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Thrombophilia - A Review

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Definition:

Conditions that predispose to an increased risk for thrombosis either venous (most common), arterial or both. These conditions are being identified more frequently and may be classified as inherited or acquired.

History

- Susruta (Ayurveda physician and surgeon, 600-1000 B.C.) – first demonstrated patient with a "swollen and painful leg that was difficult to treat"
- Giovanni Battista Morgagni, 1761- recognized clots in pulmonary arteries after sudden death, but did not make the connection to DVT
- Rudolf Virchow "Discovered" PE in 1846 – "the detachment of larger or smaller fragments from the end of a softening thrombus which are carried along the current of blood and driven into remote vessels.
- Kakker in 1969 described in his paper, 30% of post-op patients developed clot in calf vein, 35% of these lysed within 72 hours and 15% of patients developed with persistent thrombosis.
- In 1856, Rudolf Virchow postulated a triad of factors that leads to intravascular coagulation Figure 1 :

1. Local trauma to the vessel wall.
2. Hypercoagulability (Thrombophilia).
3. Stasis.

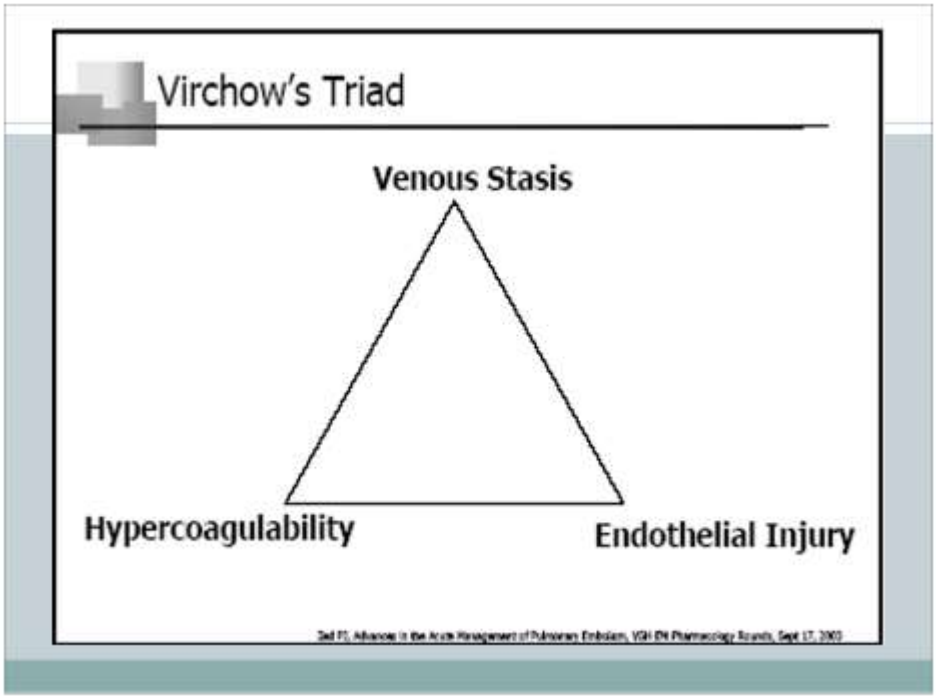

Figure 1.

The major components of a hemostatic system are as below:

1. The vessel wall.
2. Platelets (and other blood elements).
3. Plasma proteins (coagulation and fibrinolytic factors).

Stasis may occur due to Immobility, paralysis (e.g. CVA), Obesity, postoperative casting, heart and respiratory failure.

Classification: Thrombophilia is classified as inherited or acquired Fig. 2.

Inherited

Venous	Arterial and venous
Factor V Leiden mutation	Homocystinuria
Prothrombin G20210A	Hyperhomocystenemia
Protein C and Protein S deficiincy	Dysfibrinogenemia
Antithrombin deficiency	
Elevated Factor VIII activity	

Fig.2

Acquired

Risk factors:

Age

Prior thrombosis

Immobilization

Major surgery

Malignancy

Estrogens

Antiphospholipid antibody syndrome

Prolonged air travel

Heparin –induced thrombocytopenia

Myeloproliferative disorders

Risk factors for venous thrombosis may be as follows:

Acquired

Inherited

Mixed/ unknown

Fig. 3

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Prevalence of Defects in Patients with Venous Thrombosis	
Thrombophilic Defect	**Relative Risk**
Antithrombin Deficiency	8-10
Protein C Deficiency	7-10
Protein S deficiency	8-10
Factor V Leiden/APC Resistance	3-7
Prothrombin 20210 A mutation	3
Elevated Factor VIII	2-11
Lupus anticoagulant	11
Anticardiolipin antibody	1.6 – 3.2
Hyperhomocysteinemia	2.5

Protein C Deficiency

Protein C is a vitamin K dependent glycoprotein produced in the liver. The activation of protein C, thrombin binds to thrombomodulin, a structural protein on the endothelial cell surface. This complex then converts protein C to activated protein C. For protein C to bind, cleave and degrade factors Va and VIIIa, protein S must be available. Protein C deficiency, whether inherited or acquired, may cause thrombosis when levels drop to 50% or below. Protein C deficiency also occurs with surgery, trauma, pregnancy, oral contraceptive pill (OCP), liver or renal failure, disseminated intravascular coagulopathy (DIC), or warfarin. In the activation of protein C, thrombin binds to thrombomodulin, a structural protein on the endothelial cell surface. This complex then converts protein C to activated protein C (APC), which degrades factors Va and factor VIIIa limiting thrombin production. Protein C deficiency causes thrombosis when levels drop to 50% or less. Acquired Protein C deficiency occurs with surgery, trauma, pregnancy, oral contraceptive pills, liver or renal failure, disseminated intravascular coagulopathy (DIC) or warfarin.

Protein S Deficiency

Protein S is an essential cofactor in the protein C pathway. The remaining protein S, called free PS, is the functionally active form of protein S. Inherited PS deficiency is an autosomal dominant disorder, causing thrombosis when levels drop to 50% or lower.

Causes of acquired protein S:

May be due to elevated C4bBP, decreased PS synthesis, or increased PS consumption. C4bBP is an acute phase APC, is an anticoagulant which inactivates factors Va and VIIIa in the presence of its cofactor, protein S.

Alterations of the factor V molecule at APC binding sites (such as amino acid 506 in Factor V Leiden) impair, or resist APC's ability to degrade or inactivate factor Va. It is the functional form of naturally occurring, vitamin K dependent anticoagulant protein C. APC is an anticoagulant which inactivates factors Va, VIIIa in presence of protein S.

Activated Protein C (APC) Resistance Due to Factor V Leiden

Activated protein C (APC) is the functional form of the naturally occurring, vitamin K dependent anticoagulant, protein C. APC is an anticoagulant which inactivates factors Va and VIIIa in the presence of its cofactor, protein S. Alterations of the factor V molecule at APC binding sites (such as amino acid 506 in Factor V Leiden) impair, or resist APC's ability to degrade or inactivate factor Va

Prothrombin G20210A Mutation

It is a A G-to-A substitution in nucleotide position 20210 which is responsible for a factor II polymorphism. The presence of one allele (heterozygosity) is associated with a 3-6 fold increased for all ages and both genders. The mutation causes a 30% increase in prothrombin levels.

Antiphospholipid Syndrome

This is characterized by any of the following:

- Thrombosis—arterial or venous
- Pregnancy
- Laboratory Criteria: IgG or IgM anticardiolipin antibody-medium or high titer Lupus Anticoagulant

Investigations:

- DRVVT- venom activates F. X directly; prolonged by LAC's
- APTT- Usually prolonged, does not correct in 1:1 mix
- Prothrombin Time- seldom very prolonged

Treatment:

- Patients with thrombosis- anticoagulation (target, INR 3)
- Anticoagulation is long-term—risk of thrombosis is 50% at 2 years after discontinuation
- Women with recurrent fetal loss and APS require LMW heparin and low-dose heparin during their pregnancies

Heparin–induced thrombocytopenia (HIT)

The released PF4 reacts with heparin to form heparin-PF4 complexes, which serve as additional sites for HIT antibody binding. Diagnosis is made on clinical grounds. HIT usually results in thrombosis rather than bleeding. Diagnosis should be confirmed by either immunoassay (ELISA) or functional tests (14C serotonin release assay). Treatment involves cessation of heparin, treatment with an alternative drug, e.g. argatroban, and switching to warfarin. This is mediated by an antibody that reacts with a heparin-platelet factor complex to form antigen-antibody complexes. These complexes bind to the platelet via its Fc receptors. Cross linking the receptors leads to platelet aggregation and release of platelet factor 4 (PF4). The released PF4 reacts with heparin to form heparin-PF4 complexes which serve as additional sites for HIT antibody binding.

Diagnosis of thrombophia

- Diagnosis should be confirmed by either immunoassay (ELISA) or functional tests (14C serotonin release assay)
- Treatment involves cessation of heparin, treatment with an alternative drug, e.g. argatroban, and switching to warfarin

Who to test?

Site of thrombosis

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin G20210A	-	+
Antithrombin deficiency	-	+
Protein C deficiency	-	+
Hyperhomocysteinemia	+	+
Lupus Anticoagulant	+	+

Pro

Improve understanding of pathogenesis of thrombosis

Identify and counsel affected family members

Obviate expensive diagnostic testing (e.g. CT scans) looking for a malignancy

Con

Infrequent identification of patients with defects whose management would change

Potential for overaggressive management

Cost of testing

Routine screening of patients with VTE for an underlying thrombophilic "is not justified".

However, the risk of subsequent thrombosis over 5 years in men with idiopathic VTE is 30%. Any additional defect adds to risk and to possible need for prolongation of anticoagulation.

Furthermore, women with a history of VTE who wish to become pregnant will be treated differently if a defect were found.

Following tests may be considered:

- Genetic test for prothrombin gene mutation 20210A
- Functional assay of antithrombin
- Functional assay of protein C
- Functional assay of protein S
- Clotting test for lupus anticoagulant/ELISA for cardiolipin antibodies
- Measurement of fasting total plasma homocysteine
- Test for Factor V Leiden
- Genetic test for prothrombin gene mutation G20210A

- Measurement of fasting total plasma homocysteine
- Clotting assay for lupus anticoagulant/ELISA for cardiolipin antibodies

Screening Evaluation For "Strongly Thrombophilic" Patients

- Test for Factor V Leiden
- Genetic test for prothrombin gene mutation 20210A
- Functional assay of antithrombin
- Functional assay of protein C
- Functional assay of protein S
- Clotting test for lupus anticoagulant/ELISA for cardiolipin antibodies
- Measurement of fasting total plasma homocysteine

Management of Patients With Thrombophilia

Risk Classification	Management
<u>High Risk</u>	
2 or more spontaneous events	Indefinite Anticoagulation
1 spontaneous life-threatening event (near-fatal pulmonary embolus, cerebral, mesenteric, portal vein thrombosis)	
1 spontaneous event in association with antiphospholipid antibody syndrome, antithrombin deficiency, or more than 1 genetic defect	

Moderate Risk

1 event with a known provocative stimulus Asymptomatic	Vigorous prophylaxis in high-risk settings

Further Reading

1. Thrombotic Disorders by Subhash Varma, Anupam Chakrapani In: API Textbook of Medicine, 12th Edition 2022, 827-831
2. Thrombophilia—
   Hypercoagulable States by Shapiro Gabriel

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