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Selected Topics: Prehospital Care

A SUDDEN INCREASE IN PARTIAL PRESSURE END-TIDAL CARBON DIOXIDE ($P_{ET}CO_2$) AT THE MOMENT OF RETURN OF SPONTANEOUS CIRCULATION

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□ **Abstract—Background: Previous studies established that a level of partial pressure end-tidal carbon dioxide ($P_{ET}CO_2$) of 10 mm Hg divided patients undergoing advanced life support (ALS) into those likely to be resuscitated (values > 10 mm Hg) and those likely to die during ALS (values < 10 mm Hg). Objective: The study tested the significance of a sudden increase in the $P_{ET}CO_2$ in signaling the return of spontaneous circulation (ROSC) during ALS. Material and Methods: $P_{ET}CO_2$ values were continuously recorded during ALS in out-of-hospital patients with cardiac arrest. Constant ventilation was maintained by an automatic device. There were 108 patients, representing two extreme outcomes of ALS, who were subdivided into two groups. The first group included 59 patients with a single ROSC followed by a stable spontaneous circulation. The second group included 49 patients with no signs of ROSC. Results: ROSC was associated with a sudden increase in $P_{ET}CO_2$ that remained significantly higher than before ROSC. $P_{ET}CO_2$ did not rise during the entire ALS in the second group of patients without ROSC and was lower than in the first group of patients. Conclusions: In constantly ventilated patients, $P_{ET}CO_2$ is significantly higher (about 10 mm Hg) after ROSC than before ROSC. A sudden increase in $P_{ET}CO_2$ exceeding 10 mm Hg may indicate ROSC. Consequently, the rule of 10 mm Hg may be extended to include a sudden increase in continuously recorded $P_{ET}CO_2$ by more than 10 mm Hg as an indicator of the possibility of ROSC. © 2010 Elsevier Inc.**

□ **Keywords—cardiac arrest; advanced life support; capnography; end-tidal carbon dioxide; return of spontaneous circulation; asynchronous compression-ventilation; cardiopulmonary resuscitation**

INTRODUCTION

Outcome of advanced life support (ALS) is determined by many factors, including severity of the primary insult, time elapsed between cardiac arrest and beginning of the basic life support (BLS) and ALS itself, the efficiency of BLS and ALS, cause of the cardiac arrest, patient's general state of health, and environmental circumstances. Of these factors, only ALS efficiency is under the control of the care providers. Therefore, any information regarding efficiency of ALS during its delivery is desirable, especially because frequent pulse checking and electrocardiogram (ECG) rhythm analysis may negatively interfere with the efficiency of ALS (1).

The partial pressure end-tidal carbon dioxide ($P_{ET}CO_2$) level reflects tissue metabolism, tissue and lung perfusion, and alveolar ventilation. Under constant ventilation, $P_{ET}CO_2$ reflects the level of circulation and intensity of the body's aerobic metabolism. Spontaneous circulation (SC) has been reported to be more effective in comparison with chest compression in the level of cardiac output

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reached (2). This provided a rationale for the observation by Kalenda that an increase of $P_{ET}CO_2$ occurs after ROSC (3). This has been confirmed in both experimental and clinical studies (4–7). Two experimental and one clinical study demonstrated a linear relationship between the cardiac output and $P_{ET}CO_2$ (8–10). Some other studies on out-of-hospital and hospital resuscitations also confirmed that $P_{ET}CO_2$ level after ROSC is higher than before ROSC (6,11,12). Other studies have been aimed at using $P_{ET}CO_2$ to discriminate between patients suffering cardiac arrest with a chance for ROSC from those destined to die (13–18). These studies have concluded that a $P_{ET}CO_2$ value of 10 mm Hg may serve as such a threshold value.

The ILCOR (International Liaison Committee on Resuscitation) Consensus on Science and Treatment Recommendations in 2005 mentioned the use of capnometry as a possible early indicator of ROSC (19).

A principle goal of the present study was to analyze changes in $P_{ET}CO_2$ levels around the ROSC point with an ultimate goal of determining whether an increase in $P_{ET}CO_2$ level could be used as a reliable indicator of ROSC.

MATERIALS AND METHODS

Study Design

This was a retrospective case control study. $P_{ET}CO_2$ was continuously monitored during out-of-hospital ALS delivered to patients in cardiac arrest. Subsequently, the $P_{ET}CO_2$ recordings were analyzed in two extreme groups of cases: the first group of patients were those with a single uncomplicated ROSC followed by stable SC; the second group of patients were those with an unsuccessful ALS resuscitation without any sign of ROSC, who died at the scene. Collected data were also used to compare $P_{ET}CO_2$ levels during the chest compression period of ALS and during the SC period in successfully resuscitated patients.

The patients were resuscitated in the out-of-hospital setting by Emergency Medical Services (EMS) personnel, serving an area of 496 km^2 with 1.5 million inhabitants, responding to approximately 90,000 calls a year. The rescue team worked in a "two-tiered system" ("rendezvous") with two EMS teams, one consisting of a driver and a paramedic (a large ambulance) and the other of a physician and a paramedic (a small rapid response unit vehicle), who met at the scene.

Twelve physicians participated in collection of this study data according to a strict protocol. All the physicians were either emergency physicians or anesthesiologists skilled in tracheal intubation and providing ALS. They voluntarily agreed to follow the protocol, which included the use of constant ventilation of intubated patients by an automatic device, and use of the asynchronous ventilation/compression ALS mode.

The Ethical Committee of the EMS accepted the study protocol and approved the "no request of patient's informed consent" before beginning the study because enrolled patients were unconscious, the procedure was non-invasive, and it did not interfere with or alter the medical care provided.

The data were collected during the years 2004–2006. The European Resuscitation Council guidelines for resuscitation 2000 and 2005 (since January 2006) were followed during ALS, including its recommendation for checking the pulse and the pharmacotherapy (20,21).

$P_{ET}CO_2$ values were continuously observed by the EMS physician and also were recorded every second on a Personal Computer Memory Card International Association card (PCMCIA, Flash 4 MB; Pretec, Taipei, Taiwan). The course of ALS was monitored by a Zoll M Series instrument (ZOLL Medical Corporation, Chelmsford, MA). This device enables continuous recording of $P_{ET}CO_2$ (kPa or mm Hg) and of respiratory rate using a single solid infrared CapnoStat mainstream carbon dioxide (CO_2) sensor (Respironics Novametrix, Inc., Wallingford, CT). The capnography sensor was calibrated every morning.

Return of spontaneous circulation (ROSC) was defined by an EMS physician as a palpable central pulse (usually carotid artery) in the absence of chest compressions, and by an organized spontaneous ECG rhythm followed by a measurable blood pressure (20,21). The time when the palpable pulse was noted for the first time was marked on the ECG strip and was used as time zero in off-line analysis of the entire ALS course with ROSC.

All patients were intubated and a constant lung ventilation was maintained for each patient during the entire $P_{ET}CO_2$ recording period to avoid bias due to variation in the alveolar ventilation. The automatic ventilation device used was Oxylog 2000 (Dräger Medical AG & Co. KG, Lübeck, Germany). A tidal volume of 7–10 mL/kg, a respiratory rate of 8–12 breaths/min, and 100% oxygen (FiO_2) were applied. Chest compressions, at a rate of 100/min, were performed independent of the ventilation (20,21). The pulse checking was performed every 2 min, except in the case of $P_{ET}CO_2$ significantly increasing, at which time the pulse was checked immediately.

The study design involved collecting data from 70 cases in patients transferred to the hospital and 70 cases in patients who died at the scene. Records of patients who received ALS were reviewed regardless of age, cardiac arrest etiology, first ECG rhythm pattern, or bystander BLS. Also included were patients with other relevant ALS circumstances, such as ROSC followed by

a stable SC, and the recording time for $P_{ET}CO_2$ was longer than 6 min before and after ROSC (59 cases). In addition, records were reviewed for patients in whom no sign of ROSC was noted during the entire ALS and the duration of $P_{ET}CO_2$ recording was longer than 15 min (49 cases). Exclusion criteria included patients with either capno-sensor moisturizing or contamination with blood, as well as patients who received sodium bicarbonate. In addition, 32 records out of a total of 140 collected were excluded, from patients in whom ROSC was achieved but the ensuing SC was unstable and failed again, once or repeatedly. A total of 108 records were reviewed for the study.

Data Collection and Analysis

For each case, data recorded included the patient's age, sex, initial ECG rhythm, whether or not the arrest was witnessed, whether or not bystander BLS was provided, cause of the cardiac arrest, survival, and quality of life. All data were stored in the study database.

Continuously recorded $P_{ET}CO_2$ values for the group with ROSC were categorized as follows. Before ROSC: average value was the mean of values during the chest compression period; initial value was the first value obtained at the beginning of ALS; final value was the last value obtained during the chest compression period; maximum value was the highest value obtained during the chest compression period; minimum value was the lowest value obtained during the chest compression period. $P_{ET}CO_2$ value at the moment of ROSC was defined as the value at the moment when pulse was palpable for the first time. After ROSC: average value was the mean of values of the time interval from ROSC to the last value obtained before admission to hospital; initial value was the value obtained 2 min after ROSC; final value was the last value obtained before admission to the hospital; maximum value was the highest value obtained during the spontaneous circulation period; minimum value was the lowest value obtained during the spontaneous circulation period.

The $P_{ET}CO_2$ values for the group with no sign of ROSC were categorized as follows: average value was the mean of values from the entire ALS course; initial value was the first value obtained at the beginning of ALS; final value was the last value obtained at the moment when ALS effort was terminated; maximum value was the highest value obtained during ALS; minimum value was the lowest value obtained during ALS.

Because the study was primarily aimed at answering the question of whether a sudden increase of $P_{ET}CO_2$ level could be used as an early indicator of ROSC, all $P_{ET}CO_2$ records were analyzed in 2-min steps in the following manner. Most frequent values (modes) occurring during a 2-min interval were tested with regard to arbitrarily set threshold "increase" values of 2, 5, 10, 15, and 20 mm Hg and compared to the previous interval. A case where the increase equaled or exceeded a particular threshold value, and ROSC was diagnosed concurrently, was labeled "True Positive." When the increase occurred but ROSC was not diagnosed, the case was labeled "False Positive." "False Negative" was a case where an increase exceeding a threshold value did not occur but ROSC was diagnosed. "True Negative" was when such an increase did not occur and ROSC was not diagnosed in the particular 2-min time interval.

Statistical Analysis

The mean values and standard deviations from $P_{ET}CO_2$ measurements recorded in 59 patients before and after ROSC were compared by the two-tailed paired *t*-test using GraphPad Prism version 4.00 for Windows (GraphPad Software, Inc., San Diego, CA, www.graphpad.com). In the second group, only the mean values and standard deviations were calculated for each patient.

RESULTS

A summary of data on the 108 analyzed cases of ALS, subdivided into two groups, is presented (Table 1).

The mean duration of $P_{ET}CO_2$ recordings in 59 cases with ROSC was 18 min before ROSC and 33 min after ROSC. The average of the mean levels of $P_{ET}CO_2$ was 26.65 ± 12.00 mm Hg (3.55 ± 1.6 kPa) before ROSC and 36.60 ± 12.44 mm Hg (4.8 ± 1.66 kPa) after ROSC ($p < 0.0001$). Results of the paired *t*-test, comparing $P_{ET}CO_2$ after ROSC to its level before ROSC in individual cases, indicated that the increase in $P_{ET}CO_2$ around the moment of ROSC was significant ($p < 0.0001$). The mean difference of $P_{ET}CO_2$ level before and after ROSC was 9.95 mm Hg (1.32 kPa) and the 95% confidence interval of the difference was 6.46–13.50 mm Hg (0.86–1.8 kPa). The entire waveform of $P_{ET}CO_2$ recordings from 59 patients with restored spontaneous circulation demonstrates a significant increase at the moment of ROSC diagnosis, followed by an overshoot (Figure 1).

The mean duration of $P_{ET}CO_2$ recordings from 49 patients without any sign of ROSC was 29 min. The average of the mean levels of $P_{ET}CO_2$ was 16.68 ± 9.1 mm Hg (2.24 ± 1.21 kPa). The waveform of all $P_{ET}CO_2$ values from these patients was flat and positioned lower than in the preceding group of successfully resuscitated patients, even when comparing their mean values before

Table 1. The 108 Analyzed Cases Divided into Two Groups

	Data for Two Groups of Patients Included in the Study	
	1st Group	2nd Group
	Single ROSC Followed by a Stable Spontaneous Circulation	Without any Sign of ROSC
Number of patients (108 total)	59	49
Sex		
Male	41	40
Female	18	9
Age (years)		
Range	0.5–90	0.5–92
Mean	58	62
Body weight (kg/lb)		
Range	6 kg (13.2 lb)–140 kg (308 lb)	5 kg (11 lb)–120 kg (264 lb)
Mean	83 (182.6 lb)	83 (182.6 lb)
ECG rhythm		
AS	32	30
PEA	7	5
VF/VT	20	14
Witnessed		
Yes	48	37
No	11	12
Bystander CPR		
Yes	31	23
No	28	26
Bystander AED		
Yes	0	0
No	59	49
Etiology established by out-of-hospital providers		
Cardiac	39	39
Non-cardiac	17	8
Traumatic	3	2
Not established	0	0
Survival and quality of life (1–5) of surviving patients 6 weeks after resuscitation		
Normal life	6	0
Moderate handicap	4	0
Severe handicap	8	0
Vegetative state	40	0
Death	1	49

ROSC = return of spontaneous circulation; ECG = electrocardiogram; AS = asystole; PEA = pulseless electrical activity; VF/VT = ventricular fibrillation/ventricular tachycardia; CPR = cardiopulmonary resuscitation; AED = automated external defibrillator.

ROSC (Figure 2). Four patients who did not achieve ROSC presented with extremely high $P_{ET}CO_2$ values.

Table 2 presents the average, maximum, minimum, initial, and final levels of $P_{ET}CO_2$ for both groups of patients. In addition, for the group of patients with successful ALS courses, $P_{ET}CO_2$ level is compared in three different parts of the ALS course (before ROSC, at the moment of ROSC, and after ROSC). Comparison of the chest compression periods in successfully resuscitated patients (i.e., before ROSC) and those with no ROSC shows that mean levels of $P_{ET}CO_2$ (average, initial, final, maximum, and minimum) were always higher in patients who achieved ROSC (Table 2). However, in both cases there was a considerable overlap of absolute values.

Comparison of the period of spontaneous circulation after ROSC to the chest compression period preceding ROSC shows that the mean levels of $P_{ET}CO_2$ (average, initial, final, maximum, and minimum) were always higher during the spontaneous circulation period after ROSC.

Table 3 analyzes data with respect to an increase in $P_{ET}CO_2$ occurring during successive 2-min period and exceeding arbitrarily set threshold values. The percent frequencies of "True Positive" response in patients with ROSC and "False Positive" response in patients without ROSC are presented for the specific threshold values (Table 3).

DISCUSSION

This study applied $P_{ET}CO_2$ monitoring to out-of hospital resuscitation (ALS) of patients with cardiac arrest who

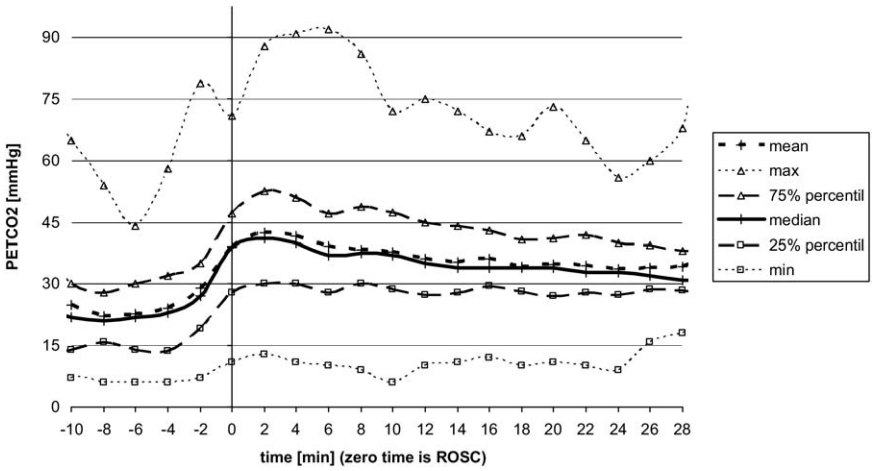

Figure 1. Diagrammatic overview of $P_{ET}CO_2$ values recorded before and after ROSC in a group of 59 patients with a single ROSC followed by a stable spontaneous circulation. The moment declared by ALS providers as ROSC was set as time zero for all analyzed patients.

were intubated and had constant lung ventilation maintained by an automatic device. The latter procedure is important because any fluctuation in the alveolar ventilation (for example, by using a self-inflating bag) may be expected to interfere with $P_{ET}CO_2$ as indicator of the cardiac output, because principle variables affecting $P_{ET}CO_2$ values are the entire body metabolism, cardiac output, and also alveolar ventilation. In comparison to previous studies aimed at evaluation of $P_{ET}CO_2$ measurements during ALS, this study concentrated on a $P_{ET}CO_2$ change at the moment of ROSC with the aim of testing whether a sudden increase in $P_{ET}CO_2$ could be used as an early indicator of ROSC (11,12).

Kalenda, in 1978, noted that ROSC was accompanied by a sudden steep increase of $P_{ET}CO_2$ (3). A positive correlation between a wide range of cardiac outputs and $P_{ET}CO_2$ values during constant ventilation has been demonstrated in both experimental and clinical studies (8–10). The ILCOR Consensus on Science and Treatment Recommendations in 2005, and others, mentioned the use of capnometry as an early indicator of ROSC (19).

Regarding capnometry use in ALS, a rule of 10 mm Hg was suggested by Wayne et al., who showed that $P_{ET}CO_2 < 10$ mm Hg is associated with a very low chance of a successful resuscitation outcome (13–18). Grmec at al. showed that the $P_{ET}CO_2$ level is about 10 mm Hg higher after ROSC than before ROSC in most cases (6,11,12). Our results thus corroborate previous reports showing that $P_{ET}CO_2$ after ROSC is associated with significantly higher values of $P_{ET}CO_2$, compared

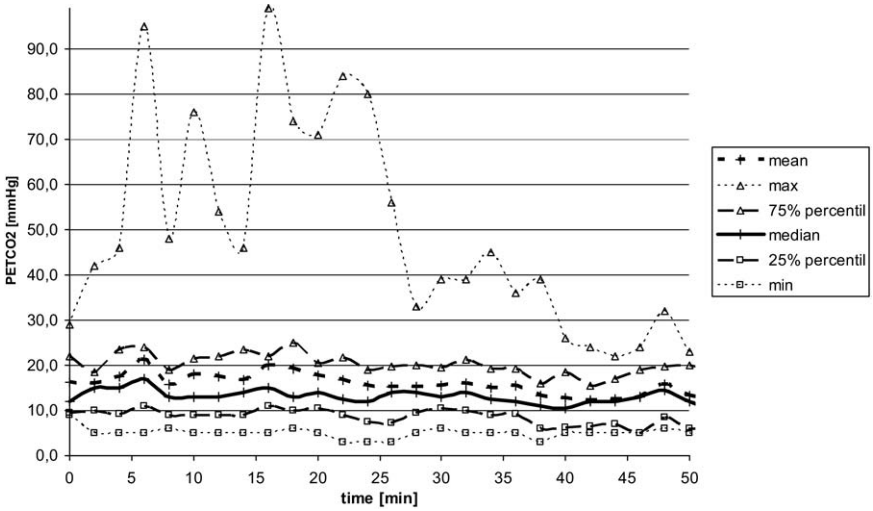

Figure 2. Diagrammatic overview of $P_{ET}CO_2$ values recorded during ALS in the group of 49 patients who failed to achieve ROSC.

Table 2. The Average, Initial, Final, Maximum, and Minimum $P_{ET}CO_2$ Values for Two Groups of Patients*

$P_{ET}CO_2$	59 Patients with ROSC Followed by Stable Spontaneous Circulation			49 Patients with No Sign or ROSC
	Before ROSC (Chest Compression Period) Average $P_{ET}CO_2$ mm Hg ± SD	ROSC (Moment of Palpable Pulse) Average $P_{ET}CO_2$ mm Hg ± SD	After ROSC (SC Period) Average $P_{ET}CO_2$ mm Hg ± SD	Entire (Chest Compression Period) Average $P_{ET}CO_2$ mm Hg ± SD
Average	26.65 ± 12.00 (range 8–65)	39.14 ± 15.37	36.6 ± 12.44 (range 12–68) $p < 0.0001$	16.68 ± 9.10 (range 6–47) $p < 0.0001$
Initial	26.78 ± 14.99 (range 5–71)		42.54 ± 18.12 (range 13–88) $p < 0.0001$	16.33 ± 10.2 (range 5–54) $p < 0.0001$
Final	28.95 ± 14.47 (range 7–79)		33.07 ± 12.55 (range 6–65) $p < 0.0001$	13.33 ± 10.53 (range 3–51) $p < 0.0001$
Maximum	35.86 ± 14.47 (range 12–79)	71	48.52 ± 18.52 (range 15–99) $p < 0.0001$	28.41 ± 18.14 (range 9–99) $p = 0.0194$
Minimum	18.69 ± 12.18 (range 0–61)	11	28.73 ± 12.19 (range 6–64) $p < 0.0001$	8.10 ± 13.74 (range 3–18) $p < 0.0001$

* The group with successful ALS courses shows $P_{ET}CO_2$ levels in three different stages of the ALS course (before ROSC period, at the moment of ROSC, and after ROSC period). ROSC = return of spontaneous circulation; $P_{ET}CO_2$ = partial pressure end-tidal carbon dioxide.

with those before ROSC (11,12). The overshoot of $P_{ET}CO_2$ after ROSC suggested by our data (summarized in Figure 1) points to an insufficiency of circulation and tissue perfusion during the chest compression period when compared to spontaneous circulation after successful ROSC.

Absolute $P_{ET}CO_2$ values should be interpreted with caution. In the present study, 6 of 59 patients from the first group, with successful and uncomplicated ROSC, started with very low (< 9.37 mm Hg, i.e., < 1.25 kPa) $P_{ET}CO_2$ values, similar to findings in some previous studies (15,16). On the other hand, 4 of 49 patients in the second group of patients presented initially with supernormal $P_{ET}CO_2$ values (> 41.25 mm Hg, i.e., > 5.5 kPa), and one patient sustained extremely high values for 16 min of ALS although no ROSC was achieved. As discussed below, this might have been due to a measurement error.

Absolute $P_{ET}CO_2$ levels depend not only on cardiac output but also on lung ventilation and other factors such as the presence and duration of asphyxia preceding ALS, or a decrease in body temperature, or eventually, peripheral vasoconstriction interfering with CO_2 release from peripheral tissues (22–25). There was a relatively large range of absolute ventilation parameters (7–10 mL/kg) in the present study, which was almost certainly caused by the fact that exact body weight was determined only later, in the intensive care unit or autopsy room.

In cases of unsuccessful ALS that did not result in any notable ROSC, the waveform of $P_{ET}CO_2$ values was flat throughout the entire ALS course (Figure 2). This confirms that steadily low $P_{ET}CO_2$ values can predict an unsuccessful ALS, as was reported previously (13–18). Four of 49 patients who did not achieve ROSC presented initially with supernormal $P_{ET}CO_2$ values. We suggest that this might be caused by a measurement error. The "main stream" sensor used in this study is more prone to contamination with foamy sputum when compared to the "side stream" sensor. Whereas its contamination with concentrated blood resulted in an error signal, its contamination with highly diluted blood made it falsely appear to be a high $P_{ET}CO_2$ value (unpublished results). This could be due to a close absorbance maximum of CO_2 (426 nm) and that of hemoglobin (430 nm).

Limitations

Limitations of the present study include the fact that only two extreme model situations were analyzed: cases where an uncomplicated ROSC was followed by stable SC, and cases with no sign of ROSC. Consequently, 32 cases were excluded on the basis of a less distinct ALS course (11 of them were admitted to the hospital). The study also did not cover cases when circulation restarted im-

Table 3. The Incidence of a Sudden Increase of $P_{ET}CO_2$, Exceeding Indicated Threshold Values for the Two Groups of Patients*

	mm Hg ≥ 2	mm Hg ≥ 5	mm Hg ≥ 10	mm Hg ≥ 15	mm Hg ≥ 20
59 patients who achieved ROSC followed by stable SC					
True positive	56	53	47	29	22
False negative	3	6	12	30	37
Sensitivity (TPR)	0.95	0.9	0.8	0.49	0.37
49 patients who did not achieve SC					
False positive	42	28	20	9	4
True negative	7	21	29	40	45
Specificity (FPR)	0.86	0.57	0.41	0.18	0.08

* The sensitivity (TPR = true positive rate) and specificity (FPR = false positive rate) are calculated with respect to the occurrence of ROSC.
ROSC = return of spontaneous circulation; $P_{ET}CO_2$ = partial pressure end-tidal carbon dioxide.

mediately after defibrillation because these patients were not intubated and, consequently, $P_{ET}CO_2$ values were not available. This causes a significant bias in the survival and outcome results presented in Table 1, as these were cases with mostly a good outcome.

CONCLUSIONS

The study demonstrates that constantly ventilated patients undergoing ALS in out-of-hospital conditions have a significantly higher $P_{ET}CO_2$ of about 10 mm Hg (1.33 kPa) after ROSC than before ROSC. It also shows that an increase in $P_{ET}CO_2 > 10$ mm Hg (1.33 kPa), coming relatively suddenly, is likely to indicate ROSC. Consequently, the rule of 10 mm Hg may be extended to include the utilization of a sudden increase of more than 10 mm Hg in continuously recorded $P_{ET}CO_2$ as an indicator of likelihood of ROSC. In addition, this may indicate a suitable moment for checking the pulse, which otherwise is measured in 2-min intervals according to present recommendations.

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ARTICLE SUMMARY

1. Why the topic is important?

From numerous factors determining success of advanced life support (ALS), only ALS efficiency is under the control of its providers. Any information regarding efficacy of ALS during its delivery is desirable. Although partial pressure end-tidal carbon dioxide ($P_{ET}CO_2$) monitoring during ALS can provide information about tissue metabolism, tissue and lung perfusion, and alveolar ventilation, it is not widely used by ALS providers.

2. What does this study attempt to show?

Whether the monitoring of $P_{ET}CO_2$ in intubated patients with constant ventilation could be utilized to detect return of spontaneous circulation (ROSC), and thus provide a suitable moment for pulse and electrocardiogram checking during ALS.

3. What are the key findings?

Trends and changes in $P_{ET}CO_2$ levels during ALS are more informative than $P_{ET}CO_2$ absolute values. A sufficiently high (10 mm Hg) and sudden increase in $P_{ET}CO_2$ may indicate ROSC.

4. How is patient care impacted?

The thorough understanding and correct interpretation of capnographic readings during ALS may contribute to better patient outcomes, and may help to avoid futile ALS interventions.