

Prediction of Pulmonary Embolism Extent by Clinical Findings, D-dimer Level and Deep Vein Thrombosis Shown by Ultrasound

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Summary

Pulmonary embolism (PE) may encompass a wide spectrum of severity. To determine whether clinical findings, D-dimer (DD) concentration, and deep vein thrombosis (DVT) shown by lower-limb venous compression ultrasonography (US) might predict the scintigraphic extent of PE, we studied 104 hemodynamically stable consecutive outpatients with acute PE diagnosed by a high-probability ventilation-perfusion lung scan. Scintigraphic extent of PE was classified into three categories: perfusion defects corresponding to <30%, 30–50%, or >50% of the total lung area. Median respiratory and heart rates were found to be significantly related to the extent of PE. Higher median alveolar-arterial oxygen difference values were observed as the proportion of lung perfusion defects increased (>50% vs. <30%, 6.3 vs. 3.6 kPa, P <.0001). Median plasma DD concentration was 7950 μg/L in patients with >50% perfusion defects compared to 2731 μg/L in those with <30% defects (P = .0001). DD levels above 4000 μg/L were associated to more extensive perfusion defects (>50% vs. <30% defects, OR 30; 95% CI 5.8–155). Finally, a proximal DVT was more likely among patients with larger perfusion defects (>50% vs. <30% defects, OR 4.5; 95% CI 1.5–13.6). In conclusion, clinical signs such as tachypnea and tachycardia, alveolar-arterial oxygen difference, plasma DD concentration, and presence of DVT on US are predictors of a larger PE, as assessed by the extent of perfusion defects on high probability lung scans.

Introduction

Pulmonary embolism (PE) encompasses a wide spectrum of clinical presentations, ranging from isolated chest pain without significant consequences on gas exchange or hemodynamics to severe hypoxemia and circulatory collapse (1, 2). Clinical evaluation of patients with suspected PE has long been considered unreliable (3). However, clinical assessment combining patient characteristics either empirically (4-7) or by a standardized scoring procedure (8-10) has been shown to be of value in test selection and interpretation. New diagnostic strategies combining clinical probability of PE with noninvasive instruments such as plasma D-dimer (DD) measurement and lower-limb venous compression ultrasonography (US) have therefore been recently proposed and validated (5-9).

The role of echocardiography in assessing the presence of right ventricular (RV) dysfunction in response to acute PE has been established (11-13). Several studies have reported a significant correlation between the extent of pulmonary vascular obstruction and echocardiographic evidence of RV overload (11-15), a finding which appears to be correlated with a higher adverse outcome rate (13, 16-18). However, echocardiography is not widely available.

Limited data are found in the literature (1, 19, 20) regarding the association between features such as clinical data, DD concentration, and presence of deep vein thrombosis (DVT) on US examination, and the extent of PE. Moreover, the performances of diagnostic tests have been shown to be strongly influenced by the disease's clinical spectrum (21). Therefore, we determined whether clinical findings, DD levels, and detection of DVT by US might predict the extent of PE, as assessed by the degree of lung scan perfusion defects in a subset of consecutive outpatients with acute PE and a high-probability lung scan.

Materials and Methods

Patients

Data of the current study were derived from a previous prospective management trial on the diagnosis of PE (22), including seven hundred forty-two consecutive outpatients referred to the emergency department of the University Hospital of Geneva, Switzerland, between October 1st, 1992, and March 31st, 1995, for clinically suspected PE. One-hundred and three patients met exclusion criteria (22), leaving 671 patients available for analysis, of whom 196 (29%) had a PE. Herein, we studied only the 104 patients (53% of patients with PE) in whom PE was established by a high-probability lung scan.

Diagnostic Studies

Clinical probability of PE was assessed empirically by the physician in charge in the emergency room, based on risk factors, symptoms and signs frequently encountered in PE, blood gases, electrocardiogram, and description of chest X-ray findings (7). Clinical probability was rated as low (0–20%), intermediate (21–79%), or high (80–100%). Clinical information included symptoms of PE such as dyspnea, pleuritic pain, cough, hemoptysis, and leg pain or swelling; signs of PE such as tachypnea (respiratory rate ≥20 per min), tachycardia (heart rate ≥100 per min), temperature, and arterial hypotension (systol-

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Table 1 Characteristics of the study population

Patient Characteristics	Lung scan perfusion defects *			
	All	**< 30 %**	**30-50 %**	**> 50 %**
	n (%)	n (%)	n (%)	n (%)
Number of patients	104	27 (26)	45 (43)	32 (31)
Median (range) age in years	74 (19-89)	69 (19-89)	75 (20-89)	74 (21-88)
Male/Female	46/58	12/15	21/24	13/19
Clinical probability of PE				
Low	5 (5)	4 (15)	1 (2)	0 (0)
Intermediate	74 (71)	17 (63)	34 (77)	23 (72)
High	25 (24)	6 (22)	9 (20)	9 (28)
Deep Vein Thrombosis on US	63 (61)	8 (30)	34 (76)	21 (66)
Risk Factors for PE **				
History of PE	18 (19)	2 (8)	12 (30)	4 (14)
History of DVT	31 (33)	6 (25)	17 (42)	8 (28)
Venous insufficiency	44 (47)	12 (50)	19 (47)	13 (45)
Surgery	13 (14)	7 (29)	4 (10)	2 (7)
Immobilization	29 (31)	9 (37)	11 (27)	9 (31)
Cancer	10 (11)	1 (4)	5 (12)	4 (14)
Estrogen use †	9 (10)	4 (17)	4 (10)	1 (3)

PE for pulmonary embolism; US for lower-limb venous compression ultrasonography.

* Proportion of the total lung area.

** Data missing for 11 patients.

† Contraceptive pill or hormone replacement therapy.

ic blood pressure ≤90 mmHg); as well as chest radiograph abnormalities such as atelectasis, pleural effusion, and elevated diaphragm.

Alveolar-arterial oxygen difference [(A-a)O_2D] was established on the basis of the blood gas measurement obtained while breathing room air. The (A-a)O_2D was calculated according to the following equation: (A-a)O_2D = PIO_2-($PaCO_2$/0.8)-PaO_2 where PIO_2 was estimated as 18.6 kPa, PaO_2 corresponding to the partial pressure of oxygen in arterial blood (kPa) and $PaCO_2$ to the partial pressure of carbon dioxide in arterial blood (kPa).

Plasma DD levels were measured using an enzyme-linked immunosorbent assay (ELISA) method (Asserachrom D-Di enzyme immuno-assay kit, Diagnostica Stago, Asnières-sur-Seine, France), by a technician unaware of the clinical probability, the lung scan result, and the final diagnosis.

Lower-limb venous compression ultrasonography was performed by trained staff within 24 h. The examination consisted of a real-time B-mode venous compression test of the common femoral and popliteal veins. The criterion for diagnosing DVT was noncompressibility of the vein (23).

Ventilation-perfusion lung scan and pulmonary angiography were performed using techniques described elsewhere (24). In the original study, lung scans were interpreted according to the PIOPED interpretation criteria (4). For the purposes of this study, all lung scans categorized as high-probability were reevaluated by an experienced nuclear medicine physician (JPP), who confirmed the previous interpretation in all cases. Then, each high-probability scan was scored for the extent of PE, blinded to all other data, including other test results and clinical information. The proportion of perfusion defects was assessed visually using a semiquantitative segmental scoring of the six available views. Lung scans were classified into three categories: perfusion defects corresponding to <30%, 30–50%, or >50% of the total lung area.

Statistical Analysis

Descriptive statistics were applied for all variables collected. For continuous variables (described as median, range), differences between the three perfusion defect groups were tested for significance by means of the Kruskal-Wallis rank test. When appropriate, groups were compared pairwise through use of the Mann-Witney U test. These analyses were performed using StatView® statistical software (Abacus Concepts, Inc., Berkeley, Calif.). For nominal variables, the Chi-Squared test for proportions was used. The results are presented as odds ratios (ORs), the corresponding exact 95% confidence intervals (CIs) for proportions being calculated from the binomial distribution with the Confidence Interval Analysis (CIA) Software (BMJ, London, 1989). A P value <.05 was considered to indicate statistical significance.

Results

The series included 104 hemodynamically stable consecutive outpatients in whom diagnosis of PE was based on a high-probability lung scan. Demographic and clinical characteristics of the study population are summarized in Table 1.

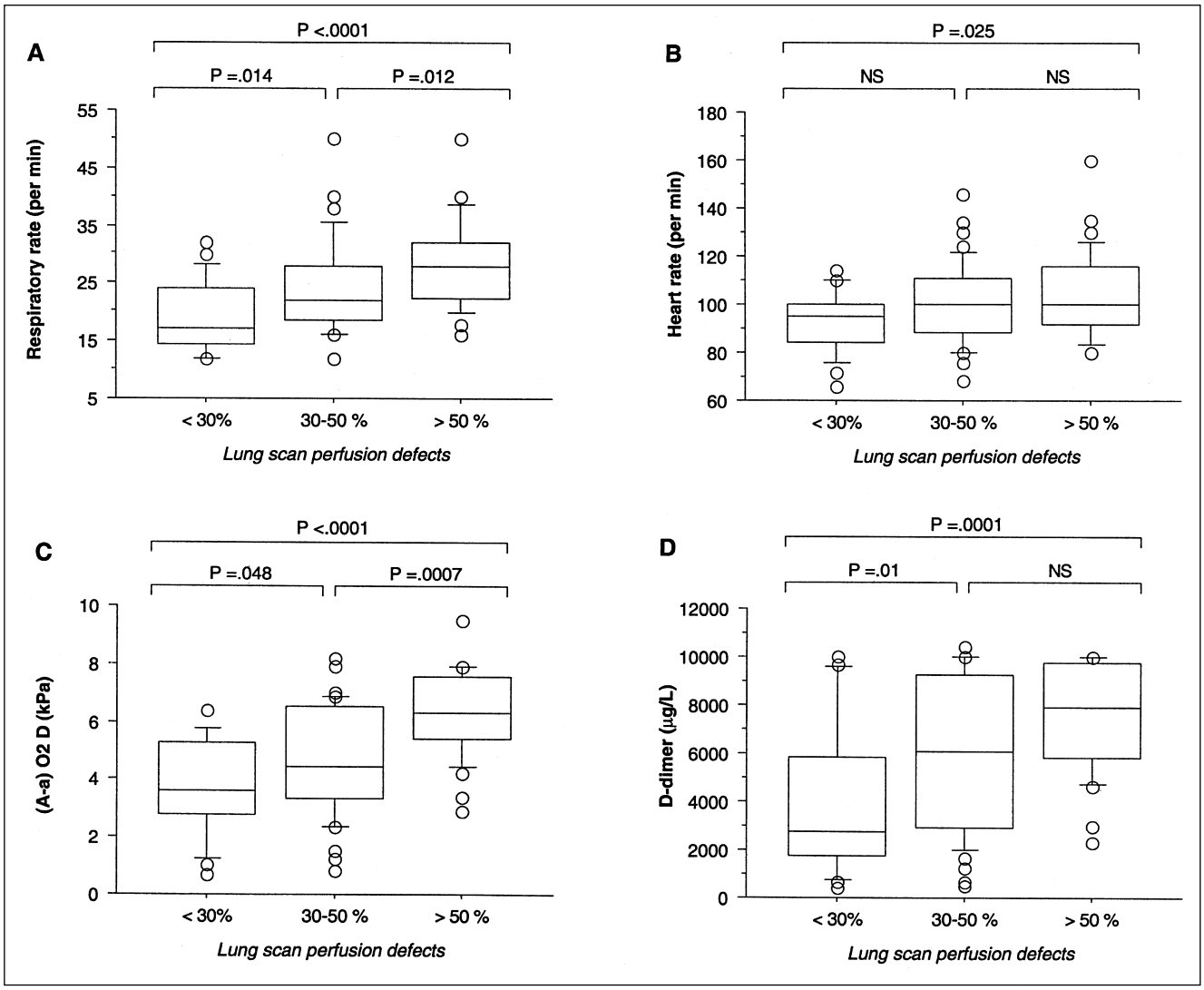

Fig. 1 Respiratory rate (A), heart rate (B), alveolar-arterial oxygen difference (C), and D-dimer levels (D) according to the proportion of perfusion defects on lung scan. Results are presented as box-plots of medians with 25th and 75th percentiles, whiskers showing points that are 1.5 times the interquartile range below the 25th percentile or above the 75th percentile

Clinical Features of PE

Overall, median respiratory rate was 24 per min (12-50) and heart rate was 100 per min (66-160). As shown in Fig. 1A, median respiratory rate was significantly higher in patients with >50% perfusion defects (28 per min, 16-50) than in those with 30-50% (22 per min, 12-50) or <30% defects (17 per min, 12-32). Furthermore, heart rate appeared to be higher in patients with >50% perfusion defects (100 per min, 80-160) when compared to those with <30% defects (95 per min, 66-114) (Fig. 1B).

Median (A-a)O_2D was 5.2 kPa (0.7-9.5) in the entire cohort. The median (A-a)O_2D differed significantly between patients with >50% perfusion defects (6.3 kPa, 2.9-9.5) and those with 30-50% (4.4 kPa, 0.8-8.2) or <30% defects (3.6 kPa, 0.7-6.4), as well as between patients with 30-50% and <30% perfusion defects (Fig. 1C).

In contrast, no statistically significant differences were observed between the three categories of perfusion defects with respect to symptoms of PE such as dyspnea, pleuritic pain, cough, hemoptysis, and leg pain or swelling; signs of PE such as fever and arterial hypotension; and chest radiograph abnormalities such as atelectasis, pleural effusion, and elevated diaphragm.

D-dimer Level

Overall, median DD level was 5995 µg/L (384-10400). As shown in Fig. 1D, patients with >50% perfusion defects had significantly higher DD (7950 µg/L, 2350-10000) than did those with <30% defects (2731 µg/L, 384-10000). Higher DD levels were also obtained in patients with 30-50% perfusion defects (6090 µg/L, 521-10000) when compared to those with <30% defects (2731 µg/L, 384-10000).

Sixty-nine patients (66%) had a DD concentration above 4000 µg/L. As shown in Table 2, the proportion of patients with DD levels above that value was significantly greater in the >50% perfusion defect group than in the <30% (OR 30; 95% CI 5.8–155) or in the 30-50% defect group (OR 7.5; 95% CI 1.6-35.7). Prevalence of DD above 4000 µg/L was also higher among patients with 30–50% perfusion defects as compared to those with <30% defects (OR 4; 95% CI 1.4-11).

Table 2 Results of D-dimer levels according to the extent of lung perfusion defects

Lung perfusion defects	DD ≥ 4000 µg/L	DD < 4000 µg/L	Odds ratio	P value
	n	n	(95 % CI)	
> 50 %	30	2	30 (5.8 - 155) *	< 0.0001
			7.5 (1.6 - 35.7) **	0.005
30-50 %	30	15	4.0 (1.4 - 11) *	0.006
< 30 %	9	18	1.0	

DD for D-dimer.

* Compared to < 30% perfusion defects.

** Compared to 30-50% perfusion defects.

Lower-limb Venous Compression Ultrasonography

Overall, 63 patients (61%) had proximal DVT shown on US in the entire cohort. As detailed in Table 3, the proportion of patients with DVT was significantly greater in the >50% than in the <30% perfusion defect group (OR 4.5; 95% CI 1.5-13.6), and in those with 30-50% perfusion defects when compared with those with <30% defects (OR 7.3; 95% CI 2.5-21.4). Nevertheless, 11 of 32 patients in the >50% defects group did not have a DVT.

Discussion

The current study indicated that clinical signs such as tachypnea and tachycardia, alveolar-arterial oxygen difference, DD levels, and presence of DVT on US were strongly related to the extent of PE, as assessed by the degree of perfusion defects on lung scan. Although not unexpected, these findings had never been systematically reported.

Our data showed significantly higher median respiratory rate, heart rate, and $(A\text{-}a)O_2D$ values in relation with increasing lung perfusion defect categories (Fig. 1). Therefore, our findings support and extend previous suggestions (1, 19, 20) that some clinical findings may be of value in predicting the extent of PE. Stein and Henry (1) described trends towards a higher prevalence of certain clinical characteristics in patients with increasing clinical severity of PE. Furthermore, in a study focusing on blood gases, Stein et al. (20) have also demonstrated that the magnitude of the alveolar-arterial oxygen gradient was related to indices of PE severity, as determined by the pulmonary artery mean pressure and the number of mismatched vascular perfusion defects on lung scan. Finally, other studies have reported a correlation between hemodynamic (14) or echocardiographic (12, 15) evidence of right ventricular overload and dysfunction with the degree of pulmonary vascular obstruction on lung scan.

More interestingly, our data revealed that plasma DD concentration and presence of DVT on US were strongly related to the scintigraphic extent of PE. One may suppose that degradation of larger thrombi, associated to more extensive PE, are indeed able to induce a greater DD release. Moreover, our findings imply that a plasma DD concentration above 4000 µg/L can be considered as a valuable predictor of a larger PE among patients with the disease (Table 2). The prevalence of DVT was significantly higher in patients with >50% or 30–50% lung perfusion defects when compared to those with <30% defects (Table 3). This may partly be explained by the fact that a larger PE usually results from a more extensive DVT, which is more likely to be detected by US. Hence, our data strongly suggest that DVT shown on US is a predictor of a larger PE. Moreover, presence of DVT on US has recently been shown to be independently associated with adverse outcome of PE (25). Nevertheless, 11 of 32 patients (34%) with >50% perfusion defects did

Table 3 Results of US examination according to the extent of lung perfusion defects

Lung perfusion defects	DVT on US	No DVT on US	Odds ratio	P value
			(95 % CI)	
> 50 %	21	11	4.5 (1.5 - 13.6) *	.006
			0.6 (0.2 - 1.7) **	.342
30-50 %	34	11	7.3 (2.5 - 21.4) *	.0001
< 30 %	8	19	1.0	

US for lower-limb venous compression ultrasonography; DVT for deep vein thrombosis.

* Compared to < 30% perfusion defects.

** Compared to 30-50% perfusion defects.

not have proximal DVT on US, suggesting that even in major PE, a negative US does not rule out the diagnosis.

Our conclusions might yet be challenged on the basis of three main limitations. First, given the relatively small sample size, additional less strong associations with other clinical characteristics of PE might have been masked. Second, the study population consisted exclusively of outpatients, which restricts our conclusions to that subgroup of patients. Third, classifying the scintigraphic extent of PE into three categories is obviously arbitrary. Besides these potential limitations, the strength of our series lies in the fact that the cohort included unselected consecutive outpatients with objectively confirmed PE. Our conclusions may therefore be generalized to similar patient populations.

In summary, we found that clinical signs such as tachypnea, tachycardia, elevated alveolar-arterial oxygen difference, plasma D-dimer concentration above a cutoff value of 4000 μg/L, and presence of deep vein thrombosis on ultrasound are predictors of a large PE involving more than 50% of the total lung area, as assessed by the extent of perfusion defects on high probability lung scans.

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