Pathophysiology of venous thromboembolism

KK Hampton

Venous thromboembolism remains an important cause of morbidity and mortality for surgical and non-surgical patients, and its pathophysiology in acutely ill, non-surgical patients is not well understood. The clinically silent nature of thromboembolism makes it a significant threat to hospital patients.

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE), remains an important cause of morbidity and mortality for surgical and non-surgical patients alike. This is despite rapid progression in the understanding of the disorder (Rosendaal, 1999; Geerts et al, 2001; Seligsohn and Lubetsky, 2001) and in the ability to prevent and treat VTE (Geerts et al, 2001; Nicolaides, 2001). Progress in understanding the biology of clot formation and an improved definition of thromboembolic risk factors have led to a general acceptance that VTE is a multifactorial disorder with a complex, and as yet incompletely understood, pathophysiology (Rosendaal, 1999).

VTE occurs with a broad range of clinical manifestations, from asymptomatic calf vein thrombosis through to life-threatening, acute, massive PE. Substantial changes in attitudes to the prevention and treatment of VTE have occurred in recent years and have been reflected in the development of local, national (www.sign.ac.uk) (Second Thromboembolic Risk Factors Consensus Group, 1998), and international clinical guidelines (Geerts et al, 2001). This review summarizes current understanding of the pathophysiology of VTE and the relationship between DVT and PE, and examines current thinking on the impact it exerts on the morbidity and mortality of hospital patients.

PATHOPHYSIOLOGY OF VTE

Virchow's (1856) observation that a triad of factors influences the pathogenesis of VTE remains valid today. Procoagulant changes in the blood coupled with stasis and vascular trauma are central influences on thrombus formation. Venous thrombi tend to form in the deep veins of the leg, often in the slow flow behind a venous valve. In the prothrombotic state, the thrombus may extend, usually proximally, to involve the femoral and iliac veins (Kesteven, 2000). This may be followed by embolization leading to an acute PE, with potentially fatal consequences (Hirsh and Hoak, 1996). VTE occurs as a complication of trauma (physical trauma and surgery) and in association with non-traumatic medical conditions. Each has a complex but separate pathophysiology that has not been fully defined.

Trauma-related VTE

Trauma and surgery are recognized as important risk factors for VTE. Patients undergoing surgery are exposed to different degrees of risk, with those undergoing major orthopaedic surgery at highest risk because of the highly traumatic nature of the procedure (Second Thromboembolic Risk Factors Consensus Group, 1998). VTE after orthopaedic surgery has a complex pathophysiology. Stasis as a result of surgery and concomitant anaesthesia set the scene for thrombus formation. Venographic studies show delayed clearance of blood from the soleal sinuses of the calf muscle in supine surgical patients (Lindstrom et al, 1977) and anaesthesia has been shown to result in vasodilation, increased venous capacitance and a compromised venous return (Lindstrom et al, 1984).

Research suggests that a persistent hypercoagulable state affecting both venous and arterial circulations occurs as a consequence of major bone trauma (Dahl, 1997, 1999, 2000). In particular, the vasculature of the lungs appears to play a key role in this process. The immediate consequence of bone trauma is a marked local activation of coagulation and fibrinolysis at the site of operation. This is believed to result from tissue damage leading to the release of large amounts of tissue factor and the exposure of procoagulant proteins

Dr KK Hampton is Senior Lecturer and Consultant Haematologist, Division of Genomic Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF

in the sub-endothelium to blood. At the same time, large amounts of procoagulant cellular debris from bone marrow are released into the circulation. As this passes through the capillaries of the lungs thrombin is generated, leading to a substantial intrapulmonary activation of coagulation. A persistent hypercoagulable state is believed to result, which exposes patients to the danger of VTE for a considerable period after the operation.

Medical illness-related VTE

In comparison with trauma-related conditions, the pathophysiology of VTE in the acutely ill, non-surgical patient is less well understood. Non-specific factors, such as the production of acute phase reactants, are known to be procoagulant (Munford, 2001) and haemodynamic compromise through stasis is a likely contributory factor, but the aetiology of the procoagulant state in non-surgical patients remains poorly defined.

In the MEDENOX trial (Samama et al, 1999), which examined the efficacy of the low molecular weight heparin enoxaparin for the prevention of VTE in acute medical conditions, patients received low dose (20 mg once daily) and high dose (40 mg once daily) therapy or placebo. The study found no difference in efficacy between the 20 mg dose and placebo, despite a correlation between anti-Xa levels and dose (Bara et al, 2001). This absence of a dose response contrasts with the findings in surgical patients and suggests a distinct pathophysiology in acutely ill medical patients.

Some medical conditions have specific features that may predispose to the development of VTE. Chronic hypoxaemia resulting from obstructive pulmonary disease can lead to the development of secondary polycythaemia. The resulting rise in haematocrit and red cell mass leads to an increase in blood viscosity within the pulmonary circulation, reducing pulmonary blood flow. Chronic obstructive pulmonary disease is also thought to induce a procoagulant state through biochemical changes (Alessandri et al, 1994) including altered platelet function (Gazzaniga et al, 1993). Chronic heart disease, especially associated with right ventricular failure, results in stasis within the venous circulation, leading to impaired venous return and increased blood stasis. Although likely contributory factors can be identified in some conditions, the pathophysiology of VTE in acutely ill medical patients remains poorly understood.

VTE and malignancy

An association between VTE and malignancy was first proposed by Trousseau (1865) and VTE has long been recognized as a frequent complication of malignant disease. A hypercoagulable state exists in malignant disease that predisposes cancer patients to the development of VTE. Patients are at highest risk following surgery and during chemotherapy (Geerts et al, 2001). Cytotoxic drugs (Lee and Levine, 1999), hormonal chemotherapy in breast cancer (Pritchard et al, 1996) and the use of central venous catheters (Monreal et al, 1996) are also associated with increased risk.

The pathogenesis of the hypercoagulable state in malignancy is complex and involves activation of the coagulation and fibrinolytic systems by procoagulant proteins secreted by tumour cells. Vascular trauma and venous stasis caused directly or indirectly by the presence of a tumour are also contributory factors (Rickles and Falanga, 2001).

Tissue factor, the primary cellular activator of blood coagulation, is highly expressed by many tumours cells (Kakkar et al, 1995). It also promotes tumour angiogenesis and is involved in cell adhesion and migration (Ott et al, 1998; Abe et al, 1999). Tumour cells also secrete cysteine and serine proteases. One of the best characterized is cancer procoagulant, a cysteine endopeptidase that activates factor X by a unique mechanism (Gordon and Mourad, 1991). Adenocarcinoma of the upper gastrointestinal tract may be mucin secreting and are associated with a procoagulant effect mediated, at least in part, by prothrombin activation and cysteine protease activation of factor X (Letai and Kuter, 1999). Tumour cells also interact with endothelial and mononuclear cells and platelets, directly through cell–cell interactions and indirectly through the release of cytokines (Rickles and Falanga, 2001).

Pregnancy-associated thrombosis

All three elements of Virchow's triad contribute to the enhanced risk of VTE during pregnancy (Greer, 1999a). Venous stasis is evident from the first trimester and vessel damage, particularly in the pelvic vessels, can occur following vaginal or abdominal delivery. In addition, changes in the coagulation system occur as part of the physiological preparation for birth and contribute to the development of a procoagulant state. These include increases in the levels of a number of procoagulant factors including von Willebrand factor, factor VIII, factor V and fibrinogen. An acquired resistance to the endogenous anticoagulant protein C and a fall in free protein S may accompany these. Elevated levels of plasminogen activator inhibitor 1 and 2 also contribute through impaired fibrinolysis.

Additional mechanisms of hypercoagulability

It is widely accepted that the pathogenesis of VTE involves a genetic component with studies showing that up to 30% of cases are familial in nature (Bertina, 2001). Thrombophilia is the term used to describe an inherited predisposition to VTE (Lensing et al, 1999). A number of inherited gene defects have been identified that are prothrombotic in nature and promote the existence of a hypercoagulable state in carriers. Almost all are associated with defects in the pathways that regulate the activities of coagulation factors (Seligsohn and Lubetsky, 2001) (*Table 1*).

The first inherited defects associated with thrombophilia to be described were antithrombin III deficiency and dysfibrinogenaemia, which were identified in the 1960s (reviewed by Seligsohn and Lubetsky, 2001). Later, in the 1980s, heterozygous deficiencies of protein C (Griffin et al, 1981) and protein S (Comp and Esmon, 1984) that conferred an inherited predisposition to VTE were characterized. However, these abnormalities are rare and did not account for all the cases of thrombophilia seen, suggesting the existence of additional genetic factors (Seligsohn and Lubetsky, 2001).

The 1990s saw the identification of the first common inherited defect associated with thrombophilia. The factor V Leiden mutation is a G→A base substitution at nucleotide 1691 of the factor V gene which causes the replacement of arginine 506 with glutamine in the factor V polypeptide chain. The mutation is procoagulant resulting in the synthesis of factor V protein that is resistant to inactivation by activated protein C (Bertina et al, 1994). The mutation is carried by about 5% of Caucasian populations and in its heterozygous form confers an estimated 5–10-fold increased risk of VTE.

A second common thrombophilic defect results from a single base substitution mutation in the 3'-untranslated region of the prothrombin (factor II) gene (PT20210A) and was identified soon after the factor V Leiden mutation. PT20210A is associated with elevated plasma levels of prothrombin and is carried by about 2% of Caucasian populations. Heterozygous carriers have an estimated 2–3-fold enhanced risk of VTE (Poort et al, 1996). Hyperhomocysteinaemia, which may result from genetic as well as acquired factors, has been associated with the occurrence of VTE. Homozygosity for a C→T mutation at nucleotide 677 of methylenetetrahydrofolate reductase causes mild hyperhomocysteinaemia and this has been linked to venous thrombosis (Alhenc-Gelas et al, 1999). However, the majority of individuals with hyperhomocysteinaemia do not have a genetic reason, but other metabolic reasons commonly resulting from folate deficiency and insufficient dietary uptake of vitamins B_6 or B_{12}.

It is increasingly accepted that VTE is a multifactorial disorder involving multiple acquired and genetic risk factors that interact in a dynamic fashion (Rosendaal, 1999). Consistent with this idea is the observation that co-inheritance of multiple genetic risk factors is associated with a higher risk of VTE and that interaction of risk factors occurs. Rosendaal noted:

> **'interaction occurs when the two risk factors in combination produce an effect that exceeds the sum of their separate effects'.**

The co-inheritance of factor V Leiden and deficiencies of antithrombin III, protein C or protein S results in an elevated risk of VTE that surpasses the sum of the risks (Seligsohn and Lubetsky, 2001). Similar interactions occur between factor V Leiden and PT20210A. The combination of protein C deficiency, factor V Leiden or PT20210A and use of oral contraceptive results in a 30–150-fold increased risk of VTE in comparison to individuals with no thrombophilia and not taking oral contraceptives (de Bruijn et al, 1998; Martinelli et al, 1998). Such increases in risk through the interaction of risk factors are much higher than the individual risks involved, and highlight that, although lifetime risks of thrombosis can be offered to those with multiple congenital thrombophilias, additional acquired risk factors can interact, resulting in much-increased thrombosis potential (Rosendaal, 1999).

DVT and PE: manifestations of a single disease process

DVT and PE are the most common clinical manifestations of VTE and are widely recognized as inter-related forms of a single disease process (Perrier, 2000; Geerts et al, 2001). Although small distal clots found in calf veins are often

TABLE 1.
Inherited thrombophilic defects and estimated prevalence

Inherited/genetic	General population	VTE population
Antithrombin deficiency	0.3%	3%
Protein C deficiency	0.3%	3%
Protein S deficiency	0.3%	3%
Factor V Leiden	4–6%	10–18%
Prothrombin G20210A	2–3%	6–18%
Hyperhomocysteinaemia	5%	10–18%
Elevated factor VIIIc	6–8%	10–15%

VTE = venous thromboembolism. Adapted from Barger and Hurley (2000)

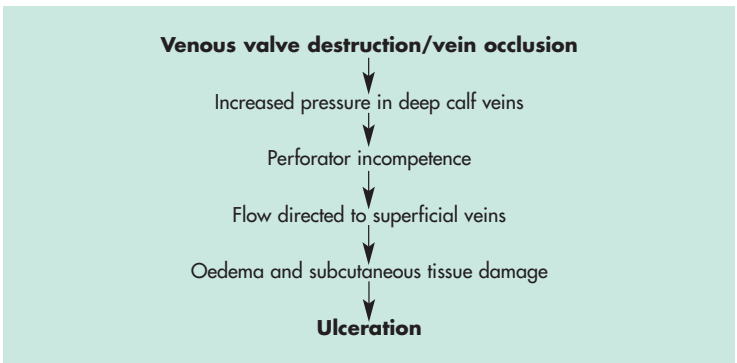
clinically asymptomatic, many will extend into the proximal veins of the leg and may subsequently embolize, resulting in a PE.

This was illustrated by Girard et al (1999) who found a high prevalence of lower limb DVT in patients with acute PE. Among 228 consecutive patients with proven PE, venography confirmed the presence of a DVT in 174 (82%). Cases of PE where the presence of a DVT is not immediately obvious may reflect the lack of an objective diagnostic test, a failure to dissect the lower limb deep veins at autopsy, or possibly total thrombus detachment and migration (British Thoracic Society, 1997), a phenomenon found especially in surgical patients (Task Force on Pulmonary Embolism, European Society of Cardiology, 1997). Evidence suggests that the clinical manifestation of VTE may depend on the risk profile of an individual. For example, the high incidence of factor V Leiden associated with DVT is not reflected in patients presenting with an apparently isolated PE (Margaglione et al, 2000; Perrier, 2000).

Thrombus location can be correlated with the incidence and severity of PE. In a prospective clinical study, Kohn et al (1987) described the occurrence of PE in patients with DVT. The prevalence of PE was 46% in those with isolated calf vein thrombi, 67% in cases where the DVT extended into the thigh, and up to 77% in those with pelvic vein involvement. This is consistent with autopsy data that show an increasing number of PE derived from pelvic vein (periprostatic and periuterine plexus) thromboembolism (Morpurgo et al, 1998). Upper extremity DVT, often associated with indwelling venous catheters, is now more frequently described, and also appears to be associated with a high risk of PE (Prandoni et al, 1997).

The prevalence of PE at autopsy in hospitalized patients is high (more than 10%) and has remained largely unchanged during the last 30 years (Stein, 2000). In many cases PE remains unrecognized and hence untreated, often with fatal consequences (Task Force on Pulmonary Embolism, European Society of Cardiology, 2000). The International Cooperative Pulmonary Embolism Registry (ICOPER) study, which described outcome in 2500 patients with PE, found a cumulative mortality rate at 3 months of more than 17% (Goldhaber et al, 1999). Evidence has confirmed that PE is frequently clinically 'silent'. Meignan et al (2000) found that up to 45% of patients presenting with proximal DVT had silent PE. The high percentage of deaths showing DVT postmortem that was not recognized antemortem suggests that silent DVT should be a major concern in hospitalized patients. This is borne out by the ICOPER findings, where the clinical diagnosis of DVT inversely correlated with mortality. The poorer outcome in those PE patients in whom symptoms of DVT were not manifest supports the view that effective thromboprophylaxis is required in hospitalized patients perceived to be at risk of VTE.

Figure 1. The pathogenesis of post-thrombotic syndrome.



MORBIDITY AND MORTALITY

Morbidity associated with VTE

Morbidity as a result of an acute VTE is associated with immediate clinical consequences, long-term problems caused by recurrent symptomatic VTE and post-phlebitic or post-thrombotic syndrome (PTS). Acute PE results in complex, multifactorial changes to cardiovascular and respiratory function with a wide prognostic spectrum. In those who survive an initial thromboembolic episode and receive antithrombotic therapy, recurrent non-fatal VTE, fatal PE, and chronic thromboembolic pulmonary hypertension may complicate the course. The consequences of PE are related to the number and size of thrombi and the condition of the organ systems (Task Force on Pulmonary Embolism, European Society of Cardiology, 2000).

Post-thrombotic syndrome

PTS is thought to result from a combination of venous hypertension and abnormalities of the microcirculation (*Figure 1*). Clinical manifestations range from mild oedema to acute pain and ulceration (Brandjes et al, 1997). Damage to, and subsequent incompetency of, venous valves results in venous flow directing into the superficial venous system during muscular contraction. This results in oedema, compromising the viability of subcutaneous tissue, and in the most severe form, venous ulceration (Hirsh and Hoak, 1996). More rarely, venous hypertension will result from persistent venous obstruction, for example because of a large proximal thrombus causing outflow obstruction.

The prevalence of PTS in the general population has been estimated at 1–2%. The prevalence

after a documented episode of DVT is not precisely known (Hirsh and Hoak, 1996). In a large study published in 1996, the clinical course of 355 patients was followed for 8 years (Prandoni et al, 1996). Eighty three patients developed PTS, with 24 patients experiencing severe post-thrombotic complications. The cumulative incidence at 2 years was 22.8%, rising to 29.1% after 8 years.

Graduated compression stockings are considered the mainstay of therapy for PTS and are often routinely applied to patients shortly after DVT is diagnosed. In a randomized trial evaluating the use of compression stockings, the rate of mild PTS was significantly lower in the group wearing stockings (20%) than in a comparator group without stockings (47%). A significantly lower incidence of severe PTS was also demonstrated in the patients given stockings (11%) relative to the comparator group (23.5%) (Brandjes et al, 1997).

The results of this study, however, are in contrast to those of a more recent randomized trial which found that most patients (83%) do not develop PTS following proximal DVT and that in those who do develop the condition no benefit could be demonstrated from the use of compression stockings (Ginsberg et al, 2001).

Perioperative death from fatal PE

All hospitalized patients, both surgical and medical, are at risk of fatal PE, but the risks vary substantially (Geerts et al, 2001). Historically, hip replacement has been regarded as a procedure particularly prone to thromboembolic complications. Reviewing studies from the early days of hip replacement shows that fatal PE contributed substantially to postoperative mortality (Salvati et al, 2000). A study of a series of 7959 total hip replacements performed between 1962 and 1973 described a prevalence of fatal PE of 1.04% (Johnson et al, 1977, 1978). Of 1174 patients who did not receive thromboprophylaxis, fatal PE was found in 2.3%. In 1973, fatal PE was described in 2.2% of a series of 2012 consecutive hip replacement patients (Coventry et al, 1973). These patients were followed postoperatively and it was shown that fatal PE occurred in two patients out of 62 who received no prophylactic anticoagulation, a prevalence of more than 3%.

The benefits of thromboprophylaxis were first confirmed in the 1970s when the landmark International Multicenter Trial proved that heparin significantly reduces the incidence of fatal PE (Anonymous, 1975; Kakkar et al, 1977). Including figures from an additional publication in that era (Gruber et al, 1977) suggests the prevalence of fatal PE was reduced from 0.84% to 0.27% after heparin.

In the 1980s, two meta-analyses reviewed trials published in the 1970s and 1980s comparing rates of fatal PE in surgical patients in the presence or absence of heparin thromboprophylaxis. One study (Clagett and Reisch, 1988) examined rates of fatal PE in moderate- to high-risk general surgery patients, excluding orthopaedic procedures. Rates of about 0.7% were seen in patients receiving no thromboprophylaxis compared with about 0.2% in those receiving heparin (*Figure 2*). The other meta-analysis examined fatal PE rates in patients undergoing general, orthopaedic and urological surgery (Collins et al, 1988). Including all patients, the rate of fatal PE was about 0.9% in those who received no thromboprophylaxis and about 0.2% in those receiving heparin. However, a separate review of the 21 trials that examined orthopaedic patients shows substantially higher rates of 1.9% in the patients receiving no thromboprophylaxis and 0.6% in those receiving heparin. These figures compare with those obtained in more recent studies (Warwick et al, 1995; Ansari et al, 1997), particularly by Warwick et al, who reported fatal PE rates in the region of 0.4% in patients undergoing total hip or knee replacement in the absence of thromboprophylaxis. A large proportion of the trials reviewed in these meta-analyses had low autopsy rates and both rigorously excluded endpoints that were not fully substantiated. It therefore seems likely that the true prevalence of fatal PE was underestimated in these analyses.

In a double-blind study, rates of fatal PE were examined in more than 23 000 surgical patients receiving heparin thromboprophylaxis (Haas et al, 1999). The study was supported by an exceptional and uniquely high autopsy rate of 70% and reported an overall incidence of fatal PE of 0.2%

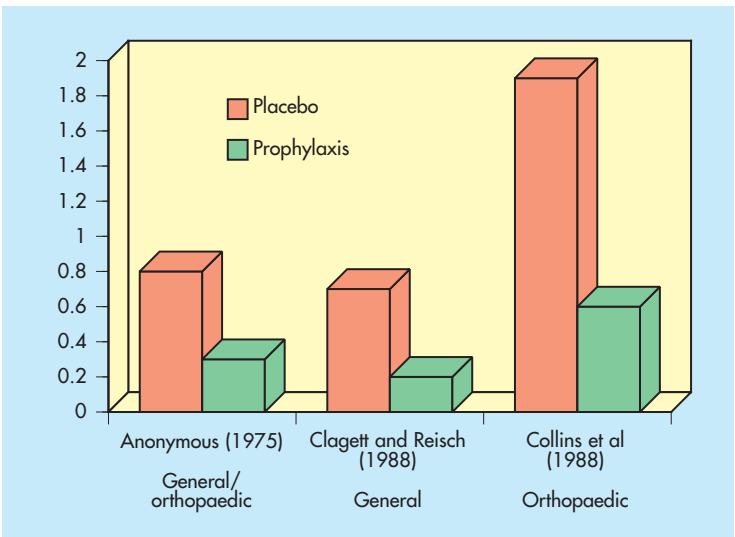


Figure 2. Thromboprophylaxis and the incidence of fatal thromboembolism after surgery.

at 14 days after the end of thromboprophylaxis. This figure represents the incidence of fatal PE in the 1990s in patients receiving guideline-recommended thromboprophylaxis. A sub-group analysis also revealed that the incidence of fatal PE in patients undergoing orthopaedic surgery (hip or knee replacement and hip fracture) was considerably higher than previously published estimates.

The studies described confirm that orthopaedic surgery is associated with a high-risk of VTE, and that death from thromboembolism is a significant problem. More sub-study analyses, particularly of the Haas trial, are required to better define those patients at highest risk of fatal PE and improve risk stratification.

Non-surgical patient mortality from PE

Compared to surgical patients, only a limited number of studies have published data on the prevalence of fatal PE in general medical patients. Most of the information available is derived from studies examining the efficacy of heparin thromboprophylaxis in patients with acute medical illnesses.

In a European study of hospitalized medical patients with acute cardiac or pulmonary disease, cancer or non-pulmonary sepsis, 2474 patients were randomized to receive the low molecular weight heparin nadroparin 7500 IU once daily or placebo for 21 days (Bergmann and Caulin, 1996). The primary efficacy endpoint of the study was mortality up to the end of the treatment period. Death occurred in 124 of 1230 (10.1%) patients receiving nadroparin and in 128 of 1244 (10.3%) patients receiving placebo. Autopsy was performed after 123 of the deaths and fatal PE was found in 27 cases, accounting for 22% of the deaths in which autopsy was performed.

In the Swedish heparin prophylaxis study, more than 11 000 patients over 55 years of age, hospitalized as a result of infectious disease, were randomized to receive unfractionated heparin 5000 IU twice daily for 3 weeks or no treatment in an open design (Gardlund, 1996). The primary endpoint of the study was autopsy-verified PE. Autopsy was performed in 56.8% of the placebo group deaths and in 63.8% of the UFH group. Overall mortality was similar in the heparin and control groups (5.3 *vs* 5.6%). A total of 31 cases of fatal PE were identified.

The PRIME study looked at 959 bedridden patients hospitalized as a result of acute medical illness who had at least one additional predefined thromboembolic risk factor (Lechler et al, 1996). The mean age of the patients was 74 years, and there was an average of 3.4 predefined risk factors per patient. The majority of patients (70%) had been hospitalized because of acute heart failure. Two cases of symptomatic PE occurred but no cases of fatal PE were described.

The MEDENOX trial examined the efficacy and safety of the low molecular weight heparin, enoxaparin, in the prevention of VTE in acutely ill medical patients (Samama et al, 1999). The study population included patients hospitalized because of acute cardiac or respiratory failure or an infectious or rheumatic disorder in association with a pre-defined thromboembolic risk factor. The study showed that patients with acute medical illnesses are at substantial risk of VTE. There were a small number of deaths from fatal PE (4 of 866 patients; 0.5%).

In a randomized comparison of nadroparin with placebo for the prevention of DVT in patients mechanically ventilated for acute, decompensated chronic obstructive pulmonary disease, no proven cases of PE were observed (Fraisse et al, 2000). However, there was no systematic investigation by objective tests, and autopsy was not routinely performed after death.

Goldhaber et al (2000) examined new onset VTE among hospitalized patients at Brigham and Women's Hospital, Boston, USA. The study identified 384 patients with VTE, mostly among those using general medical or medical oncology services. Death as a result of fatal PE occurred in 3.4% of patients. However, almost all the patients had received some form of physical or chemical thromboprophylaxis.

The studies carried out to date show that VTE is a significant problem in acutely ill medical patients and that PE accounts for a proportion of the deaths in these patients. However, more studies are required to obtain reliable estimates of fatal PE rates. The MEDENOX study showed that mortality at 3 months was in the range 11.4–14.7%, suggesting that thromboprophylaxis was worthwhile in this defined patient group in whom more than 85% of patients survived beyond 3 months.

Fatal PE in pregnancy

Although the incidence of fatal PE in pregnancy is low, thromboembolic complications remain the major cause of maternal death (Department of Health, 1998). The overall incidence of fatal PE has fallen since the 1950s but since the 1980s there has been a reversal in the downward trend, highlighting an ongoing need for improved methods of diagnosis and management of thrombosis in pregnancy. The underlying rate of DVT in pregnancy is around 0.1% and varies depending on a range of factors including age, method of delivery, body weight and a personal or family history of thrombosis (Greer, 1999b).

Fatal PE in critically ill patients

VTE is an important cause of morbidity and mortality among critically ill patients admitted to intensive care units as a result of major trauma, spinal cord injury or following neurosurgery. Approximately 10% have proximal DVT on admission and are further predisposed to DVT during their stay as a result of prolonged immobilization, sepsis and vascular injury from indwelling venous catheters and other interventions. It is estimated that between 22 and 80% of critically ill patients will develop DVT, depending on the nature of their condition. Fatal PE occurs in 0.5–2.0% of critically ill patients and is the third most common cause of death in those who survive beyond the first day (Attia et al, 2001).

CONCLUSION

The pathophysiology of VTE is complex and remains incompletely understood. VTE is manifested clinically as DVT and PE – different but inter-related outcomes of a single disease process. The clinically silent nature of VTE and its substantial morbidity and mortality make it a significant threat to the health of hospital patients. The classical 'at-risk' patient undergoing traumatic surgery experiences both localized and systemic activation of coagulation that, in conjunction with other acquired and inherited risk factors, sets the scene for clot formation. Medical illness results in a procoagulant state that is poorly understood, but places hospitalized patients at substantial risk of VTE.

Modern medical care and up-to-date attitudes to thromboprophylaxis, particularly use of heparins, have reduced the incidence of fatal PE. Clinical studies in surgical patients have allowed accurate determination of mortality rates and show a reduction in fatal PE from around 0.7% to about 0.2% using heparins. However, fatal PE is more common in medical than surgical patients. Effective risk stratification and implementation of thromboprophylaxis in non-surgical groups, especially those with an acute medical illness in whom thromboprophylaxis is not always implemented, is required to reduce hospital mortality. HM

Conflict of interest: none.

Abe K, Shoji M, Chen J et al (1999) Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor. *Proc Natl Acad Sci USA* **96**(15): 8663–8

Alessandri C, Basili S, Violi F, Ferroni P, Gazzaniga PP, Cordova C (1994) Hypercoagulability state in patients with chronic obstructive pulmonary disease. Chronic Obstructive Bronchitis and Haemostasis Group. *Thromb Haemost* **72**(3): 343–6

Alhenc-Gelas M, Arnaud E, Nicaud V et al (1999) Venous thromboembolic disease and the prothrombin, methylene tetrahydrofolate reductase and factor V genes. *Thromb Haemost* **81**(4): 506–10

Anonymous (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin – An international multicentre trial. *Lancet* **ii:** 145–51

Ansari S, Warwick D, Ackroyd CE, Newman JH (1997) Incidence of fatal pulmonary embolism after 1390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. *J Arthroplasty* **12**(6): 599–602

Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH (2001) Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* **28**(161): 1268–79

Bara L, Boutitie F, Samama MM et al (2001) Correlation of plasma coagulation parameters with treatment, patient characteristics and outcome in the medenox trial. *Thromb Haemost* abstract 2306

Barger AP, Hurley R (2000) Evaluation of the hypercoagulable state. Whom to screen, how to test and treat. *Postgrad Med* **108(4):** 59–66

Bergmann JF, Caulin C (1996) Heparin prophylaxis in bedridden patients [letter; comment]. *Lancet* **348**: 205–6

Bertina RM (2001) Genetic approaches to thrombophilia. Thromb. *Haemost* **86**(1): 92–103

Bertina RM, Koeleman BP, Koster T et al (1994) Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* **369**: 64–7

Brandjes DP, Buller HR, Heijboer H et al (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* **349**: 759–62

British Thoracic Society (1997) Standards of Care Committee. *Thorax* **52:** S3–S24

Clagett GP, Reisch JS (1988) Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. *Ann Surg* **208**(2): 227–40

Collins R, Scrimgeour A, Yusuf S, Peto R (1988) Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* **318**: 1162–73

Comp PC, Esmon CT (1984) Recurrent venous thromboembolism in patients with a partial deficiency of protein S. *N Engl J Med* **311**: 1525–8

Coventry MB, Nolan DR, Beckenbaugh RD (1973) 'Delayed' prophylactic anticoagulation: a study of results and complications in 2,012 total hip arthroplasties. *J Bone Joint Surg Am* **55:** 1487–92

Dahl OE (1997) The role of the pulmonary circulation in the regulation of coagulation and fibrinolysis in relation to major surgery. *J Cardiothorac Vasc Anesth* **11**(3): 322–8

Dahl OE (1999) Mechanisms of hypercoagulability. *Thromb Haemost* **82**(2): 902–6

Dahl OE (2000) Thromboembolism and thromboprophylaxis in high risk surgery: facts and assumptions--a topic for emotions? *Eur J Anaesthesiol* **17**(6): 343–7

de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP (1998) Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. *Br Med J* **316:** 589–92

Department of Health (1998) *Why Mothers Die: Report of the Confidential Enquiries into Maternal Deaths 1994-1998.* HMSO, London

Fraisse F, Holzapfel L, Couland JM et al (2000) Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med* **161**(4 Pt 1):1109–14

Gardlund B (1996) Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in

KEY POINTS

- Venous thromboembolism (VTE) is a multifactorial disorder with a complex and incompletely understood pathophysiology.
- Deep vein thrombosis and pulmonary embolism are interrelated forms of a single pathophysiological process.
- Acute medical illness results in a procoagulant state that places hospitalized patients at risk of VTE.

patients with infectious diseases. The Heparin Prophylaxis Study Group. *Lancet* **347**: 1357–61
Gazzaniga PP, Basili S, Ferroni P et al (1993) Chronic obstructive pulmonary disease. A possible correlation between platelet aggregation tests and respiratory indexes. ECOB Group. *Clin Ter* **142**(6): 507–16
Geerts WH, Heit JA, Clagett GP et al (2001) Prevention of venous thromboembolism. *Chest* **119(1):** 132S–75S
Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, Gent M (2001) Prevention and treatment of postphlebitic syndrome: Results of a 3-part study. *Arch Intern Med* **24**(161): 2105–9
Girard P, Musset D, Parent F, Maitre S, Phlippoteau C, Simonneau G (1999) High prevalence of detectable deep venous thrombosis in patients with acute pulmonary embolism. *Chest* **116**(4): 903–8
Goldhaber SZ, Visani L, De Rosa M (1999) Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* **353**: 1386–9
Goldhaber SZ, Dunn K, MacDougall RC (2000) New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest* **118**(6): 1680–4
Gordon SG, Mourad AM (1991) The site of activation of factor X by cancer procoagulant. *Blood Coagul Fibrinolysis* **2**(6): 735–9
Greer IA (1999a) Thrombosis in pregnancy: maternal and fetal issues. *Lancet* **353:** 1258–65
Greer IA (1999b) Confidential enquiry into maternal mortality. *Hosp Med* **60**(3): 221
Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C (1981) Deficiency of protein C in congenital thrombotic disease. *J Clin Invest* **68**(5): 1370–3
Gruber UF, Duckert F, Fridrich R, Torhorst J, Rem J (1977) Prevention of fatal postoperative pulmonary embolism by dextran 40, low doses of heparin or xantinol nicotinate. *Lancet* **i:** 207–10
Haas SK, Wolf H, Encke A, Fareed J (1999) Prevention of fatal postoperative pulmonary embolism by low molecular weight heparin - a double blind comparison of certoparin and unfractionated heparin. *Thromb.Haemost* **82:** abstract 1548
Hirsh J, Hoak J (1996) Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. *Circulation* **93**(12): 2212–45
Johnson R, Green JR, Charnley J (1977) Pulmonary embolism and its prophylaxis following the Charnley total hip replacement. *Clin Orthop* **127:** 123–32
Johnson R, Carmichael JH, Almond HG, Loynes RP (1978) Deep venous thrombosis following Charnley arthroplasty. *Clin Orthop* **132:** 24–30
Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Thirwell J (1977) Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. *Lancet* **i**: 567–9
Kakkar AK, DeRuvo N, Chinswangwatanakul V, Tebbutt S, Williamson RC (1995) Extrinsic-pathway activation in cancer with high factor VIIa and tissue factor. *Lancet* **346**: 1004–5
Kesteven PL (2000) Traveller's thrombosis. *Thorax* **55**(Suppl 1): S32–S36
Kohn H, Konig B, Mostbeck A (1987) Incidence and clinical feature of pulmonary embolism in patients with deep vein thrombosis: a prospective study. *Eur J Nucl Med* **13**(Suppl): S11–S15
Lechler E, Schramm W, Flosbach CW (1996) The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. *Haemostasis* **26**(Suppl 2): 49–56
Lee AY, Levine MN (1999) The thrombophilic state induced by therapeutic agents in the cancer patient. *Semin Thromb Hemost* **25**(2): 137–45
Lensing AW, Prandoni P, Prins MH, Buller HR (1999) Deep-vein thrombosis. *Lancet* **353**(9151): 479–85
Letai A, Kuter DJ (1999) Cancer, coagulation, and anticoagulation. *Oncologist* **4**(6): 443–9
Lindstrom B, Ahlman H, Jonsson O, Sivertsson R, Stenqvist O (1977) Blood flow in the calves during surgery. *Acta Chir Scand* **143**(6): 335–9
Lindstrom B, Ahlman H, Jonsson O, Stenqvist O (1984) Influence of anaesthesia on blood flow to the calves during surgery. *Acta Anaesthesiol Scand* **28**(2): 201–3
Margaglione M, Brancaccio V, De Lucia D et al (2000) Inherited thrombophilic risk factors and venous thromboembolism: distinct role in peripheral deep venous thrombosis and pulmonary embolism. *Chest* **118**(5): 1405–11
Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci P (1998) High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med* **338:** 1793–7
Meignan M, Rosso J, Gauthier H et al (2000) Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. *Arch Intern Med* **160:** 159–64
Monreal M, Alastrue A, Rull M et al (1996) Upper extremity deep venous thrombosis in cancer patients with venous access devices--prophylaxis with a low molecular weight heparin (Fragmin). *Thromb Haemost* **75**(2): 251–3
Morpurgo M, Schmid C, Mandelli V (1998) Factors influencing the clinical diagnosis of pulmonary embolism: analysis of 229 postmortem cases. *Int J Cardiol* **65**(Suppl 1): S79–S82
Munford RS (2001) Statins and the acute-phase response. *N Engl J Med* **344**(26): 2016–8
Nicolaides AN (2001) Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. *Int Angiol* **20**(1): 1–37
Ott I, Fischer EG, Miyagi Y, Mueller BM, Ruf W (1998) A role for tissue factor in cell adhesion and migration mediated by interaction with actin-binding protein 280. *J Cell Biol* **140**(5): 1241–53
Perrier A (2000) Deep vein thrombosis and pulmonary embolism: a single disease entity with different risk factors? *Chest* **118**(5): 1234–6
Poort SR, Rosendaal FR, Reitsma PH, Bertina RM (1996) A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* **88**(10): 3698–703
Prandoni P, Lensing AW, Cogo A (1996) The long-term clinical course of acute deep-vein thrombosis. *Ann Intern Med* **125:** 1–7
Prandoni P, Polistena P, Bernardi E et al (1997) Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med* **157**(1): 57–62
Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J (1996) Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. *J Clin Oncol* **14**(10): 2731–7
Rickles FR, Falanga A (2001) Molecular basis for the relationship between thrombosis and cancer. *Thromb Res* **102:** V215–V224
Rosendaal FR (1999) Venous thrombosis: a multicausal disease. *Lancet* **353**: 1167–73
Salvati EA, Pellegrini VD Jr, Sharrock NE et al (2000) Recent advances in venous thromboembolic prophylaxis during and after total hip replacement. *J Bone Joint Surg Am* **82**(2): 252–70
Samama MM, Cohen AT, Darmon JY et al (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* **341**(11): 793–800
Second Thromboembolic Risk Factors (THRiFT II) Consensus Group (1998) Risk of and prevention for venous thromboembolism in hospital patients. *Phlebology* **13:** 87–97
Seligsohn U, Lubetsky A (2001) Genetic susceptibility to venous thrombosis. *N Engl J Med* **344**(16): 1222–31
Stein PD (2000) Silent pulmonary embolism. *Arch Intern Med* **160**(2): 145–6
Task Force on Pulmonary Embolism, European Society of Cardiology (2000) Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J* **21**(16): 1301–36
Trousseau A (1865) Phlegmasia alba dolens. Cliniques Medicales de l'Hotel-Dieu de Paris, London 3, 94
Virchow R (1856) *Gessamelte Abhanlungen zur Wissenschaftlischen Medicine.* Meidinger, Frankfurt
Warwick D, Williams MH, Bannister GC (1995) Death and thromboembolic disease after total hip replacement. A series of 1162 cases with no routine chemical prophylaxis. *J Bone Joint Surg Br* **77**(1): 6–10