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CLINICAL RESEARCH STUDY

Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II

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ABSTRACT

BACKGROUND: Selection of patients for diagnostic tests for acute pulmonary embolism requires recognition of the possibility of pulmonary embolism on the basis of the clinical characteristics. Patients in the Prospective Investigation of Pulmonary Embolism Diagnosis II had a broad spectrum of severity, which permits an evaluation of the subtle characteristics of mild pulmonary embolism and the characteristics of severe pulmonary embolism.

METHODS: Data are from the national collaborative study, Prospective Investigation of Pulmonary Embolism Diagnosis II.

RESULTS: There may be dyspnea only on exertion. The onset of dyspnea is usually, but not always, rapid. Orthopnea may occur. In patients with pulmonary embolism in the main or lobar pulmonary arteries, dyspnea or tachypnea occurred in 92%, but the largest pulmonary embolism was in the segmental pulmonary arteries in only 65%. In general, signs and symptoms were similar in elderly and younger patients, but dyspnea or tachypnea was less frequent in elderly patients with no previous cardiopulmonary disease. Dyspnea may be absent even in patients with circulatory collapse. Patients with a low-probability objective clinical assessment sometimes had pulmonary embolism, even in proximal vessels.

CONCLUSION: Symptoms may be mild, and generally recognized symptoms may be absent, particularly in patients with pulmonary embolism only in the segmental pulmonary branches, but they may be absent even with severe pulmonary embolism. A high or intermediate-probability objective clinical assessment suggests the need for diagnostic studies, but a low-probability objective clinical assessment does not exclude the diagnosis. Maintenance of a high level of suspicion is critical. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Clinical diagnosis; Deep venous thrombosis; Pulmonary embolism; Venous thromboembolism

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Acute pulmonary embolism in patients with severe or fatal pulmonary embolism at autopsy is generally unrecognized antemortem.[1-4] Advances in the diagnostic methods for acute pulmonary embolism should affect this high rate of underdiagnosis.[5-8] However, the successful use of diagnostic pathways requires recognition of patients with possible acute pulmonary embolism on the basis of the clinical characteristics.

The clinical characteristics of patients with acute pulmonary embolism in the first Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), an accuracy study of ventilation-perfusion scintigraphy, were described in all enrolled patients,[9] patients with no previous cardiopulmonary disease,[10] patients grouped according to the presenting syndromes of pulmonary embolism,[11] and the elderly.[12] One of the strengths of the data from PIOPED II is that many patients with mild pulmonary embolism were included, which permits the identification of subtle clinical characteristics. However, the clinical characteristics of patients with pulmonary embolism in PIOPED,[9-12] as in PIOPED II and other investigations of patients enrolled in clinical trials,[13,14] were sufficient to alert attuned physicians to the diagnosis and characteristics of patients who met the inclusion criteria. Patients who were too ill to participate, who died suddenly, or who were not identified because the clinical findings were mild or atypical were not included. With these constraints in mind, we describe the clinical characteristics of patients enrolled in PIOPED II.

CLINICAL SIGNIFICANCE

- In patients with pulmonary embolism only in the segmental pulmonary branches, generally recognized symptoms may be mild or absent, leading to underdiagnosis.
- Absence of symptoms is most common in patients with pulmonary embolism only in the segmental pulmonary branches, but this also occurs in patients with proximal pulmonary embolism.
- A low-probability objective clinical assessment does not exclude pulmonary embolism, even in the proximal pulmonary arteries.

PATIENTS AND METHODS

PIOPED II was a prospective multicenter investigation of multidetector computed-tomography angiography alone and combined with venous phase imaging of the pelvic and thigh veins for the diagnosis of acute pulmonary embolism.[5] A composite reference test was used.[5] Patients aged 18 years or more with clinically suspected acute pulmonary embolism were potentially eligible.[5] Exclusion criteria included an inability to complete tests within 36 hours, critical illness, ventilatory support, shock, recent myocardial infarction, abnormal serum creatinine, allergy to contrast material, pregnancy, treatment with long-term anticoagulants, inferior vena cava filter, and deep venous thrombosis of the upper extremity.

To avoid confusing clinical findings of pulmonary embolism with comorbid conditions, we evaluated patients with no prior cardiopulmonary disease in addition to evaluating all patients. No prior cardiopulmonary disease was defined as no current asthma, pneumonia, history of chronic bronchitis, emphysema, chronic obstructive pulmonary disease, current or history of right or left-sided heart failure, lung cancer, or prior pulmonary embolism.

The circulatory collapse syndrome was defined as loss of consciousness or systolic blood pressure of 80 mm Hg or less. The hemoptysis/pleuritic pain syndrome (previously termed the pulmonary infarction syndrome)[13] was defined as patients with either hemoptysis or pleuritic pain in the absence of circulatory collapse. The uncomplicated dyspnea syndrome was defined as dyspnea in the absence of hemoptysis, pleuritic pain, or circulatory collapse.

Measurements of arterial blood gases were obtained while the patient was breathing room air. The alveolar-arterial (A-a) oxygen difference was calculated as follows:[15]

$$\text{A-a oxygen difference (mm Hg)} = 150 - 1.25\,P_{ACO_2} - P_{aO_2}$$

where P_{ACO_2} = partial pressure of carbon dioxide in arterial blood (mm Hg), and P_{aO_2} = partial pressure of oxygen in arterial blood (mm Hg).

Statistical Methods

The chi-square test was used to compare the prevalence of clinical features in patients with and without pulmonary embolism. Because of the large number of comparisons, *P* values are underestimates. Comparisons of continuous variable means were made with the 2-tailed Student unpaired *t* test.

RESULTS

Acute pulmonary embolism was present in 192 patients, among whom 133 (69%) had no prior cardiopulmonary disease. Pulmonary embolism was excluded in 632 patients, among whom 366 (58%) had no prior cardiopulmonary disease.

Syndromes of Pulmonary Embolism

The syndrome of hemoptysis or pleuritic pain occurred in 41% of patients with no prior cardiopulmonary disease and in 44% of all patients with pulmonary embolism (Table 1). The uncomplicated dyspnea syndrome occurred in 36% of patients with no prior cardiopulmonary disease and in 36% of all patients with pulmonary embolism. The circulatory collapse syndrome was uncommon: 8% in patients with no prior cardiopulmonary disease and 8% in all enrolled patients with acute pulmonary embolism. The presentations of 19 patients (14%) with pulmonary embolism and no prior cardiopulmonary disease differed from these syndromes. The presenting findings in some of these patients were

Table 1 Syndromes of Acute Pulmonary Embolism

	PE No Prior CPD N = 133 n (%)	No PE No Prior CPD N = 366 n (%)	PE All Patients N = 192 n (%)	No PE All Patients N = 632 n (%)
Hemoptysis or pleuritic pain	55 (41)	196 (54)‡	84 (44)	357 (56)§
Uncomplicated dyspnea	48 (36)	93 (25)‡	70 (36)	163 (26)§
Circulatory collapse	11 (8)	21 (6)	15 (8)	33 (5)
Different presentation	19 (14)*	56 (15)	23 (12)†	79 (13)

CPD = cardiopulmonary disease; PE = pulmonary embolism.
*Tachypnea or tachycardia and signs or symptoms of DVT in 3; $Pa_{O2} < 80$ mm Hg and signs or symptoms of DVT in 1.
†Tachypnea or tachycardia and signs or symptoms of DVT in 8; $Pa_{O2} < 80$ mm Hg and signs or symptoms of DVT in 1.
‡$P < .025$.
§$P < .01$.

tachypnea, tachycardia, or a Pa_{O_2} less than 80 mm Hg with signs or symptoms of deep venous thrombosis (Table 1).

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

The partial pressure of oxygen in arterial blood (Pa_{O_2}) while breathing room air was measured in 74 patients with pulmonary embolism and in 48 patients with pulmonary embolism and no prior cardiopulmonary disease (Table 2). The Pa_{O_2} while breathing room air was 80 mm Hg or more in 32% of all patients with pulmonary embolism and 80 mm Hg or more in 38% of patients with no prior cardiopulmonary disease. The A-a oxygen difference was 20 mm Hg or less in 32% of all patients with pulmonary embolism and in 35% of patients with pulmonary embolism and no prior cardiopulmonary disease (Table 2).

Risk Factors for Pulmonary Embolism

Immobilization (bed rest within past month for the most of the day for ≥ 3 consecutive days) was the most frequent risk

Table 2 Arterial Blood Gases and Alveolar-Arterial Oxygen Difference While Breathing Room Air

	PE No Prior CPD N = 48 n (%)	No PE No Prior CPD N = 88 n (%)	PE All Patients N = 74 n (%)	No PE All Patients N = 186 n (%)
Pa_{O_2} (mm Hg)				
≤49	1 (2)	2 (2)	4 (5)	17 (9)
50-59	6 (13)	12 (14)	12 (16)	32 (17)
60-69	15 (31)	14 (16)*	20 (27)	35 (19)
70-79	8 (17)	13 (15)	14 (19)	32 (17)
≥80	18 (38)	47 (53)	24 (32)	70 (38)
Pa_{CO_2} (mm Hg)				
≤35	30 (63)	39 (44)*	42 (57)	65 (35)‡
36-39	12 (25)	17 (19)	18 (24)	39 (21)
≥40	6 (13)	32 (36)	14 (19)	82 (44)§
pH (units)				
<7.35	0 (0)	7 (8)*	0 (0)	13 (7)†
7.35-7.45	29 (60)	60 (68)	41 (55)	131 (70)†
>7.45	19 (40)	21 (24)	33 (45)	42 (23)§
A-a O_2 difference (mm Hg)				
≤20	17 (35)	44 (50)	24 (32)	70 (38)
21-30	4 (8)	10 (11)	5 (7)	32 (17)*
31-40	11 (23)	13 (15)	18 (24)	30 (16)
41-50	9 (19)	13 (15)	14 (19)	32 (17)
51-60	5 (10)	6 (7)	10 (14)	17 (9)
≥61	2 (4)	2 (2)	3 (4)	5 (3)

CPD = cardiopulmonary disease; PE = pulmonary embolism.
*$P < .05$.
†$P < .025$.
‡$P < .01$.
§$P < .001$.

Table 3 Risk Factors

	PE No Prior CPD N = 131-133 n (%)	No PE No Prior CPD N = 361-366 n (%)	PE All Patients N = 185-192 n (%)	No PE All Patients N = 588-632 n (%)
Age	56 ± 16	47 ± 16‖	57 ± 17	50 ± 17‖
Sex (female)	82 (62)	225 (61)	112 (58)	394 (62)
Immobilization*	27 (20)	60 (16)	48 (25)	121 (19)
Travel ≥ 4 h in last month	19 (14)	74 (20)	23 (12)	105 (17)
Surgery (≤3 mo)	30 (23)‡	53 (14)**	41 (21)§	83 (13)¶
Malignancy (excluding lung cancer)†	29 (22)	44 (12)#	37 (19)	82 (13)**
Thrombophlebitis, ever	11 (8)	10 (3)#	19 (10)	27 (4)#
Trauma (≤3 mo) Lower extremities and pelvis	14 (11)	27 (7)	16 (8)	49 (8)
Other	4 (3)	14 (4)	5 (3)	21 (3)
Smoke (ever)	55 (42)	156 (43)	90 (47)	321 (51)
<1 pack/d	29 (22)	74 (20)	43 (22)	122 (19)
1-2 packs/d	20 (15)	62 (17)	37 (19)	152 (24
>2 packs/d	0 (0)	5 (1)	1 (1)	19 (3)
Central venous instrumentation (≤3 mo)	12 (9)	17 (5)	22 (12)	35 (6)#
Stroke, paresis, or paralysis	4 (3)	10 (3)	7 (4)	17 (3)
Prior pulmonary embolism	–	–	7 (4)	19 (3)
Heart failure	–	–	10 (5)	60 (10)
COPD	–	–	10 (5)	58 (9)
Lung cancer	–	–	5 (3)	8 (1)

CPD = cardiopulmonary disease; PE = pulmonary embolism; COPD = chronic obstructive pulmonary disease.
*Bed rest within past month for the most of the day for ≥3 consecutive days.
†Actively treated in last 3 months.
‡Among patients with PE and no prior CPD who had surgery as a risk factor (n = 30), the prevalence of heart, abdominal, pelvic, hip/knee-open, hip/knee-replacement, and neurosurgery ranged from 3 to 5.
§Among all patients with PE who had surgery as a risk factor (n = 41), 9 had abdominal surgery and heart, pelvic, hip/knee-open, hip/knee-replacement, and neurosurgery ranged from 3 to 5.
‖$P < .0001$.
¶$P < .001$.
#$P < .01$.
**$P < .05$.

factor assessed in patients with pulmonary embolism, and surgery was the usual cause of immobilization (Table 3). One or more of the assessed risk factors were reported in 92% of patients with pulmonary embolism and no prior cardiopulmonary disease. Among all patients with pulmonary embolism, 94% had 1 or more of the assessed risk factors.

Symptoms of Pulmonary Embolism

New dyspnea at rest or on exertion was the most frequent symptom in patients with pulmonary embolism and no prior cardiopulmonary disease (73%) (Table 4). Dyspnea only on exertion was observed in 16% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 16% of all patients with pulmonary embolism (Table 4). Two-pillow orthopnea was often present (Table 4). Orthopnea occurred in 37 of 97 patients (38%) with dyspnea who had pulmonary embolism and no prior cardiopulmonary disease and in 11 of 21 patients (52%) with dyspnea only on exertion.

The onset of dyspnea was rapid (within seconds or minutes) in 72% of patients with pulmonary embolism and no prior cardiopulmonary disease, and in 67% of all patients with pulmonary embolism (Table 5). The onset was within seconds, minutes, or hours in 83% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 87% of all patients with pulmonary embolism. In some, however, the onset of dyspnea occurred over days.

Pleuritic chest pain was more frequent than hemoptysis (Table 4). Cough, when present, was usually nonproductive, but purulent sputum and clear sputum also were reported. Hemoptysis may have been pinkish, blood streaked, or all blood. Hemoptysis of pure blood occurred in only 1 patient with pulmonary embolism and no prior cardiopulmonary disease, and it was less than 1 teaspoonful. Thigh pain and swelling were rarely described in the absence of calf pain or swelling.

Signs of Pulmonary Embolism

Tachypnea was present in approximately one half of the patients with pulmonary embolism (Table 6). Tachycardia was present in approximately one fourth. Clinical evidence of pulmonary hypertension (accentuated pulmonary component of the second sound), right ventricular pressure overload or enlargement (right ventricular lift), or elevated right atrial pressure (jugular venous distension) was shown in

Table 4 Symptoms of Pulmonary Embolism

	PE No Prior CPD N = 127-133 n (%)	No PE No Prior CPD N = 361-366 n (%)	PE All Patients N = 184-191 n (%)	No PE All Patients N = 622-632 n (%)
Dyspnea				
Dyspnea (rest or exertion)	97 (73)	248 (68)	151 (79)	459 (73)
Dyspnea (at rest)#	73 (55)	167 (46)	117 (61)	338 (54)
Dyspnea (exertion only)#	21 (16)	73 (20)	31 (16)	111 (18)
Orthopnea (≥2-pillow)	37 (28)	88 (24)	69 (36)	220 (35)
Pleuritic pain	58 (44)	207 (57)^	89 (47)	376 (59)^
Chest pain (not pleuritic)	25 (19)	80 (22)	33 (17)	130 (21)
Cough	45 (34)*	103 (28)**	82 (43)†	248 (39)††
Wheezing	27 (21)	66 (18)	58 (31)	193 (31)
Calf or thigh swelling	52 (41)	62 (17)^^	72 (39)	126 (20)^^
Calf and thigh swelling	9 (7)	14 (4)	15 (8)	35 (6)
Calf or thigh pain	56 (44)	83 (23)^^	78 (42)	156 (25)^^^
Calf and thigh pain	22 (17)	24 (7)^^	30 (16)	61 (10)^^^

CPD = cardiopulmonary disease; PE = pulmonary embolism.

*Hemoptysis, PE, no CPD: 2 = slightly pinkish, 4 = blood-streaked, 1 = all blood (<1 tsp).

**Hemoptysis, no PE, no CPD: 1 = slightly pink, 2 = streaked, 7 = all blood (1 patient, too little to quantify; 1 patient, <1 tsp; 4 patients, 1 tsp to ½ cup; 1 patient, >½ cup).

†Hemoptysis, PE, all patients: 3 = slightly pinkish, 6 = blood-streaked, 2 = all blood (<1 tsp).

††Hemoptysis, No PE, all patients: 7 = slightly pinkish, 9 = blood streaked, 9 = all blood (1 patient, too little to quantify; 3 patients, <1 tsp; 4 patients, 1 tsp to ½ cup; 1 patient, >½ cup).

#Information not available in some.

^$P < .01$.

^^$P < .001$.

^^^$P < .025$.

21% of patients with no prior cardiopulmonary disease and in 22% of all patients with pulmonary embolism. Lung examination was abnormal in 29% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 37% of all patients with pulmonary embolism. Crackles and decreased breath sounds were the most frequent lung findings. Rhonchi and wheezes occurred uncommonly. Signs of deep venous thrombosis (edema, erythema, tenderness, or palpable cord) in the thigh, in the absence of deep venous thrombosis in the calf, were rare (Table 6). Among all patients with pulmonary embolism, calf swelling plus pain with palpation of the deep veins occurred in 32%.

Combinations of Signs and Symptoms

Either dyspnea or tachypnea was present in 84% of patients with pulmonary embolism and no prior cardiopulmonary disease, and in 86% of all patients with pulmonary embolism. Dyspnea, tachypnea, or pleuritic pain was present in 92% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 92% of all patients with pulmonary embolism. One or more of these signs and symptoms or signs of deep venous thrombosis were present in 98% of patients with pulmonary embolism and no prior cardiopulmonary disease, and in 97% of all patients with pulmonary embolism.

Table 5 Rate of Onset of Dyspnea

	Patients with Dyspnea and PE No Prior CPD N = 92 n (%)	Patients with Dyspnea and No PE No Prior CPD N = 242 n (%)	All Patients with Dyspnea and PE N = 143 n (%)	All Patients with Dyspnea and No PE N = 450 n (%)
Seconds	42 (46)	109 (45)	59 (41)	206 (46)
Minutes	24 (26)	69 (29)	37 (26)	117 (26)
Hours	10 (11)	35 (14)	20 (14)	70 (16)
Days	16 (17)	29 (12)	27 (19)	57 (13)

CPD = cardiopulmonary disease; DVT = deep vein thrombosis; PE = pulmonary embolism.

All differences not significant.

Table 6 Signs of Pulmonary Embolism

	PE No Prior CPD N = 128-132 n (%)	No PE No Prior CPD N = 350-365 n (%)	PE All Patients N = 184-191 n (%)	No PE All Patients N = 602-629 n (%)
General				
Tachypnea (≥20/min)	71 (54)	155 (43)#	108 (57)	296 (47)§
Tachycardia (>100/min)	32 (24)	52 (14)§	49 (26)	98 (16)§
Diaphoresis	3 (2)	27 (7)**	8 (4)	40 (6)
Cyanosis	0 (0)	1 (0.003)	1 (1)	1 (0)
Temperature > 38.5°C (>101.3°F)	1 (1)	12 (3)	3 (2)	14 (2)
Cardiac examination (abnormal)	28 (21)	39 (11)§	42 (22)	72 (12)‖
Increased P2†	15 (15)	14 (5)¶	22 (15)	27 (5)‖
Right ventricular lift‡	4 (4)	6 (2)	8 (5)	9 (2)#
Jugular venous distension	18 (14)	27 (8)**	25 (13)	50 (8)**
Lung examination (abnormal)	38 (29)	94 (26)	70 (37)	227 (36)
Rales (crackles)	23 (18)	52 (14)	40 (21)	112 (18)
Wheezes	2 (2)	12 (3)	6 (3)	54 (9)#
Rhonchi	2 (2)	8 (2)	9 (5)	32 (5)
Decreased breath sounds	22 (17)	42 (12)	40 (21)	109 (17)
Pleural friction rub	0 (0)	3 (1)	2/ (1)	5 (1)
DVT signs††				
Calf or thigh	62 (47)*	77 (21)‖	90 (47)	146 (23)‖
Calf and thigh	18 (14)	16 (4)‖	23 (12)	30 (5)‖

CPD = cardiopulmonary disease; PE = pulmonary embolism; P2 = pulmonary component of second sound; DVT = deep venous thrombosis.
*Number of patients with PE and no CPD who had 1 or more signs of DVT: edema = 55, erythema = 5, tenderness = 32, palpable cord = 2.
†Data in 103 patients with PE and no CPD, 293 with no PE and no CPD, 145 with PE all patients, 512 no PE all patients.
‡Data in 110 patients with PE and no CPD, 301 with no PE and no CPD, 155 with PE all patients, 529 no PE all patients.
§$P < .01$.
‖$P < .001$.
¶$P < .0001$.
#$P < .025$.
**$P < .05$.
††Edema, erythema, tenderness, or palpable cord.

Patients with Circulatory Collapse

Among patients with circulatory collapse with pulmonary embolism and no prior cardiopulmonary disease, dyspnea was present in 9 of 11 (82%), dyspnea or tachypnea was present in 10 of 11 (91%), and dyspnea, tachypnea, or pleuritic pain was present in 10 of 11 (91%). All 11 patients had dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis.

Among all patients with circulatory collapse and pulmonary embolism, dyspnea was present in 13 of 15 (87%), dyspnea or tachypnea was present in of 14 of 15 (93%), and dyspnea, tachypnea, or pleuritic pain was present in 14 of 15 (93%). All 15 patients had dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis.

Clinical Characteristics According to Location of Pulmonary Embolism

Among 150 patients with pulmonary embolism in whom images were classifiable, main or lobar (proximal) pulmonary arteries showed pulmonary embolism by computed tomography angiography in 116 (77%). The largest affected branch was segmental in 32 patients (21%) and subsegmental in 2 patients (1%). Among all patients with pulmonary embolism in proximal arteries, 94% presented one of the typical syndromes (hemoptysis/pleuritic pain syndrome, uncomplicated dyspnea syndrome, or circulatory collapse syndrome), whereas in patients with segmental pulmonary embolism, only 72% had one of these presentations. The others with segmental emboli had only calf swelling.

Dyspnea or tachypnea occurred in 92% of all patients with pulmonary embolism in whom the pulmonary embolism was proximal, but in only 65% with segmental pulmonary embolism. Dyspnea, tachypnea, or pleuritic pain occurred in 97% of patients with proximal pulmonary embolism and in 77% of patients with segmental pulmonary embolism. Dyspnea at rest or during exertion, dyspnea at rest, orthopnea, tachypnea, and Pa_{CO_2} of 35 mm Hg or less were more frequent in patients with proximal pulmonary embolism, and Pa_{CO_2} of 40 mm Hg or more was less frequent than in patients with segmental pulmonary embolism.

Signs, Symptoms, and Combinations According to Age

Most symptoms and all signs occurred with similar frequencies in patients aged 70 years or more and younger patients

Table 7 Symptoms in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age

	≥70 Y N = 33-35 n (%)	<70 Y N = 93-98 N (%)
Dyspnea		
Dyspnea (rest or exertion)	23 (66)	74 (76)
Dyspnea (at rest)*	17 (49)	56 (58)
Dyspnea (exertion only)*	5 (14)	16 (16)
Orthopnea (≥2-pillow)	8 (23)	29 (30)
Pleuritic pain	12 (35)	45 (46)
Chest pain (not pleuritic)	6 (18)	20 (20)
Cough	10 (29)	35 (36)
Wheezing	3 (9)	24 (24)
Calf or thigh swelling	9 (26)	43 (44)
Calf or thigh pain	9 (26)	46 (47)†

*Information not available in some.
†$P<.05$ age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

(Tables 7 to 10). In patients with no prior cardiopulmonary disease and in all patients with pulmonary embolism, the combination of dyspnea or tachypnea occurred less frequently in elderly patients than in younger patients.

Objective Clinical Assessment in Patients with Pulmonary Embolism

The majority of patients with pulmonary embolism (113/176, 64%) had a moderate probability of pulmonary embolism by the Wells clinical scoring system.[7] The remaining patients with pulmonary embolism were equally divided with a high-probability clinical assessment (32/176,18%) and a low-probability clinical assessment (31/176,18%). Comparable proportions were found among patients with no prior cardiopulmonary disease, elderly patients, younger patients, and patients who presented with the various syndromes. Among patients with pulmonary embolism in the main or lobar pulmonary arteries in whom an objective clinical assessment was recorded, 16 of 107 (15%) had a low-probability objective clinical assessment by the Wells scoring system.[7]

Table 8 Symptoms in All Patients with Pulmonary Embolism According to Age

	≥70 Y N = 53-55 n (%)	<70 Y N = 130-137 n (%)
Dyspnea		
Dyspnea (rest or exertion)	41 (75)	110 (80)
Dyspnea (at rest)*	33 (60)	84 (61)
Dyspnea (exertion only)*	7 (13)	24 (18)
Orthopnea (≥2-pillow)	17 (31)	52 (39)
Pleuritic pain	18 (33)	71 (52)†
Chest pain (not pleuritic)	7 (13)	26 (19)
Cough	24 (44)	58 (43)
Wheezing	13 (25)	45 (33)
Calf or thigh swelling	14 (26)	61 (46)†
Calf or thigh pain†	15 (28)	62 (46)

*Information not available in some.
†$P<.025$ age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

Table 9 Signs in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age

	≥70 N = 33-35 n (%)	<70 N = 91-98 n (%)
General		
Tachypnea (≥20 min)	16 (47)	55 (57)
Tachycardia (>100 min)	8 (23)	24 (25)
Diaphoresis	1 (3)	2 (2)
Cyanosis	0 (0)	0 (0)
Temperature > 38.5°C (>101.3°F)	0 (0)	3 (3)
Cardiac examination (any)	8 (23)	20 (21)
Increased P2*	3 (12)	12 (16)
Right ventricular lift†	0 (0)	4 (5)
Jugular venous distension	7 (20)	11 (12)
Lung examination (any)	15 (43)	23 (23)‡
Rales (crackles)	9 (26)	14 (15)
Wheezes	1 (3)	1 (1)
Rhonchi	0 (0)	2 (2)
Decreased breath sounds	8 (23)	14 (15)
Pleural friction rub	0 (0)	0 (0)

*Data in 26 patients ≥ 70 years, 77 patients < 70 years.
†Data in 30 patients ≥ 70 years, 80 patients < 70 years.
‡$P<.05$ age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

Table 10 Signs in All Patients with Pulmonary Embolism

	≥70 y N = 52-55 n (%)	<70 y N = 130-137 n (%)
General		
Tachypnea (≥20 min)	28 (51)	80 (59)
Tachycardia (>100 min)	11 (21)	38 (28)
Diaphoresis	1 (2)	7 (5)
Cyanosis	0 (0)	1 (1)
Temperature > 38.5°C (>101.3°F6)	0 (0)	3 (2)
Cardiac examination (any)	12 (22)	30 (23)
Increased P2*	3 (7)	19 (18)
Right ventricular lift†	2 (4)	6 (5)
Jugular venous distension	10 (19)	15 (11)
Lung examination (any)	25 (45)	44 (32)
Rales (crackles)	14 (26)	36 (27)
Wheezes	2 (4)	4 (3)
Rhonchi	3 (6)	6 (4)
Decreased breath sounds	16 (29)	24 (18)
Pleural friction rub	1 (2)	1 (1)

All differences between age groups not significant.
*Data in 42 patients ≥ 70 years, 103 patients < 70 years.
†Data in 45 patients ≥ 70 years, 110 patients < 70 years.

DISCUSSION

The data show a broad range of severity of clinical findings in patients with pulmonary embolism. The syndrome of pleuritic pain or hemoptysis, in the absence of circulatory collapse, was the most frequent mode of presentation in PIOPED, occurring in 65% of patients with pulmonary embolism and no prior cardiopulmonary disease.[10] The present data from PIOPED II showed somewhat fewer patients with pleuritic pain or hemoptysis, and more had the uncomplicated dyspnea syndrome. Circulatory collapse was an uncommon mode of presentation in PIOPED[10] and PIOPED II because of selection criteria. Patients with hemoptysis or pleuritic pain syndrome have been shown to have less severe pulmonary embolism than patients with uncomplicated dyspnea according to an objective pulmonary angiography scoring system.[13] Patients with circulatory collapse had the most severe pulmonary embolism based on the angiographic score, but the score was not statistically significantly more than in patients with uncomplicated dyspnea.[13] The absence of dyspnea did not exclude pulmonary embolism, even in patients with circulatory collapse.[11]

Typically, among patients with acute pulmonary embolism, the $Pa{O_2}$ is low.[10] However, acute pulmonary embolism cannot be excluded on the basis of a normal $Pa{O_2}$. This was shown in the present study and in PIOPED,[10] in which 26% of such patients with acute pulmonary embolism and no prior cardiopulmonary disease who had measurements of the $Pa{O_2}$ while breathing room air had a $Pa{O_2}$ of 80 mm Hg or more. Even among patients with submassive or massive acute pulmonary embolism in the Urokinase Pulmonary Embolism Trial, 12% had a $Pa{O_2}$ of 80 mm Hg or more.[16] In patients with pulmonary embolism breathing room air, the A-a oxygen difference closely correlates with the $Pa{O_2}$[17] and has no greater diagnostic value.

The present data show that patients with pulmonary embolism may have dyspnea only on exertion. Orthopnea also was shown to be a symptom of pulmonary embolism. Orthopnea occurred in patients with pulmonary embolism who had dyspnea only on exertion and in those with dyspnea at rest. Typically, the onset of dyspnea occurred over seconds, minutes, or hours, but in some it occurred over days. Compared with patients who had only segmental pulmonary artery pulmonary embolism, patients with proximal pulmonary embolism (main or lobar pulmonary embolism) more often had typical signs, symptoms, and blood gases. Patients with pulmonary embolism even in the main or lobar pulmonary arteries may have a low-probability objective clinical assessment.

In both PIOPED and PIOPED II, pleuritic chest pain was more frequent in patients with pulmonary embolism than hemoptysis.[9,10] Hemoptysis, when present, occurred only in small amounts. Examination of the lungs was abnormal in a minority (29% with no prior cardiopulmonary disease) of patients with pulmonary embolism.

Signs of deep venous thrombosis in patients with no prior cardiopulmonary disease were more frequent in PIOPED II than in PIOPED (47% vs 11%), as were symptoms of deep venous thrombosis (44% vs 26%). However, in PIOPED II the frequency of signs of deep venous thrombosis (41%) and symptoms of deep venous thrombosis (39%) were similar to those in the Urokinase Pulmonary Embolism Trial.[10,13]

Dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis were seen in the majority of patients with pulmonary embolism in PIOPED[9,10] and in the present data from PIOPED II. Conversely, in the absence of dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis, pulmonary embolism was infrequently diagnosed.[9,10]

The diagnosis of pulmonary embolism among elderly patients has been thought to be particularly difficult because the expected signs and symptoms may be absent or ignored.[18-20] This did not seem to be the case in the experience of PIOPED[12] or in the present experience of PIOPED II, although among patients with pulmonary embolism the combination of dyspnea or tachypnea was present in fewer elderly patients than younger patients. In the absence of dyspnea or tachypnea among elderly patients in PIOPED, unexplained radiographic abnormalities were important diagnostic clues.[12] When the diagnosis of pulmonary embolism is uncertain, computed tomography angiography can be performed with the same sensitivity and specificity in elderly patients as in younger patients,[21] although renal failure was a problem among elderly patients who underwent conventional angiography.[12]

CONCLUSIONS

Symptoms may be mild and generally recognized symptoms may be absent in patients with the largest pulmonary embolism in the segmental pulmonary branches, but typical symptoms may be absent even in patients with large emboli. A high or intermediate-probability objective clinical assessment may suggest the need for diagnostic studies, but a low-probability objective clinical assessment was sometimes present, even in patients with proximal pulmonary embolism. Maintenance of a high level of suspicion is critical for the identification of patients in whom diagnostic tests may be necessary.

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References

1. Goldhaber SZ, Hennekens CH, Evans DA, et al. Factors associated with correct antemortem diagnosis of major pulmonary embolism. *Am J Med.* 1982;73:822-826.
2. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest.* 1995;108:978-981.
3. Rubenstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients. An autopsy study. *Arch Intern Med.* 1988;148: 1425-1426.

4. Attems J, Arbes S, Bohm G, et al. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wien Med Wochenschr.* 2004;154:159-162.
5. Stein PD. Fowler SE, Goodman LR, et al. for the PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism (PIOPED II). *N Engl J Med*. 2006;354:2317-2327.
6. Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. *Am J Med.* 2006;119:1048-1055.
7. Wells PS, Anderson DR, Rodger M, et al. 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.
8. Wicki J, Pernerger TV, Junod AF, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med.* 2001;161:92-97.
9. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol.* 1991;68:1723-1724.
10. Stein PD, Terrin ML, Hales CA, et al. 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.
11. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest.* 1997;112:974-979.
12. Stein PD, Gottschalk A, Saltzman HA, et al. Diagnosis of acute pulmonary embolism in the elderly. *J Am College Cardiol.* 1991;18: 1452-1457.
13. Stein PD, Willis PW III, DeMets DL. History and physical examination in acute pulmonary embolism in patients without preexisting cardiac or pulmonary disease. *Am J Cardiol.* 1981;47:218-223.
14. Wenger NK, Stein PD, Willis PW III. Massive acute pulmonary embolism: The deceivingly nonspecific manifestations. *JAMA.* 1972; 220:843-844.
15. Guenter CA. Respiratory function of the lungs and blood. In: Guenter CA, Welch MH, eds. *Pulmonary Medicine, 2nd Ed*. Philadelphia: JB Lippincott; 1982:168.
16. National Cooperative Study. The Urokinase Pulmonary Embolism Trial. *Circulation.* 1973;47/48 (Suppl II):II-81-II-85.
17. Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Chest.* 1995; 107:139-143.
18. Taubman LB, Silverstone FA. Autopsy proven pulmonary embolism among the institutionalized elderly. *J Am Geriatr Soc.* 1986:34:752-756.
19. Morrell MT. The incidence of pulmonary embolism in the elderly. *Geriatrics.* 1970;25:138-153.
20. Busby W, Bayer A, Pathy J. Pulmonary embolism in the elderly. *Age Ageing.* 1988;17:205-209.
21. Stein PD, Beemath A, Quinn DA, et al. Usefulness of multidetector spiral computed tomography according to age and gender for diagnosis of acute pulmonary embolism. *J Cardiol.* 2007;99:1303-1305.