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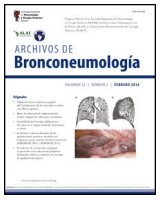

Scientific Letter

The Predictive Value of $PaCO_2$ in Patients With Pulmonary Embolism: Data From RIETE Registry

Dear Editor,

Hypocapnia and respiratory alkalosis are common arterial blood gas (ABG) abnormalities in patients with acute pulmonary embolism (PE) [1]. While the exact mechanisms leading to hypocapnia in this context are not fully understood, a response to hypoxia and complex chemosensitive neural reflexes triggered by thrombi are thought to induce hyperventilation [2]. Additionally, the arterial partial pressure of CO_2 ($PaCO_2$) serves as a surrogate marker for dead space ventilation and may help estimate the degree of pulmonary artery obstruction [2]. Indeed, a $PaCO_2$ value of ≤30 mmHg has been associated with obstruction of more than 50% of the pulmonary arterial bed [3].

Although the clinical significance of hypocapnia at diagnosis is well-established [1], less attention has been given to its prognostic value over time in acute PE [4]. Our aim was to evaluate the association between initial $PaCO_2$ levels and all-cause mortality at 7, 30, and 90 days in patients with acute PE. Additionally, we explored whether this relationship varied by PE risk stratification. Data were obtained from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry.

ABG analysis was performed within the first six hours of PE diagnosis at the discretion of the treating physician; the timing of anticoagulation in relation to ABG collection was not consistently recorded in the registry. After excluding 176 patients with implausible $PaCO_2$ values (<20 or >140 mmHg), 28,883 patients diagnosed from March 2001 to April 2023 were included.

PE severity was classified according to the European Society of Cardiology (ESC) guidelines. Low-risk PE was defined as a simplified Pulmonary Embolism Severity Index (sPESI) of zero with no right ventricular (RV) dysfunction and no elevated troponin. High-risk PE was defined by systolic blood pressure < 90 mmHg; all others were considered intermediate risk.

We performed multivariable logistic regression to assess the association between $PaCO_2$ values and all-cause mortality at 7, 30, and 90 days. The models were adjusted for the following covariates: age (>80 vs. ≤80 years), sex, RV dysfunction, troponin levels (elevated vs. normal), active cancer, chronic respiratory disease, chronic heart failure, heart rate (≥110 vs. <110 per minute), systolic blood pressure (≥100 vs. <100 mmHg), renal dysfunction (creatinine clearance <60 vs. ≥60 mL/min), oxygen saturation (<90% vs. ≥90%), and $PaCO_2$ category. $PaCO_2$ was stratified into three clinically relevant categories: <30 mmHg, 30–39 mmHg, and ≥40 mmHg.

In univariable analysis, patients with $PaCO_2$ < 30 mmHg had significantly higher mortality at 7 days (odds ratio [OR]: 2.46; 95%CI: 2.05–2.96), 30 days (OR: 1.70; 95%CI: 1.50–1.93), and 90 days (OR: 1.59; 95%CI: 1.43–1.76), compared with those with $PaCO_2$ 30–39 mmHg. Patients with $PaCO_2$ ≥40 mmHg also showed increased mortality at 7 days (OR: 1.94; 95%CI: 1.60–2.35), 30 days (OR: 1.56; 95%CI: 1.38–1.77), and 90 days (OR: 1.48; 95%CI: 1.34–1.64). In multivariable analysis, both low and high $PaCO_2$ values remained significantly associated with higher mortality compared to the reference group (30–39 mmHg). Specifically, $PaCO_2$ < 30 mmHg was associated with increased mortality at 7 days (adjusted OR [aOR]: 1.92; 95%CI: 1.59–2.32), 30 days (aOR: 1.38; 95%CI: 1.21–1.58), and 90 days (aOR: 1.33; 95%CI: 1.19–1.49). Similarly, $PaCO_2$ ≥ 40 mmHg was associated with higher mortality at 7 days (aOR: 1.76; 95%CI: 1.45–2.14), 30 days (aOR: 1.46; 95%CI: 1.28–1.66), and 90 days (aOR: 1.43; 95%CI: 1.28–1.60).

Other variables independently associated with increased 7-day mortality included: age > 80 years (aOR: 1.69; 95%CI: 1.41–2.02), male sex (aOR: 1.30; 95%CI: 1.10–1.53), elevated troponin (aOR: 1.23; 95%CI: 1.03–1.47), active cancer (aOR: 2.54; 95%CI: 2.13–3.03), heart rate ≥110 per minute (aOR: 1.57; 95%CI: 1.33–1.87), systolic blood pressure < 100 mmHg (aOR: 2.33; 95%CI: 1.91–2.84), creatinine clearance < 60 mL/min (aOR: 2.47; 95%CI: 2.04–2.99), and oxygen saturation < 90% (aOR: 1.85; 95%CI: 1.57–2.17).

Our results show that both low (<30 mmHg) and high (≥40 mmHg) $PaCO_2$ levels were independently associated with increased mortality at all time points compared with the reference group (30–39 mmHg). This pattern was observed in the overall population and within most PE risk groups, particularly among intermediate-risk patients. Adjusted odds ratios (with 95% confidence intervals) and event rates are presented in Table 1.

To further illustrate the time-dependent relationship between $PaCO_2$ and outcomes, we constructed a Kaplan–Meier curve for cumulative all-cause mortality, stratified by $PaCO_2$ category. As shown in the Fig. 1, mortality increased progressively over 90 days in all groups but was consistently higher in patients with $PaCO_2$ < 30 mmHg or ≥40 mmHg. At 30 days, cumulative mortality reached 7.1% in the <30 mmHg group and 6.6% in the ≥40 mmHg group, compared with 4.3% in the reference category. The difference across groups was statistically significant (log-rank $p < 0.001$).

To our knowledge, this is the largest study to date evaluating $PaCO_2$ as a prognostic biomarker in acute PE. Our findings reveal a non-linear (U-shaped) relationship between $PaCO_2$ and mortality, with both hypocapnia and hypercapnia independently associated with adverse outcomes. Interestingly, initial $PaCO_2$ levels were not aligned with ESC risk stratification, and their prognostic value appeared to be independent. For instance, among patients, classified as low-risk according to ESC guidelines, those with $PaCO_2$ ≥ 40 mmHg still had a significantly higher 30-day mortality (adjusted OR: 2.05; 95%CI: 1.15–3.68). This suggests that

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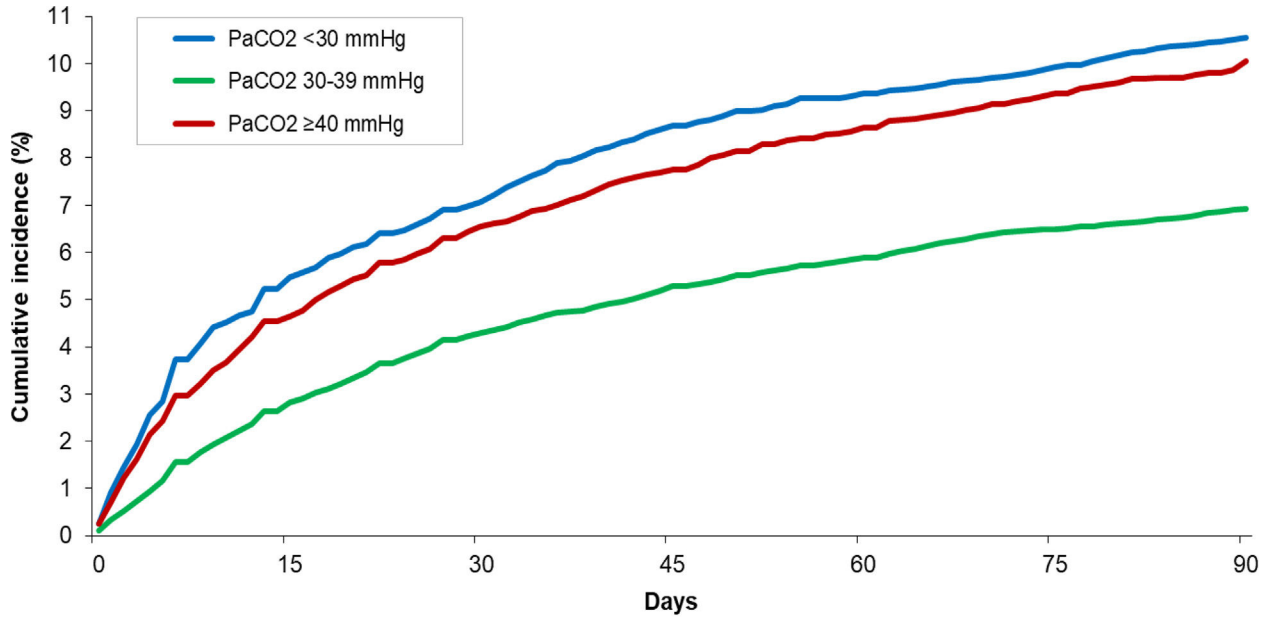
Table 1
All-cause mortality at 7, 30, and 90 days according to baseline $PaCO_2$ categories.

	N	7-Days death		30-Day death		90-Day death	
		Death	aOR (95%CI)	Death	aOR (95%CI)	Death	aOR (95%CI)
All patients	***28,883***	***664 (2.3%)***		***1531 (5.3%)***		***2361 (8.2%)***	
$PaCO_2$ < 30 mmHg	5791	216 (3.7%)	1.92 (1.59–2.32)‡	407 (7.0%)	1.38 (1.21–1.58)‡	601 (10.4%)	1.33 (1.19–1.49)‡
$PaCO_2$ 30–39 mmHg	16,713	259 (1.5%)	Ref.	710 (4.2%)	Ref.	1137 (6.8%)	Ref.
$PaCO_2$ ≥ 40 mmHg	6379	189 (3.0%)	1.76 (1.45–2.14)‡	414 (6.5%)	1.46 (1.28–1.66)‡	623 (9.8%)	1.43 (1.28–1.60)‡
Low-risk PE	**6281**	**22 (0.35%)**		**60 (0.96%)**		**88 (1.4%)**	
$PaCO_2$ < 30 mmHg	921	5 (0.54%)	1.74 (0.61–4.99)	10 (1.09%)	1.26 (0.61–2.58)	15 (1.6%)	1.26 (0.70–2.27)
$PaCO_2$ 30–39 mmHg	4216	12 (0.28%)	Ref.	32 (0.76%)	Ref.	48 (1.1%)	Ref.
$PaCO_2$ ≥ 40 mmHg	1144	5 (0.44%)	1.51 (0.53–4.30)	18 (1.57%)	2.05 (1.15–3.68)*	25 (2.2%)	1.91 (1.17–3.12)*
Intermediate-risk PE	**20,645**	**540 (2.6%)**		**1291 (6.3%)**		**2033 (9.8%)**	
$PaCO_2$ < 30 mmHg	4417	180 (4.1%)	2.00 (1.63–2.47)‡	350 (7.9%)	1.41 (1.22–1.62)‡	527 (11.9%)	1.35 (1.20–1.53)‡
$PaCO_2$ 30–39 mmHg	11,491	210 (1.8%)	Ref.	600 (5.2%)	Ref.	979 (8.5%)	Ref.
$PaCO_2$ ≥ 40 mmHg	4737	150 (3.2%)	1.72 (1.38–2.13)‡	341 (7.2%)	1.41 (1.23–1.63)‡	527 (11.1%)	1.41 (1.25–1.59)‡
High-risk PE	**1028**	**86 (8.4%)**		**130 (12.6%)**		**165 (16.1%)**	
$PaCO_2$ < 30 mmHg	305	25 (8.2%)	1.38 (0.79–2.43)	38 (12.5%)	1.15 (0.73–1.82)	46 (15.1%)	1.03 (0.68–1.56)
$PaCO_2$ 30–39 mmHg	486	30 (6.2%)	Ref.	53 (10.9%)	Ref.	72 (14.8%)	Ref.
$PaCO_2$ ≥ 40 mmHg	237	31 (13.1%)	2.09 (1.21–3.60)†	39 (16.5%)	1.47 (0.93–2.33)	47 (19.8%)	1.32 (0.87–2.02)

Abbreviations: PE, pulmonary embolism; Ref., reference; aOR, adjusted odds ratio; CI, confidence intervals.
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.



	7 days	30 days	60 days	90 days
$PaCO_2$ <30 mmHg	216 (3.7%)	407 (7.1%)	536 (9.4%)	601 (10.6%)
$PaCO_2$ 30-39 mmHg	259 (1.6%)	710 (4.3%)	972 (5.9%)	1,137 (6.9%)
$PaCO_2$ ≥40 mmHg	189 (3.0%)	414 (6.6%)	543 (8.6%)	623 (10.1%)

Fig. 1. Kaplan–Meier curve of 90-day mortality stratified by $PaCO_2$ categories.

elevated $PaCO_2$ may help identify additional risk not captured by standard ESC classification.

Previous studies examining the prognostic value of $PaCO_2$ in acute PE have yielded inconsistent results [4,5]. In some cases, transcutaneous CO_2 monitoring has been used as a non-invasive surrogate for arterial $PaCO_2$. However, this method may be less reliable in hypocapnic states, where it tends to underestimate true $PaCO_2$ levels due to technical and physiological limitations [6]. Additionally, long-term outcomes such as chronic thromboembolic pulmonary can influence mortality and may confound the interpretation of short-term prognostic markers like baseline $PaCO_2$ [7,8].

Although $PaCO_2$ was independently associated with mortality after adjusting for established risk factors, we did not formally assess whether its inclusion improved overall model performance. Further work is needed to evaluate whether $PaCO_2$ adds incremental predictive value beyond current ESC-based risk stratification tools.

This study has limitations. We relied on a single baseline $PaCO_2$ value. Prior research suggests that temporal trends in $PaCO_2$ may

be more informative [5]. Additionally, the registry did not systematically record FiO_2 or supplemental oxygen use at the time of ABG. Finally, we could not assess the arterial-venous CO_2 gap, which has been shown to correlate with hemodynamic severity in PE.

In conclusion, our findings demonstrate that initial $PaCO_2$ values outside the 30–39 mmHg range are independently associated with increased short- and mid-term mortality in patients with acute PE. $PaCO_2$ may serve as a valuable early marker of adverse outcomes and should be considered in future prognostic assessments of PE.

Author contribution

DRC Wrote and revised the manuscript. Conceived and designed the study and supervised, contributed to interpreting the results.

JGG Contributed to interpreting the results, read and agreed to the published version of the manuscript.

KK contributed to interpreting the results, read and agreed to the published version of the manuscript.

BB read and agreed to the published version of the manuscript.

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ALR read and agreed to the published version of the manuscript.

HMB read and agreed to the published version of the manuscript.

MM Wrote and revised the manuscript. Conceived and designed the study and supervised. Contributed to interpreting the results, read and agreed to the published version of the manuscript.

Artificial intelligence involvement

No AI was involvement in this work.

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Conflict of interest

There are no conflicts of interest to report.

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