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Diagnosis of Pulmonary Embolism in the Coronary Care Unit

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Abstract

The clinical diagnosis of pulmonary embolism (PE) is difficult in the coronary care unit (CCU) because many findings of PE are similar to acute coronary syndrome and heart failure. Immobilization of only 1 or 2 days may predispose to PE. Heart failure and acute myocardial infarction add to the risk. Dyspnea may be absent or occur only with exertion. The onset of dyspnea may occur over seconds to days. Orthopnea occurs with PE as well as heart failure. When the clinical probability and results of objective testing are discordant, the post-test probability of PE may be neither sufficiently high nor sufficiently low to permit therapeutic decisions. Objective scoring systems for clinical assessment have not been developed for patients in a CCU. D-dimer is likely to be of little value for exclusion of PE in the CCU, because elevations occur with heart failure, unstable angina, and myocardial infarction. Computed tomographic (CT) pulmonary angiography with venous phase imaging of the low pelvic and proximal leg veins (CT venography) are recommended for imaging. Scintigraphy in women <aged 50 years with a normal or nearly normal chest radiograph may be the preferred imaging test to reduce the risk of radiation. Echocardiography with leg ultrasonography is a rapidly obtainable combination of bedside tests that may be useful for young patients and patients in extremis. In conclusion, the choice of diagnostic tests depends on the clinical probability of PE, condition of the patient, availability of diagnostic tests, risks of iodinated contrast material, radiation exposure, and cost.

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Keywords

Coronary care unit; pulmonary embolism; deep venous thrombosis; CT angiography; CT venography; D-dimer; Electrocardiography

Pulmonary embolism (PE) is a major cause of morbidity and mortality in hospitalized patients with heart disease.¹ Among 198 patients with severe congestive heart failure in a coronary care unit (CCU), 9.1% developed PE during the hospitalization even though the majority had received thromboprophylaxis.² Among 1032 hospitalized cardiac patients who died and underwent autopsy, 24.4% had PE and 9.7% had massive PE.¹ Among those with massive PE, the diagnosis was unsuspected antemortem in 82%.¹

The clinical diagnosis is particularly difficult in the CCU because of many findings of acute PE are similar to acute coronary syndrome or heart failure. A need for increased vigilance of the possibility of PE is critical.³ Occasionally patients with acute PE have chest pain and electrocardiographic (ECG) changes suggestive of acute coronary syndrome. In patients with such findings in whom the coronary angiogram is normal, PE would be a diagnostic possibility.

Predisposing Factors

Immobilization of only one or two days may predispose to PE.⁴ Among patients in whom immobilization was a predisposing factor, 65% were immobilized ≤ 2 weeks.⁴ The risk of PE in patients hospitalized with heart failure is twice that of hospitalized patients who do not have heart failure.⁵ The lower the ejection fraction, the greater the risk of venous thromboembolism.⁶

Symptoms of Acute Pulmonary Embolism

Clinical findings such as unexplained dyspnea, tachypnea, or chest pain, are useful for the selection of patients for further diagnostic testing.^{4,7} Dyspnea is not a universal finding. It occurred in 73% of patients with PE and no prior cardiopulmonary disease.^{4,7} Dyspnea may occur only with exertion.⁷ The onset of dyspnea occurred over seconds or minutes in 72% of patients with no prior cardiopulmonary disease and seconds, minutes or hours in 83%. In some, however, the onset of dyspnea occurred over days.⁷

Orthopnea is a symptom of PE as well as heart failure, and may occur in those who have dyspnea at rest or only on exertion.⁷ Pleuritic chest pain occurs more frequently than hemoptysis in patients with PE.^{4,7}

Nonpleuritic chest pain may occur in a minority of patients with PE and the characteristics are highly variable.⁷ It has been described as substernal, left anterior, right anterior, left posterior, right posterior, left lateral and right lateral. The pain usually does not radiate. It may, however, radiate to the back, neck, and rarely left or right arm.⁷ Cough may be a symptom of PE.⁷ It is usually nonproductive, but it may be productive of clear, purulent, blood streaked, or less frequently completely bloody sputum. Calf pain occurred in 39% of patients with PE, and 17% had calf pain and thigh pain, but thigh pain alone was uncommon.⁷

Signs of Acute Pulmonary Embolism

Tachypnea (respiratory rate ≥ 20 /min) occurred in 54% to 70% of patients who did not have prior cardiopulmonary disease.^{4,7} Tachycardia (heart rate > 100 /min) occurred less frequently (24% to 30%).^{4,7} One of the signs of right atrial, right ventricular or pulmonary artery pressure elevation (neck vein distension, right ventricular lift, accentuated pulmonary component of the

second sound) was documented in only 21% of patients who did not have prior cardiopulmonary disease.⁷

Lung examination showed an abnormality in 30% of patients with PE.⁷ Rales (crackles) and decreased breath sounds were the most frequently detected abnormalities.⁷ Wheezes and rhonchi were heard occasionally.⁷ A pleural friction rub was rare.⁷

Fever can be the presenting physical finding in patients with venous thromboembolism especially in the intensive care unit. Fever occurred with similar frequency among those with pulmonary hemorrhage/infarction and those with PE who did not have pulmonary hemorrhage/infarction.⁸ The fever was usually low grade.⁸ Signs of DVT were observed in 15% to 47% of patients with acute PE.^{7,9}

Combinations of Signs and Symptoms

Either dyspnea or tachypnea was shown in over 80% of patients with acute PE.^{4,7} However, even among patients with circulatory collapse, the most severe presentation of acute PE, both dyspnea and tachypnea may be absent.^{7,10} Dyspnea or tachypnea or pleuritic pain was shown in over 90%. One of these findings or signs of DVT were found in 96% of patients with PE.^{4,7}

Unexplained changes on the chest radiograph or unexplained shock or loss of consciousness may suggest PE.^{4,10}

Initial a priori assessment of the probability of acute PE is strongly recommended.¹¹⁻¹⁴ Guidelines for diagnosis recommend that before any diagnostic tests are performed, the clinical probability of acute PE should be assessed.¹¹⁻¹⁴ When the clinical probability and results of objective testing are discordant, the post-test probability of PE may be neither sufficiently high nor sufficiently low to permit therapeutic decisions.¹⁵ Under these circumstances further objective testing is mandatory.¹¹ Objective scoring systems for clinical assessment, although generally preferable to intuitive assessment, have not been developed for patients in a CCU. In non-CCU patients, physicians with experience in PE showed similar results with empirical assessment^{16,17} and assessment with objective scoring systems.¹⁷⁻¹⁹

Partial Pressure of Oxygen in Arterial Blood and Alveolar-Arterial Oxygen Difference

The partial pressure of oxygen in arterial blood (P_aO_2), when low in patients with suspected acute PE, is a helpful adjunct in the diagnostic assessment.²⁰ However, patients with acute PE may have a normal P_aO_2 .^{4,20} A normal alveolar-arterial oxygen difference (alveolar-arterial oxygen gradient) also does not exclude acute PE.^{4,21} It was normal in 14% of patients with PE.⁴

Electrocardiogram

In patients with mild to massive PE, a normal electrocardiogram was shown in 30%.⁴ Atrial flutter or atrial fibrillation in patients with acute PE is infrequent in patients with no prior heart disease.²² Abnormalities of the ST segment and T wave are by the most frequent electrocardiographic manifestation of PE.^{4,22}

Electrocardiographic manifestations of acute cor pulmonale ($S_1Q_3T_3$, complete right bundle branch block, P pulmonale, or right axis deviation) occurred in 26% to 32% of patients with submassive or massive acute PE who did not have associated cardiac or pulmonary disease.²²

The problem of distinguishing the prominent Q waves known to occur with PE from those of myocardial infarction has been recognized for many years.²² The electrocardiogram may simulate infarction in any-region of the heart.²²

Leftward shifts of the frontal plane axis in PE are frequent in acute PE and were observed more frequently than a rightward shift.²³ Low voltage frontal plane QRS complexes may be a sign of acute PE²² although it is uncommon.

Chest Radiograph

Some of the nonspecific radiographic abnormalities combined with symptoms and ECG abnormalities may suggest that PE is present.⁴ The chest radiograph, in addition, is useful for the exclusion of conditions that mimic acute PE (pneumonia, pneumothorax, pleurisy) or to evaluate co-morbid or predisposing conditions (heart failure), as well as to aid in the diagnostic interpretation of some imaging tests (pulmonary scintigraphy).

Most patients with acute PE and no prior cardiopulmonary disease have an abnormal plain chest radiograph, although a normal chest radiograph was observed in 24%.²⁴ An elevated hemidiaphragm is readily observed, and occurs in 28% to 41% of patients with acute PE.^{4,24} An elevated hemidiaphragm, consolidation, pleural effusion, or atelectasis occurred in about two-thirds with acute PE.²⁴ A plural based density or costophrenic density suggest pulmonary infarction (Hampton's Hump). Among those with a pleural effusion, only blunting of the costophrenic angle was shown in 86% of patients with PE.⁴ No patients with PE and no prior cardiopulmonary disease had a pleural effusion that occupied more than one-third of a hemithorax.⁴

Either focal oligemia or distension of the proximal portion of the pulmonary artery or both (Westermark's sign) occurred more frequently among patients with massive PE than submassive PE (42% vs 26%).²⁴ Alveolar pulmonary edema may occur, but it is rare (1%) and interstitial edema is uncommon (3%).⁴

Cardiac Troponin

It has been thought for many years that some of the electrocardiographic changes in acute PE reflect myocardial ischemia.²⁵ Myocardial infarction has been shown at autopsy of patients who died of PE and had normal coronary arteries.²⁵ Coronary artery spasm does not occur in experimentally induced PE in animals. In fact, experimentally induced PE in dogs²⁶ and pigs²⁷ showed that both left and right coronary artery blood flow increased concordantly with increasing pulmonary artery pressure and decreasing P_aO_2 . This suggests that right ventricular strain in combination with hypoxemia may cause myocardial damage and release of chemical markers. In a CCU, if acute coronary syndrome is excluded, elevated chemical markers of ischemia may suggest acute PE.^{28,29} Pooled data among patients with PE and an elevated troponin I showed an in-hospital all cause mortality of 22% versus 6% among patients with a normal troponin I.³⁰ Among PE patients with an elevated troponin T, in-hospital all cause mortality was 17% vs. 3%³¹ among patients with a normal troponin T.

Myoglobin

Among 21 patients with PE who had right ventricular distention and an elevated myoglobin level, in-hospital all cause mortality was 33% versus no deaths among 25 such patients who had a normal myoglobin level.³²

Natriuretic Peptides

Elevations in brain natriuretic peptides (BNP)³³ and N-terminal-proBNP³⁴ are associated with right ventricular dysfunction in acute PE. Natriuretic peptide levels are also increased in patients with right ventricular pressure overload due to causes other than PE, including primary pulmonary hypertension, chronic thromboembolic hypertension, congenital heart disease, and chronic lung disease.³⁵ Brain natriuretic peptides in patients with PE, when low, predict a benign clinical outcome, with few in-hospital deaths from PE.³⁵

D-Dimer

A negative D-dimer test, measured by any method, in combination with a low probability clinical assessment, provides a reasonable certainty for excluding PE.³⁶ An intermediate clinical probability would also exclude PE with reasonable certainty if D-dimer were measured by rapid enzyme linked immunosorbent assay (ELISA)^{36,37} or, in the opinion of some, a quantitative latex agglutination test.³⁷ If clinical assessment is high probability, a negative D-dimer test does not exclude PE¹¹ and further diagnostic tests are indicated.

Unfortunately, hospitalized patients often have disorders that cause a positive D-dimer test³⁸, and D-dimer is particularly likely to be elevated in patients in the CCU. Exclusion of PE on the basis of a negative D-dimer and clinical assessment would be cost effective. The charge for a D-dimer is about 1% the charge (including physician fees) for a CT angiogram, 3% the charge for a ventilation-perfusion (V-Q) scan and about 4% the charge for a bilateral venous ultrasound.¹¹

D-dimer may be elevated in patients with unstable angina.³⁹ Some observed elevations of D-dimer in patients with myocardial infarction⁴⁰, although others observed elevations of D-dimer infrequently among conventionally treated patients.⁴¹ Congestive heart failure also causes elevations of D-dimer.⁴²

Role of CT Angiography and CT Venography

Contrast enhanced CT angiography has become the reference standard for diagnosis of acute PE^{13,14} and under most circumstances is the imaging test of choice. The combination of contrast-enhanced multidetector computed tomographic pulmonary angiography (CT angiography) and venous phase imaging of the low pelvic and proximal leg veins (CT venography) is recommended for patients in the CCU.⁴³ Even though the diagnostic yield of CT venous phase venography was small (1.3%) in patients with a negative 64-detector CT angiogram, the proportion of diagnoses of venous thromboembolism was 10.3%.⁴⁴

Based on data with mostly 4-slice CT, if PE was shown in a main or lobar pulmonary artery, the positive predictive value was 97%.⁴⁵ Since the rate of false positive diagnoses increases with decreasing vessel size, it is important to ascertain the radiologist's degree of certainty for a diagnosis of PE in segmental or subsegmental pulmonary artery branches. If the diagnosis is not unequivocal, further testing may be necessary. Positive CT angiographic findings may be relied upon if the clinical impression indicates a high probability for PE (96% had PE).⁴⁵ If the CT angiogram /CT venogram combination is negative in a patient with a high probability clinical assessment, the false negative rate is 18% and further evaluation is recommended by V-Q scan, serial ultrasound or conventional angiography.¹¹

If the clinical assessment indicates an intermediate probability of PE, most patients with a positive CT angiogram (92%) have PE and treatment is indicated.¹¹ If the apparent PE is only in a segmental or subsegmental branch, further testing is optional. A negative CT angiogram/

CT venogram combination excluded PE in 92% of patients with a moderate probability clinical assessment, and no treatment is necessary in such patients.¹¹

If clinical assessment indicates a low probability for PE, the CT angiogram can be considered diagnostic if the PE is shown in a main or lobar pulmonary artery, but if the apparent PE is in a segmental or subsegmental branch, the confidence in the CT diagnosis must be reassessed and further evaluation may be necessary.¹¹ If the CT angiogram/ CT venogram combination is negative in a patient with a low probability clinical assessment, PE was excluded in 97% of patients and treatment is not indicated.¹¹

Optional Pathways

A venous ultrasound prior to imaging with CT angiography or CT angiography/CT venography is optional and may guide treatment if positive. Venous ultrasound detected deep venous thrombosis in 15% of patients with suspected PE⁴⁶ and in 29% with proven PE⁴⁶ thereby allowing treatment with no further obligatory testing.

Patients with Allergy to Iodinated Contrast Material

With severe iodine allergy, pulmonary scintigraphy may be a useful alternative. A low probability V-Q lung scan combined with a low probability clinical assessment showed PE in only 4%.¹⁶ A high probability V-Q scan in a patient with a high probability clinical assessment showed PE in 96%.¹⁶ With other combinations, PE was present in 16%-88% and further evaluation is needed. Further evaluation may include serial venous ultrasound.¹¹

Patients with Impaired Renal Function

For patients with impaired renal function, venous ultrasound is recommended and if positive, treatment is indicated. Pulmonary scintigraphy is recommended if venous ultrasound is negative. Serial venous ultrasound is an option if scintigraphy is equivocal.

Digital Subtraction Pulmonary Angiography

Conventional pulmonary angiography is rarely considered necessary now a days, but continues to have the advantage of a radiologist being with the patient during the entire procedure to assess the need for additional injections and/or views or superselective injections when initial results are nondiagnostic.

Ventilation-Perfusion Lung Scans

Among patients who suffered loss of consciousness on the day of study entry, the V-Q lung scan was interpreted as high probability for PE in 4 of 5 (80%)¹⁰ Although this is a small number of patients, it is clear that the lung scan may not show a high probability interpretation in patients with severe PE. Most patients on ventilatory support, 41 of 46 (89%) showed nondiagnostic (intermediate or low probability) V-Q scans.⁴⁷

Scintigraphy in patients with a normal or nearly normal chest radiograph may be the imaging test of choice in women under 50 years of age because of the risk of radiation with CT angiography, particularly radiation of the breasts. Breast radiation with V-Q scintigraphy is approximately 0.28–0.9 mGy⁴⁸, which is not more than 0.5% to 5% the radiation dose to the breasts resulting from CT angiography.¹⁵ Although in PIOPED, V-Q scans gave a definitive diagnosis in only 28% of patients¹⁶, in a more recent investigation, 46% had a definitive diagnosis by V-Q scan.⁴⁹ Retrospective analysis of data from PIOPED II (75% outpatients) showed a definitive V-Q scan in 74% of patients.⁵⁰ If the chest radiograph was normal or nearly

normal, a definitive reading of the V-Q scan was shown in 91%⁵¹ of patients. A very low probability interpretation of the V-Q scan is as reliable as CT angiography in excluding PE when the clinical probability is low or moderate.⁵²

A normal perfusion lung scan excludes PE with a negative predictive value close to 100%.¹⁶ The ventilation scan can be eliminated when perfusion scan is normal in most patients without reducing diagnostic accuracy.⁵³ It is arguable that the benefits of more comprehensive imaging with CT angiography would outweigh the smaller risks of radiation in an older population, and in men of all ages.

Echocardiography

Right ventricular distention on the echocardiogram may suggest acute PE if unexplained by other findings. Right ventricular dysfunction in a patient with PE and normal systolic blood pressure has been classified as “impending hemodynamic instability”.⁵⁴ In-hospital prognosis is good, however, in patients with PE and right ventricular enlargement (based on data from CT angiography) if not in shock, acutely ill, on ventilatory support, or having had recent myocardial infarction or life threatening arrhythmia.⁵⁵ Right ventricular enlargement alone in patients with PE, therefore, does not appear to indicate a poor prognosis or an indication for thrombolytic therapy.

Transesophageal echocardiography (TEE) may be useful in patients with suspected massive PE who require immediate and aggressive therapy.⁵⁶ Because of the high prevalence of bilateral central thromboemboli in such patients, TEE allowed a definitive diagnosis in 92%.⁵⁶ Other than in patients with massive PE, TEE had limited accuracy in comparison to CT.⁵⁷

Role of Magnetic Resonance Angiography

Investigations in a few patients showed sensitivity for the detection of PE with gadolinium enhanced magnetic resonance angiography of 77% to 100% and specificity of 95% to 98%.⁵⁸ There is concern about nephrogenic systemic fibrosis/ nephrogenic fibrosing dermopathy (NSF/NFD), which occurs rarely in patients with poor renal function who receive gadolinium-containing contrast material (215 patients reported world-wide).⁵⁹ Among the reports that included information about renal status, all patients had acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²), renal dysfunction due to the hepato-renal syndrome or renal dysfunction in the perioperative liver transplantation period.⁶⁰ The vast majority of patients were receiving hemodialysis.⁶⁰ To date, there has not been a report of NSF/NFD in a patient with normal renal function or mild to moderate renal insufficiency following exposure to gadolinium-containing contrast agents.⁶⁰ The length of magnetic resonance angiographic examinations, the difficulties with close monitoring, and the need for nonmagnetic support equipment make this modality of limited use for the CCU patient.

Recommendations for Patients in Extremis

Echocardiography with leg ultrasonography are recommended as rapidly obtainable bedside tests.¹¹ Right ventricular enlargement or poor right ventricular function, in a proper clinical setting, can be interpreted as resulting from PE.¹¹ A positive venous ultrasound in the appropriate clinical setting also indicates PE.¹¹ If both the echocardiogram and compression ultrasound are negative, appropriate imaging studies should be performed when the patient stabilizes.¹¹ A portable perfusion scan may give diagnostic information at the bedside. Some recommend immediate transfer to an interventional catheterization laboratory.

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References

1. Pulido T, Aranda A, Zevallos MA, Bautista E, Martínez-Guerra ML, Santos LE, Sandoval J. Pulmonary embolism as a cause of death in patients with heart failure. An autopsy study. *Chest* 2006;129:1282–1287. [PubMed: 16685020]
2. Darze ES, Latado AL, Guimarães AG, Guedes RA, Santos AB, de Moura SS, Passos LC. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. *Chest* 2005;128:2576–2580. [PubMed: 16236926]
3. Goldhaber SZ. Diagnosis of acute pulmonary embolism: always be vigilant. *Am J Med* 2007;120:827–828. [PubMed: 17904448]
4. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, Weg JG. Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest* 1991;100:598–603. [PubMed: 1909617]
5. Beemath A, Stein PD, Skaf E, Al Sibae MR, Alesh I. Risk of venous thromboembolism in patients hospitalized with heart failure. *Am J Cardiol* 2006;98:793–795. [PubMed: 16950187]
6. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol* 2001;54:810–8166. [PubMed: 11470390]
7. Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, Hull RD, Leeper KV Jr, Sostman HD, Tapson VF, Buckley JD, Gottschalk A, Goodman LR, Wakefield TW, Woodard PK. Clinical characteristics of patients with acute pulmonary embolism: Data from PIOPED II. *Am J Med* 2007;120:871–879. [PubMed: 17904458]
8. Stein PD, Afzal A, Henry JW, Villarreal C. Fever in acute pulmonary embolism. *Chest* 2000;117:39–42. [PubMed: 10631196]
9. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol* 1991;68:1723–1724. [PubMed: 1746481]
10. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest* 1997;112:974–979. [PubMed: 9377961]
11. Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, Sos TA, Quinn DA, Leeper KV Jr, Hull RD, Hales CA, Gottschalk A, Goodman LR, Fowler SE, Buckley JD. PIOPED II investigators. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. *Am J Med* 2006;119:1048–1055. [PubMed: 17145249]
12. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003;58:470–484. [PubMed: 12775856]
13. Remy-Jardin M, Pistolesi M, Goodman LR, Gefter WB, Gottschalk A, Mayo JR, Sostman HD. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement of the Fleischner Society. *Radiology* 2007;245:315–329. [PubMed: 17848685]
14. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Andreotti F, Ascherman M, Athanassopoulos G, De Sutter J, Fitzmaurice D, Forster T, Heras M, Jondeau G, Kjeldsen K, Knuuti J, Lang I, Lenzen M, Lopez-Sendon J, Nihoyannopoulos P, Perez Isla L, Schwehr U, Torracca L, Vachiery JL. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of

the European Society of Cardiology (ESC). Guidelines on the diagnosis and management of acute pulmonary embolism. *Euro Heart J* 2008;29:2276–2315.

15. Stein PD, Sostman HD, Bounameaux H, Buller HR, Chenevert TL, Dalen JE, Goodman LR, Gottschalk A, Hull RD, Leeper KV Jr, Pistoletti M, Raskob GE, Wells PS, Woodard PK. Challenges in the diagnosis of acute pulmonary embolism. *Am J Med* 2008;121:565–571. [PubMed: 18589050]
16. PIOPED Investigators. Value of the ventilation-perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753–2759. [PubMed: 2332918]
17. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward. A simple score. *Arch Intern Med* 2001;161:92–97. [PubMed: 11146703]
18. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs MJ. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001;135:98–107. [PubMed: 11453709]
19. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006;144:165–171. [PubMed: 16461960]
20. Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest* 1996;109:78–81. [PubMed: 8549223]
21. Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Chest* 1995;107:139–143. [PubMed: 7632205]
22. Stein PD, Dalen JE, McIntyre KM, Sasahara AA, Wenger NK, Willis PW 3rd. The electrocardiogram in acute pulmonary embolism. *Progress in Cardiovascular Diseases* 1975;17:247–257. [PubMed: 123074]
23. Lynch RE, Stein PD, Bruce TA. Leftward shift of frontal plane QRS axis as a frequent manifestation of acute pulmonary embolism. *Chest* 1972;61:443–446. [PubMed: 5046842]
24. Stein PD, Willis PW III, DeMets DL, Greenspan RH. Plain chest roentgenogram in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Am J Noninvas Cardiol* 1987;1:171–176.
25. Weber DM, Phillips JH Jr. A re-evaluation of electrocardiographic changes accompanying acute pulmonary embolism. *Am J Med Sci* 1966;251:381–398. [PubMed: 5910224]
26. Stein PD, Alshabkhoun S, Hatem C, Pur-Shahriari AA, Haynes FW, Harken DW, Dexter L. Coronary artery blood flow in acute pulmonary embolism. *Am J Cardiol* 1968;21:32–37. [PubMed: 5634740]
27. Stein PD, Alshabkhoun S, Hawkins HF, Hyland JW, Jarrett CE. Right coronary blood flow in acute pulmonary embolism. *Am Heart J* 1969;77:356–362. [PubMed: 5766721]
28. Tapson VF. Diagnosing and managing acute pulmonary embolism: role of cardiac troponins. *Am Heart J* 2003;145:751–753. [PubMed: 12766729]
29. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. *Arch Intern Med* 2002;162:79–81. [PubMed: 11784223]
30. Stein, PD. *Pulmonary Embolism*. Vol. 2. Blackwell Futura; Oxford: 2007. p. 25p. 221
31. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jäckle S, Binder L. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation* 2002;106:1263–1268. [PubMed: 12208803]
32. Pruszczyk P, Bochowicz A, Kostrubiec M, Torbicki A, Szulc M, Gurba H, Kuczyńska K, Berent H. Myoglobin stratifies short-term risk in acute major pulmonary embolism. *Clin Chim Acta* 2003;338:53–56. [PubMed: 14637265]
33. Tulevski II, Hirsch A, Sanson BJ, Romkes H, van der Wall EE, van Veldhuisen DJ, Büller HR, Mulder BJ. Increased brain natriuretic peptide as a marker for right ventricular dysfunction in acute pulmonary embolism. *Thromb Haemost* 2001;86:1193–1196. [PubMed: 11816706]
34. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation* 2003;107:1576–1578. [PubMed: 12668488]

35. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. *Circulation* 2003;108:2191–2194. [PubMed: 14597581]
36. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V, Kalra NK. D-dimer for the exclusion of deep venous thrombosis and acute pulmonary embolism: a systematic review. *Ann Intern Med* 2004;140:589–602. [PubMed: 15096330]
37. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost* 2007;5:296–304. [PubMed: 17155963]
38. Schrecengost JE, LeGallo RD, Boyd JC, Moons KG, Gonias SL, Rose CE Jr, Bruns DE. Comparison of diagnostic accuracies in outpatients and hospitalized patients of d-dimer testing for the evaluation of suspected pulmonary embolism. *Clin Chem* 2003;49:1483–1490. [PubMed: 12928229]
39. Shitrit D, Bar-Gil Shitrit A, Rudensky B, Sulkes J, Tzivony D. Determinants of ELISA D-dimer sensitivity for unstable angina pectoris as defined by coronary catheterization. *Am J Hematol* 2004;76:121–125. [PubMed: 15164376]
40. Lippi G, Filippozzi L, Montagnana M, Salvagno GL, Guidi GC. Diagnostic value of D-dimer measurement in patients referred to the emergency department with suspected myocardial ischemia. *J Thromb Thrombolysis* 2008;25:247–250. [PubMed: 17541763]
41. Lew AS, Berberian L, Cercek B, Lee S, Shah PK, Ganz W. Elevated serum D dimer: a degradation product of cross-linked fibrin (XDP) after intravenous streptokinase during acute myocardial infarction. *J Am Coll Cardiol* 1986;7:1320–1324. [PubMed: 3711489]
42. Cugno M, Mari D, Meroni PL, Gronda E, Vicari F, Frigerio M, Coppola R, Bottasso B, Borghi MO, Gregorini L. Haemostatic and inflammatory biomarkers in advanced chronic heart failure: role of oral anticoagulants and successful heart transplantation. *Br J Haematol* 2004;126:85–92. [PubMed: 15198737]
43. Goodman LR, Sostman HD, Stein PD. CT venography: a necessary adjunct to CT pulmonary angiography or a waste of time, money, and radiation? *Radiology* 2009;250:327–330. [PubMed: 19188309]
44. Stein PD, Matta F, Yaekoub AY, Kazerooni EA, Cahill JE, Goodman LR, Sostman HD, Hales CA, Denier JE, Weg JG, Ghumman D, Chan KM, Woodard PK. CT venous phase venography with 64-slice CT angiography in the diagnosis of acute pulmonary embolism. *Clin Appl Thromb Hemost*. In press
45. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, Leeper KV Jr, Popovich J Jr, Quinn DA, Sos TA, Sostman HD, Tapson VF, Wakefield TW, Weg JG, Woodard PK. PIONEER II Investigators. Multidetector computed tomography for acute pulmonary embolism. *N Eng J Med* 2006;354:2317–2327.
46. Turkstra F, Kuijter PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997;126:775–781. [PubMed: 9148650]
47. Henry JW, Stein PD, Gottschalk A, Relyea B, Leeper KV Jr. Scintigraphic lung scans and clinical assessment in critically ill patients with suspected acute pulmonary embolism. *Chest* 1996;109:462–466. [PubMed: 8620723]
48. Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). *Ann ICRP* 1998;28:1–126.
49. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, Lang E, Stiell I, Kovacs G, Dreyer J, Dennie C, Cartier Y, Barnes D, Burton E, Pleasance S, Skedgel C, O'Rourke K, Wells PS. Computerized tomographic pulmonary angiography versus ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *J Am Med Assoc* 2007;298:2743–2753.
50. Sostman HD, Stein PD, Gottschalk A, Matta F, Hull R, Goodman L. Sensitivity and specificity of ventilation–perfusion scintigraphy for acute pulmonary embolism in PIONEER II. *Radiology* 2008;246:941–946. [PubMed: 18195380]
51. Forbes KP, Reid JH, Murchison JT. Do preliminary chest X-ray findings define the optimum role of pulmonary scintigraphy in suspected pulmonary embolism? *Clin Radiol* 2001;56:397–400. [PubMed: 11384139]

52. Gottschalk A, Stein PD, Sostman HD, Matta F, Beemath A. Very low probability interpretation of ventilation-perfusion lung scans in combination with low probability clinical assessment reliably excludes pulmonary embolism: Data from PIOPED II. *J Nucl Med* 2007;48:1411–1415. [PubMed: 17785726]
53. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, Allesscia G, Tonelli L, Sostman HD, Giuntini C. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). *Am J Respir Crit Care Med* 1996;154:1387–1393. [PubMed: 8912753]
54. Cannon CP, Goldhaber SZ. Cardiovascular risk stratification of pulmonary embolism. *Am J Cardiol* 1996;78:1149–1151. [PubMed: 8914880]
55. Stein PD, Beemath A, Matta F, Goodman LR, Weg JG, Hales CA, Hull RD, Leeper KV Jr, Sostman HD, Woodard PK. Enlarged right ventricle without shock in acute pulmonary embolism: prognosis. *Am J Med* 2008;121:34–42. [PubMed: 18187071]
56. Krivec B, Voga G, Zuran I, Skale R, Pareznik R, Podbregar M, Noc M. Diagnosis and treatment of shock due to massive pulmonary embolism: approach with transesophageal echocardiography and intrapulmonary thrombolysis. *Chest* 1997;112:1310–1316. [PubMed: 9367474]
57. Steiner P, Lund GK, Debatin JF, Steiner D, Nienaber C, Nicolas V, Bücheler E. Acute pulmonary embolism: value of transthoracic and transesophageal echocardiography in comparison with helical CT. *AJR Am J Roentgenol* 1996;167:931–936. [PubMed: 8819386]
58. Stein PD, Woodard PK, Hull RD, Kayali F, Weg JG, Olson RE, Fowler SE. Gadolinium enhanced magnetic resonance angiography for detection of acute pulmonary embolism: and in depth review. *Chest* 2003;124:2324–2328. [PubMed: 14665516]
59. Public Health Advisory. Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy. [November 4, 2008]. www.fda.gov/cder/drug/advisory/gadolinium_agents_20061222.htm
60. Information for Healthcare Professionals Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance). [November 4, 2008]. www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705.htm. Date created: May 23, 2007, updated June 4, 2008

ABBREVIATIONS

BNP	brain natriuretic peptides
CCU	coronary care unit
CT	computed tomography
DVT	deep venous thrombosis
NSF/NFD	nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy
P_aO₂	partial pressure of oxygen in arterial blood
PE	pulmonary embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis

TEE

transesophageal echocardiography