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Clinical paper

Abrupt rise of end tidal carbon dioxide level was a specific but non-sensitive marker of return of spontaneous circulation in patient with out-of-hospital cardiac arrest☆

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of an abrupt and sustained increase in end-tidal carbon dioxide ($ETCO_2$) to indicate return of spontaneous circulation (ROSC) during resuscitation of patient with out-of-hospital cardiac arrest.
Design: Cross-sectional study.
Setting: Emergency department of two regional hospitals.
Methods: Patients with age ≥18 years old, suffered non-traumatic out-of-hospital cardiac arrest with active resuscitation and endotracheal intubation performed in emergency department, were included. $ETCO_2$ value was charted throughout resuscitation. Time of ROSC was remarked. $ETCO_2$ levels before and after ROSC were compared. Diagnostic accuracy of $ETCO_2$ rise ≥10 mmHg, $ETCO_2$ rise ≥20 mmHg, and $ETCO_2$ rise to the level ≥40 mmHg were evaluated for indicating ROSC.
Results: $ETCO_2$ level immediately after ROSC was higher as compared to the value before return of circulation (median $ETCO_2$ was 32 mmHg and 41 mmHg respectively, $p = 0.033$). With $ETCO_2$ rise ≥10 mmHg, the sensitivity was low (33%, 95% CI 22–47%), while specificity was 97% (95% CI 91–99%). Positive and negative predictive values were 83% (95% CI 62–95%) and 74% (95% CI 66–81%) respectively. The diagnostic accuracy was higher in cardiac arrest with presumed non-cardiac etiology (sensitivity 45%, specificity 100%) as compared to those with cardiac etiology (sensitivity 18%, specificity 97%).
Conclusions: The feature of an abrupt rise of $ETCO_2$ was a specific but non-sensitive marker of ROSC in patient with out-of-hospital cardiac arrest.

Introduction

Measurement of end-tidal of carbon dioxide ($ETCO_2$) level was a non-invasive method, recommended in the ACLS resuscitation guidelines of the American Heart Association[1,2] for monitoring the resuscitation process for patients with cardiac arrest. $ETCO_2$ had been recommended as one of the marker for early prognostication of patients with cardiopulmonary arrest.[3–7] The ACLS 2015 guideline stated that $ETCO_2$ after 20 min of cardiopulmonary resuscitation (CPR) is an important early prognosticator.[1] The European Resuscitation Council (ERC) resuscitation guideline 2015 also recommended $ETCO_2$ as part of a multi-modal approach to decision-making for ending resuscitative efforts.[3]

Another use of $ETCO_2$ during resuscitation was to indicate return of spontaneous circulation (ROSC) when there is an abrupt and sustained rise of $ETCO_2$.[8–13] The 2005 ILCOR consensus statement firstly incorporated the abrupt and sustained rise of $ETCO_2$ >40 mmHg as a bedside indicator of ROSC.[14] The ERC guideline recommended to withhold the dose of adrenaline if ROSC is suspected during CPR and deliver adrenaline if cardiac arrest is confirmed at the next rhythm check.[3] Theoretically, if this is sensitive and specific enough, it would be able to replace regular pulse checks and thus further minimize the interruption of chest compressions. However, there was limited evidence in the literature to evaluate the accuracy of this to indicate ROSC. A retrospective case control study had demonstrated a sudden increase of $ETCO_2$ ≥10 mmHg had 80% sensitivity and 40% specificity indicating ROSC.[8] However, there was major limitation of generalization with the study design and inclusion criteria. There is no strong evidence to evaluate the

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accuracy of the feature of suddenly increased $ETCO_2$ to detect ROSC in patients with OHCA.

The objective of our study was to evaluate the $ETCO_2$ profile for patients of OHCA with or without ROSC, and evaluate the diagnostic characteristics of the features of abrupt increase in $ETCO_2$ in diagnosis of ROSC.

Methods

Study design and setting

This is a cross-sectional study, being performed in emergency departments of two regional hospitals in Hong Kong. The study period was from July 2012 to June 2013. The two hospitals provide emergency service for a region with population of over one million. All cardiac arrest patients occurred in the area were delivered by the Emergency Medical Services provided by the Fire Services Department to these two receiving hospitals. All patients were resuscitated on scene by pre-hospital personnel according to the basic life support protocol. Automated external defibrillators were utilized and defibrillation would be performed if indicated. After arrival to hospital, patients were resuscitated according to the ACLS guideline with endotracheal intubation and chest compression. Patients were ventilated with mechanical ventilator (Dräger Oxylog® 1000) with fixed minute ventilation during resuscitation before ROSC. Tidal volume was tailored for individual patients according to estimated body weight. Ventilation rate was set between 8 and 10 breaths per minute. Patients were ventilated in an asynchronous ventilation compression according to the ACLS protocol. End-tidal capnography was applied immediately after endotracheal intubation. Nellcor™ Microstream model N85 by the Medtronic was utilized as the end-tidal capnography in the study. The Nellcor N85 provides continuous end-tidal capnography for the range from 0 to 99 mmHg with the accuracy of ±2 mmHg or 5%.

Ethics approval was obtained from the local institutional review board. The study was performed according to the ethical principles in the Declaration of Helsinki and the Good Clinical Practice guideline of the International Conference on Harmonization.

Patients' inclusion

Inclusion criteria were patients with age at least 18 years old, suffered non-traumatic out-of-hospital cardiac arrest with active resuscitation and endotracheal intubation performed in emergency department. Exclusion criteria were those with regain of spontaneous circulation before arrival to hospital and those without satisfactory documentation of $ETCO_2$ values. Patients who were ventilated by manual bag-valve-mask but not constantly ventilated by mechanical ventilator were also excluded.

Definition

Return of spontaneous circulation (ROSC) was defined as the restoration of a spontaneous circulation with a palpable pulse or arterial waveform in the absence of chest compressions, and an organized spontaneous ECG rhythm followed by a measurable blood pressure.[15] Duration was not taken into account as the primary research question is to assess the accuracy of change in $ETCO_2$ at the time of return of circulation.

An abrupt and sustained rise of $ETCO_2$ was defined as the rise of $ETCO_2$ values equal or more than a threshold valve (10 mmHg and 20 mmHg) as measured by the capnometer on subsequent occasions, and the observed value did not drop for more than 10 mmHg after three minutes.

When the $ETCO_2$ increased for more than the threshold value (10 mmHg and 20 mmHg), where ROSC was diagnosed concurrently, it would be classified as "true positive". When there was increase in $ETCO_2$ values but there was no ROSC, it would be classified as "false positive". "True negative" would be defined when there was neither $ETCO_2$ increase nor ROSC occurred. "False negative" was defined as ROSC occurred but there was no increase in $ETCO_2$ values. Sensitivity was defined as the number of patients with RSOC and $ETCO_2$ increased more than the threshold value (true positive) divided by the total number of patients with ROSC. Specificity was defined as the number of patients without increase in $ETCO_2$ and no ROSC (true negative) divided by total number of patients without ROSC.

Etiology of cardiac arrest was presumed as follow. Cardiac causes would be presumed if it was a witnessed arrest, patients with shockable cardiac rhythm or electrocardiographic evidence of myocardial infarction, patients had preceding chest pain before cardiac arrest, and those confirmed as cardiac causes by autopsy. Non-cardiac causes included those arrest associated with poisoning, intracranial lesions, sepsis, electrolyte disturbances, respiratory/asphyxiation or other non-cardiac causes based on clinical findings. The judgment was performed by the attending emergency physician.

Data collection

Variables collected include patients' age, gender, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), initial cardiac arrest rhythm, defibrillation in pre-hospital phase and in emergency department were recorded. Data were prospectively collected in standardized forms of the local cardiac arrest registry. Outcome variables were traced by electronic hospital records, including survival to hospital admission and survival to hospital discharge.

$ETCO_2$ data was gathered and documented in a specifically designed resuscitation chart by the attending nurse. Prior training sessions were arranged for the proper use of capnography. $ETCO_2$ readings were recorded whenever there was significant change (defined as change of $ETCO_2$ $\geq$10 mmHg) or every 3 min. Regular pulse checks were adopted every 3 min. Time of ROSC was recorded down. All $ETCO_2$ data was collected prospectively while the outcome and demographics were retrieved from the local cardiac arrest registry, which was a database prospectively collecting data of patients of OHCA in Utstein template.

Statistical analysis

Baseline characteristics and outcomes were compared between the ROSC and no-ROSC group. Categorical data would be presented in the form of frequency or percentage and analyzed using the Fisher's exact test or the chi-square test with Yate's correction where appropriate. Continuous variables were presented in the form of mean and standard deviation and were compared by independent sample *t*-test if normally distributed.

The group of patients with sustained ROSC (those with recurrent cardiac arrest were excluded) was further analyzed. Boxplot was created to illustrate the distribution of $ETCO_2$ values just before and after ROSC. Median and interquartile range were calculated. They were compared using Wilcoxon signed rank test. The $ETCO_2$ values before ROSC and after ROSC were analyzed by repeated measure analysis of variance. The Mauchly's test was adopted to evaluate the assumption of sphericity. Pairwise comparisons with Bonferroni method would be subsequently carried out. Line charts were created to illustrate the trend of $ETCO_2$ throughout the resuscitation in the group with single ROSC and those without ROSC.

Diagnostic characteristics of $ETCO_2$ to predict ROSC were calculated, including sensitivity, specificity, positive and negative predictive values along with the 95% confidence interval. Positive

likelihood ratio was defined as sensitivity divided by one minus specificity. Negative likelihood ratio was defined as one minus sensitivity divided by specificity. Diagnostic characteristics were calculated for $ETCO_2$ rise ≥10 mmHg, $ETCO_2$ rise ≥20 mmHg, $ETCO_2$ rise ≥10 mmHg to a value ≥40 mmHg, and $ETCO_2$ rise ≥20 mmHg to a value ≥40 mmHg.

Subgroup analysis was carried out for those with presumed cardiac and non-cardiac etiology. Changes in $ETCO_2$ level at ROSC would be compared in two groups. Diagnostic characteristics of $ETCO_2$ indicating ROSC would also be calculated in both groups.

Results

Totally 178 cases were included. Fig. 1 showed the recruitment of patients and the outcome. With high exclusion rate due to inadequate documentation, comparison between the included cohort and those excluded was required. There were no significant differences with reference to baseline characteristics and outcome between the included cohort and those excluded.

For the included cohort, sixty patients (34%) had ROSC. Table 1 illustrated the characteristics and outcomes. $ETCO_2$ rise was more prevalent in the ROSC group as compared to the contrary group, in both classification at 10 mmHg, 20 mmHg and second value ≥40 mmHg. Table 2 illustrated the diagnostic characteristics of $ETCO_2$ indicating ROSC. With reference to $ETCO_2$ rise ≥10 mmHg, the sensitivity was low (33%, 95% CI 22–47%), while specificity was 97% (95% CI 91–99%). Positive and negative predictive values were 83% (95% CI 62–95%) and 74% (95% CI 66–81%) respectively. The specificity was similar (98%) with cut-off of $ETCO_2$ rise at 20 mmHg but the sensitivity dropped to 20%. With addition of stringent criteria of $ETCO_2$ rise to value ≥40 mmHg, the specificity went higher (99%) but with even lower sensitivity (15%).

Forty-six patients had sustained ROSC without recurrent cardiac arrest. Analysis of the $ETCO_2$ values in this group of patients at the juncture of ROSC was performed and illustrated in Fig. 2. The median $ETCO_2$ level just before ROSC was 32 mmHg as compared to the level immediately after ROSC (41 mmHg, $p = 0.033$). Analysis of two $ETCO_2$ levels just before ROSC and another two $ETCO_2$ values after ROSC was carried out with repeated measures ANOVA. The Mauchly's test of sphericity indicated the data violated the assumption of sphericity ($p < 0.001$). Repeated measures using ANOVA and Greenhouse–Geisser correction, the mean $ETCO_2$ were statistically significantly different between two groups ($p = 0.012$). Pair wise comparisons with Bonferroni correction showed that there was a significant difference between the $ETCO_2$ level just before and after ROSC (mean difference 13.5, $p = 0.047$). Fig. 4 illustrated the $ETCO_2$ trend throughout the resuscitation for those with single ROSC versus those without ROSC. The rise of $ETCO_2$ at the juncture of ROSC was well demonstrated.

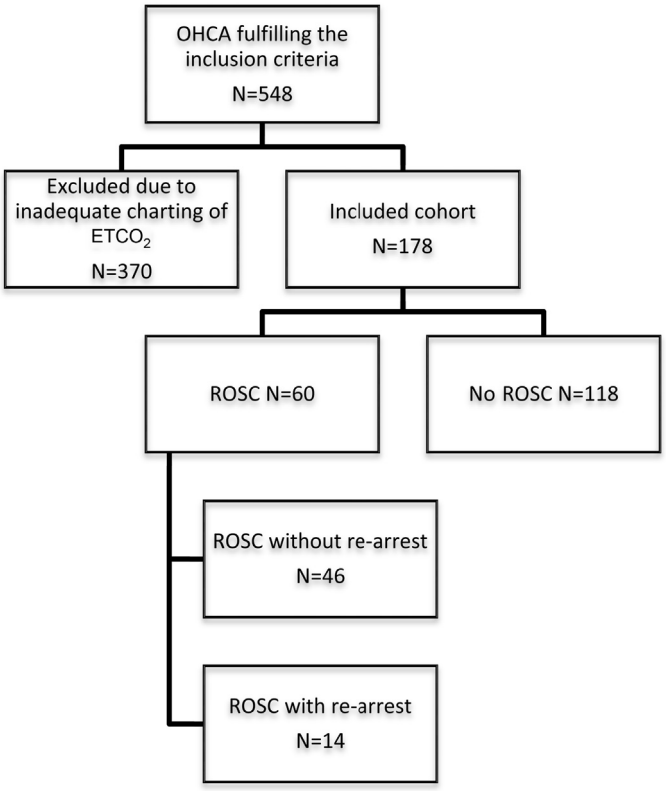

Fig. 1. Inclusion of the cohort and outcome.

Table 1
Baseline characteristics, $ETCO_2$ change and outcome of the cohort.

Parameters	All ($N = 178$)	ROSC group ($N = 60$)	No ROSC group ($N = 118$)	p Value
Age (mean, SD)	72, 20	74, 16	71, 21	0.369
Gender, male	83 (47%)	27 (45%)	56 (48%)	0.879
Witnessed arrest	88 (49%)	42 (70%)	46 (39%)	<0.001
Bystander CPR	38 (21%)	13 (22%)	25 (21%)	1.000
Initial documented cardiac rhythm				0.791
VF/VT	18 (10%)	7 (12%)	11 (9%)	
PEA	8 (5%)	2 (3%)	6 (5%)	
Asystole	152 (85%)	51 (85%)	101 (86%)	
Defibrillation				
Prehospital	22 (12%)	8 (13.3%)	14 (11.9%)	1.000
In ED	21 (11.8%)	8 (13.3%)	13 (11%)	0.836
Presumed etiology				–
Non-cardiac	26 (15%)	11 (18%)	15 (12.7%)	
Cardiac	56 (32%)	23 (38%)	33 (28.0%)	
Unknown	95 (53%)	26 (43%)	69 (58.5%)	
$ETCO_2$ change observed during resuscitation				
$ETCO_2$ rise ≥10 mmHg	24 (13.5%)	20 (33%)	4 (3%)	<0.001
$ETCO_2$ rise ≥20 mmHg	14 (8%)	12 (20%)	2 (2%)	<0.001
$ETCO_2$ rise ≥10 mmHg and latter $ETCO_2$ ≥40 mmHg	13 (7%)	11 (18%)	2 (2%)	<0.001
$ETCO_2$ rise ≥20 mmHg and latter $ETCO_2$ ≥40 mmHg	10 (6%)	9 (15%)	1 (0.8%)	<0.001
ROSC	60 (34%)	–	–	–
Survival to admission	57 (32%)	–	–	–
Survival to discharge	2 (1.2%)	–	–	–

Table 2
Diagnostic characteristics of $ETCO_2$ change indicating ROSC.

	$ETCO_2$ rise ≥10 mmHg	$ETCO_2$ rise ≥20 mmHg	$ETCO_2$ rise ≥10 mmHg and $ETCO_2$ value ≥40 mmHg	$ETCO_2$ rise ≥20 mmHg and $ETCO_2$ value ≥40 mmHg
Sensitivity, 95% CI	33% (22–47%)	20% (11–33%)	18% (10–31%)	15% (8–27%)
Specificity, 95% CI	97% (91–99%)	98% (93–100%)	98% (93–100%)	99% (95–100%)
Positive predictive value, 95% CI	83% (62–95%)	86% (56–97%)	85% (54–97%)	90% (54–99%)
Negative predictive value, 95% CI	74% (66–81%)	71% (63–77%)	70% (63–77%)	70% (62–76%)
Positive likelihood ratio, 95% CI	9.8 (3.5–27.5)	11.8 (2.7–51)	10.8 (2.5–47.2)	17.7 (2.3–136.5)
Negative likelihood ratio, 95% CI	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.8–1)

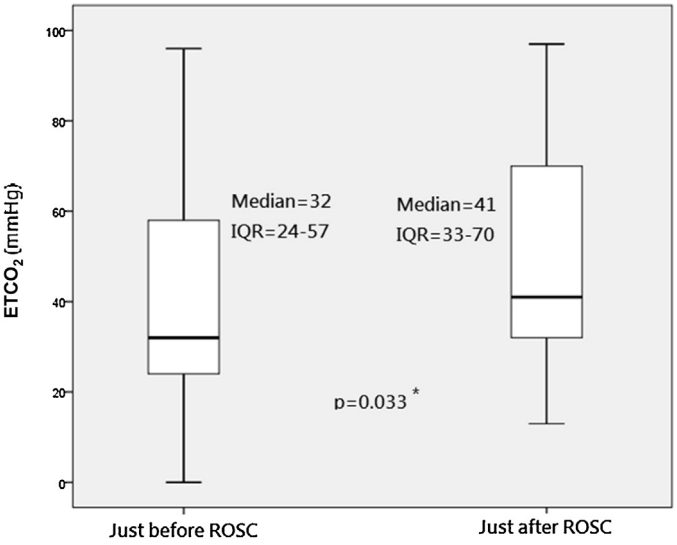

Fig. 2. $ETCO_2$ levels before and after ROSC. *Wilcoxon signed rank test.

Subgroup analysis for the group with presumed cardiac and non-cardiac etiology was shown in Table 3 and Fig. 3. Fig. 3 illustrated the change in $ETCO_2$ level at the juncture of ROSC. The rise of $ETCO_2$ was higher in non-cardiac group (median $ETCO_2$ rise 17.5 mmHg) as compared to the cardiac group (median $ETCO_2$ rise 5 mmHg, $p = 0.066$). In Table 3, the sensitivity and specificity of $ETCO_2$ rise ≥10 mmHg for ROSC were 45% (95%CI 18–75%) and 100% (95% CI 75–100%) in non-cardiac group, and were 18% (95% CI 6–41%) and 97% (95% CI 83–100%) in cardiac group respectively.

Discussion

The value of capnography during resuscitation of cardiopulmonary arrest was first recognized as dated back in 1987 by Garnett et al.[11] which stated that $ETCO_2$ was often the first bedside indicator of ROSC. The 2005 AHA guideline started to incorporate the abrupt and sustained rise of $ETCO_2$ >40 mmHg as a bedside indicator of ROSC.[14] It was stated in AHA resuscitation guidelines in 2010 that the use of $ETCO_2$ as clinical indicator of ROSC with Level IIa recommendation (LOE B). Nowadays, continuous quantitative waveform capnography has become the standard practice in resuscitation of cardiac arrest in most centers.

Another use of $ETCO_2$ in resuscitation of OHCA patients would be the indication of ROSC with abrupt and sustained rise of $ETCO_2$ during resuscitation.[8–13] Various studies had confirmed that $ETCO_2$ level was higher after ROSC.[8,11–13] $ETCO_2$ level during OHCA reflects tissue metabolism, alveolar ventilation, tissue and lung perfusion. Under constant ventilation, $ETCO_2$ level would correlate with the level of circulation and the aerobic metabolism of the entire body. It had been shown that spontaneous circulation was much more effective than chest compressions in terms of cardiac output.[16] This provided the biological rationale for the observation that $ETCO_2$ was higher after ROSC, which was an observation as early as 1978 by Kalenda et al.[17] In fact, the absolute $ETCO_2$ level during any time point of resuscitation of OHCA patients would basically depend on the body's aerobic metabolism rate, alveolar ventilation, systemic and pulmonary circulation. However, there are more complicating factors, including existence of ventilation-perfusion mismatch, peripheral vasoconstriction interfering CO_2 release from peripheral tissues (and the use of vasopressors), the presence of airway obstructing pathologies and the use of sodium bicarbonate during resuscitation.[18,19] How "abrupt" of the $ETCO_2$ increase during ROSC depends on the difference in pulmonary circulation before and after ROSC, which depends on the how effective is the chest compression before ROSC and the cardiac output immediately after ROSC. $ETCO_2$ increase at ROSC would be highly variable among different patients, and a single cut-off of the $ETCO_2$ increment would result in an inaccurate differentiation of ROSC during the resuscitation course as demonstrated in our study.

For the use of $ETCO_2$ to diagnose ROSC, most of the studies in literature were either animal studies or experiments under controlled environment[20–22] or had concluded that the $ETCO_2$ level was higher after ROSC.[8–13] There was only one retrospective case control study by Pokorna et al to directly evaluate

Table 3
Diagnostic characteristics of $ETCO_2$ rise ≥10 mmHg for ROSC in OHCA patients with presumed non-cardiac vs. cardiac etiology.

	Cardiac	Non-cardiac
Sensitivity, 95% CI	18% (6–41%)	45% (18–75%)
Specificity, 95% CI	97% (83–100%)	100% (75–100%)
Positive predictive value, 95% CI	80% (30–99%)	100% (46–100%)
Negative predictive value, 95% CI	65% (50–77%)	71% (48–88%)
Positive likelihood ratio, 95% CI	6.2 (0.7–51.7)	Infinity
Negative likelihood ratio, 95% CI	0.8 (0.7–1)	0.5 (0.3–0.9)

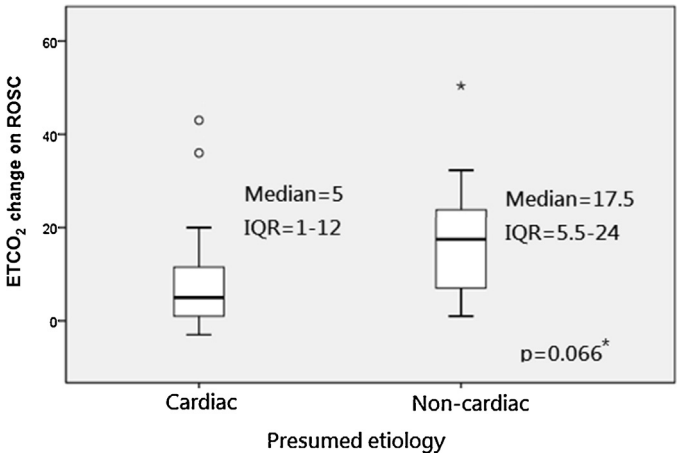

Fig. 3. Changes in $ETCO_2$ level on ROSC for cardiac arrest patients with presumed cardiac vs. non-cardiac etiology. *Wilcoxon rank sum test.

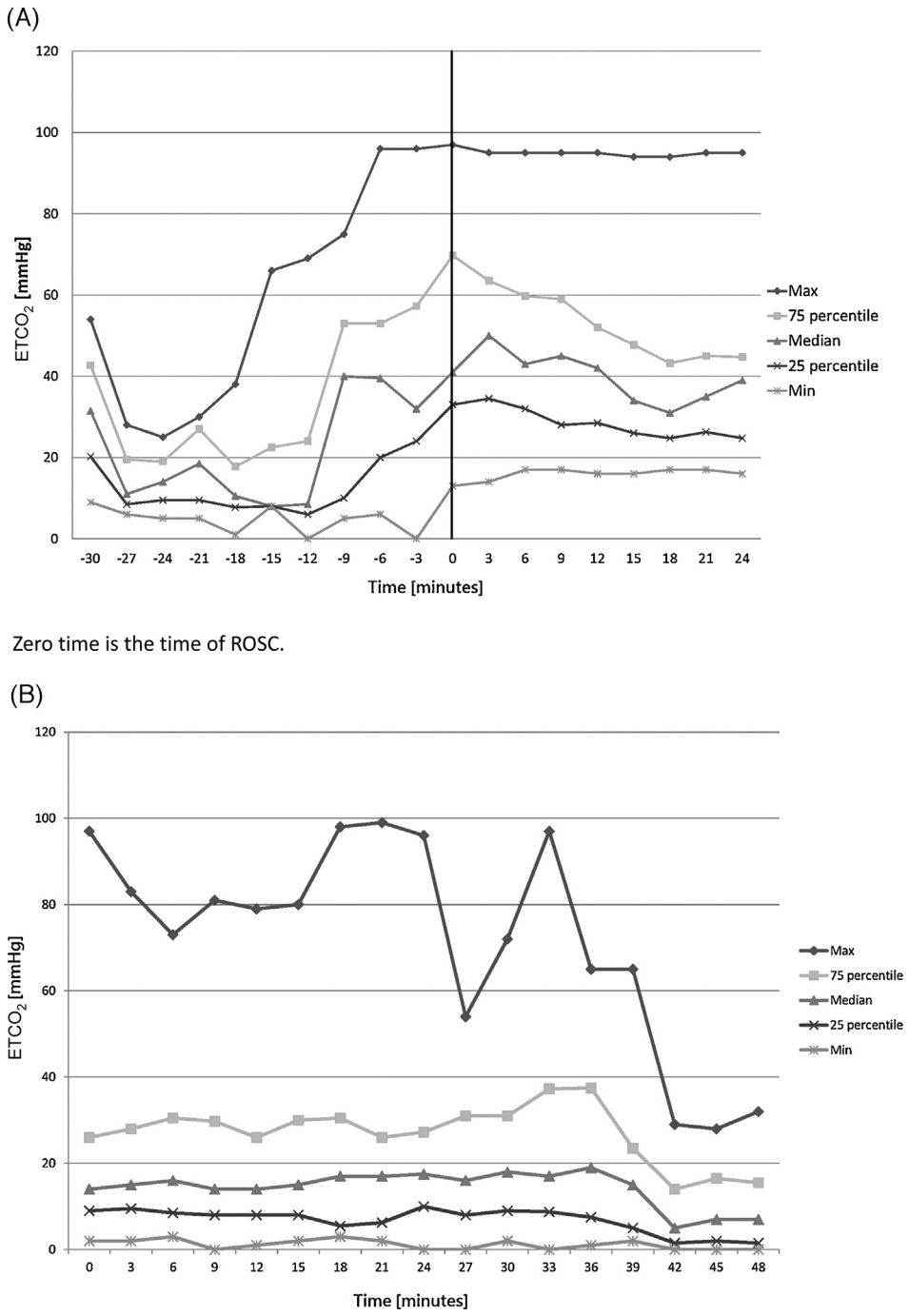

Fig. 4. Line charts illustrating $ETCO_2$ values throughout resuscitation of OHCA. (A) In patients with single ROSC followed by stable spontaneous circulation ($N = 46$). Zero time is the time of ROSC. (B) In patients without ROSC ($N = 118$).

the diagnostic accuracy of "abrupt sustained $ETCO_2$ increase" in ROSC.[8] The reported accuracy for $ETCO_2$ increase $\geq$10 mmHg had 80% sensitivity and 40% specificity. The reported sensitivity and specificity with 20 mmHg cut-off were 37% and 8% respectively. The result was different from our study. Our reported sensitivity and specificity with 10 mmHg cutoff of $ETCO_2$ increase was 33% and 97% respectively. With 20 mmHg cut-off, our reported values of sensitivity and specificity were 20% and 98%. We proposed the feature of abrupt $ETCO_2$ increase is a specific but non-sensitive marker for diagnosis of ROSC during resuscitation of OHCA. It appears reasonable that with higher cut-off of $ETCO_2$ increase, specificity would be better but with lower sensitivity. With more stringent criteria by addition of the end value to $\geq$40 mmHg, it is expected to enhance the specificity but further jeopardize the sensitivity. Theoretically, with a marker that is accurate enough to diagnose ROSC, it would replace the need for regular pulse check and therefore, minimize the interruption of chest compressions. In our study, it is shown that the $ETCO_2$ increase is not a sensitive marker to replace regular pulse checks. But the $ETCO_2$ increase was is demonstrated to be highly specific to indicate ROSC in our study.

Pokorna et al. reported for $ETCO_2$ increase $\geq$10 mmHg had 80% sensitivity and 40% specificity to detect ROSC.[8] The reported sensitivity and specificity with 20 mmHg cut-off were 37% and 8% respectively. The result had gross difference from that of our study. We hypothesized that the possible reasons include the difference in study design, inclusion criteria, the characteristic and aetiology

of arrest in the included patients. The study by Pokorna et al was a retrospective case control study conducted in the arrest scene outside hospital. It recruited the "case" group of patients of OHCA resuscitated at the scene with a single uncomplicated ROSC, and the "control" group of patients with unsuccessful ALS resuscitation without any signs of ROSC who were died at the scene. Our study setting was an in-hospital setting in the emergency department and our design was a prospective cohort study. We included out-of-hospital cardiac arrest of all clinical courses including the protracted cardiac arrest with multiple ROSC. In addition, the aetiology of arrest was not discussed in the study by Pokorna et al.

The $ETCO_2$ level in OHCA patients had significant variations and may depends on the etiology of cardiac arrest. Heradstveit et al had illustrated that the level of $ETCO_2$ depends on the cause of the arrest in a retrospective study.[7] Respiratory arrests had higher levels than cardiac, and pulmonary embolism had the lowest levels. It is not unexpected that for diseases resulting in significant ventilation-perfusion mismatch, the $ETCO_2$ would be low. A systematic review had stated no single cut-off value could be established for prognostication due to variation in etiology.[5] The sensitivity of the $ETCO_2$ rise in ROSC also differs with variation in etiology. Our study had shown that the feature was non-sensitive in patients with presumed cardiac etiology (18% sensitivity), while the sensitivity was better in the contrary group of non-cardiac causes. The specificity in cardiac and non-cardiac groups was high (97% and 100% respectively). The result indicates that the feature of $ETCO_2$ rise was more accurate in OHCA of non-cardiac etiology.

Limitation of study

Improper documentation of the use of $ETCO_2$ leads to possible selection bias. In our study, less than one third of all patients of OHCA were included during the study period, due to lack of proper $ETCO_2$ documentation. The potential selection bias may affect the prevalence of ROSC in the cohort and the interpretation of diagnostic accuracies of $ETCO_2$.

The quality of chest compressions was not controlled or measured in the study, which may affect the $ETCO_2$ level. The ventilation for OHCA in our cohort may have significant variations as the range of tidal volume had been recommended to be 6–8 ml/kg, and they were based on the estimation by the attending emergency physicians as the body weight can never be accurately measured during resuscitation. The variation in ventilation may have bias in the $ETCO_2$ level measured. In addition, use of sodium bicarbonate and vasopressors may also have effects on the $ETCO_2$ level which was not controlled in the study. For the subgroup analysis comparing cardiac versus non-cardiac causes of arrest, we adopt the composite non-cardiac group rather than respiratory causes due to limitation in sample sizes.

Conclusion

The feature of an abrupt rise of $ETCO_2$ was a specific but non-sensitive marker of ROSC in patient with out-of-hospital cardiac arrest.

Conflict of interest statement

All authors did not have conflict of interest with any parties. There was no funding for the research.

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