THROMBOPROPHYLAXIS PART I
ANAESTHESIA TUTORIAL OF THE WEEK 223

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation.

1. Which of the following statements is correct?
    a. The annual incidence of venous thromboembolism is 20/100,000
    b. The risk of a DVT after a hip replacement is around 50%
    c. 90-day mortality from a treated PE is 10%
    d. Factor II is also known as prothrombin

2. Are proteins C and S pro-coagulant or anticoagulant?

3. Which of the following are major risks factors for venous thromboembolism?
    a. Malignancy
    b. Varicose veins
    c. Post-operative intensive care
    d. Thoracic surgery

INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has an annual incidence in Europe of 60 -70 per 1000, 000 inhabitants. Half of these occur in hospitalised patients or those in care homes, and 25% in people with no recognised risk factors[1]. The risk in the post-operative population is higher still, with the incidence of subclinical DVT after total knee arthroplasty or hip fracture surgery between 40-60% and an incidence of PE in the same group of 4-10%[2]. In the UK, patients with a PE who receive treatment, have 14- and 90-day mortality rates of approximately 10% and 20%, respectively[3]. The House of Commons Health Committee reported in 2005 that an estimated 25,000 people in the UK die from preventable hospital-acquired VTE every year[4]. It is our duty to do what we can to reduce the incidence of VTE by both understanding the mechanism of formation, and ensuring correct prophylaxis is received. There have recently been a number of advances in the prevention of VTE, and this two-part series aims to summarise these, as well as reviewing older prophylactic strategies.

This first tutorial will discuss the pathophysiology of VTE, identification of high risk populations, and the presentation of DVT and PE. It will then briefly cover the treatment of these conditions. In the second tutorial, the mechanical and pharmacological methods of prevention will be discussed.

THROMBOGENESIS

Thrombogenesis is a normal mechanism by which the body maintains haemostasis is response to injury. Venous thromboembolism, however, is the abnormal development and propagation of a clot which is not useful. The thrombus itself can cause local problems relating to mechanical obstruction or blood flow. In this situation, fragments of the thrombus can break off and cause further harm by

similar means. The formation of a thrombus and its subsequent embolisation was first described by Rudolph Virchow in 1856. He subsequently described the eponymously named Virchow's triad. In an environment where one or more of the following conditions are met, there is a risk of thrombogenesis; venous stasis, damage or dysfunction of the endothelium and hypercoagulability. The risk factors for thrombosis are listed in table 1 below.

	EPITHELIAL DISRUPTION	HYPERCOAGULABILITY	VENOUS STASIS	OTHER
Acquired	**Malignancy** 2^{o} to extension into the vasculature	**Malignancy** 2^{o} to treatment	**Malignancy** 2^{o} extrinsic vascular compression (pelvic/abdominal)	**Previous VTE**
	Trauma (**fracture**)	**Pregnancy/Puerperium/ Caesarian section**	**Post-operative intensive care**	Age > 60 yrs
	Surgery (**major abdominal/ pelvic/ hip or knee replacement**)	Thrombophilia (Nephrotic syndrome, Antiphospholipid syndrome, Paroxysmal nocturnal haemoglobinuria)	**Varicose veins**	
	Indwelling central venous catheter	Dehydration	Immobilisation/long distance travel	
		Myeloproliferative syndrome	Heart failure	
		Oestrogen containing hormone replacement	Neurological disability	
		Polycythemia	Atrial Fibrillation	
			Obesity (BMI > 30Kg/m^2)	
Inherited		Factor V Leiden mutation (activated protein C resistance)		
		Prothombin mutation		
		Cambridge mutation		
		Deficiencies in Antithrombin III, Protein C, Protein S		
		Dysfibrinogenaemia		
		Hyperhomocysteinaemia		

Table 1: Risk factors for venous thromboembolism. British Thoracic Society[1] major risk factors in bold.

Activation of the coagulation cascade

Tissue factor is located in the smooth muscle and adventitial layers or vessel walls; collagen is located in the subendothelial matrix. When the endothelium is disrupted, the revelation of either of these compounds can initiate thrombus formation via platelet activation. Coagulation can also be activated inappropriately, not just by trauma to the endothelium, but by disruption, such as that caused by atherosclerotic plaques, turbulent blood flow or immunological damage. Stagnant blood allows

accumulation of activated clotting factors which may precipitate thrombus formation.

Platelets

Platelets are formed from the fragmentation of a precursor called a megakaryocyte and have a life span of only 5 -9 days. The main function of a platelet is to maintain haemostasis. Platelets are responsible for synthesis of Thromboxane A2 and within the cell there are granules containing many of the mediators of coagulation; calcium, ADP, von Willebrand Factor, fibrinogen, factors V and XIII. The initial tethering of platelets to the site of injury is mediated by glycoprotein Ib receptors and Von Willebrand Factor (vWF). As the platelet plug forms there is a conformational change cause by actin and myosin filaments within the cell. Contraction of the plug acts to reduce the size of the vessel defect and stabilise the plug.

Von Willebrand Factor

Von Willebrand Factor (vWF) is found in plasma, the endothelium and megakaryocytes. The binding of vWF to collagen or platelet glycoprotein complexes, facilitates the formation of a thrombus. Absence of vWF factor causes a defect in primary haemostasis and coagulation as seen in von Willebrand Factor deficiency.

Formation of the thrombus

After initial adhesion of platelets to the site of injury, amplification of the coagulation process must occur for a stable plug to form. The platelet integrin, glycoprotein IIb/IIIa, is the main receptor for adhesion and aggregation but other autocrine and paracrine mediators, including thrombin, thromboxane A2, epinephrine and adenosine diphosphate aid the haemostatic process.

The formation of thrombin

Thrombin is a potent initiator and amplifier of the coagulation cascade. When tissue factor is exposed, three substrates, factor VII, factor IX and factor X interact to form factor Xa which converts prothrombin to thrombin. Thrombin then activates the flowing factors; V, VIII, XI, as well as initiating the conversion of fibrinogen to fibrin.

Factor Va amplifies the conversion of prothrombin to thrombin. In its absence, the generation of thrombin is 1% the rate of generation when factor Va is present.

Fibrinogen

Fibrinogen, a soluble plasma glycoprotein, is converted to fibrin by the action of thrombin and plays a great role in providing stability to the platelet plug by bridging glycoprotein IIb/IIIa integrins.

Modulators

Calcium is an important co-factor in the coagulation cascade without which haemostasis would falter. It is only in the presence of both calcium and factor Va that factor Xa can convert prothrombin to thrombin on the cell membrane.

Vitamin K is a fat soluble vitamin that is involved in the carboxylation of glutamate residues on factors II, VII, IX, X and proteins C and S.

Negative feedback and inhibition

Haemostasis is an incredibly careful balance between pro- and anti-coagulant factors that are omnipotent within the plasma and endothelium. As soon as the coagulation cascade is initiated, the inhibitory mechanism is also activated.

When bound to thrombomodulin (found in the endothelium), thrombin activates protein C, an inhibitor of the coagulation cascade and in this way provides negative feedback, halting the haemostatic process. The action of Protein C (inactivation of factors Va and VIIIa) is slightly increased in the presence of Protein S. Antithrombin III, circulating in plasma, is also a potent inactivator of thrombin.

Plasmin, derived from the cleavage of plasminogen by tissue plasminogen activator (t-PA) in the endothelium, is responsible for fragmenting fibrin and destabilising the thrombus.

ASSESSMENT OF RISK

The National Institute of Clinical Excellence (NICE) recently passed guidance relating to VTE. All patients admitted to hospital in the United Kingdom should have their risk of VTE assessed on admission, allowing adequate thromboprophylaxis to be instituted immediately[4]. Those at increased risk include: any patient expected to have significantly reduced mobility for > 3 days, ongoing mobility less than normal and one risk factor(see table 1), any patient undergoing surgery where total anaesthetic and surgical time is > 90minutes or 60 minutes if involving the abdomen or pelvis, any surgical admission with inflammatory or intra-abdominal condition or any surgical patient with one or more risk factors. Along with stratification of VTE risk, an assessment of bleeding risk should also be made to prevent the complications of pharmacological thromboprophylaxis.

Part 2 of this tutorial series will examine methods by which a patients risk of VTE can be reduced.

DIAGNOSIS OF VTE

VTE has a variety of clinical presentations and is often asymptomatic. Symptomatic venous thrombosis carries a considerable risk of long term morbidity, due to venous ulceration and development of post-thrombotic limb secondary to venous insufficiency.

Signs and symptoms of DVT and PE

Signs and symptoms of a DVT or PE may be very subtle and unless actively searched for, can easily be missed. Symptoms of a DVT include painful, red, swollen limb. On examination the limb may be tender on palpation, hardened or distended veins may be identified and there may be discolouration or cyanosis.

The clinical presentation of a pulmonary embolus may be even more vague. Symptoms and signs include dyspnoea, tachypnoea, chest pain, cough, haemoptysis, tachycardia, raised jugular venous pressure, cyanosis, fever and circulatory collapse.

There are a number of scoring systems to help guide investigation of a suspected PE, the one reproduced in the box below is that which is recommended by the British Thoracic Society (BTS)[1]:

- The patient must have clinical features compatible with PE breathlessness and/or tachypnoea with or without pleuritic chest pain and/or haemoptysis
- plus two other factors:
  (a) the absence of another reasonable clinical explanation
  (b) the presence of a major risk factor.
- Where (a) and (b) are both true the probability is high; if only one is true the probability is intermediate; and if neither is true the probability is low.

Investigations

Leg Ultrasound

For suspected DVT, duplex ultrasonography of femoral and popliteal veins has a sensitivity and specificity of around 97% in a symptomatic patient[5]. Unfortunately there is limited accuracy in compression ultrasound in detecting asymptomatic proximal DVT and a single normal leg ultrasound, should not therefore, be used to exclude a subclinical thrombus[1].

D-dimer

D-dimer is a degradation product of cross-linked fibrin. Raised D-dimer levels do not infer VTE as they are present in many conditions such as pregnancy, peripheral vascular disease, cancer, inflammatory conditions and hosptalised patients. Newer second generation rapid D-dimer tests show sensitivities of 87-98% and combined with a low clinical probability (using a scoring system such as the one discussed earlier), a negative D-dimer can have a negative predictive value of 97%. If all patients with high, intermediate and low clinical probabilities are included, then the negative predictive value drops to 85% (using the SimpliRED assay)[1]. The BTS recommend that the D-dimer is only used in cases where clinic suspicion of a PE or DVT is low.

Isotope Lung Scanning

Isotope tests are reported as having high, intermediate and low probability of pulmonary embolism. A normal or low probability isotope or ventilation/perfusion scan, reliably excludes a PE. A high probability lung scan is not, however, diagnostic of one[1]. The BTS recommends that an isotope scan should only be the initial imaging investigation if there is: a normal, contemporaneous chest x-ray, no significant, symptomatic cardiopulmonary disease, facilities are available on site, standardized reporting criteria are used and a non-diagnositc test is followed by further imaging. This technique is useful in those patients who would benefit from the lower radiation exposure as compared to the CTPA, such as obstetric patients.

Computed tomography pulmonary angiogram (CTPA)

The availability of fast multi-slice scanners has increased in the northern hemisphere and it is now the recommended first line imaging technique for PE. It's superiority to the isotope scan is not only that it has a greater sensitivity and specificity for PE but that, in the advent of a negative scan, it often reveals the true diagnosis. The CTPA identifies a greater number of emboli, but without improving outcome, when compared to the ventilation/perfusion scan[6]. A proximal clot can be reliably identified in around 95% of studies and if the CTPA is negative further treatment is not required[1].

Echocardiography

ECHO can be diagnostic in massive PE and may give prognostic information, however, it is less useful in most other cases[1].

Other Investigations

Contrast venography is the gold standard for DVT diagnosis in all veins but is rarely carried out. Alternate investigations include measurement of the thrombus burden, using radionuclide venography and impedance plethysmography. Both are sensitive in detecting proximal but not distal thrombosis.
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Pulmonary angiography is seen as the gold standard for PE diagnosis but there is inter-observer disagreement in up to a third of subsegmental thrombi. It is still, however, more sensitive to subsegmental thrombi than a CTPA.

In patients with a PE the electrocardiogram often demonstrates only a tachycardia. Infrequently there may be right axis deviation, large S deflection in lead I, a Q wave in lead III and inverted T wave in lead III. T wave inversion in inferior and anterioseptal leads may also be indicative of PE.

Chest X-ray is invariably unhelpful in the diagnosis of a PE although it can demonstrate Westermark sign (proximal dilation and distal constriction of the pulmonary vasculature) and Hampton's Hump (wedge shaped opacification associated with pulmonary infarction). Although rare, if seen, these signs have high specificities for PE. Although it may not be of use in diagnosis of PE, a chest x-ray may well elucidate an alternative diagnosis.

TREATMENT OF VTE

The initial treatment of any patient follows the ABC approach . Patients suspected VTE may need supportive therapy and treatment based on clinical judgement prior to definitive diagnosis. Therapy may include: oxygen, fluid, inotropes and analgesia. In the future there may be a place for pulmonary vasodilators in treatment of a massive PE but currently, along with supportive management, the goals of treatment are to prevent further thrombus formation, and in some circumstances precipitate breakdown of the thrombus.

These recommendations for treatment of an acute VTE are taken from the American College of Chest Physicians[2] (ACCP) who issued guidelines in 2008. The British Thoracic Society guidelines[1] date from 2003 and differ only slightly. NICE are in the process of developing guidelines for the treatment of VTE.

Anticoagulation

The ACCP guidelines state that anticoagulation with unfractionated heparin (UFH), low molecular heparin (LMWH) and factor Xa inhibitors is better than no anticoagulation for an acute PE or DVT. The treatment of choice, however, is LMWH without regular factor Xa assays. Direct thrombin inhibitors are also useful as the initial treatment of VTE, although these are not mentioned in the guidelines. If LMWH is unavailable and there is no ability to monitor anti-Xa activity then subcutaneous, fixed dose UFH can be used (initial dose 333U/Kg followed twice daily 250U/Kg). A vitamin K antagonist (VKA) should be started on day one and dual therapy continued until the international normalised ratio (INR) is > 2 for more than 24 hours.

In the case of massive PE then an IV bolus of UFH may be given immediately as it is more rapid in onset than the LMWH. Where the clinical suspicion of VTE is high, then treatment should be started before definitive diagnosis.

In renal failure there is some evidence to suggest that UFH is safer than LMWH.

Thrombolysis

For the majority of patients with VTE, thrombolysis is not recommended, however, the clinician's decision must be based on severity of the condition, prognosis and risk of bleeding. There is a small population of patients that may benefit from thrombolysis, namely any patient with haemodynamic compromise including cardiac arrest, unless contraindicated due to bleeding risk. If administering thrombolysis then a peripheral vein is preferred to a central catheter. 50mg Altepalase (a plasminogen activator) is recommended by the BTS in the emergent situation.

Caval filters and embolectomy

In highly compromised patients who cannot receive thrombolytic therapy then catheter extraction or embolectomy may be considered.

The routine placement of a vena caval filter is not recommended but in a patient with a high risk of bleeding, obviating the use of anticoagulation, then an inferior vena caval filter may be used.

Long term treatment

VKA, most commonly warfarin, provide the mainstay of long term prophylaxis against further VTE. Anticoagulation with VKA for at least 3 months, with a target INR 2.5, is recommended for all patients (BTS advise 6 weeks in those with no risk factors). Long term anticoagulation must be assessed in conjunction with the individual patient's risk of bleeding and on-going risk factors for VTE.

IMPORTANT POINTS/SUMMARY BOX

- VTE is a major cause of mortality and morbidity
- Appropriate thromboprophylaxis should be considered for patient admitted into hospital
- Appropriate diagnostic tests and imaging depends on the findings of a targeted clinical history and examination

ANSWERS TO QUESTIONS

1. F/T/F/T
2. Proteins C and S are anticoagulant co-factors
3. malignancy, varicose veins, post-operative intensive care

REFERENCES and FURTHER READING

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