CHAPTER 145

Acute Deep Venous Thrombosis: Epidemiology and Natural History

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Acute venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), are the most common preventable cause of hospital death[1] and a source of substantial long-term morbidity.[2-4] The impact on health is so great that the Surgeon General of the United States issued a "Call to Action" to combat VTE.[5] An understanding of the risk factors and natural history of VTE is essential in guiding prophylaxis, diagnosis, and treatment. In addition, recognizing underlying risk factors and the multifactorial nature of VTE may aid in the identification of situations likely to provoke thrombosis in both high-risk individuals and those with unexplained thromboembolism. Furthermore, understanding the natural history of VTE is important in defining the relative risks and benefits of anticoagulation, as well as the duration of treatment in individual patients.

EPIDEMIOLOGY

Incidence

The incidence of recurrent, fatal, and nonfatal VTEs is estimated to exceed 900,000 cases annually in the United States alone.[6] A 35-year population-based study using the Rochester Epidemiology Project database of Olmsted County Minnesota demonstrated an overall average age- and sex-adjusted annual VTE incidence of 122 per 100,000 person-years (DVT, 56 per 100,000; PE, 66 per 100,000).[7] This study also demonstrated higher age-adjusted rates among men than women (134 vs. 115 per 100,000, respectively). First-time VTEs are approximated to occur in 250,000 US white individuals annually.[8] When compared with other racial populations, whites have a lower incidence of VTE than do African Americans (104 vs. 141 per

Abstract

The incidence of recurrent, fatal and nonfatal venous thromboembolism (VTE) is estimated to exceed 900,000 cases annually. VTE is associated with a number of risk factors. These include age, immobilization, travel, history of VTE, malignancy, surgery, trauma, pregnancy, oral contraceptives and hormonal therapy, blood group, geography and ethnicity, inflammatory bowel disease, systemic lupus erythematosus, varicose veins, iliac vein compression, popliteal vein entrapment, among others. The main complications of VTE include recurrent thrombosis and mortality, especially related to pulmonary embolism, along with post-thrombotic morbidity related to deep venous thrombosis.

Keywords

venous thromboembolism
recurrent thrombosis
DVT
PE
risk factors

100,000) and a higher incidence of VTE than do Hispanics and Asian/Pacific Islanders combined (104 vs. 21 per 100,000).[9] However, the problem of VTE is not just isolated to the United States; it is a global issue. The estimates of VTE across the European Union were 684,019 cases of DVT, 434,723 cases of PE, with 543,454 VTE-related fatalities.[10]

Populations Affected

The incidence of VTE varies with the population studied, use of thromboprophylaxis, the intensity of screening, and the accuracy of the diagnostic test employed. For example, individuals with acute spinal cord injury who were screened systematically with venography demonstrated DVT at a rate of 81%.[11] However, medical-surgical intensive care unit (ICU) patients who received thromboprophylaxis had a DVT rate reported at 10% to 18%,[12] compared with those who were not given DVT prophylaxis having a rate of 25% to 32%.[12,13] Interestingly, the risk of VTE in the critically ill is not limited to the time actually spent in the ICU. A single-center study showed that of the VTEs diagnosed in the critically ill, 64% were diagnosed with a VTE after discharge from the ICU. It is suggested that prolonged immobility after discharge from the ICU may have contributed to the high rate of DVT.[14] Similarly, prolonged immobility contributes to increased rates of VTE in nursing home residents.[15] In summary, it appears that medical-surgical ICU patients are at lower risk for DVT compared with acute spinal cord injury, trauma, or neurosurgery patients, but at a comparable risk to patients who have had major orthopedic surgery, and at higher risk than medical-surgical ward patients.[13,16] Furthermore, a more recent study noted a high (15.2%) rate of DVT in critically ill trauma patients within the first week that did not vary regardless of whether or not prophylaxis was used.[17]

TABLE 145.1 Risk Factors for Acute Deep Venous Thrombosis and Pulmonary Embolism

Risk Factor for DVT or PE	Odds Ratio	95% Confidence Interval
Hospitalization		
With recent surgery	21.72	9.44-49.93
Without recent surgery	7.98	4.49-14.18
Trauma	12.69	4.06-39.66
Malignant Neoplasm		
With chemotherapy	6.53	2.11-20.23
Without chemotherapy	4.05	1.93-8.52
Prior central venous catheter or pacemaker	5.55	1.57-19.58
Prior superficial vein thrombosis	4.32	1.76-10.61
Neurologic disease with extremity paresis	3.04	1.25-7.38
Varicose Veins		
Age 45 years	4.19	1.56-11.30
Age 60 years	1.93	1.03-3.61
Age 75 years	0.88	0.55-1.43
Congestive Heart Failure		
Thromboembolism not categorized as a cause of death at postmortem	9.64	2.44-38.10
Thromboembolism categorized as a cause of death at postmortem	1.36	0.69-2.68

DVT, Deep venous thrombosis; *PE*, pulmonary embolism.
Modified from Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160:809.

Risk Factors

DVT occurring in the setting of a recognized risk factor is often defined as a secondary event, whereas those that occur in the absence of risk factors is termed primary or idiopathic.[18] Known risk factors for DVT are listed in Table 145.1.

The high incidence of acute DVT in hospitalized patients, the availability of objective diagnostic tests, and the existence of clinical trials evaluating prophylactic measures have helped to more readily identify high-risk groups in this population compared with the outpatient population. Malignancy, surgery, and trauma within the previous 3 months remain significant risk factors for outpatient thrombosis, whereas the prevalence of surgery and malignancy is higher among inpatients with DVT.[19,20] Approximately 47% of outpatients with a documented DVT have one or more recognized risk factors.[19] The incidence of VTE proportionally increases with the number of risk factors.[21] The 2005 Caprini score is currently the most used system in the country (Fig. 145.1).[12,22]

Age

VTE occurs in all ages, although a higher incidence has consistently been associated with advanced age. In a community-based study of phlebographically documented DVT, the yearly incidence of DVT was noted to increase progressively from almost 0 in childhood to 7.65 cases per 1000 in men and 8.22 cases per 1000 in women older than 80 years.[23] The incidence of DVT increased 30-fold from those age 30 years to those older than 80 years. Rosendaal[24] similarly noted an incidence of 0.006 per 1000 children younger than 14 years, which rose to 0.7 per 1000 among adults 40 to 54 years old. Furthermore, Hansson and colleagues[25] found the prevalence of objectively documented thromboembolic events among men increased from 0.5% at age 50 years to 3.8% at age 80 years.

The influence of age on the incidence of VTE is likely multifactorial. The number of thrombotic risk factors increases with age, with three or more risk factors being present in only 3% of hospitalized patients younger than 40 years but in 30% of those 40 years and older.[21] Interestingly, it also appears that the number of risk factors required to precipitate thrombosis decreases with age.[24] This may be related to an acquired prothrombotic state associated with aging because higher levels of thrombin activation markers are found among older people.[26] Advanced age also has been associated with anatomic changes in the soleal veins

Patient's name:_____ Age: ___ Sex: ___ Wgt: ___ lbs

Choose all that apply

Each risk factor represents 1 point
- Age 41–60 years
- Minor surgery planned
- History of prior major surgery
- Varicose veins
- History of inflammatory bowel disease
- Swollen legs (current)
- Obesity (BMI >30)
- Acute myocardial infarction (<1 month)
- Congestive heart failure (<1 month)
- Sepsis (<1 month)
- Serious lung disease incl. pneumonia (<1 month)
- Abnormal pulmonary function (COPD)
- Medical patient currently at bed rest
- Leg plaster cast or brace
- Other risk factors_____

Each risk factor represents 3 points
- Age over 75 years
- Major surgery lasting 2–3 hours
- BMI >50 (venous stasis syndrome)
- History of SVT, DVT/PE
- Family history of DVT/PE
- Present cancer or chemotherapy
- Positive factor V leiden
- Positive prothrombin 20210A
- Elevated serum homocysteine
- Positive lupus anticoagulant
- Elevated anticardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia
  Type_____

Each risk factor represents 2 points
- Age 60–74 years
- Major surgery (>60 minutes)
- Arthroscopic surgery (>60 minutes)
- Laparoscopic surgery (>60 minutes)
- Previous malignancy
- Central venous access
- Morbid obesity (BMI >40)

Each risk factor represents 5 points
- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (<1 month)
- Stroke (<1 month)
- Multiple trauma (<1 month)
- Acute spinal cord injury (paralysis) (<1 month)
- Major surgery lasting over 3 hours

For women only (each represents 1 point)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant

Total risk factor score ☐

Please see following page for prophylaxis safety considerations
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Prophylaxis regimen

Total risk factor score	Incidence of DVT	Risk level	Prophylaxis regimen	Legend
0–1	<10%	Low risk	No specific measures; early ambulation	**ES** — Elastic stockings **IPC** — Intermittent pneumatic compression **LDUH** — Low dose unfractionated heparin **LMWH** — Low molecular weight heparin **Fac Xa** — Factor X inhibitor
2	10–20%	Moderate risk	ES or IPC or LDUH, or LWMH	
3–4	20–40%	High risk	IPC or LDUH, or LMWH alone *or* in combination with ES or IPC	
5 or more	40–80% 1–5% mortality	Highest risk	Pharmacological: LDUH, LMWH*, Warfarin*, or Fac Xa* alone *or* in combination with ES or IPC	

Prophylaxis safety considerations: Check box if answer is 'YES'

Anticoagulants: Factors associated with increased bleeding
☐ Is patient experiencing any active bleeding?
☐ Does patient have (or has had history of) heparin-induced thrombocytopenia?
☐ Is patient's platelet count <100,000/mm^3?
☐ Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, clopidigrel, salicylates)?
☐ Is patient's creatinine clearance abnormal? If yes, please indicate value ————————
If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures.

Intermittent pneumatic compression (IPC)
☐ Does patient have severe peripheral arterial disease?
☐ Does patient have congestive heart failure?
☐ Does patient have an acute superficial/deep vein thrombosis?
If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures.

Figure 145.1 The Caprini risk factor tool to predict the risk of venous thromboembolism. *DVT,* Deep venous thrombosis; *PE,* pulmonary embolism. (From Wakefield T, Henke P. *Complications in Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011:353.)

and more pronounced stasis in the venous valve pockets.[27,28] We have also noted biologic changes with aging in our research laboratory, such as elevations in P-selectin, tissue factor (TF), antiphospholipid antibodies, and procoagulant microparticles, supporting the effect of age on venous thrombogenesis.

Venous diseases, including VTE, are usually regarded as rare in young children,[3] with an incidence of 0.006 per 1000 children younger than 14 years,[24] whereas the incidence in hospitalized children younger than 18 years has been estimated to be 0.05%.[29] Early mobilization and discharge may partially explain the lower incidence in children.[29] However, the diagnosis is often not considered in pediatric patients, and few studies have systematically evaluated children for DVT. Over time the number of recognized cases in hospitalized children has increased from 0.3 to 28.8 per 10,000 from 1992 to 2005.[30]

VTE in children is almost always associated with recognized thrombotic risk factors,[24,31-33] and multiple risk factors are often required to precipitate thrombosis.[24] DVT may occur in as many as 3.7% of pediatric patients immobilized in halo-femoral traction for preoperative treatment of scoliosis,[34] 4% of children hospitalized in the ICU,[35] and 10% of children with spinal cord injuries.[36,37] Symptomatic postoperative DVT is regarded as unusual in children, although there are few data from studies using routine surveillance,[38] and autopsy-identified PE is approximately four times more frequent in pediatric patients who have undergone surgery than in the general pediatric medical population.[31] Other thrombotic risk factors in hospitalized children are local infection and trauma, immobilization,[33] inherited hypercoagulable states,[24] oral contraceptive use,[39] lower limb paresis,[34] and the use of femoral venous catheters.[40] Outpatient DVT is often associated with a prior DVT and thrombophilia.[30]

Immobilization

Immobilization is a risk factor for VTE. Stasis in the soleal veins and behind the valve cusps is worsened by inactivity of the calf muscle pump,[28] which is associated with an increased risk of DVT. The prevalence of lower extremity DVT in autopsy studies also parallels the duration of bed rest, with an increase during the first 3 days of confinement and a rapid rise to very high levels after 2 weeks. DVT was found in 15% of patients dying after 0 to 7 days of bed rest, in comparison with 79% to 94% of those dying after 2 to 12 weeks.[27] Preoperative immobilization is also associated with a twofold increase in risk of postoperative DVT,[41] and DVT among stroke patients is significantly more common in paralyzed or paretic extremities (53% of limbs) than in nonparalyzed limbs (7%).[42] Patients with neurologic disease and extremity paresis or plegia have a threefold higher risk for DVT and PE, which appears to be independent of hospital confinement.[43]

Travel

Immobilization as a thrombotic risk factor extends to include prolonged travel, particularly the "economy class syndrome," which occurs in people who have sat in a cramped position during extended aircraft flights.[44] Several case series have reported the occurrence of PE in relation to extended travel,[44-49] although none has rigorously examined the prevalence relative to that of the general population, and few have thoroughly reported the presence of other risk factors. A high prevalence of preexisting venous disease and other thrombotic risk factors in this group of patients has sometimes been noted.[26,49] The question of prolonged travel as a risk factor is moderated by observations that extreme duration of venous stasis alone may fail to produce thrombosis[50] and that no consistent rheologic or prothrombotic changes have been demonstrated during prolonged travel.[26,51] However, PE is the second leading cause of travel-related death, accounting for 18% of 61 deaths, suggesting that a relationship cannot be excluded.[48]

More evidence that a connection between travel and DVT and PE has accumulated. In a case-control study, Ferrari and associates found[52] that long distance travel increased the risk of DVT, with an odds ratio (OR) of 4.0, and Samama[53] made similar observations (OR, 2.3). Scurr and colleagues[54] found a 10% risk of calf DVT in patients who traveled without compression stockings. Lapostolle and coworkers[55] observed that over an 86-month period, 56 of 135.3 million airline passengers had severe PE. The frequency among those who traveled more than 5000 km was 150 times as high as those who traveled less than 5000 km. In another case-control study, Paganin and associates[56] observed a high incidence of VTE in patients with risk factors for DVT who traveled long distances: in particular, history of previous VTE (OR, 63.3), recent trauma (OR, 13.6), presence of varicose veins (OR, 10), obesity (OR, 9.6), immobility during flight (OR, 9.3), and cardiac disease (OR, 8.9) increased the risk of DVT. These investigators concluded that low mobility during flight was a modifiable risk factor for development of PE and that travelers with risk factors should increase their mobility.[57]

After a consensus meeting, the World Health Organization published the following conclusions: an association probably exists between air travel and DVT; such an association is likely to be small and mainly affects passengers with additional risk factors for VTE; similar links may exist for other forms of travel.[58] The available evidence does not permit an estimation of actual risk.

History of Venous Thromboembolism

Approximately 23% to 26% of patients presenting with acute DVT have a previous history of thrombosis,[23,59] and histologic studies confirm that acute thrombi are often associated with fibrous remnants of previous thrombi in the same or nearby veins.[60] Depending on sex and age, population-based studies have demonstrated that recurrent VTE occurs in 2% to 9% of people.[3]

The risk of recurrent VTE is higher among patients with idiopathic DVT.[61] In addition, primary hypercoagulability appears to have a significant role in many recurrences. Simioni and associates[61] reported the cumulative incidence of recurrent thrombosis among patients who are heterozygous for the factor V Leiden mutation to be 40% at 8 years of follow-up, 2.4-fold higher than in patients without the mutation, although the importance of heterozygous factor V Leiden to recurrent thrombosis has been questioned.[62] den Heijer and colleagues[63] estimated that 17% of recurrent thromboembolic events may

be due to hyperhomocysteinemia. A similar relationship between impaired fibrinolysis and recurrent DVT has been suggested by several investigators, although the methodologic validity of these findings has been questioned.[64]

Malignancy

Approximately 20% of all first-time VTE events are associated with malignancy.[65] An estimated 1 in 200 individuals with malignancy will develop either DVT or PE, a fourfold higher risk than those without malignancy.[43] Considering all-cause mortality of in-hospital death for cancer patients, one in seven will die of PE.[66] Strikingly, the discovery of an occult malignancy associated with an otherwise first-time idiopathic VTE is as high as 12% to 17% in some series.[67,68] In another 5% to 11% of patients, malignancy appears within 1 to 2 years of presentation for DVT.[67-69] Several series have documented a significantly higher risk of malignancy in patients with presumed idiopathic DVT.[67,70] Among such patients, 7.6% have been noted to have a malignancy during follow-up, with an OR of 2.3 in comparison with those with secondary thrombosis.[68] The incidence of occult malignancy diagnosed within 6 to 12 months of an idiopathic DVT is 2.2 to 5.3 times higher than that expected from general population estimates.[71,72] The highest rates of VTE are associated with pancreatic malignancies, followed by kidney, ovary, lung, and stomach.[73]

The underlying mechanisms contributing to the hypercoagulable state in malignancy have been well studied and are multifactorial. Venous compression secondary to tumor growth, cancer-associated thrombocytosis, immobility, indwelling central lines, and chemotherapy or radiation therapy are all risk factors that increase the possibility of VTE.[74] However, the systemic prothrombotic response seen in malignancy is mediated by cytokines, inhibitors of fibrinolysis, and procoagulants.[75]

Tumor cells can directly initiate hemostasis through constitutive expression of TF. TF is not normally expressed on resting vascular endothelium but rather induced by chemical mediators during times of inflammation or vessel damage to bind factors VII and VIIa. This complex of TF and factor VII activates factors X and XI through proteolysis, leading to the generation of thrombin.[76] Another mediator in malignancy-associated VTE is cancer procoagulant (CP). The role of CP in coagulation is limited to its association with malignancy because it has not been identified in normal healthy tissue. CP serves as a direct activator of factor X, independent of the presence of factor VIIa. The platelet adhesion molecules glycoprotein Ib and glycoprotein IIb/IIIa (GPIIb/IIIa) have also been identified on tumor cells, allowing for platelet activation and aggregation.[77]

The prothrombotic contribution of cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) mediate their actions through induction of TF on vascular endothelium, monocytes, and leukocytes.[76,78] In addition, IL-1 and TNF-α downregulate the expression of thrombomodulin, the receptor for thrombin, on the endothelial surface. This results in a decrease in thrombin-thrombomodulin complexes, the activating complex of protein C, a natural anticoagulant.[76,78] Furthermore, IL-1 and TNF-α stimulate the production of plasminogen activator inhibitor 1 (PAI-1), the main physiologic inhibitor of fibrinolysis.[79]

As many as 90% of patients with cancer have abnormal coagulation parameters, including increased levels of coagulation factors, elevated fibrinogen or fibrin degradation products, and thrombocytosis.[80] Elevated fibrinogen and thrombocytosis are the most common abnormalities, perhaps reflecting an overcompensated form of intravascular coagulation.[80] Levels of the coagulation inhibitors antithrombin, protein C, and protein S also may be reduced in malignancy.[81]

Markers of activated coagulation are elevated in the majority of patients with solid tumors and leukemia.[80] Fibrinopeptide A levels reflect tumor activity, decreasing or increasing in response to treatment or progression of disease, suggesting that tumor growth and thrombin generation are intimately related.[80] Furthermore, these levels may fail to normalize after administration of heparin to patients with cancer and DVT, perhaps explaining why these DVTs may be refractory to anticoagulants.[80]

VTE is also associated with the treatment of some cancers. DVT complicates 29% of general surgical procedures for malignancy.[81] Preoperative activation of the coagulation system, as reflected by elevated thrombin-antithrombin complex values, is associated with a 7.5-fold increased risk of postoperative DVT.[80] Some chemotherapeutic regimens also predispose to DVT, and thrombotic complications may be as common as the more widely recognized infectious complications.[82] VTE has been reported in up to 6% of patients undergoing treatment for non-Hodgkin's lymphoma, and in 17.5% of those receiving therapy for breast cancer.[83] Among patients with stage II breast cancer, thrombosis was significantly more common in those randomly assigned to 36 weeks of chemotherapy (8.8%) than in those receiving only 12 weeks of treatment (4.9%).[82] Potential thrombogenic mechanisms associated with chemotherapy include direct endothelial toxicity, induction of a hypercoagulable state, reduced fibrinolytic activity, tumor cell lysis, and use of central venous catheters.[83,84] Some intravenous chemotherapeutic agents are associated with activation of coagulation and increased markers of thrombin generation, a response that is blocked by pretreatment with heparin.[85] An additional risk factor in some cancer patients is an elevated soluble P-selectin.[86]

Surgery

The high incidence of postoperative DVT, as well as the availability of easily repeatable, noninvasive diagnostic tests, has allowed a greater understanding of the risk factors associated with surgery than in other conditions. Surgery constitutes a spectrum of risk that is influenced by patient age, coexistent thrombotic risk factors, type of procedure, extent of surgical trauma, length of procedure, and duration of postoperative immobilization.[87] The type of surgical procedure is particularly important.[41] Historically, the overall incidence of DVT is approximately 19% in patients undergoing general surgical operations, 24% in those having elective neurosurgical procedures; and 48%, 51%, and 61% among those undergoing surgery for hip fracture, hip arthroplasty, and knee arthroplasty, respectively.[87] On the basis of these data, patients can be classified as being at low, moderate, or high risk for thromboembolic

complications. Approximately half of postoperative lower extremity thrombi develop in the operating room, with the remainder occurring over the next 3 to 5 days.[88] However, the risk for development of DVT does not end uniformly at hospital discharge. In one study, 51% of the thromboembolic events occurred after discharge from gynecologic surgical procedures.[89] Similarly, up to 25% of patients undergoing abdominal surgery have DVT within 6 weeks of discharge.[90] Heit and associates found a nearly 22-fold higher risk of DVT and PE among patients who were hospitalized following previous surgery.[89]

All components of the Virchow triad may be present in the surgical patient—perioperative immobilization, transient changes in coagulation and fibrinolysis, and the potential for gross venous injury. Immobilization is associated with a reduction in venous outflow and capacitance during the early postoperative period.[91] Surgery is also accompanied by a transient, low-level hypercoagulable state, presumably mediated by the release of TF, which is marked by a rise in thrombin activation markers shortly after the procedure begins.[91] The thrombogenic potential of different surgical procedures appears to differ, with greater rises in thrombin activation markers during hip arthroplasty than after laparotomy.[92] Increased levels of PAI–1 are also associated with a decrease in fibrinolytic activity on the first postoperative day, the "postoperative fibrinolytic shutdown."[93] This relationship between impaired fibrinolysis and postoperative DVT may be particularly important,[64] with preoperative and early postoperative elevations in PAI-1 correlating with the development of thrombosis in orthopedic patients.[93] Complications are also an important trigger: in a large VA study involving more than 76,000 patients, the strongest predictors of postoperative VTE included myocardial infarction, blood transfusion (>4 units), and urinary tract infection.[94]

Trauma

The prevalence of DVT among autopsied trauma casualties has been reported to be as high as 65%, comparable to the 58% incidence among injured patients in modern venographic series.[11] Substantially lower DVT rates, ranging from 4% to 20%,[95] have been noted in series using duplex ultrasonography, although many patients studied were receiving prophylaxis and the limitations of ultrasound in screening asymptomatic patients are well recognized. Recent trauma was associated with nearly a 13-fold increase in risk.[89]

Although the risk of DVT may be less than 20% in some injured patients,[11] certain subgroups are at particularly high risk. Age (OR, 1.05 for each 1-year increment), blood transfusion (OR, 1.74), surgery (OR, 2.30), fracture of the femur or tibia (OR, 4.82), and spinal cord injury (OR, 8.59) have been significantly associated with the development of DVT in this population.[11] Other reported risk factors are a hospital stay longer than 7 days,[96] increased Injury Severity Score (ISS),[96-98] pelvic fractures,[99] major venous injury,[100] presence of femoral venous lines,[101] the duration of immobilization,[102] and prolongation of the partial thromboplastin time.[103]

As with postoperative DVT, several pathophysiologic elements may be responsible for the high incidence of DVT in trauma patients. Immobilization by skeletal fixation, paralysis, and critical illness are associated with venous stasis, whereas mechanical injury is important after direct venous trauma and central venous cannulation. Less well appreciated is the hypercoagulable state after depletion of coagulation inhibitors and components of the fibrinolytic system. Fibrinopeptide A levels rise after injury,[104] consistent with activation of coagulation, whereas fibrinolytic activity has been found to increase initially and then decrease.[105,106]

Pregnancy

The incidence of VTE in the pregnant population is 6 to 10 times greater than matched controls[107] and causes approximately 10% of all maternal deaths.[108] Using clinical evaluation, VTE has been reported at a rate of 1.3% to 7% during pregnancy and 6.1% to 23% in the postpartum period.[109] However, studies that used venography, Doppler ultrasonography, or ventilation-perfusion scans for evaluation of clinically suspected thromboembolism have suggested an incidence of 0.029% to 0.055% in this population.[110] The risk of thrombosis appears to be two to three times greater during the puerperium, with the highest incidence found after cesarean section.[111] Interestingly, when VTE has been objectively documented, the occurrence of thrombosis is equally distributed throughout all three trimesters.[112]

DVT in pregnancy has been attributed to impaired venous outflow due to uterine compression because 97% of reported thromboses have been isolated to the left leg.[112] Furthermore, pregnancy is associated with a transient hypercoagulable state due to increases in the levels of fibrinogen, von Willebrand factor, and factors II, VII, VIII, and X. Compounding this acquired functional resistance to activated protein C is also seen during pregnancy.[113] Similarly, protein S levels are decreased by 50% to 60% early during pregnancy, with free protein S levels comparable with hereditary heterozygous protein S deficiency.[114,115] The fibrinolytic system is also altered in pregnancy: levels of tissue plasminogen activator (tPA) are decreased and PAI-1 and PAI-2 increased.[116]

Both retrospective and prospective studies have demonstrated that between 30% and 50% of women with a pregnancy-associated VTE also have an inherited thrombophilia. This high incidence has led to the recommendation of screening for thrombophilia in those pregnant patients with a personal or family history of VTE.[117,118] The risk of puerperal DVT also increases with maternal age, suppression of lactation, hypertension, and assisted delivery but not with the number of pregnancies.[119]

Oral Contraceptives and Hormonal Therapy

As suggested by case reports in the early 1960s, further studies have now established the use of oral contraceptives as an independent risk factor for the development of DVT. These studies noted ORs of 3.8 to 11.0 for thrombosis,[120] and an unweighted summary relative risk among 18 controlled studies was 2.9.[121] Approximately one-quarter of apparently idiopathic thromboembolic events among women of childbearing age have

been attributed to oral contraceptives. Early studies also suggested that thromboembolism is responsible for approximately 2% of deaths in young women, with contraceptive-associated mortality rates of 1.3 and 3.4 per 100,000 among women aged 20 to 34 and 35 to 44 years, respectively.[122] The increased risk of thromboembolism appears to diminish soon after oral contraceptives are discontinued and is independent of the duration of use.[123]

Risk is correspondingly higher when oral contraceptive use is combined with other factors, such as surgery[124] and inherited inhibitor deficiencies.[125] The factor V Leiden mutation may be particularly important in this regard; resistance to activated protein C has been reported in up to 30% of patients with contraceptive-associated thromboembolism.[126] The use of third-generation oral contraceptives may act synergistically with the factor V Leiden mutation, raising thromboembolic risk 30- to 50-fold.[127-129]

Estrogenic compounds also increase the risk of VTE when used for lactation suppression[119] in treatment of carcinoma of the prostate and as postmenopausal replacement therapy.[130] Although estrogen doses used for postmenopausal replacement therapy are approximately one-sixth those in oral contraceptives, some data support an increased thromboembolic risk at these doses as well. Several studies show a twofold to fourfold higher risk of VTE among women taking hormone replacement therapy.[130-134] This increased risk is greatest during the first year of treatment.[131,134] However, given the relative infrequency of thromboembolism, this risk represents only one or two additional cases of thromboembolism per year in every 10,000 women in this age group.

Estrogen in pharmacologic doses is associated with alterations in the coagulation system that may contribute to this thrombotic tendency. Such alterations include decreases in PAI-1[135] and increases in blood viscosity, fibrinogen, plasma levels of factors VII and X, and platelet adhesion and aggregation.[136,137] An associated prothrombotic state is implied by rises in markers of activated coagulation occurring in conjunction with elevations of circulating factor VIIa and decreases in antithrombin and protein S inhibitor activity.[136,138] The extent to which antithrombin and protein S are depressed is significantly less with lower-estrogen preparations.[139]

Blood Group

There also appears to be a relationship between VTE risk and the ABO blood groups, with a higher prevalence of blood type A and correspondingly lower prevalence of blood type O groups.[140,141] In reviewing the literature, Mourant and colleagues[142] found the relative incidence of type A to be 1.41 times higher among patients with thromboembolism than among controls. The effect of blood type was greater in young women who were taking oral contraceptives or were pregnant; the relative incidence of type A among patients with thromboembolism was 3.12 in those taking oral contraceptives and 1.85 in those who were pregnant. A relationship between soluble endothelial cell markers and ABO blood group is known to exist, with significantly lower levels of von Willebrand factor among those with type O blood.[143]

Geography and Ethnicity

There are also geographic differences in the frequency of VTE, as the incidence of postoperative DVT in Europe has been noted to be nearly twice that of North America.[81,87] Higher rates of thromboembolism have also been noted in the central United States compared with either coast.[144] Autopsy series suggest that although the prevalence of thromboembolism is identical among American black and white patients, it is significantly higher than in a matched Ugandan black population.[145] A similar autopsy series noted the prevalence of thromboembolism to be 40.6% in Boston and 13.9% in Kyushu, Japan.[146]

Unfortunately, regional variations in underlying medical and surgical conditions, as well as in prophylactic measures and diagnostic methods, may confound any apparent differences in the incidence of thromboembolism among different ethnic and geographic groups. Nevertheless, it is certainly conceivable that differences between ethnic groups might arise from either genetic and/or environmental factors. Such differences seem likely based on recognized geographic differences in the spectrum of mutations leading to congenital anticoagulant deficiencies.[147] Such theoretical concerns are also supported by geographic variability in the incidence of the factor V Leiden mutation. The factor V Leiden allele has a prevalence of 4.4% in Europeans, corresponding to a carrier rate of 8.8%, but the allele has not been identified in Southeast Asian or African populations.[148]

Inflammatory Bowel Disease

Clinical series have reported VTE to complicate inflammatory bowel disease (IBD) in 1.2% to 7.1% of cases.[149,150] Crohn disease has incidence rates of 31.4/10,000 person-years and 10.3/10,000 person-years for DVT and PE, respectively. Ulcerative colitis also has a high incident rate of 30.0/10,000 and 19.8/10,000 person-years for DVT and PE, respectively. Such thromboses frequently occur among young patients, are more common with active disease, and may affect unusual sites, such as the cerebral veins.[149,150] Greater extent of colonic disease in ulcerative colitis portends a higher risk of VTE. Most cases are not associated with inherited hypercoagulable states. However, fibrinopeptide A elevations in IBD suggest that active inflammation is associated with activation of coagulation, possibly mediated by endotoxin-induced monocyte activation.[149-151]

Systemic Lupus Erythematosus

A syndrome of arterial and venous thrombosis, recurrent abortion, thrombocytopenia, and neurologic disease may complicate systemic lupus erythematosus (SLE) when accompanied by the presence of antiphospholipid antibodies.[152] Lupus anticoagulant and anticardiolipin antibodies may be seen in association with SLE; with other autoimmune disorders; with nonautoimmune disorders, such as syphilis and acute infection, with drugs, including chlorpromazine, procainamide, and hydralazine; and with older age.[153]

Lupus anticoagulant is present in 34% of patients with SLE and anticardiolipin antibodies in 44%, in comparison with 2% and 0% to 7.5%, respectively, of the general population.[153]

Among patients with SLE, those with lupus anticoagulant are at a sixfold higher risk for VTE, whereas those with anticardiolipin antibodies are at a twofold greater risk.[154] The incidence of arterial or venous thrombosis is 25% in patients with lupus anticoagulant and 28% in patients with anticardiolipin antibodies.[153]

Varicose Veins

Varicose veins are also included as a risk factor for acute DVT, although frequently only as a marker of either previous venous disease.[155] Most studies evaluating thrombotic risk have been performed in inpatients with other major risk factors for DVT. Such studies have inconsistently supported varicose veins as a risk factor in postoperative, post-stroke, or postmyocardial infarction cases.[155-157] The importance of varicose veins in otherwise healthy outpatients with DVT has been questioned by some researchers[158] because varicose veins were not identified as independent risk factor in young women,[159] although some studies of postmenopausal women have reported varicose veins or superficial thrombophlebitis to be associated with ORs of 3.6 to 6.9 for the development of thromboembolism.[131,134]

However, Heit and associates[160] found that varicose veins were independent predictors of DVT. They also reported that age is an important factor in these patients, reporting a higher correlation between DVT and varicosity in young patients. For example, 45-year-old patients with varicose veins had a fourfold higher risk of VTE, 60-year-old patients had a twofold greater risk, and 75-year-old patients had no increase in risk. This group also found that patients with previous superficial vein thrombosis were more than four times more likely to have DVT or PE.[160] See Chapter 150.

Iliac Vein Compression

The association of VTE and anatomic anomalies or syndromes represents a congenital risk factor responsible for DVT in both the upper and lower extremities. Left iliac vein compression by the right iliac artery and fifth lumbar artery was first described by May and Thurner in cadavers who hypothesized that chronic pulsation of the right iliac artery and mechanical obstruction led to intimal hypertrophy of the vein wall and subsequent venous obstruction.[161] In actuality, it was Virchow who had initially observed iliofemoral vein thrombosis was five times more likely to occur in the left leg than in the right leg over a century earlier.[162] Although left lower extremity venous hypertension associated with or without left iliofemoral DVT has come to be known as May-Thurner syndrome, it is important to recognize, if only for historical nomenclature, that a similar syndrome was described by Cockett in 1965 (Cockett syndrome) and took popularity over the term May-Thurner syndrome in Europe. However, it was Cockett who associated the acute phase of iliofemoral DVT secondary to compression of the iliac vein with the long-term consequence of chronic venous insufficiency (CVI). In addition, it was Cockett who noted surgical intervention for the purpose of alleviating the skin ulcers and varicosities associated with iliac vein compression was ineffective unless the underlying disease process was identified.[163]

May-Thurner syndrome is more common in young to middle-aged women, especially after multiple pregnancies. The presenting symptom is often acute onset of left leg pain and swelling secondary to thrombosis. Atypically, patients may present with symptoms of CVI that are unresponsive to compression stockings, leg elevation, and a calf exercise program.[164] Early 20th century postmortem dissections revealed a 22% to 32% incidence of left iliac vein compression.[165] Modern computed tomography imaging has revealed that in an asymptomatic population, the average amount of compression on the left iliac vein was 35%, and 24% of this population demonstrated greater than 50% compression.[165] Although individuals in such series were asymptomatic, the incidence of symptomatic left common iliac vein compression presenting with either edema or DVT is estimated to be between 37% and 61%.[166,167] Interestingly, the presence of an abdominal aortic aneurysm was associated with a significantly less amount of compression on the left common iliac vein by the right common iliac artery secondary to a higher prevalence of tortuosity in that artery.[168]

Popliteal Vein Entrapment

Although arterial entrapment syndrome is well described in the literature, popliteal vein entrapment has been reported to occur either alone or with the artery in 10% of cases.[169] Anatomic anomalies of the medial head of the gastrocnemius have been associated with popliteal vascular entrapment. However, when venous entrapment occurs in a setting without arterial entrapment, both the medial or the lateral head of the gastrocnemius have been shown to contribute.[170] Bony tumors and hypertrophied fibrous fascia have also been associated with isolated venous involvement.[171,172] Traditionally, popliteal artery entrapment has been more associated with the male gender; venous entrapment has been reported to occur 70% of the time in females.[173] The presentation is often that of a young adult with signs of CVI, including leg swelling varicosities, skin changes, and DVT.

Other Risk Factors

Risk factors for VTE covered in other sections in this book include inherited thrombophilias (Chapter 38), thoracic outlet syndrome (Chapter 123), central venous catheters (Chapter 149), and inferior vena cava anomalies (Chapter 163). Traditional risk factors for VTE have included obesity and cardiac disease; however, the evidence supporting these risk factors remains equivocal. Among postmenopausal women, a body mass index of greater than 25 to 30 kg/m^2 has been associated with a significantly increased risk of VTE.[132,134] Some investigators have reported obesity to be associated with a twofold greater risk for postoperative DVT, although multivariate analyses by others has not shown obesity to constitute an independent risk.[155] Obesity (and past tobacco smoking) was not an independent risk factor of DVT in the Olmsted County study[160] and has not been proven to be a risk factor for the development of DVT after stroke.[157] However, obesity is a risk factor for recurrent DVT.[174]

Systemic hypercoagulability, congestive heart failure, and enforced bed rest may predispose patients who are hospitalized with acute myocardial infarction to DVT. The incidence of DVT in this population has been reported to be 20% to 40%.[87,156,175] Some investigators have noted the incidence of DVT to be higher among patients in whom myocardial infarction was confirmed (34%) than in those in whom the diagnosis was excluded (7%). The prevalence of PE among autopsied patients has also not differed substantially from that in other inpatients.[144,145]

Although MI as a risk factor may be in question, those older than 60 years with congestive heart failure have a DVT rate of 54%.[176] However, the evidence supporting congestive heart failure as an independent risk factor for DVT is also conflicting. A variety of thromboembolic complications account for nearly half the deaths among patients who did not undergo anticoagulation after hospitalization for congestive heart failure, but congestive heart failure has not been identified as an independent risk factor for postoperative DVT. The balance of evidence suggests that severely ill medical patients are at significant risk for VTE,[177] although it is difficult to define the additional risk associated with cardiac disease.

NATURAL HISTORY

The relative balance between organization, thrombolysis, propagation, and rethrombosis determines outcomes after human thrombosis. From a clinical perspective, the most important events after thrombosis are recanalization and recurrent thrombosis.

Recanalization

Impedance plethysmography was the first widely available noninvasive test permitting serial evaluations of outflow obstruction due to an acute DVT. Although this test could not distinguish between recanalization and the development of collateral venous outflow, results of such studies were found to normalize in 67% of patients by 3 months and in 92% of patients by 9 months.[178] Venous duplex ultrasonography allows individual venous segments to be observed over time and has further documented that recanalization does occur in most patients after acute DVT. In 21 patients monitored prospectively with duplex scanning, recanalization occurred in 44% of patients at 7 days and in 100% of patients by 90 days after the acute event.[179] Several additional studies[180,181] confirm the histologic findings that recanalization begins early after an acute DVT, with the greatest reduction in thrombus load occurring within 3 months of the event. Complete thrombus resolution has been reported in 56% of patients monitored for 9 months.[179,182] However, recanalization may continue for months to years after the acute event.[181]

Recurrent Venous Thrombosis

Nearly 30% of patients will develop a recurrence within a 10-year time span.[183] Recurrences are more likely with the same event type as the incident event; for example, those who initially developed a PE are more likely to develop another PE instead of a DVT.[184] Independent predictors for recurrent DVT include increasing age, obesity, malignant neoplasm, and extremity paresis. In a series of landmark trials, among patients with proximal DVT, recurrent thromboembolic events were found in 5.2% of patients treated with standard anticoagulation for 3 months, compared with 47% of patients treated with a 3-month course of low-dose subcutaneous heparin.[185,186]

Despite the significance of these observations, reports of serial noninvasive follow-up examinations suggest that these studies may underestimate the incidence of new thrombotic events. In a series of 177 patients, most of whom were treated with standard anticoagulation measures, recurrent thrombotic events were observed in 52% of patients.[187] New thrombi were observed in 6% of uninvolved contralateral extremities, whereas propagation of thrombi to new segments occurred in 30% of involved limbs and rethrombosis of a partially occluded or recanalized segment in 31% of extremities. Propagation in the ipsilateral limb tended to occur as an early event at a median of less than 40 days after presentation, whereas rethrombosis and extension to the contralateral limb tended to occur sporadically as late events.

Mortality

The severity of PE is shown in 30-year autopsy studies, which demonstrated a 26% incidence of PE in hospitalized patients, of which 9% was fatal. This translates to a 1% incidence of PE and a 0.36% incidence of death from PE in all hospitalized patients per year.[188] See Chapter 151.

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A complete reference list can be found online at www.expertconsult.com.

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