Preventing venous thromboembolism in the critically ill – can we do more?

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Pulmonary embolism is the most common preventable cause of hospital death; and of all the different patient groups, the critically ill are particularly at risk of venous thromboembolism. Most critically ill patients have multiple risk factors. Clinical trials have shown that the use of low molecular weight heparin (LMWH) is safer than unfractionated heparin in this population. Further trials are required to look at the risks and benefits of dose adjusting LMWH at the extremes of weight, in patients with renal failure and those on antiplatelet agents. Heparin-induced thrombocytopenia is still a risk with LMWHs so a safer anticoagulant such as fondaparinux and even the new oral anticoagulants merit trials. Further evidence is also needed for the use of graduated compression stockings and pneumatic devices.

Keywords: *inferior vena cava filter; venous thromboembolism; low molecular weight heparin; unfractionated heparin; thromboprophylaxis*

A systematic review by the US Agency for Healthcare Quality and Research of 79 safety interventions for hospital patients, ranked pulmonary embolism (PE) as the most common preventable cause of hospital death, and thromboprophylaxis (TP) as the number one strategy to improve patient safety in hospitals.[1] Of all the hospital patient groups, the critically ill are particularly at increased risk of venous thromboembolism (VTE) which contributes significantly to their morbidity and mortality. PE is frequently seen at post mortem in these patients, the incidence being as high as 27%.[2] The incidence of image-proven deep venous thrombosis (DVT) in critically ill patients ranges from <10% to almost 100% depending upon the screening methods and diagnostic criteria used.

Most critically ill patients have multiple risk factors for VTE. Many risk factors predate intensive care unit (ICU) admission, in particular recent surgery, trauma, sepsis, malignancy, immobilisation, increased age, heart or respiratory failure and previous VTE, so that about 5% have evidence of DVT on ultrasound scanning on admission.[3] Other risk factors are acquired on the ICU including immobilisation, pharmacological paralysis, central venous catheterisation, additional surgical procedures, sepsis, vasopressors and haemodialysis.[4] Hospitalised patients recovering from major trauma have the highest risk of developing VTE; with a risk of DVT exceeding 50% without thromboprophylaxis, explaining why PE is the third leading cause of mortality after the first day.

Mechanical measures of thromboprophylaxis

Immobility increases the risk of DVT tenfold.[5,6] Mechanical methods of thromboprophylaxis act by reducing venous stasis in the leg. The major advantage of these methods is the avoidance of systemic anticoagulation and thus the incumbent risk of bleeding. However studies suggest the benefits of mechanical methods in reducing VTE are small or negligible. A meta-analysis of the only two randomised controlled trials performed, showed both graduated compression stockings (GECs) and intermittent pneumatic compression devices (IPC) produced no benefit.[7]

GECs have been shown to reduce the incidence of post-operative DVT in general surgery and neurosurgery. However there are no good RCTs as yet of GECs in medical patients, apart from the CLOT study[8] which showed no reduction in VTE in stroke patients using GECs, but actual harm due to skin damage. CLOT 3 randomised IPC versus no IPC in over 2800 stroke patients and the rate of proximal DVT decreased from 12.1% to 8.5% and possibly improved survival.[9] In a recent study in 798 intensive care patients using multiple propensity scores adjusted analysis, the use of IPC but not GECs was associated with a lower VTE incidence regardless of type of pharmacological thromboprophylaxis used.[10]

Pharmacological methods of thromboprophylaxis

Aspirin

Aspirin's importance in the primary and secondary prevention of atherosclerotic disease is well established, but it only reduces risk of VTE by about 25%[11] whereas low molecular weight heparin (LMWH) reduces risk by 60-70%, so why would one use such an inferior agent? Furthermore, critically ill patients are more likely to suffer the deleterious consequences of aspirin therapy, including increased risk of haemorrhage, and reduced urinary prostaglandin synthesis decreases glomerular filtration, further restricting its use in critically ill patients.

Unfractionated heparin (UFH) and LMWH

Three randomised clinical trials compared UFH to placebo in intensive care patients.[12-14] The largest by Kapoor *et al*, studied 791 patients; DVT was detected in 31% of the placebo-treated group but only 11% of the UFH group (RRR 65%, p=0.001) and PE was reduced from 5% to 2% in the treated group.[14] Similar trials against placebo have been conducted with LMWH. For example Fraisse *et al* randomised 223 patients receiving mechanical ventilation for exacerbations of COPD to receive nadroparin or placebo.[15] DVT was detected by routine venography in 28% of the placebo group and 15% of those treated with nadroparin, a relative risk reduction of 45% (p=0.045%), with no difference in the major bleeding between the two groups.

UFH has an inferior safety profile when compared to LMWH for it has a tenfold increased incidence of fatal heparin-induced thrombocytopenia (HIT) when compared to LMWH. Prior to the PROTECT study, one study compared UFH to LMWH in 325 medical intensive care patients. DVT was detected by ultrasound in 16% of patients receiving UFH compared to 13% on LMWH, with no differences noted in the rates of proximal DVT or major bleeding.[16] The PROTECT study[17] was a landmark study that randomised 3764 patients to 5,000u dalteparin versus

unfractionated heparin twice daily. The rate of proximal DVT on ultrasound was similar (5.1% with dalteparin *vs* 5.8% with UF heparin), although the rate of PE was significantly lower (1.3% dalteparin *vs* 2.3% UF heparin, hazard ration 0.51, p=0.01). Rates of major bleeding were also similar but as expected HIT was less common with dalteparin.

A previously discussed limitation of LMWH in the intensive care population is the risk of drug accumulation in patients with renal impairment leading to an unpredictable and excessive anticoagulation. Nevertheless in the PROTECT study 6.7% of patients receiving dalteparin 5,000 IU required renal dialysis during their stay. It was noted in a later publication from the PROTECT study that renal replacement therapy was a minor risk factor for bleeding (HR 1.75, 1.2-2.56).[18] Paradoxically there is also concern that the use of vasopressors and the metabolic condition of some critically ill patients may reduce the effectiveness of pharmacological prophylaxis. The putative mechanism is decreased absorption of LMWH from the subcutaneous tissues due to reduced perfusion caused by the vasopressor. Multiple organ dysfunction may alter drug metabolism, distribution and binding to albumin and acute phase proteins.

Vitamin K antagonists

Treatment with adjusted-dose oral vitamin K antagonists with a target INR is not recommended in the critically ill because dosing is difficult and unpredictable with a significant risk of both over- and under-anticoagulation.

Fondaparinux

No studies have been undertaken using fondaparinux in an intensive care population although a study in 849 older acute medical patients versus placebo showed that it is effective in this group and there was no increased bleeding when compared to placebo.[19]

Bleeding risk and side effects

Many critically ill patients have increased risk of bleeding and therefore pharmacological thromboprophylaxis may be relatively or absolutely contraindicated in those with:

- Thrombocytopenia with a platelet count <50 × 10^9/L
- Underlying coagulopathy
- Evidence of active bleeding
- Known bleeding disorder
- Uncontrolled hypertension
- Use of oral anticoagulation
- Lumbar puncture/epidural/spinal analgesia within the previous four hours
- New ischaemic or haemorrhagic CVA.

Due to the risk of HIT with heparin, patients should have regular full blood counts to ensure they are not becoming thrombocytopenic.

The role of IVC filters

These are discussed in detail in other articles in this supplement. Briefly, despite insurance payments in the USA for using inferior vena cava (IVC) filters for primary prophylaxis in trauma patients, a meta-analysis of prospective studies found no difference in the rates of PEs among such patients and bariatric patients with and without prophylactic IVC filters.[20,21]

The main indication for IVC filters is for the prevention of PE in patients with established VTE who have a contraindication to anticoagulation.[22] Most guidelines recommend that anticoagulation be considered in all patients with an IVC filter once a temporary contraindication to anticoagulation has passed and that IVC filter insertion is not indicated in unselected patients with VTE who will receive standard anticoagulant therapy.

The long-term use of IVC filters has been disappointing. Decousus et al 1998[23] studied a mixed population of surgical and medical patients who had a proven DVT and underwent randomisation with regards to insertion of an IVC filter. Both groups were anticoagulated with either heparin or LMWH. Patients with a contraindication to anticoagulation were excluded from the study. At 12 days 1.1% of the patients with an IVC filter had suffered a PE compared to 4.8% in the group without a filter. After two years' follow up however, 20.8% of the filter group and 21% of patients in the non-filter group had gone on to suffer a further PE.

In summary, where possible and whenever the contraindication to anticoagulation is transient, a retrievable filter should be favoured and anticoagulation commenced when it is no longer contraindicated.

Future directions

Many questions around thromboprophylaxis in intensive care patients remain and the absence of evidence supporting this area is striking. The benefits of mechanical thromboprophylaxis remain uncertain, current data suggests IPCs may have some benefit. For the moment the use of LMWHs is the preferred pharmacological agent, but because the risk of VTE is high in intensive care, the question remains as to whether higher doses would reduce the rate of VTE further, or would this lead to an unacceptable bleeding rate? The use of LMWHs at the extremes of body weight, in those with renal insufficiency and on antiplatelet agents remains insufficient and high-quality studies are needed to inform clinicians about dosing in these groups. HIT remains a risk with LMWHs so a safer anticoagulant would be preferable – would fondaparinux fit this role? Will the new oral anticoagulants be suitable for thromboprophylaxis in intensive care patients? There is currently inadequate data on safely reversing the new orals, so perhaps we should await this data before contemplating trials.

After total hip replacement or cancer surgery, extended duration thromboprophylaxis, given for 28-35 days post surgery, usually after 4-6 days admission, ie 3-4 weeks at home, significantly reduce the risk of VTE when compared to standard use of LMWH. It appears reasonable that intenisve care patients who fall into this group should be considered for extended prophylaxis, provided there is no increased bleeding risk. No clinical trials have assessed the benefits of extended duration prophylaxis after other illnesses requiring ICU admission and would be welcomed.

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Current status of inferior vena cava filters

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Pulmonary embolism (PE) is a common cause of death. Treatment and prevention from a known deep venous thrombosis (DVT) is usually by anticoagulation. However, in some patients anticoagulation is not possible or effective and IVC filters are used as an alternative or adjunct. Inferior vena cava (IVC) filters have become widely used but are controversial with limited data on their efficacy, indications and safety.

Keywords: *inferior vena cava filter; IVC filter; pulmonary embolism*

IVC filter design and development

Surgical interruption of the inferior vena cava (IVC) to prevent pulmonary embolus (PE) was first performed in 1893. Unsurprisingly, this did not gain widespread acceptance. In 1959, a surgically placed external clip was used to reduce the IVC to a slit. The first transvenous IVC filter, the Mobin-Uddin filter, was introduced in 1967. Transvenous devices were attractive as although a surgical femoral vein cutdown and a large sheath (24F) were required, no laparotomy or general anaesthetic was necessary. The Mobin-Uddin filter quickly fell out of favour due to the high incidence of IVC occlusion. It was soon followed by the stainless steel, Kimray-Greenfield filter that was used and refined over subsequent years.

Despite the lack of evidence for their use and growing awareness of complications, IVC filters became widely used. There have been several generations of IVC filters as designs have evolved and been refined. Designers initially focused on effectiveness of clot filtration and reducing the size of the delivery system (now typically 9F allowing true percutaneous insertion). Subsequent focus has been on reducing complications such as migration and caval perforation.

About 10 years ago permanent/retrievable IVC filters became available. These could be removed percutaneously, when no longer required, or could be left in permanently (although the long-term safety profile of these devices was unknown). The technical success rate of IVC filter retrieval is high, (even with tilting and caval perforation) although decreases with time from insertion (over 90% at three months to less than 40% at 12 months). These permanent/retrievable devices currently account for the majority of IVC filters inserted. However, it has become apparent that there are significant issues with these devices with low retrieval rates and complications. A quick trawl of the internet reveals multiple legal actions being brought against IVC filter manufacturers in the USA.

The current generation of filters have features to prevent caval perforation (and hence tilting, which reduces filtration efficiency and can make retrieval impossible) and migration. Most are based on the metal alloy 'wire' cone shape (eg Bard – Denali – **Figure 1**) while others are a very different design (Crux Biomedical – Crux). Some manufacturers are exploring bioconvertible/bioabsorbable filters that resorb over time (eg the Novate Medical filter is a filter within a stent, the filter resorbs after 60 days leaving a stent which is incorporated into the caval wall). Other manufacturers have explored devices that can be placed at the bedside without radiological guidance (using either intravascular ultrasound or by judging implant level from the patient's height – the Angel® Catheter (BiO_2 Medical) – where a filter is combined with a central line).

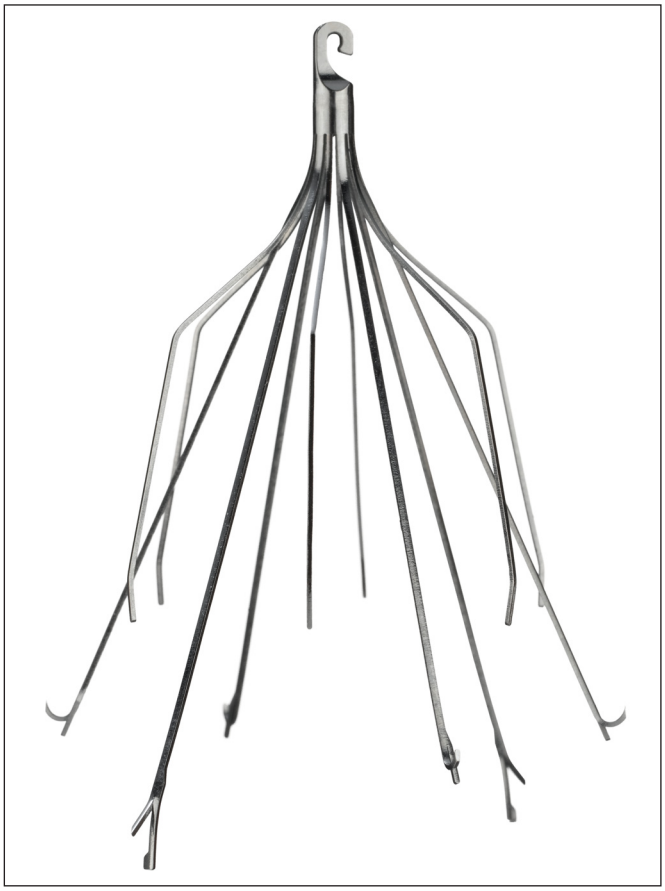

Figure 1 Bard Denali IVC filter.

Efficacy and indications

For such a widely used device there is an astonishing lack of evidence of efficacy,[1] with only two small randomised studies of limited usefulness. The PREPIC study of 400 anticoagulated patients randomised to receive IVC filter, or no IVC filter demonstrated a significant reduction in the incidence of PE (to approximately half) but no reduction in mortality, either short- or long-term (possibly reflecting the old age of the patients with the majority of deaths due to cancer or cardiovascular disease).[2,3] The PREPIC study has been influential but has been criticised for being underpowered and biased. The second randomised study of

Common
Acute PE or proximal DVT with absolute contra-indication to anti-coagulation (including need for major surgery)
Controversial
Acute PE or proximal DVT despite anticoagulation
Acute PE or proximal DVT in pregnancy
Previous PE or proximal DVT due for major surgery
Prophylaxis in poly trauma or neurosurgical setting
During percutaneous DVT thrombectomy

Table 1 Indications for inferior vena cava filters.

prophylaxis in hip fracture showed reduction in pulmonary embolism but not mortality – however this study is compromised by short follow-up (34 days), small numbers and bias.[4] Neither study reflects commonly used indications for filter placement. A large retrospective study found reduced inpatient mortality when filters were inserted in stable and unstable patients having thrombolytic therapy and unstable patients unsuitable for thrombolytic therapy.[5]

The use of IVC filters is increasing and in the US has doubled over the last decade. One US study found no clear indication for 50% of IVC filter placements.[6,7] The lack of reliable data indicating clear benefit is probably the cause of the marked differences in IVC filter use from one hospital to another.[8]

The lack of evidence makes it difficult to list indications but some cited indications are given in **Table 1**.

Complications

Although popular and widely accepted, IVC filters have come under renewed scrutiny with the growing awareness of complications.[9] These include, failure to protect from PE, IVC occlusion, filter fragmentation and embolisation of fragments to the heart and lungs and caval perforation into adjacent structures (many have been described including the aorta and duodenum) (**Table 2**). Attempted retrieval of IVC filters also has complications and fatalities have been reported. In addition to these problems it has become apparent that many (often the majority) of retrievable IVC filters are not being retrieved. The reason for this is multifactorial – including loss to follow-up, no formal system for arranging retrieval and the perception that IVC filters are harmless. This has led to warnings and new instructions from both the FDA and MHRA. Dedicated longitudinal follow-up programmes with formal arrangements for filter retrieval and early filter removal (as soon as the filter is no longer necessary) are advised.

The risk of deep venous thrombosis (DVT) doubles with the presence of an IVC filter. IVC thrombosis can occur and is associated with increased risk of PE, post thrombotic syndrome and phlegmasia cerulea dolens (blue oedema). For this reason patients with IVC filters should be anticoagulated as soon as the contraindication to anticoagulation resolves. Special care should be taken when inserting a central venous catheter in a patient with an IVC filter as the guide wire can become caught in the filter and impossible to remove or may displace the filter.

Conclusion

IVC filters have been in use for more than 45 years and yet for such a widely used device, we have little data on their efficacy or indications for use. However, most practitioners advocate their use in acute PE or proximal DVT with an absolute contra-indication to anticoagulation. We have better data on their complications and although the risk of serious complications is relatively low, these cannot be ignored and there have been recent warnings from the FDA and MHRH. One large area of concern is the widespread non-retrieval of retrievable filters for a variety of reasons and measures to address this have been advised. Patients with IVC filters should be anticoagulated when safe to do so and temporary filters should be removed as soon as possible (usually when anticoagulation is effective).

Failure to protect from PE (2%)
DVT (5%)
IVC thrombosis/occlusion (3%)
Migration
Fracture/embolisation of fragments
Caval perforation

Table 2 Complications from inferior vena cava filters.

Declaration

No conflict of interest or financial support.

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Angel® Catheter – a solution to pulmonary embolism prophylaxis in the critically ill patient

LF Angel

Pulmonary embolism (PE) is a serious complication among critically ill patients. Despite the recommended and effective use of prophylactic anticoagulation, new options are required, particularly for critically ill patients with absolute or temporary contraindications to the use of anticoagulation. The Angel® Catheter (BiO_2 Medical, Inc. San Antonio, Texas) is intended for these critically ill patients, allowing early PE prophylaxis without additional bleeding risk. The device is inserted at the bedside, provides both central venous access and inferior vena cava filtration, and can be successfully removed in all instances. Clinical experience and ongoing research will help define the role of the Angel Catheter in PE prophylaxis for critically ill patients.

Keywords: *pulmonary embolism; Angel Catheter; thrombophrophylaxis; intensive care unit; inferior vena cava filters*

Introduction

The management of the critically ill patient in the ICU is challenging, particularly with regard to the prevention, diagnosis, and treatment of venous thromboembolism (VTE). VTE has been described as the 'last frontier for prophylaxis'[1] due to the complexity of the condition of most severely ill patients and because of their high risk of both pulmonary embolism (PE) and bleeding complications.[2,3] Early thromboprophylaxis is desirable for critically ill patients, as more than 70% of embolic events occur during the ICU stay and their occurrence peaks during the first 4-7 days after admission.[4,5] This early occurrence of events supports the use of prophylactic measures as soon as possible and in particular during the time frame in which the patients are most critical, and have the highest risk of bleeding or contraindications to the use of anticoagulation. Nevertheless, even though multiple studies demonstrate a significant reduction in the incidence of embolic events with the use of prophylactic anticoagulation, and even though multiple international guidelines recommend such use, the results of recent studies show that more than 30% of patients at highest risk of both PE and bleeding do not receive any thromboprophylaxis.[6,7] Currently, a clinical diagnosis of PE is made for approximately 4% to 6% of critically ill patients,[5,8,9] and the occurrence of PE is confirmed by autopsy for 13% of patients who die in the ICU, despite the use of prophylactic measures.[9,10]

The available alternatives for the prevention of PE in patients for whom anticoagulation is contraindicated are limited to mechanical thromboprophylaxis with compression stockings and inferior vena cava (IVC) filters. Few or no existing randomised studies have compared the outcomes achieved with these available alternatives to the outcomes achieved by anticoagulation; thus, the benefit of these alternatives for critically ill patients has not been clearly demonstrated. The effectiveness of mechanical thromboprophylaxis with antiembolic stockings or pneumatic compression has been called into question by the *Clots in Legs or Stockings after Stroke Trials* and by the American College of Physicians' *Clinical Practice Guidelines for the Prevention of VTE in Hospitalised Patients*.[11] IVC filters are approved for patients with VTE and contraindications to anticoagulation, but they are more commonly used prophylactically. Clinical evidence for the use of filters is lacking, and their general use is not recommended.[12]

The reported frequency of clinically significant PE in patients with IVC filters is relatively low (1.1-1.3%) and comparable to rates achieved with anticoagulation.[13,14] The primary clinical problem with the use of IVC filters is related to the associated temporarily high risk of PE and to their long-term use.[13] Retrievable filters have been designed to offer the possibility of removing the IVC filter once the risk of PE has decreased or the patient can receive anticoagulation therapy. Despite this clinical advantage, most IVC filters are not removed; retrieval rates range from 12-45%.[13]

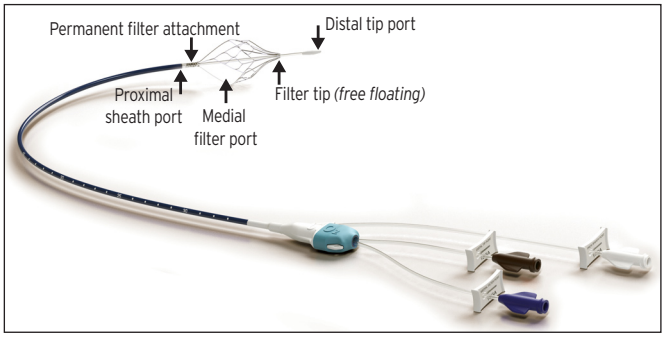

Figure 1 The Angel Catheter.

Device objectives and description

The Angel Catheter was developed as an alternative for critically ill patients at high risk of PE for whom the use of anticoagulation is temporarily or absolutely contraindicated. It combines the features of an IVC filter and a central venous catheter (CVC). It is intended for bedside placement with standard venous access techniques and/or ultrasound guidance, and can be removed (IVC filter is permanently attached to the CVC) once the risk of PE has decreased or prophylactic anticoagulation can be initiated.

The Angel Catheter (**Figure 1**) consists of a self-expanding Nitinol filter permanently attached to a multilumen CVC and is designed for femoral venous access only. The filter is deployed through an attached sheath (length, 35 cm; outer diameter, 9F) that is placed intravenously over a 0.035-in guidewire, and the sheath remains in place until the filter is removed. The catheter component is a triple-lumen CVC with ports proximal to, within, and distal to the filter. Both the sheath and the catheter are made of polyether block amide (PEBAX®) resins and are flexible and kink-resistant. The filter has a self-centering closed design without barbs or hooks. It is secured in place by the catheter and is recaptured by withdrawal into the 9F sheath.

Clinical experience

The first in-man pilot clinical trial was conducted to assess the safety of the device for severely ill medical and surgical patients at increased risk of PE.[15] This pilot trial enrolled eight critically ill medical and surgical patients considered at high risk of PE who were not candidates for medical thromboprophylaxis. The average age was 35 years old. Six of the eight patients had experienced major trauma, and at the time of insertion three patients had active bleeding and one had a PE. All of the filters were inserted at the bedside without placement-related complications. No repositioning of the device was required for any patient. All eight study devices were retrieved without complications, with a mean time to catheter retrieval of four days. In one patient a large clot was trapped by the Angel Catheter (**Figure 2**); the device was retrieved without complications after placement of a traditional retrievable IVC filter and initiation of anticoagulation. No new PEs, major bleeding, or catheter-related bloodstream infections or deep venous thromboses (DVTs) occurred in any of the patients during the study period.

Opportunities for enhanced PE prevention

VTE is considered the leading cause of preventable hospital death. Greater and more consistent use of anticoagulation therapy as the standard of care for ICU patients is effective in preventing a significant number of PE events. However, there is a portion of underserved patients who are vulnerable to VTE and for whom the current standard of care may not be suitable. These include, but are not limited to, patients with haemorrhagic stroke, GI bleeds or liver lacerations, neurovascular trauma, hepatic insufficiency, coagulopathy, patients allergic to anticoagulants, and post-orthopaedic surgery patients. Anticoagulation is contraindicated for many in these patient groups, either initially upon admission to the ICU or for the full duration of their ICU or hospital stay. The Angel Catheter has been designed to protect patients at high risk for PE not protected by current standards of care.

Conclusions

New alternatives for early PE prophylaxis are necessary for critically ill patients for whom well-studied anticoagulation options are contraindicated. IVC filters are effective in preventing PE but are not commonly used because their insertion is commonly delayed and complex for critically ill patients and their use is associated with long-term complications. The Angel Catheter is intended for this critically ill population.

Declaration

Dr Angel is the Chief Medical Officer and co-founder of BiO_2 Medical, Inc.

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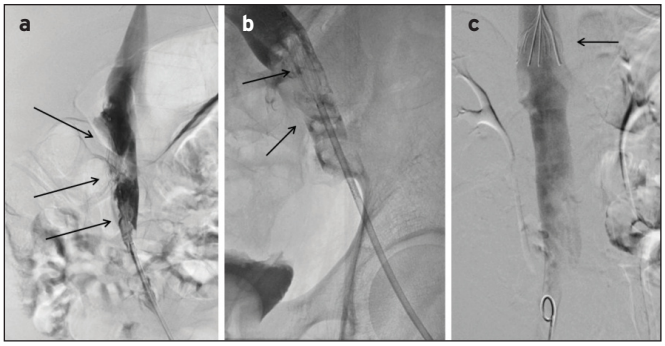

Figure 2 a. Cavogram showing a large clot captured in the filter (arrows show the clot). **b.** Cavogram with the Angel Catheter pulled back into the left iliac/femoral vein. **c.** Cavogram obtained after placement of an additional retrievable filter in the IVC, with no visible clot. The traditional retrievable filter was removed three weeks later with no captured clot and no evidence of lower extremity DVT.

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Case reports

Angel® Catheter thromboprophylaxis support in a polytrauma patient

D De Backer, FS Taccone, S Brimioulle, J-L Vincent

A 24-year-old-male was admitted following a car accident. He was unconscious on the scene and presented with a brief cardiac arrest upon arrival of the medical team. Return of spontaneous circulation was obtained after one minute of CPR. On admission at the hospital he was comatose (Glasgow Coma Score E1 M1 V1) with reactive pupils. Blood pressure was maintained with low doses of noradrenaline. The injuries identified were head trauma (diffuse axonal lesions), spinal injury (fracture of C1 without displacement but medullary contusion identified on NMR), severe thoracic trauma with multiple rib fractures on the right side and flail chest, haemopneumothorax and lung contusion, and abdominal trauma with retroperioneal haemorrhage due to right kidney laceration. The right pleural space was drained and intracranial pressure was monitored but the patient did not require any other urgent surgical procedure. The patient was haemodynamically stabilised after administration of packed red blood cells, fresh frozen plasma, platelets and tranexamic acid, but he still required moderate doses of noradrenaline for hypotension related to the spinal injury. He had respiratory failure due to spinal injury, lung contusion and ARDS.

Since prophylactic anticoagulation was impossible initially, an Angel® Catheter was inserted via a left femoral approach on day 1 after admission. It was inserted at the bedside under ultrasound guidance by the attending staff member. The catheter was inserted using the Seldinger technique to 29 cm depth (based on the patient's height of 185 cm) and then deployed by withdrawing the outer sheath. The position was then confirmed by abdominal X-ray showing the tip of the catheter at the level of the first lumbar vertebra.

ICP monitoring was discontinued on day 4. On day 5, prophylactic anticoagulation was initiated. Caval angiography showed the presence of the fully expanded filter and a fully patent vena cava (**Figure 1**). The catheter was removed into the sheath and withdrawn without any resistance. On inspection there was no clot present in the filter after removal. On day 5 the patient was fully awake. However weaning from mechanical ventilation was not possible at this time. Tracheostomy was performed on day 10 and spinal surgery was performed on day 15. The patient had a slow improvement in neurological function, with progressive recovery of motor function of the lower limbs initially, followed later by the upper limbs. He was discharged from the ICU on day 56 and transferred to a rehabilitation centre on day 71.

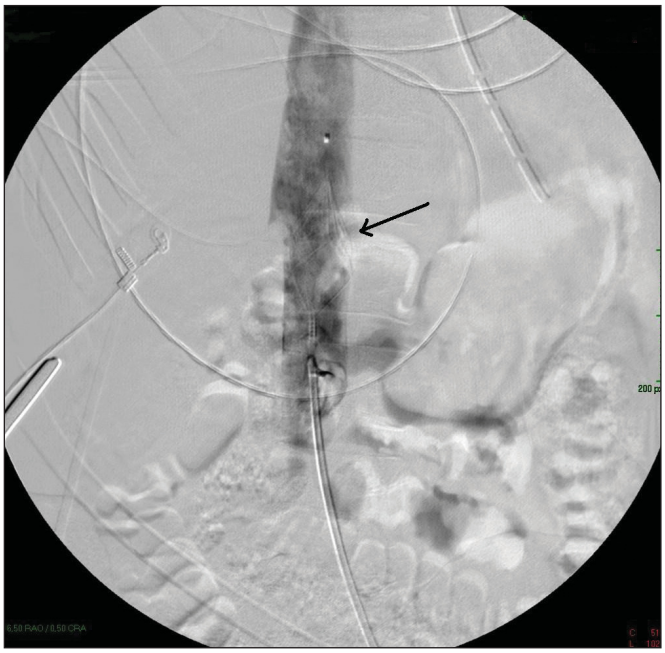

Figure 1 Angiography of the inferior vena cava. The catheter is inserted via the left femoral vein. The arrows denotes the fully deployed filter.

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Angel® Catheter for urgent orthopaedic surgery in a patient anti-coagulated for pulmonary emboli

R Hatch, C Waldmann

A 46-year-old male presented acutely to hospital following trauma to the left lower limb. Past medical history included a significant history of alcohol use, established atrial fibrillation and a possible cardiomyopathy that was currently under investigation.

On admission he was hypotensive, hypoxic, delirious and had sustained a closed compound proximal tibial fracture on the left side. Further investigations revealed a transaminitis, initially attributed to established alcoholic liver disease. Considering the nature of the injury and the degree of hypoxia the diagnosis of fat embolus was also considered. In view of the degree of organ dysfunction on admission his initial management was conservative. The patient was resuscitated and admitted to a higher monitoring area and subsequently a trauma ward. The limb was reduced and placed into a cast.

Admission to the intensive care department occurred four weeks post initial presentation for respiratory failure secondary to hospital-acquired pneumonia. Management consisted of intubation, positive pressure ventilation, intravenous antibiotics and inotropic support. Subsequent CT scan revealed bilateral pulmonary emboli, bilateral consolidation and small bilateral effusions. The initial transaminitis had now completely resolved and in retrospect was likely the result of a hypotensive liver injury rather than chronic alcoholism. The patient was started on therapeutic tinzaparin; initial attempts to wean from the ventilator failed due to sputum retention necessitating emergency re-intubation.

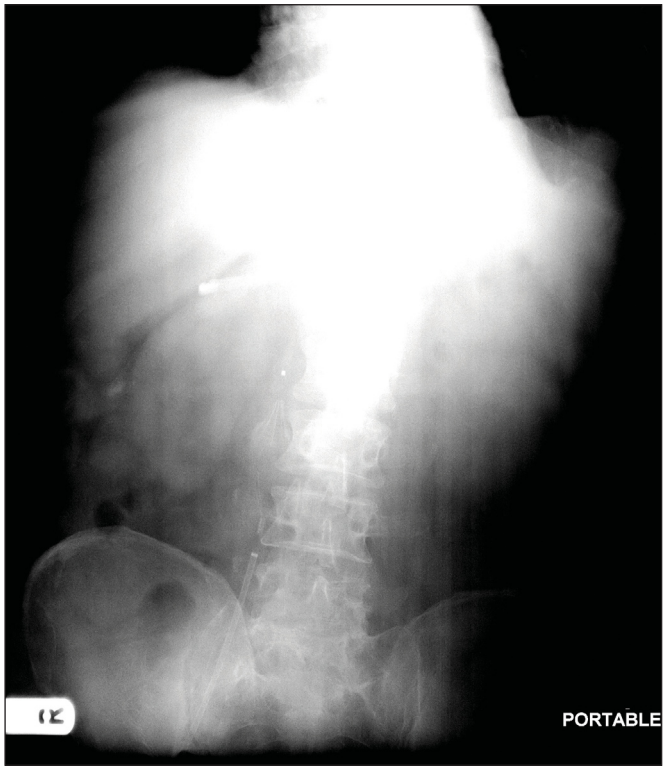

Figure 1 Mobile X-ray of the abdomen showing the filter tip at the level of the first lumbar vertebra near to the midline.

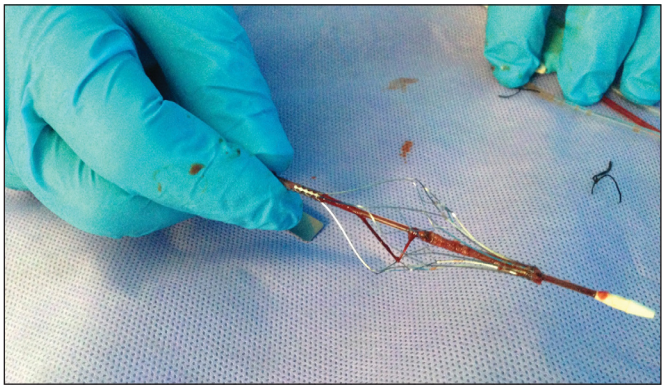

Figure 2 The Angel Catheter immediately post removal at the patient's bedside.

At six weeks post initial injury the patient had established respiratory failure and an immobilised unfixed limb. The decision to perform external fixation and insertion of a tracheostomy was made. An Angel® Catheter was inserted via a right femoral approach using the Seldinger technique in strict aseptic conditions. The catheter was inserted by the on-call intensive care trainee using ultrasound guidance under direct supervision of the duty consultant. As the patient was of average height the Angel Catheter was initially inserted to the catheter hub and then the filter was deployed by withdrawing the outer sheath and suturing in place. Insertion was straight forward and uncomplicated.

Adequate deployment of the filter tip was confirmed at the level of the first lumbar vertebra near to the midline (**Figure 1**) with a mobile abdominal X-ray. Following deployment and confirmation of placement, anticoagulation was ceased 48 hours prior to transfer to the operating theatre. Percutaneous tracheostomy was performed on the morning of surgery and following external fixation of the limb, anticoagulation was resumed 24 hours later, after assessment by the duty orthopaedic consultant.

Removal of the Angel Catheter was performed on day two after surgery and full anticoagulation re-commenced. There was no resistance to the collapse of the IVC filter into the sheath, and the acting physician decided to remove the catheter at the patient's bedside. On inspection, there was no obvious clot present in the filter (**Figure 2**). The patient made an uneventful recovery and continued weaning from ventilation with the help of the tracheostomy.

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Angel® Catheter thromboprophylaxis support in surgery for adenocarcinoma of the colon

A Walden, J Hughes, S Patel, L Keating, M Gibson, C Waldmann

An 80-year-old Caucasian lady presented to the Royal Berkshire Hospital with a short history of rectal bleeding, abdominal pain, altered bowel habit and weight loss. In her past medical history she had ischaemic heart disease, mitral valve regurgitation, pulmonary hypertension, permanent pacemaker insertion, hypertension and depression.

Following surgical review in the emergency department, a provisional diagnosis of perforated viscus was made and she was sent for a CT scan of her abdomen and pelvis. This revealed an inflammatory mass associated with her sigmoid colon, which was felt was most likely to represent a perforated carcinoma.

She responded well to initial resuscitation with intravenous fluids and antibiotics and was taken to theatre for an exploratory laparotomy. This confirmed the presence of a perforated colon secondary to an obstructing sigmoid tumour that looked malignant. This was later confirmed as an adenocarcinoma on histology. A Hartmann's procedure was performed and she was admitted to ICU postoperatively. The surgeons were concerned about her rectal bleeding and felt that heparin should not be given in the immediate postoperative period.

On admission she was breathing spontaneously with oxygen saturations of 98% on 24% fractional inspired oxygen. She was hypotensive despite a total of 3.5 L fluid resuscitation intra-operatively and intravenous pressor therapy was required to maintain her mean arterial BP at 65 mm Hg.

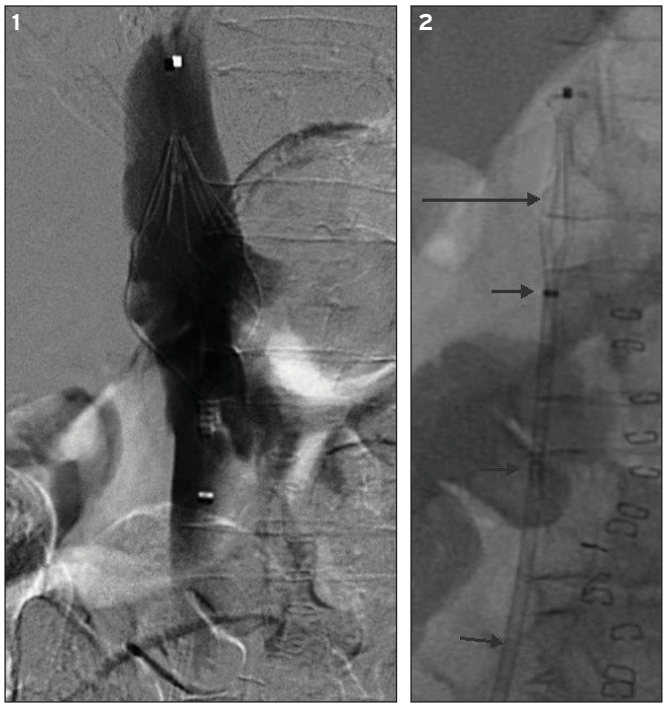

Figure 1 Inferior venocavogram showing the Angel Catheter's filter in inferior vena cava with no thrombus within it. **Figure 2** Angel Catheter's filter (long arrow) being retracted into catheter (short arrows).

In view of her high venous thromboembolic risk due to malignancy, advanced age and major surgery, a reluctance to start heparin prophylaxis and the need for central venous access for pressor therapy, we elected to insert an Angel® Catheter via the femoral route. We explained the novel nature of the procedure and device to the patient who gave informed consent for us to proceed.

The Angel Catheter was inserted via a right femoral approach under strict aseptic conditions and with direct ultrasound-guided placement by the duty consultant. Venous access was achieved at the first pass. The depth of catheter placement was determined by the patient's height. The filter device was deployed easily despite this being the first such device inserted by the operator. An abdominal X-ray demonstrated adequate deployment with the filter tip at the level of the first lumbar vertebra near to the midline. No complications of bleeding, pain or infection were noted.

When the perioperative risk of bleeding had passed, over the next 24 hours the patient was weaned off pressor therapy and was taken to the interventional radiology suite where the Angel Catheter was removed under direct screening to ensure that clot was not adherent to the end of the filter. A venogram was performed demonstrating no clot in the IVC filter (**Figure 1**) and the catheter was removed easily by collapsing the deployed filter into the sheath with no resistance and then removing the entire device. (**Figure 2**).

The patient continued to make a good recovery and was discharged from the ICU on day three and from hospital on day 38, following a period of rehabilitation. She remains well to this day.

This is a good example of using a device like the Angel Catheter to provide protection from emboli migrating to the lungs in a patient at high risk of venous thromboembolism (VTE) at a time when anti-coagulation therapy posed a risk of bleeding and destabilisation of the patient. The Angel Catheter enabled the short time period without thromboprophylaxis and high VTE risk to be bridged without the need for out-of-hours interventional radiology. The ease of removal further demonstrated that interventional radiology may not be required, providing that alternative imaging technologies are used to assess whether a thrombosis is present prior to removal. This was the first Angel Catheter to be successfully used in Europe.

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Angel® Catheter thromboprophylaxis support in a patient with subarachnoid haemorrhage

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A 51-year-old woman was admitted to another hospital for convulsions. The admission CT scan showed diffuse subarachnoid haemorrhage and intraparenchymal haematoma in the left temporal lobe. On admission to the hospital, she was awake (Glasgow Coma Score E4 M5 V6) with reactive pupils. CT-angiography showed a ruptured aneurysm of the middle cerebral artery. During transfer to our hospital, she rapidly deteriorated (GCS E1 M4 V1). On admission, a second CT-scan demonstrated an extension of the intraparenchymal haematoma and blood in the ventricular space. She was immediately operated on – clipping of the ruptured aneurysm, drainage of the haematoma and monitoring of intracranial pressure with an intraventricular catheter.

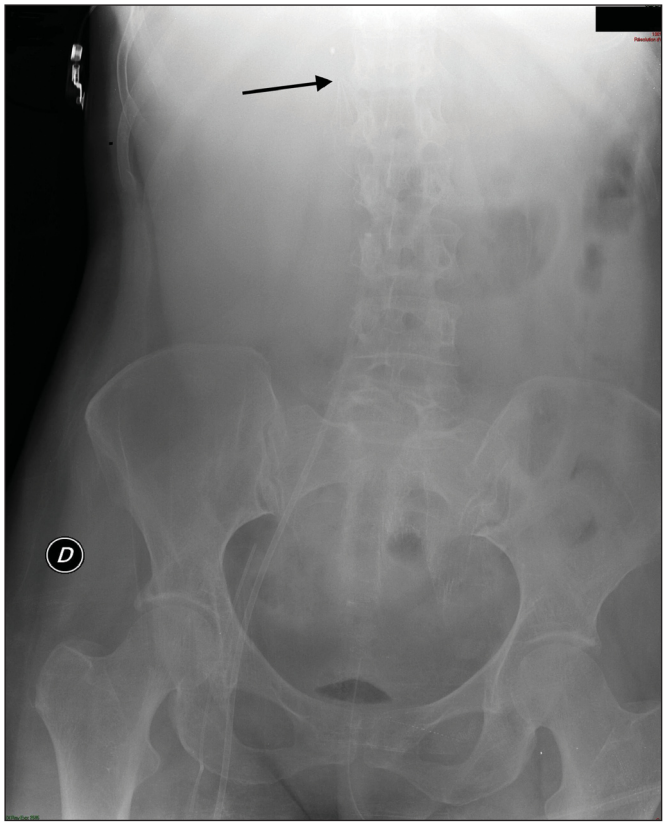

Figure 1 Position of Angel Catheter on X-ray. The catheter is inserted via the right femoral vein and the tip is positioned at the level of the junction between the first and second lumbar vertebrae (arrow).

Due to relative contraindications to rapidly initiating prophylactic anticoagulation, an Angel® Catheter was inserted via a right femoral approach day 1 after admission. The catheter was inserted at the bedside under ultrasound guidance by the attending staff member. The catheter was inserted using the Seldinger technique to 27 cm depth (based on the patient's height of 170 cm) and then deployed by withdrawing the outer sheath. The position was then confirmed by abdominal X-ray showing the tip of the catheter at the level of the junction between the first and second lumbar vertebrae (**Figure 1**).

After nine days, prophylactic anticoagulation was initiated. The next day, caval angiography showed the presence of the fully expanded filter and a fully patent vena cava. The catheter was removed into the sheath and withdrawn after 10 days of insertion without any resistance. On inspection there was no clot present in the filter after removal.

Unfortunately the patient had a poor neurological course. At day 12, brain death was diagnosed. She was considered for organ donation but an abdominal ultrasonography disclosed abnormalities on the right kidney, confirmed with CT-scan. Organ donation was not performed. At autopsy, a carcinoma of the right kidney, associated with metastatic emboli in the liver, was observed.

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Angel® Catheter as a preventative measure for pulmonary embolism in a major burn patient

A Owen, N Abeysinghe

A 47 year-old-male was admitted to our hospital with self-inflicted 54% body surface area burns involving all four limbs, face and torso, having covered himself in petrol and ignited it. He was intubated in the pre-hospital environment due to concerns regarding airway compromise. His treatment in the emergency department included vascular access and fluid resuscitation using the Parkland Formula as per local protocols. The patient was transferred to theatre within one hour of arrival and received wound cleaning and debridement, and escharotomies to his right arm and hand, left hand, neck and chest. Postoperatively he remained sedated and was taken to intensive care.

Ongoing care consisted of fluid therapy, cardiovascular support with noradrenaline and multiple return trips to theatre for dressing changes and skin grafting. Oxygen requirements remained at an FiO_2 of 0.35. Thromboprophylaxis could not be started due to ongoing bleeding from the extensive wounds.

During a routine line change on day 16 after admission a suspected right femoral venous clot was noted and confirmed by formal ultrasound by the on-call radiologist. It was decided that the risk of anticoagulation was still too high and so an inferior vena cava filter should be inserted to prevent pulmonary embolism.

The Angel® Catheter was inserted via a left femoral approach under strict aseptic conditions and with direct ultrasound placement by the on-call consultant intensivist. Venous access was achieved at the first pass. The depth of catheter placement was determined by the patient's height. A plain abdominal X-ray was used to confirm catheter position and the filter subsequently deployed. No complications of bleeding or infection were noted.

On day 3 after insertion of the Angel Catheter a venogram performed showed clot capture in the filter. On day 5 following insertion it was felt that the bleeding had improved enough to enable formal anti-coagulation and enoxaparin was commenced at a dose of 1 mg/kg BD on advice of the Burns Team. Unfortunately over the next few days the patient deteriorated due to sepsis secondary to his burns and subsequently died of multi-organ failure.

This is a good example of a novel indication for the use of the Angel Catheter, where a patient was hypercoaguable and had proven femoral venous clots, but could not be initially anti-coagulated due to the nature of his injuries.

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Incidence and treatment options for massive pulmonary embolism in Sweden

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Swedish Healthcare is organised by relatively independent counties which are responsible for the appropriateness of delivered care. As a consequence, few formal guidelines are issued by national authorities or professional societies, which is the case for the treatment of pulmonary embolism (PE). The yearly incidence of PE in Swedish adults was 86/100,000 in 2011, corresponding to approximately 6000 cases with an overall mortality of 6.5%. Acute massive PE with circulatory shock carries mortality up to 50% but its true incidence in Sweden is not known. First-line treatment is intravenous thrombolysis but non-pharmacological alternatives for cases where thrombolysis has no effect or is contraindicated have recently undergone technical development. This includes catheter fragmentation, surgical embolectomy and extracorporeal circulatory support, which may be used as a bridge to further treatment in very unstable patients. This article summarises the treatment options for acute massive PE and their rationale as seen from a Swedish perspective.

Keywords: *pulmonary embolism; thrombolytic therapy; mechanical thrombolysis; embolectomy; extracorporeal membrane oxygenation*

Introduction

The incidence of pulmonary embolism (PE) in Sweden has increased from 54 to 86/100,000 citizens between 2001 and 2011 (www.socialstyrelsen.se/statistikdatabas; accessed October 25, 2013) which is in line with European numbers and often attributed to the increased use of computed tomography for diagnosis. During the same period, development of surgical and radiological techniques, pumps and filters for extracorporeal support and medical (air) transportation, has resulted in non-pharmacological treatment emerging as an alternative for selected cases.

Acute PE with circulatory failure

In accordance with European[1] and American[2,3] guidelines the first-line treatment for acute PE with circulatory failure is IV thrombolysis. The main idea behind fibrinolytic therapy is to achieve a pharmacological fragmentation of fresh, centrally located thrombi so that they can disperse and resolve in the periphery of the lungs. If fibrinolysis is contraindicated or does not have sufficient effect, surgical embolectomy or catheter fragmentation by a radiologist are the next options. There are no studies indicating superiority of either procedure and both require resources and skills that are normally found only in tertiary centres in Sweden. Since they infer risk of PE recurrence during or after the procedures, especially if anticoagulation needs to be interrupted, insertion of an inferior vena caval filter is mandatory. In the case of surgical embolectomy, preoperative filter insertion consumes valuable time and sometimes needs to be omitted.

Radiological fragmentation of thrombi can be achieved using a variety of catheter designs, some of which include elimination of the detached material by suctioning as opposed to endogenous lysis after peripheral dispertion.[4] Swedish interventionists and X-ray laboratories are gradually acquiring this capacity with much of the introductory work done in Lund, where 8-12 patients are treated yearly. Surgical embolectomy, by its nature, is available only in thoracic surgery centres among which Stockholm, Lund and Gothenburg are the most prominent in Sweden. The Stockholm Department of Thoracic Surgery recently reported a total of 12 cases of embolectomy performed between 1957 and 1996 with only two deaths related to the hospitalisation for PE.[5] This could be compared to international numbers for mortality around 35% over that period of time.[6] The use of cardiopulmonary bypass is a requisite for allowing a reasonable period of good surgical access.

ECMO therapy

When massive PE causes severe circulatory failure or circulatory arrest, extracorporeal membrane oxygenation (ECMO) can restore and maintain adequate perfusion.[7] Once the circuit is established, additional investigations and review for further treatment can be undertaken. While surgical or radiological interventions are probable options, it has been observed that centrally located emboli may dissolve spontaneously during ECMO treatment with heparin.[8] The equipment is readily ambulant and can be applied to the patient in his/her present location, provided that the nearest thoracic surgery unit has the necessary resources to mobilise. In the patient at imminent risk of circulatory collapse and cardiac arrest, preparatory access to the femoral vein and artery can be achieved with small-bore catheters before the ECMO team arrives. If regional capacity is low, the Swedish ECMO centre in Stockholm, may also be asked to assist with on-ECMO transportation to the nearest thoracic facility.

Management algorithm

We recently introduced a comprehensive algorithm for the management of patients in circulatory failure due to massive PE (**Figure 1**). In line with other recent proposals,[9] it includes ECMO as a bridge to non-pharmacological treatment but also as a primary means of saving the patient in circulatory arrest, when PE can be judged probable. IV thrombolysis is the primary treatment but if it is contraindicated or unsuccessful and time is running out, interdisciplinary consultation is advocated to establish the basis of all further management. The following recent case from Gothenburg illustrates these aspects.

Case report

A 50-year-old male deficient of protein S and with earlier thromboembolism had developed ulcerative colitis and anticoagulant therapy had not been consistent due to recurrent bleeding. One month previously, he was diagnosed with acute and chronic PE that was successfully treated with tinzaparin under in-

hospital supervision. The patient had been discharged with further injections prescribed but subsequently turned up in the emergency department short of breath. Vital signs were normal except pulse 118/min and respiratory rate 26/min and he complained about chest pain. Analysis of anti-Xa levels indicated that there had been compliance with the prescribed injections. Echocardiography revealed increased distension of the right ventricle compared to one week earlier and pulmonary arterial pressure had increased from 60 to 80 mm Hg. An interdisciplinary review deemed thrombolysis contraindicated and the patient was assigned to catheter fragmentation.

An inferior vena caval filter was installed and fresh thrombi in the left lung were successfully fragmented. However, the angiography revealed that the right lung was hardly perfused due to chronic thrombi adherent to the vessel walls. Pulmonary arterial pressure did not decrease postoperatively and IV epoprostenol and oral sildenafil were attempted, albeit unsuccessfully.

On the fourth day of re-hospitalisation, increased signs of right ventricular failure prompted thoracic surgery in an attempt to extract chronic and remaining fresh thrombi. It was successful although surgery was extended and failure of the right heart necessitated postoperative ECMO support. Unfortunately, pulmonary hypertension persisted due to peripheral chronic embolism that had gone too far and the patient succumbed. However, management illustrates that interdisciplinary consultation made all treatment options available to the patient.

Conclusion

The regional organisation of Swedish Healthcare affiliates every ICU to a tertiary centre where non-pharmacological treatment of acute massive PE can be initiated. If resources are not primarily available there, assistance can be expected to be offered from other regions when contacted. Long-haul transportation is coordinated on a national basis and can be mobilised quite readily. The main function of the proposed algorithm does not lie in medical advice but in its informative function as to possible use of these resources. We think that a few Swedish cases among patients with massive PE could be salvaged by better communication and interdisciplinary consultation between colleagues and hospitals involved in this chain of events.

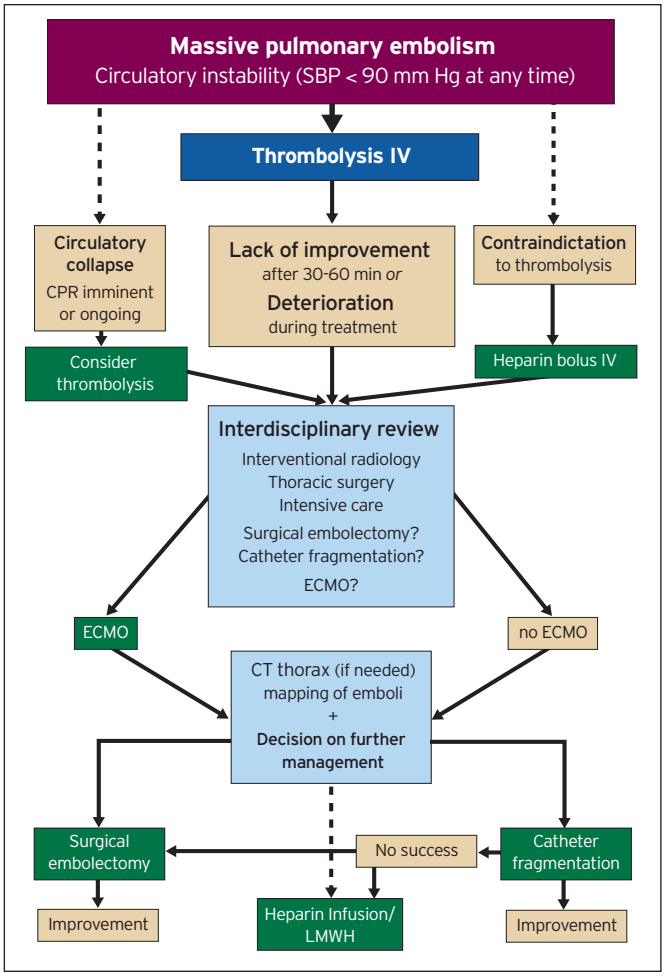

Figure 1 Algorithm for the management of patients in circulatory failure due to massive pulmonary embolism. Published with the permission of the Sahlgrenska University Hospital.

Declarations

All authors declare that they have no conflict of interest. This work did not receive any kind of financial support.

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