Patient Stratification by Cardiopulmonary Status in the Diagnosis of Pulmonary Embolism

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The purpose of this investigation is to provide further evidence in support of the interpretation of ventilation/perfusion (V/Q) lung scans on the basis of criteria dependent on whether or not the patient has prior cardiopulmonary disease (CPD). **Methods:** Data are from the collaborative PIOPED study. We evaluated the original PIOPED database to obtain the consensus probability estimates of pulmonary embolism (PE) among patients stratified according to the presence or absence of prior CPD. **Results:** Among patients with no prior CPD, nuclear physicians consistently underestimated the probability of PE (odds ratio 1.62, 95% confidence interval 1.10–2.38, p = .014). **Conclusion:** Past experience guided nuclear physicians into correctly estimating the probability of acute PE on V/Q scans of patients with prior CPD. The criteria they subjectively used was inadequate for estimating the probability of acute PE in patients with no prior CPD. Different criteria, therefore, apply to the interpretation of V/Q scans in these two groups.

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

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We evaluated data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) (*1*) and found that less stringent criteria for the ventilation/perfusion (V/Q) scan diagnosis of pulmonary embolism (PE) should be applied to patients with no prior cardiopulmonary disease than to those patients who have had previous cardiopulmonary disease (*2,3*). Fewer mismatched perfusion defects are required for a high probability interpretation of the V/Q scan in patients with no prior cardiopulmonary disease than in patients with prior experiences. Use of less strict criteria in patients with no prior cardiopulmonary disease results in a higher sensitivity for PE without a reduction of the specificity or positive predictive value (*2,3*).

Based on analysis of receiver operating characteristic (ROC) curves constructed on the basis of the final V/Q scan category interpretations for all PIOPED patients (randomized for pulmonary angiography and referred for pulmonary angiography), Worsley et al. (*4*) have recently found no difference in the sensitivity and specificity of the V/Q scan diagnosis for PE between patients with and patients without prior cardiopulmonary disease. When constructed on the basis of V/Q scan categories, however, the area under ROC curves depends heavily upon diagnoses made in the intermediate, low, near normal/normal and normal range. Subtle differences in the high probability interpretations, upon which our concept of stratification according to prior cardiopulmonary disease depends, may not be evident as a difference of area under the ROC curves. Nevertheless, because the concept of stratification according to prior cardiopulmonary disease has been called into question, further evaluation seems appropriate.

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To investigate further whether different criteria may be applied to the V/Q diagnosis of PE in patients with prior cardiopulmonary disease and patients with no prior cardiopulmonary disease, we now present an entirely different approach. The subjective percent probability estimates for acute PE (consensus probability) made by the nuclear physicians who were the readers of the V/Q lung scans in PIOPED will be analyzed. These estimates of probabilities of acute PE will be evaluated separately among patients with and patients without prior cardiopulmonary disease. Failure to correctly assess one of the stratified groups would imply a need for revision of the diagnostic criteria in that group.

METHODS

Patients in the PIOPED study included in this analysis were limited to 722 patients who were randomly selected for obligatory pulmonary angiography upon suspicion of acute PE and abnormal V/Q scans (*1*). All of these patients had pulmonary angiograms performed.

The consensus percent probability estimate for PE from the PIOPED scan forms was evaluated among patients with prior cardiopulmonary disease and patients with no prior cardiopulmonary disease. The consensus probability estimate of the probability of PE was made by two members of the nuclear medicine working group as they prepared their description of the V/Q scan on a computer-compatible form previously described (*5*). The consensus probability was the final subjective estimate of PE of two nuclear physicians from the nuclear medicine working group of PIOPED who jointly evaluated the likelihood of acute PE based on their intuitive feeling about the V/Q scan. These intuitive estimates of probability did not require formal criteria.

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 sided heart failure prior to the episode of suspected acute PE (*3*). 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 acute respiratory distress syndrome at the time of evaluation for the suspected PE. These patients also had no history of a previous PE.

Statistical Analysis

The likelihood of a difference of the incidence of angiographically proven PE versus the subjective consensus percent probability estimate of PE among patients with prior cardiopulmonary disease and patients with no prior cardiopulmonary disease was made using a logistic regression model. The outcome represented by PE and cardiopulmonary disease, or no cardiopulmonary disease, was used as the two predictors. The consensus probability was considered a covariate in this circumstance.

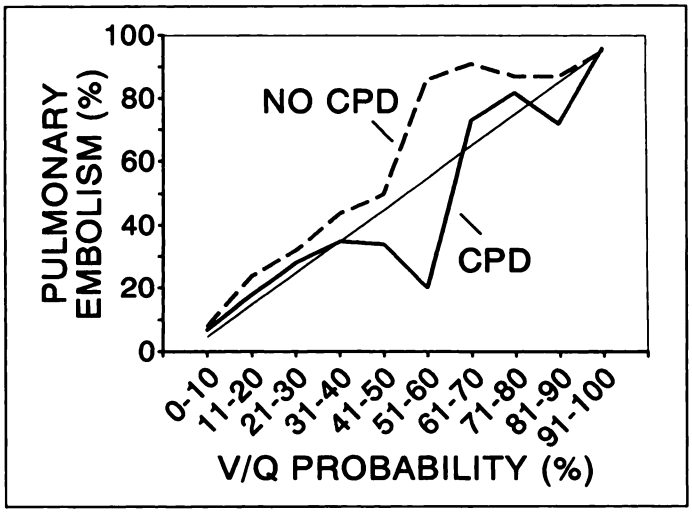

FIGURE 1. V/Q scan consensus probability for PE is shown on the x-axis for patients with no prior cardiopulmonary disease (NO CPD) and patients with prior cardiopulmonary disease (CPD). Frequency of PE, as indicated by pulmonary angiography, is shown on the y-axis. For patients with no prior CPD, the probability of acute PE was consistently higher than that predicted by consensus probability estimates. The data used to construct these curves are shown in Table 1.

RESULTS

When nuclear physicians intuitively estimated the likelihood of acute PE, they were generally correct if the patients had prior cardiopulmonary disease. Among patients with no prior cardiopulmonary disease, however, the nuclear physicians consistently underestimated the probability of acute PE (Fig. 1, Table 1). All of the data points for the patients without prior cardiopulmonary disease fell above the line of identity, while those for patients with cardiopulmonary disease showed a mixture of some locations above and some below the line of identity (Fig. 1).

Based on a logistic regression model, the odds ratio for PE among patients with no prior cardiopulmonary disease versus patients with prior cardiopulmonary disease was 1.618 (95% confidence interval 1.10–2.38) ($p = 0.014$).

TABLE 1
Consensus Estimates of Probability of Pulmonary Embolism on V/Q Lung Scans in Patients Stratified According to Prior Cardiopulmonary Disease

Consensus probability	CPD (n = 430)		No CPD (n = 292)	
	PE/total	(%)	PE/total	(%)
0%–10%	9/105	(9)	10/85	(12)
11%–20%	19/108	(18)	18/80	(23)
21%–30%	17/68	(25)	12/36	(33)
31%–40%	19/49	(39)	7/12	(58)
41%–50%	8/24	(33)	4/8	(50)
51%–60%	2/7	(29)	7/9	(78)
61%–70%	6/7	(86)	6/6	(100)
71%–80%	8/10	(80)	8/9	(89)
81%–90%	16/21	(76)	19/21	(90)
91%–100%	29/31	(94)	24/26	(92)
Totals	132/430	(31)	115/292	(39)

CPD = cardiopulmonary disease; consensus probability = the subjective estimate of PE agreed upon by the two PIOPED nuclear physicians interpreting the V/Q scan; PE+/TOTAL = angiographically proven PE divided by the total number of patients examined by pulmonary angiography for each 10% probability estimate.

DISCUSSION

The prevalence of PE was higher in the group with no prior cardiopulmonary disease than in the group with prior cardiopulmonary disease, 115 of 292 (39%) versus 132 of 430 (31%) ($p < 0.02$). This can contribute to the odds ratio for PE among patients with no prior cardiopulmonary disease versus patients with prior cardiopulmonary disease. We believe that patients with no prior cardiopulmonary disease who are suspected of having PE will always have a higher prevalence of PE because they have less reason to have other causes for the clinical manifestations that suggest PE to the clinician. For example, the sudden onset of unexplained dyspnea may suggest to the referring physician a need for a V/Q lung scan because of possible PE. Patients with prior cardiopulmonary disease in whom PE is suspected have a likelihood that the dyspnea is caused by their underlying disease, and not PE. Such is not the case, however in patients with no prior cardiopulmonary disease who are suspected of having PE. Although the overall prevalence of PE might differ in community hospitals versus tertiary care centers, patients with prior cardiopulmonary disease in whom PE is suspected should always have a lower prevalence of PE than patients with no prior cardiopulmonary disease in whom PE is suspected.

Among patients from PIOPED who were randomized for angiography and patients who were referred for angiography, we previously constructed ROC curves based on the number of mismatched segmental equivalent perfusion defects (*3*). These ROC curves did not depend upon the scan categories of high, intermediate, low, near normal or normal. We observed a statistically significant difference of the areas under the ROC curves of patients with no prior cardiopulmonary disease versus those with prior cardiopulmonary disease, and these data were independent of prevalence (*3*).

The intuitive estimate by nuclear physicians of the probability of acute PE on V/Q scans was based on their experience. These estimates of the probability for PE did not require categorization of the V/Q scans into high, intermediate, low, near normal or normal. Their judgement demonstrably was modified by experience associated with patients who had associated cardiac or pulmonary disease. In patients with no associated cardiopulmonary disease, the likelihood of PE was higher than the prediction based upon their intuitive estimate. This suggests the necessity of modification of the diagnostic criteria in this group.

When ROC analysis was performed on the basis of the PIOPED scan categories of high, intermediate, low, near normal or normal, the data failed to support the use of different criteria for interpretation of the V/Q scans among patients stratified according to the presence or absence of prior cardiopulmonary disease (*4*). Analysis of the receiving operating curves using this technique also showed no differences of the probability of PE on V/Q scans among patients with and without a history of prior PE (*4*). Data from the PIOPED, however, showed that in patients with prior PE, the positive predictive value for acute PE of a high probability V/Q scan was statistically significantly different from the positive predictive value of a high probability V/Q scan in patients with no prior PE (*1*).

ROC curves based on V/Q scan categories in PIOPED contain data from intermediate, low, nearly normal and normal categories, as well as high probability. Important, though subtle, regions of interest related just to the high probability V/Q scan may be masked by including intermediate, low, nearly normal and normal V/Q interpretations in the ROC curve.

Our data indicate that patients with and without prior cardiopulmonary disease can be stratified into distinct groups for

which different diagnostic criteria for the V/Q scan can be applied. In patients with no prior cardiopulmonary disease, fewer mismatched perfusion defects indicate a higher probability of PE than among patients with prior cardiopulmonary disease. Among patients with no prior cardiopulmonary disease, the use of fewer mismatched perfusion defects for a high probability assessment results in a higher sensitvity with no reduction of the specificity or positive predictive value (*2,3*). The same number of mismatched perfusion defects in a patient with prior cardiopulmonary disease results in a lower probability of PE.

CONCLUSION

The data presented here strengthen the validity of stratification according to prior cardiopulmonary disease for a better diagnostic interpretation of the V/Q lung scan.

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Myocardial Metabolic Changes in Hypertrophic Cardiomyopathy

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We evaluated myocardial blood flow, glucose and oxygen metabolism using PET in hypertrophic cardiomyopathy (HCM). **Methods:** PET studies using ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-acetate were performed at rest in patients with HCM and normal subjects as a control group. The metabolic rate of glucose (MRGlu), K mono value as a marker of oxidative metabolism, and myocardial blood flow were estimated from serial dynamic FDG and ^{11}C-acetate PET studies. **Results:** Myocardial blood flow (%) did not differ significantly in hypertrophic and nonhypertrophic myocardium (90.3 ± 3.1 versus 91.7 ± 3.4). The MRGlu in hypertrophic myocardium, however, was lower than that in nonhypertrophic and normal myocardium (0.44 ± 0.10 versus 0.52 ± 0.15 and 0.53 ± 0.15 μmole/min/g, respectively, $p < 0.05$). The K mono values were also lower in hypertrophic myocardium than in nonypertrophic and normal myocardium (0.05 ± 0.010 versus 0.066 ± 0.0011 and 0.065 ± 0.017 per min, respectively, $p < 0.05$). The %FDG/%perfusion values in hypertrophic myocardium did not differ significantly from those in nonhypertrophic myocardium (0.96 ± 0.10 versus 1.02 ± 0.07). **Conclusion:** Myocardial ischemia at rest is observed less frequently in patients with HCM. Impairment of oxidative and glucose metabolism may precede decreased blood flow. Primary metabolic impairment is considered to be dominant in hypertrophic myocardium.

Key Words: PET; hypertrophic cardiomyopathy; myocardial metabolism; carbon-11-acetate; fluorine-18-FDG

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Hypertrophic cardiomyopathy is a primary myocardial disease of unknown etiology and pathogenesis (*1,2*). Patients with hypertrophic cardiomyopathy often complain of chest pain. Exercise studies using ^{201}Tl have also suggested myocardial perfusion abnormalities mainly in the hypertrophied myocardium in these patients (*3,4*). Hemodynamic and metabolic evidence of pacing-induced myocardial ischemia was also demonstrated in such patients (*5,6*). Camici et al. (*7*) also suggested that coronary vasodilator reserve is impaired in patients based on ^{13}N-ammonia PET studies. Thus, it is generally accepted that flow reserve impairment is present in patients with hypertrophic cardiomyopathy.

Whether true ischemia at rest is present in patients with hypertrophic cardiomyopathy and contributes to pathogenesis remains controversial. In ischemic coronary heart disease, preserved ^{18}F-fluorodeoxyglucose (FDG) uptake in the segments with reduced myocardial perfusion, known as perfusion-metabolism mismatch, has been proposed as a marker of ischemic but viable myocardium (*8–11*). Some investigations based on PET findings using ^{13}N-ammonia and FDG suggest the presence, and others the absence, of ischemia in patients (*12,13*). In addition, metabolic alteration, including oxidative metabolism, has not been fully investigated in these patients.

Therefore, the purposes of this study were to evaluate both the presence or absence of resting ischemia and energy alterations, including glucose and oxidative metabolism, in hypertrophic myocardium.

METHODS

Subjects

The study group consisted of 20 patients (10 men, 10 women; aged 13–82 yr; mean 42.6 yr). Hypertrophic cardiomyopathy was defined as hypertrophied and nondilated left ventricle in the absence of any other cardiac or systemic disease that itself produces left ventricular hypertrophy (*14,15*). The diagnosis of hypertrophic cardiomyopathy was made based on the clinical course and the results of echocardiography, electrocardiography

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