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REVIEW

Investigation and management of pulmonary embolism 2: specific clinical conditions

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Abstract

Pulmonary embolism remains a common and potentially deadly disease, despite advances in diagnostic imaging, treatment and prevention. Managing pulmonary embolism requires a multifactorial approach involving risk stratification, determining appropriate diagnostics and selecting individualised therapy. The first part of this article reviewed the pathophysiology, risk factors, clinical presentation, diagnostic evaluation and therapeutic management and early outpatient management of pulmonary embolism. This second part summarises pulmonary embolism in the setting of pregnancy, COVID-19, recurrent disease and chronic thromboembolic pulmonary hypertension.

Key words: Ambulatory management; Chronic thromboembolic pulmonary hypertension; Computed tomography pulmonary angiogram; COVID-19; Pregnancy; Pulmonary embolism; Ventilation/perfusion scan

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Introduction

Pulmonary embolism is a common acute cardiovascular disorder with high mortality rates. The incidence is estimated to be 60 per 100 000 (Oger, 2000) and pulmonary embolism has been found in up to 14.6% of hospitalised patients at post-mortem (Stein and Henry, 1995). It accounted for nearly 28 000 NHS hospital admissions and 250 000 bed days in 2011 (British Lung Foundation, 2019), and is the third most common acute cardiovascular disorder behind myocardial infarction and stroke (Raskob et al, 2014). The first of these two articles (https://doi.org/10.12968/hmed.2021.0286b) outlined modern probability-based approaches to the investigation of pulmonary embolism and discussed management options, including early outpatient management. This second part summarises pulmonary embolism in the setting of pregnancy, COVID-19, recurrent disease and chronic thromboembolic pulmonary hypertension.

Pregnancy

Venous thromboembolism is the highest direct cause of maternal mortality during pregnancy and the puerperium in the UK (Knight et al, 2017) with overall risk of venous thromboembolism 4–5 times greater than that of non-pregnant women of a similar age. Risk is increased 20-fold in the first 6 weeks postpartum (Heit et al, 2005). Assessment and management can be complex. A suggested treatment pathway is shown in Figure 1.

The clinical features of venous thromboembolism have considerable overlap with 'normal' pregnancy phenomena, which may lead to delayed diagnosis. D-dimer levels progressively increase with advancing gestation and the Royal College of Obstetricians and Gynaecologists (2015) advises against the use of serum D-dimer measurement in pregnancy.

Investigation

The choice of radiological modality should limit the radiation dose to both mother and fetus, but the overall risk of radiation is low.

Compression Doppler ultrasonography

In the presence of signs and symptoms of deep vein thrombosis, bilateral lower limb compression Doppler ultrasonography carries little risk and is the first step of investigation. If deep vein thrombosis is confirmed, pulmonary embolism can be assumed and treated for, avoiding further investigation (Harris et al, 2018).

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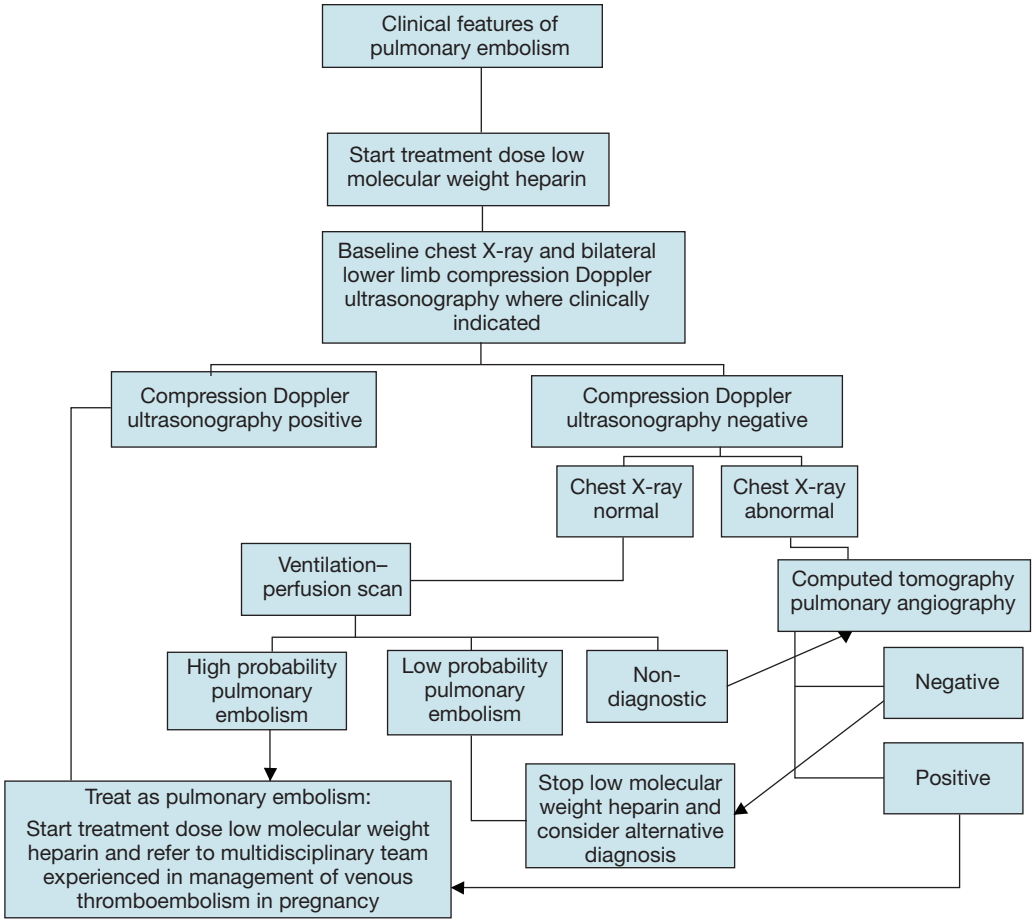

Figure 1. Suggested pathway for investigation and management of pulmonary embolism in pregnancy.

Chest X-ray

With minimal radiation exposure, a baseline chest X-ray is performed to rule out common differential diagnoses and will guide subsequent radiological investigation (Harris et al, 2018).

Ventilation/perfusion scan

Ventilation/perfusion scanning has a higher diagnostic yield in pregnant women than their non-pregnant counterparts and specificity is highest in patients with a normal baseline chest X-ray. Both fetal and maternal exposure is low (0.32–0.76 Gy and 0.9 msv respectively), with no increase to the background risk of breast cancer (Harris et al, 2018) but slightly higher risk of childhood cancer (Royal College of Obstetricians and Gynaecologists, 2015).

Computed tomography pulmonary angiogram

Computed tomography pulmonary angiogram has lower diagnostic yield in pregnant women because of poor vessel opacification secondary to a physiological increase in cardiac output. The diagnostic yield is significantly higher in patients with abnormal chest X-ray (Cahill et al, 2009) and should be reserved for this cohort and patients whose ventilation/perfusion was non-diagnostic. Fetal radiation exposure is low (0.003–0.131 Gy) but in pregnancy, computed tomography pulmonary angiogram increases the risk of breast cancer by 14% over the overall background risk and patients should be counselled accordingly (Harris et al, 2018). A modified protocol with reduced radiation dose may be considered.

Management

Warfarin and direct oral anticoagulants cross the placenta and confer risk of both fetal haemorrhage and teratogenicity. Therapeutic low-molecular weight heparin is the treatment of choice in pregnancy and should be started as soon as pulmonary embolism is suspected,

with dosage based on the patient's early pregnancy weight (Royal College of Obstetricians and Gynaecologists, 2015). Once pulmonary embolism is confirmed, treatment should be continued until at least 6 weeks postpartum, with a minimum of 3 months treatment completed. Referral to a specialist multidisciplinary team is vital to ensure safe delivery plans are in place and anticoagulation is managed accordingly (Konstantinides et al, 2019). In the event of high-risk pulmonary embolism, intravenous unfractionated heparin is the preferred treatment, although thrombolysis should be considered if it is life threatening. Postpartum patients may be offered a choice of low-molecular weight heparin or warfarin, which are safe in breastfeeding. Direct oral anticoagulants are not safe to use in lactation and should not be offered (Royal College of Obstetricians and Gynaecologists, 2015).

Management of pulmonary embolism in patients with malignancy

Occult cancer will be present in 4–10% of patients presenting with idiopathic venous thromboembolism (Otten and Prins, 2001). Those with cancer are more likely to develop recurrent venous thromboembolism and suffer bleeding secondary to anticoagulants (Farge et al, 2016). A Cochrane review concluded that there was insufficient evidence that extended testing for occult cancer in a first episode of venous thromboembolism reduced cancer- or venous thromboembolism-related morbidity and mortality (Robertson et al, 2018).

The CLOT study identified lower rates of venous thromboembolism recurrence in patients receiving low-molecular weight heparin and highlighted the difficulties in achieving adequate anticoagulation with vitamin K antagonists in cancer-associated thrombosis (Lee et al, 2003). Data on the use of direct oral anticoagulants in cancer-associated thrombosis remain limited. The Hokusai VTE Cancer trial (Raskob et al, 2018) showed that edoxaban was associated with statistically fewer episodes of recurrence than dalteparin alone. The occurrence of major bleeding was higher with edoxaban, but was limited to patients with gastrointestinal cancer. Edoxaban or rivaroxaban may be used as an alternative to low-molecular weight heparin in cancer-associated thrombosis except in patients with gastrointestinal cancer (Konstantinides et al, 2019).

The duration of therapy remains controversial and bleeding risk vs risk of cancer-associated thrombosis recurrence should be discussed with the patient. In the event of recurrent venous thromboembolism while on maintenance therapy, switching from direct oral anticoagulant to low-molecular weight heparin should be considered, or increasing the dose of low-molecular weight heparin in patients already established on this (Fernandes et al, 2019).

COVID-19

COVID-19 infection is associated with increased risk of pulmonary embolism, particularly in critical care (Sakr et al, 2020). In addition to acute illness risk factors (immobility, sepsis, respiratory failure) the virus itself induces a hypercoagulable state (Tang et al, 2020). Clinicians should have a high index of suspicion for those patients in whom oxygen requirements are disproportionate to the severity of radiological changes or in patients who develop sudden worsening hypoxia, hypotension or tachycardia (British Thoracic Society, 2021). Several studies have connected poorer patient outcomes with raised D-dimer levels in COVID-19, but the British Thoracic Society (2021) guidance does not support the routine use of D-dimer measurement in isolation to guide decisions regarding pulmonary embolism investigation and anticoagulation.

Acutely unwell patients admitted to hospital with COVID-19 should receive prophylactic low-molecular weight heparin following assessment of their bleeding risk. Thromboprophylaxis should be continued for the duration of admission or for 7 days, whichever is longer (National Institute for Health and Care Excellence, 2021). Pulmonary embolism has been reported in some patients despite thromboprophylaxis, so an intermediate dose (double the standard prophylactic dose) of low-molecular weight heparin may be considered in patients deemed high risk (National Institute for Health and Care Excellence, 2021).

Where possible, radiological diagnosis should be sought via computed tomography pulmonary angiogram (Kaminetzky et al, 2020). However, as with other high-risk pulmonary embolism, diagnostic delay should not postpone therapeutic anticoagulation. Choice and duration of anticoagulation and long-term follow up should follow the same guidance as non-COVID-19 pulmonary embolism (British Thoracic Society, 2021). In the event of massive, life-threatening pulmonary embolism, thrombolysis should be considered if clinically appropriate, as COVID-19 does not confer any additional contraindications (Sakr et al, 2020).

Recurrent disease

In patients with a first episode of unprovoked venous thromboembolism who completed at least 3 months of anticoagulant treatment, the risk of recurrent venous thromboembolism was 10% in the first year after treatment, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent venous thromboembolism events resulting in death (Khan et al, 2019). Recurrence is highest after unprecipitated events (Baglin et al, 2003), and in those who present with symptomatic pulmonary embolism compared to those with deep vein thrombosis alone (Eichinger et al, 2004).

A meta-analysis found that patients who received anticoagulation beyond the conventional 3–6 months were at reduced risk of recurrent venous thromboembolism (Ost et al, 2005), which typically mandates lifelong anticoagulation. However, anticoagulation-associated haemorrhage risk increases with time (Lecumberri et al, 2013), so careful consideration of indefinite anticoagulation must be made in an aging cohort. In these individuals, direct oral anticoagulants may provide a safer bleeding profile than warfarin (Moodley and Goubran, 2015).

Chronic thromboembolic pulmonary hypertension

Persistent symptoms after pulmonary embolism are common, occurring in around 50% of patients. Chronic thromboembolic pulmonary hypertension is a rare but important long-term sequela of pulmonary embolism and occurs in approximately 4% of cases (Gall et al, 2017). It is characterised by persistent obstruction of the pulmonary vasculature by organised thrombi, altering blood flow distribution resulting in remodelling of the pulmonary vascular bed and a progressive increase in pulmonary vascular resistance and pulmonary hypertension (Konstantinides et al, 2019). Late presentation is common, coinciding with progression of pulmonary hypertension.

Echocardiography can be used to evaluate the presence and extent of pulmonary hypertension. Common echocardiographic findings include raised pulmonary arterial pressure, dilated right ventricle, reduced right ventricular systolic function, flattening of the interventricular septum and dilatation of the inferior vena cava (Gopalan et al, 2016). Ventilation/perfusion scans are both highly sensitive and highly specific and a negative ventilation/perfusion scan essentially rules out chronic thromboembolic pulmonary hypertension. If a ventilation/perfusion scan suggests chronic thromboembolic pulmonary hypertension, referral to a specialist pulmonary hypertension service is required for diagnostic right heart catheterisation. In addition to lifelong anticoagulation, pulmonary endarterectomy is the treatment of choice resulting in significantly improved 3-year mortality. For inoperable chronic thromboembolic pulmonary hypertension, medical management with anticoagulation, oxygen, diuretics and riociguat with or without balloon pulmonary angioplasty is offered (Kim et al, 2019).

Conclusions

The management of pulmonary embolism varies according to special clinical circumstances, including pregnancy and cancer-associated thrombosis. Particular care should be taken with regards to choice of radiological modality and anticoagulant therapy. Individual risk stratification should also be used to guide therapeutic management.

Thromboprophylaxis is vital in the prevention of venous thromboembolism in patients admitted with acute COVID-19 infection. A high index of suspicion for concurrent pulmonary embolism ought to be considered for this novel disease.

Key points

- A ventilation/perfusion scan is the radiological modality of choice in pregnant women with a normal baseline chest X-ray. Both fetal and maternal exposure is low, with no increase to the background risk of breast cancer.
- Direct oral anticoagulants may be used as an alternative to low molecular weight heparin in the management of cancer-associated thrombosis, except in the case of gastrointestinal cancer.
- COVID-19 infection is associated with an increased risk of pulmonary embolism and acutely unwell patients admitted to hospital should receive thromboprophylaxis for 7 days or the duration of their admission, whichever is longer.
- Persistent symptoms are common after a pulmonary embolism, occurring in around 50% of patients.
- Evaluation with echocardiogram and ventilation/perfusion scan is used to identify the presence and extent of chronic thromboembolic pulmonary hypertension. If confirmed, lifelong anticoagulation should be commenced and referral to a specialist pulmonary hypertension unit should be considered.

Despite adequate treatment, complications after pulmonary embolism are common. Clinicians should remain vigilant in identifying recurrent disease and chronic thromboembolic pulmonary hypertension.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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