Thrombophilia: From Benchside To Bedside

Satyabrata Ganguly

The concept of thrombophilia or “State of hypercoagulability” dates back to 1854, when German Pathologist Rudolph Virchow Postulated that thrombosis resulted from and in turn precipitated by three interrelated factors:

(Virchow’s traid ¹)
1. Decreased blood flow (Venous Stasis)
2. Inflammation of or near the blood vessels (Vascular endothelial injury)
3. Intrinsic alternation in the nature of the blood itself.

Thrombophilia can be defined as a group of inherited or acquired conditions that are associated with a predisposition to venous thrombosis, arterial thrombosis.

Most hypercoagulable states alter the blood itself whereas others affect the vasculature directly². Although patients with hypercoagulable states are at great risk for developing a thrombotic event. Then those without such disorders, not all persons with a well-defined hypercoagulable state will develop an overt thrombosis³.

AETIOLOGY
Hypercoagulable states can be inherited, acquired, or both.

Established or potential hypercoagulable states

- Factor VII excess
- Factor VIII excess
- Factor XI excess
- Heparin cofactor II deficiency
- Hyperhomocysteinemia⁸
- Hyperfibrinogenemia
- Lupus anticoagulants
- Plasminogen deficiency
- Protein C deficiency ⁶
- Protein S deficiency ⁶
- Prolong use of oral contraceptive

PREVALENCE (Fig.1)
The prevalence of hypercoagulable states depends on the ethnicity and clinical history of the studied population. Prevalence is lowest in the general population, greater in individuals with a single VTE and greatest in those with recurrent VTEs or from known thrombophilic families.

Activated protein “C” resistance due to factor V Leiden is the most common inherited predisposition to hypercoagulability in caucasian populations of north European background⁴.

Factor V Leiden follows a geographic and an ethnic distribution, if occurs most frequently in Northern and Western Europe.

PATHOPHYSIOLOGY (Fig.2)
Primary hemostasis consists of three events that lead to the formation of a platelet “plug” namely platelet adhesion, activation and aggregation. Platelets adhere to the vascular subendothelium by attaching to subendothelial
Once adherent, platelets are activated by a number of agonists including (thrombin, collagen, epinephrine, and thromboxane A2) and are stimulated to release their alpha and dense-granule contents, which further promote platelet recruitment, activation and aggregation.

Secondary hemostasis consists of a series of sequential reactions (coagulation cascade) in which inactive protease. Zymogens are converted to active serine protease ultimately resulting in the production of thrombin and covalently cross-linked fibrin.

The natural anticoagulants function to contine thrombus formation to the site of vascular injury and to limit thrombus size while promoting. Ongoing coagulation by a number of positive feedbacks, thrombin also provides an important negative feedback to limit thrombus promotion by binding to thrombomodulin on endothelial cells. The complex thrombin : thrombomodulin then converts protein C to APC. Antithrombin and protein C are the major natural anticoagulants, while protein S serves as a vital cofactor for APC mediated inactivation of factors Va and VIIIa.

Vascular endothelial disruption triggers not only coagulation reactions but also the fibrinolytic pathways. Physiologic fibrinolysis is initiated by endothelial- cell- derived tissue plasminogen activator (EPA) mediated conversion of plasmiogen to plasmin, which can degrade both fibrinogen and fibrin, thus limiting the size of a thrombus and helping to clear a thrombus once the vascular injury has been repaired.

Therefore the human hemostatic system can be defined as consisting of multiple independent yet integrally related cellular and protein components that function to maintain blood fluidity under normal conditions and to promote localized, temporary thrombus formation at sites of vascular injury. This highly regulated hemostatic system maintains a delicate balance between a prohemorrhagic state and a prothrombotic state. This balance is maintained by the concomitant actions of platelets, coagulation factors. (Fig.3)

Marked thrombocytosis, accentuated platelet aggregation, increased activity levels of coagulation factors and excess plasma levels of fibrinolytic inhibitors may lead to pathologic thrombosis. Like wise, qualitative or qualitative deficiency of a natural anticoagulant, coagulation factor resistance to inactivation by a natural anticoagulant and deficiency of a fibrinolytic protein may all be associated wish a “State of hyper coagulability”.

vonwillebrand factor molecules exposed at a site of vascular injury.
SIGNS AND SYMPTOMS
There are no specific signs or symptoms associated with hypercoagulable states.

The finding of livedo reticulosis upon examination of the skin has been frequently associated with the presence of antiphospholipid antibody.

The most common clinical manifestation of an underlying hypercoagulable state is lower extremity deep venous thrombosis with or without pulmonary embolism.

The cases of arterial thrombosis presents as cerebrovascular accidents (strokes in young) or symmetrical peripheral gangrene.

DIAGNOSIS
Laboratory testing for hypercoagulable states can uncover an inherited abnormality in more than 60% of patient presenting with a first VTE (Venous Thrombo Embolism).

Who should be tested
Selected testing should be considered mainly in the following circumstances
1. Idiopathic VTE
2. VTE at young age (<45yrs)
3. Recurrent VTE
4. Recurrent Pregnancy loss

What tests should be performed
Testing for hypercoagulable states is best performed in stages. Screening tests should be performed first and if positive, should be followed by appropriate confirmatory tests (Table I).

When should tests be performed
Ideally, testing should be performed in the outpatient setting at least 4 to 6 weeks after any acute thrombotic event. This is because acute illness states, including VTEs can cause elevations of a number of acute-phase reactants, including factor VIII, fibrinogen and IgM anticardiolipin antibodies, all of which may interfere with testing and often to false-positive diagnosis.

CONCLUSION
Current treatment for thrombophilias involves both prophylaxis with low-molecular-weight heparin and treatment involving heparin, warfarin or purified factor concentrate. The presence of an inherited thrombophilia should not alter the intensity of anticoagulant therapy, given that antithrombin, protein C, or protein S deficiency, factor V Leiden, and the prothrombin G20210A mutation are not unusually anticoagulant resistant. However, they can increase the optimal treatment duration after a first thromboembolic event.

Clinical trials on treatment are essential since they will provide physicians with the information to determine whether or how they should modify their clinical practice. Correctly identifying hereditary risk factors, together with appropriate genetic evaluation and counseling, will allow the informed patient and physician to work together for effective management of thrombophilia and prevention of subsequent thrombotic events.

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<th>Confirmatory Test</th>
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<td>Activated protein C resistance</td>
<td>Factor V Leiden PCR</td>
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<td>Screening tests for lupus anticoagulants (sensitive</td>
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<td>aPTT, aPTT mixing studies, dilute Russell viper</td>
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<td>venom time)</td>
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<td>Anticardiolipin antibody testing by ELISA</td>
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REFERENCES


