THROMBOPHILIA

MOLECULAR BIOLOGY OF THROMBOSIS: PRESENT AND FUTURE

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Families with with several members affected by thrombosis were described approximately one century ago, and antithrombin deficiency, the first cause of heritable thrombophilia was discovered in 1965, followed by identification of deficiencies of protein C and protein S in the early 1980s. Athough these defects were not frequent or even rare, their contribution as risk factors for thrombosis was remarkable, which favored their detection. The characterization of hundreds of mutation in these genes has contributed to define the thrombophilic nature of these deficiencies. Over the last decade several new risk factors for venous thrombosis have been identified, particularly functional polymorphisms in the FV and Prothrombin genes, which are common, confer a modest risk factors for thrombosis, and act probably in combination with other genetic and acquired components. Genome-wide approaches have identified several condidate loci that could produce the so called quantitative traits (QTL). Although these studies could introduce more genetic determinants, and could advance our knowledge of etiology of thrombotic disorders, they are far from having produced new markers of risk. A good example is offered by the study of genetic components of FVIII plasma levels, a recognized risk factor for venous thrombosis. Family studies suggested that the G allele of the 3951C/G (D1241E) FVIII polymorphism is associated to lower FVIII activity. We investigated in case-control studies both biological effects (FVIII levels and activated protein C sensitivity ratio) and clinical associations (venous thromboembolism) of the D1241E change. The 1241E allele was associated with significantly reduced (11%) FVIII levels. However, the effect on activated protein C sensitivity ratio was not statistically significant. Carriership of the 1241E allele, potentially conferring protection from thrombosis, was found in 22.8% of controls and in 15.3% of cases. In an additional cohort of factor V Leiden carriers, carriership of the 1241E allele was 25.2% among asymptomatic subjects and 17.1% among thrombotic patients. These genotype distributions suggest a mild protective effect from venous thrombosis conferred by 1241E FVIII, masked by other genetic and/or environmental components. Our findings point toward the presence of genetic determinants of coagulation factor levels with a biologically significant role, but with a poor predictive value to estimate thrombotic risk beyond established risk factors. Although high throughput systems help us to detect very high number of genetic markers, this could be not sufficient to reach clinical significance. Plasma and endothelial proteome approaches could help us to partially overcome this *genetic* barrier. Novel techniques could assist us to evaluate multiple protein factors in patients with thrombosis. Promising results have been obtained in other disease models by multianalyte (bed) array detection systems, which could serve as sensitive tools for the simultaneous detection of a very high number of factors from a small, single biological sample. These approaches would also enable us to monitor factor variation over time and to evaluate coherent protein variations, an aspect so far poorly investigated. Improved/new functional assays, able to evaluate and integrate the multiple enzymatic and cellular interactions characterizing blood coagulation and fibrinolysis, are also in the pipeline to boost our knowledge of this old and fashionable field.

SCREENING FOR VENOUS THROMBOPHILIA: PROS

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Among the categories of individuals who may benefit from screening of thrombophilia, the first might be that of patients who develop an episode of VTE. In this group, in fact, the identification of inherited thrombophilic defects can clarify the etiology of the first thrombotic event. It is less clear whether screening of symptomatic patients can be useful in decision-making for secondary prophylaxis of VTE. In fact, data on the risk of recurrences in symptomatic patients who are carriers of the most common inherited thrombophilic conditions are still conflicting. However, it is commonly maintained that symptomatic carriers of combined thrombophilic defects (homozygous or double heterozygous) as well as carriers of antithrombin defects present with an increased risk of recurrences. In these subjects, prolonged anticoagulation is usually suggested. Thus, screening for thrombophilia allows the identification of such a group at higher risk for VTE recurrences.

A second category can be represented by family members who are symptomatic carriers of thrombophilia. Screening allows the identification of those family members who are carriers of the same defect. In addition, in families with severe thrombotic manifestations, combined thrombophilic defects are often identified. Asymptomatic family members who are carriers of thrombophilia may take advantage of this information for prevention of VTE in situations involving high risk. Prophylaxis with LMWH or UFH should be given to all individuals older than 40-45 years during risk situations, even though this is not often the case. In individuals belonging to thrombophilic families who are less than 45 years (and older than 15), primary VTE prophylaxis should be considered in risk situations. This can be particularly true of women in the post-partum period and of those during pregnancy who are carriers of severe thrombophilic conditions. In fertile age women belonging to thrombophilic families, screening for thrombophilia may be useful for counselling on administration of oral contraceptives or hormonal replacement therapy. Asymptomatic women with severe thrombophilic defects should be discouraged from using hormonal therapy. In very rare situations, in which hormones have to be given despite the high thrombotic risk, concomitant anticoagulant prophylaxis should be considered. In the majority of cases, however, asymptomatic women identified following family screening are carriers of less severe thrombophilic defects. Appropriate counselling on the relative risk of VTE should be given to these women when hormonal therapy is required. The decision on whether or not hormonal therapy is to be given should be based on accurate evaluation of the risk to benefit ratio of the treatment. Even in the presence of single, less severe thrombophilic defects in women belonging to families with a strong history of thrombotic manifestations, the use of hormonal therapy should be discouraged because of the possible co-existence of other unknown thrombophilic defects.

Universal screening before the administration of hormonal therapy is maintained not to be cost-effective. This is mainly based on the analysis of costs required to identify women at higher risk because carriers of thrombophilia and to avoid a single hormonal related VTE in these subjects. Selective screening of post-menopausal women with a family history of thrombosis before administration of hormonal replace-

ment therapy is the most cost-effective approach among those which can be considered before administration of any hormonal therapy (oral contraceptives or hormonal replacement therapy). Under these circumstances, however, recommendation for (selective) screening is based on how much one is willing to spend to prevent one VTE event.

NO INDICATION FOR THROMBOPHILIA SCREENING

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Thrombophilia can be defined as a tendency toward venous thromboembolism (VTE). There are several well characterized abnormalities in the coagulation system that have been established to increase the risk of a first episode of VTE. These conditions, referred to as inherited thrombophilia are present in approximately 15% of the healthy population, and in about 60% of patients with VTE.

However, there is a paucity of evidence about how the clinical management of patients with thrombophilia and VTE differs from those individuals who do not have a specific inherited thrombophilic defect. This uncertainty relates to the only modest risk increase for recurrent VTE, the unclear benefit of prolonging anticoagulant treatment after a first episode of VTE for a definite period of time, and the bleeding risks associated with use of prolonged anticoagulant medication. Other groups of interest to consider thrombophilia screening in are healthy relatives of symptomatic thrombophilic patients, women prior to using oral contraceptives, hormone replacement therapy, or pregnancy, and patients who have suffered recurrent miscarriages or vascular pregnancy complications. For the first two groups however, the low absolute risks for VTE, and the absence of evidence about specific beneficial interventions in the latter do not justify thrombophilia testing.

SCREENING FOR ARTERIAL THROMBOPHILIA

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We have become better informed about the increased risk of the cardiovascular disease, the most important cause of death in the world today, with a lifetime risk at age 40 of 1 in 2 for men and 1 in 3 for women in developed countries. The large number of determinants of thrombosis known today has led to the concept of thrombosis as a multigenic and multicausal disease, i.e. disease will only develop in the presence of several interacting risk factors. The familial aggregation of cardiovascular disease can be accounted for in large part by clustering of cardiovascular disease risk factors. Differences in lifestyle, such as diet composition, smoking habits, stress and obesity may reflect changes in incidence rate. However, changes in lifestyle only partially might explain these differences, suggesting that several additional factors might be involved arterial thrombotic process, for instance, behaviour of plasmatic coagulation activation, local blood flow conditions, and genetic factors. The aggregation of ischemic disease in families and the observation that the blood levels of factors considered as risk factor for cardiovascular and cerebrovascular disease are genetically determined, generated the hypothesis that the susceptibility to atherothrombotic disease could also be determined by genetic factors. Since there are many physiological and biochemical pathways involved in the development of arterial thrombosis and the human species is relatively old, with many population subdivisions and environmental changes, there are quite likely to be, on a worldwide scale, different mutations and gene combinations contributing to cardiovascular and cerebrovascular disease. It is conceivable that large populations typically carry an array of alternative forms of genes that would never result in or contribute to cardiovascular disease if not coupled with the right environment or gene combination. This concept implies that an allele at some locus makes it more likely that a person will become ill with a disease, but the presence of that allele is not the determining factor in disease expression. It merely is not necessary nor sufficient for the disease expression but lowers the threshold for the disease.

SCREENING FOR ARTERIAL THROMBOPHILIA

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A large number of candidate gene association studies have attempted to identify genes implicated in arterial thrombosis, but there have been few replicable and robust associations reported. The skantness of replicable associations partly relates to poor study design. Important methodological considerations include adequate sample size, the selection of appropriate controls, careful clinical phenotyping using standardized classification systems. It is essential that positive associations are replicated in independent populations, and appropriate methodology is used in such studies. To be of use for others, association studies should meet certain standards. In particular, genetic association studies should enable replication studies and meta-analyses.

At present, available data suggest that the effect of most haemostatic polymorphisms on arterial thrombotic diseases are likely to be at best small, at worst insignificant. Any effects of polymorphisms are likely to be mediated through interaction with other risk factors. Better designed studies are required. Currently, no evidence exists to support value in patient management.

No relevant role for arterial thrombosis is played by physiological inhibitors of coagulation such as antithrombin, protein C and protein S. From a clinical point of view determination of antiphospholipid antibodies (APAs) and homocysteine (Hcy) in blood might be useful. Actually, the presence of Lupus Anticoagulant, anticardiolipin antibodies or anti-beta2 glycoprotein I antibodies (confirmed in two occasions) allow to establish a diagnosis of antiphospholipid syndrome with consequences in both diagnostic and therapeutic approach to the patient. On the other hand, the identification of hyperhomocysteinemia may allow an inexpensive and simple, although controversial, vitamin treatment and hopefully a reduction in the global risk.

VENA CAVA FILTERS

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The appropriate use of caval vein filters in patients at risk for PE or to prevent recurrent PE controversial. While, the attractiveness of filters is appealing due the lack of bleeding complications, as with anticoagulant treatment, once inserted, and their physical protection for clots that are destined for the pulmonary circulation, their use is not based on sound evidence. There are multiple reports of case series of patients who were treated with caval vein filters that show minimal rates of complications. However, the single large randomized trial showed that an initial benefit (reduction of pulmonary embolism) was lost due to an excess of recurrent deep vein thrombosis later on, with no difference in mortality.

However, the appraisal of the data is challenging, since new developments on technology of caval vein filters are rapid, both in insertion techniques, retrieval techniwues for temporary filters, and minimization of coagulant potential of the filters surface. Hence, future clinical trials with these devices in patients at a high riskof (fatal) recurrent pulmonary embolism seem worthwhile.

Currently, it seems best to reserve the use of caval vein filters for the rare cases of patients with venous thromboembolism who cannot be treated with anticoagulants. It is likely that in case of a reversible condition that prohibits current use of anticoagulants the use of a truly retrievable filter is the treatment of choice. Another, situation where the application of a caval filter seems appropriate is the situation where recurrent disease occurred during adequate treatment with anticoagulants as a third line option (first line: vitamin K antagonists; second line: long term low molecular weight heparin).

In conclusion, routine use of caval vein filters is not appropriate; they may be used in rare clinical situations where anticoagulant treatment is impossible, or adequate anticoagulant treatment failed.

PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM

THE FIRST AMBULATORY SCREENING ON THROMBOEMBOLISM (FAST): A MULTICENTRE, CROSS-SECTIONAL, OBSERVATIONAL STUDY ON RISK FACTORS FOR VENOUS THROMBOEMBOLISM

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Summary. Objectives: to assess the prevalence of risk factors for venous thromboembolism and the prevalence of recent (<1 year) venous thromboembolism (VTE) (including superficial vein thrombosis, deep vein thrombosis and pulmonary embolism) amongst patients attending general practitioner surgeries. Design: multicentre, cross-sectional, observational study. Setting: 1,536 general practitioner surgeries. Participants: 15,180 adult, co-operative subjects, who had consulted their general practitioner for a health disorder and signed the informed consent form.

Interventions. None

Main outcome measures. Prevalence of known VTE risk factors graded according to importance, and prevalence of recent (<1 year) VTE events (including superficial vein thrombosis), based on interviews.

Results. About 1:5 patients had at least one strong risk factor and about 1:20 had at least two risk factors, with no difference between sexes. The prevalence of strong risk factors increased with age. Most were related to medical conditions: history of superficial venous thrombosis and/or deep vein thrombosis /pulmonary embolism, heart failure and malignancy. About 3:4 women and 2:3 men had at least one moderate to weak risk factor; nearly 1:2 women and 1:3 men had at least two moderate to weak risk factors. The most common were: history of VTE, smoking, history of miscarriage, oestrogen therapy, obesity and varicose veins. Overall, 80% women and 67% men had at least one risk factor, and 50% women and 35% men had at least two risk factors.

The prevalence of recent (<1 year) VTE was 3.4% in women and 2.4% in men, and increased with age. The majority of cases were superficial venous thrombosis in both sexes (2.5% in women and 1.5% in men).

Conclusions. The prevalence of risk factors for VTE amongst patients attending general practitioner surgeries is high. General practitioners should bear this in mind during their daily practice.

THE OPTIMAL DURATION OF ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH VENOUS THROMBOEMBOLISM

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It has been clearly demonstrated that patients with acute venous thromboembolism (VTE) who are treated with full doses of unfractionated or low-molecular-weight heparin have a very high rate of recurrence unless effective anticoagulant therapy is continued after the initial treatment. The