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Original Article

Transcutaneous *carbon dioxide monitoring* as a predictive tool for all-cause 6-month mortality after acute pulmonary embolism

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ABSTRACT

Background: Pulmonary embolism (PE) frequently remains undiagnosed. The partial pressure of carbon dioxide (Pa_{CO2}), a surrogate of dead-space ventilation, is useful in the evaluation of the degree *of* pulmonary artery occlusion. At present, there is no knowledge about the prognostic role of Pa_{CO2} variations during the first hours of an acute PE. Transcutaneous measurement of CO_2 (Ptc_{CO2}) is a simple, non-invasive method that correlates well with Pa_{CO2} levels, evaluated in this study for the first time in patients with PE.

Purpose: To assess the correlation between Ptc_{CO2} and Pa_{CO2} levels in the acute phase of PE and the role of Ptc_{CO2} in predicting 6-months mortality.

Methods: This was a pilot study including 53 patients with acute PE who hospitalized in Respiratory Medicine Department at University Hospital of Larissa in central Greece during 15 months. Ptc_{CO2} was constantly monitored for four hours after PE diagnosis with the TCM40 monitoring system (SmartCal). Simultaneous arterial blood gas measurements were performed. Each patient was prospectively recorded for six months via standard telephone calls.

Results: Pa_{CO2} and Ptc_{CO2} values were well-correlated in the acute phase of PE. Decreased Ptc_{CO2} levels in the first monitoring hour were associated with a higher risk of mortality. In the PE subgroup who died, the lower Ptc_{CO2} level in the first hour of PE was a predictor of shorter survival time independently of gender, age, comorbidities, and smoking status.

Conclusion: Ptc_{CO2} measurement, especially in the first hour after PE, seemed to be a valid tool in predicting all-cause 6-month mortality.

1. Introduction

Pulmonary embolism (PE) is the third most common cardiovascular disorder in industrialized countries with a total annual incidence of 62 to 112 cases per 100,000 inhabitants [1–3]. However, the actual incidence is likely to be more as it is frequently undiagnosed or diagnosed only at autopsy [4]. PE imposes a substantial social, economic burden with increased resource utilization, a broad spectrum of clinical outcomes, and a high mortality rate [1].

PE remains a major *diagnostic challenge*. It is known that patients with PE had non-specific clinical signs and symptoms [5]. In most patients with a final diagnosis of PE, symptoms and initial investigation results can mislead to the diagnosis of acute coronary or lung disease. The contribution of biochemical laboratory tests to the diagnosis of PE is also weak. Computerized tomography pulmonary angiography (CTPA) remains the gold standard in PE diagnosis; nevertheless, it requires specialized staff and expensive equipment. Imaging techniques are also user-dependent, and they can cause technical biases for risk stratification [5].

One commonly held misconception is that the air-blood gas analysis is of limited diagnostic value in patients with suspected PE [6]. However, hypocapnia and respiratory alkalosis are typical *blood gas abnormalities* seen in patients with PEs, as even patients with restrictive lung disease will reduce their arterial blood partial pressure of CO_2

Abbreviations: AUCg, Area Under the Curve with respect to ground; AUCi, Area Under the Curve with respect to increase; CCI, Commodity Channel Index; CTPA, Computerized Tomography Pulmonary Angiography; Pa_{CO2}, arterial blood partial pressure of CO_2; PE, Pulmonary Embolism; PESI, Pulmonary Embolism Severity Index; Pet_{CO2}, end-tidal carbon dioxide; P_{O2}, partial pressure of oxygen; Ptc_{CO2}, transcutaneous measurement of CO_2; Sat_{O2}, oxygen saturation; sPESI, simplified PESI

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(Pa_{CO2}) level after experiencing a PE [7]. The mechanisms causing hyperventilation in PE patients are incompletely understood, but increased physiologic dead space and chemo-sensitivity seemed to play an important role [8].

Pa_{CO2} and end-tidal carbon dioxide (Pet_{CO2}) are surrogates for dead space ventilation that could be useful in the evaluation of the degree of pulmonary artery occlusion [9,10]. Specifically, it has been demonstrated that a Pa_{CO2} value of 30 mmHg or less is highly suggestive of an obstruction index of > 50% of the arterial bed [11]. Furthermore, it has been suggested that the combined assessment of a positive D-dimer test and abnormal end-tidal alveolar dead space fraction, as determined by Pet_{CO2} measurement in exhaled gas, increase the specificity for diagnosing PE compared with the D-dimer test alone [12,13].

The above-mentioned gas exchange abnormalities seen in patients with PE are associated with the size of the emboli, embolization time, and the underlying cardiopulmonary disease [14]. Indeed, the pulmonary artery obstruction index developed by Qanadli et al. is significantly correlated with all blood gas values [15]. Approximately 10% of symptomatic PE is fatal within an hour after the onset of symptoms [16]. The severity of acute PE is determined primarily by its hemodynamic impact, presenting as sudden pulmonary hypertension due to both pulmonary bed obstruction and reflex and humoral pulmonary vasoconstriction [17]. It is well known that pulmonary hypertension influences Pa_{CO2} values. Hoeper et al. reported a significant correlation between Pa_{CO2} and cardiac output [18]. Therefore, hyperventilation and consequently decreased Pa_{CO2} are features of heart failure and pulmonary hypertension; thus may be related to PE severity and prognosis [18].

Non-invasive transcutaneous measurement of CO_2 (Ptc_{CO2}) has been proven accurate in the assessment of ventilation and oxygenation of acute respiratory disorders like asthma and pneumonia when compared with arterial blood gases [19,20]. Ptc_{CO2} is a simple, bedside non-invasive surrogate measure that correlates well with Pa_{CO2} levels on arterial blood gas analysis; avoiding pain, infection, iatrogenic anemia that are associated with frequent arterial stabs and arterial catheterization [19–22]. To our knowledge, no study exists, recording the kinetics of Ptc_{CO2} in the first hours of an acute PE in non-intubated patients. Moreover, Ptc_{CO2} has been evaluated in this study for the first time in patients with acute PE, while there is no data regarding the role of Ptc_{CO2} in the risk stratification of PE. The aims of this study were to assess the correlation between Ptc_{CO2} and Pa_{CO2} values within first four hours after an acute PE and evaluate whether the Ptc_{CO2} monitoring upon patients' admission could be used as a tool for predicting all-cause 6-month mortality in patients with PE.

2. Material and methods

2.1. Ethics

Verbal and written informed consent was obtained from all subjects before the study, according to the Helsinki declaration. The protocol was approved by the Larissa University Hospital Ethics Committee.

2.2. Participants and study design

This was a pilot, non-interventional observational study, including a total of 53 patients diagnosed with acute PE on CTPA. All participants had been hospitalized at the Respiratory Medicine Department of the University of Thessaly during a 15-month period; from December 2014 to March 2016.

Upon presentation to the emergency department, a room air arterial blood gas was performed. The Wells and Geneva pre-test probability scores were calculated. Routine laboratory tests (blood, biochemical and coagulation tests) and d-dimer concentrations were measured on admission. Hemodynamically unstable patients were excluded from the study as it is known that shock affects the Ptc_{CO2} measurements. Specifically, when cardiac output decreases, a disproportionate fall in Ptc_{CO2} occurs.

After the diagnosis of PE was established by CTPA, detailed documentation of patient's demographics, medical history and comorbidities were collected. The pulmonary embolism severity index (PESI), simplified PESI (sPESI), and *Commodity Channel Index* (CCI) were subsequently calculated [23].

Each patient was prospectively recorded for a six-month follow-up period via standard telephone calls. All patients were re-evaluated three months after the diagnosis of PE for d-dimers, and comparisons were made with initial values.

2.3. Ptc_{CO2} monitoring system

Ptc_{CO2} was monitored continuously for four hours, immediately after CTPA diagnosis. Simultaneous arterial blood gas measurements were performed. Ptc_{CO2} levels were collected using the TCM40 monitoring system (SmartCal) according to the manufacturer's instructions [24–26].

The Ptc_{CO2} measurement was performed by a Severinghaus-type CO_2 electrode. The function of the electrode is based on pH measurement. It consists of a pH-sensitive glass element surrounded by a silver leaf (Ag) conjugated with silver chloride (AgCl). The silver element (Ag) serves to heat the skin, thus resulting in increased local capillary perfusion. This increases the metabolic rate of the skin and the solubility of CO2 [24–26].

The SmartCal was calibrated before each use, and the calibration gas mix was set to 20.9% O_2, 7,5% CO_2 and 71,6% N_2. After the in vitro calibration, Ptc_{CO2} and Pa_{CO2} values were registered at the same time as a blood sample from each patient, in order to check that Ptc_{CO2} is closer to the actual Pa_{CO2} rates (in vivo calibration). In other words, Ptc_{CO2} was validated by comparing its values with air-blood gas results on *room air* at a baseline measurement and periodically thereafter. Ptc_{CO2} should have an acceptable agreement with Pa_{CO2} with limits of agreement of plus or minus 5 mmHg [27].

The preferred measuring area was the skin of the lateral aspect of the upper abdomen as the distal placement of the electrode in the presence of vasoconstriction underestimates Ptc_{CO2} levels. However, in case of thickened or oedematous skin or subcutaneous tissue, to avoid inaccurate readings, alternatives highly vascularized locations such as the earlobe or the inner aspect of the thigh or forearm were chosen. The electrode was clipped on the selected area after the skin was carefully cleaned with alcohol and dried well with a gauze pad. Two drops of contact liquid were used and then the sensor was placed. The sensor temperature was between 42 °C and 44 °C and the physiological stabilization time for the Ptc_{CO2} reading was 10 min [24–27]. After clip removal, the condition of the underlying skin was recorded.

2.4. Statistical analyses

Quantitative variables were expressed as mean ± standard deviation (SD). Qualitative variables were expressed as absolute and relative frequencies. Paired *t*-tests were used for the comparison of paired data. Mann-Whitney test was used for the comparison of continuous variables between two groups when the distribution was not normal. For the comparisons of proportions, chi-square tests and Fisher's exact tests were used. Pearson's correlation coefficients (r) were used to test the association of two continuous measures.

Ptc_{CO2} variables were tested for their ability to predict death events using receiver operating characteristic (ROC) curves. The overall performance of the ROC analysis was quantified by computing area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different from chance. The area under the curve with respect to ground (AUCg) and the area under the curve with respect to increase (AUCi) formulas were also used to analyze the repeated measures of Ptc_{CO2}, as previously reported [28,29].

AUCg for Ptc_{CO2} is the formula that calculates the total area under the curve of all the measurements in the observing period. It thus takes into account the difference between the single measurements from each other (i.e., the change over time) and the distance of these measures from the ground and is independent of increases or decreases over time. In other words, it is a formula which allows summarizing information that can be derived from repeated measurements. In contrast to AUCg, AUCi ignores the distance from zero for all measurements, thereby emphasizing how the Ptc_{CO2} levels changed over time [28,29].

Using ROC analysis was determined the optimal sensitivity and specificity of using various cut-off values for the prediction of deaths. Life table analyses were used to calculate cumulative survival rates (standard errors) for specific time intervals. The prognostic value of each variable for survival was first assessed by univariate Cox regression analysis. Variables that showed significant association with the outcome were included in the multivariate Cox proportional-hazard model in a stepwise method. The assumption of proportional hazards was evaluated by testing for interaction with a continuous time variable. Hazard ratios (HR) with 95% confidence intervals (95% CI) were computed from the results of the Cox regression analyses. Kaplan – Meier survival estimates for survival were graphed over the follow-up period. Predictors regarding all-cause related death in the PE subgroup who died were assessed by multivariate linear regression analyses calculating the corresponding 95% confidence intervals. *P* values reported are two-tailed. Statistical significant level was set at 0.05, and analysis was conducted using SPSS 19.0 (SPSS, Chicago, IL, USA) Statistical Software.

3. Results

3.1. Study participants characteristics

Data from 53 subjects (28 men and 25 women) were analyzed. Sample characteristics of the total sample and according to gender, are presented in Table 1.

All patients were hemodynamically stable without requiring thrombolytic treatment. 24.5% of the sample were smokers and 18.9% had undergone surgery during the previous six months. Hypertension, coronary disease, cerebrovascular disease were present in 26.4%, 15.1% and 11.3%, respectively. 22.6% and 26.4% had a high score on Genova and Wells indices, respectively, while 26.4% of the patients were grouped into classes 4 (high risk) and 5 (very high risk) as indicated by the PESI score.

The reference concentration of D-dimer was < 255 ng/mL. All patients with PE had a positive serum D-dimer result. Mean D-dimer values in PE patients on admission and after three months of the diagnosis were 1892.35 ng/ml and 255.38 ng/ml, respectively. A statistically significant difference in the mean D-dimer level between two observation periods was observed (−1636.97 ng/mL, $p < .001$). No association between D–dimer levels on admission and demographics (gender, age, smoking status), comorbidities (cerebrovascular disease, coronary disease, hypertension), or various predisposing factors for PE (surgical procedure within the last 6 months, malignancy, prolonged immobilization) was detected. The mean oxygen saturation (Sat_{O2}), partial pressure of oxygen (P_{O2}), Pa_{CO2}, pH, and *lac*tate on admission were 93.7 ± 4.9, 71.5 ± 17.4, 35.4 ± 7.5, 7.44 ± 0.05, and 2.1 ± 0.8 respectively.

3.2. Comparison between Pa_{CO2} and Ptc_{CO2}

As shown in Fig. 1, Pa_{CO2} and Ptc_{CO2} measurements were well-correlated ($r = 0.67$, $p < .001$).

3.3. Overall survival rates

The mean follow-up period was 6 ± 0.3 months. The cumulative

Table 1
Sample characteristics of the total sample ($N = 53$) and according to gender.

	Total	Men (n = 28)	Women (n = 25)	*p*-value
	N (%)			
Age (years)				
20–30	4 (7.5)	1 (3.6)	3 (12.0)	NSǂ
30–40	3 (5.7)	2 (7.1)	1 (4.0)	–
40–50	3 (5.7)	2 (7.1)	1 (4.0)	–
50–60	7 (13.2)	4 (14.3)	3 (12.0)	–
60–70	9 (17.0)	6 (21.4)	3 (12.0)	–
70–80	12 (22.6)	8 (28.6)	4 (16.0)	–
80–90	15 (28.3)	5 (17.9)	10 (40.0	–
Smoking status				
No smokers	27 (51.0)	6 (21.4)	21 (84.0)	< 0.001*
Current smokers	13 (24.5)	9 (32.1)	4 (16.0)	–
Ex-smokers	13 (24.5)	13 (46.4)	0	–
Comorbidities				
Cerebrovascular Disease	6 (11.3)	2 (7.1)	4 (16.0)	NSǂ
Coronary disease	8 (15.1)	6 (21.4)	2 (8.0)	NSǂ
Hypertension	14 (26.4)	8 (28.6)	6 (24.0)	NS*
Pulmonary embolism risk factors				
Surgical procedure within the last 6 months	10 (18.9)	5 (17.9)	5 (20.0)	NSǂ
Malignancy	7 (13.2)	4 (14.3)	3 (12.0)	NSǂ
Prolonged immobilization	9 (17.0)	4 (14.3)	5 (20.0)	NSǂ
Oral contraceptives	1 (1.9)	0	1 (4.0)	NSǂ
Postpartum period	3 (5.7)	0	3 (12.0)	NSǂ
Clinical prediction rules				
Wells score				
Low	29 (54.7)	19 (67.9)	10 (40.0)	0.042*
Intermediate	24 (45.3)	9 (32.1)	15 (60.0)	–
High	0	0	0	–
Geneva score				
Low	5 (9.4)	3 (10.7)	2 (8.0)	NSǂ
Moderate	36 (67.9)	19 (67.9)	17 (68.0)	–
High	12 (22.6)	6 (21.4)	6 (24.0)	–
Prognostic assessment tools				
PESI				
Class 1	11 (20.8)	5 (17.9)	6 (24.0)	NSǂ
Class 2	15 (28.3)	6 (21.4)	9 (36.0)	–
Class 3	13 (24.5)	10 (35.7)	3 (12.0)	–
Class 4	9 (17.0)	4 (14.3)	5 (20.0)	–
Class 5	5 (9.4)	3 (10.7)	2 (8.0)	–
sPESI				
Low risk	8 (15.1)	4 (14.3)	4 (16.0)	NSǂ
High risk	45 (84.9)	24 (85.7)	21 (84.0)	–
CCI, mean ± SD	5.0 ± 2.6	5.11 ± 2.3	4.6 ± 2.75	NS‡

ǂFisher's exact test; *chi-square test; ‡Student's t-test.
CCI: Charlson Comorbidity Index; **PESI:** Pulmonary Embolism Severity Index; **sPESI:** simplified Pulmonary Embolism Severity Index.

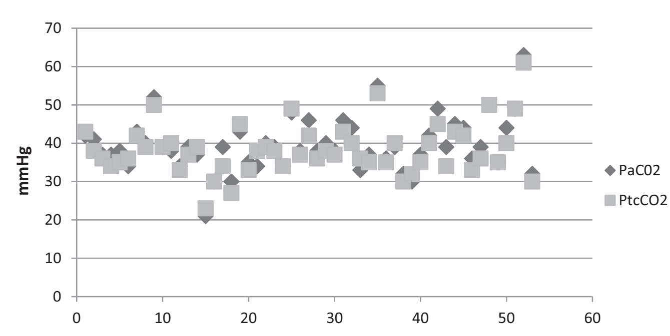

Fig. 1. Scatter plot of agreement between the Ptc_{CO2} and Pa_{CO2} measurements ($N = 53$).

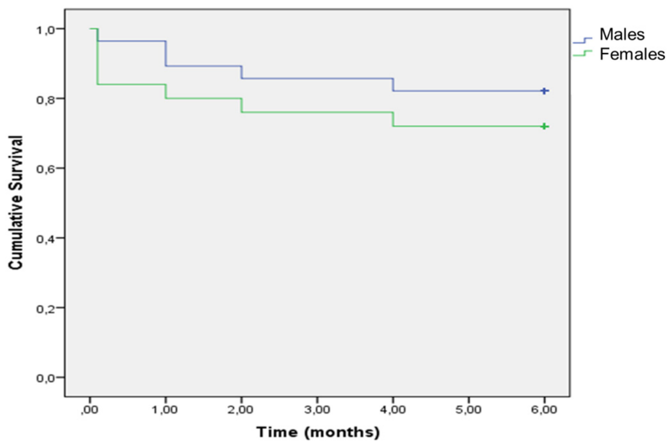

Fig. 2. Kaplan -Meier 6-month survival curve for males (n = 28) and females (n = 25).
‡The survival plot shows how survival declines with time measured in months.

event-free rate for the first month was 88.9% (SE = 4.3%), for two months 83.3% (SE = 5.1%) and for three months 79.6% (SE = 5.5%). Kaplan – Meier survival estimates for survival were graphed over the follow-up period. No significant difference was found regarding survival between males and females (log-rank test, p = .354) (Fig. 2).

3.4. *Results from Ptc_{CO2} monitoring*

Table 2 shows descriptive statistics of Ptc_{CO2} measurements during the first 4 h of monitoring. Ptc_{CO2} measures were not correlated with PESI, sPESI and CCI prognostic rules of mortality. No association between Ptc_{CO2} levels and clinical prediction rules was found. No association between recorded Ptc_{CO2} levels and laboratory data or d-dimers was detected.

Ptc_{CO2} levels significantly decreased from baseline to first hour (p < .001) as well as for all sequential measurements (p < .001) in a gender-**in***dependent* manner imaged in Fig. 3.

3.5. *Assessment of the association of Ptc_{CO2} measurements during the 4 h monitoring with survival*

The association of Ptc_{CO2} measurements during the 4 h monitoring with survival are presented in Table 3. Increased Ptc_{CO2} in the first monitoring hour and AUCg for PtcCO2 were associated with a lower risk of death.

ROC curve analysis showed that the optimal-cut off Pt_{CO2} value in the first hour for predicting mortality was 32.5 mmHg (sensitivity equal to 53.8% and specificity equal to 90.4%). The area under the curve

Table 2
Descriptive statistics of Ptc_{CO2} measurements (mmHg) during the 4 h of monitoring.

	Mean ± SD
Ptc_{CO2} (baseline)	39.7 ± 7.5
Ptc_{CO2} (1st hour)	38.1 ± 7.5
Ptc_{CO2} (2nd hour)	36.3 ± 6.9
Ptc_{CO2} (3rd hour)	34.8 ± 6.9
Ptc_{CO2} (4th hour)	32.9 ± 7.7
mean Ptc_{CO2}	36.0 ± 6.9
AUCg	8532.8 ± 1845.9
AUCi	6583.1 ± 2146.8
Change from baseline to the1st hour	−1.6 ± 2.9
Change from baseline to the 4th hour	−7.1 ± 5.5

AUCg: Area under the curve with respect to ground; **AUCi:** Area under the curve with respect to increase.

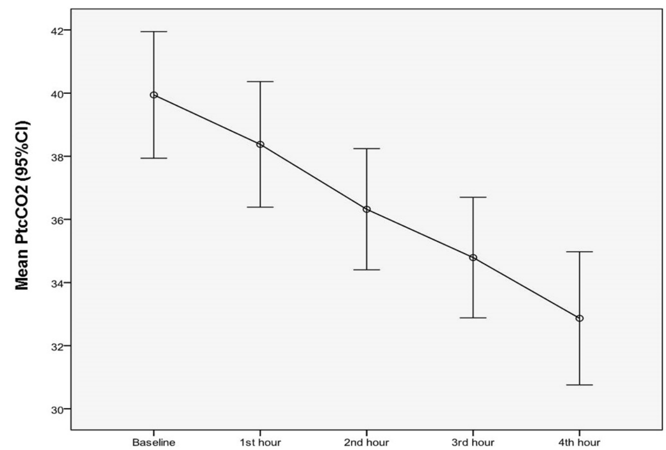

Fig. 3. Mean transcutaneous measurement of CO2 (Ptc_{CO2}) values (mmHg) during the 4 h of monitoring for the study group (N = 53).

Table 3
Association of transcutaneous measurement of CO2 (Ptc_{CO2}) measurements/hour, mean Ptc_{CO2}, minimum and maximum values of Ptc_{CO2}, AUCg, AUCi and change of Ptc_{CO2} levels from baseline to 1st and 4th hour with survival.

	HR (95% CI)[a]	*p-value*
Ptc_{CO2} (baseline)	0.93 (0.84–1.02)	0.130
Ptc_{CO2} (1st hour)	0.89 (0.81–0.98)	**0.017**[b]
Ptc_{CO2} (2nd hour)	0.92 (0.83–1.02)	0.107
Ptc_{CO2} (3rd hour)	0.92 (0.83–1.01)	0.090
Ptc_{CO2} (4th hour)	0.96 (0.89–1.03)	0.256
mean Ptc_{CO2}	0.91 (0.82–1.01)	0.056
min Ptc_{CO2}	1.00 (0.92–1.09)	0.982
max Ptc_{CO2}	0.92 (0.84–1.01)	0.086
AUCg (for 100 unit increase)	0.96 (0.94–0.99)	**0.012**[a]
AUCi (for 100 unit increase)	0.98 (0.96–1.01)	0.137
Change from baseline to 4th hour	0.99 (0.90–1.09)	0.797
Change from baseline to 1st hour	0.90 (0.76–1.07)	0.236

[a] Hazard Ratio (95% Confidence interval).
[b] Increased PtcCO2 in the first hour of monitoring and increased AUCg for ptCO2 were associated with a lower risk of death.

(AUC) was 0.73 (95% CI: 0.55–0.91), which significantly differs from 0.5 (p = .014). Concerning AUCg for CO2, ROC analysis demonstrated a cut-off value equal to 7272.8 (sensitivity 53.8% and specificity 87.8%).

When multiple Cox regression analysis was conducted, it was found that AUCg for Ptc_{CO2} and PESI were independently associated with survival (Table 4). Increased PESI was associated with worse outcome, while increased AUCg for Ptc_{CO2} was associated with a better outcome. Patients with Ptc_{CO2} in the first hour below the cut off value of 32.5 mmHg, had a six-fold greater risk of death (HR = 6.42, 95%CI: 2.13–19.32, p = .001).

Table 4
Results from multiple Cox regression analysis in a stepwise method of the relationship between the AUCg for Ptc_{CO2} AUCg cut-off value > 7272.8, PESI score with all-cause 6-month mortality after diagnosis of pulmonary embolism.

	HR (95%CI)[a]	*p-value*
AUCg (for 100 unit increase)	0.97(0.94–0.99)	0.033
AUCg > 7272.8	0.18(0.06–0.55)	0.002
PESI	2.32(1.22–4.41)	0.010

[a] Hazard ratios (95% confidence interval).

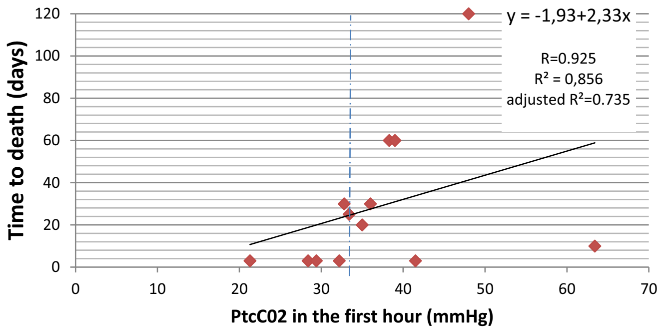

Fig. 4. Multivariate linear regression model of time to death (days).The fitted line plot shows that Ptc_{CO2} level at the first hour was an independent predictor of early death.

a. Predictors: (Constant), Gender, Age (years), Ptc_{CO2} at baseline, Ptc_{CO2} at the 1st hour, Ptc_{CO2} at the 2nd hour.

b. Dependent Variable: Time to death (months).

c. Excluded variables: comorbidities, smoking, Ptc_{CO2} at the 3rd hour, Ptc_{CO2} at the 4th hour.

R - 0.925, R^2–0.856, adjusted R^2–0.735.

3.6. Assessment of the association of Ptc_{CO2} measurements during the 4 h monitoring with survival in the PE subgroup who died

During the follow-up period, 13/53 patients (24.1%) died. For these patients, the mean survival period was 38 ± 40.2 days. Mean Pt_{CO2} value in the first hour was 36.14 ± 10.2 mmHg. 46% (6/13) died during hospitalization. 67% (4/13, 2 males and 2 females) had Pt_{CO2} value at the first hour below the cut-off value of 32.5 mmHg and all four patients died within 3 days.

Regarding the group of patients who died, in the multivariate linear regression model, the lower Ptc_{CO2} levels in the first hour was an independent predictor of early death (B = 2.33, p = .035) (Fig. 4). In other words, we found that survival increased by an average of 2.3 months for each 1 mmHg increase of Ptc_{CO2} in the first hour. Conversely, gender, age, Ptc_{CO2} at baseline and Ptc_{CO2} at second hour were not significant predictors of survival in this group of patients.

4. Discussion

At present, little is known about the variation of blood Pa_{CO2} and Pet_{CO2} during the first hours of an acute PE. Furthermore, the prognostic importance of Pa_{CO2} variation is unknown. It has been reported that Ptc_{CO2} correlates well with Pa_{CO2} levels. In the current study, for the first time, Ptc_{CO2} parameter was assessed in patients with acute PE. We investigated the correlation between Ptc_{CO2} and Pa_{CO2} values during the acute phase of PE and evaluated the usefulness of Ptc_{CO2} monitoring as a predictive tool of all-cause 6-month mortality in patients with PE.

We confirmed that Pa_{CO2} and Ptc_{CO2} values were well correlated in the acute phase of PE; thus, Ptc_{CO2} measurement can be used alternatively as an effective, well-tolerated method for determining alveolar dead space.

The evidence to date supporting Ptc_{CO2} measurement as an alternative to arterial gas sampling has been contradictory, coming from small studies with patients who were often medically stable [19,30–33]. It has been reported that the Ptc_{CO2} method could not be reliably used to suggest a trend or direction of change in CO2 level in medical patients admitted to hospital acutely. In contrast, Lambert et al. proposed that a transcutaneous monitor should be used as a trending device [19]. The overall consensus is that transcutaneous monitors can be used to trend the patients' status but should not be relied on to make significant changes to patient care without corroborating information, preferably from blood gas analysis [19]. The contradictory findings may be explained by the different temperature of the Ptc_{CO2} electrode in various studies. However, in our study, the sensor temperature was between 42 °C and 44 °C, and we found that there was an accuracy of Ptc_{CO2} values compared with capillary blood gases in patients with acute PE. Hence, we suggest that Ptc_{CO2} is a simple, painless bedside non-invasive surrogate measure that correlates well with Pa_{CO2} levels on arterial blood gas analysis. Besides, Ptc_{CO2} monitors have been widely used in neonatal intensive care units, reducing the need for frequent blood drawing and painful punctures, providing a continuous estimation of Pa_{CO2}. Furthermore, the superiority of Ptc_{CO2} over Pet_{CO2} measurement for monitoring respiratory failure has been demonstrated in non-intubated patients, for the assessment of hypoventilation during weaning from mechanical ventilator support, or during procedures that require sedation and sleep studies [34,35].

We monitored Pt_{CO2} levels in acute PE patients and found that the mean Pt_{CO2} levels significantly decreased from baseline to the first hour as well as for all sequential measurements. There are only two studies of Glenski et al., in 1986, reported that Ptc_{CO2} values were reliable in identifying hypocarbia, normocarbia and hypercarbia monitoring trends in hemodynamically stable anesthetized adult patients, being, however, no sensitive in detecting venous air embolism or the degree of immediate physiologic threat in humans and experimental models [36,37]. On the contrary, according to our results, Ptc_{CO2} trend curve monitoring might provide clinically useful "online" information regarding the risk stratification of PE, in accordance with a previous study regarding Pet_{CO2} monitoring [38,39].

According to our results, Ptc_{CO2} measurement, especially in the first hour after a PE, seemed to be a valid tool in predicting all-cause 6-month mortality. The majority of studies have used various prognostic models to predict 30-day or 90-day mortality after acute PE; thus, follow-up is limited to the first 1–3 months of treatment. Only a few studies evaluated the relationship between the prognostic models and 6-month mortality. The ongoing follow-up after acute PE has a significant impact on the long-term management of patients after acute PE. There are studies reporting that PE patients have reduced survival compared to the background population, even after excluding early deaths and malignancies.

Until now, there is no knowledge regarding the usefulness of Ptc_{CO2} monitoring as a predictive tool of mortality for patients with PE. One of our main findings was that decreased Ptc_{CO2} levels in the first monitoring hour after PE diagnosis were associated with a higher risk of death for the first six months. We found that Ptc_{CO2} levels below 32.5 mmHg in the first monitoring hour were associated with a higher risk of death for the first six months with high specificity. In patients who died lower Ptc_{CO2} levels constituted an independent factor of early 6-month out-of-hospital all-cause mortality. These findings are in contrast with the study of Ozsu S et al., who reported that Pa_{CO2} levels above 30 mmHg constitute an independent mortality predictor for in-hospital and out of hospital all-cause deaths [40].

Furthermore, we found that increased AUCg for Ptc_{CO2} -that expressed the values of Ptc_{CO2} among multiple measurements from baseline to the 4th hour- was associated with a lower risk of mortality. Remarkably, in a Cox proportional hazards regression, the risk of death was smaller (3% risk reduction) in the PE group with increased AUCg for Ptc_{CO2} as compared to the PE group with decreased AUCg for Ptc_{CO2}. By integrating over time rather than looking at time-point measurements, a more accurate estimate of the variation could be obtained. However, the prognostic cut-off Ptc_{CO2} value at the 1st hour is a more friendly tool in clinical practice than the AUCg estimation. Remarkably, focusing on the PE subgroup who died we found that lower Ptc_{CO2} level measured in the first hour of an acute PE constituted a predictor of shorter survival time after the event independently of gender, age, comorbidities, and smoking status.

During PE, significant disorders of blood flow together with a ventilation-perfusion (V/Q) mismatch lead to increase of alveolar dead space to an extent that can be measured [41]. The increase in alveolar dead space volume is proportional to the severity of pulmonary vascular obstruction. From a pathophysiological point of view, increased dead space impairs the efficient elimination of carbon dioxide and leads to an increase in Pa_{CO2} [42]. However, medullary chemoreceptors sense any elevation in arterial Pa_{CO2}, and they subsequently enhance the total minute ventilation, thereby lowering Pa_{CO2} to normal and often below normal [42]. Hence, the increase in minute alveolar ventilation and the consequent decrease in Pa_{CO2} may indirectly reflect an extension of the alveolar dead space. Accordingly, the sensitivity of Pa_{CO2} varies widely depending on the degree of embolic obstruction. Alveolar-arterial (AaDO2) gradient has been proposed as a simple measurement in the diagnosis and risk stratification of patients with PE, assessing the degree of shunting and V/Q mismatch, constituting, however, only a one-point reflection of intrapulmonary shunting [43].

One limitation of this study is that we did not include hemodynamically unstable patients as it is known that shock affects the Ptc_{CO2} measurements. Evaluation of CO2 measures in this group of patients as a predictive factor of mortality indicates a potential pathway for further research as it is known that although patients with an acute PE usually show an arterial blood gas pattern consistent with respiratory alkalosis, patients with severe right pulmonary artery occlusion showed steadily increased Pa_{CO2} values [44]. Another major limitation of the study is the small number of subjects included. Our study constitutes a pilot study reporting that Ptc_{CO2} measurement, especially in the first hour after PE seems to be a valid tool in predicting 6-month mortality; a finding, which merits further analyses in larger scale studies. Finally, we did not include data regarding in-hospital mortality and its correlation with Ptc_{CO2} due to the small sample. Increasing the sample size will avoid misleading statistics regarding in-hospital and out-hospital mortality and its correlation with Ptc_{CO2}.

5. Conclusions

Acute PE pulmonary embolism is a common, potentially life-threatening disease with a high risk for short and long-term death. We showed that Pa_{CO2} and Ptc_{CO2} values were well-correlated in the acute phase of PE; thus Ptc_{CO2} measurement can be alternatively used as an effective, non-invasive method for determining $Pa_{CO2,}$ a marker of alveolar dead-space ventilation. One of our main findings was that decreased Ptc_{CO2} levels in the first monitoring hour were associated with a higher risk of all-cause 6-month mortality. Moreover, we showed that increased AUCg for Ptc_{CO2} was associated with a lower risk of mortality. Focusing on the PE subgroup who died we found that lower Ptc_{CO2} level measured in the first hour after an acute PE was a predictor of shorter survival time after the event independently of gender, age, comorbidities, and smoking status. In summary, these results indicate that the Ptc_{CO2} measurement in the first hour after an acute PE can be used as a valid predictive tool of 6-month mortality.

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Contribution

O.S.Kotsiou analyzed data and wrote the manuscript. V. Karadontas designed and performed research, and K·I Gourgoulianis planned research and analyzed data. All authors edited the final manuscript.

Declaration of Competing Interest

None.

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