Prognostic Role of Alveolar-Arterial Oxygen Pressure Difference in Acute Pulmonary Embolism

Jen Te Hsu, MD; Chi Ming Chu, PhD*; Shih Tai Chang, MD; Hui Wen Cheng, MD;
Nye Jan Cheng, MD**; Wan-Ching Ho, MD**; Chang Min Chung, MD

Background This study investigated the utility of the alveolar–arterial oxygen pressure difference (AaDO₂) in predicting the short-term prognosis of acute pulmonary embolism (PE).

Methods and Results This study retrospectively enrolled 114 consecutive patients with acute PE, diagnosed by either spiral computed tomography or high probability ventilation–perfusion lung scans. During the first 24 h of admission, all patients had initial artery blood gas collected under room air. Patient exclusion criteria were chronic lung disease, septic emboli, and moderate and low probability lung scans. Patients were assigned to 2 groups based on either 30-day death or a 30-day composite event. Receiver operating characteristic analyses was used to determine the AaDO₂ cut-off value for predicting primary and composite endpoints. Statistical analysis demonstrated significant differences in AaDO₂ between the 30-day composite endpoint group and the 30-day composite event-free survival group ($p=0.012$). The AaDO₂ had a strong trend between the 30-day death group and the survival group ($p=0.062$). The best cut-off value for AaDO₂ was 53 mmHg and using this, the positive predictive value for 30-day death was 25% and the negative predictive value was 92%. For the 30-day composite endpoint, the positive predictive value for AaDO₂ was 35%, and the negative predictive value was 84%. In this study, thrombocytopenia was also an indicator of poor prognosis for patients with acute PE.

Conclusion The AaDO₂ measurement is a highly useful and simple measurement for predicting short-term prognosis in patients with acute PE. It has high negative predictive value and moderate positive predictive value for 30-day death and 30-day composite event. Aggressive thrombolytic treatment strategies should be considered for patients with an initial poor prognostic parameter (ie, AaDO₂ ≥ 53 mmHg). (Circ J 2006; 70: 1611–1616)

Key Words: Acute pulmonary embolism; Alveolar–arterial oxygen pressure difference; Arterial–alveolar oxygen tension ratio

Acute pulmonary embolism (PE) has high incidence and mortality rates in the United States. The International Cooperative Embolism Registry of 2,454 patients reported a high 90-day all-cause mortality rate of 17.4%.¹ PE is associated with surgery, trauma, immobilization, cancer, oral contraceptives, pregnancy, and postmenopausal hormone replacement therapy, as well as air travel.²

Most patients with acute PE have a low partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂) in the arterial blood and elevated alveolar–arterial oxygen pressure difference (AaDO₂).³ These parameters typically improve with recovery.⁴ Arterial blood gas measurements have proved disappointing as diagnostic modalities: normal values for the alveolar–arterial oxygen gradient do not exclude acute PE,⁵ and hypoxemia discriminates poorly between those with and without acute PE.⁶ Substantial evidence exists to indicate that the absence of such abnormal values for arterial

blood gas analysis, alone or in combination, does not exclude PE.

Several studies have suggested that AaDO₂ has a linear correlation to actual perfusion defect and is a sensitive indicator of resolved emboli.^{4–6} In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, a linear correlation existed between AaDO₂ and PE severity, as determined by pulmonary artery mean pressure, and with the number of mismatched perfusion defects.⁷

There is continued interest, however, in the possibility that different gradients of AaDO₂ or other arterial blood gas analyses can be used to predict the prognosis of acute PE. The purpose of this study was to determine the efficacy of individual blood gas measurements in predicting morbidity and mortality of patients with acute PE.

Methods

Study Sample

This study retrospectively identified 114 consecutive patients hospitalized at Chang Gung Memorial Hospital, Taiwan, between May 2001 and July 2003 with acute PE diagnosed by spiral computed tomography (CT) or high probability ventilation–perfusion lung scan. During the first 24 h of admission, all enrolled patients underwent the first arterial blood gas analysis under room air. Patients with intermediate or low probability lung scans were excluded, as were patients with clinical suspicion of septic emboli or a history of chronic lung disease.

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Division of Cardiology, Chiayi Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Chai Yi Hsien, *Section of Health Informatics, Institute of Public Health, National Defense Medical Center and University and **First Division, Cardiovascular Section, Lin-Kou Medical Center, Chang-Gung Memorial Hospital, Taipei, Taiwan

Mailing address: Chang Min Chung, MD, Divisions of Cardiology, Chiayi Chang Gung Memorial Hospital, 6, Sec. West Chai-Pu Road, Pu-TZ City, Chai Yi Hsien, Taiwan. E-mail: cmchung02@hotmail.com

Table 1 Clinical Characteristics, Echocardiographic Parameters, and Cardiac TnI Levels in Patients With Acute Pulmonary Embolism

Variable	30-day survival (n=94)	30-day death (primary end point) (n=20)	p value
<i>Clinical characteristics</i>			
Age (years)	62.35±14.91	63.95±18.12	0.676 ^a
Duration of symptoms (days)	7.78±9.64	9.20±14.58	0.588 ^a
Women	46 (32%)	10 (50%)	0.1779 ^b
Cancer	11 (11%)	9 (45%)	0.0002 ^{b, **}
Hypotension (SBP <100 mmHg)	3 (3%)	7 (35%)	<0.0001 ^{b, ***}
Diabetes mellitus	17 (17%)	5 (25%)	0.4018 ^b
Hypertension	26 (27%)	3 (15%)	0.2597 ^b
Congestive heart failure	8 (8%)	1 (5%)	0.6432 ^b
DVT	33 (35%)	7 (35%)	1.0000 ^b
CAD	3 (3%)	1 (5%)	0.6518 ^b
Renal insufficiency	13 (14%)	6 (3%)	0.1703 ^b
Recent surgery/immobilization	12 (13%)	2 (10%)	0.7123 ^b
Thrombocytopenia	18 (19%)	11 (55%)	0.0008 ^{b, **}
<i>Arterial blood gas analysis</i>			
PaO ₂	57.32	55.45	0.556 ^a
PaCO ₂	31.05	27.29	0.031 ^{a, *}
Aa-DO ₂	53.60	60.17	0.062 ^{a, #}
Aa-DO ₂ ≥53 mmHg	47/94 (50%)	16/20 (80%)	0.0143 ^{b, *}
a/APO ₂	0.52	0.48	0.154 ^a
a/APO ₂ <0.49	36/94 (38%)	13/20 (65%)	0.0280 ^{b, *}
PO ₂ /FiO ₂	272.94	264.05	0.556 ^a
<i>Thrombolysis</i>			
Tissue plasmin activator	6 (6%)	1 (5%)	0.8623 ^b
Echocardiography and TnI RVD (RV/LV ≥1)	15 (16%)	6 (30%)	0.1428 ^b
TnI ≥0.4 ng/ml	27 (28%)	17 (85%)	<0.0001 ^{b, ***}

TnI, troponin I; ^a, t-test; ^b, proportion test; SBP, systolic blood pressure; DVT, deep vein thrombosis; CAD, coronary artery disease; RVD, right ventricular dilatation; RV, right ventricular; LV, left ventricular.

p*<0.05, *p*<0.001, ****p*<0.0001, #*p*<0.08 is borderline.

Acute PE was treated pharmacologically in all cases. During the acute phase, all patients received anticoagulant therapy with either unfractionated heparin dosed according to the activated partial thromboplastin time or weight-adjusted low-molecular heparin administered subcutaneously. Thrombolysis, which was required by 8 patients, consisted of a 2-h intravenous infusion of 100 mg recombinant tissue plasminogen activator without concomitant heparin. Oral warfarin with an international normalized ratio 2.0–3.0 was used for at least 6 months in all discharged patients. The hospital's Human Research Committee approved the study and all participants gave oral informed consent.

Clinical Features and Biochemical Data

Clinical characteristics of all enrolled patients were recorded: gender, age, duration of symptoms, underlying disease, and possible risk factors. Baseline biochemical data, such as blood urea nitrogen, serum creatinine, troponin I, D-dimer, arterial blood gas, and platelet count, were also recorded. Electrocardiography, chest X-ray and echocardiography findings were also reviewed.

The alveolar–arterial oxygen gradient was calculated as follows:

$$\text{AaDO}_2 (\text{mmHg}) = 150 - 1.25\text{PaCO}_2 - \text{PaO}_2.$$

The arterial/alveolar oxygen tension ratio (a/APO₂) was also calculated:

$$\text{a/APO}_2 = 1 - \text{AaDO}_2/\text{PAO}_2,$$

where PaCO₂ is the partial pressure of carbon dioxide in arterial blood (mmHg), PaO₂ is the partial pressure of oxygen in arterial blood (mmHg), and PAO₂ is the partial pressure of oxygen in the alveoli. Measurements of arterial blood

gases were obtained while the patient breathed room air. All measurements were obtained within 24 h prior to commencing anticoagulant therapy.

Clinical Endpoints

The primary endpoint was 30-day all-cause death and the secondary endpoint was a composite of 30-day death and in-hospital complications, including cardiopulmonary resuscitation, mechanical ventilation and vasopressors for systemic arterial hypotension. All enrolled patients were followed for >1 year.

Statistical Analysis

The Student's t-test was used to compare continuous variables, and the proportion test to compare proportional differences for categorical variables between different groups according to the primary and secondary endpoints. The chi-square test was also used for categorical variables.

Receiver operating characteristic (ROC) analyses were used to determine the high sensitivity of AaDO₂ and a/APO₂ cutoff value for predicting the primary and composite endpoints. The a/APO₂-R was the reciprocal of a/APO₂, which equals 1/(a/APO₂). The reciprocal a/APO₂ (a/APO₂-R) was used to demonstrate the mirror curve of a/APO₂ at the opposite side of the ROC analysis and was used to compare the predictive power of different ROC curves for AaDO₂ and a/APO₂.

Multivariate Cox regression analyses were used to estimate the cumulative probability of the primary and composite endpoints in patients with and without elevated AaDO₂ and a/APO₂. The Cox proportional hazard model was used to calculate the hazard ratios of clinical variables and AaDO₂ and a/APO₂ for predicting primary and composite

Table 2 Clinical Characteristics, Echocardiographic Parameters, and Cardiac TnI Levels in the 30-Day Composite-Event Free Group vs the 30-Day Composite Event Group

Variable	30-day free of composite end point (n=84)	30-day composite end point (n=30)	p value
<i>Clinical characteristics</i>			
Age	62.21±15.40	63.80±15.76	0.631 ^a
Duration of symptoms (day)	7.19±9.17	10.37±13.78	0.248 ^a
Women	37 (44%)	19 (63%)	0.0739 ^{b, #}
Cancer	9 (11%)	11 (37%)	0.0014 ^{b, **}
Hypotension (SBP <100 mmHg)	1 (1%)	8 (27%)	<0.0001 ^{b, ***}
Diabetes mellitus	14 (17%)	8 (40%)	0.0102 ^{b, *}
Hypertension	24 (28%)	5 (17%)	0.2330 ^b
Congestive heart failure	6 (7%)	3 (1%)	0.2128 ^b
DVT	33 (39%)	7 (23%)	0.1143 ^b
CAD	2 (2%)	2 (7%)	0.1892 ^b
Renal insufficiency	10 (12%)	9 (30%)	0.0234 ^{b, *}
Recent surgery/immobilization	9 (11%)	5 (17%)	0.3949 ^b
Thrombocytopenia	16 (19%)	13 (43%)	0.0095 ^{b, *}
<i>Artery blood gas analysis</i>			
PaO ₂	58.18	53.66	0.175 ^a
PaCO ₂	31.04	28.59	0.105 ^a
Aa-DO ₂	52.76	60.33	0.012 ^{a, *}
Aa-DO ₂ ≥53 mmHg	41/84 (48%)	22/30 (73%)	0.0182 ^{b, **}
a/APO ₂	0.53	0.47	0.017 ^{a, *}
a/APO ₂ <0.49	30/84 (36%)	19/30 (63%)	0.0104 ^{b, **}
PO ₂ /FiO ₂	277.04	255.54	0.175 ^a
<i>Thrombolysis</i>			
Tissue plasmin activator	2 (2%)	5 (17%)	0.0029 ^{b, *}
Echocardiography and TnI RVD (RV/LV ≥1)	11 (13%)	10 (33%)	0.0149 ^{b, *}
TnI ≥0.4 ng/ml	20 (24%)	24 (80%)	<0.0001 ^{b, ***}

Abbreviations see in Table 1.

p*<0.05, *p*<0.001, ****p*<0.0001, #*p*<0.08 is borderline.

endpoints. Multivariable analysis was then performed to identify predictors of 30-day death, using the proportional hazards model with calculation of 95% confidence intervals (CI). As 30-day endpoint data were complete for all study patients, no patient was censored.

Results

In total, 114 patients were enrolled and subject to analyses. Of them only 1 patient had an AaDO₂ <20 mmHg. Follow-up assessment of patients was performed after at least 1 year. Table 1 shows the patients clinical characteristics according to the primary endpoint and Table 2 shows them according to the 30-day composite endpoint. There was a significant difference between the 2 groups for AaDO₂ (*p*=0.012). A strong but insignificant trend existed for AaDO₂ between the primary endpoint group and the 30-day survival group (*p*=0.062). All-cause 30-day mortality was 17.5%. The 30-day composite event rate was 26.3%. Five clinical characteristics had a significant effect on the 30-day survival rate: presence of cancer, hypotension, thrombocytopenia, low PaCO₂, and elevated troponin I. Other additive clinical characteristics affected the 30-day composite events: diabetes mellitus, AaDO₂, a/APO₂, renal insufficiency and right ventricular dilatation (RVD).

Statistical analysis demonstrated that thrombocytopenia and renal insufficiency were significantly different between the 30-day composite endpoint group and the 30-day composite event-free group (unpubl data). The incidence of thrombocytopenia was strongly and significantly different between both the 30-day mortality vs survival, and the 30-day composite event vs event-free. The odds ratio for 30-day mortality was 4.49 (95% CI 1.86–10.87) and for 30-

day composite endpoint was 2.96 (95% CI 1.44–6.11).

This study used ROC curves to demonstrate differences in arterial blood gas variables (Fig 1). The AaDO₂ was best at predicting the 30-day composite endpoint. Reciprocal a/APO₂ instead of a/APO₂ was used to compare the prognostic effect of AaDO₂ and a/APO₂ (Fig 2). The area under the ROC curve for a/APO₂-R was slightly smaller than that for AaDO₂ (0.650 vs 0.657). The ROC curves determined that AaDO₂ was best at predicting short-term mortality. The optimal cut-off value for AaDO₂ was 53 mmHg and using that to separate 30-day mortality and survival, the incidence of AaDO₂ ≥53 mmHg also showed a significant difference between the 2 groups (Table 1). With 53 mmHg as the cut-off value for AaDO₂, the positive predictive value for 30-day death was 25%, and the negative predictive value was as high as 92%. For the 30-day composite endpoint, the positive predictive value of AaDO₂ was 35%, and the negative predictive value was 84%. A prognostic cut-off value of the a/APO₂ ratio was 0.49. When a/APO₂ was used instead of AaDO₂, the positive predictive value for the primary endpoint was 26.5%, and negative predictive value was 89%. Moreover, for the secondary endpoint, the positive predictive value of a/APO₂ was 39%, and negative predictive value was 83%.

Figs 3 and 4 show the respective short-term and 1-year survival curves for mortality and the composite event. These curves also demonstrate a significant difference between both 30-day mortality vs survival, and the 30-day composite event vs event-free, based on the cut-off value for AaDO₂ after adjusting for other significant interfering factors. For 30-day death, the hazard ratio of AaDO₂ ≥53 mmHg was 3.55 (95% CI 1.19–10.62), and for the 30-day composite event, the hazard ratio of AaDO₂ ≥53 mmHg

Fig1. Receiver operating characteristic curve of ability of arterial blood gas analysis parameters to predict 30-day composite endpoint. AaDO₂, alveolar–arterial oxygen pressure difference; FiO₂, fractional inspired oxygen concentration.

Fig2. Receiver operating characteristic curve of ability of AaDO₂ and a/APO₂-R to predict 30-day composite endpoint (See text for details).

was 2.55 (95% CI 1.14–5.74).

Discussion

Role of AaDO₂ Analysis in Patients With PE

The AaDO₂ is typically used as an index of gas exchange, and the factors influencing it are diffusion gradient, ventilation–perfusion imbalance and true shunt. The combination of AaDO₂ and pulmonary artery pressure has been used for classifying PE.⁸ Kunieda et al identified a positive correlation between AaDO₂ and increased pulmonary vascular obstruction.⁴ Although Paul et al observed that a normal AaDO₂ did not exclude a diagnosis of acute PE, they also demonstrated a linear correlation between AaDO₂, pulmonary artery pressure and the number of mismatched vascular

Fig3. Survival curves at 1 year, based on a cut-off values of AaDO₂ ≥53 mmHg vs AaDO₂ <53 mmHg (See text for details).

Fig4. Composite event-free survival curves at 1 year, based on cut-off values of AaDO₂ ≥53 mmHg vs AaDO₂ <53 mmHg (See text for details).

perfusion defects.⁶ The present study further assessed the utility of using AaDO₂ to predict morbidity and mortality, and found that the optimal cut-off value for was 53 mmHg for 30-day mortality and a composite endpoint. We used different variables for arterial blood gas analysis (PaO₂, PaCO₂, AaDO₂ and a/APO₂) to evaluate the ability of each to predict short-term mortality and morbidity. The AaDO₂ with a cut-off value of 53 mmHg was the best at predicting short-term mortality and morbidity. It had a high negative predictive rate and moderate positive predictive rate. Any patient with AaDO₂ ≥53 mmHg has a moderate probability of morbidity and mortality. Mortality or morbidity was uncommon for any patient with AaDO₂ <53 mmHg during the first 24 h of admission. Thus, AaDO₂ can be used in combination with other parameters, such as hypotension,

high troponin I, RVD, to improve the accuracy of prognostic evaluation. Additionally, Masami et al have documented that inverted T waves have prognostic significance in acute PE.⁹ Therefore, the combination of initial AaDO₂ and ECG findings may provide another approach for predicting clinical prognosis. Aggressive thrombolytic therapy should be considered for patients with an AaDO₂ $\geq$ 53 mmHg.

Role of a/APO₂ Analysis in Patients With PE

Gilbert et al¹⁰ investigated the impact of fractional inspired oxygen concentration (FiO₂) on the AaDO₂ gradient and a/APO₂ ratio in normal subjects. They demonstrated that a/APO₂ provides a uniform guide to gas exchange function over the range of FiO₂ used in clinical practice. Gilbert et al defined the lower limit of normal for the ratio as approximately 0.75, and indicated that the a/APO₂ ratio is relatively unaffected by FiO₂. Retrospective analysis of patient data in the present study showed that many patients underwent their first blood gas analysis under varying concentrations of oxygen support in the emergency room (ER). As the influence of inspired oxygen on the AaDO₂ has been documented, the study group was screened using the same oxygen concentration (room air) to avoid the influence of varying FiO₂. In the real world, blood gas analysis could be checked under variable FiO₂. When patients arrive at the ER with acute illness, oxygen will be administered by the first-line physician. Therefore, the present study also assessed the predictive power of a/APO₂ and notably, it had similar but less predictive power than AaDO₂ for the short-term composite endpoint. The a/APO₂ was better than other blood gas analysis variables for predicting the short-term composite endpoint. The ROC curves determined that the prognostic cut-off value of a/APO₂ ratio was 0.49, which may be another method for adjusting the impact of different FiO₂ in clinical practice. To examine this issue, future research will require an increased number of patients who were administered different oxygen ratios.

Conflicting Result for Hypoxemia

Although a normal PaO₂ does not rule out PE, elevated PaO₂ can assist in determining the hemodynamic severity in patients with documented PE.⁹ In the Geneva score, hypoxemia is an important predictor of death.¹¹ Analysis of the results of the present study demonstrated that hypoxemia was not significantly different between short-term mortality vs survival groups and the composite endpoint vs composite event-free survival groups. This conflict was likely caused by different patient selection methods. We enrolled patients having a high probability lung scan or positive spiral CT, which is more severe disease than in other studies. In the landmark PIOPED study, only 41% of patients with PE had a high-probability lung scan; most (57%) had an intermediate-probability or low-probability scan.⁷

Mechanism for Widening AaDO₂ and Hypoxemia

Acute PE impairs the efficient transfer of oxygen and carbon dioxide across lungs. Decreased arterial PO₂ (hypoxemia) and increased AaDO₂ gradient are the most common gas exchange abnormalities. There are controversial statements about the mechanism of hypoxemia and increased AaDO₂. D'Alonzo et al concluded that hypoxemia and increased AaDO₂ was explained by large shunts.¹² Manier et al had another rationale for the mechanism of hypoxemia and increased AaDO₂. They proposed that decreased mixed venous O₂ plays a major role in patients with acute PE.

Hypoxemia and increased AaDO₂ are promoted by a moderate increase in the fraction of blood flowing through low ventilation-perfusion units. Diffusion impairment plays only a minor role in the mechanism.¹³ A low oxygen pressure in the venous blood may also contribute to arterial hypoxemia when PE causes right ventricular (RV) failure. Low cardiac output results in increased extraction of oxygen by the tissues, thereby reducing the partial oxygen pressure in venous blood below normal levels. Moreover, the importance of ventilation-perfusion inequality has also been addressed by other studies.^{14,15} When ventilation and perfusion are mismatched, blood flow from the obstructed pulmonary arteries is redirected to other gas exchange units, and shunting of venous blood into the systemic circulation can occur.

Significant Role of Thrombocytopenia in Acute PE

In the present study thrombocytopenia was associated with the severity of acute PE, as finding that has rarely been mentioned in the literature. Platelet reduction has been observed in patients with post-traumatic pulmonary microembolism.¹⁶ In the present series there was a significant difference in the incidence of thrombocytopenia between the short-term morbidity and short-term composite endpoint groups. This phenomenon can be explained by increased platelet consumption in severe PE. Adverse consequences result from reduction of blood flow through the pulmonary vasculature because of mechanical obstruction, and local pulmonary vasoconstriction resulting from platelet-mediated release of humoral substances, including serotonin, adenosine diphosphate, prostaglandins, and thromboxane.¹⁷⁻²⁰ Several physiological responses to platelet activation, such as pulmonary hypertension, bronchoconstriction, and RV failure, have been identified.²¹

Study Limitations

First, the limited sample size. A larger sample size would increase the difference in the AaDO₂ between groups. Second, this uncontrolled retrospective study had a selection bias. According to the inclusion criteria, the patients had severe PE. In the landmark PIOPED study, most patients with PE (57%) had an intermediate- or low-probability scan, and 11-14% of the 280 patients had a normal AaDO₂. In contrast, only 1 of 114 patients in the present study had a normal AaDO₂.

Conclusion

Measurement of AaDO₂ is a highly useful and simple measurement for predicting short-term mortality and composite events. It has high negative predictive value and moderate positive predictive value for 30-day death and 30-day composite events. The a/APO₂ has a predictive ability that is similar to AaDO₂, but further study is required to make a clear conclusion. Thrombocytopenia was also an indicator of poor prognosis for patients with acute PE and aggressive thrombolytic therapy should be considered for patients with an initial poor prognostic parameter of AaDO₂ $\geq$ 53 mmHg.

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