). The EkoSonic Endovascular System

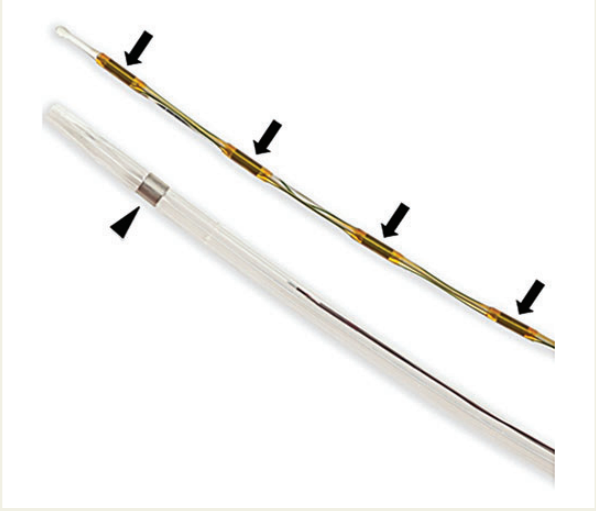

Figure 1 Tip of the ultrasound-assisted thrombolysis catheter, EkoSonic® Endovascular System (EKOS Corporation; Bothell, WA, USA). The catheter is composed of a 5.2-Fr multi-sidehole drug infusion catheter (treatment zone marker delineated with an arrow head) and a microsonic core wire containing the ultrasound elements (marked with small arrows). During ultrasound-assisted thrombolysis, the multi-element ultrasound core wire is placed inside the infusion catheter.

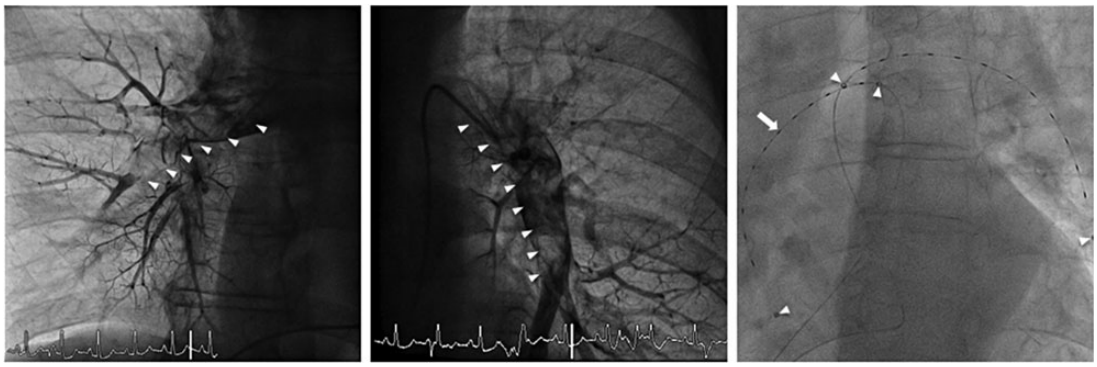

Figure 2 (left panel) Baseline selective conventional pulmonary angiography showing a near complete filling defect of the right main and lower lobe pulmonary artery (thrombus delineated by arrow heads). (middle panel) Baseline selective pulmonary angiography showing a partially occlusive thrombus in the left main and lower lobe pulmonary artery, respectively (thrombus delineated by arrow heads). (right panel) Fluoroscopic anterio-posterior view after placement of two 12-cm treatment zone EkoSonic devices with radio-opaque treatment zone markers (delineated with arrow heads) and ultrasound elements (one of them marked with a small arrow).

was cleared by the US FDA in 2008 for the infusion of solutions into the pulmonary arteries and is C.E. certified for intravascular applications.

The superiority of ultrasound-assisted thrombolysis over conventional CDT has not yet been proved in a clinical setting. Two randomized controlled trials are ongoing, one in patients with ilio-femoral deep vein thrombosis (NCT01482273) and one in patients with thrombosed infra-inguinal native arteries or bypass grafts (ISRCTN72676102). In a non-randomized, retrospective study of 25 patients with acute PE, ultrasound-assisted thrombolysis provided better thrombus removal, and both thrombolytic infusion time and treatment-related complications were reduced compared with CDT alone.[25]

Ultrasound-assisted thrombolysis for acute pulmonary embolism

Overall, seven studies with a total of 197 patients treated by ultrasound-assisted CDT were published (*Table 1*).[21,25–30] Thirty-five (18%) of the treated patients had high-risk PE. Recombinant tissue plasminogen activator (rt-PA) was used as thrombolytic drug in 195 (99%) patients with a mean total dose ranging from 17.2 to 35.1 mg. In two studies, an intrapulmonary bolus of rt-PA was administered prior to ultrasound-assisted thrombolysis in high-risk PE patients.[21,29] Treatment duration varied largely between the studies and was often guided by improvement in clinical or angiographic parameters.[25–28] Two studies used a fixed-dose treatment regimen with 10 mg of rt-PA per treated lung over the course of 15 h.[21,30]

An increased right-to-left ventricular end-diastolic diameter ratio (RV/LV ratio) assessed by echocardiography or chest CT as a sign of right ventricular dysfunction is a validated parameter which predicts short-term mortality for PE patients.[31,32] In the three studies reporting the RV/LV ratio before and after ultrasound-assisted thrombolysis, the pooled mean RV/LV ratio decreased from 1.36 to 1.03 (*Table 1*).[21,29,30] This reduction is similar to the treatment effect observed in the randomized controlled Tenecteplase Italian Pulmonary Embolism (TIPES) trial, comparing weight-adjusted i.v. tenecteplase vs. standard therapy with unfractionated heparin alone in patients with intermediate-risk PE. The RV/LV ratio decreased from 1.36 at baseline to 1.04 over 24 h in the tenecteplase group, while no significant reduction of the RV/LV ratio was observed in the control group (1.32–1.22).[33]

Compared with baseline values, mean pulmonary artery pressure significantly decreased, and cardiac index increased at completion of ultrasound-assisted thrombolysis in two studies.[21,30] Although the long-term benefit of early haemodynamic improvement is a matter of debate, there is evidence to suggest that a revascularization therapy with early improvement of haemodynamic parameters potentially reduces the incidence of chronic pulmonary hypertension, a rare but serious long-term complication.[34–36]

In four studies, pulmonary thrombus load was assessed pre- and post-ultrasound-assisted CDT using various angiographic scores. Relative reduction in the pulmonary occlusion score ranged from 32 to 69% (*Figure 3*).

In the pooled analysis of available ultrasound-assisted CDT studies, the rate of major bleeding complications was 3.6% (95% CI: 1.4–7.2%) (*Table 1*). Of note, none of the studies reported fatal or intracranial bleedings. Procedure-related minor bleedings occurred in 10.7% (95% CI: 6.7–15.8%). Overall mortality rate at 3 months was 3.6% (95% CI: 1.4–7.2%). Although the overall complication rate with ultrasound-assisted CDT for PE seems to be low, more data are required to confirm the favourable safety profile. A single-arm, multicentre trial (NCT01513759) designed to confirm the safety of ultrasound-assisted CDT for patients with acute intermediate- and high-risk PE is ongoing.

ULTIMA trial

The ULTrasound accelerated thrombolysIs of pulMonAry embolism (ULTIMA) trial is the first randomized catheter intervention study for patients with acute PE.[30] This multicentre trial performed in Switzerland and Germany investigated whether ultrasound-assisted CDT is

Table 1 Summary of published studies on ultrasound-assisted thrombolysis for acute pulmonary embolism

First author and year of publication	No. of patients	Patients with high-risk PE	Total rt-PA dose (mg)	Total thrombolysis duration (h)	RV/LV ratio		Mean pulmonary artery pressure (mmHg)		Cardiac index (l/min/m^2)		Relative reduction in pulmonary occlusion score (%)	Bleeding complications		Mortality at 3 months
					Before	After	Before	After	Before	After		Minor	Major	
Chamsuddin *et al.* (2008)[26]	10	NA	21.8	24.8 ± 8.4	NA	NA	NA	NA	NA	NA	NA	2 (20)	0 (0)[a]	0 (0)
Lin *et al.* (2009)[25]	11	2 (18)	17.2 ± 2.4	17.4 ± 5.2	NA	NA	NA	NA	NA	NA	69.0[b]	0 (0)	0 (0)[c]	1 (9)
Engelhardt *et al.* (2011)[29]	24	5 (21)	33.5 ± 15.5	19.7 ± 8.1	1.33 ± 0.24[d]	1.0 ± 0.13[d]	NA	NA	NA	NA	51.1[e]	2 (8)	4 (17)[f]	0 (0)
Quintana *et al.* (2013)[27]	10	2 (20)	18 (7–38)[g]	20.8 (12–49)[g]	NA	NA	NA	NA	NA	NA	41.9[h]	2 (20)	0 (0)[i]	0 (0)
Kennedy *et al.* (2013)[28]	60	12 (20)	35.1 ± 11.1	19.6 ± 6.0	NA	NA	27 ± 9	20 ± 6	NA	NA	32.0[b]	1 (2)	1 (2)[a]	4 (7)
Engelberger *et al.* (2013)[21]	52	14 (27)	21.0 ± 5.7	15.2 ± 1.7	1.42 ± 0.21[j]	1.06 ± 0.23[j]	37 ± 9	25 ± 8	2.0 ± 0.7	2.7 ± 0.9	NA	11 (21)	2 (4)[k]	2 (4)
Kucher *et al.* (2013)[30]	30	0 (0)	20.8 ± 3.0	15.0 ± 1.0	1.28 ± 0.19[j]	0.99 ± 0.17[j]	30 ± 9	24 ± 7	2.5 ± 0.5	3.9 ± 2.3	NA	3 (10)	0 (0)[k]	0 (0)
Total[l]	197	35 (18)	26.9[m]	17.8[m]	1.36 ± 0.21	1.03 ± 0.20	31.3 ± 9.0	22.7 ± 6.9	2.2 ± 0.7	3.1 ± 1.3	41.2	21 (10.7)	7 (3.6)	7 (3.6)

Data presented as number (%) or means ± standard deviation if not otherwise stated; NA, not available; rt-PA, recombinant tissue plasminogen activator; RV/LV-ratio, right-to-left ventricular end-diastolic diameter ratio.
[a]As defined by the Society of interventional Radiology.[41]
[b]Assessed by angiographic Miller index.[38]
[c]Major bleeding defined as intracranial bleeding or bleeding resulting in death, transfusion, surgery, or unplanned cessation of thrombolytic drug.
[d]Assessed by chest computed tomography.
[e]Assessed by modified Miller score.[39]
[f]Defined as intracranial bleeding or bleeding severe enough to warrant cessation of therapy or blood transfusion.
[g]Median dose and (range).
[h]Assessed by Mastora score.[40]
[i]No clear definition of major bleeding available.
[j]Assessed by echocardiography.
[k]As defined by the International Society on Thrombosis and Haemostasis.[42]
[l]Pooled means ± standard deviation derived from pooled variance analysis.
[m]Pooled mean without study by Quintana *et al.*[27]

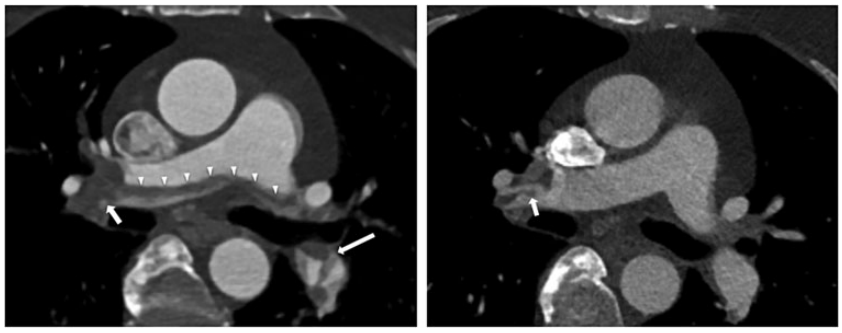

Figure 3 (left panel) Baseline contrast-enhanced chest computed tomography of the same patient as in *Figure 2* showing a saddle embolus (delineated with arrow heads), a near complete occlusion of the right main pulmonary artery (small arrow) and a partial occlusion of the left lower lobe pulmonary artery (large arrow). (right panel) Follow-up contrast-enhanced chest computed tomography from the same patient 24 h after termination of ultrasound-assisted catheter-directed thrombolysis showing resolution of the saddle embolus and evidence of residual non-obstructive embolus in the right lower lobe pulmonary artery (small arrow).

superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk PE patients. The authors hypothesized that ultrasound-assisted CDT would have a similar effect on reducing RV/LV ratio at 24 h when compared with i.v. tenecteplase and used the mean and standard deviations of the difference in the RV/LV ratio of the tenecteplase (0.31 ± 0.20) and heparin groups (0.10 ± 0.30) from the TIPES trial.[33] The estimated sample size was 24 per group using a power of 80% at a two-sided *P*-value of 0.05 by the *t*-test. Patients with acute symptomatic PE (symptom duration of <14 days) confirmed by contrast-enhanced CT with embolus located in at least one main or proximal lower lobe pulmonary artery and an RV/LV ratio ≥ 1 obtained from the echocardiographic apical four-chamber view were included. Patients with known significant bleeding risk or intolerance to the administered treatment drugs were excluded. Ultrasound-assisted CDT was performed according to a standardized treatment protocol over the course of 15 h with a rt-PA dose of 20 ± 1 mg for patients with bilateral device placement and 10 ± 0.5 mg for patients with unilateral device placement. A total of 59 patients were randomized, 30 in the interventional group and 29 in the control group. In the interventional group, the RV/LV ratio was reduced from 1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 h ($P < 0.001$), while in the control group no significant decrease of the RV/LV ratio was observed at 24 h (1.20 ± 0.14 vs. 1.17 ± 0.20; $P = 0.31$). The mean difference in the RV/LV ratio from baseline to 24 h was 0.30 ± 0.20 vs. 0.03 ± 0.16 ($P < 0.001$), respectively. Although there was a late 'catch-up' in patients with heparin alone, there was a trend for greater improvement in the RV/LV ratio from baseline to 90 days in favour of ultrasound-assisted CDT (0.35 ± 0.22 vs. 0.24 ± 0.19; $P = 0.07$). Right ventricular systolic function was graded in four categories by the core laboratory: normal, mild, moderate, or severe dysfunction. There was significantly improved right ventricular systolic function at 90 days in favour of ultrasound-assisted CDT (2.2 ± 0.9 vs. 1.5 ± 0.9 categories; $P = 0.01$). In both study groups, bleeding complications were rare, with three (10%) minor bleedings in the interventional group and one (3%) in the control group. There was no major bleeding. The authors concluded that a standardized ultrasound-assisted thrombolysis treatment regimen for patients with intermediate-risk PE was superior to anticoagulation alone in reversing right ventricular dilatation at 24 h without increasing the bleeding risk.

Practical aspects for ultrasound-assisted thrombolysis

Patients undergoing invasive pulmonary angiography and catheter intervention require continuous haemodynamic and electrocardiographic monitoring.[18] Venous access is usually obtained at the common femoral vein using a 6 French introducer sheath for patients who are scheduled for unilateral catheter placement or a 10 French double-lumen introducer sheath for those who were scheduled for bilateral catheter insertion. Duplex sonography is recommended in patients with leg swelling to rule out concomitant ilio-femoral deep vein thrombosis before obtaining venous access. In patients with concomitant ilio-femoral deep vein thrombosis, the contralateral common femoral vein may be used for venous access. A standard 5-French angiographic catheter can be used with manual injections of a small amount of iodine contrast medium for localizing the embolic occlusion. A 12-cm treatment zone catheter is appropriate in most cases. To minimize the risk of pulmonary artery perforation, only the main and lower lobe pulmonary arteries should be considered for catheter placement and segmental branches with a diameter of <6 mm should not be approached.[37] An intrapulmonary bolus of thrombolytic drug (e.g. 2–5 mg rt-PA per catheter) may be injected prior to initiating ultrasound-assisted thrombolysis in patients with high-risk PE. In most patients with intermediate-risk PE, the initial bolus should be omitted. Infusion of the thrombolytic drug (e.g. rt-PA at 0.5–1.0 mg/h per catheter) and saline coolant (e.g. at 35 mL/h per catheter) over 15–24 h is initiated. Thereafter, the patient should be continuously monitored in an intermediate or intensive care unit. Treatment duration can be guided by clinical parameters, alternatively, a fixed-dose 15-h regimen as in the ULTIMA trial may be used. It is suggested to measure pulmonary artery

pressure pre- and post-ultrasound-assisted CDT to confirm treatment success.

Limitations of ultrasound-assisted thrombolysis for acute pulmonary embolism

Although 18% of the treated patients were at high risk, it remains unclear if ultrasound-assisted CDT including an intrapulmonary bolus of thrombolytic drug acts fast enough to prevent haemodynamic deterioration and death in unstable patients. In these patients, systemic thrombolysis or surgical embolectomy remains the preferred therapeutic options. Additional limitations of ultrasound-assisted CDT include long duration of the procedure (15–24 h), limited availability in the majority of hospitals, high costs, learning curve, and no long-term data with regard to recurrent PE, mortality, and the risk of chronic thrombo-embolic pulmonary hypertension.

Conclusion

In PE patients at intermediate risk of death, catheter-based therapy has emerged as alternative revascularization strategy to systemic thrombolysis or surgical embolectomy. Ultrasound-assisted CDT is superior to anticoagulation alone in reversing RV dilatation in patients with intermediate-risk PE. Available data suggest a low major bleeding rate following ultrasound-assisted thrombolysis, but clinical outcome studies are warranted to confirm a favourable safety profile. For unstable patients with high-risk PE, ultrasound-assisted thrombolysis is a potentially promising but unproven technique. In practice, ultrasound-assisted CDT may be indicated in selected patients with intermediate- or high-risk PE if the bleeding risk under systemic thrombolysis is increased. Ideally, these procedures are performed in experienced centres with around-the-clock availability of catheter therapy and surgical embolectomy.

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CARDIOVASCULAR FLASHLIGHT

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Coronary artery disease in systemic sclerosis not clinically apparent: findings from optical coherence tomography

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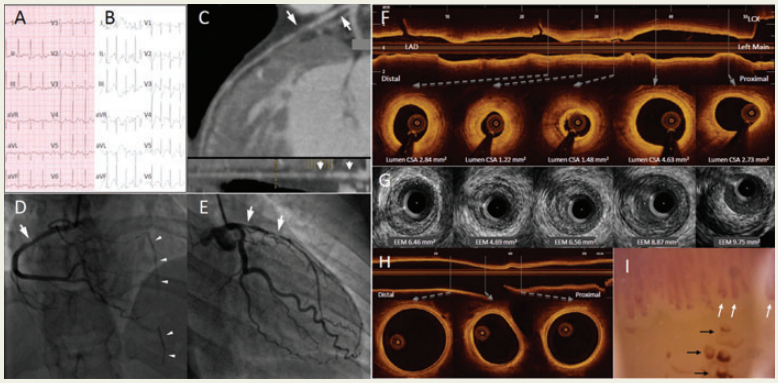

A 42-year-old female was referred for intermittent effort angina. She had low body mass index, no coronary risk factors and an unremarkable past medical history except for a Raynaud's phenomenon. Owing to a normal exercise stress test (*Panel A*), symptoms were initially attributed to anxiety. However, a 24h-EKG monitoring revealed diffuse ST-segment depression during physical activity (*Panel B*). On admission, CT scan showed low-density areas at proximal/mid segments of the left anterior descending artery (LAD), without calcifications (*Panel C*). At coronary angiography LAD presented with a long, subocclusive stenosis (*Panels D* and *E*) with collaterals from the right coronary artery. Optical coherence tomography (OCT) demonstrated diffuse intimal-medial thickening of the LAD, a finding suggestive for a fibrotic process involving the vessel (*Panel F* and Supplementary material online, *Video S1*). Intravascular ultrasound showed constrictive vessel remodeling (*Panel G*). Two everolimus-eluting stents were implanted in overlap in the LAD with optimal final result (Supplementary material online, *Figures S1* and *S2*). An OCT pullback of the radial artery documented focal intimal thickening, suggesting different stages of vascular involvement of the medium-small arteries (*Panel H*). A videocapillaroscopy (*Panel I*) identified typical features of early scleroderma peripheral microangiopathy, with giant capillaries and haemorrhages. Systemic sclerosis (SSc)-related autoantibodies were still negative.

Systemic sclerosis has a strong macrovascular component with an increased risk of heart attack. Involvement of the medium-small arteries is one of the earliest features of SSc preceding the widespread fibrosis. The present case demonstrates how OCT may orient in the diagnosis and treatment of an uncommon cause of CAD such as SSc not clinically apparent yet.

Supplementary material is available at *European Heart Journal* online.