Seminar

Pulmonary embolism

Samuel Z Goldhaber

Pulmonary embolism (PE) is a common illness that can cause death and disability. It is difficult to detect because patients present with a wide array of symptoms and signs. The clinical setting can raise suspicion, and certain inherited and acquired risk factors predispose susceptible individuals. D-dimer concentration in blood is the best laboratory screening test, and chest CT has become the most widespread imaging test. Treatment requires rapid and accurate risk stratification before haemodynamic decompensation and the development of cardiogenic shock. Anticoagulation is the foundation of therapy. Right-ventricular dysfunction on echocardiography and higher than normal concentrations of troponin identify high-risk patients who might need escalation of therapy with thrombolysis or embolectomy even if the blood pressure is normal on presentation. When patients are admitted to medical wards or when patients undergo surgery, their physicians should prescribe prophylactic measures to prevent PE. After hospital discharge, prophylaxis should continue for about a month for patients at high risk of thromboembolism.

Pulmonary embolism (PE) is a common, potentially life-threatening cardiopulmonary illness that has only recently attracted the attention of the general public, when a healthy young woman died of PE shortly after a flight from Australia to the UK. Although PE can be difficult to diagnose, early recognition is important because prompt medical or surgical intervention can be life-saving. Therefore, physicians, health-care providers, and the public need to understand the rapidly progressing advances in PE epidemiology, pathophysiology, diagnosis, treatment, and prevention strategies. The interdisciplinary nature of PE means that knowledge about this disease can no longer be consigned to the domain of specialists.

Epidemiology

Although PE and deep venous thrombosis (DVT) can be notoriously difficult to diagnose,[1] hospital admission rates for venous thromboembolism (VTE) increased in the UK in the 1990s.[2] Despite challenges in detection of VTE, cohort studies show consistency in incidence estimates among western populations. In the Brest district of France, the annual incidence was 1·83 per 1000.[3] In Olmsted County, MN, USA, the most recent annual incidence estimate was 1·22 per 1000 among adults.[4] In the Longitudinal Investigation of Thromboembolism Etiology, which combined two separate US cross-sectional studies totalling 148 054 person-years, the annual incidence was 1·45 per 1000.[5] If the annual incidence of recognised VTE is 1·50 per 1000, and if only one of every three cases of VTE is detected, the USA, with a population of almost 300 million, has about 450 000 recognised incident cases and 900 000 unsuspected incident cases, totalling about 1 350 000 VTE cases each year.

Mortality from recognised PE is higher than generally acknowledged. In a population-based cohort study from Olmsted County, the 30-day mortality rate after PE or DVT was 28%.[6] In the International Cooperative Pulmonary Embolism Registry of 2454 consecutive patients from 52 institutions in seven countries, the 3-month mortality rate was 17·4 %.[7] In a Japanese registry of 533 patients with PE, the in-hospital mortality rate was 14·0%.[8] Many patients die from underlying comorbid disorders, especially cancer and cardiorespiratory diseases.[9] The mortality from PE in registries such as the international one mentioned above, which enrol consecutive patients without any exclusions, is far higher than that in selective registries such as the Prospective Investigation of Pulmonary Embolism Diagnosis, in which the 1-year mortality rate from PE was 2·5%.[10] In an overview of 1302 patients in five clinical studies of PE, 19 died of PE and there were 11 other sudden deaths, giving a low overall mortality rate of only 2·3%.[11]

Risk factors

Understanding of risk factors for VTE[12,13] will increase the likelihood that DVT and PE can be diagnosed and prevented. These factors include environmental, natural, and hormonal influences (panel 1).

Travel

Long-haul air travel is a rare (0·4 cases per million passengers) risk factor for massive PE.[14] The risk increases substantially with flight distances of 5000 km or more.

Search strategy and selection criteria

I subscribe to about 15 journals in internal medicine, cardiology, haematology, and pulmonary disease. I use a "tear and file" system to track relevant articles. To ensure that I have not missed important articles in other journals, I check the venous thrombosis articles weekly on the AMEDEO web page. For selection in this seminar, I searched MEDLINE (1993–2003) with the search terms "pulmonary embolism" and "clinical" and "OVID full text". I chose mostly recent articles published in 2000–2003. I emphasised papers from journals with high impact factors that add critical knowledge to this field. I also included 22 articles recommended by the reviewers of this seminar.

Lancet 2004; **363:** 1295–305

Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA (S Z Goldhaber MD)

Correspondence to: Dr Samuel Z Goldhaber, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA (e-mail: sgoldhaber@partners.org)

Passengers at particularly high risk include those older than 50 years, and individuals with a history of previous VTE, thrombophilia, limitation of mobility, cancer, or large varicose veins.

Obesity

The magnitude of risk associated with obesity is related to the body-mass index. The Nurses' Health Study identified risk factors for PE among a cohort of initially healthy female nurses, with 1 619 770 person-years of follow-up.[15] The relative risk of PE was 1·7 (95% CI 1·1–2·7) for those with a body-mass index of 25·0–28·9 kg/m^2 and 3·2 (1·7–6·0) for those with a body-mass index of 29·0 kg/m^2 or higher. In the International Cooperative Pulmonary Embolism Registry, the proportion of patients with a body-mass index of 29·0 kg/m^2 or higher was 29%.[7] Even in Japan, with a much leaner population than western countries, a prospective PE registry found that body-mass index was 25·3 kg/m^2 or higher in 34% of cases.[8]

Panel 1: **Risk factors for PE**

Environmental
- Long-haul air travel
- Obesity
- Cigarette smoking
- Hypertension
- Immobility

Natural
- Increasing age

Women's health
- Oral contraceptives, including progesterone-only and especially third-generation pills
- Pregnancy
- Hormone replacement therapy

Medical illness
- Previous PE or DVT
- Cancer
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Inflammatory bowel disease
- Antipsychotic drug use
- Chronic in-dwelling central venous catheter
- Permanent pacemaker
- Internal cardiac defibrillator
- Stroke with limb paresis
- Nursing-home confinement or current or repeated hospital admission
- Varicose veins

Surgical
- Trauma
- Orthopaedic surgery, especially total hip replacement, total knee replacement, hip fracture surgery, knee arthroscopy
- General surgery, especially for cancer
- Gynaecological and urological surgery, especially for cancer
- Neurosurgery, especially craniotomy for brain tumour

Thrombophilia
- Factor V Leiden mutation
- Prothrombin gene mutation
- Hyperhomocysteinaemia (including mutation in methylenetetrahydrofolate reductase)
- Antiphospholipid antibody syndrome
- Deficiency of antithrombin III, protein C, or protein S
- High concentrations of factor VIII or XI
- Increased lipoprotein (a)

Non-thrombotic
- Air
- Foreign particles (eg, hair, talc, as a consequence of intravenous drug misuse)
- Amniotic fluid
- Bone fragments, bone marrow
- Fat
- Cement

Women's health

Oral contraceptives, pregnancy, and postmenopausal hormone replacement therapy raise the risk of PE. Inherited prothrombotic states further increase the risk.

First-generation oral contraceptives contained more than 50 μg oestrogen. They were associated with an alarming increase in the frequency of massive PE and were withdrawn from the market in 1989. Second-generation oral contraceptives, containing less than 50 μg oestrogen, were introduced in the USA in 1967, but an excess, albeit lower, risk of VTE persisted. Third-generation oral contraceptives contain newer progestagens, such as desogestrel or gestodene, which improve acne and hirsutism. However, they cause adverse haemostatic changes, including acquired resistance to activated protein C[16] and therefore increase the risk of VTE more than second-generation pills. Increasing age and cigarette smoking further increase the thrombotic risk among users of oral contraceptives.[17]

Despite the increased relative risk of VTE from oral contraceptives, the absolute risk of fatal PE is low. In a New Zealand study, the absolute risk of death from PE in current users was estimated as one per 100 000 woman-years. Among the women who died, the median age was 29 years. The risk of fatal PE was twice as high among women taking third-generation oral contraceptives.[18]

A history of PE or DVT is an absolute contraindication to oral contraceptives. Relative contraindications include a strong family history of VTE or an inherited prothrombotic state, such as factor V Leiden or the prothrombin gene mutation. Whether women with a family history but no personal history of VTE should be screened for prothrombotic states is controversial. Overall, oral contraceptives are safe and effective. The absolute risk of VTE is very low.

In pregnancy, the risk of PE increases with time, and most cases of VTE occur during pregnancy rather than post partum. Increasing maternal age and caesarean-section delivery increase the likelihood of VTE.[19] Inherited prothrombotic states are associated with obstetric complications[20] and with late fetal loss.[21]

The Women's Health Initiative is a randomised placebo-controlled primary prevention trial that enrolled 16 608 women to assess the major benefits and risks of postmenopausal hormone replacement therapy.[22] The trial used a combined oestrogen and progesterone preparation that is most commonly prescribed in the USA. Though the trial duration was planned to be 8·5 years, the study was stopped early because overall health risks exceeded benefits after an average of 5 years of follow-up. The hazard ratio for PE in the treated group was twice that for controls. The absolute excess risk of PE was 8·0 per 10 000 woman-years. In a meta-analysis of 12 studies, the relative risk of VTE was 2·1 among current users and was highest (3·5) during the first year of use.[23]

Selective oestrogen-receptor modulators such as raloxifene increase the risk of PE. In a study on prevention of breast cancer, 7705 postmenopausal women were

assigned raloxifene or placebo; by 40 months of follow-up the rate of PE was three times higher in patients assigned raloxifene than in those assigned placebo (0·3% *vs* 0·1%). The rate of DVT was also three times higher (0·7% *vs* 0·2%).[24]

Oestrogen agonists-antagonists such as tamoxifen are used to treat or prevent breast cancer. In a trial of 7152 women randomly assigned tamoxifen or placebo, the VTE rate was 2·5 times greater in the tamoxifen group (1·20% *vs* 0·47%).[25]

Cancer

In patients with known cancer who develop VTE, recurrence and bleeding complications are common with conventional heparin followed by oral anticoagulation.[26] Low-molecular-weight heparin as monotherapy without oral anticoagulation can halve the rate of recurrence compared with oral anticoagulation.[27]

Cancer, occult at the time of PE diagnosis in many cases, predisposes to PE. In the Swedish Cancer Registry, the risk of discovering a newly diagnosed cancer was increased for at least 2 years after the diagnosis of VTE.[28] However, when such cancers are discovered, they generally become apparent at an advanced stage and confer a poor prognosis.[29] Cancer should be suspected, especially in patients who have idiopathic VTE and recurrence during follow-up.[30]

Thrombophilia

Inherited and acquired risk factors for PE commonly interact. In most inherited thrombophilias, impaired neutralisation of thrombin or failure to control thrombin generation causes VTE.[31] To help define the role of heritability of the prethrombotic state, quantitative genetic-model fitting for hypercoagulability was done among participants in the St Thomas' UK Adult Twin Registry.[32] There was a high degree of heritability for markers of coagulation and inhibition of fibrinolysis, indicating substantial genetic control over fibrin formation and fibrinolysis.

Factor V Leiden is an autosomal dominant single point mutation (G→A) that brings about resistance to activated protein C and an increased predisposition to VTE (roughly three times). The carrier frequency ranges from 3% to 7%, and the mutation is especially prevalent in northern European people.[33] Among participants in the Physicians' Health Study, the carrier frequency was 5·3% for white Americans, 2·2% for hispanic Americans, 1·2% for African Americans, 0·45% for Asian Americans, and 1·2% for native Americans.[34] There is conflicting evidence on whether patients with VTE and factor V Leiden have an increased rate of recurrence after anticoagulation is discontinued compared with individuals who do not have this mutation.[35,36]

A single point mutation (G→A at position 20210) has been identified in the prothrombin gene, which causes an increased risk of VTE.[37] As with factor V Leiden, inheritance is autosomal dominant. However, the magnitude of the effect is slightly less than that of factor V Leiden.[38]

Hyperhomocysteinaemia is associated with VTE and is most commonly caused by an acquired nutritional deficiency of folate exacerbated by inadequate intake of vitamin B_{12} or vitamin B_6. Folate antagonists, such as methotrexate and phenytoin or vitamin B_6 antagonists, such as oestrogens, tobacco, or theophylline, also raise homocysteine concentrations. Impaired renal function can cause hyperhomocysteinaemia because homocysteine is predominantly metabolised by the kidneys.[39]

The antiphospholipid antibody syndrome, an acquired disorder, is the most ominous hypercoagulable state for PE. Anatomically large and recurrent VTE is the most common clinical manifestation of this syndrome, but increases in antibodies to cardiolipin are also associated with myocardial infarction, stroke, and first-trimester miscarriage.[40]

Despite advances in laboratory diagnosis of hypercoagulability, predisposing thrombophilic states are identifiable in only a minority of patients with VTE. Therefore, the most important action is to obtain a careful family history. Patients and their families should be reassured that some asymptomatic carriers of prethrombotic genetic risk factors will never develop clinical evidence of PE or DVT. There is no published evidence to support screening of first-degree relatives of patients with thrombophilia.[41]

Pathophysiology

Venous stasis and endothelial damage predispose to VTE, especially among patients with underlying hypercoagulable states. Those with previous PE or DVT are particularly susceptible to recurrences. Most cases of PE result from thrombi that originate in the pelvic region or deep veins of the leg. When venous thrombi become dislodged from their sites of formation, they move through the venous system to the pulmonary arterial circulation. Extremely large emboli can lodge at the bifurcation of the pulmonary artery, forming a "saddle embolus". More commonly, however, a pulmonary vessel of second, third, or fourth order is affected. In rare cases, thrombi in the axillary, subclavian, or other arm veins embolise to the pulmonary arteries.[42]

PE can have the following pathophysiological effects: increased pulmonary vascular resistance resulting from vascular obstruction, neurohumoral agents, or pulmonary-artery baroreceptors; impaired gas exchange caused by increased alveolar dead space from vascular obstruction and hypoxaemia from right-to-left shunting, as well as impaired transfer of carbon monoxide due to loss of gas exchange surface; alveolar hyperventilation owing to reflex stimulation of irritant receptors; increased airway resistance resulting from bronchoconstriction; and decreased pulmonary compliance caused by lung oedema, lung haemorrhage, and loss of surfactant.

Right-ventricular dysfunction

The haemodynamic response to PE depends on the size of the embolus, coexisting cardiopulmonary disease, and neurohumoral activation. Pulmonary-artery obstruction and circulating neurohumoral substances decrease the pulmonary vascular bed and cause an increase in right-ventricular afterload. As right-ventricular and pulmonary-artery pressures rise, the right ventricle dilates, becomes hypokinetic, and ultimately fails. Progressive right-heart failure leads to reduced forward cardiac output and is the cause of death from acute PE in most cases.

Sudden increases in right-ventricular pressure adversely affect left-ventricular function because of the anatomical juxtaposition of the two ventricles and ventricular interdependence. Moderate right-ventricular hypertension can displace the interventricular septum towards the left ventricle, resulting in decreased left-ventricular diastolic filling and end-diastolic volume. The subsequent reduction in coronary-artery perfusion pressure to the overloaded right ventricle can cause progressive right-ventricular ischaemia and failure. Ultimately, right-ventricular infarction, circulatory arrest, and death can ensue.[43]

Diagnosis

Clinical suspicion

Diagnosis of PE poses a major challenge because classic symptoms and signs are not present in many cases. PE can present with subtle findings in young, previously healthy patients who have excellent cardiac reserve. With increasing age, PE tends to masquerade as other illnesses such as acute coronary syndrome or exacerbation of chronic obstructive pulmonary disease. Accurate diagnosis of PE is particularly difficult when patients present with two concurrent illnesses, such as obvious pneumonia plus occult PE or obvious congestive heart failure plus occult PE. Such patients may not improve clinically despite appropriate treatment for the apparent illness, until the PE is also recognised and treated.

Detection of PE begins with consideration of VTE as a diagnostic possibility. The clinical scenario is crucial in assessing the likelihood of PE. Wells and colleagues[44] have developed a rapid seven-feature bedside assessment that is useful because almost half of their study patients could be classified as "PE unlikely". The researchers designated a score of 4·0 or less as PE unlikely. In this low-risk group, only about 5% of patients were subsequently found to have PE. The seven features are: clinical signs and symptoms of DVT (3·0 points); an alternative diagnosis is less likely than PE (3·0 points); heart rate above 100 bpm (1·5 points); immobilisation or surgery in the previous 4 weeks (1·5 points); previous DVT or PE (1·5 points); haemoptysis (1·0 point); and cancer, being treated currently or within the previous 6 months or palliative (1·0 point).

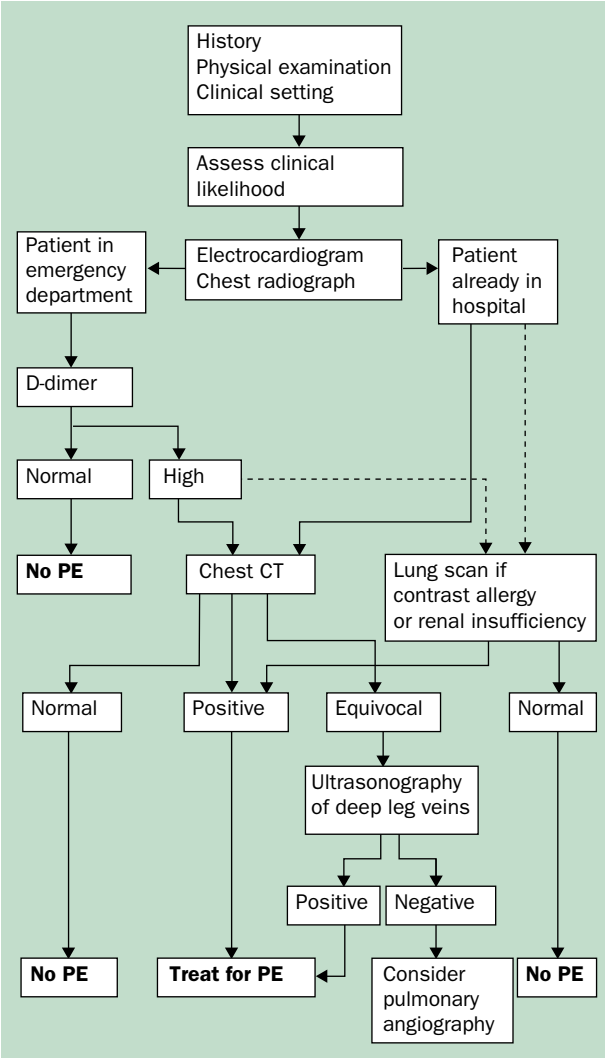

Figure 1: **Diagnostic algorithm for suspected PE**

For optimum diagnostic accuracy, symptoms and signs should be integrated with appropriate laboratory tests, including electrocardiography, chest radiography, and, when available, D-dimer testing. In many cases, no further diagnostic investigation is warranted. When appropriate, though, imaging tests, such as a chest CT or lung scan, should be done (figure 1).

Initial diagnostic studies

The electrocardiogram (figure 2) is useful to help exclude a myocardial infarction with ST-segment elevation and acute pericarditis. In patients with large PE, pulmonary hypertension and right-ventricular strain cause incomplete or complete right bundle-branch block, T-wave inversion in leads V1 to V4, an S wave in lead I, and both a Q wave and an inverted T wave in lead III.[45] A normal electrocardiogram is very unusual in patients with acute PE.

The chest radiograph cannot be used to diagnose or exclude PE. It is useful in the differential diagnosis because it can detect pneumonia, pneumothorax, rib fracture, and congestive heart failure. Common abnormalities in patients with large PE include cardiac enlargement, pulmonary-artery enlargement, and oligaemia of the embolised lung.[46] In patients with small PE, a small wedge-shaped density at the periphery of the lungs indicates pulmonary infarction—"Hampton's hump".

Laboratory studies

Testing of the arterial blood for hypoxaemia and calculation of the alveolar–arterial oxygen gradient have been basic tools in the investigation of PE for a long time. However, comparison of blood gas results with pulmonary angiography has shown that hypoxaemia is not specific and does not serve as a useful triage tool in patients with suspected PE.[47] Furthermore, the alveolar–arterial oxygen gradient is normal in about 20% of patients with angiographically proven PE.[48]

The D-dimer blood test has practical usefulness in the diagnostic investigation of some patients with suspected PE. Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin.[49] Among most patients with PE, endogenous fibrinolysis (which was clinically ineffective in preventing thromboembolism) results in a rise in the amount of D-dimer circulating in plasma. By contrast, a normal D-dimer concentration has a very high negative predictive value for excluding the diagnosis of PE. However, raised D-dimer concentrations are not specific for PE and are observed among patients with myocardial infarction, pneumonia, sepsis, and cancer, during the second and third trimesters of pregnancy, and after surgery. Therefore, this test is most useful in the setting of the emergency department, because most patients already in hospital have raised D-dimer concentrations.

At the Emergency Department of Brigham and Women's Hospital, we introduced a requirement that the D-dimer ELISA was done for all patients with suspected acute PE.[50] After a year, we found that 559 of 1106 D-dimer assays had raised results and 547 were normal. Only two patients with normal D-dimer concentrations had PE. Thus, the sensitivity of the D-dimer ELISA for acute PE was 96·4%, and the negative predictive value was 99·6%. Therefore, chest CT and lung scanning are

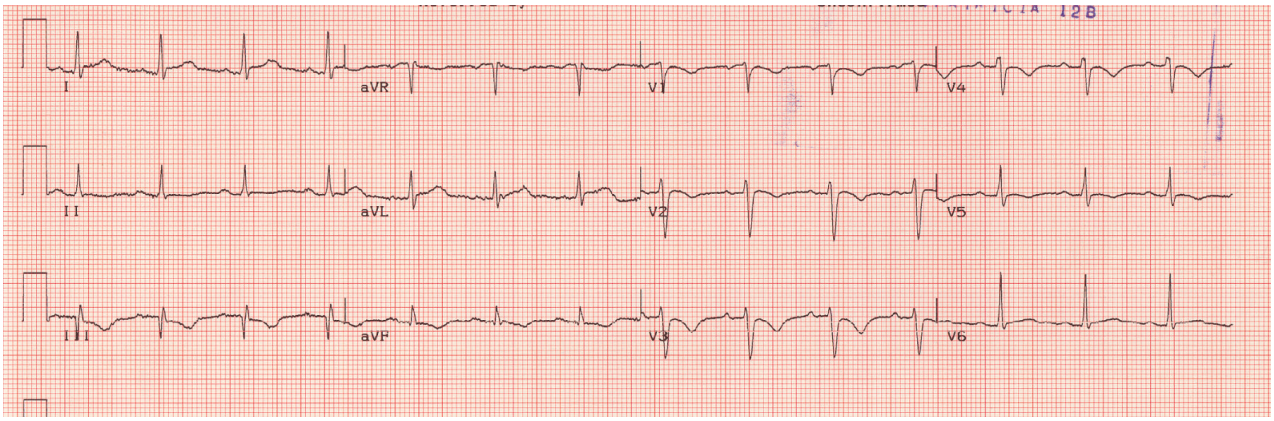

Figure 2: **Electrocardiogram of a haemodynamically stable 63-year-old woman**
The patient presented with acute PE and moderately severe right-ventricular dilatation and dysfunction on echocardiography. The electrocardiogram shows an S wave in lead I, Q wave in lead III, and T-wave inversion in leads III, AVF, and V1–V4 (the McGinn-White pattern), which is typical of right-ventricular strain due to massive PE.

not indicated for most patients with normal D-dimer results. This strategy may improve diagnostic efficiency and reduce costs. However, there is not yet enough evidence to stop the investigation for PE in patients with high clinical probability and normal D-dimer concentrations.[51,52] Such evidence may soon emerge.

Cardiac biomarkers

Cardiac biomarkers are being used with increasing frequency to assess prognosis in patients with newly diagnosed PE. In the Management Strategies and Prognosis of Pulmonary Embolism 2 study,[53] raised troponin concentrations were related to overall mortality and a complicated in-hospital course, presumably because troponin serves as a marker of right-ventricular microinfarction.

Low concentrations of pro-brain natriuretic peptide predict a benign clinical outcome in patients with acute PE.[54] Conversely, high concentrations of brain natriuretic peptide predict an adverse outcome.[55,56]

Imaging studies

The traditional imaging test for suspected PE has been the ventilation/perfusion lung scan. High-probability lung scans and normal lung scans are well validated with paired contrast pulmonary angiograms for diagnosis and exclusion of PE, respectively.[57] The main difficulty with lung scanning is that most scans are of intermediate or indeterminate probability. These non-diagnostic scans can cause consternation among clinicians who have either to undertake additional imaging tests or to decide empirically to diagnose or exclude acute PE.

Because of frustration with lung scanning and the clinical need for definitive diagnosis or exclusion of PE, chest CT is rapidly replacing lung scanning as the main imaging test for suspected acute PE. Lung scanning is becoming a second-line test reserved for patients with a history of allergy to contrast agent or renal insufficiency. Chest CT has two other advantages over lung scanning: thrombus can be directly visualised (figure 3); and alternative diagnoses can be established on lung parenchymal images that are not evident on chest radiography.

Chest CT takes less than 30 s with a single breath-hold to minimise respiratory motion. Although excellent vascular opacification of the pulmonary arteries with contrast agent can be achieved in most cases, the major limitation of conventional chest CT has been failure to detect PE beyond third-order pulmonary arterial branches.[58] In a prospective study with first-generation CT, the sensitivity of CT compared with angiography was 70%.[58] Other management studies are needed to show the safety of withholding anticoagulant therapy in patients with normal chest CT. With the newer multi-row detector CT scans, four slices can be acquired simultaneously during each rotation of the X-ray source. The total examination time is eight times faster than with conventional single-row detector systems. Fewer motion artifacts occur; resolution increases from 5·00 mm to 1·25 mm; and subsegmental vessels can generally be well visualised. Compared with conventional CT, the

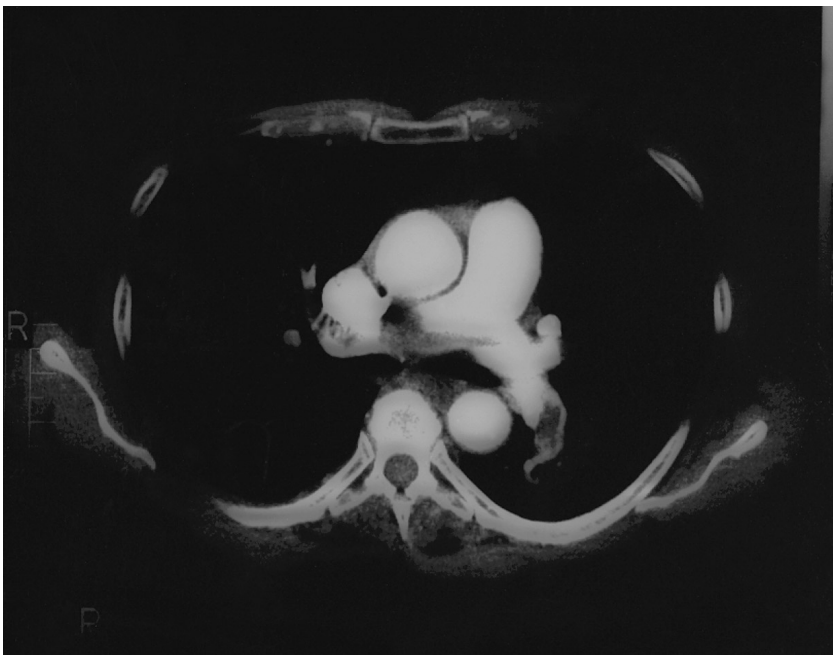

Figure 3: **Chest CT of the patient whose electrocardiogram is shown in figure 2**
The scan shows bilateral central PE, with larger thrombus burden in the left than in the right pulmonary artery.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.