

## **A Silent Killer—Often Preventable**

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## CARDIOLOGY CASEBOOK

A regular feature of the *American Journal of Critical Care*, Cardiology Casebook is intended to enhance practitioners' knowledge and critical thinking. Stylized case studies are accompanied by self-assessment quizzes. We welcome letters to the editors regarding this feature.

### A SILENT KILLER—OFTEN PREVENTABLE

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A 73-year-old, slightly obese woman arrived at Chicago's O'Hare International Airport after a long nonstop flight from Tokyo, Japan. She had been confined to a coach seat between 2 moderately overweight passengers and as a result was immobilized in a cramped space for a prolonged period of time. While going through customs, she noted a heaviness and soreness in the calf of her right leg and because the symptoms were mild she dismissed them as a possible bruise. That evening she was concerned when she developed a persistent nonproductive cough. On the advice of her family she went to the nearest emergency department, where alert personnel made an early presumptive diagnosis of venous thromboembolism (VTE).

The frequency of VTE has increased in the general population as a result of longevity and the long hours of air flight by a greater number of travelers. VTE is often a clinically silent disease in which the initial manifestation can be a fatal pulmonary embolus (PE). VTE is prevalent in hospitalized patients, but contrary to general thought, 75% of VTE occurs on the medical service and not on the surgical service.<sup>1</sup> Surgeons may be more aware than physicians in other specialties of this complication and better at prophylaxis and diagnosis.

#### QUESTIONS

1. The prevalence of VTE is due to which factors?
  - a. hospitalized seriously ill patients
  - b. the aging population
  - c. longer survival of patients with cancer or heart disease
  - d. failure to diagnose
  - e. underutilization of protocols for prophylaxis of deep vein thrombosis (DVT)
  - f. long hours of air flight
  - g. all of the above
2. Which of the following is/are the most serious complication(s) of DVT?
  - a. stroke
  - b. PE
  - c. gangrene of the affected extremity
  - d. myocardial infarction
3. Risk factors of DVT include which of the following?
  - a. increasing age, prolonged immobility
  - b. obesity
  - c. myocardial infarction, stroke, paralysis
  - d. cancer, major surgery, trauma
  - e. inflammatory conditions, thrombophilia
  - f. pregnancy, estrogen use
  - g. lipoprotein (a) [Lp(a)]
  - h. all of the above
4. Which of the following procedure(s) is/are preferred in the diagnosis of PE due to DVT?
  - a. venography, ventilation-perfusion (V/Q) scintigraphy
  - b. predictive testing, risk factor assessment, clinical algorithms
  - c. D-Dimer assays, venous ultrasonography
  - d. computed tomography (CT), pulmonary angiography (PA), magnetic resonance PA
  - e. PA, CT venography
5. Which of the following is/are considered appropriate for DVT prophylaxis?
  - a. aspirin
  - b. low-molecular-weight heparin (LMWH)
  - c. elastic stockings
  - d. tissue-type plasminogen activator (t-PA)
  - e. clopidogrel
  - f. intermittent pneumatic compression (IPC) devices
  - g. unfractionated heparin (UFH)
  - h. Flite Tabs

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6. Management of VTE involves which of the following?
  - a. daily dose of a LMWH
  - b. immediate administration of warfarin
  - c. a continuous infusion of intravenous UFH followed by oral anticoagulation
  - d. a continuous infusion of intravenous UFH
  
7. Long-term low-intensity warfarin therapy is just as effective as full-dose warfarin in preventing recurrent VTE.
  - a. True
  - b. False

## ANSWERS

1. g. all of the above

Venous pulmonary thromboembolism is a common complication of DVT in hospitalized patients, as well as outpatients, and is a major potential cause of mortality and morbidity.<sup>2</sup> Seriously ill patients, medical or surgical, are at equal risk. VTE affects 2 million people, accounts for more than 250 000 hospitalizations, and may contribute to the mortality of 200 000 patients annually.<sup>3-6</sup> Failure to routinely screen, diagnose, and initiate prophylactic care compromises hospital course and outcome.<sup>7</sup> The prevalence of VTE is escalating as the population ages due to the longer survival of patients with cardiac disease or cancer, as well as to the increase in the number of travelers on long hours of air flight. Epidemiological trends have not changed significantly in more than 30 years despite improved prophylactic therapies, identification of DVT risk factors, aggressive diagnostic evaluation, and available evidence-based practice protocols.<sup>7</sup> The diagnosis and treatment of DVT are integral in all emergency departments, where physicians and nurses are positioned to play leading roles in screening and identifying patients with DVT and VTE.

2. b. PE

The first manifestation of VTE can be fatal due to PE. More than one third of all deaths due to PE occur on the day of presentation. Hospitalized patients who may be at risk for VTE should be identified early and prophylaxis initiated promptly. The 3-month mortality rate in PE is as high as 17%, which makes it imperative to initiate therapy for DVT early.<sup>8</sup> PE is one of the most preventable causes of hospital-associated deaths; however, detection can be elusive, and the diagnosis is often made at autopsy.

3. h. all of the above

Identification of specific risk factors inherent in certain patient populations is the basis for initiating prophylactic therapy. Key considerations when evaluating the risk of VTE include (1) the risk factor profile, (2) unusual aspects, such as an episode of VTE while therapeutically anticoagulated, and (3) anticoagulation when the risk of thrombosis exceeds the risk of hemorrhage.<sup>7</sup> The clinical risk factors for VTE are increasing age, prolonged immobility, stroke, myocardial infarction, paralysis, previous VTE, cancer, cancer therapy, major surgery (especially surgeries involving abdomen, pelvis, and lower extremities), trauma (especially fractures of the hip, pelvis, or leg), critical illness, obesity, varicose veins, congestive heart failure, indwelling central venous catheters, inflammatory bowel disease, nephrotic syndrome, pregnancy, and estrogen use.<sup>9</sup> Additional risks related to surgery are the site, the technique, the type of anesthesia, the presence of infection, and the degree of postoperative immobilization.

Obesity was the most common comorbidity in more than 4000 patients with DVT confirmed by ultrasound. Women with DVT were more likely to be obese than were their male counterparts. Similar risk factors found in the overweight group were a history of DVT and a positive family history of VTE.<sup>10</sup>

Elevated levels of a hereditary but infrequent blood lipid abnormality, Lp(a), can be found more often in patients with premature coronary disease. Lp(a) is LDL (low-density lipoprotein), plus an additional protein apo (a). Patients with elevated levels of Lp(a) have an increased tendency to venous and arterial thromboembolism. Special serum studies should be done to assess Lp(a) levels when the routine blood lipid values are normal and premature coronary disease is suspected.

Inherited forms of VTE include any alteration in DNA that leads to a hypercoagulable or thrombophilic state and that can predispose to VTE. Factor V Leiden, the most common cause of familial thrombophilia, refers to the resistance to activated protein C. Thrombophilic, indicating the tendency to venous thrombosis, is a term that includes thrombosis at a young age, recurrent thrombosis, heparin resistance, thrombosis at unusual sites, and a family history of thrombosis.<sup>11</sup> Thrombotic events during pregnancy or while taking estrogens, often mistakenly considered to be idiopathic, are in fact due to familial thrombophilia.

Prolonged immobility, frequent during air travel, increases the risk of DVT and PE. Most after-flight DVTs are asymptomatic (89%) and thus neglected. Prolonged bending and compression of veins on the edge of seats are contributing factors to stasis and thrombosis. Blood concentration due to limited fluid

intake and a dry cabin atmosphere are additional factors on long flights. Immobility and relative hypoxia can alter fibrinolytic activity and cause release of vein wall factors that lead to stasis and thrombosis.

#### 4. d. CT PA, magnetic resonance PA

The incidence of DVT varies with the population. In the majority of postoperative patients, DVT is confined to the calves, and 10% to the proximal veins. Symptomatic PE develops in 30% of patients with DVT. The diagnosis is often elusive because DVT and PE produce few specific signs and symptoms. Routine screening for asymptomatic DVT is not recommended because it is neither clinically effective nor cost-effective. Immobilized patients with congestive heart failure, chronic respiratory failure, systemic and pulmonary infections, and malignancy are at greatest risk for VTE. Clinical algorithms that incorporate risk factor assessment, D-dimer assays, and ultrasonography have been developed in an attempt to standardize the assessment of patients presenting with suspected DVT. Low-risk patients have a 5% probability of DVT; high-risk patients, an 85% probability.

Venous ultrasonography is the most widely used modality in the diagnosis of acute DVT and has replaced conventional venography as the first-line diagnostic test for DVT. Ultrasound imaging can be performed at the bedside, does not involve ionizing radiation, and is noninvasive and relatively inexpensive. Sensitivities and specificities of venous ultrasonography for the diagnosis of symptomatic DVT are 97% and 94%, respectively. The various types of ultrasonography available have various sensitivities and specificities for detecting DVT in the different segments of an extremity. Proximal deep veins (common femoral, femoral, and popliteal) are best evaluated with compression ultrasound. Duplex ultrasound and color Doppler imaging is more often used to interrogate the calf and iliac veins. The utility of ultrasonography is affected by several factors: morbid obesity, lower extremity edema and tenderness, and the presence of bandages or other immobilization devices. A venous duplex examination of the calf and proximal veins is used to exclude the presence of DVT. Serial duplex scans are indicated in patients suspected of having DVT when a limited proximal vein ultrasound examination was negative. Of all the ultrasound examinations performed for suspected DVT, only 12-25% are positive.<sup>12</sup>

CT venography provides direct imaging of the inferior vena cava, pelvic veins, and lower extremity veins and can be performed immediately after CT PA without an additional injection. A single examination

can evaluate the pulmonary arterial system, as well as the pelvic and lower extremity venous system, a distinct advantage over the other tests. However, approximately 150 mL of iodinated contrast material is required to produce adequate opacification of the pulmonary arteries and the veins of the pelvis and lower extremities. Nephrotoxic effects of contrast media can occur in critically ill patients with underlying renal insufficiency; therefore, minimizing the dose is necessary. CT venography has a sensitivity between 89% and 100% and a specificity between 94% and 100%.

D-Dimer assay is a relatively sensitive, but non-specific marker for DVT. D-Dimer is a fibrin-specific degradation product that detects cross-linked fibrin resulting from endogenous fibrinolysis. Assays are performed as a means to reduce the number of serial ultrasound studies in patients with suspected acute DVT. The negative predictive power of the D-dimer enzyme-linked immunosorbent assay (ELISA) varies according to the pretest probability of disease. In low-risk patients, the negative predictive value of a D-dimer ELISA is exceptionally good; its predictive value is unacceptable in high-risk groups.<sup>11,12</sup>

VTE has been an elusive diagnostic entity. Historically, venography was the standard of accuracy in the diagnosis of DVT; however, because it was invasive, costly and technically difficult, venography is no longer considered suitable for routine clinical evaluation of DVT.<sup>12</sup> Impedance plethysmography has a low sensitivity and is considered a poor method of detecting DVT. I-fibrinogen leg scanning, once used in the evaluation for DVT, has also been discarded because it had high false-negative and false-positive results.<sup>8</sup>

Pulmonary embolism, the most common cause of death following VTE, is the most common preventable hospital mortality.<sup>7</sup> The diagnosis of PE can not be established without objective testing. Several studies have evaluated the utility of duplex ultrasound of lower extremity proximal veins in patients with suspected PE. However, these tests, as well as nuclear medicine-based V/Q scanning, are being replaced by current procedures that incorporate magnetic resonance PA or CT PA. Many consider PA the gold standard; however, PA will fail in the diagnosis of subsegmental PE. If future studies substantiate the superiority of CT PA multislice technology to PA at the subsegmental level, this procedure may become the initial and only imaging study needed for the diagnosis of acute PE.<sup>13</sup>

Catheter-based PA is a valuable tool in the diagnosis of PE. In many centers, catheter-based PA is employed when less invasive imaging modalities, such as CT PA or magnetic resonance PA are impractical or have failed to provide definitive information, or when

a negative study conflicts with strong clinical signs of PE. The classical angiographic appearance of PE is one or more intraluminal filling defects with diminished distal contrast enhancement. Chronic PEs are more difficult to identify than acute occlusions and are identified as stenoses, webs, or mural thickening. Fat emboli are not generally seen on angiography.

Traditional PA is superior to CT or magnetic resonance for identification of small or subtle abnormalities (peripheral or chronic emboli, emboli in vessels on the axial plane). In addition, pulmonary catheterization allows direct measurement of pulmonary artery pressure. Because of its high rate of indeterminate findings, V/Q scintigraphy is now reserved for patients in whom motion artifact or poor function of the right ventricle limit the quality of CT examination and when use of intravenous radiographic contrast material is contraindicated. Helical or spiral CT PA has supplanted the V/Q scan as the initial imaging study of choice in patients with suspected PE. CT PA provides visualization of the pulmonary arterial system in the axial plane. Three-dimensional reconstructions can be generated from the raw data to enhance diagnostic accuracy. The cardinal sign of acute PE on CT PA is an intravascular filling defect in a pulmonary artery that partially or completely occludes the vessel and is often associated with an increased diameter of the affected vessel.<sup>14</sup> For the diagnosis of PE, CT PA has a sensitivity of 53% to 100% and a specificity of 67% to 100%, varying with several factors that include patient selection, extent of thrombus, and experience of the reader. Technological advances have affected diagnostic outcomes as resolution and multislice imaging improves and acquisition time shortens. Together, sensitivities of 94% to 96% and specificities of 94% to 100% have been achieved.

Although magnetic resonance imaging produces high tissue contrast without ionizing radiation, the technique of magnetic resonance PA and venography is currently less popular than CT for evaluation of acute VTE because of technical limitations (spatial resolution, breath-holding), higher cost, limited availability, and other logistical considerations.<sup>14</sup> As technology improves, magnetic resonance PA and venography may play a greater role in the evaluation of patients with VTE. Although a diagnosis of DVT by ultrasonography may indirectly suggest a diagnosis of PE in a symptomatic patient, the utility of ultrasound is limited. Some patients with a diagnosis of DVT and pulmonary symptoms may have hemodynamic instability from other causes. Even when PE has been confirmed, DVT of the proximal lower extremity veins is only detectable by compression ultrasound in 50% of

patients, making it likely that PE may have originated from pelvic veins or embolized completely from a lower extremity vein.

5. b. LMWH
- c. elastic stockings
- f. IPC devices
- h. Flite Tabs

The combination of pharmacological and mechanical methods of prophylaxis provides greater protection than any one method.

LMWH (enoxaparin, dalteparin) is the treatment of choice for DVT and PE. Its use has reduced the length of hospital stays and made outpatient or short-stay DVT programs possible.<sup>15</sup> LMWHs are composed of smaller molecules with significantly less binding to plasma proteins and other vascular factors. These characteristics result in a more prolonged and predictable anticoagulant effect and less bleeding. LMWHs have minimal effects on platelets; as a result, the incidence of thrombocytopenia is diminished. LMWH requires only one daily subcutaneous administration, which reduces consumption of human and laboratory resources. Enoxaparin is the only LMWH approved for the prevention of DVT in medically ill or surgical patients. Enoxaparin (40 mg subcutaneously once daily), when given to medically ill patients (eg, congestive heart failure, severe respiratory disease) during prolonged bed rest, was as effective and safe as UFH therapy (5000 IU subcutaneously 3 times daily) in the prevention of thromboembolic events.<sup>16</sup> LMWH is excreted by the kidney, and caution is required in the presence of severe renal insufficiency (creatinine >3 mg/dL). A cost-analytical model of various studies comparing UFH and LMWH therapies suggests that LMWH has a better risk-benefit ratio and was cost neutral compared with UFH in prevention of DVT.

Heparin has several potential adverse effects such as heparin-induced thrombocytopenia, increased cholesterol levels, osteoporosis, and skin lesions. Renal insufficiency must be considered when ordering heparin, because all forms of heparin are eliminated via the kidneys. Dosing by body size is difficult in obese patients. The variable anticoagulant effect, increased risk of bleeding, and the delivery demands of UFH (constant infusion) all preclude outpatient anticoagulant therapy or timely hospital discharge.

In addition to UFH and LMWHs, therapy for primary thromboprophylaxis also includes the use of vitamin K antagonists (eg, warfarin). Warfarin is commonly used in orthopedic surgery, followed by the use of LMWH.<sup>17</sup> Warfarin therapy is widely used up to 6 weeks

postoperatively for the prevention of VTE following hip and knee replacement.<sup>17</sup> However, the optimal duration of this type of thromboprophylaxis, especially following major orthopedic surgery, is controversial.

Breakthroughs in polysaccharide chemistry made possible the synthesis of a new class of antithrombotic compounds, synthetic oligosaccharides. Fondaparinux, the first of this new class, is a selective inhibitor of factor Xa and is the most advanced in clinical development. The rationale for designing a specific factor Xa inhibitor was that factor Xa is positioned at the start of the common coagulation cascade pathway, thus playing a central role in thrombin formation. Although fondaparinux has no direct activity against thrombin or any other coagulation factors, inhibition of factor Xa results in effective and linear dose-dependent inhibition of thrombin generation, but does not affect thrombin activity. It does not bind to platelets and thus has no effect on platelet function. Currently, fondaparinux has been approved for use in thromboprophylaxis after major orthopedic surgery.<sup>18</sup> It is given as a once-daily subcutaneous 2.5-mg injection. Clinical trials of patients undergoing major orthopedic surgery demonstrated that fondaparinux was more effective than enoxaparin in preventing VTE without increasing clinically relevant bleeding.<sup>19</sup> The optimal timing for the first doses of LMWH prophylaxis or of fondaparinux is controversial. Peri-operative doses given within 2 to 6 hours of surgery increase bleeding with no effective increase in prophylaxis. In contrast, doses initiated 6 hours postoperatively provide effective prophylaxis and are not associated with increased bleeding.

Hospital patients at risk for VTE should continue prophylaxis after discharge. The greater the number of days of postoperative prophylaxis, the lower the prevalence of asymptomatic DVT. However, questions remain as to which high-risk patients should receive postdischarge prophylaxis, which agent should be used, and the duration of posthospital prophylaxis.<sup>20</sup> Aspirin as an antithrombotic agent is ineffective in preventing VTE following general surgery. However, when a decision is made not to continue anticoagulation (LMWH, warfarin, fondaparinux) past the post-operative 7 to 10 days, aspirin for 1 month is recommended.<sup>21</sup> In the event that pharmacological anticoagulation can not be employed, other adjunctive therapies are advised, for example, elastic stockings, IPC devices, and foot pumps. IPC is effective in preventing DVT during general surgery, as well as in surgical patients with malignant diseases. Graded compression elastic stockings can reduce the incidence of leg DVT and enhance the effects of low-dose UFH. Stockings counteract venous stasis and augment venous return.<sup>22</sup> Data on the use of

stockings are insufficient as they relate to proximal DVT and PE. Inferior vena cava filters prevent thrombus from embolizing to the pulmonary vasculature and are useful when other conventional means of thrombotic prevention are not possible or are unsuccessful. Placement of an inferior vena cava filter is reserved for patients with contraindications to anticoagulation, or those who develop complications while receiving anticoagulants, and in those at high risk of mortality from recurrent PE.<sup>7</sup> A randomized controlled trial in 2003, "The Long-Haul Flights with Flite Tabs (LONFLIT)" evaluated the development of leg edema and superficial and DVT prophylaxis in high-risk patients on long-haul flights with an oral fibrinolytic agent 150 mg pinokinase. The study concluded that prophylactic use of pinokinase 150 mg tablets is effective in reducing the incidence of flight-related DVT in high risk subjects on 7 to 8 hour flights. There were no adverse effects.<sup>22</sup> Currently advisories suggest the routine practice of standing, stretching, exercising, drinking water, and the avoidance of restricted clothing and alcohol during travel. Established guidelines for DVT prophylaxis can be found in journals.<sup>23,24</sup>

6. c. a continuous infusion of intravenous UFH followed by oral anticoagulation

Pharmacological treatment of VTE includes a short course of UFH followed by a prolonged course of oral anticoagulation therapy with full-dose warfarin. Since the introduction of warfarin in 1950, management of VTE consists in bed rest, a bolus followed by a continuous infusion of intravenous UFH for 5 to 6 days (adjusted to maintain an activated partial thromboplastin time [aPTT] of 60 to 80 seconds, or 1.5-2.5 times the control) followed by a prolonged period of anticoagulation with warfarin. The therapeutic target for warfarin therapy is defined as an international normalized ratio (INR) of 2.0 to 3.0, maintained for 3 to 12 months. UFH dosage by body weight (introduced in 1993) achieved a more rapid therapeutic aPTT.

7. a. True

The standard therapy to prevent recurrent VTE is warfarin at a target INR of 2.0 to 3.0 given for 3 to 12 months. Recurrent thromboembolism occurs in 6% to 9% of patients after completing anticoagulation therapy; consequently, this group will require long-term therapy. Full-dose warfarin for more than 1 year can prevent further embolic events, but carries a substantial risk of major hemorrhage. However, long-term, low-intensity warfarin (INR 1.5-2.0) is equally effec-

tive in preventing recurrent VTE, has a lower risk of bleeding, and requires less frequent monitoring.<sup>25</sup>

## SUMMARY

Deep vein thrombosis and its potentially fatal complication, PE, accounts for more than 250 000 hospitalizations annually in the United States. Pulmonary embolism is the most serious complication and has a 3-month mortality of 17%. Two million people each year are affected by VTE, and the prevalence is rising because of the aging population.<sup>3-6</sup> Deep vein thrombosis and its potential complication, PE, is preventable. However, there still is widespread failure to screen, diagnose, and initiate prophylactic therapy in patients at risk. This failure can be corrected by development of a heightened awareness of risk factors among emergency department physicians and nurses and by similar personnel caring for bedridden hospitalized patients. A recent landmark study Prophylaxis in Medical Patients With Enoxaparin Study (MEDENOX) revealed the risk factors of VTE in order of frequency: (1) previous VTE, (2) acute infectious disease, (3) cancer, (4) age greater than 75 years, and (5) chronic respiratory disease. This study confirmed the effectiveness of a LMWH, enoxaparin, in the prevention of VTE.<sup>26,27</sup>

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