

EDUCATION SESSION 6: THROMBOSIS



Risk Factors for Thrombosis in the Young

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Venous thrombosis occurs in about one per 1,000 individuals per year, with approximately 1-2% of cases developing a fatal pulmonary embolism. As a consequence of deep vein thrombosis about 20-40 % of patients in the long term develop the so-called post phlebotic limb syndrome with limb discoloration, pain, and swelling, and a small percentage progress over the years to develop venous ulceration mainly around the ankles. Risk factors are conditions associated with an increased incidence of venous thromboembolism; risk predictors or risk markers are specific factors, that are associated with a increased disease frequency. For an individual patient the absolute risk is the most relevant, although very often there may be two or more compounding elements associated with the development of acute thrombosis.

Virchow in 1856 postulated three main groups of causes of thrombosis: reduced blood flow, changes in the vessel wall, and changes in blood composition. Most of the risk factors for venous thrombosis are caused by stasis or changes in overall total blood coaguability.

Acquired Causes of Thrombosis

The risk of thrombosis increases sharply with age from roughly 1 per 10,000 people per year before the age of 40 to up to 1 in 100 per year for those over the age of 75. The most frequently encountered acquired causes of thrombosis are listed in **Table 1**. Immobilisation is an important cause of thrombosis and is obviously associated with prolonged bed rest and may well be a major initiating factor

during prolonged and complicated operative procedures. Recent problems associated with long-haul airline travel (particularly in the cramped seating of economy class travel) and even a prolonged car or coach journey in cramped conditions, often associated with dehydration and excess alcohol intake, interferes with the function of the calf muscles in pumping the blood upstream through the veins and leads to prolonged stasis and excessive activation of the coagulation system in the relatively static areas associated with the valve cusps. Major surgery is another strong risk factor for venous thromboembolism particularly with orthopaedic surgery of the hip and knee, where the risk maybe as high as 50%. Other high-risk situations include abdominal, gynaecological, and neurological surgery and it is also high after major trauma including spinal injury and pelvic fractures. Venous thrombosis is a common complication in cancer patients with probably multiple inter-related mechanisms. These include the tumour itself, which may produce pro-coagulant material, mechanical effects due to venous obstruction by the tumour, and also the general effect of an acute phase reaction, reduced mobility, and the direct effects of treatment, particularly radiotherapy and chemotherapy.

The increased risk of thrombosis in pregnancy has been known for many years with a further increased risk associated with caesarean section and in particular a 3- to 5-fold higher risk in the immediate six-week post-partum period following delivery. The combined oral contraceptive pill

Table 1. Acquired Risk Factors for Thrombosis

Age
Previous Thrombosis
Immobilisation
Major Surgery
Orthopedic Surgery
Malignancy
Oral contraceptives
Hormone Replacement Therapy
Antiphospholipid Syndrome
Myeloproliferative Disorders
Polycythemia Vera

Table 2. Inherited Risk Factors for Venous Thrombosis

Inherited	Mixed/Unknown
Factor V Leiden	
Prothrombin 20210A	
Anti-thrombin Deficiency	
Protein C Deficiency	
Protein S Deficiency	
Dysfibrinogenemia	Hyperhomocysteinemia
High levels of factor VIII:C	
APC-resistance in the absence of FVL	
Blood Group	

has been known since 1961 to be associated with an increased risk of venous thrombosis. The main effects of the estrogen content of the contraceptive pill is that it increases the synthesis of certain circulating coagulation factors, particularly fibrinogen, factors II, VII, IX and X and factor XII. Associated with this increased level, usually within the normal range, of these pro-coagulant clotting factors, there is a mild decrease of the natural occurring circulating anticoagulants, antithrombin III, and protein S. It is generally accepted that there are no appreciable changes in protein C activity and that the platelet count and platelet function remain unaltered. Some protective activity is offered by a slight overall increase in fibrinolytic potential. In 1995 several large epidemiological studies showed that so-called third-generation contraceptive pills containing the progestogens gestodene or desogestrel approximately doubled the risk of venous thromboembolism compared to so-called second-generation contraceptive pills mainly containing the progestogen, levonorgestrel. The exact biological explanation for this increased risk associated with third-generation pills has not been conclusively demonstrated, although Rossing and colleagues have shown that endogenous thrombin potential by activation of the extrinsic system is increased in patients taking the third-generation contraceptive pill and this is associated with acquired activated protein C resistance, which is markedly protein S sensitive.

The risk of thrombosis is also markedly increased in patients who develop antiphospholipid antibodies. The antiphospholipid antibody syndrome is defined by the persistent presence of a positive lupus anticoagulant test (which has to be defined by a positive confirmatory test such as the dilute Russel viper venom time with a platelet neutralisation procedure) and persistently positive anticardiolipin antibodies (either IgG or IgM) associated with the recently described positive anti- β 2-glycoprotein 1 antibody. The presence of these antibodies either in the primary form or associated with other autoimmune diseases such as SLE gives an incidence of thrombotic events in about 30-40% of individuals. These antibodies are also associated with recurrent miscarriages often associated with reduced placental blood flow or thrombosis, infertility, immune type thrombocytopenia and a variety of neurological syndromes including migraine.

Genetic Causes of Thrombosis

Traditionally genetic causes of thrombosis and thrombophilia were suspected by a strong family history of thrombosis, particularly thrombosis presenting at a young age. Often with an associated triggering environmental acquired

factor, the definite and suspected inherited abnormalities associated with an increased incidence of thrombosis are listed in **Table 2**. Among Caucasian populations the factor V Leiden mutation (factor V R506Q) is the most common genetic defect, occurring in about 5% of the population. Heterozygous factor V Leiden increases the risk of thrombosis 3- to 8-fold, whereas homozygous individuals have approximately an 80-fold increased risk. Although the definitive diagnosis of the factor V Leiden mutation is dependant on PCR technology, the mutation leads to so-called activated protein C resistance, which can be readily detected by an APTT based coagulation test. Other inherited specific defects include the prothrombin 20210A mutation, which occurs in approximately 1% of the population and is associated with an increased circulating level of prothrombin activity. Other specific inherited defects include antithrombin deficiency (formally known as anti-thrombin III) and protein C and S deficiency, each of which are present in approximately one in 2,000-3,000 of the overall population. Additional rare inherited causes of thrombosis include dysfibrinogenemia and hyperhomocysteinaemia. However, hyperhomocysteinaemia may also be an acquired defect associated with low vitamin B6, B12, or folic acid intake and maybe related to a common genetic defect of the methylene tetrahydrofolate reductase (MTHFR) gene. Additional risk factors for thrombosis that may have a genetic cause include a high circulating level of factor VIII:C activity and also the ABO blood group of an individual, with those who are blood group O having the lowest risk. Non-O blood groups are related to high levels of von Willebrand factor, which in turn may be a major determinant of plasma factor VIII:C activity.

Conclusion

Venous thrombosis is a multi-factorial disease with risk factors resulting from environment, genetics, and behaviour, any of which may precipitate thrombosis. When risk factors exert their action these effects may interact and indeed synergistically further increase the risk development of venous thrombosis. For an individual patient risk assessment must include detailed haemostatic testing that takes into account the specific age, sex and racial group of the individual and any other associated medical condition. By such an approach the long-term treatment and prophylaxis of a patient with anti-thrombotic medications and also the course of action in high risk situations such as surgery and pregnancy can be more carefully coordinated and the risk of further clinical thrombotic episodes reduced.