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Original Contribution

The gradient between arterial and end-tidal carbon dioxide predicts in-hospital mortality in post-cardiac arrest patient

Yong Won Kim, MD, Sung Oh Hwang, MD, Hee Seung Kang, MD, Kyoung-Chul Cha, MD *

Department of Emergency Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

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ABSTRACT

Purpose: We investigated the predictive value of the gradient between arterial carbon dioxide ($PaCO_2$) and end-tidal carbon dioxide ($ETCO_2$) ($Pa\text{-}ETCO_2$) in post-cardiac arrest patients for in-hospital mortality.
Methods: This retrospective observational study evaluated cardiac arrest patients admitted to the emergency department of a tertiary university hospital. The $PaCO_2$ and $ETCO_2$ values at 6, 12, and 24 h after return of spontaneous circulation (ROSC) were obtained from medical records and $Pa\text{-}ETCO_2$ gap was calculated as the difference between $PaCO_2$ and $ETCO_2$ at each time point. Multivariate logistic regression analysis was performed to verify the relationship between $Pa\text{-}ETCO_2$ gap and clinical variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value of $Pa\text{-}ETCO_2$ for predicting in-hospital mortality.
Results: The final analysis included 58 patients. In univariate analysis, $Pa\text{-}ETCO_2$ gaps were significantly lower in survivors than in non-survivors at 12 h [12.2 (6.5–14.8) vs. 13.9 (12.1–19.6) mmHg, $p = 0.040$] and 24 h [9.1 (6.3–10.5) vs. 17.1 (13.1–23.2) mmHg, $p < 0.001$)] after ROSC. In multivariate analysis, $Pa\text{-}ETCO_2$ gap at 24 h after ROSC was related to in-hospital mortality [odds ratio (95% confidence interval): 1.30 (1.07–1.59), $p = 0.0101$]. In ROC curve analysis, the optimal cut-off value of $Pa\text{-}ETCO_2$ gap at 24 h after ROSC was 10.6 mmHg (area under the curve, 0.843), with 77.8% sensitivity and 85.7% specificity.
Conclusion: The $Pa\text{-}ETCO_2$ gap at 24 h after ROSC was associated with in-hospital mortality in post-cardiac arrest patients.

1. Introduction

End-tidal carbon dioxide ($ETCO_2$) is useful for monitoring the quality of cardiopulmonary resuscitation (CPR) during resuscitation and ventilation status in post-cardiac arrest patients [1-4]. $ETCO_2$ is also a valuable predictor for in-hospital mortality in post-cardiac arrest patients [5-8]. In general, $ETCO_2$ correlates with arterial partial pressure of carbon dioxide ($PaCO_2$) and the gradient between the two variables should be 2–5 mmHg [9-11]. However, the gradient may be increased by respiratory dead space or low pulmonary circulation and can present as a ventilation/perfusion (V/Q) mismatch [12-17]. Patients with a V/Q mismatch or increased gradient between $PaCO_2$ and $ETCO_2$ ($Pa\text{-}ETCO_2$ gap) have a high probability of in-hospital mortality [18,19]. This phenomenon may occur in post-cardiac arrest patients because of traumatic lung injury secondary to vigorous chest compression, early-onset pneumonia due to aspiration, pulmonary interstitial edema secondary to ischemia-reperfusion injury, or myocardial stunning, which can lead to deterioration of pulmonary function [20-25]. We investigated the predictive value of the $Pa\text{-}ETCO_2$ gap for in-hospital mortality in post-cardiac arrest patients.

2. Material and methods

2.1. Study design

This retrospective observational study evaluated cardiac arrest patients admitted to the emergency department of a tertiary university hospital between March 2011 and February 2017. The study protocol was approved by Institutional Review Board of Wonju Severance Christian Hospital (YWMR-CR317049).

In the Wonju region, patients with out-of-hospital cardiac arrest (OHCA) are managed by emergency medical technicians (EMTs) dispatched from a fire department. EMTs provide both basic and advanced life support, including defibrillation and advanced airway management for a minimum of 5 min at the scene. If they cannot achieve return of spontaneous circulation (ROSC), the patient is transported to the nearest emergency department (ED) while the EMTs continue to perform cardiopulmonary resuscitation (CPR) in the ambulance. Once ROSC is achieved, the patient is referred to our hospital. In the hospital, the patient received comprehensive post-cardiac arrest care including therapeutic hypothermia at 32–34 °C or targeted temperature

* Corresponding author at: Department of Emergency Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Republic of Korea.
E-mail address: chaemp@yonsei.ac.kr. (K.-C. Cha).

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management (TTM) at 33 °C or 36 °C. Ventilator support to achieve normoxia and normocarbia is provided during ED and intensive care unit (ICU) stays. The tidal volume, respiratory rate, and positive end-expiratory pressure are controlled to achieve a target arterial oxygen saturation (SaO_2) of 94–98%, $ETCO_2$ of 30–40 mmHg and $PaCO_2$ of 35–45 mmHg. Pulse oximetry (Tram-rac 4A, GE Medical Systems, WI, USA) and $ETCO_2$ (CAPNOSTAT mainstream CO_2 module, GE Medical Systems, WI, USA) were monitored continuously, and sequential arterial blood gas analysis (ABGA) was performed at 6, 12, and 24 h after ROSC, followed by at every 24 h. Patient care and other ancillary tests were decided by the intensivist on duty.

We included patients older than 18 years who had survived for >24 h after successful resuscitation from out-of-hospital non-traumatic cardiac arrest. Patients transferred from other hospitals or without matched data for $ETCO_2$ and ABGA were excluded.

2.2. Study variables

Clinical data obtained from medical records included age, sex, history of previous pulmonary disease, witnessed cardiac arrest, bystander CPR, initial presenting rhythm, etiology of arrest, estimated total collapse time, total duration of CPR, cumulative number of defibrillation attempts, temperature of therapeutic hypothermia or targeted temperature management (TTM), and in-hospital mortality. Previous pulmonary disease was confirmed by medical records and chest X-ray or computed tomography (CT) reviewed by an independent radiologist to our study. Pre-arrest pulmonary dysfunction was defined as history of previous pulmonary disease or cardiac arrest caused by acute respiratory failure due to lung parenchymal or pulmonary vascular disease. The values of $PaCO_2$ and $ETCO_2$ at 6, 12, and 24 h after ROSC were also obtained from medical records, and Pa-$ETCO_2$ gap was calculated as the difference between $PaCO_2$ and $ETCO_2$ at each time point.

2.3. Data analysis

Continuous variables were reported as median values (interquartile range: IQR) and were compared with the Mann-Whitney *U* test. Nominal data were calculated as percentage of frequency of occurrence and compared using chi-square or Fisher's exact test, as appropriate. Linear mixed model analysis was used to compare $PaCO_2$, $ETCO_2$, and Pa-$ETCO_2$ gap at 6, 12, and 24 h after ROSC between survivors and non-survivors. Multivariate logistic regression analysis was performed to determine whether age, sex, witnessed cardiac arrest, bystander CPR, initial presenting rhythm, estimated total collapse time, total duration of CPR, TTM, or pre-arrest pulmonary dysfunction affected in-hospital mortality. The resulting odds ratios (ORs) are presented with 95% confidence intervals (95% CIs). A two-sided *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using R version 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. General characteristics

During the study period, 590 non-traumatic OHCA patients over 18 years old adult patients were visited to our ED from scene. Among them, 227 (38.5%) patients archived ROSC and 66 patients (11.2%) of them survived >24 h after ROSC. 8 patients were excluded due to mismatched sampling times for $ETCO_2$ and $PaCO_2$. Finally, 58 patients were analyzed. There were no differences in general characteristics, except age, between survivors and non-survivors. Survivors were younger than non-survivors ($p = 0.010$) (Table 1).

3.2. Comparison of $PaCO_2$, $ETCO_2$, and Pa-$ETCO_2$ gap in survivor and non-survivor groups

There were no differences in $PaCO_2$ at 6, 12, and 24 h after ROSC between survivors and non-survivors. $ETCO_2$ at 6 h [32.0 (27.0–37.0) mmHg vs. 27.0 (20.0–33.0) mmHg, $p = 0.023$], 12 h [33.0 (30.0–35.0) mmHg vs. 26.0 (23.0–30.0) mmHg, $p = 0.001$], and 24 h (37.0 (32.0–40.0) mmHg vs. 28.0 (21.0–33.0) mmHg, $p < 0.001$] was significantly higher in survivors than in non-survivors. Pa-$ETCO_2$ gaps at 12 h [12.2 (6.5–14.8) mmHg vs. 13.9 (12.1–19.6) mmHg, $p = 0.040$] and 24 h [9.1 (6.3–10.5) mmHg vs. 17.1 (13.1–23.2) mmHg, $p < 0.001$] after ROSC were significantly lower in survivors than in non-survivors. There were no group-time interactions for $PaCO_2$, $ETCO_2$, and Pa-$ETCO_2$ ($p = 0.237$, 283, and 0.207 respectively) (Fig. 1).

3.3. Predictive value of Pa-ETCO2 gap for in-hospital mortality

Multivariate logistic regression analysis revealed that the Pa-$ETCO_2$ gap [OR (95% CI): 1.30 (1.07–1.59), $p = 0.010$] at 24 h after ROSC was related to in-hospital mortality (Table 2). The Pa-ETCO2 gap had an area under the receiver operating characteristic curve of 0.842 at 24 h, and the optimal cut-off value of Pa-$ETCO_2$ gap at 24 h was 10.6 mmHg, with 77.8% sensitivity and 85.7% specificity (Fig. 2).

4. Discussion

The Pa-$ETCO_2$ gap at 24 h after ROSC was associated with in-hospital mortality in post-cardiac arrest patients in this study. Previous studies observed that the Pa-$ETCO_2$ gap increased when dead space ventilation increased or cardiac output decreased, demonstrating its value as a predictor of disease severity or outcomes in critically ill patients [15-18]. In

Table 1
General characteristics.

	Total ($n = 58$)	Survivors ($n = 15$)	Non-survivors ($n = 43$)	*p*-value
Age (y)	60 (53–75)	54 (51–60)	71 (55–76)	0.010
Male gender, no. (%)	41 (70.7)	13 (86.7)	28 (65.1)	0.188
Witnessed, no. (%)	44 (75.9)	12 (80.0)	32 (74.4)	0.742
Bystander CPR, no. (%)	32 (55.2)	10 (66.7)	22 (51.2)	0.374
Shockable rhythm, no. (%)	7 (12.1)	3 (20.0)	4 (9.3)	0.360
Cumulative number of defibrillation attempts	1 (1–4)	3 (2–6)	1 (1–3)	0.714
Cardiac etiology, no. (%)	19 (32.8)	7 (46.7)	12 (27.9)	0.213
Estimated total collapse time (min)	31 (22–44)	29 (20–39)	34 (23–44)	0.494
Total CPR duration (min)	28 (19–35)	27 (20−31)	28 (19–35)	0.644
Therapeutic hypothermia or TTM, no. (%)	53 (91.4)	14 (93.3)	39 (90.7)	1.000
33 °C	50 (94.3)	13 (92.9)	37 (94.9)	1.000
36 °C	3 (5.7)	1 (7.1)	2 (5.1)	1.000
Pre-arrest pulmonary dysfunction, no. (%)	18 (31.0)	3 (20.0)	15(34.9)	0.348

*Variables are presented as median (interquartile range) or frequency (%).
§CPR: cardiopulmonary resuscitation, TTM: targeted temperature management.

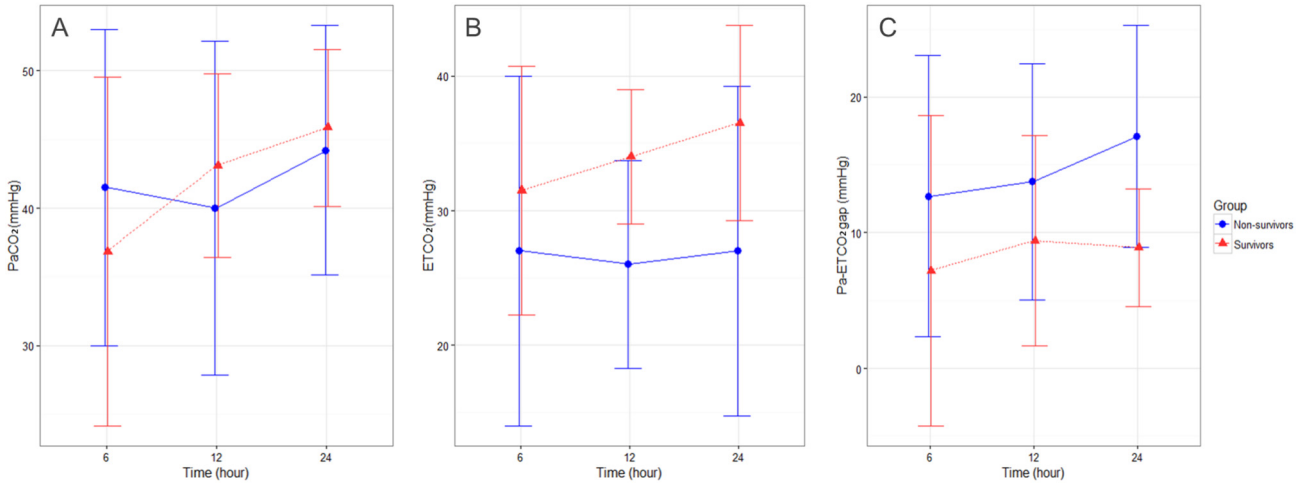

Fig. 1. Trends of $PaCO_2$ (A) $ETCO_2$ (B) and Pa-$ETCO_2$ gap (C) of survivors and non-survivors during 24 h after ROSC. There was no group-time interaction in all variables. ($p = 0.237$, 283 and 0.207 respectively). *ROSC: return of spontaneous circulation.

Table 2
Multivariate logistic regression analysis of Pa-$ETCO_2$ gap at each time point for prediction of in-hospital mortality.

Variables (mmHg)	Odds ratio (95% CI)	*p*-value
6h Pa-$ETCO_2$ gap	1.11(0.99–1.26)	0.073
12h Pa-$ETCO_2$ gap	1.08(0.97–1.20)	0.186
24h Pa-$ETCO_2$ gap	1.30(1.07–1.60)	0.010

post-cardiac arrest patients, global ischemia and reperfusion injury can deteriorate pulmonary and cardiovascular function, which might be presented as increased Pa-$ETCO_2$ gap. [26]. Patients who do not overcome these critically adverse events tend to deteriorate over time, as demonstrated by the increased Pa-$ETCO_2$ gap in this study.

Post-cardiac arrest patients with poor neurologic outcomes can be a burden to their families and society responsible for their care [27]. Various prognostic tools have been used to predict patient outcomes,

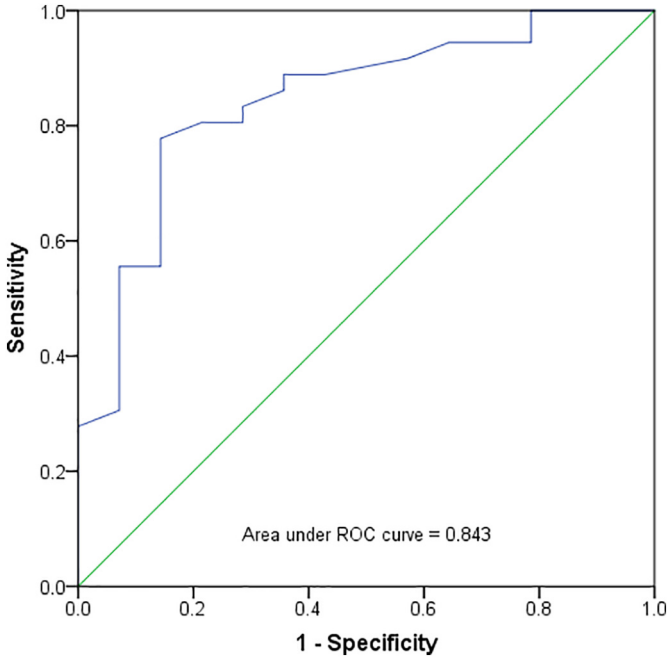

Fig. 2. Analysis by receiver operating characteristic curve for 24 h Pa-$ETCO_2$ gap for predicting in-hospital mortality.

including bedside neurologic examination, somatosensory evoked potentials, electroencephalography (EEG), brain CT, magnetic resonance imaging (MRI), and biochemical markers, but they have limitations [28-33]. Sedatives or neuromuscular blocking agents might mask a patient's response, and there is risk in moving critically ill patients from the ICU to a CT or an MRI facility for neuroimaging. Several studies indicated that continuous EEG monitoring is the most reliable prognostic tool, but EEG requires specialist review [34]. The Pa-$ETCO_2$ gap can be easily obtained at any time, and any medical personnel can objectively review the results, making it a useful to identify patients at higher likelihood of in-hospital mortality and in need of additional therapeutic intervention.

In our study, increased Pa-$ETCO_2$ gap was mainly caused by reduction of $ETCO_2$. Guidelines for post-cardiac arrest patient care recommend continuous monitoring of $ETCO_2$ to promote cerebral perfusion by maintaining an optimal $PaCO_2$ level [34]. Thus, an increased Pa-$ETCO_2$ gap would be a clue indicating uncorrected adverse event occurrence. Therefore, to clarify whether the Pa-$ETCO_2$ gap is increasing, $PaCO_2$ should be determined if the $ETCO_2$ remains decreased in a post-cardiac arrest patient dependent on a mechanical ventilator. It is insufficient to monitor the $ETCO_2$ alone to optimize the $PaCO_2$ level, and factors causing deterioration in a patient's condition should be identified and corrected.

This study had several limitations. First, it is possible that mismatched $PaCO_2$ and $ETCO_2$ values were included in analysis, even though data were prospectively collected using a clinical practice protocol. Second, even though we excluded patients with pulmonary dysfunction to minimize bias due to a mismatch between $PaCO_2$ and $ETCO_2$ values, it is possible that patients with undetected pulmonary dysfunction were included. Third, characteristics of enrolled patients might affect the Pa-$ETCO_2$ gap or in-hospital mortality because the majorities were male, non-shockable rhythm or non-cardiac etiology even though these variables did not related with in-hospital mortality in multivariate logistic regression analysis. Fourth, this study might not be generalized for all patients with cardiac arrest because we included patients who survived >24 h after ROSC only. Finally, this was a single-center, observational study with a small sample size. A larger, population-based, multi-center study is needed to generalize our results.

5. Conclusions

The gradient between $PaCO_2$ and $ETCO_2$ at 24 h after ROSC is associated with in-hospital mortality in post-cardiac arrest patients. It might be useful predictor of in-hospital mortality in post-cardiac arrest patients because it can be obtained easily and evaluated objectively.

Sources of support

There was no source of support.

Conflict of interest

All authors have nothing to declare on conflict of interest.

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