Acquired Risk Factors for Venous Thromboembolism in Medical Patients

Paolo Prandoni

Acute venous thromboembolism (VTE) is a serious and potentially fatal disorder, which often complicates the course of hospitalized patients, but may also affect ambulatory and otherwise healthy people. While the introduction of thromboprophylactic measures is expected to have reduced the occurrence of postoperative VTE, there is an increasing awareness of the importance of medical conditions in determining thromboembolic events. Among the conditions that predispose patients to VTE are increasing age, cancer and its treatment, prolonged immobility, stroke or paralysis, previous VTE, congestive heart failure, acute infection, pregnancy or puerperium, dehydration, hormonal treatment, varicose veins, long air travel, acute inflammatory bowel disease, rheumatologic disease, and nephrotic syndrome. Other factors that have recently been associated with an increased risk of VTE disorders include persistent elevation of D-dimer and atherosclerotic disease. Recognition of the incidence and clinical importance of thrombosis will most likely encourage more widespread use of antithrombotic prophylaxis in medical patients.

Acute venous thromboembolism (VTE) is a serious and potentially fatal disorder, which often complicates the course of hospitalized patients, but may also affect ambulatory and otherwise healthy people. In 1884, Rudolph Virchow first proposed that thrombosis was the result of at least one of three underlying etiologic factors: vascular endothelial damage, stasis of blood flow, and hypercoagulability. In the last century, there has been increased recognition that all risk factors for venous thromboembolism (VTE) are mediated by these underlying pathophysiologic processes and that VTE does not usually develop in their absence.[1] In a review of 1231 consecutive patients treated for VTE, 96% had at least one recognized risk factor.[2] Furthermore, there is convincing evidence that risk increases in proportion to the number of predisposing factors.[1,3]

According to recent epidemiological data collected in two Swedish cities, VTE is to be expected in 1.6-1.8 per 1000 inhabitants per year.[4,5]

Classic risk factors for VTE include cancer, surgery, prolonged immobilization, fractures, puerperium, paralysis, use of oral contraceptives, and the antiphospholipid antibody syndrome.[1,3] These states not only predispose apparently normal patients to thrombosis but are also likely to trigger this condition in people with inherited thrombophilic abnormalities.[1,3] Combined genetic defects, as well as the combination of a genetic defect with one or more acquired risk factors, and the combination of two acquired risk factors result in a risk of VTE that exceeds the sum of the separate effects of the single factors.[3] This is the case of the combination of highly prevalent defects, such as factor V Leiden and prothrombin mutation, with even minor risk factors such as oral contraceptive pill, or the combination of oral contraceptive pill with even minor surgery or injury.

The majority of clinically recognized instances of VTE are suspected because of typical signs and symptoms in individuals who present to an outpatient clinic or hospital emergency department.[1] Hospitalization for surgery and for medical illnesses account for similar proportions of cases.[6]

Not infrequently, VTE affects ambulant and otherwise healthy individuals.[7]

This review focuses on old and new acquired hypercoagulable states that can be responsible for VTE disorders in both hospitalized and ambulant "medical" patients.

Cancer

Since the initial observation by Armand Trousseau in 1865, numerous studies have addressed the relationship between cancer and VTE. VTE is either a frequent complication in cancer patients, or sometimes acts as an epiphenomenon of a hidden cancer, in such a way offering opportunities for anticipated cancer diagnosis and treatment.[8] In patients with malignancy VTE represents an important cause of morbidity and mortality. It has been estimated that 1 in every 7 hospitalized cancer patients who dies, does so from pulmonary embolism.[9] Of these patients, 60% have localized cancer or limited metastatic disease, which would have allowed for longer survival in the absence of a fatal PE. According to the "Medicare Provider Analysis and Review Record," a database that records the primary discharge diagnosis and an additional four discharge diagnoses in the US, the rate

Correspondence: Paolo Prandoni, MD, PhD, Department of Medical and Surgical Sciences, 2nd Chair of Internal Medicine, University of Padua (Italy), Via Ospedale Civile, 105, Padua 35128, Italy; Phone (+39)0498212656; Fax (+39)0498212661, paoloprandoni@tin.it

of initial or recurrent thromboembolism in patients with cancer greatly exceeds that recorded in those without malignancy, and occurs with similar frequency among cancers of virtually all body systems.[10]

Although the true rate of VTE in cancer patients is virtually unknown, because of the surprising lack of information in almost all studies dealing with the natural history of malignant diseases, the majority of thrombotic episodes occur spontaneously, i.e., in the absence of triggering factors that commonly account for thromboembolic complications in subjects without cancer.[11] This is confirmed by the high frequency of patients with known malignancy referred to clinicians for the development of VTE.[12] The most common situations that make cancer patients at higher risk of VTE include immobilization, surgery, chemotherapy with or without adjuvant hormone therapy, and the insertion of central venous catheters.[8]

The strong association between cancer and venous thromboembolism is further emphasized by the high rate of cancer development in patients with venous thrombosis. According to the results of the most important studies, this risk has been consistently found to be 4-5 times higher in patients with idiopathic than in patients with secondary thrombosis.[8] These data have recently found important confirmation in three very large, retrospective, population-based studies.[13-15] Of interest, although the risk for developing cancer was particularly high in the first 6 months after the diagnosis of VTE, a significant effect persisted for up to 10 years, suggesting that either a malignant disorder can induce hypercoagulability many years prior to its overt clinical development or that cancer and thrombosis share common risk factors. A recent investigation has indeed provided direct genetic evidence for the link between oncogene activation and thrombosis.[16]

Medically Ill Patients

While the introduction of thromboprophylactic measures has most likely reduced the occurrence of postoperative VTE, there is an increasing awareness of the importance of medical conditions in determining thromboembolic events, as appropriate thromboprophylaxis is rarely administered to patients from medical wards.

Three large-scale prevention studies involving over 5500 medically ill patients have shown that 11%-15% will have VTE and 4%-5% will have proximal-vein thrombosis as identified by screening studies in the absence of prophylaxis.[17-19] Additionally, the US national DVT Free Registry found that 60% of patients diagnosed with an acute DVT were in the peri-hospitalization period. Approximately 60% of the cases occurred in non-surgical patients.[20]

Current literature highlights numerous risk factors for VTE in the medically ill patient. These clinical risk factors include increasing age, acute respiratory failure, congestive heart failure, prolonged immobility, stroke or paralysis, previous VTE, cancer and its treatment, acute infection, dehydration, hormonal treatment, varicose veins, acute inflammatory bowel disease, rheumatologic disease, and nephrotic syndrome.[21,22] Patients with (mostly asymptomatic) proximal-vein thrombosis may carry an unexpectedly high risk of in-hospital death.[23] Recent data suggest that current practice is associated with important uncertainty leading to both overuse and underuse of thromboprophylaxis in patients hospitalized in medical wards.[24] Of interest, the institution of computer-alert programs has the potential to increase physicians' use of prophylaxis and markedly reduce the rate of VTE arising among hospitalized patients at risk.[25]

As anticipated, VTE can affect apparently healthy people. Besides circumstantial events, those additional risk factors for VTE that increase the thromboembolic risk in these individuals do not substantially differ from those accounting for VTE in the hospital setting. The most common are old age, varicose veins, cancer, heart failure, peripheral artery disease, and previous VTE.[26,27] Of interest, in this context obesity, smoking, and hypertension have been found to be associated with an increased VTE risk.[5,28]

Pregnancy, Puerperium and Hormonal Treatment

The absolute risk of developing VTE during pregnancy or the puerperium is low. Despite the low incidence, pulmonary embolism is a leading cause of maternal death after childbirth, with approximately 1 clinically recognized pulmonary embolism per 1000 births and 1 fatal pulmonary embolism per 100,000 births.[1]

Women taking hormonal treatment either for contraception or as replacement therapy have a 2- to 4-fold increased risk of VTE compared with control women. This risk is dramatically increased by the carriership status of a thrombophilic abnormality.[1,3]

Air Travel

There has been recent attention in the popular press about the risks of VTE associated with long-duration air travel—the so-called economy class syndrome.[1] The general consensus is that clinically important VTE after air travel is rare. Case reports suggest that most cases of travel-related thrombosis affected people at risk because of previous VTE or other predisposing factors.

Inflammation

In a recent population-based case-control study, van Aken et al showed that subjects with elevated interleukin-8 levels have an increased risk of venous thrombosis, thus lending some support to the role of inflammation in the pathogenesis of venous thrombosis.[29] It is not surprising, therefore, that subjects with inflammatory bowel disorders, Behçet disease, human immunodeficiency virus (HIV) infection, and other infectious diseases exhibit an increase risk of VTE. It should be noted, however, that in a recent prospective investigation markers of inflammation such as fibrinogen, C-reactive protein levels, or white cell count were not associated with VTE.[30]

D-Dimer

In a recent case-control study investigators from the Thrombophilia Leiden Study showed an intriguing association between elevated levels of D-dimer and the risk of venous thrombosis.[31] These findings have been confirmed by those of a recent prospective investigation.[32] It is quite evident that D-dimer cannot by itself represent the cause of venous thromboembolism, but should be interpreted as a marker of hypercoagulability often detectable in disease states as well as in otherwise healthy people. These studies open new interesting perspectives for future research.

Atherosclerosis

Although acquired and/or inherited risk factors potentially responsible for VTE are identifiable in the majority of patients, the disease remains without an apparent explanation in up to 30% of patients. We found an unexpected association of VTE with atherosclerosis.

Ultrasonography of the carotid arteries was performed in 299 unselected patients with DVT of the lower extremities free from symptomatic atherosclerosis and in 150 control subjects.[33] The presence of plaques in patients with spontaneous venous thrombosis was compared with that of patients with venous thrombosis secondary to acquired risk factors and that of control subjects. At least one carotid plaque was detected in 72 of the 153 (47.1%) patients with spontaneous thrombosis, in 40 of the 146 (27.4%) with secondary thrombosis (overall response [OR], 2.3; 95% confidence interval [CI], 1.4 to 3.7), and in 48 of the 150 (32.0%) control subjects (OR, 1.8; 95% CI, 1.1 to 2.9). In a multivariate analysis taking into account risk factors for atherosclerosis, the strength of this association did not change. The association between spontaneous venous thrombosis and carotid plaques increased with age.

In a recent multicenter prospective Italian study dealing with the long-term follow-up of patients with pulmonary embolism, those patients who had an idiopathic episode had a statistically significant and clinically relevant increased risk of fatal and non-fatal cardiovascular events, including atherosclerotic complications.[34]

We speculate that either atherosclerotic disease induces venous thrombosis or the two conditions share common risk factors.

Conclusions

VTE is a serious and potentially fatal disorder that complicates the course of hospitalized patients and may also affect ambulant and otherwise healthy people. The risk factors that predispose patients to thrombosis are numerous. Recognition of the incidence and clinical importance of thrombosis will most likely encourage more widespread use of antithrombotic prophylaxis in the future.

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