Prognostic Value of Arterial/Alveolar Oxygen Tension Ratio (a/APO₂) in Acute Pulmonary Embolism

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Background Because the arterial/alveolar oxygen tension ratio (a/APO₂) is relatively constant throughout the entire range of fractional inspired oxygen concentration (FiO₂), its use in determining the prognosis of acute pulmonary embolism (APE) was investigated.

Methods and Results This study retrospectively assessed 202 consecutive patients with APE confirmed by computed tomography or high probability lung scintigraphy. All patients underwent initial arterial blood gas analysis during the first 24 h of admission. Receiver-operating characteristic analyses were performed to determine the a/APO₂ cut-off value for predicting 30-day death or 30-day composite events. Cut-off values for a/APO₂ were used to determine stability in all patients and 2 subgroups (0.49 for all patients; 0.49 for FiO₂=0.21; 0.46 for FiO₂>0.21). Using the cut-off value of a/APO₂<0.49 for predicting 30-day death, the negative predictive value (NPV) was 90%, and the positive predictive value (PPV) was 30.3%. For the 30-day composite end point, the NPV was 81.3%, and the PPV was 40.9%. Excluding massive APE, the a/APO₂ also had high NPV and moderate PPV in predicting short-term prognosis. This study additionally demonstrated a linear relationship between platelet count and a/APO₂.

Conclusions The cut-off value of a/APO₂<0.49 exhibits stability at variable FiO₂ values and is a useful prognostic predictor in APE. (Circ J 2007; 71: 1560–1566)

Key Words: Acute pulmonary embolism; Alveolar–arterial oxygen pressure difference (AaDO₂); Arterial/alveolar oxygen tension ratio (a/APO₂); Thrombocytopenia

Short-term mortality is high in patients with a pulmonary embolism (PE). The International Cooperative Embolism Registry (ICOPER) of 2,454 patients reported that the short-term cumulative mortality because of PE was 11.4% at 2 weeks and 17.4% at 3 months! Acquired predisposing factors include surgery, trauma, immobilization, cancer, oral contraceptive use, pregnancy, postmenopausal hormone replacement therapy and frequent air travel? Accurate risk stratification is of paramount importance in selecting the optimal management strategy for patients with acute PE (APE) and a rapid, noninvasive and inexpensive screening test is urgently needed. Although arterial blood gas (ABG) measurements have proved disappointing for excluding APE,³ both the alveolar–arterial oxygen gradient (AaDO₂) and the arterial/alveolar oxygen tension ratio (a/APO₂) have demonstrated efficacy for prognosis of APE.⁴ The previous study by Hsu et al was limited to patients breathing room air.⁴ Although AaDO₂ is believed to measure the severity of APE, it is strongly

dependent on the fraction of inspired oxygen (FiO₂).^{5,6} The a/APO₂ has proven in several studies to be a more reliable predictive index in patients with abnormal lung gas exchange.^{5–7}

Therefore, the purpose of the present investigation was to use an FiO₂ expanded from 0.21 to 1.0 to explore further the prognostic value of a/APO₂.

Methods

Study Sample

We assessed 202 consecutive patients admitted to Chang Gung Memorial Hospital (CGMH), Taiwan, between March 2000, and July 2005, with APE confirmed by computed tomography (CT) or high-probability ventilation–perfusion lung scan. During the first 24 h of admission, all enrolled patients underwent initial ABG analysis under either room air or oxygen support. Patients with an intermediate- or low-probability lung scan, clinical suspicion of septic emboli, recurrent PE or history of chronic lung disease were excluded.

APE was treated pharmacologically in all cases; that is, anticoagulant therapy with unfractionated heparin dosed according to activated partial thromboplastin time, or weight-adjusted low-molecular heparin administered subcutaneously. Thrombolysis, which 16 patients underwent, consisted of a 2-h intravenous infusion of 100 mg recombinant tissue plasmin activator (tPA) without concomitant heparin.

Oral warfarin at an international normalized ratio of 2.0–3.0 was used for at least 6 months in all discharged patients. The Human Research Committee approved the study and

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Table 1 Clinical Characteristics, Arterial Blood Gas Analysis, Echocardiographic Parameters and Cardiac TnI Levels in Patients Who Survived 30 Days or Died 30 Days After Acute Pulmonary Embolism

	30-day survival (n=157)	30-day death (n=45)	p value
<i>Clinical characteristics</i>			
Age (years)	62.80±15.68	62.42±17.40	0.891*
Duration of symptoms (days)	6.33±8.29	6.80±10.65	0.755*
Women	81 (51%)	23 (51%)	1.000**
Cancer	21 (13%)	19 (42%)	<0.001**
SBP	131.29±27.71	116.49±27.21	0.002*
Shock (SBP <90 mmHg)	8 (5%)	11 (24%)	<0.001**
Diabetes mellitus	28 (18%)	9 (20%)	0.827**
Hypertension	44 (28%)	8 (18%)	0.182**
Congestive heart failure	12 (8%)	2 (4%)	0.740**
Deep vein thrombosis	53 (34%)	12 (27%)	0.470**
Coronary artery disease	7 (4%)	1 (2%)	0.687**
Renal insufficiency	22 (14%)	7 (16%)	0.811**
Recent surgery/immobilization	18 (11%)	5 (11%)	1.000**
Thrombocytopenia	35 (22%)	22 (49%)	0.001**
<i>Arterial blood gas analysis</i>			
FiO2	0.28±0.13	0.34±0.20	0.023*
PaO2	69.25±40.02	59.87±26.74	0.141*
PaCO2	31.20±6.92	30.05±10.49	0.390*
AaDO2	94.38±70.68	146.09±132.47	0.001*
a/APO2	0.46±0.15	0.36±0.16	<0.001*
a/APO2 <0.49	85 (54%)	37 (82%)	<0.001**
PaO2/FiO2	252.26±79.93	205.60±90.74	0.001*
<i>Thrombolysis</i>			
Tissue plasmin activator	12 (8%)	4 (9%)	0.759**
<i>Echocardiography and TnI</i>			
RVD (RV/LV ≥1)	31 (20%)	17 (38%)	0.017**
TnI ≥0.4 ng/ml	86 (55%)	34 (75%)	<0.001**

TnI, troponin I; SBP, systolic blood pressure; RVD, right ventricular dilatation; RV, right ventricle; LV, left ventricle.

See text for definitions of arterial blood gas analysis.

*Student's t-test, **proportional test.

all participants gave informed consent.

Clinical Features and Biochemical Data

Recorded clinical data including the following: age, gender, duration of symptoms, underlying disease and possible risk factors. Baseline biochemical data, such as blood urea nitrogen, serum creatinine, troponin I (TnI), ABG and platelet count were also examined before treatment. Electrocardiography, chest X-ray and echocardiographic findings were also reviewed.

The AaDO2 was calculated as:

$$\text{AaDO}_2 (\text{mmHg}) = \text{PAO}_2 - \text{PaO}_2$$

$$\text{PAO}_2 = (\text{P}_\text{B} - \text{P}_\text{H}_2\text{O}) (\text{FiO}_2) - 1.25\text{PaCO}_2$$

and the a/APO2 as:

$$\text{a/APO}_2 = \text{PaO}_2 / \text{PAO}_2$$

where P_B is barometric pressure (assuming 760 torr), $\text{P}_\text{H}_2\text{O}$ is the water vapor partial pressure (47 torr at 37°C), FiO_2 is fractional inspired oxygen concentration, PaCO_2 is partial pressure of carbon dioxide in arterial blood (mmHg), PaO_2 is partial pressure of oxygen in arterial blood (mmHg) and PAO_2 is partial pressure of oxygen in alveolar. ABGs were measured while the patient breathed room air or was on oxygen support. All measurements were obtained within 24 h prior to anticoagulant therapy.

Clinical Endpoints

The 30-day all-cause death was the primary endpoint. The secondary endpoint was a composite endpoint of 30-day death and in-hospital complications, including cardiopulmonary resuscitation, mechanical ventilation and vasopressors for systemic arterial hypotension. Because this study

was a retrospective observational study, the decision to start thrombolysis was based on the clinical assessment of the individual patient by the physician in charge. To minimize selection bias, thrombolysis was not included in the composite endpoint. All enrolled patients received follow-up treatment for at least 1 year.

Statistical Analysis

Continuous variables were compared by Student's t-test, and categorical variables between groups were compared by proportion test according to primary and secondary endpoints.

Receiver-operating characteristic (ROC) analyses was used to determine the a/APO2 cut-off value for predicting primary and composite endpoints. The reciprocal AaDO2 (AaDO2-R) was reciprocal for AaDO2, which equaled $1/\text{AaDO}_2$. The AaDO2-R was used to demonstrate the mirror curve of AaDO2 at the opposite side of ROC analyses. This analysis was used to compare the predictive power of different ROC curves of AaDO2 and a/APO2.

Cumulative probability of the primary and composite endpoints in patients with and without decreased a/APO2 were estimated by multivariate Cox regression analysis. The hazard ratio (HR) of a/APO2 was calculated by the Cox proportional hazard model to predict primary and composite endpoints. Multivariate analysis was then performed to identify predictors for 30-day death using the proportional hazards model with 95% confidence intervals (CI).

The strength of linear relationships between platelet count and a/APO2 was estimated on the basis of Pearson correlation coefficients.

Table 2 Clinical Characteristics, Arterial Blood Gas Analysis, Echocardiographic Parameters and Cardiac Troponin I in the 30-Day Composite-Event-Free Group vs 30-Day Composite-Event Group

	30-day free of composite endpoint (n=137)	30-day composite endpoint (n=65)	p value
<i>Clinical characteristics</i>			
Age (years)	62.70±15.70	62.74±16.83	0.988*
Duration of symptoms (days)	6.05±8.05	7.25±10.35	0.371*
Women	65 (47%)	39 (60%)	0.100**
Cancer	18 (13%)	22 (34%)	0.001**
SBP	132.69±28.36	118.09±25.31	0.001*
Shock (SBP <90 mmHg)	7 (5%)	12 (18%)	0.002**
Diabetes mellitus	23 (17%)	14 (22%)	0.440**
Hypertension	37 (27%)	15 (23%)	0.608**
Congestive heart failure	9 (7%)	5 (8%)	0.772**
Deep vein thrombosis	49 (36%)	16 (25%)	0.147**
Coronary artery disease	6 (4%)	2 (3%)	1.000**
Renal insufficiency	16 (12%)	13 (20%)	0.134**
Recent surgery/immobilization	15 (11%)	8 (12%)	0.814**
Thrombocytopenia	28 (20%)	29 (45%)	<0.001**
<i>Arterial blood gas analysis</i>			
FiO ₂	0.28±0.12	0.34±0.19	0.006*
PaO ₂	68.16±27.65	65.07±53.03	0.587*
PaCO ₂	31.29±7.10	30.21±9.23	0.362*
AaDO ₂	90.44±68.91	138.49±118.40	<0.001*
a/APO ₂	0.48±0.14	0.36±0.17	<0.001*
a/APO ₂ <0.49	72 (53%)	50 (77%)	<0.001**
PaO ₂ /FiO ₂	256.67±74.89	210.65±95.10	<0.001*
<i>Thrombolysis</i>			
Tissue plasmin activator	7 (5%)	9 (14%)	0.048**
<i>Echocardiography and troponin I</i>			
RVD (RV/LV ≥1)	25 (18%)	23 (35%)	0.013**
TnI ≥0.4 ng/ml	73 (53%)	47 (72%)	<0.001**

Abbreviations see in Table 1.

*Student's t-test, **proportional test.

Fig 1. Receiver-operating characteristic (ROC) analysis curves for variable arterial blood gas analysis in all patients. *Area under the ROC curve. a/APO₂, arterial/alveolar oxygen tension ratio; AaDO₂-R, reciprocal the alveolar–arterial oxygen gradient; AaDO₂, alveolar–arterial oxygen gradient; FiO₂, fractional inspired oxygen concentration.

Results

Tables 1 and 2 show the baseline characteristics of the study population of 202 patients according to the primary and secondary endpoints, respectively.

In the 202 patients, diagnosis of PE was based on a high-probability lung scan in 121 (60%) and a positive CT scan in 81 (40%). The 30-day mortality rate was 22.3%, and the 30-day composite event rate was 32.2%. The clinical parameters that differed significantly between the 30-day death group and the 30-day survival group included cancer, systolic blood pressure (SBP), shock (SBP <90 mmHg), thrombocytopenia, FiO₂, AaDO₂, a/APO₂, PaO₂/FiO₂, right ventricular (RV) dilatation and elevated TnI level. The only additional significant parameter between the 30-day composite event group and the 30-day event-free survival was the rate of thrombolysis. In the 30-day composite event group, the rate of tPA treatment was higher than in the 30-day composite-event-free group. In ABG analysis, FiO₂ was higher in the 30-day death group than in the 30-day survival group (p=0.023). Moreover, the FiO₂ was also higher in the 30-day composite-event group than in the 30-day event-free group (p=0.006).

This study used ROC curves to demonstrate differences in ABG variables. All patients (n=202) were assigned to 1 of 2 subgroups according to FiO₂ level. The first subgroup included patients breathing room air (FiO₂=0.21, n=114), and the second subgroup included patients breathing a higher oxygen supplement (FiO₂ ranging from 0.28 to 1.0, n=88).

Optimal cut-off values of a/APO₂ and AaDO₂ were calculated in all patients and the separate subgroups (Figs 1,2).

Fig2. Receiver-operating characteristic (ROC) analysis curves for variable arterial blood gas analysis in 2 subgroups: (A) fractional inspired oxygen concentration (FiO_2)=0.21, (B) $\text{FiO}_2 > 0.21$. *Area under the ROC curve. a/APO2, arterial/alveolar oxygen tension ratio; AaDO2-R, reciprocal the alveolar–arterial oxygen gradient; AaDO2, alveolar–arterial oxygen gradient.

Fig3. Survival curves at 1 year based on cut-off value of arterial/alveolar oxygen tension ratio (a/APO2) <0.49 vs a/APO2 $\geq$ 0.49. HR, hazard ratio.

Fig4. Composite event-free survival curves at 1 year based on cut-off values of arterial/alveolar oxygen tension ratio (a/APO2) <0.49 vs a/APO2 $\geq$ 0.49. HR, hazard ratio.

Cut-off values of a/APO2 were stable in the total patient cohort and in the 2 subgroups. (0.49 for all patients; 0.49 for $\text{FiO}_2=0.21$; 0.46 for $\text{FiO}_2 > 0.21$); the optimal cut-off values of AaDO2 were highly variable in the total group and the 2 subgroups (135 mmHg for all patients; 53 mmHg for $\text{FiO}_2=0.21$; 207 mmHg for $\text{FiO}_2 > 0.21$).

Fig 1 shows the differences in ABG variables in all patients. AaDO2-R instead of AaDO2 was used to compare the prognostic effect of AaDO2 and a/APO2. The area under the ROC curve for a/APO2 was higher than that for AaDO2-R (0.682 vs 0.646). The ROC curves indicated that a/APO2 was the best predictor of short-term mortality. The optimal cut-off value for a/APO2 was 0.49. Using the cut-

off value to distinguish 30-day mortality and survival, the incidence of a/APO2 <0.49 also revealed a significant difference between the 2 groups ($p < 0.001$, Table 1). The incidence of a/APO2 <0.49 also differed significantly between the 30-day composite event group and the event-free group ($p < 0.001$, Table 2).

The cut-off value of a/APO2 <0.49 used to predict 30-day death demonstrated a sensitivity of 82% and a specificity of 45.8%. The negative predictive value (NPV) was 90%, and the positive predictive value (PPV) was 30.3%. The 30-day composite endpoint, a/APO2 <0.49, demonstrated a sensitivity of 76.9% and a specificity of 47.4%. The NPV was 81.3%, and the PPV was 40.9%.

Fig 5. Platelet count as a function of arterial/alveolar oxygen tension ratio (a/APO2) in patients with acute pulmonary embolism. Correlation coefficient (r)=0.233, $p<0.01$.

Patients in shock were classified as massive PE and excluded from the normotensive subgroup analysis ($n=19$). Using the cut-off value ($a/APO_2 < 0.49$) to analyze normotensive APE ($n=183$), the cut-off value for 30-day death had a sensitivity of 85.3% and a specificity of 48.3%. The NPV was 93.5%, and the PPV was 27.3%. For the 30-day composite endpoint, $a/APO_2 < 0.49$ had a sensitivity of 77.3% and a specificity of 50.0%. The NPV was 84.4%, and the PPV was 38.7%.

Figs 3 and 4 show the short-term and 1-year survival curves for mortality and composite events, respectively. These survival curves also demonstrated a significant difference between 30-day mortality vs survival, as well as for 30-day composite-event vs event-free, based on the cut-off value for a/APO_2 after adjusting for other significant interfering factors and age. For 30-day death, the HR of $a/APO_2 < 0.49$ was 2.17 (95% CI 1.25–3.77); for the 30-day composite event, the HR of $a/APO_2 < 0.49$ was 2.19 (95% CI 1.32–3.62).

In addition, the incidence of thrombocytopenia significantly differed between both 30-day mortality vs survival and 30-day composite-event vs event-free. The odds ratio for 30-day mortality was 1.52 (95% CI 1.17–1.97). The odds ratio for 30-day composite endpoint was 2.25 (95% CI 1.38–3.68). A linear relationship between platelet count and a/APO_2 level was also noted (Fig 5). Linear regression analysis revealed regression coefficients of 0.233 between platelets and a/APO_2 ($p<0.01$).

Discussion

Mechanisms of Impaired Gas Exchange and Index of Gas Exchange in APE

Large shunt has proved to be the major cause of hypoxemia and impaired gas exchange in APE.^{8,9} An increased area of pulmonary artery obstruction destabilizes normal distribution of ventilation/perfusion and increases shunt. The lung regions exhibit alveolar dead space with high ventilation/perfusion ratios and shunting because of perfusion of atelectatic areas.⁹ Other proposed mechanisms have been reported and revealed minor roles.^{10–13}

Several parameters are derived from ABG analysis. Hypoxemia and impaired gas exchange indices calculated as a function of inspired oxygen concentration include PaO_2/FiO_2 , a/APO_2 and $AaDO_2$.^{5,13,14} In the present study, ROC curve analysis found that PaO_2/FiO_2 was inferior to both the a/APO_2 and $AaDO_2$ for comparing gas exchange under room air. If FiO_2 was more than 0.21, the area under the ROC curve for PaO_2/FiO_2 was slightly smaller than that for a/APO_2 (0.709 vs 0.714). This finding was compatible with the report of Gowda et al.¹⁵ In addition, the unit of PaO_2/FiO_2 was confusing and did not account for different levels of $PaCO_2$. Because this, the PaO_2/FiO_2 was not favorable for predicting the short-term prognosis of APE.

Although $AaDO_2$ has been correlated with perfusion defects, including acute and chronic PE,¹⁴ $AaDO_2$ would increase as FiO_2 increased. Compared with $AaDO_2$, a/APO_2 was more consistent for identifying lung gas exchange under differing FiO_2 .^{5–7}

Role of a/APO_2 in APE

In 1974, Gilberts and Keighley demonstrated that a/APO_2 was more stable than $AaDO_2$ at various levels of FiO_2 .⁵ The lower limits of normal were determined to be 0.75. Their method was based on demonstrating that the ratio of arterial to alveolar oxygen tension is a reliable and consistent index of respiratory impairment over the range of FiO_2 from 0.21 to 1.0.

Subsequent studies by Gilberts et al proved that the constancy of the a/APO_2 ratio depends on the amount of shunting and ventilation/perfusion inequality.⁶ It was found that a/APO_2 was most useful at FiO_2 levels greater than 0.3 and PaO_2 levels less than 100 torr. The greatest constancy of a/APO_2 was noted in patients with large shunts, whereas $AaDO_2$ shows the greatest variability under these circumstances.

In the emergency room, APE patients present with variable acuity and require different ventilation methods and oxygen treatment. Although a/APO_2 is not independent of FiO_2 , it is clearly less dependent on FiO_2 than $AaDO_2$, and may be useful on this basis alone.

The present study also demonstrated consistent cut-off

values of a/APO2 at different FiO2 levels. Conversely, the AaDO2 cut-off values were highly variable at different FiO2 levels, which indicates that a/APO2 is best for assessing the prognosis of APE because of its stability over a wide range of inspired oxygen concentrations.

Role of a/APO2 in APE in Normotensive Patient

Many reports has used echocardiography for risk stratification of in-hospital death and patients with echocardiographic evidence of RV dysfunction have a 4.6–12.6% PE-related in-hospital mortality rate.^{16–19} The treatment strategy still remains controversial for normotensive patients with APE, especially if it is submassive.^{20,21} There is a need for a rapid, noninvasive, inexpensive screening test for risk stratification of APE.

Compared with the reported average in-hospital mortality of 8.6%,^{18,19} a/APO2 can be used for further risk stratification in normotensive APE. Excluding acute, massive APE with shock, in the present study the 30-day outcome of the remaining 183 patients with normotensive PE were analyzed using the same cut-off value of a/APO2 <0.49. This group included small to submassive APE.

The 30-day death result also showed a high NPV of 93.5% and a PPV of 27.3%. For the 30-day composite event, the PPV was 38.7%, and the NPV was high at 84.4%.

Based on the above analytical results, a/APO2 can help differentiate the high-risk group of APE without hypotension. In daily practice, initial ABG analysis can quickly identify the high-mortality group of normotensive, ensuring that clinicians treat these patients more aggressively with thrombolytic agents.

Kunieda et al have reported that an initially elevated index of gas exchange (AaDO2) would decrease according to recovery of APE, with a linear correlation to the resolved perfusion defect.⁴ Moreover, serial a/APO2 analysis may also reveal dynamic change in the severity of APE. However, the initial selection criteria in the present study included either a positive CT scan (n=81) or high-probability lung perfusion scan (n=121), which resulted in an inconsistent presentation in the extent of PE for these 2 diagnostic tools. Although the a/APO2 supposedly correlates well with the extent of PE, conducting the analysis was limited by the inclusion criteria. A further prospective study is needed to confirm this hypothesis.

Platelets

Platelet activation occurs in the initial phase of venous thrombus formation. Urinary excretion of thromboxane B2, a marker of platelet activation in the early phases of thrombus formation, increases in APE.²² Modig et al reported a reduced platelet count in pulmonary microembolism after trauma.²³ McCarthy et al has reported that low platelet counts was related to high AaDO2 values in post-trauma PE.²⁴ In an animal study, significant platelet and fibrinogen consumption occurred after thrombin injection.²⁵ Physiological responses to platelet activation include pulmonary hypertension, bronchoconstriction and RV failure.^{25,26} Thrombocytopenia in APE could be explained by intravascular coagulation and platelet consumption. Further analysis in the present study revealed a relationship between platelet count and a/APO2, suggesting that the degree of thrombocytopenia is related to severity of impaired gas exchange in APE. Moreover, this finding also means that the severity of APE is reflected in the degree of thrombocytopenia.

Linear regression analysis revealed a significant relation-

ship between platelet and a/APO2, although the correlation was weak. Two explanations are possible. First, this study analyzed the relationship between a/APO2 and post-embolism platelet count, not absolute platelet consumption. Absolute platelet consumption is calculated by pre-embolism platelet count minus post-embolism platelet count. Because the pre- and post-embolism platelet counts vary widely between patients, the severity of APE is more appropriately evaluated by absolute platelet consumption than post-embolism platelet count. Takayoshi et al also demonstrated a strong correlation between physiologic dead space and thromboxane B2 concentration, which was related to the fall in platelet count in an earlier animal study.²⁶ However, the pre-embolism platelet count is difficult to determine in APE patients, even in a prospective study design.

Second, multiple factors contributed to the final result for impaired gas exchange. The APE causes cardiopulmonary dysfunction that may result from mechanical obstruction, neurogenic factors and local pulmonary vasoconstriction resulting from platelet-mediated release of humoral substances, including serotonin, adenosine diphosphate, prostaglandins, thromboxane and platelet-activating factor.^{29,30} The correlation between platelet count and a/APO2 would be affected by initial platelet consumption, release of humoral factors, thrombus formation and late-developing events. This impressive linear relationship has never been documented previously.

Hypotension and Short-Term Prognosis of APE

Some of the parameters identified as predictors of adverse outcome include RV dysfunction,^{17–19,21} T-wave inversion,³¹ elevated troponin level, elevated brain natriuretic peptide,³² hypotension¹ and abnormal gas exchange.⁴

Hemodynamic instability has been identified as an important risk factor for in-hospital mortality or escalation of treatment.^{1,33,34} The present study also demonstrated the importance of SBP in the short-term prognosis of APE patients. The prevalence of hypotension (SBP <90 mmHg) significantly differed between the 30-day survival group and the 30-day death group ($p < 0.001$, Table 1), as well as between the 30-day composite event-free group and the 30-day composite event group ($p = 0.002$, Table 2).

The mechanisms of hypotension depend on the initial mechanical obstruction, as well as on the subsequent neurohumoral stimuli and hypoxic effects.²⁹ The direct effect of vascular obstruction causes RV dilation and dysfunction, decreasing preload and impairing the gas exchange.^{1,14,16} Subsequent pulmonary hypertension and ventricular interdependency results in underfilling and decreased end-diastolic volume of the left ventricular. These mechanisms may all cause ischemia and possibly cardiogenic shock.

Massive PE with RV dysfunction and systemic hypotension has a poor prognosis.^{1,33,34} Although the rate of thrombolytic therapy was relatively low in the present study, currently available data indicate that thrombolytic treatment should be performed for hemodynamic instability on presentation.^{33,34}

Study Limitations

First, this was a retrospective observational study. Thrombolysis was performed by the managing physician based on individual clinical presentation, so the clinical indications of thrombolysis were not uniform. Thus, the parameter “tPA” was not included in the composite endpoint. Further-

more, predisposing factors were not thoroughly examined in every patient.

Second, there was selection bias in this study. The inclusion criteria allowed enrollment of patients with more severe PE than general APE. According to the analytical results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED),²⁷ 57% patients with APE present with low- or intermediate-probability lung perfusion scan. Moreover, Kline et al have reported that approximately 15% of patients with PE have a normal index of lung gas exchange (AaDO₂).²⁸ However, in the present study only 3 patients had a normal a/APO₂ ratio (>0.75).

Third, the number of subjects was limited. The sample size was not sufficiently large to allow detailed statistical investigation of all different FiO₂ levels. Future studies should analyze a larger study population at every FiO₂ level to further demonstrate the consistency of a/APO₂.

Fourth, a previous prospective study proved that the gas exchange index (AaDO₂) was valuable for clinically assessing resolved emboli in the recovery phase of APE.¹⁴ In our retrospective study, not all included patients underwent post-treatment ABG analysis. Subsequent analysis was performed according to clinical presentation of the patients and the decision of the managing physician, which limited the observation of dynamic change in a/APO₂ during APE treatment.

Conclusion

This study has revealed that a/APO₂ not only indicates the severity of lung gas exchange, but is also a predictor of in-hospital mortality and composite events. For the purpose of predicting short-term prognosis, a/APO₂ is more consistent than AaDO₂ at different FiO₂.

The cut-off value (a/APO₂ <0.49) was characterized by a high NPV and moderate PPV in all patients and in the subgroup of normotensive patients with APE. The platelet count presented a linear relationship with severity of a/APO₂. a/APO₂ is a quick and clinically useful blood test for short-term risk stratification of APE and gives an important insight to the further treatment strategy.

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