Alveolar-Arterial Oxygen Gradient in the Assessment of Acute Pulmonary Embolism*

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Purpose: The purpose of this investigation is to evaluate the utility of the alveolar-arterial (A-a) oxygen gradient in the diagnosis of acute pulmonary embolism (PE) among patients who participated in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).

Methods: Pulmonary embolism was diagnosed (n=280) or excluded (n=499) by angiography in all patients. Patients were then categorized as (1) the entire cohort, (2) no prior cardiopulmonary disease and no prior PE, and (3) no prior PE or deep venous thrombosis. Normal values of the A-a gradient were defined in three ways: (1) values ≤20 mm Hg; (2) values ≤age/4+4; and (3) values based on age from the literature.

Results: When a normal A-a gradient was defined as ≤20 mm Hg, 11 to 14% of patients with PE in the three categories of patients had a normal A-a gradient. When the equation age/4+4 was used, 8 to 10% of patients with PE in the three categories of patients had a normal A-a gradient. With age-related values from the literature, 20 to 23% of patients with PE in the three categories of patients had a normal A-a gradient. The A-a gradient was normal in comparable percentages of patients who did not have PE.

Conclusion: Normal values of the A-a gradient did not exclude the diagnosis of acute PE.

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Key words: pulmonary embolism; alveolar-arterial oxygen gradient; thromboembolism; deep venous thrombosis

Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) showed that among patients with no prior cardiopulmonary disease, the distribution of the alveolar-arterial (A-a) gradient in patients with acute pulmonary embolism (PE) and patients in whom PE was suspected and excluded was similar.1 An A-a gradient ≤20 mm Hg occurred in 14% of patients with PE. The diagnosis of acute PE, therefore, could not be reliably excluded on the basis of a normal A-a gradient. Subsequent to this publication, there has been rekindling of interest in the ability of a normal A-a gradient to exclude PE. McFarlane and Imperiale2 indicated that only 1.9% (95% confidence interval, 0.1 to 11.2%) with a normal A-a gradient and no history of prior PE or prior deep venous thrombosis had PE. They concluded that a normal A-a gradient among patients suspected of PE with no prior PE or prior deep venous thrombosis mitigated against further diagnostic evaluation. The purpose of the present investigation is to explore further the value of the A-a gradient among patients in PIOPED by using an expanded PIOPED database.

METHODS

Data in this study are from the multicenter collaborative study of PIOPED.3 In the prior evaluation of the A-a gradient,1 data were used only from patients randomized for angiographic pursuit, as described in the primary PIOPED report.3 We now utilize data from all patients in PIOPED, including those who were not randomized for angiographic pursuit, but who had pulmonary angiograms if requested by the attending physician. Such requests for angiography were based on the physicians' assessment of the need for angiography in their particular patients.

The diagnosis of acute PE was established or excluded in all patients on the basis of pulmonary angiography. There were 280 patients with PE who had an A-a gradient calculated on the basis of measurements obtained while breathing room air. Patients with blood gas values obtained while breathing oxygen were excluded because of potential inaccuracy in the calculation of the A-a gradient in such patients.

Among the 280 patients with PE and A-a gradients measured while breathing room air, 130 patients had no prior cardiopulmonary disease as defined previously.1 Also, among these 280 patients, 190 had no prior PE or prior deep venous thrombosis. Patients with no prior cardiopulmonary disease, as we defined it, had no prior PE, but they may have had prior deep venous thrombosis.

For comparison, we evaluated patients with suspected PE in

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whom the diagnosis was excluded by pulmonary angiography. There were 499 such patients who had an A-a gradient measured while breathing room air. Among these, 200 had no prior cardiopulmonary disease and no prior PE, but they may have had prior deep venous thrombosis. Also, among the 499 patients, 365 had no prior PE or prior deep venous thrombosis, but they may have had prior cardiopulmonary disease other than PE.

Evaluations of the ability of the A-a gradient to exclude PE were made among all patients, patients with no prior cardiopulmonary disease, and patients with no prior PE or prior deep venous thrombosis.

The magnitude of the A-a gradient was evaluated in relation to indices of severity of PE. Indices of the severity of PE were the pulmonary artery mean pressure, number of mismatched vascular perfusion defects on the ventilation/perfusion lung scan, and partial pressure of oxygen in arterial blood (PaO₂). In these evaluations, patients were grouped according to whether they had prior cardiopulmonary disease. Pulmonary artery mean pressure was measured at the time of pulmonary arteriograms in all patients with fluid-filled catheters. All measurements were made just prior to the injection of contrast material. A mismatched vascular perfusion defect on the ventilation/perfusion lung scan was defined as either a large or moderate size mismatched segmental perfusion defect.

\( \text{PaO}_2 \) and A-a Oxygen Gradient

The A-a oxygen gradient was calculated according to the following equation:

\[ \text{A-a gradient (mm Hg)} = \frac{\text{PaCO}_2 - \text{PaO}_2}{100} \]

Where \( \text{PaCO}_2 \) is partial pressure of carbon dioxide in arterial blood (mm Hg), and \( \text{PaO}_2 \) is partial pressure of oxygen in arterial blood (mm Hg). Measurements of arterial blood gases were obtained with the patient breathing room air. All six PIOPED centers were roughly at sea level. All measurements were obtained within 24 h prior to the diagnostic pulmonary angiogram. This may have been as long as 48 h after the onset of symptoms, although usually it was less than 36 h after the onset of symptoms.

Statistical Methods

A \( \chi^2 \) with Yates' correction was used to compare the values of the proportion of patients with a normal A-a gradient among patients with PE vs those without PE. The strength of the linear relationships was estimated on the basis of Pearson correlation coefficients.

Normal Values of A-a Gradient

The normal A-a gradient increases with age. Most patients have an A-a gradient \( \leq 20 \) mm Hg.6,9 Analyses, therefore, were made on the basis of an assumed normal A-a gradient being \( \leq 20 \) mm Hg. Analyses were also made on the basis of normal values of the A-a gradient, defined as age/4+4, as employed by others.5,10 Finally, analyses were made on the basis of normal age-related values obtained from data reported by Mellemgaard.6 Patients 15 to 19 years of age had an A-a gradient \( \leq 14 \) mm Hg; patients 20 to 29 years of age had an A-a gradient \( \leq 20 \) mm Hg; and patients \( \geq 30 \) years of age (with one exception) had an A-a gradient \( \leq 27 \) mm Hg.6 These values correspond closely with normal age-related values of the A-a gradient reported by Harris and associates7 and Kanber and associates.8 Others reported somewhat lower normal values of the A-a gradient, which did not exceed 20 mm Hg in subjects 23 to 60 years of age.8

RESULTS

All Patients

Among 280 patients with acute PE, irrespective of the presence of prior cardiopulmonary disease (including prior PE and/or prior deep venous thrombosis), 33 of 280 (12%) had an A-a gradient \( \leq 20 \) mm Hg vs 82 of 499 (16%) among patients who did not have PE (NS) (Table 1, Fig 1). If a normal A-a gradient is defined on the basis of the equation age/4+4, then 23 of 280 (8%) with PE had a normal A-a gradient vs 59 of 499 (12%) who did not have PE (NS). Among patients with a normal A-a gradient based on reported age-related values, 57 of 280 (20%) with PE had a normal A-a gradient vs 123 of 499 (25%) among patients who did not have PE (NS).

Among patients with PE who had an A-a gradient \( \leq 20 \) mm Hg, 27 of 33 (82%) had ventilation/perfu-

\[ r = 0.328, P < 0.005 \]

**Figure 1.** Alveolar-arterial (A-a) oxygen gradient shown as a function of age among all patients with pulmonary embolism. Correlation coefficient \((r) = 0.328, p < 0.005\).

**Table 1—Frequency of Normal A-a Gradients Among Patients With PE and Patients With No PE**

<table>
<thead>
<tr>
<th>A-a Gradient Normal ( \leq 20 ) mm Hg</th>
<th>A-a Gradient Normal ( \leq \text{Age/}4+4 )</th>
<th>A-a Gradient Normal=Age-Related Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PE</strong></td>
<td><strong>No PE</strong></td>
<td><strong>PE</strong></td>
</tr>
<tr>
<td>No. of Pts (%)</td>
<td>No. of Pts (%)</td>
<td>No. of Pts (%)</td>
</tr>
<tr>
<td>All patients</td>
<td>33/280 (12)</td>
<td>82/499 (16)</td>
</tr>
<tr>
<td>No prior CPD</td>
<td>18/130 (14)</td>
<td>40/200 (20)</td>
</tr>
<tr>
<td>No prior PE or DVT</td>
<td>21/190 (11)</td>
<td>55/365 (15)</td>
</tr>
</tbody>
</table>

*CPD = cardiopulmonary disease; DVT = deep venous thrombosis; Nl = normal; Pts = patients. All differences (PE vs no PE), not significant.*
sion lung scans interpreted as intermediate, low, or nearly normal probability for PE.

Patients With No Prior Cardiopulmonary Disease

Among 130 patients with no prior cardiopulmonary disease, 18 of 130 (14%) with an A-a gradient ≤20 mm Hg had acute PE vs 40 of 200 (20%) among patients who did not have PE (NS) (Table 1, Fig 2). Using the age/4+4 equation to define normal values of the A-a gradient, 13 of 130 (10%) with PE had normal values of the A-a gradient vs 24 of 200 (12%) among patients who did not have PE (NS). Among patients with a normal A-a gradient on age-related values, 30 of 130 (23%) with PE had a normal A-a gradient vs 54 of 200 (27%) with no PE (NS).

Patients With No Prior PE or Prior Deep Venous Thrombosis

Among 190 patients with no prior PE or prior deep venous thrombosis, 21 of 190 (11%) with acute PE had an A-a gradient ≤20 mm Hg vs 55 of 365 (15%) who did not have PE (NS) (Table 1, Fig 3). Based on the equation for age-corrected values of the A-a gradient, 15 of 190 (8%) with PE had a normal A-a gradient vs 40 of 365 (11%) with no PE (NS). Among patients with a normal A-a gradient based on reported age-related values, 38 of 190 (20%) had PE and 86 of 365 (24%) did not have PE.

Among patients with PE who had no prior PE or prior deep venous thrombosis, 17 of 21 (81%) had ventilation/perfusion scans that were interpreted as intermediate, low, or nearly normal probability for PE.

Relation of A-a Oxygen Gradient to Indices of the Severity of Acute PE

The A-a gradient showed a linear correlation with the pulmonary artery mean pressure (PAP) among patients with PE and no prior cardiopulmonary disease (r=0.32, p<0.005) and among patients with PE and prior cardiopulmonary disease (r=0.34, p<0.005). Among patients with PE no prior cardiopulmonary disease who had an A-a gradient ≤20 mm Hg, the pulmonary artery mean pressure was 18±6 mm Hg and ranged as high as 34 mm Hg. Patients with PE with prior cardiopulmonary disease and an A-a gradient ≤20 mm Hg had a pulmonary artery mean pressure of 19±10 mm Hg and may have had a pulmonary artery mean pressure as high as 37 mm Hg.

The A-a gradient showed a linear correlation with the number of mismatched vascular perfusion defects on the ventilation/perfusion lung scan among patients with PE and no prior cardiopulmonary disease (r=0.40, p<0.005). A linear correlation was also shown among patients with PE and who had prior cardiopulmonary disease (r=0.39, p<0.005). Patients with no prior cardiopulmonary disease and an A-a gradient ≤20 mm Hg had 2±3 mismatched vascular defects (mean±SD) and may have had as many as 11 mismatched vascular perfusion defects. Patients with prior cardiopulmonary disease and an A-a gradient ≤20 mm Hg had 1±1 mismatched vascular defects, and all had ≤3 mismatched vascular perfusion defects.

The A-a gradient showed a strong inverse linear correlation with the PaO₂ among patients with PE and no prior cardiopulmonary disease (r=-0.92, p<0.005) (Fig 4). The A-a gradient also showed a strong inverse linear correlation with the PaO₂ and patients with PE who had prior cardiopulmonary disease (r=-0.84, p<0.005) (Fig 5). Among 33
patients with an A-a gradient $\leq 20$ mm Hg, the PaO$_2$ was $\geq 80$ mm Hg in 31 patients and it was 76 mm Hg in 2 patients.

**DISCUSSION**

A normal value of the A-a gradient did not distinguish patients with acute PE from patients with no acute PE. Irrespective of how normal was defined, and irrespective of whether the categories of patients included all patients or only those with no prior cardiopulmonary disease or those with no prior PE or deep venous thrombosis, comparable percentages of patients with normal A-a gradients had PE or no PE.

When we defined a normal A-a gradient as $\leq 20$ mm Hg, 11 to 14% of patients with PE had a normal A-a gradient. This applied to all patients, those with no prior cardiopulmonary disease, and those with no prior PE or deep venous thrombosis. When we defined normal as age/4+4, only 8 to 10% of patients with PE in the three categories had PE. However, this definition is restrictive and would have excluded 22 of 80 (28%) normal patients described by Mellemgaard,\textsuperscript{6} 7 of 35 (20%) described by Kanber and associates,\textsuperscript{9} 13 of 48 (27%) described by Harris and associates,\textsuperscript{7} and 3 of 19 (16%) described by Filley and associates.\textsuperscript{8} Averaging these data, the age-corrected equation would incorrectly define as abnormal 19% of patients. Use of this restrictive equation for the definition of a normal A-a gradient contributed to the low frequency of normal A-a gradients in patients with PE observed by McFarlane and Imperiale.\textsuperscript{2}

The A-a gradient showed a linear correlation with the severity of the PE, as assessed by the pulmonary artery mean pressure and by the number of mismatched vascular perfusion defects on the ventilation/perfusion lung scan. Patients with less severe PE were more likely to have a normal A-a gradient than those with more severe PE.

McFarlane and Imperiale\textsuperscript{2} seem to have included relatively few patients with PE who had ventilation/perfusion lung scans interpreted as non-high probability. In PIOPED, 59% of patients with PE had non-high probability interpretations of the ventilation/perfusion lung scans.\textsuperscript{3} Such patients are particularly likely to have a normal A-a gradient. This may explain why our results differ. Our data show that among all patients with PE and an A-a gradient $\leq 20$ mm Hg, 82% had non-high probability ventilation/perfusion lung scans. Among patients with no prior PE and no prior deep venous thrombosis who had PE and an A-a gradient $\leq 20$ mm Hg, 81% had non-high probability ventilation/perfusion lung scans.

According to the PIOPED protocol, symptoms may have occurred within 24 h prior to the ventilation/perfusion lung scan, and the blood gas determinations were performed within 24 h prior to pulmonary angiography. There may have been 48 h, therefore, between the onset of symptoms and obtaining the sample of blood for PaO$_2$. It is possible that the PaO$_2$ and the A-a gradient improved in the interim between the onset of symptoms and measurement of arterial blood gases.

Some of the patients in this study were in the arm of PIOPED that selected patients for pulmonary angiography at the request of their physicians. If this introduced bias, it presumably would have been a more frequent selection of patients for pulmonary angiography among patients with more severe symptoms, a lower PaO$_2$, and a higher A-a gradient. Patients with a low A-a gradient would have been less likely to have undergone pulmonary angiography, which would have decreased the likelihood of diagnosing PE in such patients. Potential bias caused by including patients from the nonrandomized arm of PIOPED, therefore, would have diminished the likelihood of observing a normal A-a gradient among patients with acute PE. The advantage of using patients from the nonrandomized arm of PIOPED was that more data were available for evaluation.

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**Figure 4.** Alveolar-arterial (A-a) oxygen gradient shown as a function of the partial pressure of oxygen in arterial blood (PaO$_2$) among patients with no prior cardiopulmonary disease (no CPD). Correlation coefficient ($r$)=−0.917 (p<0.005).

**Figure 5.** Alveolar-arterial (A-a) oxygen gradient shown as a function of the partial pressure of oxygen in arterial blood (PaO$_2$) among patients with any prior cardiopulmonary disease (CPD). Correlation coefficient ($r$)=−0.842 (p<0.005).
The A-a gradient among patients with acute PE showed a strong inverse linear correlation with the PaO₂. A low PaO₂ may strengthen the clinical suspicion of acute PE. However, among patients with no prior cardiopulmonary disease, 26% of patients with PE had a PaO₂ ≥80 mm Hg. Even among patients with massive or submassive PE in the Urokinase Pulmonary Embolism Trial, 12% had a PaO₂ ≥80 mm Hg. In the present investigation, 25% of patients with PE and no prior cardiopulmonary disease and 15% of patients with PE and prior cardiopulmonary disease had a PaO₂ ≥80 mm Hg. The limitations of both tests for screening for acute PE are similar. Neither can be used to exclude acute PE.

Our data indicate that the A-a gradient may be included among many laboratory test results that usually are abnormal in patients with acute PE, but the A-a gradient may be normal in such patients. Normal values of an A-a gradient do not exclude the diagnosis of acute PE.

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