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Clinical paper

Hypothermia is associated with a low $ETCO_2$ and low pH-stat $PaCO_2$ in refractory cardiac arrest

T. Darocha[a,1], G. Debaty[b,1], F.X. Ageron[c], P. Podsiadło[d], A. Hutin[e], H. Hymczak[f,g], M. Blancher[b], S. Kosiński[h], K. Mendrala[a], P.N. Carron[c], L. Lamhaut[e], P. Bouzat[i], M. Pasquier[c,]*

[a] *Department of Anaesthesiology and Intensive Care, Medical University of Silesia, Katowice, Poland*
[b] *Department of Emergency Medicine, University Hospital of Grenoble Alps/CNRS/TIMC UMR 5525, Grenoble, France*
[c] *Department of Emergency Medicine, Lausanne University Hospital and University of Lausanne, BH09, 1011 Lausanne, Switzerland*
[d] *Department of Emergency Medicine, Jan Kochanowski University, Kielce, Poland*
[e] *Adult Intensive Care Unit, Department of Anaesthesiology - SAMU de Paris, Assistance Publique - Hôpitaux de Paris, University Hospital Necker, Paris, France*
[f] *Department of Anesthesiology and Intensive Care, John Paul II Hospital, Krakow, Poland*
[g] *Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[h] *Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland*
[i] *Department Anesthesia and Critical Care, University Hospital, Grenoble, France*

Abstract

Aims: The end-tidal carbon dioxide ($ETCO_2$) is frequently measured in cardiac arrest (CA) patients, for management and for predicting survival. Our goal was to study the $PaCO_2$ and $ETCO_2$ in hypothermic cardiac arrest patients.

Methods: We included patients with refractory CA assessed for extracorporeal cardiopulmonary resuscitation. Hypothermic patients were identified from previously prospectively collected data from Poland, France and Switzerland. The non-hypothermic CA patients were identified from two French cohort studies. The primary parameters of interest were $ETCO_2$ and $PaCO_2$ at hospital admission. We analysed the data according to both alpha-stat and pH-stat strategies.

Results: We included 131 CA patients (39 hypothermic and 92 non-hypothermic). Both $ETCO_2$ ($p < 0.001$) and pH-stat $PaCO_2$ ($p < 0.001$) were significantly lower in hypothermic compared to non-hypothermic patients, which was not the case for alpha-stat $PaCO_2$ ($p = 0.15$). The median $PaCO_2$-$ETCO_2$ gradient was greater for hypothermic compared to non-hypothermic patients when using the alpha-stat method (46 mmHg vs 30 mmHg, $p = 0.007$), but not when using the pH-stat method ($p = 0.10$). Temperature was positively correlated with $ETCO_2$ ($p < 0.01$) and pH-stat $PaCO_2$ ($p < 0.01$) but not with alpha-stat $PaCO_2$ ($p = 0.5$). The $ETCO_2$ decreased by 0.5 mmHg and the pH-stat $PaCO_2$ by 1.1 mmHg for every decrease of 1° C of the temperature. The proportion of survivors with an $ETCO_2 \leq 10$ mmHg at hospital admission was 45% (9/25) for hypothermic and 12% (2/17) for non-hypothermic CA patients.

Conclusions: Hypothermic CA is associated with a decrease of the $ETCO_2$ and pH-stat $PaCO_2$ compared with non-hypothermic CA. $ETCO_2$ should not be used in hypothermic CA for predicting outcome.

Keywords: Cardiac arrest, Capnometry, Capnography, $ETCO_2$, Extracorporeal Life Support, Hypothermia, Accidental, Resuscitation, Triage

* Corresponding author.
E-mail addresses: tomekdarocha@wp.pl (T. Darocha), GDebaty@chu-grenoble.fr (G. Debaty), Francois-Xavier.Ageron@chuv.ch (F.X. Ageron), alice.hutin@aphp.fr (A. Hutin), hymczak@op.pl (H. Hymczak), MBlancher@chu-grenoble.fr (M. Blancher), sylweriusz.kosinski@uj.edu.pl (S. Kosiński), Pierre-Nicolas.Carron@chuv.ch (P.N. Carron), lionel@lamhaut.fr (L. Lamhaut), PBouzat@chu-grenoble.fr (P. Bouzat), Mathieu.Pasquier@chuv.ch (M. Pasquier).
[1] Co-first authors.

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Introduction

End-tidal carbon dioxide ($ETCO_2$) is the level of carbon dioxide that is released at the end of an exhaled breath. $ETCO_2$ is routinely measured and monitored in intubated patients in the emergency setting.[1,2] It is recommended for confirmation of correct endotracheal tube placement and monitoring of ventilation.[1–3] The use of $ETCO_2$ monitoring in the ED has great potential as a method of non-invasive monitoring of patients in shock.[4] In the specific case of cardiac arrest (CA), $ETCO_2$ may be used to assess CPR quality and to detect return of spontaneous circulation (ROSC).[1–3] It is also used as a predictor of survival and as a criterion for withholding and termination of resuscitation. Failure to achieve an $ETCO_2$ > 10 mmHg in an intubated patient after 20 min of CPR is indicative of a poor chance of survival.[3] An $ETCO_2$ of >10 mmHg is also frequently used as an inclusion criterion for extracorporeal cardiopulmonary resuscitation (ECPR) for refractory CA.[5,6]

Hypothermic CA is a special circumstance of CA. ECPR combined with rewarming is the treatment of choice for patients suffering hypothermic CA. Patient selection is different than for ECPR in CA of cardiac origin. Patients with hypothermic CA have more favourable outcomes.[7,8] Observational data suggest that the $PaCO_2$ - $ETCO_2$ gradient is increased in non-CA patients with severe hypothermia.[9] The objectives of the study were to assess the relation between $PaCO_2$ and $ETCO_2$ in both hypothermic and non-hypothermic cardiac arrest patients and to assess $ETCO_2$ as a predictor of survival in hypothermia.

Methods

We retrospectively analysed patients with refractory CA assessed for ECPR in the emergency department in whom $ETCO_2$ and $PaCO_2$ measurements were available at the time of admission. We included hypothermic CA patients from a previous prospective study[10] and from the Severe Accidental Hypothermia Center, Krakow - Department of Anesthesiology and Intensive Care, John Paul II Hospital, Krakow, Poland. For the non-hypothermic CA patients we analysed de-identified individual patient level data from two primary cohort studies of refractory out-of-hospital cardiac arrest (OHCA) treated with ECPR. The rationale, data collection methods, verification procedures, and primary outcomes have been reported in detail elsewhere.[11–15] The databases for the two observational studies consisted of consecutive, prospectively enrolled refractory OHCA patients. Amongst non-hypothermic CA patients, we excluded patients with prehospital ECPR, CA of non-cardiac or unknown origin, ROSC before hospital admission, patients for whom $ETCO_2$ or $PaCO_2$ was not available, or whose core temperature was <32 °C, to exclude cases in which hypothermia could have been a cause or contributor to CA. A missing temperature at hospital admission was not an exclusion criterion, if CA was from a cardiac cause.

We collected the following data: age, sex, first prehospital rhythm (shockable or not), whether the CA was witnessed or not, CPR duration (defined as the time from beginning of CPR to hospital admission), core temperature at hospital admission, and whether the patient underwent ECPR or ECLS rewarming. The primary parameters of interest were $ETCO_2$ and $PaCO_2$. We used the first $ETCO_2$ value recorded on the admission and the first $PaCO_2$ measured in the arterial blood gas. Depending on the origin of the data, the $PaCO_2$ was originally either measured at 37 °C and not corrected to the patient's temperature (alpha-stat) or corrected to the patient's temperature (pH-stat). Additional parameters from the arterial blood gas (ABG), such as PaO_2, HCO_3, base excess (BE), potassium, haemoglobin, and lactate, were also evaluated. In the absence of $ETCO_2$ monitoring on admission, values recorded in the prehospital phase were analysed.

The primary outcome of our study was survival at hospital discharge. Secondary outcomes included intensive care unit (ICU) length of stay, and survival at discharge with favourable neurological outcome using Cerebral Performance Category (CPC).[16] A CPC of 1 or 2 was considered to be a favourable neurological outcome.[8,17,18]

Ethical committee approval was obtained for data collection for all patients (Switzerland CER-VD N° 2016 01760, France ID-RCB: 2016-A01762–49, and Krakow, Poland N° 1072.6120.344.2018).

Statistical analysis

To analyse the data according to both alpha-stat and pH-stat strategies,[9,19,20] we converted the $PaCO_2$ originally measured with the alpha-stat method to pH-stat using the following formula: pH-$PaCO_2$ = alpha-$PaCO_2$*10EXP(0.021x(temperature-37)). We converted the $PaCO_2$ originally measured with the pH-stat method to alpha-stat using the following formula: alpha-$PaCO_2$ = pH-$PaCO_2$/10EXP(0.021x(temperature-37)). The $PaCO_2$ was originally measured with the alpha-stat method in 31 patients, and with the pH-stat method in 100 patients. Because temperature values were missing in 29 patients without hypothermia, it was not possible to estimate the values of $PaCO_2$ alpha-stat in those patients. We used multiple imputation to estimate the missing temperature values in order to apply the alpha-stat and pH-stat method in all patients.

Two groups of patients, either with or without hypothermia, were identified. We described continuous variables with mean and standard deviation or median and interquartile range and compared variables with Student t-test or Wilcoxon rank sum test when appropriate. We described categorical variables with frequency, percentage and 95% confidence intervals and compared variables with Fisher's exact test by doubling the exact one-tailed probability. Firstly, we explored the relationship between $ETCO_2$ or $PaCO_2$ and temperature by using a generalized linear model (GLM). The assumption of a linear relationship is required for a GLM. To explore the relationship of between continuous variables, a common approach is to dichotomize or split variables in several categories. However, this approach can lead to loss of information. Because we expected that the relationship was not linear, we used a restricted cubic spline with 3 knots. A restricted cubic spline is a transformation with a cubic polynomial in each spline to model a non-linear relationship in a regression model. We also expected that the relationship between $ETCO_2$, $PaCO_2$ and temperature might be confounded. We fitted a regression model including age, witnessed cardiac arrest, CPR duration and initial shockable rhythm and adjusted the exposure variable ($ETCO_2$ and $PaCO_2$) by adding the residuals to the mean value of the exposure variable. We graphically assessed linearity between adjusted $PaCO_2$ and $ETCO_2$ on the y-axis and temperature on the x-axis. As linearity seemed reasonable, we then

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fitted the GLM between $ETCO_2$ and $PaCO_2$. We also used a logistic regression model to assess the association between survival and temperature and $ETCO_2$. Because we expected overfitting of the model with a limited number of events in the regression equation, we performed crude (overall) analysis and bivariable analysis with potential confounders one at a time for patients with hypothermia to assess whether each confounder did or did not change the association. The confounders were witnessed cardiac arrest, CPR duration, initial shockable rhythm, and age. We performed multiple imputation by chained equations to estimate missing values for temperature, witnessed cardiac arrest, CPR duration and included survival, hypothermia, pH and initial rhythm as independent variables. We generated 20 imputed datasets. We imputed 56 missing values for 56 incomplete observations. All statistical analyses were performed using STATA software (version 16.0; Stata corp, College Station, TX, USA).

Results

A total of 131 patients were enrolled in the study, including 39 hypothermic and 92 non-hypothermic CA patients (Fig. 1). The general characteristics of the study population are shown in Table 1. Both $ETCO_2$ and pH-stat $PaCO_2$ were significantly lower in hypothermic CA than in non-hypothermic CA. The median $ETCO_2$ was 12 mmHg versus 18 mmHg ($p < 0.001$), and the median pH-stat $PaCO_2$ was 30 mmHg versus 43 mmHg ($p < 0.001$). Alpha-stat $PaCO_2$ showed a trend to being higher in hypothermic CA. The difference was not statistically different. The median alpha-stat $PaCO_2$ - $ETCO_2$ gradient was 30 mmHg (IQR 21–52) for non-hypothermic CA patients and 46 mmHg (IQR 29–70) for hypothermic CA patients ($P = 0.007$). The median pH-stat $PaCO_2$ - pH-$ETCO_2$ gradient was 23 mmHg (IQR 13–42) for non-hypothermic CA patients and 16 mmHg (IQR 7–31) for hypothermic CA patients ($p = 0.10$). The relationships between temperature and $ETCO_2$ and $PaCO_2$ adjusted for age, witnessed cardiac arrest, CPR duration and initial shockable rhythm are shown in Fig. 2. We thought that the assumption of linearity was reasonable. While $ETCO_2$ and pH-stat $PaCO_2$ decrease as temperature decreases, alpha-stat $PaCO_2$ increases.

The main outcomes are presented in Table 2. The proportion of survivors with $ETCO_2 \leq 10$ mmHg at hospital admission was 45% (9/20) for patients in hypothermic CA and 12% (2/17) for patients in non-hypothermic CA.

Hypothermic CA was associated with an $ETCO_2$ that was 4.8 mmHg lower than in patients with non-hypothermic CA in the generalized linear model, and a pH-stat $PaCO_2$ that was 10.5 mmHg lower (Table 3). Hypothermia was not associated with any change of alpha-stat $PaCO_2$ (Table 3). Temperature was significantly associated with $ETCO_2$ ($p < 0.01$) and pH-stat $PaCO_2$ ($p < 0.01$) but not alpha-stat $PaCO_2$ ($p = 0.5$). The $ETCO_2$ decreased by 0.5 mmHg for every decrease of 1 °C in temperature, and the pH-stat $PaCO_2$ decreased by 1.1 mmHg for every decrease of 1 °C in temperature (Table 3).

After adjusting for age, witnessed cardiac arrest, cardiopulmonary resuscitation duration and initial shockable rhythm, there was no association between $ETCO_2$ and survival among patients with hypothermia (Table 4).

Discussion

In the present study of patients with cardiac arrest, we showed that hypothermia is associated with a decrease in both $ETCO_2$ and pH-stat $PaCO_2$, but not alpha-stat $PaCO_2$, resulting in a larger measured $PaCO_2$ - $ETCO_2$ gradient in hypothermic patients when using the alpha-stat strategy. About half the survivors from hypothermic CA had an $ETCO_2 \leq 10$ mmHg at hospital admission. The value of $ETCO_2$ did not predict survival.

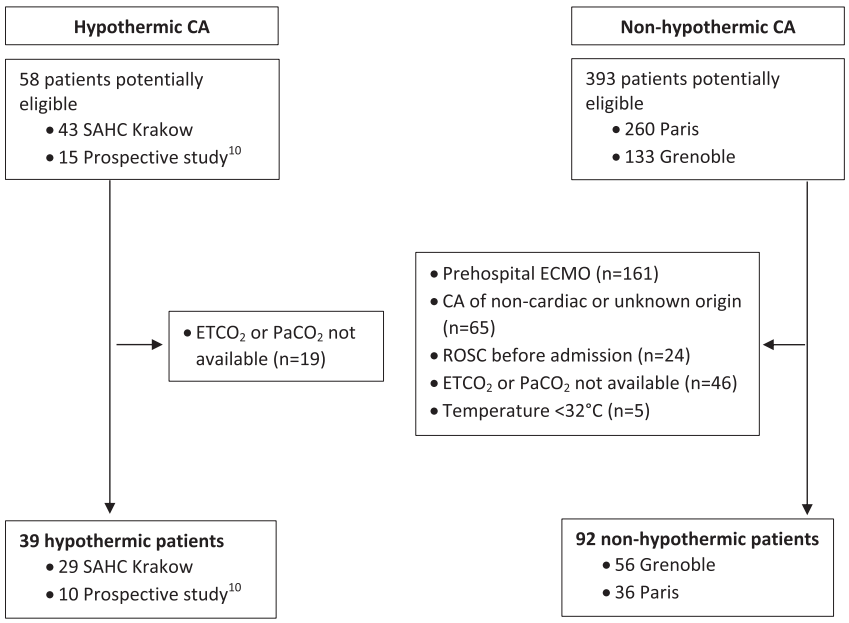

Fig. 1 – Flowchart of the study patients. CA: cardiac arrest; ECMO: extracorporeal membrane oxygenation; ROSC: return of spontaneous circulation; SAHC: Severe Accidental Hypothermia Centre.

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Table 1 – Characteristics of the study population. CA: cardiac arrest; CPR: cardiopulmonary resuscitation; IQR: interquartile range; SD: standard deviation.

	Missing	Overall (n = 131)	Hypothermic CA (n = 39)	Normothermic CA (n = 92)	p-value
Overall characteristics					
Age (years), mean (SD)	0	51 (13)	56 (15)	49 (12)	0.01
Sex male, n (%)	0	110 (84)	29 (74)	81 (88)	0.10
Initial shockable rhythm, n (%)	29	81 (79)	4 (40)[a]	77 (84)	0.01
Witnessed cardiac arrest, n (%)	25	96 (91)	32 (82)	64 (96)	0.06
CPR duration (min), median (IQR)	1	100 (80–125)	135 (81–180)	95 (79–108)	0.01
Temperature (°C), mean (SD)	29	30 (5)	24 (3)	34 (1)	<0.001
Blood gas analysis					
$ETCO_2$ (mmHg), median (IQR)	0	15 (10–27)	12 (8–15)	18 (12–30)	<0.001
$PaCO_2$ alpha-stat (mmHg), median (IQR)[b]	29	56 (42–77)	57 (43–81)	53 (41–70)	0.15
$PaCO_2$ pH-stat (mmHg), median (IQR)[c]	0	40 (30–57)	30 (21–45)	43 (35–62)	<0.001
pH, mean (SD)	0	7.02 (0.22)	6.96(0.23)	7.04 (0.21)	0.06
PaO_2 (mHg), median (IQR)	0	98.7 (60.8–217)	66 (51–89)	137 (78–225)	<0.001
HCO_3 (mmol/L), median (IQR)	8	12 (9–16)	11.5 (10–15)	12.5 (9–17)	0.52
Potassium (mmol/L), mean (SD)	5	4.7 (1.7)	4.9 (2.4)	4.6 (1.2)	0.34
Haemoglobin (g/L), median (IQR)	12	122(110–141)	115 (99–143)	123 (111–140)	0.20
Lactate (mmol/L), median (IQR)	1	13 (9–16)	10 (7–15)	13 (9–17)	<0.01

[a] The initial CA rhythm was available for only 10/39 of the hypothermic patients.

[b] Because of missing data for the temperature in 29 patients, the original values measured with the pH-stat $PaCO_2$ method could not be estimated to correspond to alpha-stat $PaCO_2$ values.

[c] Includes 31 patients with alpha-stat $PaCO_2$ These values were converted to pH-$PaCO_2$.

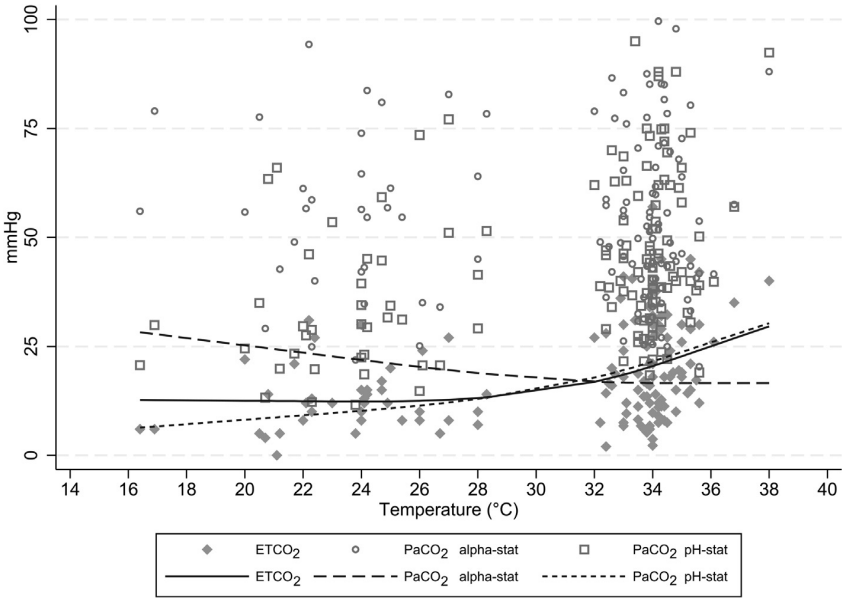

Fig. 2 – Relationship between $ETCO_2$ or $PaCO_2$ (alpha-stat or pH-stat) and temperature at hospital admission for cardiac arrest patients. The dots represent the unadjusted data. The two dashed lines represent the $PaCO_2$ (alpha-stat or pH-stat) adjusted for age, witnessed cardiac arrest, CPR duration and initial shockable rhythm.

The physiologic $PaCO_2$ - $ETCO_2$ gradient is approximately 0–5 mmHg in normothermia.[1,2,21]. In a study of normothermic patients undergoing polysomnography and breathing ambient air, the mean $PaCO_2$ - $ETCO_2$ gradient was of 2.3 (SD 8.4) mmHg.[22] These values are much lower than the median $PaCO_2$ - $ETCO_2$ we found in CA patients. An increase in the $PaCO_2$ - $ETCO_2$ gradient has been observed in several clinical situations. For example, mean $ETCO_2$ was 10 mmHg lower than mean $PaCO_2$ (34 vs 44 mmHg) in a study of intubated patients following burns or trauma.[23] In another study of trauma patients admitted to the operating room, the initial mean $PaCO_2$ - $ETCO_2$ gradient was 6.8 (SD 9.5) mmHg in patients who survived, and 12.4 (SD 13.3) mmHg in those who died ($p = 0.03$).[24] We were unable to find data on the $PaCO_2$ - $ETCO_2$ gradient in CA or on hypothermic CA patients.

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Table 2 – Hospital outcomes of hypothermic and non-hypothermic cardiac arrest patients admitted to the hospital. CA: cardiac arrest; CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range.

	Missing	Overall (n = 131)	Hypothermic CA (n = 39)	Non-hypothermic CA (n = 92)	p value
ECMO duration (days), median (IQR)	21	2 (1–5)	12 (5–27)	1.3 (0.5–2.6)	<0.001
ICU duration (days),median (IQR)	99[a]	8 (2–17)	8 (2–17)	-	-
Survival, n (%)	0	37 (28)	20 (51)	17 (18)	<0.001
CPC	19				0.58
1–2, n (%)		34 (92)	19 (95)	15 (88)	
3–4, n (%)		3 (8)	1 (5)	2 (12)	

[a] The ICU duration was not available for the non-hypothermic CA patients, and missing for 7 hypothermic CA patients

Table 3 – Relationship between $ETCO_2$ or $PaCO_2$ (alpha-stat or pH-stat) and temperature for hypothermia in cardiac arrest patients.

	$ETCO_2$		$PaCO_2$ alpha-stat		$PaCO_2$ pH-stat	
	Coefficient of linear regression (95% CI)	p-value	Coefficient of linear regression (95% CI)	p-value	Coefficient of linear regression (95% CI)	p-value
Temperature (for 1 °C increase)	+0.5 (0.1; 0.8)	0.007	−0.6 (−1.4;0.3)	0.178	1.1 (0.5;1.7)	0.001
Hypothermia	−4.8 (−8.7; −0.1)	0.015	+7.0 (−1.9;15.9)	0.124	−10.5 (−17.3; −3.7)	0.003

Multivariate generalized linear models with random effect on origin of the data; covariables are age, CPR duration, initial shockable rhythm, and witnessed cardiac arrest (N = 131). Model 1 includes temperature and model 2 includes hypothermic or non-hypothermic groups as exposure.

Table 4 – Association between survival and ETCO2 using logistic regression model among patients in hypothermia. Survival is the dependent variable.

$ETCO_2$	Odds ratio	95% CI	p-value
Crude analysis	1.02	0.94–1.11	0.575
Adjusted for age	1.03	0.94–1.12	0.525
Adjusted for witnessed cardiac arrest	1.04	0.94–1.13	0.452
Adjusted for shockable rhythm	1.02	0.93–1.11	0.696
Adjusted for CPR duration	1.03	0.94–1.12	0.558

By decreasing metabolic rate, hypothermia leads to decreases in $PaCO_2$ and $ETCO_2$.[2,25–27] Hypothermia increases the solubility of CO_2, decreasing the partial pressure of CO_2 for a given blood CO_2 content.[28] At core temperatures lower than 37 °C, the $PaCO_2$, can be measured at 37 °C (uncorrected, alpha-stat), or measured values can be corrected to actual core temperature (pH-stat). We did not observe a decrease in uncorrected values of $PaCO_2$ in hypothermic patients. In a study of mild induced hypothermia a decrease in core temperature led to a decrease of $ETCO_2$, corrected $PaCO_2$ and intracranial presure.[27] A decrease of 3 °C in core temperature led to decreases of $ETCO_2$ and a decrease in corrected $PaCO_2$ but not uncorrected $PaCO_2$. Changes in arterial pH corrected for temperature and cerebral hemodynamics were correlated with changes in $PaCO_2$ but not with changes in core temperature. Using uncorrected $PaCO_2$ to calculate the $PaCO_2$ - $ETCO_2$ gradient, increases the measured gradient compared to using corrected $PaCO_2$.[26] In contrast, the $PaCO_2$ - $ETCO_2$ gradient did not change when corrected $PaCO_2$ was used for the calculation. In a study of 13 hypothermic patients with signs of shock, but not in cardiac arrest, an increased alpha-stat $PaCO_2$ - $ETCO_2$ gradient was reported, with maximum values as high as 36 mmHg.[9] Our study confirmed, that $ETCO_2$ reflects the corrected $PaCO_2$ more closely than the uncorrected $PaCO_2$. Hypothermia did not affect the corrected $PaCO_2$ - $ETCO_2$ gradient in hypothermic CA.

$ETCO_2$ is used routinely to make clinical decisions.[1–3] Our study demonstrated that patients in hypothermic CA have a low $ETCO_2$ compared to patients in non-hypothermic CA. Low $ETCO_2$ levels have been linked to poor outcomes in normothermic CA.[2,29,30] In intubated normothermic CA patients, $ETCO_2$ < 10 mmHg may be one of the criteria for terminating resuscitation.[3,30] $ETCO_2$ should be used with extreme caution as a prognostic factor for poor outcome in hypothermic CA. Low $ETCO_2$ may indicate a lack of perfusion during CA but may also be caused by other factors such as ventilation/perfusion mismatch.[1,29,31] This can be also observed in severely hypothermic patients without cardiac arrest. Our study showed that $ETCO_2$ should not be used to predict survival in hypothermic CA or as a marker for good quality resuscitation in deep hypothermia.

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A patient in cardiac arrest that may have been caused by hypothermia should be transported directly to an ECLS centre regardless of the $ETCO_2$. In the prehospital setting, or more often at hospital admission, $ETCO_2$ is often one of the criteria for use of ECPR in non-hypothermic patients in cardiac arrest from cardiac causes.[6,30,32] $ETCO_2$ < 10 mmHg may be one of the criteria for disqualification from extracorporeal cardiopulmonary resuscitation (ECPR) with veno-arterial extracorporeal membrane oxygenation (ECMO) in refractory cardiac arrest.[5,6,33–36] However, European Resuscitation Council recommends predicting the outcome of ECLS rewarming of a patient in hypothermic cardiac arrest using a multivariable decision tool such as the HOPE (Hypothermia Outcome Prediction after ECLS rewarming) scale. The HOPE score has been validated.[7,8,17] Our findings do not support the use of the $ETCO_2$ value as a guiding factor for the use of ECPR for patients in hypothermic cardiac arrest. In our study, about half of the patients who survived hypothermic CA had an $ETCO_2$ value that would have been a contraindication to ECPR for non-hypothermic patients in cardiac arrest.

$ETCO_2$ monitoring should be used to confirm proper position of the endotracheal tube in a normothermic patient but should not be used to confirm proper placement of the endotracheal tube in a patient in hypothermic CA.[3] In an intubated patient in hypothermic CA, an $ETCO_2$ < 10 mmHg does not necessarily indicate malposition. The differential diagnosis of an $ETCO_2$ < 10 mmHg in an intubated patient in CA should include hypothermia as well as pulmonary embolism, haemorrhage, equipment problems, and kinking of the tube. Hypothermia should also be suspected in the ED if the $PaCO_2$ - $ETCO_2$ gradient is high. The classic reasons for an increase in the normally minimal $PaCO_2$-$ETCO_2$ fall into three main categories: global or regional decrease in pulmonary perfusion, increased V/Q mismatch and measurement error.[37] Based on our study, increased $PaCO_2$ - $ETCO_2$ gradient can also be caused by accidental hypothermia, especially with alpha-stat $PaCO_2$.

Because $ETCO_2$ correlates with $PaCO_2$, it can be used to guide ventilation in prehospital care. The Wilderness Medical Society guidelines for prehospital management of hypothermia recommend that in a patient with an advanced airway, $ETCO_2$ should be maintained in the normal range.[38] Because the $PaCO_2$ - $ETCO_2$ gradient may be elevated in hypothermia, we recommend using a weight-based estimate of minute ventilation instead. The ideal minute volume is not known but may be lower than in normothermia.

Once available, usually in hospital, the $PaCO_2$ is used instead of the $ETCO_2$ to guide ventilation. It is not known whether the pH stat or the alpha-stat strategy is better for guiding acid-base management in hypothermic CA patients. Based on experience with mild to moderate induced hypothermia for cardiac surgery and in post-arrest targeted temperature management, the alpha-stat strategy seems to be superior. It does not lead to significantly impaired autoregulation of cerebral perfusion and preserves neuronal electroneutrality.[39,40] In deep hypothermia, however, the differences between actual $PaCO_2$ and measured $PaCO_2$ may be very high. The pH strategy should be used to ensure cerebral protection.[41]

One of the strengths of our study was that we used accurate data from prospective studies published in peer-reviewed journals. We used a rigorous method to model the associations among temperature, $PaCO_2$ and $ETCO_2$ using a multivariable regression model. We were careful to use polynomial regression with spline to model continuous variables.

Limitations

Although $ETCO_2$ closely approximates $PaCO_2$ in normal physiologic conditions, it is influenced by several factors in CA, especially by the quality of chest compressions and by the ventilation rate.[1,2,29,31,42] We did not adjust for these potential confounders. This may have introduced a systematic bias. The potential time lag between the measurements of $ETCO_2$ and $PaCO_2$ might have introduced inaccuracies and reporting bias. The two measurements were not always taken simultaneously. This may have created a systematic bias. In addition, we used the first measurement at hospital admission and not several measurements. Random error measurement might lead to regression dilution bias that would be expected to decrease the observed association.[43] Using a different formula for temperature correction can result in different values of $PaCO_2$.[44] Our study had only 131 subjects. This limits the statistical robustness of our data. In the non-hypothermic group, a missing temperature was not an exclusion criterion if the cause of CA was identified as cardiac. Our data came from only three European countries, limiting the external validity of our study. Also, there were significant differences in the characteristics of patients in hypothermic and non-hypothermic CA. For example, the median duration of CPR in patients with hypothermic CA undergoing ECPR was about 120 minutes, while a long duration of CPR was a contraindication to ECPR in patients with non-hypothermic CA.[45,46] The inclusion of potential confounders in our multivariable analysis may have only partially overcome these limitations.

Conclusions

We found that $ETCO_2$ and pH-stat $PaCO_2$ are decreased in hypothermic patients in CA, but not in normothermic patients. Because alpha-stat $PaCO_2$ did not change in hypothermic CA, the alpha stat - $ETCO_2$ gradient was increased in severely hypothermic patients in CA. $ETCO_2$ should not be used to predict outcomes in hypothermic CA. $ETCO_2$ < 10 mm Hg should not be used in hypothermic CA patients as a criterion for stopping CPR in prehospital care or for withholding ECLS rewarming in hospital.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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