**REVIEW**

**Treatment options and strategies for acute severe pulmonary embolism**


Department of Cardiology, Pulmonary Hypertension and Lung Transplantation Unit and Centre for Cardiovascular Imaging, The Prince Charles Hospital, Brisbane, Queensland, Australia and Department of CardioThoracic Surgery, Papworth Hospital, UK

**Key words**
pulmonary embolism, pulmonary hypertension.

**Correspondence**
Christian R. Hamilton-Craig, Rode Road, Chermside, Qld 4032, Australia.
Email: christian_hamilton-craig@health.qld.gov.au

Received 24 July 2007; accepted 18 January 2008.

**Abstract**
Pulmonary thromboembolism (PE) is the third most frequent cause of cardiovascular death after ischaemic heart disease and stroke. In fatal PE, 2/3 of patients die within first hour of presentation. There is a clinical impetus to rapidly recognize, risk-stratify and appropriately treat patients with acute severe PE. Current recommendations present conflicting classification systems, and there is often some confusion in the clinical evaluation and management of patients with acute severe PE. This review presents a series of real clinical cases, which illustrate the available treatment options, ranging from conservative therapy to thrombolysis through to percutaneous catheter fragmentation and open surgical embolectomy. We evaluate the evidence for the various strategies and propose an algorithm for clinicians with a focus on early risk stratification and timely referral. This is particularly relevant to regional and remote centres, as well as secondary and tertiary institutions.

**Introduction**

Acute severe pulmonary embolism (PE) is a life-threatening condition. There are several treatment options and strategies for improving outcomes in patients with severe PE. This article aims to assist physicians faced with the challenges of managing these acutely unwell patients.

Pulmonary thromboembolism (PE) is the third most frequent cause of cardiovascular death after ischaemic heart disease and stroke. The true incidence of PE is not known, but it is estimated that there are more than 600,000 cases each year in the USA alone.1 The International Cooperative Pulmonary Embolism Registry studies showed a mortality of 17.4% for all acute severe PE and the Management and Prognosis in Pulmonary Embolism Trial studies showed a 31% mortality if haemodynamic instability was present.2,3 In fatal PE, two-thirds of patients die within the first hour of presentation. Of the survivors, 70% fail to have the diagnosis made and the mortality rate in that group may approach 30%.1–4 In the elderly population, less than 30% of PE are diagnosed on the index visit.5

Risk factors for PE are well recognized and include surgical procedures, trauma, protracted bedrest, malignancy and specific prothrombotic disorders; however, there are many other common conditions that strongly predispose to PE, including congestive heart failure, pregnancy, use of oral contraceptive agents, chronic obstructive pulmonary disease, obesity and advanced age.2,6

There is a clinical imperative to rapidly recognize, risk-stratify and appropriately treat patients with acute severe PE. Current recommendations present conflicting classification systems and differ in management strategies.6–8 There is often confusion in the clinical evaluation and management of PE (either massive, submassive or severe), as individual patients may present with different manifestations of this condition.

Younger patients with otherwise normal hearts can often tolerate the haemodynamic stress created by PE and therefore frank right heart failure and haemodynamic collapse may be absent in this group.9 However, when PE occurs in a patient with underlying cardiopulmonary disease and reduced functional reserve, there may be a rapid onset of ventricular dysfunction and systemic compromise requiring urgent and aggressive treatment strategies.2,10

The authors recognize the need to better understand the treatment options and strategies available in the
management of acute severe PE in Australian and international clinical practice. The Prince Charles Hospital is one of the largest quaternary programmes for Pulmonary Hypertension and Interventional Cardiology in Australia, catering for more than 400 patients with pulmonary hypertension and conducting 5500 invasive cardiac procedures and over 15,000 echocardiograms annually. The following clinical cases illustrate the available treatment for patients presenting with acute severe PE and aim to help guide the clinician in choosing the right therapy at the right time.

Clinical cases

Case 1: early thrombolysis

A 44-year-old man was transferred by ambulance from home to the emergency department with sudden-onset dyspnoea and chest pain. He had a history of treated hypertension and recent orthopaedic surgery (hip replacement for congenital hip dysplasia 7 weeks earlier). His blood pressure (BP) was 98/54, significantly lower than usual. Oxygen saturation was 90% on arrival. Electrocardiogram (ECG) showed sinus tachycardia with a deep S wave in lead I, Q wave in lead III and T-wave inversion in V2 and V3, and intermittent right bundle branch block (Fig. 1). D-dimer was 11.46 mg/L.

Computed tomography pulmonary angiogram (CTPA) showed bilateral proximal pulmonary emboli. Trans-thoracic echocardiography carried out in the emergency department showed a severely dilated right ventricle with normal wall thickness. He was treated with thrombolysis using alteplase 100 mg, i.v. unfractionated heparin and monitored in the intensive care unit (ICU). There were no bleeding complications and his oxygen exchange improved within 24 h and right ventricular (RV) function normalized on subsequent testing after 72 h. He was discharged on long-term warfarin and the follow up will be for 5 years, including repeat echocardiography and ventilation–perfusion scans to monitor for development of chronic thromboembolic pulmonary hypertension (CTEPH).

Comment

This patient had an acute severe PE with moderate haemodynamic compromise, who presented early and was successfully thrombolysed without incident. As noted, younger patients with functional reserve can better tolerate the haemodynamic stress of severe PE; therefore,
relative hypotension in a patient with no previous lung disease is an indicator of PE severity, reflecting the degree of RV strain. Clinical indicators for early aggressive intervention for massive PE require one or more of the following features:8,14

- Arterial hypotension (<90 mmHg systolic or drop of >40 mmHg from usual value)
- Cardiogenic shock with peripheral hypoperfusion and hypoxia
- Circulatory collapse, including syncope or need for cardiopulmonary resuscitation
- Echocardiographic findings indicating RV dilatation and/or pulmonary hypertension
- Widened arterial–alveolar O₂ gradient (>50 mmHg)

Patients with these parameters should be considered for thrombolysis and/or early referral to specialist centres. The indications and contraindications for thrombolysis in acute severe PE are shown in Table 1. All patient receiving thrombolysis should receive i.v. heparin infusion to maintain the partial thromboplastin time at 1.5–2.5 times the upper normal limits and either alteplase (rt-PA) 10 mg as an i.v. bolus for more than 1–2 min, followed by 90 mg as an i.v. infusion for more than 2 h or urokinase infusion of 250 000 IU/h mixed with 2000 IU of heparin for more than 2 h, followed by an infusion of 100 000 IU/h of urokinase for 12–24 h.

Limitations of thrombolysis include the need for observation in an intensive-care/high-dependency environment, the availability of alteplase in regional centres and the risk of haemorrhage. Patients who require thrombolysis should ideally be transferred to larger centres with experience in the evaluation and monitoring of acute severe PE and that can manage haemorrhagic complications should the need arise.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Indications and contraindications for thrombolysis in pulmonary embolism (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td></td>
</tr>
<tr>
<td>Massive PE: first-line treatment</td>
<td></td>
</tr>
<tr>
<td>Haemodynamic compromise</td>
<td></td>
</tr>
<tr>
<td>Failure to respond to anticoagulants</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td>Recent major trauma, major operation or non-compressible vascular puncture (within 10 days)</td>
<td></td>
</tr>
<tr>
<td>Recent stroke (within 2 months) or any history of haemorrhagic stroke</td>
<td></td>
</tr>
<tr>
<td>Active internal bleeding</td>
<td></td>
</tr>
<tr>
<td>Significant bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>Relative</td>
<td></td>
</tr>
<tr>
<td>Prolonged cardiopulmonary resuscitation</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Diabetic proliferative retinopathy</td>
<td></td>
</tr>
</tbody>
</table>

**Electrocardiogram**

The ECG findings in the patient were similar to the classic ‘‘S1Q3T3’’ pattern of right heart strain, more accurately termed acute cor pulmonale. This is seen when sudden pressure and volume overload from RV outflow obstruction causes repolarization abnormalities. It is associated with massive or submassive PE and portends a poor prognosis.11 Notably, the most common ECG abnormalities in patients with pulmonary emboli are sinus tachycardia with entirely non-specific ST-wave and T-wave changes.12

**Case 2: surgical embolectomy**

A 35-year-old woman presented to our emergency department with a history of syncope 12 h earlier. On arrival, she was in respiratory distress with oxygen saturation of 84% breathing room air. She was haemodynamically compromised with BP 85/45 mmHg and clinically in extremis. A CTPA showed large obstructive filling defects in the left and right main pulmonary arteries. Emergency echocardiography showed a severely dilated right ventricle with normal wall thickness and estimated right ventricular systolic pressure (RVSP) of 44 mmHg (Fig. 2).

After consultation with a multidisciplinary team, including the pulmonary hypertension unit, echocardiologist and cardiothoracic surgeon, the consensus was for primary open surgical embolectomy (Fig. 3).

Ten days postembolectomy repeat echocardiography showed normalized RV size and function, with an estimated RVSP of 29 mmHg. A thrombophilia screen showed significant Protein S deficiency and the patient had been taking the oral contraceptive pill, a recognized high-risk combination for PE. She was commenced on lifelong antiplatelet therapy.
warfarin, advised against further pregnancy or use of oral contraceptives and an inferior vena cava (IVC) filter was inserted before discharge 10 days after the index event.

Comments

This patient had symptoms of a recent onset shown by unheralded haemodynamic compromise in a young patient with normal cardiorespiratory reserve. Right heart strain was shown on both the ECG and the echocardiogram and she was in impending cardiogenic shock. The thrombus burden was large and there was concern that thrombolysis, although a valid therapeutic option in this setting, may not have resulted in full thrombus dissolution. Owing to the availability of a cardiothoracic surgeon with considerable experience in the surgical treatment of both acute PE (embolectomy) and CTEPH (pulmonary endarterectomy), this patient benefited from complete surgical removal of thrombus burden (embolectomy) with normalization of function. This also reflects the advantage of consultation with a multidisciplinary team experienced in the options for treating acute severe PE.

Surgical embolectomy

Surgical embolectomy has been compared with medical thrombolysis in only a handful of clinical trials. The largest, anon-randomized trial comparing 37 consecutive patients with severe PE, showed successful medical treatment (i.v. rt-PA infusion) in 75% of patients, with a mortality rate of 33%, whereas surgical treatment was successful in 85%, with a mortality rate of 23%. These figures reflect high death rates in both groups, signifying the significant dangers of acute severe PE. The authors suggested that medical treatments were associated with a higher mortality, increased risk of major haemorrhage and increased recurrence of PE. The patient groups in this study were not comparably matched, which may have created a bias towards treating patients with more severe PE and those with more comorbidity with thrombolysis. The data do suggest, however, that surgical embolectomy in experienced hands has both good short-term and medium-term outcomes and is a valid and useful option. Many patients, however, will undergo thrombolysis as it is more readily available. Early referral to a centre with expertise in both surgical and medical options is desirable.

Right ventricular assessment

Echocardiography is an important tool in the early risk stratification of patients with acute PE and is recommended by guidelines. Distinguishing between minor, sub-massive and massive PE depends on the presence or absence and degree of right heart dysfunction. Acute RV pressure overload (as a result of obstruction to RV outflow) causes a vicious cycle of increased myocardial oxygen demand, ischaemia, loss of left ventricular (LV) preload and falling cardiac output, leading ultimately to cardiogenic shock. RV failure with haemodynamic instability is associated with a very poor prognosis. With mortality rates of up to 65%, RV hypokinesis is an independent predictor of 30-day mortality. It is clear that in patients with significant RV dysfunction early and aggressive intervention before LV decompensation and loss of cardiac output is critical. Of note, however, a recent meta-analysis of all randomized controlled trials comparing thrombolysis with heparin alone in patients with acute PE and preserved BP and RV function concluded that the benefits of thrombolysis still remain unclear in this group. Patients presenting with acute severe PE should therefore have formal assessment of RV function.

The American Society of Echocardiography has published normal values for RV size based on the major axis, basal diameter and mid-cavity diameter. Echocardiographic quantification of RV function requires some experience in interpretation because of the unusual geometry of the right ventricle and the heavy trabeculation of the wall. Multislice helical CTPA is currently the mainstay for diagnostic evaluation of suspected acute PE and can also give helpful information on RV size. The CT image axis can be manipulated on the reporting workstation to give a four-chamber view similar to echocardiography and the right and LV dimensions can be quantified. This approach has been shown to give prognostically significant information when the RV/LV ratio is in excess of 0.9, giving an odds ratio for major adverse events (death, ventilation, inotropic support, rescue thrombolysis or...
surgical embolectomy) of 4.02 (95% confidence interval 1.06–15.19; \( P = 0.041 \); Fig. 4). A significant limitation is that CT images are not ECG-gated and therefore ventricular dimensions can vary depending on the phase of the cardiac cycle. Increased RV size on CT should cue the ordering of urgent echocardiography and physicians should be encouraged to query the reporting radiologist about RV size as well as clot burden. Echocardiography in experienced hands remains the gold standard for evaluation of RV function in acute PE as supported by current guidelines. When in doubt, patients should be transferred to larger centres for evaluation.

**Genetic prothrombotic disorders**

Genetic predispositions to venous thromboembolism are relatively rare, but these patients have a high risk of recurrent events. Patients with an unexplained thrombotic episode below the age of 40 years, with recurrent deep vein thrombosis (DVT) or PE and those with a positive family history should be investigated for prothrombotic genetic disorders. The most common prothrombotic genetic defects that have been identified are resistance to activated protein C (due to the factor V Leiden mutation in 90% of cases), deficiencies of antithrombin III, protein C and protein S, hyperhomocysteinaemia and the prothrombin gene mutation. Table 2 illustrates the standard tests that should be carried out before commencement of coumadin-based anticoagulation in these patients.

**Case 3: catheter fragmentation of PE**

A 37-year-old man was transferred in extremis from another institution 3 weeks after having had a major motor vehicle accident. He sustained complex fractures of the left tibia with vascular compromise and had undergone orthopaedic surgery with a popliteal artery bypass. He had received postoperative prophylaxis with low-dose s.c. enoxaparin. On postoperative day 10, he suddenly developed cardiogenic shock with systolic BP 80 mmHg and severe hypoxaemia. He was admitted to the ICU and deteriorated, requiring mechanical ventilation, high-dose inotropic support and inhaled nitric oxide therapy. CTPA confirmed a saddle PE subtotally obstructing outflow from the right heart. Echocardiography showed a massively dilated and hypocontractile right ventricle. There was reluctance to thrombolise because of recent major arterial surgery despite ongoing clinical deterioration and the patient was transferred to our institution for catheter-based intervention. Formal pulmonary angiography confirmed a large thrombus in the saddle position. Using a stiff Amplatzer wire (AGA Medical, MN, USA), the thrombus was dislodged from the main pulmonary artery, breaking up into fragments that lodged mainly in the right proximal pulmonary tree. This was associated with immediate and marked improvement in haemodynamics and reduction in inotropic requirements. We then proceeded to fragment and aspirate the thrombus from the right pulmonary branches (Fig. 5). A pigtail catheter was placed within the body of the remaining thrombus and a urokinase infusion commenced at 4400 IU/kg/h i.v. for 12 h. There were no bleeding complications and the patient was extubated on day 2 after the procedure with no ongoing oxygen requirements. On follow-up echocardiography, RV size, systolic pressure and function had returned to normal. An IVC filter was placed before discharge on long-term warfarin.

**Table 2 Testing for prothrombotic disorders**

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden (activated protein C resistance)</td>
</tr>
<tr>
<td>Protein C and S levels†</td>
</tr>
<tr>
<td>Prothrombin gene mutation (20210A)</td>
</tr>
<tr>
<td>Autoantibodies (ANA, ENA, anticardiolipin/lupus inhibitor)‡</td>
</tr>
<tr>
<td>Homocystein MTHFR mutation</td>
</tr>
<tr>
<td>Plasminogen level</td>
</tr>
<tr>
<td>Fibrinogen level‡</td>
</tr>
<tr>
<td>Factor XII (for deficiency)</td>
</tr>
<tr>
<td>Factor VIII (for level &gt;150%)</td>
</tr>
<tr>
<td>CRP</td>
</tr>
</tbody>
</table>

†Affected by warfarin. ‡Associated with spontaneous arterial thrombosis.

ANA, antinuclear antigen; CRP, C reactive protein; ENA, extractable nuclear antigen; MTHFR, methylenetetrahydrofolate reductase.

Figure 4 Positive computed tomography pulmonary angiogram scan reformatted to 4-chamber view for ventricular dimensions, right ventricle—left ventricle ratio 1.02 (courtesy of Medical Imaging Department, The Prince Charles Hospital).
In cases of massive PE, the aim is to rapidly relieve central obstruction and prevent the onset or progression of cardiogenic shock. Percutaneous fragmentation techniques and catheter-directed thrombolysis are useful to promptly re-establish pulmonary blood flow. This is particularly valuable when systemic thrombolysis fails (or is contra-indicated) and such patients should be rapidly transferred to a quaternary centre with expertise in pulmonary hypertension management.

Mechanical fragmentation results in increased clot surface area, thereby allowing effective subsequent thrombolysis. The increased cross-sectional area of multiple small arteries (even if partially occluded by small fragments of thrombus) is significantly greater than that of the larger branch arteries, thereby providing reduction in vascular resistance and recovery of flow. Improvements in survival have not been shown, as there are no large randomized studies. However, haemodynamic theory suggests that the redistribution of larger central clots into the peripheral pulmonary bed may immediately increase total pulmonary blood flow and relieve RV afterload, which has been confirmed in vivo.

Verstraete et al. compared the effects of localized catheter-delivered thrombolysis versus i.v. infusion of rt-PA and showed no difference in efficacy or safety between the two techniques. Given the need for invasive catheter-based intervention for localized intrapulmonary thrombolysis, this technique rapidly fell out of favour. The study, however, was a relatively small trial (only 15 and 19 patients in each group, respectively), and patients had preserved systemic (systolic) BP. These results may not therefore be applicable to the patient with acute severe PE and significant haemodynamic compromise or cardiogenic shock in whom more aggressive therapy is warranted.

Catheter fragmentation followed by intrapulmonary thrombolytic infusion is a useful, and possibly underused, technique to achieve rapid resolution of thrombus and improvement in haemodynamics. Simple fragmentation using an angiography catheter may be enough to break the vicious cycle of RV outflow obstruction and consequent LV failure, as well as increasing the available surface area for effective thrombolysis. This technique should be considered in patients with failed systemic thrombolysis, but should be carried out in centres with adequate infrastructure.

**Figure 5** Aspirated portions of clot during percutaneous catheter fragmentation of pulmonary embolism (PE). Note the small fragments which have been aspirated through a large bore catheter which was used to dislodge a large thrombus occluding the main pulmonary artery.

**Comments**

In cases of massive PE, the aim is to rapidly relieve central obstruction and prevent the onset or progression of cardiogenic shock. Percutaneous fragmentation techniques and catheter-directed thrombolysis are useful to promptly re-establish pulmonary blood flow. This is particularly valuable when systemic thrombolysis fails (or is contra-indicated) and such patients should be rapidly transferred to a quaternary centre with expertise in pulmonary hypertension management.

Mechanical fragmentation results in increased clot surface area, thereby allowing effective subsequent thrombolysis. The increased cross-sectional area of multiple small arteries (even if partially occluded by small fragments of thrombus) is significantly greater than that of the larger branch arteries, thereby providing reduction in vascular resistance and recovery of flow. Improvements in survival have not been shown, as there are no large randomized studies. However, haemodynamic theory suggests that the redistribution of larger central clots into the peripheral pulmonary bed may immediately increase total pulmonary blood flow and relieve RV afterload, which has been confirmed in vivo.

Verstraete et al. compared the effects of localized catheter-delivered thrombolysis versus i.v. infusion of rt-PA and showed no difference in efficacy or safety between the two techniques. Given the need for invasive catheter-based intervention for localized intrapulmonary thrombolysis, this technique rapidly fell out of favour. The study, however, was a relatively small trial (only 15 and 19 patients in each group, respectively), and patients had preserved systemic (systolic) BP. These results may not therefore be applicable to the patient with acute severe PE and significant haemodynamic compromise or cardiogenic shock in whom more aggressive therapy is warranted.

Catheter fragmentation followed by intrapulmonary thrombolytic infusion is a useful, and possibly underused, technique to achieve rapid resolution of thrombus and improvement in haemodynamics. Simple fragmentation using an angiography catheter may be enough to break the vicious cycle of RV outflow obstruction and consequent LV failure, as well as increasing the available surface area for effective thrombolysis. This technique should be considered in patients with failed systemic thrombolysis, but should be carried out in centres with adequate infrastructure.

**Figure 6** Schematic drawing representing the effect of mechanical fragmentation of available clot surface area for thrombolysis (a) before and (b) after mechanical fragmentation. Note that several peripheral branches of the pulmonary artery are open after fragmentation of the thrombus. (Reproduced from Uflacker with permission.)
cardiothoracic surgical back-up and expertise in both catheter interventions and postprocedure management.

**Case 4: late thrombolysis**

A 64-year-old woman presented to a regional hospital 4-h drive north of our institution, with a 2-week history of a swollen right calf and progressive dyspnoea. She had medical history of hypertension and significant obesity (body mass index 40). CTPA confirmed thrombus straddling the left and right pulmonary arteries with near-complete obstruction. Doppler ultrasonography showed extensive thrombus in the deep veins of the right leg. She had been managed with therapeutic dose enoxaparin and warfarin; however, on day 2 of her admission, she had three syncopal events associated with oxygen desaturation prompting a medical arrest call. On transfer to our institution, she was tachycardic, hypotensive, $S_2O_2$ 84% on room air, with increased jugular venous pressure, a RV heave and an $S_4$ gallop audible. Troponin I level was increased and liver enzymes were deranged. Echocardiography showed a severely dilated right heart with an estimated RVSP of 60 mmHg. She was reviewed by the cardiac surgeon and not considered a suitable candidate for embolectomy because of the late time-course of her presentation and her marked obesity. She was thrombolysed with alteplase 100 mg for more than 2 h and given standard i.v. unfractionated heparin. Clinical parameters significantly improved overnight, with resolution of heart failure symptoms and repeat echo 3 days after thrombolysis showed improvement in RV function and normalization of pressures.

**Comment**

This study shows that patients presenting relatively late can still benefit from systemic thrombolysis; however, this is best judged by centres with specialist expertise. We recommend that patients with syncope, severe hypoxia, signs or symptoms of RV failure should be discussed with, or transferred to, larger institutions regularly treating patients with acute severe pulmonary emboli. Such centres should have alteplase available for systemic thrombolysis and should have appropriate protocols available to facilitate staff in rapidly thrombolysing these patients. Larger centres that may use localized intrapulmonary thrombolysis or catheter fragmentation technique should also have urokinase available.

The study also raises the issue of low-molecular-weight heparins (LMWH) in the obese patient. The initial studies evaluating LMWH had few patients at extremes of bodyweight and some manufacturers recommend dose capping of LMWH, reflecting the uncertainty of their pharmacokinetic response in larger patients. There is concern that the arbitrary capping of LMWH doses (e.g. 100 mg b.i.d. of enoxaparin) may result in undertreatment of these patients. The use of uncapped weight-based doses of LMWH (e.g. >200 IU/kg per day of dalteparin) does not appear to adversely affect clinical outcomes in patients with venous thromboembolism weighing more than 100 kg and this finding was also seen in a meta-analysis involving data on 921 overweight patients with ischaemic heart disease. Guidelines from product information as well as review articles recommend clinical monitoring of anti-Xa levels (3–4 h after dosing with LMWH) in patients at extremes of bodyweight (both high and low), age or renal function. Therapeutic drug monitoring is underutilized in these patient groups.

**IVC filters**

IVC filters have been shown in randomized controlled trials to reduce the rate of recurrence of PE. Recurrent clinically symptomatic PE after IVC filter placement is rare, being reported in only 2–5% of cases. A range of filters designed to prevent thromboembolism from the deep leg and pelvic veins is available for percutaneous insertion. The procedure is a relatively low-risk procedure through the femoral vein. Complications are rare and are mainly associated with long-term implantation (such as migration of the filter, IVC perforation and IVC thrombosis leading to phlegmasia cerulea dolens). Retrievable filters have been developed for short-term and medium-term use, such as in patients with multisite severe trauma who are at particularly high risk of thromboembolism and may receive prophylactic filters during ICU admission. To minimize exposure to potential long-term complications, it is prudent to apply strict criteria for IVC filter insertion. The relative and absolute indications for IVC filters are listed in Table 3.

**Case 5: acute-on-chronic PE**

A 52-year-old man presented to a rural hospital with a 2-month history of cough, progressive dyspnoea and syncope on exertion. He was found to have hypoxia with oxygen saturation of 90% on room air, tachycardia, with a loud second heart sound and an $S_3$ gallop. Ventilation/perfusion imaging showed multiple moderate-sized mismatched defects and he was commenced on warfarin and transferred to our institution. Echocardiography showed moderately severe RV dilatation with flattening of the interventricular septum in systole, consistent with RV pressure overload, no intracardiac shunt and an estimated RVSP of 77 mmHg. CTPA confirmed bilateral pulmonary emboli in the left lower, right middle and right lower lobes.
Cardiac magnetic resonance imaging and magnetic resonance pulmonary angiography showed a hypertrophied right ventricle with poor systolic function (RV ejection fraction 27%) and dilated pulmonary arteries with residual filling defects consistent with organizing thrombus (Fig. 7). He was diagnosed as having acute-on-chronic emboli with a significant thrombus burden and late presentation not suitable for thrombolysis. His anticoagulation was continued and sildenafil 25 mg t.i.d. was added to treat his pulmonary arterial hypertension (PAH) and provide afterload reduction to the right ventricle. After 3 months, repeat echocardiography showed some reduction in RVSP from 77 to 59 mmHg. Right heart catheter confirmed pulmonary artery pressure of 58/15 mmHg. He was advised of the diagnosis of CTEPH of moderate severity and that he may benefit from surgical pulmonary thromboendarterectomy in future. Sildenafil was continued as a bridge to surgery.

Comment

Patients with acute severe PE presenting with an RVSP on echocardiography of >50 mmHg, without clinical or echocardiographic signs of RV failure, probably have a “conditioned” right ventricle because of underlying CTEPH.\textsuperscript{30,31} Patients presenting de novo with an acute PE are unable to acutely generate and maintain an RVSP of this magnitude because of the vicious haemodynamic cycle.\textsuperscript{31}

In patients with underlying CTEPH and acute-on-chronic embolism, surgical embolectomy alone is ineffective and highly dangerous, as it removes only the acute embolus, leaving the underlying pulmonary hypertension unchanged.\textsuperscript{30} Not surprisingly, therefore, these patients have a stormy postoperative course and high mortality. Thrombolysis, however, can be effectively used to treat the acute event in the scenario of acute-on-chronic PE or in patients with a stuttering course, such as the patient of case 3 who may have had multiple sequential pulmonary emboli. There is no evidence, however, that thrombolysis is of any benefit in established chronic thromboembolic pulmonary hypertension.

An important clinical issue arises in the follow up of patients presenting with acute severe PE; specifically who should be monitored for the subsequent development of CTEPH. High-risk groups include patients with important central thromboembolic events, patients presenting with significant haemodynamic compromise and/or RV dysfunction, those with a documented thrombophilia and those with persistent abnormalities of lung perfusion on follow-up testing.\textsuperscript{30,32–34} Follow up of patients in these categories should be for a minimum of 2 years and should be comprehensively re-evaluated at any time if new symptoms develop. Most patients with an effectively treated PE return to normal, but the published figure of 3.8% progressing to develop CTEPH still is a large absolute number, given the frequency of acute PE in our population.\textsuperscript{30,35}

Sildenafil, a phosphodiesterase-5 inhibitor is effective in the treatment of PAH.\textsuperscript{36,37} Sildenafil is now Pharmaceutical Benefits Scheme listed for use in PAH (idiopathic, associated with connective-tissue disease or occurring after surgical repair of congenital systemic-to-pulmonary shunts), but not for CTEPH at this stage.\textsuperscript{37} In our institution, we have found sildenafil useful to reduce pulmonary arterial pressures in a variety of situations, such as acutely post-heart transplantation or heart–lung transplantation, after mitral valve surgery and we are currently trialling this

### Table 3 Indications for inferior vena cava filter

<table>
<thead>
<tr>
<th>Absolute indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE with contraindications to anticoagulation</td>
</tr>
<tr>
<td>Recurrent PE despite adequate anticoagulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic thromboembolic pulmonary disease (before surgery)</td>
</tr>
<tr>
<td>Massive or submassive PE with haemodynamic compromise</td>
</tr>
<tr>
<td>Large, free-floating iliocaval thrombus</td>
</tr>
<tr>
<td>Poor compliance with medications</td>
</tr>
<tr>
<td>History of PE disease with upcoming surgery</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism.
therapy in patients with CTEPH not amenable to surgery. Similarly, bosentan, an endothelin receptor antagonist also effective in the treatment of PAH, has been shown to have some efficacy in CTEPH.38,39 These PAH-specific therapies are not widely available, supporting the need for these patients to be referred early to centres with expertise in the treatment of pulmonary hypertension in general. Pulmonary thromboendarterectomy is the treatment of choice for suitable patients with CTEPH.

Conclusions

Patients presenting with acute severe PE require rapid and effective risk assessment in order to choose the appropriate management strategy. A suggested approach to assist clinicians with decision-making in the management of acute severe PE is presented as an algorithm (Fig. 8). An important message is that thrombolysis should be considered early, followed by expedited transfer to centres experienced in the management and long-term follow up of more complex cases. Perhaps, we should be thinking of acute severe PE in the same mindset as is accepted for ST-elevation myocardial infarction – time is right ventricle!

References

4 Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser K, Rauber K et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable


