the PIOPED trial, only 27 cases of V/Q-matched defects associated with pleural effusion as the sole radiographic and scintigraphic abnormalities were identified. Data from patients where bilateral effusions were seen on the chest radiograph and where perfusion defects were visualized away from the costophrenic angles when effusions were present are not discussed per se in the reports of the PIOPED investigators. Given these limitations, the PIOPED investigators initially warned that their findings concerning the modification of traditional interpretive schemes based upon effusion size required verification (*7*). Our slightly larger series does not confirm the initial findings.

A distinction must be drawn between the nature of the PIOPED study and our own. The current study is retrospective in nature and incurs all of the biases such studies entail. However, although the PIOPED trial was prospective in design, significant institutional variation in patient recruitment (33–70%) and obtaining of angiograms (64–92%) was reported (*10*). Thus, during the PIOPED study time frame, less than 50% of those eligible for enrollment actually underwent pulmonary angiography. While 39% of those in the PIOPED study had intermediate probability lung scans, those who refused or were ineligible for the study had intermediate probability scans in 22% of cases. This difference was significant ($p < 0.01$), and suggests some bias in the PIOPED trial as well.

In the present series, 45% of those with a solitary V/Q-matched defect accompanied by a pleural effusion had evidence for embolism. This represents a significantly greater percentage of thromboembolic disease than reported by Bedont and Datz (*4*). Yet, in their series, less than one-third of patients underwent pulmonary angiography, with diagnosis based in a majority of cases upon thoracentesis results or other clinical findings. Brown et al. (*11*), however, has strongly questioned the value of thoracentesis in the diagnosis of pulmonary embolism. Biello et al. (*3*) and Worsley et al. (*12*) have reported, in two large studies, that matched V/Q defects that correspond in size to all types of radiographic abnormalities are associated with a 26% chance of pulmonary embolism. Perhaps our higher incidence is due to selection bias, limiting the population to only those with effusions, different techniques of pulmonary angiography or sample size.

CONCLUSION

Pulmonary emboli are associated with pleural effusions of all sizes. Matched V/Q defects corresponding to radiographically evident pleural effusions are of intermediate probability for PE. Our data suggest that revision of the PIOPED criteria based upon pleural effusion size is not warranted.

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Small Perfusion Defects in Suspected Pulmonary Embolism

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The purpose of this investigation was to assess the diagnostic value of 1 to 3 versus >3 small subsegmental defects on perfusion lung scans of patients with suspected acute pulmonary embolism (PE). **Methods:** Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) were evaluated from patients with suspected acute PE. Angiograms, follow-up data and outcome classifications were used to determine PE status. The perfusion scan of included patients showed only small subsegmental defects (<25% of a segment) in the presence of a regionally normal chest radiograph. Findings on the ventilation scan were irrelevant. **Results:** The positive predictive value for PE of perfusion lung scans with 1–3 small subsegmental defects was 1% to 3%, depending on the group analyzed. The positive predictive value for PE of perfusion lung scans with >3 small subsegmental defects was 11% to 17% depending on the group analyzed. **Conclusion:** Perfusion lung scans with 1–3 small subsegmental defects satisfy the criterion for a very low probability (<10% positive predictive value) for PE and perfusion lung scans with >3 small subsegmental defects satisfy the criteria for a low probability (<20% positive predictive value) for PE.

Key Words: pulmonary embolism; ventilation/perfusion lung scan; thromboembolic disease

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Criteria for a low-probability interpretation of ventilation/perfusion (V/Q) lung scans in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) included small segmental perfusion defects (<25% of a segment) with a normal regional chest radiograph (*1*). If the only scintigraphic

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abnormality was 1–3 small segmental perfusion defects in the presence of a normal regional chest radiograph, the lung scan was interpreted as very low probability for pulmonary embolism (PE) (*1*). Evaluation of this criterion was independent of findings on the ventilation scan. Among 29 patients with any number of small subsegmented defects, 2 (7%) had PE. Only some of the PIOPED data were analyzed (*2*). Based on these data, any number of small subsegmental perfusion defects with a regionally normal chest radiograph, in the revised V/Q criteria resulting from PIOPED, was assigned to the criteria for a low-probability interpretation (*2*). A low-probability interpretation was defined as an interpretation with a positive predictive value of <20% for PE (*2*).

Alderson and Martin (*3*), using pooled data, calculated a positive predictive value of 0 of 33 (0%) for small V/Q mismatches defined as <25% of a segment. (The PIOPED criteria indicated that the state of ventilation is irrevelant when only small defects are present.) The number of small defects was unstated. They too recommended that such subsegmental perfusion defects be assigned as a criterion for a low-probability interpretation. They defined low probability as having a positive predictive value for PE of <10%.

Recently, based on data from PIOPED, Silberstein et al. showed PE in 2 of 80 (2.5%) patients with 1 to 3 small subsegmental perfusion defects (*4*). They did not evaluate the positive predictive value for PE of >3 subsegmental defects. Findings on the ventilation scan were irrelevant in this study.

The purpose of this investigation is to further assess the diagnostic value of small subsegmental perfusion defects on lung scans of patients with suspected acute PE.

METHODS

Patients Studied

Data from PIOPED were evaluated from patients with suspected acute PE (*1*). Angiograms, follow-up data and outcome classifications were used to determine PE status as positive for patients with angiograms that showed PE and for patients for whom outcome review established the presence of PE. PE status was determined as negative for patients with angiograms that did not show PE and no contrary outcome review and for patients who lacked a definitive angiogram reading who were discharged from the hospital without a prescription for anticoagulants and in whom no outcome event suggested PE. Among patients with small subsegmental perfusion defects, PE was diagnosed or excluded by pulmonary angiography in 47 patients and by follow-up in 48 patients.

We evaluated data from two arms of PIOPED: (a) those with suspected PE who were randomized for obligatory pulmonary angiography provided their V/Q lung scans were abnormal; and (b) those with a suspicion of PE who were referred for angiography only at the request of their physicians. The first group we term the randomized group. The randomized group plus patients referred for angiography we term the combined group. Only the randomized group was included in the original PIOPED report (*1*). The methods for obtaining V/Q lung scans and pulmonary angiograms have been described (*1*).

In the present investigation of data from PIOPED, we included patients if the lung scan showed only small subsegmental perfusion defects (<25% of a segment) in the presence of a regionally normal chest radiograph. For the evaluation of small subsegmental perfusion defects, the findings on the ventilation scan were irrelevant. These patients also had no mismatched perfusion defects, defined as segmental perfusion defects ≥25% of a segment without corresponding ventilation or radiographic abnormalities, or perfusion defects substantially larger than either matching ventilation or chest radiographic abnormalities. The patients also had no matched ventilation and perfusion abnormalities where the regional chest radiograph was clear and a ventilation abnormality was present with the perfusion defect equivalent in size or smaller, and there was no perfusion defect smaller than the radiographic abnormality. In addition, patients with small subsegmental perfusion defects had no pleural effusion and no nonsegmental abnormalities including enlarged mediastinum, heart or hilum, or elevated diaphragm.

Patients in this analysis were stratified according to the presence or absence of prior cardiopulmonary disease. One patient, however, with >3 small subsegmental perfusion defects and no PE, had no information regarding prior cardiopulmonary disease. Patients were categorized as having no prior cardiac disease if, according to the PIOPED clinical physician, they had no history or evidence of valvular heart disease, coronary artery disease, other heart disease, and no history of left- or right-side of heart failure prior to the episode of suspected acute PE. Patients were categorized as having no prior pulmonary disease if they had no history of asthma, chronic obstructive pulmonary disease, interstitial lung disease, other lung disease, and no recognized acute pneumonia or adult respiratory distress syndrome at the time of evaluation for the suspected PE and no history of a prior PE.

Statistical Methods

Positive predictive value was defined as the frequency of PE with small subsegmental defects on the perfusion lung scan. A chi square test was used to compare various positive predictive values. The 95% confidence intervals were determined on the basis of the exact binomial distribution.

RESULTS

Randomized Patients versus Referred Patients

No statistically significant differences between randomized and referred patients were shown for positive predictive values for PE of small subsegmental perfusion defects among patients evaluated by angiography or among patients evaluated by angiography or follow-up. Among patients with small subsegmental perfusion defects evaluated by pulmonary angiography 2 of 33 (6%) showed PE in the randomized group and 2 of 14 (14%) showed PE in the referred group (ns = not significant). Among such patients evaluated by angiography or by follow-up, randomized versus referred showed PE in 2 of 67 (3%) versus 2 of 28 (7%) (ns). Because no statistically significant differences of the positive predictive value of abnormalities of perfusion lung scans were shown between randomized and referred patients, data from lungs of randomized and referred patients were combined in order to enlarge the data base. All of the following data are from the combined group of randomized plus referred patients.

Patients with One to Three Small Subsegmental Perfusion Defects

Among patients in whom PE was diagnosed or excluded by pulmonary angiography, 1 of 29 (3%) with 1–3 small subsegmental perfusion defects showed PE (Table 1) (Fig. 1). Among patients in whom PE was diagnosed or excluded by pulmonary angiography or follow-up, 1 of 68 (1%) showed PE. Angiographic findings in patients who had PE are shown in Table 2. Most vessels with PE showed partial filling.

Patients with More Than Three Small Subsegmental Perfusion Defects

Among patients in whom PE was diagnosed or excluded by pulmonary angiography, 3 of 18 (17%) with more than 3 small subsegmental perfusion defects showed PE (Table 1). Among

TABLE 1
Pulmonary Embolism with Lung Scans Showing Only Small Subsegmental Perfusion Defects

Number of small subsegmental perfusion defects	Diagnosis by pulmonary angiogram PE/total (%)	Diagnosis by pulmonary angiogram or follow-up PE/total (%)
1–3	1/29 (3)	1/68 (1)*
>3	3/18 (17)	3/27 (11)
Any	4/47 (9)	4/95 (4)

*$p < 0.05$ 1–3 defects versus >3 defects.

TABLE 2
Pulmonary Angiographic Findings in Patients Showing PE and Small Subsegmental Perfusion Defects

Patient no.	Number of defects	Artery in which PE was visualized	Partial filling	100% occlusion
1	1–3	RLL, 1* SEG	X	
		RLL, Peripheral	X	
2	>3	LLL, Peripheral	X	
3	>3	RLL	X	
		RLL, 2 Seg	X	
		RLL, 1 Seg		X
4	>3	LML, Peripheral	X	
		LLL, Peripheral	X	

*Number indicates the number of segmental arteries showing PE.
LLL = left lower lobar artery; RLL = right lower lobar artery; LML = left middle lobar artery; SEG = segmental artery; PE = pulmonary embolism.

patients in whom PE was diagnosed or excluded by pulmonary angiography or follow-up, 3 of 27 (11%) showed PE. Angiographic findings in patients who had PE are shown in Table 2.

Patients with Any Small Subsegmental Perfusion Defects

Among patients in whom PE was diagnosed or excluded by pulmonary angiography, 4 of 47 (9%) with any small subsegmental perfusion defects showed PE (Table 1). Among patients in whom PE was diagnosed or excluded by pulmonary angiography or follow-up, 4 of 95 (4%) showed PE.

Lung Scans with One to Three Compared with Three or More Small Subsegmental Perfusion Defects

Among patients in whom PE was diagnosed or excluded by pulmonary angiography, lung scans with 1–3 small subsegmental perfusion defects showed a trend toward a lower positive predictive value for PE compared with lung scans that showed >3 small segmental perfusion defects (Table 1).

Among patients in whom the diagnosis was made by pulmonary angiography or follow-up, lung scans with 1–3 small subsegmental perfusion defects showed a lower positive predictive value for PE than lung scans with >3 small subsegmental perfusion defects, 1 of 68 (1%) versus 3 of 27 (11%) ($P < 0.05$) (Table 1).

Stratification According to Prior Cardiopulmonary Disease

The positive predictive value for PE of 1–3 small subsegmental perfusion defects was ≤6% in patients with no prior cardiopulmonary disease and in patients with prior cardiopulmonary disease irrespective of whether the diagnosis of PE was made by pulmonary angiography or pulmonary angiography and follow-up. No statistically significant differences were shown.

Among patients in whom PE was diagnosed or excluded by pulmonary angiography, the positive predictive value for PE of >3 small subsegmental perfusion defects in patients with no prior cardiopulmonary disease versus patients with prior cardiopulmonary disease was 3 of 11 (27%) versus 0 of 6 (0%) (ns). Among patients in whom PE was diagnosed or excluded by angiography or follow-up, the positive predictive value for PE of >3 small subsegmental perfusion defects in patients with no prior cardiopulmonary disease versus patients with prior cardiopulmonary disease was 3 of 18 (17%) versus 0 of 8 (0%) (ns).

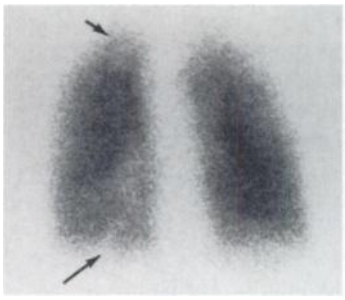

FIGURE 1. Posterior view of a perfusion lung scan. Both the round lesion in the left apex (arrow) and the retrocardiac lesion in the base of the left lung (arrow) were small segmental perfusion defects (<25% of a segment). The patient showed no PE on pulmonary angiography.

DISCUSSION

The positive predictive value for PE of lung scans with 1–3 small subsegmental perfusion defects with a regionally normal chest radiograph was 1% to 3% depending on the group analyzed. This satisfied the criterion for a very low-probability interpretation (<10% positive predictive value) (*5*). This low positive predictive value for PE is comparable to the positive predictive value reported by Silberstein (*4*). The positive predictive value for PE of lung scans with >3 small subsegmental perfusion defects with a regionally normal chest radiograph was 11% to 17% depending on the group analyzed. A perfusion lung scan with >3 small subsegmental defects satisfied the criterion for a low-probability interpretation (<20% positive predictive value for PE) (*2,5*).

Stratification according to prior cardiopulmonary disease has been shown to allow the use of different V/Q criteria for a high-probability assessment in the two stratified groups (*6,7*). This resulted in a higher sensitivity with no loss of specificity or positive predictive value among patients with no prior cardiopulmonary disease. In the present investigation, a trend suggested a higher positive predictive value for PE with >3 small subsegmental perfusion defects in patients with no prior cardiopulmonary disease than in patients with prior cardiopulmonary disease. Few patients with prior cardiopulmonary disease had perfusion scans that showed only small subsegmental defects because the criteria for inclusion required no regional parenchymal abnormalities on the chest radiograph.

CONCLUSION

Perfusion lung scans with 1–3 small subsegmental defects satisfy the criterion for a very low probability for PE and perfusion scans with >3 small subsegmental defects satisfy the criteria for a low probability for PE.

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Diagnostic Value of the Gallium-67 Pulmonary Leak Index in Pulmonary Edema

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We studied the value of a noninvasive, bedside, dual-radionuclide method (^{67}Ga-circulating transferrin and ^{99m}Tc-red blood cells) to measure pulmonary microvascular permeability in efforts to discriminate between pulmonary edema due to adult respiratory distress syndrome (ARDS) and hydrostatic pulmonary edema (HPE). **Methods:** Patients had respiratory insufficiency and bilateral alveolar pulmonary edema on chest radiographs. All patients, except one, were mechanically ventilated. Patients were divided into groups according to various sets of etiologic, hemodynamic and ventilatory factors. Group 1 (n = 8) had risk factors for HPE only. Group 2 (n = 5) had risk factors for both ARDS and HPE, such as a pulmonary capillary wedge pressure (PCWP) above 18 torr. Group 3 (n = 13) had risk factors for ARDS only and a PCWP below 18 torr. Patients were also classified on the basis of a lung injury score, using radiographic and ventilatory variables. Group 4 (n = 12) had a score below 2.5 and Group 5 (n = 14) above 2.5, arbitrarily defined as ARDS. Any radioactivity measurements over the lungs and in blood within 72 hr after admission were used to calculate the 1 hr pulmonary leak index as a measure of microvascular permeability (upper limit of normal 14.1 $\times$ $10^{-3} \cdot min^{-1}$). **Results:** The PLI ($\times 10^{-3} \cdot min^{-1}$) was median 10.2 (range 4.4–16.2) in Group 1, 26.8 (14.2–31.9) in Group 2 and 32.3 (23.0–52.4) in Group 3 ($p < 0.001$). It was 13.3 (4.4–39.9) in Group 4 and 31.1 (14.2–52.4) in Group 5 ($p < 0.01$). Using the various definitions, the sensitivity of a supranormal pulmonary leak index for ARDS was 100% and the specificity varied between 46% and 75%. In receiver operating characteristic curves, the pulmonary leak index performed best when ARDS and HPE were defined on the basis of risk factors only, and performed better than hemodynamic and equally well as ventilatory variables in discriminating between edema types, if definitions of the latter were mainly based on hemodynamic and ventilatory variables, respectively. **Conclusion:** The ^{67}Ga pulmonary leak index is a useful tool to differentiate ARDS from HPE.

Key Words: adult respiratory distress syndrome; hydrostatic pulmonary edema; protein leak; gallium-67; pulmonary leak index

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Pulmonary edema of adult respiratory distress syndrome (ARDS) supposedly results from increased permeability of the pulmonary microvasculature. ARDS is sometimes hard to differentiate from hydrostatic pulmonary edema (HPE), which is presumably caused by a high microvascular hydrostatic pressure. The diagnosis of pulmonary edema is based on the chest radiograph, even though the acute appearance of bilateral, fluffy alveolar consolidations may be caused by other factors than edema (*1–3*). Although the radiographic abnormalities may correlate somewhat with extravascular lung water and may have specific features for either type of edema, the assessment of extravascular lung water is nonspecific and the radiologic differentiation among edema types is hard, necessitating adjunct diagnostic criteria (*1–9*). Various combinations of etiologic, hemodynamic and ventilatory factors are used to help differentiating ARDS from HPE, in the absence of a standard (*1–4,6–20*). For instance, a pulmonary capillary wedge pressure (PCWP) below 15–18 torr is commonly used as a criterion for ARDS (*6–11,13–16,18–20*).

The diagnosis can also be based on the presumed difference in pathophysiology: increased protein permeability for ARDS and normal permeability for HPE. The assessment of protein contents in bronchoalveolar lavage fluids, however, may be impractical and may lack sufficient sensitivity and specificity to be clinically useful in diagnosing permeability edema associated with ARDS (*1,7*). Other methods developed to detect increased microvascular permeability noninvasively utilize intravenously injected radiolabeled proteins and radioactivity measurements over the lung and in blood over time, yielding the pulmonary leak index or analogous indices as measures of the pulmonary transvascular protein transport (*2,3,5,9–18,21–25*). The leak index, using ^{113m}In-transferrin or ^{99m}Tc-albumin may be elevated during ARDS and not during HPE but the diagnostic value is still unclear, since some patients with ARDS may have a normal pulmonary leak index, while some patients with HPE and a PCWP above 30 torr may have an elevated pulmonary leak index, possibly as a consequence of increased protein transport, i.e., solvent drag, induced by high microvascular fluid filtration pressures (*2,9–12,14,15,18,24*). Many of these methods may have methodologic drawbacks and limited clinical applicability at the bedside (*2,9–16,18,21–23*). For instance, measuring the kinetics of the intravenously injected positron emitter ^{68}Ga, binding to circulating transferrin, may be able to discriminate increased permeability from hydrostatic edema of the lungs, but PET is not widely available, cannot be applied at the bedside and the method, like others, does not incorporate an intravascular tracer to correct for potential changes in pulmonary blood volume (*5,9–13,16*). We therefore use a dual radionuclide method and a sensitive, mobile probe system to allow for bedside measurements of the kinetics of the commonly available permeable tracer, ^{67}Ga, supposed to bind

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