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Clinical paper

The association between end-tidal CO2 and return of spontaneous circulation after out-of-hospital cardiac arrest with pulseless electrical activity

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Abstract

Introduction: End-tidal carbon dioxide (ETCO2) has been suggested to have prognostic implications during out-of-hospital cardiac arrest (OHCA). Our objective was to determine if the change in ETCO2 (delta ETCO2) during resuscitation was predictive of future return of spontaneous circulation (ROSC) in patients with pulseless electrical activity (PEA) arrests.

Methods: We performed a retrospective, observational study of adult (≥18 years of age) non–traumatic PEA OHCAs in two Canadian EMS systems over a two-year time frame beginning on January 1, 2018. Cases were excluded if there was a Do Not Resuscitate order (DNR), had no advanced airway, or had less than two ETCO2 recordings. We performed multivariable logistic regression to examine the association between ETCO2 measures and ROSC. Second, we examined the prognostic performance (sensitivity, specificity, NPV, PPV) for ETCO2 at specific thresholds for predicting ROSC.

Results: A total of 208 OHCA met inclusion criteria of which 67 (32%) obtained ROSC. After adjusting for pre-determined confounders, there was an association between delta ETCO2 and ROSC (odds ratio [OR] per 10 mmHg increase in ETCO2 of 1.74 (95% confidence interval [CI] 1.35 to 2.24); P value < 0.001). We also found significant associations between both initial ETCO2 and final ETCO2 with ROSC.

Conclusion: Our analysis indicates that there is a positive linear relationship between delta ETCO2 and ROSC with values of delta ETCO2 > 20 mmHg being highly specific for ROSC in PEA patients. As such, patients with up-trending ETCO2 values should have resuscitation continued unless there is overwhelming clinical evidence to the contrary.

Keywords: ETCO2, Pulseless electrical activity, Cardiac arrest, Resuscitation, Emergency medical services, Return of spontaneous circulation

Introduction

Prognostication of cardiac arrest outcome is important in the prehospital setting to inform the decision to cease resuscitation or transport to hospital. Currently the only intra-arrest monitoring tools widely available to paramedics with prognostic value are the underlying cardiac rhythm identified on electrocardiogram (ECG) and end-tidal CO2 (ETCO2) measurement.[1,2] Shockable rhythms, ventricular fibrillation and pulseless ventricular tachycardia are associated with better outcomes than non-shockable rhythms (pulseless electrical activity (PEA) and asystole). While asystole is universally associated with a poor prognosis, PEA encompasses two physiologically different processes that have different rates of survival.[3,4]

True PEA occurs when organized electrical impulses exist but do not translate into organized cardiac contractility. This is associated

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with survival rates similar to asystole.[4] Pseudo-PEA occurs when electrical impulses result in cardiac myocyte contraction but the forward flow of blood is not significant enough to generate a palpable pulse. This entity has higher rates of return of spontaneous circulation (ROSC) and survival than true PEA and can be thought of as a profound shock state.[3–5] It is critical for paramedics to be able to differentiate between these different subtypes of PEA and identify patients that have a better chance of survival to avoid prematurely terminating resuscitation. Previously, ECG changes were thought to hold potential for prognostication in PEA patients; however, a recent prospective study found no specific association between ECG findings and survival.[6] ETCO2 may be the best tool available for this purpose in out-of-hospital cardiac arrest (OHCA).

Previous studies have examined ETCO2 readings at various times during cardiac arrest as a possible predictor of ROSC, survival to admission, and survival to hospital discharge.[1,7–11] The most comprehensive analysis of the data was compiled by Paiva et al. in their 2018 meta-analysis. They concluded that ETCO2 > 20 mmHg at time of intubation or after 20 minutes of ACLS care were the best predictors of ROSC. They also suggested that trending values may be more valuable than specific timed values in isolation but did not specifically evaluate this.[1] Three studies included in the Paiva meta-analysis looked specifically at ETCO2 in patients with PEA (see references 8,12,13), the largest of which was by Levine et al. This prospective cohort study included 150 patients in PEA and found that ETCO2 $\leq$ 10 mmHg at 20 min after advanced cardiac life support (ACLS) initiation predicted non-survival with 100% sensitivity and specificity. In this study 23.3% of patients achieved ROSC and 10.7% survived to hospital discharge.[8] Studies by Lui et al. and Pokorna et al. have investigated the magnitude of change in ETCO2 (delta ETCO2) that suggests a ROSC has already occurred and found that a rapid increase > 10 mmHg is specific for ROSC. No studies have investigated the delta ETCO2 prior to ROSC to determine what magnitude of change is predictive of a future ROSC event.[14,15]

With this in mind, the primary objective of our study was to examine the association between the change in ETCO2 during resuscitation and ROSC. Our secondary objectives were to compare the predictive value of delta ETCO2 for ROSC with that of initial ETCO2, and final ETCO2. We hypothesized that positive delta ETCO2 values would be associated with ROSC and that delta ETCO2 would be a better predictor of ROSC than single timepoint measurements.

Methods

Setting and design

We performed a retrospective cohort study of prospectively collected data between January 1, 2018, and December 31, 2019, from Peel Regional Paramedic Services and Halton Region Paramedic Services in Ontario, Canada. These paramedic services provide prehospital emergency transport to a population of 1.9 million people in urban and rural settings within a geographical area of 2200 km^2. They are the sole providers of paramedic services within their regions. Paramedics in these regions attend over 2000 OHCAs per year. For all patients, standard ACLS care (defibrillation, antiarrhythmic medication, epinephrine and appropriate airway management) was provided as necessary, in accordance with American Heart Association guidelines and local medical directives. We included adult ($\geq$18 years old) OHCA patients treated by paramedics who presented as PEA arrests. Exclusions included Do Not Resuscitate (DNR) orders, cardiac arrests of traumatic etiology, lack of an advanced airway (supraglottic airway or endotracheal tube), and patients without at least two recorded ETCO2 values between intubation and ROSC. The breakdown of cardiac arrest cases and exclusions is shown in Fig. 1. The study protocol was approved by the Sunnybrook Health Science Centre Research Ethics Board.

Outcomes and study definitions

Our primary outcome was ROSC in the prehospital setting, defined as any organized rhythm on the defibrillator file with a corresponding "pulse present" or blood pressure recorded on the paramedic electronic patient care record.

Delta ETCO2 was defined as the difference between the initial ETCO2 recording 1 min after placement of an advanced airway and the final recording 1 min prior to ROSC or at time of termination of resuscitation. ETCO2 values were obtained through mainstream technology in patients with an advanced airway (endotracheal intubation or King LT® supraglottic airway device) and automatically recorded by defibrillator software (Zoll X series defibrillator, Chelmsford, Massachusetts).

Statistical analyses

We analyzed each of our included pre-specified variables categorized by our outcomes of interest. Descriptive statistics were summarized using medians with interquartile range (IQR) or counts and percentages. Bivariate comparisons were made between groups for all variables of interest using Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables as appropriate. All statistical analyses were two-sided, with a P value < 0.05 considered statistically significant.

Our primary analysis examined the association between delta ETCO2 and prehospital ROSC. We examined this association using multivariable logistic regression while adjusting for predetermined baseline confounders. These confounders included standard Utstein data elements (age, gender, witness status, bystander CPR, EMS response time) as well as the type of advanced airway used (endotracheal intubation vs. supraglottic airway) during the cardiac arrest. Delta ETCO2 was maintained as a continuous variable, and nonlinearity was assessed with the inclusion of restricted cubic splines (3 knots). Results for ETCO2 values were presented per 10 mmHg changes.

Our secondary analyses used a similar method as described above to examine initial, and final ETCO2 values.

We examined the predictive value of ETCO2 values for ROSC by calculating the sensitivity and specificity at multiple different thresholds along with corresponding 95% confidence intervals. Overall discrimination of ETCO2 for ROSC was presented as area under the receiver operator characteristic curve (AUC/ROC).

All statistical analyses were performed using R: A Language and Environment for Statistical Computing (Vienna Austria).

Results

A total of 208 patients were included in our analysis, 67 (32%) of which obtained a prehospital ROSC (Fig. 1). The median age of included patients was 74 years (IQR 64,82 years) and 128 (60.6%) were male. Cardiopulmonary resuscitation was performed to AHA guideline recommendations: chest compression rate 111/min (IQR

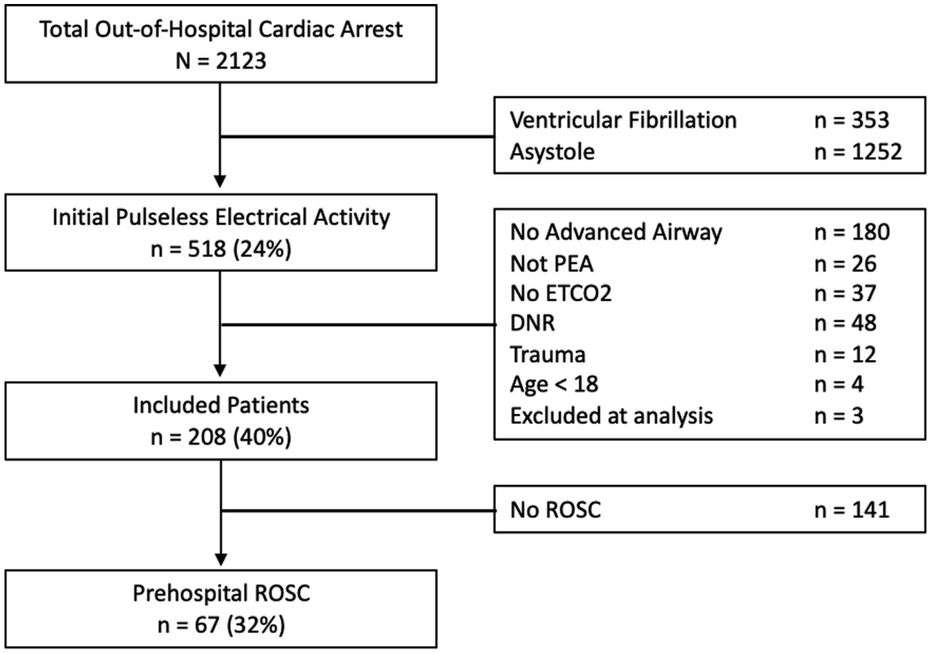

Fig. 1 – Flow Diagram.

107,115) and depth 5.6 cm (IQR 4.9,6.1). The median time to first ETCO2 reading was 24.0 minutes (IQR 20.0,30.0 minutes) after the start of resuscitation. Descriptive characteristics for included patients are reported in Table 1.

The initial ETCO2 values (mean +/- SD) were 40.5 +/- 18.5 mmHg for patients who obtained ROSC and 34.5 +/- 17.1 mmHg for patients who did not obtain ROSC. Other differences were noted in minimum ETCO2 value (mean +/- SD) during the resuscitation 32.0 +/- 17.4 mmHg vs 19.2 +/- 12.7 mmHg, maximum ETCO2 value 58.8 +/- 21.2 mmHg vs. 46.0 +/–23.1 mmHg and final ETCO2 value 51.4 +/- 21.5 mmHg vs. 30.0 +/- 19.3 mmHg. Delta ETCO2 values ranged from a low of −44 mmHg to a high of 66 mmHg (Table 1 and Fig. 2).

After adjusting for our predetermined variables of interest, we found that there was a positive association between delta ETCO2 and subsequent prehospital ROSC with an odds ratio (OR) of 1.74

Table 1 – Cardiac arrest characteristics grouped by return of spontaneous circulation.

Variable	ROSC (n = 67)	No ROSC (n = 141)	P Value
Age (years), mean (SD)	75.7 (14.3)	69.3 (15.9)	<0.05
Male Sex, n (%)	44 (65.7)	82 (58.2)	
Public Location, n (%)	3 (4.5)	25 (17.7)	<0.05
Bystander Witnessed, n (%)	44 (65.7)	72 (51.1)	
EMS Witnessed, n (%)	11 (16.4)	20 (14.2)	
Bystander CPR, n (%)	27 (48.2)	52 (43.0)	
EMS Response Interval (min), median (IQR)	9.0 (7.0,11.0)	10.0 (7.0,13.0)	
CPR depth (cm), median (IQR)	5.6 (4.8,6.1)	5.6 (5.1,6.1)	
CPR rate (/min), median (IQR)	110 (106,114)	111 (107,115)	
Compression Fraction, median (IQR)	0.87 (0.83,0.89)	0.89 (0.85,0.91)	
Time to Advanced Airway (min), mean (SD)	21.9 (7.4)	25.2 (10.9)	<0.05
Endotracheal Intubation, n (%)	50 (74.6)	103 (73.0)	
Normal Saline (ml), mean (SD)	777.4 (538)	743.6 (452)	
Epinephrine (mg), mean (SD)	3.7 (1.9)	5.0 (2.2)	<0.05
Sodium Bicarbonate, n (%)	13 (19.4)	28 (19.9)	
Calcium Gluconate, n (%)	6 (8.9)	22 (15.6)	
Time to Initial ETCO2 (min), mean (SD)	23.4 (7.3)	27.2 (10.8)	<0.05
Initial ETCO2 (mmHg), mean (SD)	40.5 (18.5)	34.5 (17.1)	<0.05
Min ETCO2 (mmHg), mean (SD)	32.0 (17.4)	19.2 (12.7)	<0.05
Max ETCO2 (mmHg), mean (SD)	58.8 (21.2)	46.0 (23.1)	<0.05
20 minute ETCO2 (mmHg), mean (SD)	44.6 (28.1)	31.5 (19.1)	
Final ETCO2 (mmHg), mean (SD)	51.4 (21.5)	30.0 (19.3)	<0.05

ROSC = Return of spontaneous circulation; SD = standard deviation; CPR = cardiopulmonary resuscitation; ETCO2 = end-tidal carbon dioxide; Min = minutes; IQR = interquartile range.

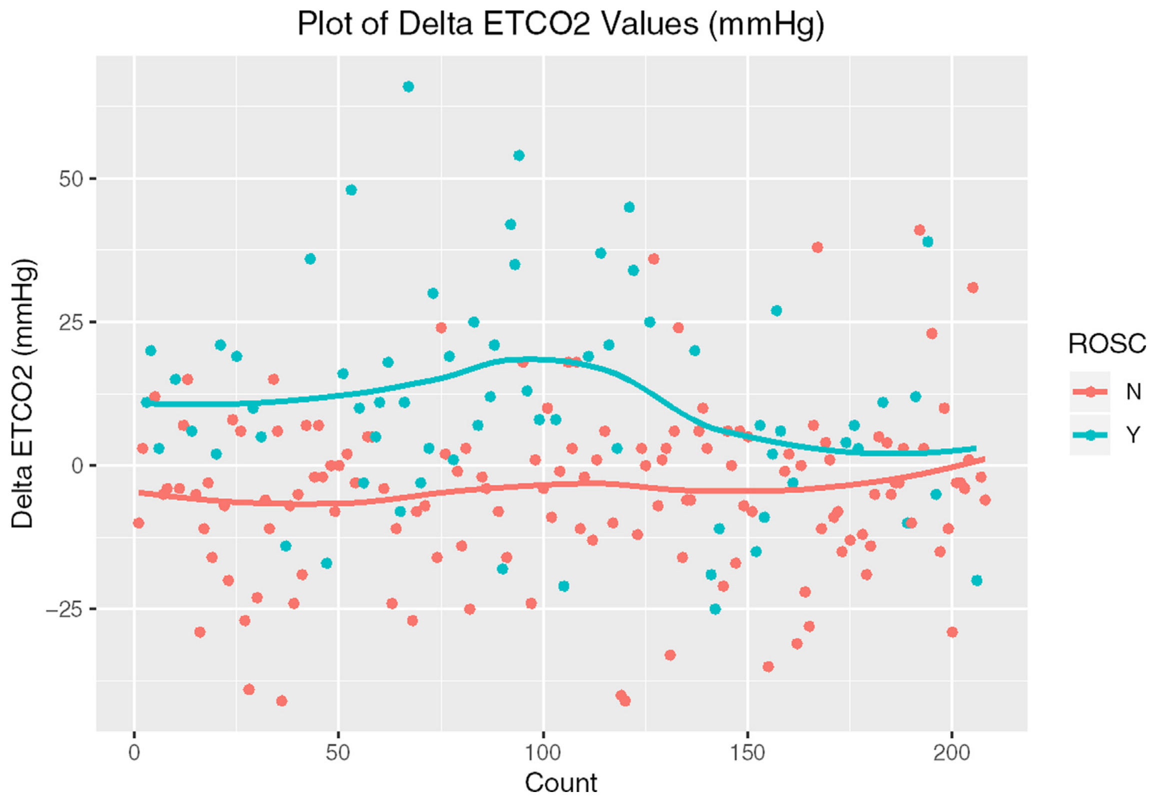

Fig. 2 – Graph of delta ETCO2 data.

(95% confidence interval [CI] 1.35 to 2.24; P value < 0.001) for every 10 mmHg increase in delta ETCO2. We did not find evidence of non-linearity in this relationship (Fig. 3) and so maintained this as a linear relationship in our model (Table 2).

In our secondary analyses we also found significant increases in odds of prehospital ROSC with increases in initial ETCO2 per 10 mmHg (OR 1.28, 95% CI 1.04 to 1.58; P = 0.02) and final ETCO2 per 10 mmHg increase (OR 1.64, 95% CI 1.35 to 2.00; P < 0.001).

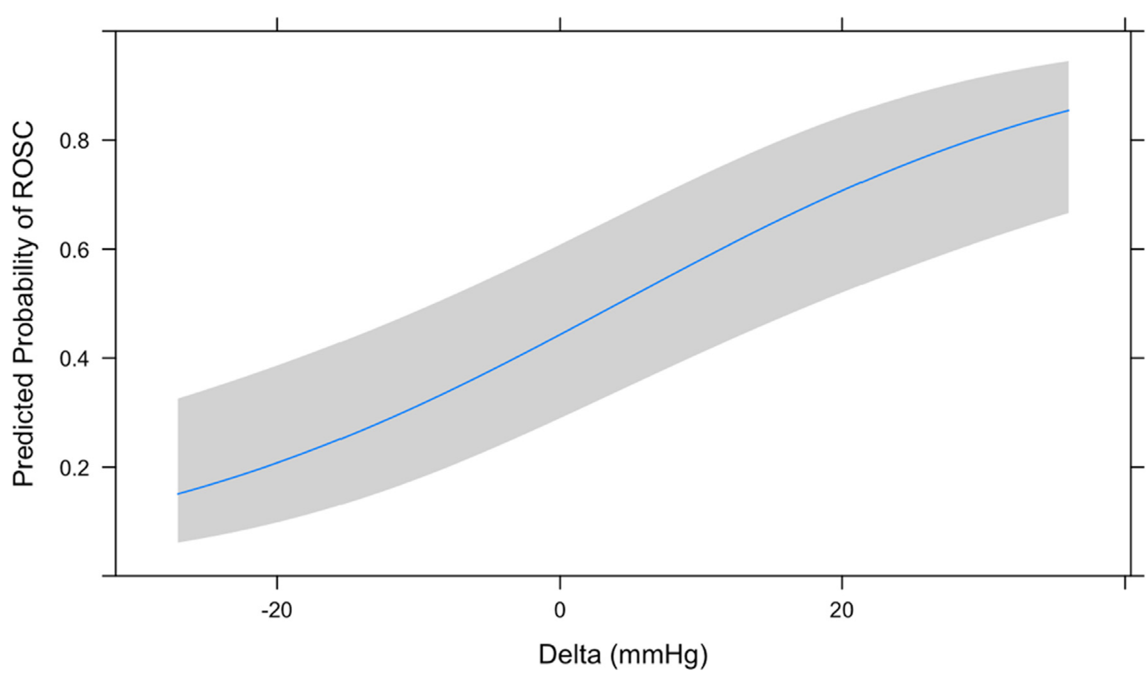

Fig. 3 – Relationship between delta ETCO2 and ROSC.

Table 2 – Multivariable logistic regression analysis for return of spontaneous circulation.

Variable	Odds Ratio	95% CI	P Value
Age (/year)	1.03	1.01, 1.06	0.015
Bystander CPR	1.12	0.54, 2.34	0.756
Male Sex	1.45	0.68, 3.08	0.34
EMS Response Time	0.95	0.84, 1.07	0.419
Witnessed	2.33	1.03, 5.28	0.043
Endotracheal Intubation	2.85	1.15, 7.06	0.024
Delta ETCO2 (/10 mmHg)	1.74	1.35, 2.24	<0.001

No evidence of interaction (airway*delta) or non-linearity with delta – P value for lrtest 0.131. CI = Confidence Interval; CPR = Cardiopulmonary Resuscitation; EMS = emergency medical services; ETCO2 = End-tidal Carbon Dioxide.

Again, no evidence of non-linear relationships between ETCO2 and prehospital ROSC. We were unable to analyze the association between ETCO2 at 20 minutes after advanced airway and outcomes because the majority of cases had ROSC or resuscitation terminated by that time.

The sensitivity, specificity, as well as positive and negative predictive values for the delta ETCO2 at different thresholds are presented in Table 3. A delta ETCO2 of >20 mmHg had a specificity of 95% for a future ROSC event (95% CI 0.90 to 0.98). The area under the receiver operator characteristic curve (ROC/AUC) for delta ETCO2 was 0.75 (95% CI 0.68 to 0.83) suggesting that delta ETCO2 had good discrimination for differentiating patients who will obtain ROSC from those who will not obtain ROSC.

Discussion

In this retrospective study assessing the relationship between ETCO2 and ROSC, we found a linear relationship between the odds of future ROSC and increasing delta ETCO2 in OHCA patients presenting with initial PEA.

When compared to other single time-point measures of ETCO2, delta ETCO2 was a stronger predictor of ROSC. A positive change in ETCO2 of 10 mmHg over the duration of resuscitation had a higher odds of ROSC than identical increases in initial or final ETCO2. An initial ETCO2 $\geq$10 mmHg was most sensitive for ROSC in our study. This value has been used in multiple prior studies but would be unhelpful in most cases as when high quality CPR is delivered, ETCO2 values are rarely less than 10 mmHg (15% of cases in our study).

The use of a single ETCO2 value 20 minutes after placement of an advanced airway is also rarely useful as arrests are not typically run that long. While we had set out to determine the association between 20 min ETCO2 and ROSC, only 22% of cardiac arrests had ongoing resuscitation 20 minutes after advanced airway placement. Most patients had either achieved ROSC or had resuscitation terminated by this time.

The ROSC rate for cases included in our analysis was 32%. This is significantly higher than the rates seen in two of the key early studies of ETCO2 in PEA by Wayne et al. who found a rate of 17.8% and Levine et al. who found a rate of 23.3%.[8,12] Another recent study by Jarmillo et al. in 2020 that examined emergency department patients with PEA arrest found ROSC in 22/55 cases (40%) which is similar to our findings.[4] We attribute our high rates of ROSC in PEA to the high-quality CPR provided by our prehospital providers and the improvements in care since the early studies on ETCO2.

Our results favor the use of guiding principles rather than hard cut-offs when it comes to interpreting ETCO2. While we have set arbitrary categorical values of delta ETCO2 to help illustrate our findings, the key message is that the larger the magnitude of increase in ETCO2, the higher the odds that a patient will achieve ROSC. Resuscitations with up-trending ETCO2 values should be continued barring overwhelming clinical evidence to the contrary. For paramedics, this may require transporting to hospital to facilitate ultrasound evaluation for cardiac activity and physician assessment.

The use of ETCO2 trends is most useful to those in prehospital settings without access to more advanced methods to detect perfusion like ultrasound or arterial blood pressure monitoring. Further studies directly correlating ETCO2 and arterial line blood pressure measurements or cardiac activity on ultrasound would help refine its use particularly to aid in distinguishing true PEA and pseudo-PEA.

Table 3 – Prognostic performance of thresholds of ETCO2 values for return of spontaneous circulation.

		Prognostic Measure (95% Confidence Interval)			
ETCO2 Value	n (n = 208)	Sensitivity	Specificity	PPV	NPV
Initial > 10 mmHg	176	0.98 (0.92, 1.00)	0.06 (0.02, 0.11)	0.33 (0.27, 0.40)	0.89 (0.52, 1.00)
Initial > 20 mmHg	167	0.84 (0.73, 0.92)	0.21 (0.15, 0.29)	0.34 (0.26, 0.41)	0.73 (0.57, 0.86)
Final > 10 mmHg	183	0.99 (0.92, 1.00)	0.16 (0.11, 0.24)	0.36 (0.29, 0.43)	0.96 (0.79, 1.00)
Final > 20 mmHg	153	0.94 (0.85, 0.98)	0.36 (0.28, 0.44)	0.41 (0.33, 0.49)	0.93 (0.82, 0.98)
Delta > 0 mmHg	101	0.76 (0.64, 0.86)	0.61 (0.52, 0.69)	0.48 (0.38, 0.58)	0.84 (0.76, 0.91)
Delta > 5 mmHg	69	0.61 (0.49, 0.73)	0.80 (0.72, 0.86)	0.59 (0.47, 0.71)	0.81 (0.74, 0.87)
Delta > 10 mmHg	45	0.48 (0.35, 0.60)	0.91 (0.85, 0.95)	0.71 (0.56, 0.84)	0.78 (0.71, 0.84)
Delta > 15 mmHg	34	0.36 (0.24, 0.48)	0.93 (0.87, 0.97)	0.71 (0.53, 0.85)	0.75 (0.68, 0.81)
Delta > 20 mmHg	24	0.25 (0.16, 0.37)	0.95 (0.90, 0.98)	0.71 (0.49, 0.87)	0.73 (0.66, 0.79)
Delta > 25 mmHg	16	0.18 (0.10, 0.29)	0.97 (0.93, 0.99)	0.75 (0.48, 0.93)	0.71 (0.64, 0.78)
Delta > 30 mmHg	14	0.15 (0.07, 0.26)	0.97 (0.93, 0.99)	0.71 (0.42, 0.92)	0.70 (0.63, 0.77)
Delta > 35 mmHg	11	0.12 (0.05, 0.22)	0.98 (0.94, 1.00)	0.73 (0.39, 0.94)	0.70 (0.63, 0.76)
Delta > 40 mmHg	6	0.07 (0.02, 0.17)	0.99 (0.96, 1.00)	0.83 (0.36, 1.00)	0.69 (0.62, 0.75)
Delta > 45 mmHg	3	0.04 (0.01, 0.13)	1.00 (0.97, 1.00)	1.00 (0.29, 1.00)	0.69 (0.62, 0.75)
Delta > 50 mmHg	2	0.03 (0.00, 0.10)	1.00 (0.97, 1.00)	1.00 (0.16, 1.00)	0.68 (0.61, 0.75)

ETCO2 = end-tidal carbon dioxide; PPV = positive predictive value; NPV = negative predictive value.

The primary limitations of our study are its retrospective design and lack of survival data. As our findings are observational, no causal effect should be implied, although our analysis did control for the most appropriate OHCA variables. We did not attempt to capture ETCO2 values prior to advanced airway placement as we hypothesized that BVM ventilation and the changes in mask seal intrinsic to the procedure would result in unreliable data. With a heightened focus on compressions prior to airway management in OHCA, a large proportion of patients were excluded because they did not have an advanced airway placed prior to ROSC. Further, because at least two measurements of ETCO2 are required to define a delta, patients that achieved ROSC rapidly after advanced airway placement and had only a single measurement were excluded. However, prediction of ROSC becomes more important in longer duration cardiac arrests when decisions about termination must be made, and this is the population that we have best captured with our study.

Conclusion

In this observational study we found a positive linear relationship between delta ETCO2 and ROSC with values of delta ETCO2 > 20 mmHg being highly specific for ROSC in PEA patients. As such, patients with up-trending ETCO2 values should have resuscitation continued unless there is overwhelming clinical evidence to the contrary.

CRediT authorship contribution statement

Crickmer: Conceptualization, Data curation, Investigaton, Methodology, Writing both draft and review editing. Drennan: Conceptualization, Formal analysis, Investigation, Methodology, Writing original draft and review editing. Turner: Data curation, Project administration, Resources, Software, Writing - review and editing Cheskes: Conceptulaiztion, Investigation, Methodology, Resources, Supervision, Writiing - draft and review and editing.

Declaration of Competing Interest

Dr. Cheskes has received a speaking honorarium for educational events on CPR quality from Zoll Medical and Stryker Corporation. Dr. Cheskes has received grant funding from the Laerdal Foundation for the DOSE VF pilot RCT. Dr. Cheskes has received grant funding from HSF Canada for the DOSE VF RCT. Dr. Cheskes has received grant funding from Zoll Medical for AED on the Fly, Community Responder Program for Peel Region and Monitoring Ventilation during OHCA research studies. Dr. Cheskes sits on the Advisory Board of Drone Delivery Canada. No other authors have any conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.08.014.

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