Pathophysiology and Investigations for Deep Venous thrombosis

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Started 1894
DVT can take place in any section of the venous system, but arises most frequently in the deep veins of the leg.

DVT is a clinical challenge for doctors of all disciplines.

It can complicate the course of a disease but might also be encountered in the absence of precipitating disorders.

Long-term morbidity due to post-thrombotic syndrome is common and can be substantial.

The major concern, however, is embolisation of the thrombus to the lung, which can be fatal.

The disorder and its sequelae are also among the best examples of preventable diseases.
PULMONARY EMBOLISM

DEEP VEIN THROMBOSIS
DVT
PATHOGENESIS:

Venous Thrombo Embolism (VTE) considered as one disease entity – comprises DVT and PE

Common but preventable

Incidence : 1-2 per 1000 person years. More in men . Risk increases with age
Venous Thromboembolism

- Annual incidence of VTE in the US: approx 900,000
- Annual mortality: 100,000
- More deaths than from breast cancer, AIDS, car accidents
What is the scenario of DVT in India?

• The incidence of DVT in India is:
  • 15 to 20 % in hospitalized patient
  • 50% in patients undergoing orthopedic surgery particularly involving the hip and knee.
  • one percent of the adult population after the age of forty
  • 40% in those patients undergoing abdominal or thoracic surgery
  • 1/100 who developed DVT die, usually from the blood clot travelled to the lungs - pulmonary embolism.
VTE in India
Retrospective data 1996-2005
Christian Medical College, Vellore

- Incidence of VTE: 17.46 per 10,000 admissions.
- Pulmonary embolism: 14.9% of the study patients. Mortality in those with confirmed pulmonary embolism was 13.5%.

VTE is no longer a rarity in India.

- General surgical operations are the most common causes of postoperative DVT.
- Pulmonary embolism continues to be 'suspected' more often than it is diagnosed.

**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Malignancy</td>
<td>31</td>
</tr>
<tr>
<td>Postoperative</td>
<td>30</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>21</td>
</tr>
<tr>
<td>Haematological conditions</td>
<td>12</td>
</tr>
<tr>
<td>Others, including trauma</td>
<td>4</td>
</tr>
</tbody>
</table>

**Postoperative status 30%**

Five per 10,000 operations
General surgery patients: 40.3%
Orthopaedic patients: 20.1%
Autopsy Data
PGIMER, Chandigarh

1997-2002

1,000 adult medical patients

• PE 159 (16%)
  • Fatal 36, significant 90, incidental 30
Clinical suspicion 30%; Ante mortem diagnosis 10%
  • Sepsis 32%, HPB 18%, Cancer 14% of PE
  • 80% < 50 years

New studies
ENDORSE
Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting
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Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting

32 countries enrolled in ENDORSE study
358 hospitals
First patient enrolled 2\textsuperscript{nd} August 2006
Last patient enrolled 4\textsuperscript{th} January 2007

Patients at risk for VTE in 32 countries

N = 35,329 (19,842 surgical and 15,487 medical)

Patients at risk for VTE receiving recommended prophylaxis in 32 countries

N = 17,732 (11,613 surgical and 6119 medical)

Pathophysiology
Virchow’s Triad (1856)

Formation of venous thrombus
Blood stasis
Surgery, Hospitalisation

Changes in coagulation
Protein C&S, Hyper-Homocystein, hormone imbalance

Venous endothelium lesion
Trauma, Surgery

Estase sangüínea

Virchow (1821-1902)

Alterações da coagulação

Lesão do endotélio venoso
Virchow’s triad and risk of thrombosis

- Abnormal blood flow
- Immobilisation and bed rest
- Vascular injury
- Surgical manipulation
- Hypercoagulability
  - Increase in coagulation factors

Risk levels:
- Very high risk
- Medium / high risk
- Low / medium risk
Initially fibrin strands, RBC, Platelets
Risk factors for thrombosis

- **Congenital-**
  1. Antithrombin deficiency
  2. Dysproteinemias - Protein c deficiency: 7 fold increased risk
  3. Coagulation factor V Leiden mutation, coagulation factor II G2021A mutation
  4. Deficiency of [antithrombin](#) III, Protein s deficiency
  5. Increased factor 8
  6. Plasminogen deficiency
  7. Thrombomodulin deficiency
  7. Raised clotting factors – raised concentration of factor VIII (150 IU/dL), factor IX (129 IU/dL), or factor XI (121 IU/dL)
  8. Homocysteinamia – 2-3 fold increased risk
  9. Hypercholesterolemia
  10. Hemoglobinopathies
  11. Disorders of histidine rich glycoproteins
• **Acquired**

1. Prolonged surgery and trauma
2. Immobilization, long distance travel (air/road)
3. Stroke
4. Cardiac failure, Respiratory failure
5. Pregnancy
6. Hormone replacement therapy
7. Oral contraceptives
8. Increased factor VIII
9. Antiphospholipid syndrome
10. Inflammatory bowel disease.
11. Active Malignancy
12. Nephrotic syndrome
13. PNH
14. Sepsis
15. Diabetes
16. Obesity
17. Varicose vein – static blood
18. Central line, pacemaker, IV drug abuser
DVT following total knee replacement
DVT after hip replacement
VTE Risk Factor Model

Intrinsic Thrombosis Risk

Genes
- Anticoagulant deficiencies
- Factor V Leiden
- Prothrombin 20210A

Acquired RFs
- Age
- Previous VTE
- Cancer
- Obesity
- Varicose Veins
- Hormone Treatments

Triggering Factors
- Pregnancy
- Surgery
- Immobilization
- Trauma
- Air Travel

Prophylaxis

Thrombosis Threshold

VTE
Diagnosis

Early accurate diagnosis important as PE can be fatal

1. Clinical assessment
2. Lab studies
3. Imaging
Clinical features

1. Pain
2. Swelling
3. Redness
4. Mild pyrexia
5. Homan’s sign unreliable
6. Clinical signs unreliable till calf veins
# DVT Diagnosis

## Wells Criteria for DVT Probability

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis / recent immobilisation (POP)</td>
<td>+1</td>
</tr>
<tr>
<td>Bedridden &gt;3 days/ Recent surgery&lt; 1mth</td>
<td>+1</td>
</tr>
<tr>
<td>Tender along deep veins</td>
<td>+1</td>
</tr>
<tr>
<td>Leg swollen</td>
<td>+1</td>
</tr>
<tr>
<td>Calf girth difference &gt;3cm</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema</td>
<td>+1</td>
</tr>
<tr>
<td>Non-varicose prominent veins</td>
<td>+1</td>
</tr>
<tr>
<td>Alternate diagnosis likely</td>
<td>-2</td>
</tr>
</tbody>
</table>

*Probability low <0 pts; moderate 1-2 pts; high >3 pts*
Diagnosis

- **BLOOD TESTS**
  - D-dimer – high negative predictive value
  - Thrombophilia profile

- **IMAGING:**
  - Ascending Venography (Gold Standard) – filling defects within vein
  - Compression Ultrasonography:
    - 97% specificity & sensitivity for proximal thrombus,
    - for calf vein – 70%: so do serial exam
  - CT – iv contrast /MRI venography
  - IVUS
  - Radio isotope imaging
  - Impedence Plethysmography
Venography:
direct evidence or indirect (collaterals, cross pelvic filling, flattening of pelvic veins

IVUS: superior.
Allows accurate measurements, external compression, images trabeculations, webs or residual thrombus, vein wall thickness, neointimal hyperplasia, movement. IVUS used to calculate diameter and length of stent required.

CT / MRI:
3 D, Underlying venous obstruction may be identified before CDT (May Thurner, IVC pathology)
Because of its high sensitivity, measurement of D-dimer (a fibrin degradation product - FDP) has gained a prominent role as a rapid, simple, and inexpensive test for ruling out acute deep vein thrombosis.
D-dimer in the diagnostic approach to Deep Vein Thrombosis

- D-dimer has high sensitivity but low specificity

D-Dimer levels remain elevated in DVT for about 7 days.
• A full thrombophilia evaluation
• Fibrinogen, antithrombin III, protein C, protein S, factor V Leiden, prothrombin gene mutation, antiphospholipid / anticardiolipin antibodies, factor VIII levels, homocysteine
• Required in high risk patients (recurrent DVT, PE etc) to evaluate duration of therapy
**IMAGING**

1st line imaging is by Duplex Ultrasonography

Sensitivity for proximal vein Deep Vein Thrombosis is 97% but only 73% for calf vein DVT.
Venous Thromboembolism suspected

Assess clinical risk
Measure D-dimer levels

D-dimer Negative
Risk Low

D-dimer Positive
US leg veins

Risk High
Treat

Risk Low

Confirm Diagnosis

D-dimer Negative Risk High

-US leg veins +/-
-CT pulmonary angiogram or V/Q scan
Protocol for diagnosis:

Ultrasonography

1st line imaging technique

Compression ultrasonography entails imaging the calf to the groin in the axial plane with a 5- to 10-MHz transducer.

Protocol for diagnosis:

Ultrasonography

- Diagnosis of DVT
  - Lack of compressibility of the vessel lumen,
  - A distended vessel,
  - Visualization: DVT may be directly visualized as moderately echoic to hyperechoic masses separate from anechoic fluid.
  - Lack of Doppler flow in the vessel.
  - Principal criterion for the diagnosis of DVT: The inability to completely compress the vein lumen.

American College of Physicians and the American Academy of Family Physicians
• Compression ultrasonography is 95-99% sensitive for proximal venous thrombus
• The iliac and pelvic veins are not imaged consistently with sonography.
• In the presence of thigh swelling or an abnormal common femoral vein, excessive interposed bowel gas - CTV or MRV are useful adjuncts.
Compression Ultrasonography
Noncompressible clot in deep vein
Noncompressible popliteal vein
Popliteal vein thrombosis. Duplex sonogram shows absent flow.
• Compared with venography, ultrasonography has a sensitivity of 97–100% and a specificity of 98–99% for detection of proximal thrombosis

• Ultrasonography is less accurate in diagnosis of distal (calf vein) thrombosis. The lower sensitivity (about 70%) carries a risk for false-negative results, whereas the low specificity (about 60%) can result in over-treatment
DVT Diagnosis

- **Ascending Venogram**
Spiral Multi Detector row CT Venography

Clot in iliac and ovarian vein

100% sensitivity and 96-97% specificity
Clot in left iliac vein
DVT left popliteal vein
Magnetic Resonance Venography Imaging

MRI
MRI is the diagnostic test of choice for suspected iliac vein or inferior vena caval thrombosis.

In suspected calf vein thrombosis, MRI is more sensitive than any other noninvasive study.

MRI is highly sensitive and relatively specific – but:
- the cost of the examination,
- the technical complexity, and
- the lack of general availability limit the use of MRV as a screening tool.

Specific indications for MRV are primarily as an alternative to CT (particularly in patients with an allergy to contrast material, in those with renal failure, and those in whom an evaluation of the iliocaval veins are required for questionable sonographic findings) or for a preinterventional evaluation of the extent of a thrombus.
INTRAVASCULAR ULTRASOUND (IVUS)

IVUS is the gold standard test for narrowed or compressed pelvic veins.
Intravascular Ultrasound (IVUS)
Plethysmography is derived from the Greek word meaning "to increase."

This procedure is based on recording changes in blood volume of an extremity, which are directly related to venous outflow.
• **Nuclear Imaging**

Nuclear medicine studies with $^{125}$I-labeled fibrinogen are not recommended now. Radioactive isotope incorporates into a growing thrombus, this test can distinguish new clot from an old clot.
CONCLUSION:

DVT is not uncommon in India

DVT can lead to PE and post thrombotic syndrome

Thrombus arises spontaneously or accentuated by risk factors eg surgery, cancer, heart failure etc

In risk factors – prophylaxis (LMWH) is effective

Diagnosis: clinical + imaging + D Dimer

Rx:
- LMWH + VKA (3-6 mths or indefinite)
- for selected cases: CDT, IVC filter
VTE Can affect athletes!! – Serena Williams
Lehmann diagnosed with deep vein thrombosis

Australia v India 2016: Darren Lehmann diagnosed with deep vein thrombosis, won’t travel for T20 series
What is the way forward?

- Creating awareness of disease and management
- Develop easy-to-use tools at primary care level for diagnosis and management
- Develop a guidance document for DVT in primary care
- Understand current limitations and ways to overcome them
Air-travellers: beware of deep venous thrombosis
Dr Harinder Singh Bedi
Knowing is not enough; we must apply. Being willing is not enough; we must do.

- Leonardo Da Vinci
Upper Extremity DVT (UE DVT)
Medical patients at risk for VTE and receiving recommended prophylaxis

Primary objectives

52% at Risk for VTE
51% receiving ACCP recommended prophylaxis

Overall (N=68,183)

Secondary objectives

Surgical

64% at Risk for VTE
59% receiving ACCP recommended prophylaxis

Medical

42% at Risk for VTE
40% receiving ACCP recommended prophylaxis

• Deaths due to VTE (543,454)/yr

Exceeds combined deaths due to: 1,2

- AIDS (5,860)
- breast cancer (86,831)
- prostate cancer (63,636)
- transport accidents (53,599)

VTE Risk Factors

- Genetic Predisposition
- Pregnancy
- Contraceptives
- HRT/SERMS
- Immobility
- Trauma or Surgery
- Cancer
- Obesity
- Age

CLOT

Genetic VTE Risk Factors

Factor V Leiden
Prothrombin 20210A

Gain of Function

Coagulation

Fibrinolysis

~35% of patients with thrombosis have one of these disorders

Loss of Function

Antithrombin
Protein C
Protein S

Gain of Function

CLOT
For many reasons, including allergic reactions, contrast-induced Deep Vein Thrombosis noninvasive studies have essentially replaced venography as the initial diagnostic test of choice.
• **Specific findings include the following:**

• **Below-the-knee thrombus:** A clot below the popliteal vein level remains an elusive area in duplex scanning. It is challenging to detect, and detection is operator dependent.
## WHO IS AT RISK?

Top risk factors and triggering events for DVT:

- Increasing age
- Prolonged immobility
- Stroke
- Paralysis
- Previous VTE
- Cancer and its treatment
- Major surgery (particularly operations involving the abdomen, pelvis and lower extremities)
- Respiratory failure
- Trauma (especially fractures of the pelvis, hip or leg)

- Obesity
- Varicose veins
- Congestive heart failure and myocardial infarction
- Indwelling central venous catheters
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy, oral contraceptives or post-menopausal hormone replacement
- Inherited predisposition for clotting\textsuperscript{11,12}
<table>
<thead>
<tr>
<th>Acquired Risk Factors</th>
<th>Hereditary Risk Factors</th>
<th>Mixed/Unknown</th>
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<tbody>
<tr>
<td>Bed rest</td>
<td>Antithrombin deficiency</td>
<td>High levels of factor VIII</td>
</tr>
<tr>
<td>Travel</td>
<td>Protein C deficiency</td>
<td>High levels of factor IX</td>
</tr>
<tr>
<td>Immobilizer or cast</td>
<td>Protein S deficiency</td>
<td>High levels of factor XI</td>
</tr>
<tr>
<td>Trauma/spinal cord injury</td>
<td>Factor V leiden (FVL)</td>
<td>High levels of factor fibrinogen</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Prothrombin gene mutation</td>
<td>Activated Protein C resistance in absence of FVL</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Dysfibrinogenemia</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Factor XIII 34val</td>
<td>High levels of plasminogen activator</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Plasminogen deficiency</td>
<td>Elevated levels of lipoprotein (a)</td>
</tr>
<tr>
<td>Hormonal replacement therapy</td>
<td></td>
<td>Low levels of tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
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<td></td>
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<tr>
<td>Myeloproliferative disorders</td>
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<tr>
<td>Polycythemia vera</td>
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<tr>
<td>Central venous catheters</td>
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<tr>
<td>Age</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Chemotherapy</td>
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<td>Heparins</td>
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<tr>
<td>Pregnancy/postpartum period</td>
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WHAT HAPPENS IN DEEP VEIN THROMBOSIS?

Deep veins of the leg

Clot forms in a deep vein of the leg (deep vein thrombosis)

PULMONARY EMBOLISM
The blood clot from the leg vein travels to the heart and is lodged inside a blood vessel in the lungs, blocking blood supply. This is a potentially fatal emergency.
Hospitalization – risk factor for VTE

Almost all hospitalized patients have one or more risk factors for VTE.

DVT is common in many hospitalized patient groups. 

**Hospital-acquired DVT and PE** are usually clinically silent.

It is difficult to predict which at-risk patients will develop symptomatic thromboembolic complications. Screening at-risk patients using physical examination or noninvasive testing is neither cost-effective nor effective.

Lab testing and Bedside Tools:

D-Dimer – 95% sensitive for VTE
But also elevated in malignancy, infection, surgery, MI

Hypoxia: highly sensitive but poorly specific

ECG:
tachycardia, S1 Q3 T3 pattern , low voltage, RBBB, pulmonary P wave
Guidance documents

• Parakh et al. VTE guidelines. JAPI 2007
References


