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Future perspectives in catheter-based treatment of pulmonary embolism

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Pulmonary embolism is the third commonest cause of cardiovascular death globally. The majority of such patients present with low-risk features and can be managed with simple anticoagulation; however, a large group of patients exhibit evidence of right ventricular dysfunction on echocardiography or CT at the time of presentation and these patients are at risk of early haemodynamic compromise, particularly in those with abnormal cardiac biomarkers. Catheter-directed thrombolysis has been proposed as a treatment-strategy for patients with pulmonary embolism with evidence of acute right ventricular dysfunction. We review the current technologies in mainstream use, the evidence base in support of their use and discuss future research requirements in this area.

Introduction

Pulmonary embolism (PE) is the third commonest cause of cardiovascular death, leading to hundreds of thousands of deaths across Europe every year.[1] It represents a significant economic burden and is an important cause of avoidable in-hospital death.[2]

The majority of PE cases (60%) are low risk with no haemodynamic consequences and can be managed with oral anticoagulation followed by immediate or next-day discharge. These patients are well managed by current health care systems and the move is increasingly towards ambulatory care for this group.[3]

At the other end of the spectrum is a very sick, but small group of patients (5% of all PEs) in whom high-risk ('massive') PE causes immediate haemodynamic collapse and shock (defined as systolic blood pressure less than 90 mmHg for more than 15 min without arrhythmia), requiring emergency full-dose systemic thrombolysis as a salvage intervention.

Many such patients die before they reach hospital and a further 30–50% will die in hospital.[4] Studies show that only a minority of such patients get life-saving thrombolysis with full-dose alteplase (typically 100 mg) due to concerns over the bleeding risks associated with high-dose tissue plasminogen activator (tPA) and, even when they do receive this drug, the life-threatening bleeding complication rates from this treatment can be as high as 20% in older patients.[4-6]

The third group of patients with intermediate-risk PE are the most difficult group to manage. These are patients with evidence of right ventricular (RV) dysfunction on either echocardiography or computed tomography (CT) pulmonary angiography and abnormal biological markers of myocardial injury, but who have preserved blood pressure (defined as systolic blood pressure greater than 90 mmHg). These patients represent a third of patients with PE, many of whom are too sick to go home but not sick enough to meet the guideline recommendations for systemic thrombolysis due to the bleeding risks involved with this approach.

Full-dose systemic thrombolysis for intermediate-high risk PE has been tested in the PEITHO study.[6] PEITHO randomized 1001 patients to either full-dose thrombolysis or placebo. Those who received full-dose thrombolysis had a significant reduction in the risk of cardiovascular collapse and/or death (from 5.6% to 2.6% incidence of death/CV collapse at 7 days), but the bleeding complications of

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receiving tPA cancelled out the benefits of the treatment, creating neutral net clinical benefit.

It seems clear, therefore, that if we had a treatment for intermediate-high risk PE that could reduce the incidence of CV collapse/death by half, but with fewer bleeding complications, we may be able to improve outcomes in this difficult to manage group of patients, whose in hospital mortality can be as high as 12%.[4]

Half-dose systemic thrombolysis has been proposed as a solution to this conundrum, with data from one open-label randomized study suggesting improved rates of pulmonary hypertension (PHT) when using thrombolytic vs. control.[7] However, this study reported much higher rates of PHT in the control arm (over half the anticoagulation-only group developed PHT) than the 3–13% (according to definition) rates seen in the much larger PEITHO study,[6,8] suggesting that the MOPETT cohort may have been unrepresentative of a typical PE patient population.

The PEITHO 3 study, randomizing patients to half-dose thrombolysis or anticoagulation, should provide an answer to the question of whether the benefits of systemic thrombolysis on prevention of CV collapse seen in PEITHO can be preserved, whilst reducing the bleedings risks of treatment through a 'half-dose' approach.

In the meantime, it seems appropriate that we continue the search for other approaches to treating intermediate-high risk PE. The goal seems clear—preserve the benefits of reperfusion whilst minimizing bleeding complications.

Low-dose catheter-directed thrombolysis

In PE, partial or complete occlusion of the main or branch pulmonary arteries creates shunting, directing blood away from the segment of lung affected by the PE towards healthy, unobstructed vessels.[9] This means that systemic thrombolysis in the bloodstream is frequently coming into contact with a limited surface area of clot within the occluded branch vessel, with most carried into an unaffected segment. Large doses of thrombolytic (with a short half-life of just a few minutes when given as a bolus) are

Figure 1 The effect of Ekos plus heparin vs. heparin alone on RV/LV ratio at 24 hours. From the ULTIMA trial (Kucher *et al.*[14]).

therefore required to 'chip away' at the clot in order to significantly debulk it.

Local administration of thrombolytic through catheter-directed thrombolysis (CDT) into the pulmonary arterial system is an attractive concept, presuming that local administration might improve the efficiency of clot breakdown whilst minimizing systemic effect.[10]

A simple pigtail catheter placed in the main pulmonary artery can deliver thrombolytic closer to the obstruction; however, the same phenomenon of shunting will carry the agent away from the clot towards unobstructed vessels, meaning relatively limited contact with the body of obstructive clot, as per systemic treatment. It would, however, produce peak concentration of a short-acting drug closer to the site of need.

The Ekos system proposes a novel mechanism of improving the process of CDT. It uses multiple ultrasound arrays within a sheath to deliver alteplase directly into the body of the clot, utilizing the process of acoustic streaming to 'inject' droplets of tPA inside the clot at fixed points along each array, thus increasing the surface area of thrombus subject to contact with tPA. This could potentially reduce the amount of thrombolytic required to disrupt obstruction to blood flow and therefore offload the right ventricle, with a presumed lower risk of bleeding through a smaller dose of administered tPA, though of course introducing an invasive nature to the treatment.[11-13]

The use of the Ekos system has been tested in several clinical studies. The ULTIMA trial randomized 59 patients with intermediate-risk PE to a standard anticoagulation protocol, or anticoagulation plus CDT with the Ekos system, using 20 mg of alteplase for bilateral PE treatment over 10 h.[14]

The primary endpoint—of reduction in the RV/left ventricular (LV) echocardiographic ratio at 24 h—was met, showing superiority of the Ekos CDT system for RV unloading with minimal bleeding complications (*Figure 1*).

The second published study using the Ekos system was the SEATTLE II study, which was a single-arm, open-label study of 150 patients receiving 24 mg of alteplase (for bilateral treatment) via the Ekos system. Again, it showed significant reductions in RV/LV ratio at 48 h by CT scanning.[15] In this study, however, a not insignificant rate of bleeding complications was observed, though some of this could be minimized through the use of ultrasound-guided micropuncture access.

Given that many operators had previously reported early clinical improvement of their patients during Ekos treatment, the OPTALYSE study was convened to test lower dose and/or more rapid treatment protocols using the Ekos system, delivering four different protocols to 101 patients.[16] These protocols for bilateral treatment of PE were:

(1) 8 mg of alteplase over 2 h
(2) 8 mg of alteplease over 4 h
(3) 12 mg of alteplase over 6 h
(4) 24 mg of alteplase over 6 h

Note that protocol 4 gave a similar dose to that used in SEATTLE II but given at twice the speed and therefore the regimens are not directly comparable between the two studies.
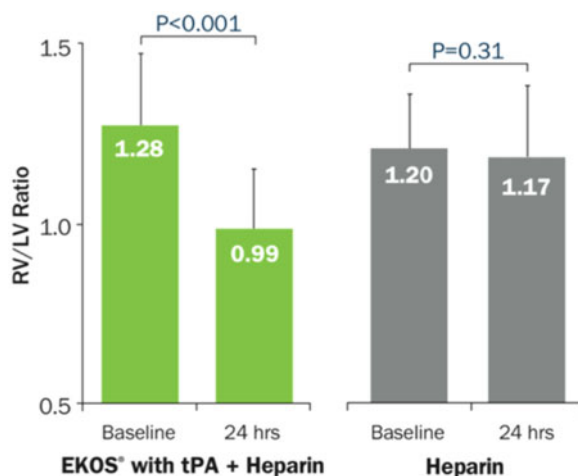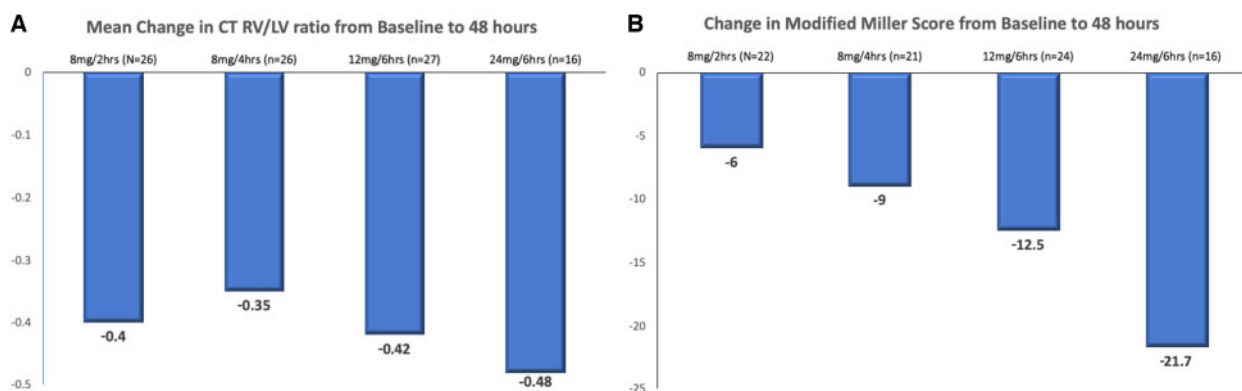
Figure 2 (A) Change in RV/LV ratio according to treatment arm in the OPTALYSE study. (B) Clot burden reduction by modified Miller score according to treatment arm (Tapson et al.[16]).

The highest dose protocol was associated with two episodes of serious bleeding and therefore was discontinued, with the other three regimens continuing until 101 patients were randomized in total.

Interestingly, each protocol showed similar reductions in the RV/LV ratio on CT scanning at 48 h. However, there was a dose/duration-of-treatment relationship between the protocol used and the degree of reduction in CT thrombus burden at 48 h, as well as on reduction in PA pressure, suggesting that reduction in RV/LV ratio alone may not be telling the whole story, with other measures of treatment success suggesting a dose–response relationship (*Figure 2*).

Whether that relationship is clinically important is unclear. RV/LV ratio is, however, a longstanding surrogate endpoint in PE research and has a strong association with outcome.[17]

After three studies published reporting six different treatment protocols for use, there remains conflicting data on the protocol of choice with this technology. The use of microbubble augmentation may also further improve the Ekos system, though whether adding another level of complexity will alter outcomes is also unclear.[18]

The opinion of the authors is that the available protocols provide a 'menu' of treatments, all of which have a good chance of offloading the right ventricle within hours of commencement of treatment, and therefore selection of protocol is patient dependent, factoring in clinical status, comorbidity status, thrombus burden, and bleeding risk.

The final point regarding the Ekos system is that it typically takes hours, rather than minutes to have measurable clinical impact. The published outcome measures are reported at 24 and 48 h. In a patient with some degree of instability, the technology cannot compare with, for example, a primary percutaneous coronary intervention procedure for ST-elevation myocardial infarction (STEMI) for speed of effect—a procedure which can produce dramatical clinical benefits within 15 min of 'needle-to-skin'.

Thrombus extraction technologies

Those cardiologists familiar with the difficulties of demonstrating clinical benefit from extraction of thrombus in the coronaries in STEMI will understand that what

should be a simple concept of 'better off out of the vessel' is sometimes not that simple.[19] Furthermore, there are several important differences between lung and myocardium.

Firstly, embolization may not be as significant in the lung as it is in a major epicardial coronary vessel supplying a third of downstream myocardium, though large numbers of patients do report 'post-PE impairment'. Whether we currently have treatments that could ameliorate that is unclear, as the mechanisms are mixed and the weighting of causation is unclear.[8]

Other differences exist between the two conditions. In STEMI, complete occlusion of the coronary artery is required to cause the clinical syndrome and death of the tissue we are attempting to preserve has mostly occurred by 6 h after onset of symptoms. In intermediate-high risk PE, whilst hypoxia is an important clinical issue, it is circulatory collapse that is the bigger concern, caused by a dramatic increase in RV afterload from obstructive thrombus in a central/proximal-bilateral position.[8]

Given the laws of fluid dynamics, it takes a relatively small reduction in obstructive burden to offload the right ventricle and therefore the ability to extract some clot from the central PA, or proximal left and/or right main pulmonary arteries, should be clinically advantageous. Again, however, we see differences between the clot in PE and the clot in STEMI.

Deep venous thrombosis can sometimes have been present for weeks before embolization takes place. This means that the material present in the pulmonary artery might be fibrotic and difficult to fragment and then extract.[18] Fresh clot is easier to disrupt, but not all large volume PEs are due to fresh clot.

Evidence to support this comes from an analysis of the limited impact of using mechanical disruption alone (e.g. with a pigtail catheter) vs. mechanical disruption with adjunctive thrombolysis, the latter of which has shown greater success.[20]

Previously deployed technologies that macerate and aspirate are not without their own risks. The Angiojet technology (Boston Scientific, Marlborough, MA, USA) now has a blackbox warning from the American FDA for complications associated with use in PE,[21] including haemoptysis and haemodynamic collapse.

Other aspiration technologies are sometimes used in an 'off-label' fashion. The Penumbra CAT 8 device (Penumbra Inc., Alameda, CA, USA) utilizes an 8-Fr lumen catheter that is connected to a pneumatic suction system able to generate close to 29 pounds per square inch (PSI) in suction power to help remove proximal and more distal clots as desired. Compared to using devices that rely on a syringe to create negative pressure within a catheter (as e.g. do most coronary aspiration catheters), the CAT 8 provides more consistent suction power that does not wane with the release of syringe.[21]

The smaller French size, variety of tip shapes and ease of use, with or without a separator system, makes it an attractive option even in urgent cases. However, size is a double-edge sword. Being only 8-Fr limits its ability to extract large volumes of clot, which necessitates multiple runs. In turn, multiple runs can often lead to significant blood loss and it is not uncommon for the procedure to be terminated if the volume suctioned exceeds 250 mL of blood (equivalent of 1 unit of PRBC).

Increasing the French size of the device to allow for more robust suction with fewer runs might lead to decreased blood loss if the ratio of clot to blood aspiration was higher. Another possibility is the development of a filtering/circulation mechanism so that suctioned blood can be reintroduced into peripheral circulation. Currently, there are no trials that have examined the role of this particular device in the treatment of intermediate-high risk PE.

The Flowtriever clot extraction system (Inari Medical, Irvine CA, USA) is a much larger system than those previously mentioned, requiring 20-Fr central venous access.[22] It utilizes negative suction created by pulling negative against a 60 mL syringe with the ability to generate up to—29 mmHg (−13.75 PSI) removing up to 86 mL of volume in one second. The device incorporates the Flowtriever catheter (*Figure 3*), which is made of three self-expanding nitinol mesh disks that are designed to engage, disrupt and deliver the clot to the guiding catheter for extraction. Given the large bore access, this device can extract much larger amounts of clot in a single pass than the other systems described above.

The downside of a larger system is the potential for more vascular complications, more arrhythmic stimulation as it passes the right ventricle/RV outflow tract and, without thrombolytic adjunctive action, a limited action on pulmonary arterial run-off.

The device does have a learning curve and is quite challenging to advance in cases where there is chronic PA dilation, especially when attempting to access the right main PA. The T-16 telescoping catheter, which can be inserted inside the T-20, has helped alleviate this issue. The 16-Fr catheter can be used as a standalone device but at the expense of suction power and is not recommended to be used routinely as such in its current iteration. An angulated tip would allow better ease of navigation/rotation and a system that recirculate the aspirated blood to avoid significant blood loss after multiple treatments would be valuable.

Given, however, that haemodynamic instability in PE occurs mostly with large volume central/proximal bilateral
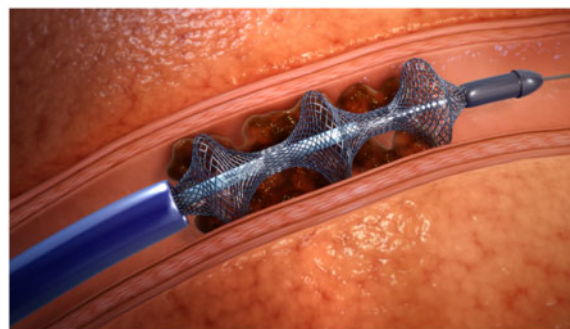

Figure 3 The Flowtriever system (Inari Medical, Irvine, CA, USA).

thrombus, the ability to significantly reduce RV afterload on the table in the cath lab with an aspiration device is attractive, rather than having to wait for thrombolytic action to take place over the course of hours.

In the FLARE study, 106 patients were treated with the Flowtriever device in a single-arm study design similar to that of SEATTLE II.[23] The device demonstrated successful reductions in RV/LV ratio by CT at 48 h, though interestingly had only a modest impact on pulmonary arterial pressures, which fell by only 2 mmHg. Whether this reflects baseline patient differences from those seen in OPTALYSE, where a 10.5 mmHg fall was seen in the group who received 12 mg of alteplase over 6 h, or whether this hints at a potential secondary benefit of low-dose thrombolytic action on the peripheral pulmonary vasculature is not clear.

Additionally, there was no change was seen in post-procedural oxygen saturations, or in heart rate and/or blood pressure in the FLARE study, raising the question of why significant thrombus extraction (without subsequent ongoing clinical action of the device outside of the lab) led to RV recovery at 48 h, but without immediate changes in bedside clinical observations at the end of the case.

The potential to alter clinical status 'on table' is, however, a valuable concept, though the catheter's bulkiness may lead to more complications in the real world than those reported in the first clinical trial experience with this device.

What is needed now

A clinical outcomes study

By some considerable distance, the most pressing need within the field of catheter-directed therapy for acute PE in patients with intermediate-high risk features is a randomized trial demonstrating improvement in robust clinical outcomes when CDT is tested against simple anticoagulation.

Most of the risk from high-risk PE is in the first few hours and most of the risk in intermediate-high risk PE is in the first few days. The 3-year follow-up from the PEITHO study suggests that the theoretical gains in long-term function and outcome may be less important than a treatment effect that happens in that first 30 days; outcomes studies should therefore principally focus on a short time horizon.[8]

There is likely to be a 'sweet spot' of risk-benefit whereby a clinical outcomes trial could demonstrate an improvement in hard outcomes. This would be in patients with intermediate-high risk PE who are stable enough to survive the peri- and post-operative period of catheter-based treatment, but in whom clinical features indicate a high risk of early haemodynamic collapse with simple anticoagulation.

A *post hoc* analysis of the PEITHO trial does point to such a group, who have relative hypotension (90-110 mmHg of systolic blood pressure), increased respiratory effort (respiratory rate >20), and those with decreased cardiac reserve (a history of congestive cardiac failure). Possessing two of those features was associated with a 20% risk of collapse in the first 7 days after hospital admission and this group represents an attractive cohort in whom we might be able to demonstrate improved clinical outcomes from catheter-directed treatments for PE against simple anticoagulation.[24] Sinus tachycardia and significant hypoxia are further potential markers of adverse outcomes and could represent additional criteria for selection.

It may also be important to intervene as early as possible in these patients given that there may be preferential improvement in haemodynamics when CDT is offered in the first 24 h of presentation.[25]

Bleeding reduction strategies when using catheter-directed thrombolysis

Whilst simple technical changes to delivery of the CDT procedure will likely result in fewer access site complications, there is more to consider than just the access site. In SEATTLE II, there were a few incidences of non-access site related serious bleeding complications[15] and therefore total dose of thrombolytic, and response of serum fibrinogen levels to ongoing treatment, may allow tailoring of treatments to individual bleeding risk.[26] Subsequent adaptation of treatment duration to real-time signals of clinical improvement may prove valuable.

OPTALYSE has suggested that very small doses of thrombolytic can potentially offload the right ventricle, though the dose-response signals seen in that study on clot burden and pulmonary arterial pressure suggest that the 12 mg dose over 6 h could be the optimal protocol.[16]

Reduced fibrogen levels predict thrombolytic associated bleeding.[26] We lack a study powered to show that adaptation of tPA duration and/or dose provides a meaningful impact on hard endpoints, but should these levels fall abruptly, discontinuation of thrombolytic treatment may reduce bleeding complications, particularly in those at high risk of bleeding.

Finally, it is not clear whether we need adjunctive heparin when delivering thrombolytic systemically or locally and if we do, the dosing remains a subject of interest.

Association of clot extraction technologies with meaningful (very) early improvements in haemodynamic status

Even with the large 20-Fr Flowtriever device able to extract large volumes of thrombus, heart rate and blood pressure were no different at the end of the procedure in the
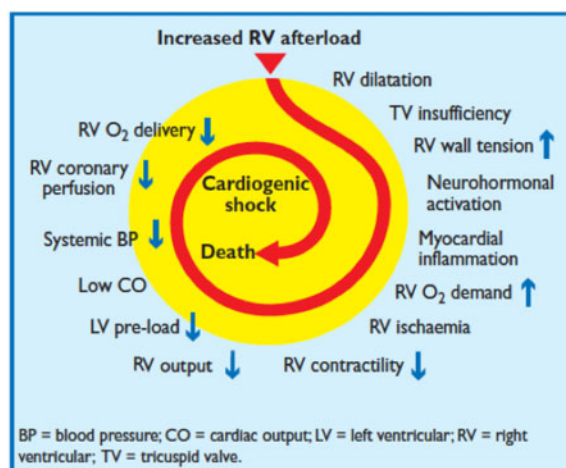

Figure 4 The spiral of RV shock in acute pulmonary embolism (Konstantinides *et al*.[27]).

FLARE study.[23] This raises several possibilities. The first is that the patients were not sick enough to see a signal. The second is that the dysfunctional RV takes time to recover. The third is that the pulmonary arteriolar run-off is more important than we think and adjunctive anticoagulation in the first 48 h could plausibly play an important synergistic role. The fourth possibility is that this was the play of chance within a small study and a larger study would show an effect on haemodynamics from clot extraction.

It is plausible that there could be a delay before clinical improvement begins with an extraction device, given the 'spiral of shock' previously described.[27] It may simply be that this spiral requires time to unwind. (*Figure 4*[27])

It is also plausible that a mixed approach in the sickest patients of clot extraction, followed by local, low-dose thrombolytic might better treat the entire pulmonary vasculature, though clearly a new dataset would be required to demonstrate safety, efficacy, and economic viability.

Comparison of catheter-directed strategies against surgical embolectomy

Surgical embolectomy is the most invasive treatment available for large volume central PE, but in haemodynamically stable patients is a relatively low-risk intervention in the modern era.[28] Individual case series suggest good results with this approach and, as with the large-bore clot extraction devices, has the attraction of a conceptually immediate impact on haemodynamics. However, it requires general anaesthesia, a potentially dangerous intervention in the decompensating PE patient,[29] mechanical ventilation (which has the attraction of improving degrees of hypoxia but the downsides of iatrogenic risk) and thoracotomy, which produces considerable morbidity.

It seems likely that centre experience - experience across the whole PE team and not just the handskills of the surgeon—may prove especially important if this approach is to achieve front line status in this area and, given the morbidity associated with this operation, clearly would need to target those with the most to gain from aggressive

treatment strategies but who could survive induction and surgery.

Medical support for the sickest PE patients in the process of clinical deterioration

In patients with a failing right ventricle, the proposed recommendations are to give a fluid bolus, start vasopressors and consider haemodynamic support[27,29] but all of these measures also possess the potential for hazard.

For many years, cardiologists gave litres of fluid to patients with RV infarction complicating inferior STEMI. However, there comes a point in this parallel condition whereby excess fluid loading causes paradoxical septal motion and begins to affect LV haemodynamics and cardiac output.[30] Current advice in RV myocardial infarction (MI) is to raise the central venous pressure to the upper limit of normal, and therefore in the failing RV caused by PE, where RV dilatation is a ubiquitous finding, it is possible that fluid administration may help initially, but that excessive fluid loading in RV shock may be detrimental.[31-33]

Vasopressors such as norepinephrine vasoconstrict the arterial system within seconds of administration and correct hypotension, maintaining essential organ perfusion. However, the problem in PE is one of afterload and excessive vasoconstriction of the peripheral arterial system will provide afterload obstruction in series in the presence of abnormal LV septal dynamics. However, systemic vasoconstriction with norepinephrine is likely preferable to excess fluid loading as a bridge to definitive therapy.[34]

The last question is regarding some sort of haemodynamic support. The two options in the area of haemodynamically significant PE are extracorporeal membrane oxygenation (ECMO) and the Impella RP device.

In massive PE, where blood pressure can be barely detectable, instigation of ECMO at the earliest timepoint appears to be a sound concept.[35-37] The failing heart does not fail purely because of afterload mechanics. There is a spiral of decline that mixes local and systemic factors, including systemic acidosis. Providing a period of stable mean arterial blood pressure with the ability to detoxify the bloodstream has obvious attractions.

The downsides of this, of course, include the nature of definitive treatment in this situation, which typically includes the use of systemic thrombolysis in the presence of large bore cannulae inserted into central veins in an unstable patient, with bleed risks apparent.[35] In an effort to minimize bleeding complications, ECMO could be combined with low-dose CDT to stabilize the sickest of PE patients, rather than considering full-dose systemic thrombolytic.[36]

The Impella RP is a micro-axial flow pump, designed to augment cardiac output in a failing right ventricle. Recent data have been supportive in the scenario of RV MI[38] though the addition of thrombolytic to a large bore device again presents bleeding risks, though early experience suggests that, in selected patients, it may be a useful adjunct to catheter-directed therapy with either low-dose CDT or clot extraction, where there is residual RV failure that might benefit from short-term haemodynamic support.[39] More data are required in this area, particularly following the recent US Food Administration caution on the use of the Impella RP.

Conclusion

Large volume central PE causing haemodynamic effect remains a major clinical problem and is one of the principal causes of avoidable in-hospital death. It typically presents in patients with comorbidities that make systemic thrombolysis unattractive and, in the majority of such patients, potentially life-saving systemic treatments are frequently withheld due to concerns over bleeding complications.

Catheter-directed treatments hold promise for patients at the sicker end of the spectrum, but we currently lack hard outcome data that would mandate it as a first-line treatment in any spectrum of the disease. Surrogate endpoints support selected use, but bigger and better trials are needed in this area.

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