



Out-of-Hospital Arterial to End-Tidal Carbon Dioxide Gradient in Patients With Return of Spontaneous Circulation After Out-of-Hospital Cardiac Arrest: A Retrospective Study

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Study objective: End-tidal carbon dioxide (etCO₂) is used to guide ventilation after achieving return of spontaneous circulation (ROSC) in certain out-of-hospital systems, despite an unknown difference between arterial and end-tidal CO₂ (partial pressure of carbon dioxide [paCO₂]-etCO₂ difference) levels in this population. The primary aim of this study was to evaluate and quantify the paCO₂-etCO₂ difference in out-of-hospital patients with ROSC after nontraumatic cardiac arrest.

Methods: This retrospective single-center study included patients aged 18 years and older with sustained ROSC after nontraumatic out-of-hospital cardiac arrest. In patients with an existing out-of-hospital arterial blood gas analysis within 30 minutes after achieving ROSC, matching etCO₂ values were evaluated. Linear regression and Bland-Altman plot analysis were performed to ascertain the primary endpoint of interest.

Results: We included data of 60 patients in the final analysis. The mean paCO₂-etCO₂ difference was 32 (±18) mmHg. Only a moderate correlation ($R^2=0.453$) between paCO₂ and etCO₂ was found. Bland-Altman analysis showed a bias of 32 mmHg (95% confidence interval [CI], 27 to 36) [the upper limit of agreement of 67 mmHg (95% CI, 59 to 74) and the lower limit of agreement of -3 mmHg (95% CI, -11 to 5)].

Conclusion: The paCO₂-etCO₂ difference in patients with ROSC after out-of-hospital cardiac arrest is far from physiologic ranges, and the between-patient variability is high. Therefore, etCO₂-guided adaption of ventilation might not provide adequate accuracy in this setting. [Ann Emerg Med. 2023;82:558-563.]

Please see page 559 for the Editor's Capsule Summary of this article.

A **podcast** for this article is available at www.annemergmed.com.

0196-0644/\$-see front matter

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<https://doi.org/10.1016/j.annemergmed.2023.03.001>

INTRODUCTION

Background

Despite constantly ongoing research efforts and concomitant improvement in patient care, only about 1 out of 10 persons suffering from sudden cardiac arrest survives to hospital discharge. Standardized postresuscitation care, representing one link of the so-called chain of survival, has a significant influence on survival and neurologic outcome. Aims of the immediate postresuscitation care include the prevention of further injury in addition to the diagnosis, and if possible, the treatment of the underlying cause of arrest. Prevention of further injury can be achieved by rapid hemodynamic stabilization, control, and optimization of the airway, as well as adequate tissue oxygenation and decarboxylation.¹ This should be initiated as soon as

possible, regardless of the location, and not be limited to the ICU.¹

After return of spontaneous circulation (ROSC) is achieved, it is recommended to target a normal (ie, 35 to 45 mmHg) arterial partial pressure of carbon dioxide (paCO₂).¹ Carbon dioxide is an important regulator of vascular tone and cerebral blood flow, which is critical after cardiopulmonary resuscitation (CPR), in which prolonged low-flow times may result in limited brain perfusion. High arterial carbon dioxide concentrations lead to an increased cerebral blood flow and blood volume, and possibly raised intracranial pressure, whereas lower concentrations result in the exact opposite. Derangements of paCO₂ with consequent pH shifts alter cardiovascular function and responsiveness to vasopressors. Hypercapnic acidosis, a

Editor's Capsule Summary*What is already known on this topic*

Arterial CO₂ is elevated post return of spontaneous circulation (ROSC) from cardiac arrest.

What question this study addressed

What is the difference between out-of-hospital contemporaneous arterial and end-tidal CO₂ measurements in adult patients after post-cardiac arrest ROSC?

What this study adds to our knowledge

In 60 patients, the mean difference between arterial and end-tidal CO₂ measurements at an average of 11 minutes post ROSC was 32 mmHg. The absolute CO₂ value and associated difference were smaller in patients who went on to survive 30 days.

How this is relevant to clinical practice

End-tidal CO₂ levels underestimate the elevated arterial CO₂ levels generally present in the first minutes post ROSC from cardiac arrest. This could help adjust ventilation.

common condition in cardiac arrest, leads to smooth muscle cell relaxation and a decrease in systemic vascular resistance.² Adaption of ventilation to counteract hypercapnia and its effects on hemodynamics is thus important, as cardiovascular instability and myocardial dysfunction are common in patients with ROSC.

Importance

Arterial blood gas (ABG) analysis is rarely available in the out-of-hospital setting; therefore, end-tidal CO₂ (etCO₂) is mostly used to guide ventilation. Under normal physiologic conditions, a difference of 2 to 5 mmHg between arterial and end-tidal CO₂ (paCO₂-etCO₂ difference) measurements has been described.³ Higher values have been shown in patients with major systemic or pulmonary disease, as well as in patients with severe traumatic brain injury, who undergo out-of-hospital emergency airway management.⁴ However, the paCO₂-etCO₂ difference in patients with ROSC after out-of-hospital cardiac arrest (OHCA) remains unknown.

Goal of This Investigation

The primary aim of this study was to evaluate and quantify the paCO₂-etCO₂ difference in out-of-hospital patients aged 18 years and older with ROSC after

nontraumatic cardiac arrest. Secondarily, the paCO₂-etCO₂ difference after achieving ROSC between patients with and without 30-day survival was compared.

METHODS**Study Design and Setting**

This study was a single-center retrospective analysis of routine data. Data from the database of the out-of-hospital emergency physician response unit located at the Medical University of Graz, Austria, were retrieved. This response unit, staffed with an out-of-hospital emergency physician and a paramedic, covers the eastern part of the city of Graz and its suburban areas with around 200,000 individuals. It is dispatched to around 2,000 missions per year, approximately 150 of which are CPRs, whereas the remainders are traumatic, neurologic, pediatric, medical, and toxicologic emergencies. Ventilatory management after achieving ROSC includes a tidal volume of 500 mL, a respiratory rate of 12 breaths/min, a positive end-expiratory pressure value of 5 mbar, and an inspired oxygen concentration of 100%, which is then adapted to achieve normocapnia (end-tidal) and an oxygen saturation rate of at least 94%.

Ethical approval was sought and granted by the Ethics Committee of the Medical University of Graz (IRB00002556, decision number: 33-590 ex 20/21) before data retrieval and study conduction. The need for informed consent was waived, because data were retrieved and analyzed retrospectively and in a pseudonymized fashion.

Selection of Participants

Data of missions between January 1, 2016, and December 31, 2021, were extracted. Patients with OHCA and CPR, who had sustained ROSC until hospital admission, were included. Patients without an ABG analysis within 30 minutes after achieving ROSC, with no etCO₂ value 0 to 5 minutes before ABG analysis, with no endotracheal intubation during cardiac arrest, under 18 years of age, or who had experienced traumatic cardiac arrest were excluded. A sensitivity analysis without patients with suspected measurement errors (a paCO₂-etCO₂ difference of below -5) was performed.

Measurements

Time-stamped paCO₂ measurements from the internal storage of the blood gas analyzer used at the physician response unit (epoc blood analysis system, Siemens Healthcare GmbH) were obtained. The etCO₂ level was measured using side-stream capnography with the monitor used at the physician response unit (Lifepak 15 Monitor; Stryker). The corresponding etCO₂ values (0 to 5 minutes before ABG analysis) from the physician response unit's

electronic record, which includes a time-stamped download of each mission's monitor data, were extracted.

Furthermore, patient-specific and case-specific data according to the Utstein style for data reporting in CPR research from the physician response unit's electronic record and medical record were obtained. The record is based on the minimal data set for emergencies laid out by the German Interdisciplinary Society of Intensive Care and Emergency Medicine, electronically collected and stored (MEDEA; iLogs). Prior to data extraction, abstractors were introduced to the standardized abstraction form and coding following the Utstein style. Thereafter, test runs were performed under the supervision of the senior author, who also solved issues regarding conflicting data and assessed abstractor performance by the evaluation of random samples.

Outcomes

The primary outcome of interest was the $\text{paCO}_2\text{-etCO}_2$ difference after achieving ROSC. The secondary outcome of interest was to compare the $\text{paCO}_2\text{-etCO}_2$ difference after achieving ROSC between patients with and without 30-day survival.

Analysis

Demographic and arrest-related data, as well as etCO_2 and ABG measurements, were presented as means and SDs, medians and interquartile ranges, or numbers (n) and percentages (%), as appropriate. A Bland-Altman plot for paCO_2 and etCO_2 measurements was created. Pearson correlation coefficient and linear regression analysis were used to assess and quantify a possible linear relationship between the variables of interest. An unpaired *t* test was used to evaluate numeric differences in the $\text{paCO}_2\text{-etCO}_2$ difference between survivors and nonsurvivors after 30 days. *P* values of below .05 were considered significant.

All analyses were performed using IBM SPSS 27 (IBM Corp), and graphs were created with Microsoft Excel 2016 (Microsoft Corp).

RESULTS

Characteristics of the Study Subjects

Out of a total of 13,660 physician response unit missions during the selected timespan, 806 CPRs could be identified and sustained ROSC was found in 180 cases. Of those 180 missions, 60 could be included in the final analysis (99 excluded as no ABG analysis was performed within 30 minutes after ROSC, 12 excluded as no endotracheal intubation was performed, 5 excluded owing to age under 18 years, and 4 excluded as traumatic cardiac arrest was suspected). The exact selection process is depicted in

Figure E1 (available at www.annemergmed.com). Patient characteristics are shown in Table, and the medical treatment received prior to ABG analysis is displayed in Table E1 (available at www.annemergmed.com).

Primary Outcome

The mean $\text{paCO}_2\text{-etCO}_2$ difference after achieving ROSC was $32 (\pm 18)$ mmHg, the mean paCO_2 was $80 (\pm 24)$ mmHg, and the mean etCO_2 was $48 (\pm 14)$ mmHg. Linear regression analysis demonstrated a moderate ($R^2=0.453$) correlation between paCO_2 and etCO_2 (Figure 1). Results were virtually identical in the sensitivity analysis (Figure E2).

Table. Patient characteristics in the overall cohort.

Characteristics	No./Value
Patients included, n	60
Male sex, n (%)	44 (73.3)
Median age, y (IQR)	73 (63.75-79.25)
Witnessed arrest, n (%)	
Bystander witnessed	43 (71.7)
EMS witnessed	5 (8.3)
Unwitnessed	12 (20.0)
Arrest location, n (%)	
Home/residence	39 (65.0)
Street/highway	9 (15.0)
Public building	6 (10.0)
Assisted living/nursing home	4 (6.7)
Sports/recreation event	2 (3.3)
Bystander CPR received, n (%)	33 (55.0)
Cause, n (%)	
Medical	53 (88.3)
Asphyxia	4 (6.7)
Drug overdose	2 (3.3)
Drowning	1 (1.7)
First monitored rhythm, n (%)	
Asystole	14 (23.3)
PEA	21 (35.0)
VF	25 (41.7)
Median response time (ALS unit), min (IQR)	8 (5-11)
Median adrenaline, mg (IQR)	2 (1-4)
Median time from ROSC to ABG analysis, min (IQR)	11 (5-16.25)
Median CPR duration until ROSC, min (IQR)	19 (14-28.25)
30-day survival, n (%)	16 (26.7)
Neurologic outcome of 30-d survivors, n (%)	
CPC 1-2	11 (68.8)
CPC 3-4	5 (31.3)

ALS, advanced life support; CPC, cerebral performance category; EMS, emergency medical service; IQR, interquartile range; PEA, pulseless electrical activity; VF, ventricular fibrillation.

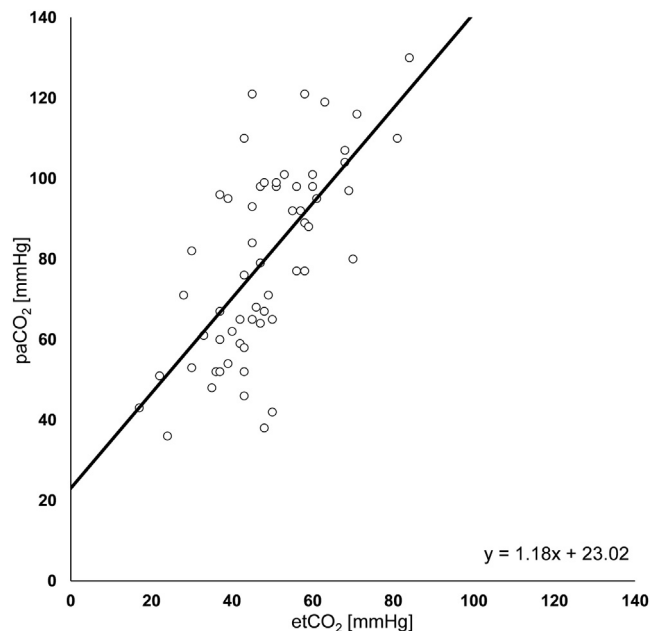


Figure 1. Linear regression model between paCO_2 and etCO_2 . X axis showing etCO_2 values, and y axis showing paCO_2 values. A moderate ($R^2=0.453$) correlation was found for the model.

Bland-Altman analysis showed a bias of 32 mmHg (95% confidence interval [CI], 27 to 36) [the upper limit of agreement of 67 mmHg (95% CI, 59 to 74) and the lower limit of agreement of -3 mmHg (95% CI, -11 to 5)] (Figure 2). Results were also very similar in the Figure E3.

Secondary Outcome

Patients who were still alive after 30 days had a significantly lower paCO_2 - etCO_2 difference than those who died within the first 30 days (23 ± 16 versus 35 ± 17 , $P=.018$).

LIMITATIONS

There are several limitations to this study. It is a retrospective single-center study and the data are therefore restricted to its originally documented content. A standardized electronic record was used and vital parameters were automatically transferred from the monitor. For that reason, the data are of good quality. To match paCO_2 and etCO_2 values, the time of ABG analysis was used, which is not necessarily identical to the time of sample collection. However, as a point-of-care device was used, and the analysis required less than a minute, this gap should only be minimal. Furthermore, not every patient with ROSC had an ABG analysis. This could have led to a selection bias, as sicker patients might be more likely to have an ABG analysis performed. Nonetheless, patient

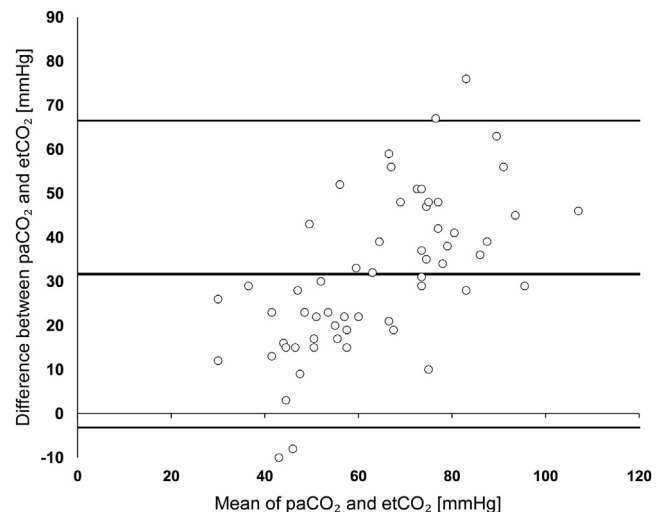


Figure 2. Bland-Altman analysis of paCO_2 and etCO_2 . The bias of 32 mmHg (95% CI, 27 to 36) is plotted as a single line, and the upper and lower limits of agreement, 67 mmHg (95% CI, 59 to 74) and -3 mmHg (95% CI, -11 to 5), respectively, are plotted as thin lines. CI, confidence interval.

characteristics between the included patients and those excluded owing to missing ABG analysis or etCO_2 data are similar (Table E2). Furthermore, the inclusion rate of about every third ROSC patient in the final analysis is similar to that in previous studies looking at the out-of-hospital paCO_2 - etCO_2 difference.^{2,4}

DISCUSSION

A high, yet variable, paCO_2 - etCO_2 difference with a mean of $32 (\pm 18)$ mmHg was found. PaCO_2 - etCO_2 difference is largely influenced by alveolar dead space, which can be increased for several reasons after CPR.³ First and foremost, a decrease in cardiac output, a common state in the immediate ROSC phase, leads to a reduction in pulmonary blood flow. This reduction in pulmonary perfusion accounts for a shift in the ventilation/perfusion balance, with a concomitant increase in alveolar dead space. Second, pulmonary embolism, with a reported incidence of up to 7% in OHCA, also leads to the enlargement of alveolar dead space.⁵ Furthermore, imbalances in coagulation with shifts toward more procoagulatory states have been shown in post-cardiac arrest syndrome.⁶ These possible microthrombi could further raise the ventilation/perfusion mismatch, leading to an increase in alveolar dead space. In addition to alveolar dead space, a right-to-left shunt can increase the paCO_2 - etCO_2 difference. Several frequently encountered complications after CPR, namely lung contusions, pneumothorax, pleural effusions, and pulmonary edema, can lead to a rise in the right-to-left shunt volume.⁷

Increased out-of-hospital $\text{paCO}_2\text{-etCO}_2$ differences—although under different circumstances—have been shown before. In a recent study examining the $\text{paCO}_2\text{-etCO}_2$ difference after OHCA using the first in-hospital ABG, a gap of 8 mmHg was found.⁸ Several factors could play a major role in the explanation of this considerable discrepancy. Delayed measurement of the difference could give more time for hemodynamic and respiratory stabilization, which is also indicated by a markedly higher mean pH (7.2 versus 6.97) and paCO_2 values closer to those of normocapnia (52 versus 80 mmHg). Higher differences with increased paCO_2 values could further indicate the existence of a proportional bias, as also shown in an adapted version of the Bland-Altman analysis (Figure E4) in the supplement.

Another study, which looked at a small cohort of patients with ROSC after in-hospital cardiac arrest, also found an increased $\text{paCO}_2\text{-etCO}_2$ difference. However, the mean difference of 16.1 (± 9.0) is less pronounced compared with the difference described in the presented data. A mean CPR duration of only 13 minutes compared with 19 minutes, with decreased metabolic derangement, as well as a $\text{paCO}_2\text{-etCO}_2$ difference calculation after 60 minutes post ROSC compared with a median of 11 minutes in this study, resulting in more time for hemodynamic stabilization, could explain these differences.⁹ Kim et al¹⁰ also looked at the in-hospital difference after OHCA, but at a later time point. In their study, a difference of around 10 mmHg was found 6 hours post ROSC. As a differing cohort was examined (24-hour survival required) and delayed time points were chosen (6, 12, and 24 hours after ROSC), direct comparison was only possible to a limited extent. A linear regression between the time of ABG analysis and CO_2 difference in the first 30 minutes after ROSC in our cohort is shown in Figure E5.

Patients who survived until day 30 had a significantly lower difference than those who did not survive. Similar results have been found in the already mentioned in-hospital cohort.⁹ This could be indicative of less deranged pulmonary perfusion and a better overall hemodynamic status in these patients.

Notably, not a single patient was hyperventilated and more than 90% had paCO_2 values above the normal range. This may in part be owing to hypoventilation during the CPR process. Furthermore, CO_2 most likely was mobilized from peripheral tissues with spontaneous circulation.² It could also indicate that higher than previously anticipated minute volumes are required when patients are artificially ventilated in the acute post-ROSC phase.

In summary, the $\text{paCO}_2\text{-etCO}_2$ difference in out-of-hospital patients with ROSC after nontraumatic cardiac

arrest was far from physiologic ranges and of high variability. Therefore, etCO_2 -guided adaption of ventilation may not provide adequate accuracy in this setting.

The authors want to thank Gerhard Prause, MD for his dedication and thrive to improve the out-of-hospital care in Austria over the last decades and all his innovative implementations, such as out-of-hospital blood gas analysis. Furthermore, the authors also want to thank all out-of-hospital emergency physicians for their respective contributions to routine patient care, which created the basis for this study.

Supervising editor: Keith A. Marill, MD, MS. Specific detailed information about possible conflict of interest for individual editors is available at <https://www.annemergmed.com/editors>.

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Author contributions: MEichlseder, PhZ, and PZ conceived and designed the study. MEichinger, MEichlseder, DF, MR, PhZ, and PZ collected the data. The data analysis was performed by MEichlseder, AP, and PZ, whereas the manuscript was drafted by MEichinger, MEichlseder, AP, DF, and MR. MEichlseder takes responsibility for the paper as a whole.

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals'* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. The authors report this article did not receive any outside funding or support.

Publication dates: Received for publication November 14, 2022. Revisions received February 13, 2023, and February 18, 2023. Accepted for publication March 1, 2023.

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