Thromboembolic Disease:
Taking things to Heart

By Patrick Duffy, MD, FRCPC, and Julie Stakiw, MD

Thrombotic disorders of the arterial and venous system are the most frequent cause of death in North America affecting over 2 million people per year with a similar number of non-fatal events. Venous thromboembolic disease (VTD) has an annual incidence greater than 1 in 1,000 (deep vein thrombosis [DVT] 48, pulmonary embolism [PE] 69 per 100,000 respectively). There is a diverse spectrum of presentations, from incidentally diagnosed asymptomatic DVT to sudden death from a fatal PE. It is estimated that PEs are responsible for 10% of hospital deaths, and are frequently unrecognized antemortem. Approximately 25% of distal vein thromboses propagate to the proximal veins, which are a major origin of subsequent pulmonary emboli (Table 1). Untreated DVT can also lead to chronic venous insufficiency, recurrent pulmonary emboli with pulmonary hypertension, or subsequent fatal PE.

How prevalent is it?

VTD affects all ages. Approximately 500,000 PEs occur each year in the U.S. and 2% to 10% of these people die as a

Mrs. Baker

Mrs. Baker, 58, presented with syncope, dyspnea and left pleural chest pain after returning from a trip to Europe. Two months prior, she had right partial lobectomy for large cell carcinoma of the lung. Subsequent to this, metastatic bone disease was diagnosed. Mrs. Baker had no prior history of thromboembolic disease or hormone replacement therapy. Her family history was unremarkable.

On examination:

- Heart rate: 102 beats per minute
- Blood pressure: 120/80 mmHg.
- Oxygen saturation 95% on room air
- Jugular vein pulse was 4 cm
- Second heart sound was loud and there was decreased breathe sounds over her right lung fields
- Her left calf was tender, erythematous, but not overtly swollen

Question 1: What is your pretest probability for thromboembolic disease in this patient?

Question 2: How would you initially evaluate this patient?

Question 3: How should this patient be treated?

Thromboembolic Disease

Table 1
Risk factors for Thromboembolic Disease

Venous Stasis

- Immobility
- Institutionalization
- Cerebrovascular Accident
- Paralysis
- Chronic heart failure
- Travel > 4hr
- Obesity
- Respiratory failure
- Varicose Veins

Endothelial Injury

- Trauma
- Atherosclerosis
- Perioperative
- Malignancy
- Post phlebetic syndrome
- Prior deep vein thrombosis
- Central venous catheter placement

Hypercoagulability

Acquired Disorders

- Post operatative
- Malignancy
- Hormone replacement therapy
- Estrogen therapy
- Antiphospholipid antibody
- Lupus anticoagulant
- Myeloproliferative disorders
- Paroxysmal nocturnal hemoglobinuria

Inherited Disorders

- Factor V Leiden - APC resistance
- Antithrombin protein C/S deficiency
- Fibrinogen/TPA/PA1 defects
- Factor XII deficiency and prothrombin gene mutation

result. The majority of deaths occur within the first hour, followed by approximately 25% mortality from recurrent emboli within the subsequent two weeks. Over 90% of pulmonary emboli originate in the deep venous system of the leg with a major source being the iliofemoral veins (Table 2). The majority of isolated calf vein thromboses are asymptomatic. Of symptomatic patients with proximal DVT, over 40% have high probability lung scans, even in the absence of respiratory symptoms. Over 25% of people with PE have no evidence of DVT on subsequent evaluation.

In one population based study, thromboembolic disease increased with age, with a male to

Table 2
Differential diagnosis of swollen leg

- Deep vein thrombosis
- Post-phlebitic syndrome
- Congestive heart failure
- Muscle injury/hematoma
- Popliteal cyst (Baker's cyst)
- Superficial phlebitis
- Capillary leak syndrome
- Nerve root irritation
- Compartment syndrome
- Superficial thromboplebitis
- Chronic venous insufficiency
- Abscess
- Hypoproteinemia
- Cellulitis
- Lymphedema
- Malignancy
- Factitious
- AV fistula
- Acute Arthritis
- Myositis
- Fracture

AV: Atrioventricular

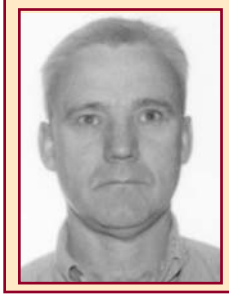

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Table 3
Clinical manifestation

	PE (%)	No PE (%)
Dyspnea	73	72
Pleuritic pain	66	59
Cough	37	36
Leg edema	28	22
Leg pain	26	24
Palpitations	10	18
Tachypnea	70	68
Tachycardia	30	24
Fourth heart sounds	24	14
Increased P2	23	13
Rales	51	40

Adapted from: Carson JL: The clinical course of pulmonary embolism. N Eng J Med 1992; 326:1240.

female ratio of 1.2:1 and PE accounted for an increasing proportion of events with increasing age for both genders.[1] This has significant implications, given the current aging trend in Canada.

PE was an independent predictor of reduced survival for up to three months after initial event. Independent predictors of reduced survival include:

- increasing age,
- male,
- recurrent PE,
- low body mass index,
- hospital admission or confinement,
- congestive cardiac failure,
- chronic lung disease,
- malignancy; and
- serious neurologic disease.

Clinical presentation of syncope and arterial hypotension predicted poor survival. This appears to support the hypothesis that deaths in

Table 4
Test results of pulmonary embolism

Pulmonary embolism is confirmed by:

- Pulmonary angiography
- Intraluminal filling defect
- Helical CT: intraluminal filling defect in a lobar or main pulmonary artery
- Ventilation-perfusion scan: high-probability scan and moderate/high clinical probability
- Diagnostic tests for deep vein thrombosis (DVT): evidence of acute DVT with nondiagnostic ventilation-perfusion scan or helical CT

Pulmonary embolism is excluded by:

- Pulmonary angiogram: normal
- Perfusion scan: normal
- D-dimer test: normal test that has very high sensitivity (≥ 98%) and at least moderate specificity (≥ 40%)
- Normal D-dimer that has at least moderately high sensitivity (≥ 85%) and specificity (≥ 70%) and:
  - low clinical suspicion for pulmonary embolism; or
  - normal alveolar dead space fraction
- Nondiagnostic ventilation-perfusion scan or normal helical CT, and normal proximal venous ultrasound scans, and:
  - low clinical suspicion for pulmonary embolism; or
  - normal D-dimer test that has at least moderately high sensitivity (≥ 85%) and specificity (≥ 70%)

Adapted from: Kearon C: Diagnosis of pulmonary embolism. CMAJ 2003; 168(2):183-94.

PE are the consequence of right heart failure, and patients with poor cardiac and respiratory reserve in particular are at high risk for fatal outcomes.

What is the approach to diagnosis?

The clinical diagnosis of DVT is unreliable in patients who commonly present with pain or swelling in the lower limb, and the differential diagnosis is wide. Kearon et al evaluated clinical assessment and D-Dimer testing in outpatients suspected of deep venous thrombosis.[2] This study evaluated 445 patients to determine pretest probability and then classified into low, moderate, or high pretest probability for DVT. A combination of low pretest clinical probability, and a negative D-dimer was sufficient to exclude DVT in a large proportion of symptomatic patients. Of these patients, 40% had low pretest probability and negative D-Dimer tests. These patients were followed for three months with only one patient subsequently developing a confirmed episode of venous thromboembolism (negative predictive value 99.4%). DVT was diagnosed in 63 patients in the moderate to high-risk group (by venous ultrasonagraphy in the majority of the patients). In clinical practice, Doppler ultrasound has an average sensitivity and specificity of 97% to 98% respectively for diagnosing symptomatic proximal DVT, but as low as 75% for symptomatic calf vein thrombosis.[3] Patients who have moderate or high pretest probability and initially negative Doppler ultrasounds should have a repeat evaluation in three to five days. In some cases, a definitive lower limb venography should be undertaken. The latter situation may arise in patients at high-risk of

Mrs. Baker's answers

1. Mrs. Baker has a high pretest probability given her diagnosis of cancer, recent travel, and clinical presentation of syncope with pleuritic chest pain.
2. Compression ultrasound confirmed the presence of occlusive thrombosis in the proximal iliofemoral vein. Due to her previous surgical resection, a spiral computed tomography scan was undertaken, and this showed a large left-sided embolism with multiple segmental emboli. It also showed pulmonary nodules consistent with metastatic disease. It is also likely that Mrs. Baker would have a high probability ventilation/perfusion scan. Metastatic disease would not have been diagnosed.
3. Mrs. Baker was admitted to hospital due to concerns with respect to her hemodynamic stability, and commenced on intravenous heparin. However, she was subsequently discharged on low molecular weight heparin. It was recommended that Mrs. Baker be maintained on this drug indefinitely, given her underlying diagnosis of malignancy associated thrombosis.

bleeding from anticoagulation, or who are at high-risk of death if they develop a subsequent PE.

As for DVT, the clinical diagnosis of PE is unreliable, and objective testing is mandated as the standard of care. Patients presenting with unexplained dyspnea, chest pain or syncope are candidates for further testing. Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study indicate that no clinical signs will reliably differentiate patients with PE from those without PE (Table 3). Although readily available, blood gases, electrocardiogram, and chest X-ray are of limited value, although they may help in providing an alterna-

tive diagnosis.[4] Arterial blood analysis is frequently used, although documentation of its usefulness is limited. In one retrospective analysis of blood gases from 78 patients with angiographically documented PE, 95% had abnormal P(A-a) oxygen gradients. Hence, a normal P(A-a) oxygen gradient makes PE unlikely.[5]

The PIOPED data has been regarded as a reference database, since its publication. However, in a study involving 750 patients with suspected PE, Miniati et al noted the sudden onset of dyspnea was present in nearly 80%, pleuritic chest pain in 60%, and syncope or presyncope in 26% of patients with PE.[6] Hemoptysis occurred in a minority of patients. The sudden onsets of chest pain, fainting, or dyspnea were present in 96% of 202 patients with PE versus 59% of negative controls. The study also found that 90% of patients with PE had a P(A-a) oxygen lower then 82 mmHg of mercury versus 50% of normal controls. Left ventricular strain, in contrast to PIOPED data was found in close to 50% of PEs versus 12% of controls. Electrocardiogram abnormalities included:

- T-wave inversion (23%),
- S1 Q3 T3 (19%)
- transient right bundle branch block (9%); and
- pseudo infarction (6%).

Sinus tachycardia (24%) and atrial fibrillation (8%) was no different in either group.

The most common radiologic features were oligemia, truncation of the hiliar arteries, or consolidation compatible with infarction (45%, 36%, and 15% respectively). Only 1% of patients without PE had these features. Hence, the absence of sudden onset of dyspnea, chest pain or fainting, a normal P(A-a) oxygen absence of ECG changes of right ventricular load has a strong negative predictive value for PE (94%).[6]

An excellent review on the strategies for diagnosing PE is provided by C Kearon in a recent publication.[7]

What's the treatment for thromboembolism?

Traditionally, patients have been admitted to hospital and treated with intravenous unfractionated heparin (UFH), bolus 60/80µ per kilogram, infusion 16µ to 18µ per kilogram, followed by warfarin for a minimum of three months. The use of low molecular weight heparin (LMWH) facilitates outpatient treatment of DVT and PE. Advantages include an easily determined weight based dosage, subcutaneous administration, and predictable anticoagulation response without the need for laboratory monitoring. A meta analysis of 10 studies showed decreased symptomatic recurrence (3.1% versus 6%), less major bleeding (0.8% versus 2.8%), and a reduced mortality (3.9% versus 7.1%). These findings have been confirmed in other studies, which also show reduction in heparin induced thrombocytopenia (relative reduction 0.85), a potentially fatal complication of heparin therapy.

Many physicians are reluctant to treat PE patients as outpatients, due to the lack of randomized control studies to support this. However, the majority of proximal DVT patients are treated as outpatients, although PEs are found in 40% of these patients if pulmonary studies are done. Admission to hospital is zero for hemodynamatically unstable patients, those at high risk of bleeding, requiring thrombolytic therapy, or have independent comorbid medical conditions, will require an admission.

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How long should therapy last?

Patients with identifiable reversible risk factors have a recurrence rate of 3% per year for thromboembolic events, and three months of therapy is adequate. Idiopathic venous thromboembolism has a recurrent rate of 5% to 25% per patient-year, and a minimum of six months therapy is recommended. Patients with idiopathic VTE[8] who have a secondary unprovoked event need life long anticoagulation. A recent randomized placebo controlled trial with long-term, low- intensity warfarin (INR 1.5 to 2.0) showed a 64% reduction rate of recurrent VTE in patients with idiopathic VTE (2.6 versus 7.2 per 100 person-years).[5] This risk reduction was also seen in patients with Factor V Leiden and G20210A prothrombin polymorphism defects. Hence, long-term low-intensity warfarin appears to provide an alternative treatment for patients who are at risk of recurrent thromboemoblism who require life long therapy. Patients with incurable malignancy and thromboemoblic disease require indefinite treatment with low molecular weight heparin since the failure rate with warfarin is high (17.4% versus 8.8%). The risk of recurrence is also high in patients with:

- antiphospholipid antibody syndrome,
- lupus anticoagulant,
- homozygous factor V Leiden,
- antithrombin deficiency.

The benefit of long-term anticoagulation has to be balanced with the risk of increased bleeding. Risk factors associated with increased bleeding including advanced age (greater than 75), malignancy, stroke, liver disease, nonsteroidal anti-inflammatory drug use, intensity of international normalized ratio, adequacy of monitoring, and patient compliance.

What now?

Physicians need to be able to rapidly define a patient's risk for thromboembolic disease, confirm or exclude a diagnosis on a timely basis, and initiate appropriate therapy. The currently available therapeutic interventions have significant drawbacks and the search for the ideal anticoagulant is ongoing. VTD should be regarded as a chronic disorder with episodic recurrence, and if untreated, has significant morbidity and mortality. CME

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Take-home message

Physicians should have a high clinical suspicion of pulmonary embolism when patients present with unexplained dyspnea, syncope, and chest pain.

A three-step approach to diagnosis of venous thromboembolism is recommended:

1. Define patients' risk category using clinical symptoms and signs.
2. Initial noninvasive testing include D-Dimer, assays, compression Doppler ultrasounds of the lower limbs, and VQ scans.
3. Definitive diagnosis of PE may require pulmonary angiogram, but physicians have to be aware of the indications and contraindications for this procedure.