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Clinical paper

End tidal CO_2 and cerebral oximetry for the prediction of return of spontaneous circulation during cardiopulmonary resuscitation

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Abstract

Background: End Tidal CO_2 ($ETCO_2$) is a reasonable predictor of Return of Spontaneous Circulation (ROSC) in cardiac arrest (CA), though with many limitations. Cerebral Oximetry (CerOx) non-invasively measures brain O_2 saturation and correlates with flow.

Objectives: This study compares $ETCO_2$ and CerOx for ROSC prediction during both out of hospital (OHCA) and emergency department cardiac arrests (EDCA).

Methods: We conducted a prospective study on CA patients resuscitated in the ED. $ETCO_2$ and CerOx simultaneously measured during ED CPR. Data was analyzed with logistic regression modeling and area under the curve (AUC).

Results: 176 patients were analyzed, 66.7% were witnessed, 52.8% had bystander CPR. EMS alert to ED arrival was 27.0 ± 10.6 min. Initial rhythm was 31.8% asystole, 27.8% PEA, 25.6% VF/VT with 26.1% achieving ROSC. AUC predictors of ROSC were: last 5 min trend [CerOx = 0.82 ; $ETCO_2$ = 0.74], delta first to last [CerOx = 0.86 ; $ETCO_2$ = 0.73], the penultimate minute [CerOx = 0.81 ; $ETCO_2$ = 0.76], and final minute [CerOx = 0.89 ; $ETCO_2$ = 0.77]. AUC comparison of simultaneous measurements (n = 125) revealed: last 5 min trend [CerOx = 0.80 ; $ETCO_2$ = 0.79], delta first to last [CerOx = 0.83 ; $ETCO_2$ = 0.75], penultimate minute [CerOx = 0.83 $ETCO_2$ = 0.74], and final minute [CerOx = 0.89 ; $ETCO_2$ = 0.75].

Conclusions: Our data shows, both ETCO2 and rSO2 are good predictors of ROSC. We found CerOx superior to $ETCO_2$ in predicting ROSC.

Keywords: Cardiac arrest, End tidal carbon dioxide, Near infrared spectroscopy, Prediction of return of spontaneous circulation

Introduction

Despite the many advances in improved emergency medical services and increased public awareness; the rate of hospital discharge after an out-of-hospital cardiac arrest (OHCA) is reported below 8%.[1] The Cardiac Arrest Registry to Enhance Survival (CARES) reports a 9.6% survival to discharge rate from out-of-hospital cardiac arrests and GWTG shows an 18% survival from in-hospital cardiac arrests (IHCA).[2] With such low survival rates, it is not surprising that many question the amount of resources utilized to treat CA patients. Though, recent research

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shows during IHCA those hospitals systems that resuscitate patients longer have higher rates of Return of Spontaneous Circulation (ROSC).[3] The decision to end resuscitation is complicated by the lack of good objective measures of futility. Currently, the American Heart Association Guidelines do not give definitive recommendations regarding termination of resuscitation, rather the decision rests with the treating physician and is based on a number of global prognostic factors.[4] Physicians during resuscitation are attempting to balance the probability of a good neurologic outcome with the utilization of current and future resources when making the decision regarding termination of resuscitation. The cost of unsuccessful resuscitation efforts has been conservatively extrapolated to be well over a billion dollars annually.[5] A proposed definition of medical futility includes the inability of a treatment to provide meaningful resuscitation in the last one hundred cases.[6] Simple pre-hospital termination of resuscitation (TOR) tools have been validated with positive predictive value of 99.5%, however the overall ROSC rate in this study was low at 5.5%.[7] This rate is much lower that the currently reported rates in the 2017 CARES registry of 31.8% ROSC. To date, the most effective way to improve ROSC rates is to deliver adequate chest compressions and early defibrillation. Studies show that CPR producing a minimum coronary perfusion pressure (CPP) of 15 mmHg is required to obtain ROSC.[9] Unfortunately, compressions during CPR are often inadequate with studies showing deficiencies of 28% in rate, 37% in depth and 24% off chest times.[10] The American Heart Association emphasizes, continuous quality compressions during CPR and the utilization of physiologic parameters to guide resuscitation.

Currently, the AHA, ERC, ILCOR have designated $ETCO_2$ to confirm the placement of the endotracheal tube and is recommended for both monitoring CPR quality and as an early indicator of ROSC.[12] $ETCO_2$ has been shown to correlate well with cardiac output and CPP.[13] Unfortunately, $ETCO_2$ is dependent on multiple variables. For example, it is directly dependent on minute ventilation, which is notoriously inconsistent in cardiac arrest resuscitations.[18] There is a discordant reduction in $ETCO_2$ values as compared to CPP after vasopressor administration in cardiac arrest, and similar discordant elevations of $ETCO_2$ values are noted after the administration of bicarbonate.[19,20] Another issue with the use of $ETCO_2$ monitoring during cardiac arrest is the mechanical obstruction of the detector inlet by aspirated gastric contents, and pulmonary secretions.

Cerebral Oximetry (CerOx) is a FDA approved, non-invasive device that estimates the regional oxygen saturation (rSO_2) in the frontal lobes of the brain by utilizing near-infrared spectroscopy. CerOx provides data relevant to cerebral oxygen supply and demand through measurement of the primarily venous weighted signal.[14] The cerebral oximetry values range from 15 to 95%, with normal values considered to be between 55–80% with an average value of 67%.[15] CerOx has been shown to have a strong correlation with jugular venous bulb saturations[15] and intra-operative oximetry desaturations predict post-operative cognitive deficits and longer hospital stays.[16,17] CerOx measurements are not dependent on pulsatile flow and an advanced airway is not required. Specifically, during the management of cardiac arrest, CerOx has been found to be feasible in the pre-hospital and hospital settings, and has the real potential to predict ROSC, direct resuscitation in the pre and post ROSC phase and also potentially predict neurological recovery.[21]

Study objective

We attempted to simultaneously collect CerOx and $ETCO_2$ to assess the ability of these modalities to predict ROSC or futility. The overall purpose of this study is to provide rescuers with an objective and reliable means to gauge the quality of their resuscitative efforts. Our attempt is to further validate ETCO2 and to compare to another modality CerOx for prediction of ROSC. The hope is to further establish values which enable rescuers to alter their resuscitation efforts as well as introduce objective measures to assist in the decision to terminate resuscitation efforts.

Methods

Study design and setting

This was an IRB approved prospective observational study of adult ($>$18 years of age), with non-traumatic, OHCA and Emergency Department Cardiac Arrests (EDCA) patients. Data was collected using Utstein criteria on a convenience sample of patients from 16 May 2010 through 15 March 2014. Only those patients whom the physician actively attempted resuscitative efforts were enrolled.

As soon as practical, research staff attached $ETCO_2$ via to an endotracheal tube utilizing the Nelcor N-85® or Philips HeartStart MRx Monitor® and placement of CerOx INVOS® sensors onto the subject's forehead. The members of the resuscitation team could utilize the $ETCO_2$ readings during their resuscitative efforts, but all were blinded to the CerOx values. Both modalities were simultaneously monitored until ROSC or death as determined by the treating physician. ROSC was defined as palpable pulse and a measurable blood pressure persisting for at least ten minutes as charted in the medical record. We defined cardiac arrest as the absence of a pulse with any cardiac rhythm and lack of response to stimuli. The pre-hospital information was gathered from EMS charts and direct provider interviews, while the demographics and hospital course were obtained from the electronic medical record. Patients were excluded if they had incomplete data sets, data was collected during a second arrest and patients who were hypothermic on arrival (Fig. 1). Detroit EMS utilizes standardized statewide BLS and ALS protocols during resuscitation. We performed two analyses, one directly comparing those subjects whom we were able to simultaneous collect $ETCO_2$ and CerOx measurements and one evaluating each modality CerOx and $ETCO_2$ separately, included within this data set are subjects with simultaneous and non-simultaneous data.

Logistic regression analysis was conducted on six parameters derived from the data recorded by each device; the trend over the last five minutes of the code, the delta from first data point to the end of the resuscitation, the maximum value recorded, the first value recorded, the average value over the final minute, and the average value over the minute prior to the final minute of the resuscitation also known as the penultimate minute. The justification for the penultimate minute is because often the recognition of ROSC is delayed. The six parameters were determined based on previous studies and in an attempt to follow recommended guidelines for $ETCO_2$ use.

This study was approved by the Wayne State University's Institutional Review Board. All patients were provided the usual

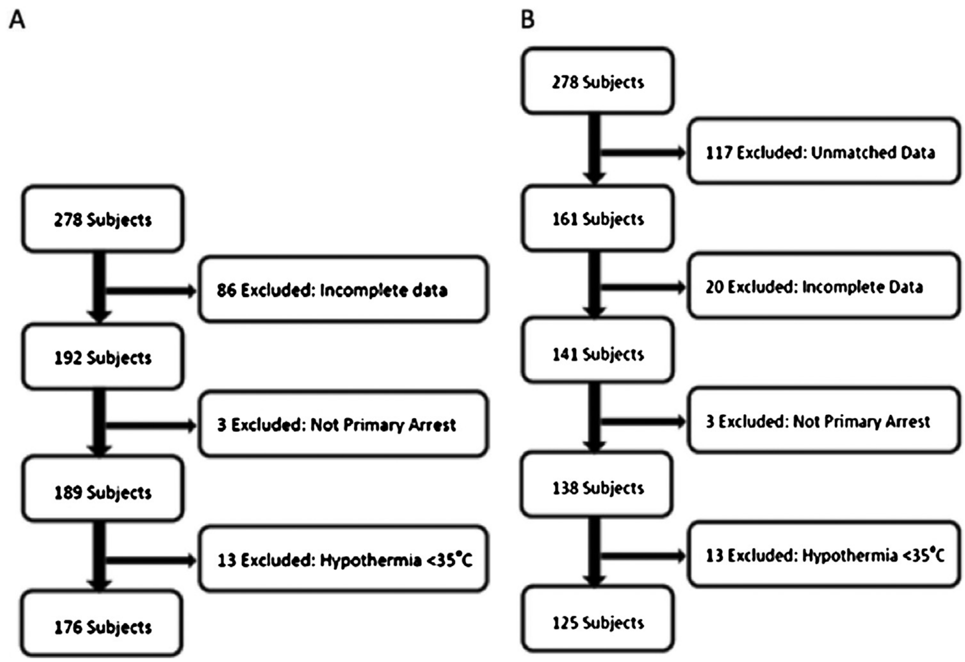

Fig. 1 – Flowchart of subject exclusion for (A) independent comparison of ROSC and (B) direct comparison of ROSC.

standard of care, and data was not gathered on patients with a "do not resuscitate" status, when resuscitative efforts were not attempted or when the survivors LAR denied consent.

Statistical analysis

The primary statistical methods involved binary logistic regression and receiver operating characteristic (ROC) curve analysis for whether CerOx and ETCO $_2$predicited ROSC status (present or absent). The ROC curve analysis provides a quantitative index of model discrimination, i.e., how well does each CerOx or $ETCO_2$ variable discriminate or differentiate the groups: ROSC present/absent. This ROC curve index is known as the area under the curve (AUC) or c-statistic. Guidelines for interpreting the magnitude of AUC are as follows[22]:

AUC = 0.50: No discrimination.
0.50 < AUC <0.70: poor discrimination.
0.70 < AUC <0.80; acceptable discrimination.
0.80 < AUC <0.90: excellent discrimination.
AUC > 0.90: outstanding discrimination.

We then compared each pairwise set of CerOx and $ETCO_2$ AUCs to determine whether one was statistically superior in discrimination, e.g., maximum CerOx versus maximum $ETCO_2$[23] Dot plots are also provided graphic depiction of the distributions.

Results

General characteristics

Of the 278 patients enrolled, we analyzed 176 data sets available for the individual variable analysis and 125 data sets were available for the simultaneous variable comparison. As an observational trial on critically ill pateints our associates were very careful as to not to interfere with patient care. As a result of this and the limitations of the technology, such as endotracheal tube secretions for $ETCO_2$, most patients were excluded due to incomplete data sets. In the larger population (N = 176) average subject age was 62.3 with a 65.3% male predominance. A majority, 89.2%, were OHCA, 66.7% were witnessed arrest and 53.8% received bystander CPR. Initial rhythms were asystole 31.8%, PEA in 27.8%, ventricular fibrillation (VF) or ventricular tachycardia (VT) 25.6%, unknown 1% and 14.8%

Table 1 – Demographics for the independent comparison of ROSC to determine FOR measures and direct comparison of ROSC to evaluate modalities.

Category	Independent comp.		Direct comp.	
	N	Statistic	N	Statistic
Age	173	62.3 (14.36)	122	62.3 (14.93)
Male sex	176	115 (65.3)	125	85 (68.0)
EMS call to ED time (min)	108	39.0 (73.0)	90	41.6 (79.5)
Arrest location	176		125	
ED		19 (10.8)		13 (10.4)
Out of hospital		157 (89.2)		112 (89.6)
Arrest witnessed	176	116 (66.7)	124	85 (68.6)
Immediate CPR performed	173	93 (53.8)	125	72 (57.6)
Initial rhythm	176		125	
Asystole		56 (31.8)		39 (31.2)
PEA		49 (27.8)		33 (26.4)
No-shock advised		26 (14.8)		19 (15.2)
VF/VT		45 (25.6)		34 (27.2)
Rate of ROSC	176	36 (20.5)	125	21 (16.8)

Statistics reported for age are mean (SD), and statistics for all other variables are N(%).

had no shock advised by an AED. Demographics and characteristics of arrest are displayed in Table 1. Also, it is important to note that though the rate of ROSC varied greatly between the ED and OHCA arrest groups, (84% and 19%, respectively) analysis with and without the ED arrest group did not significantly change the AUC or the OR for ETCO2 or CerOx.

Comparison

The analysis of the individual variable prediction of ROSC, (total patient N = 176, revealed: first value [CerOx AUC = 0.554 p = 0.1143 ; $ETCO_2$ AUC = 0.533, p = 0.3981], maximum value [CerOx AUC = 0.778 p < 0.0001; $ETCO_2$ AUC = 0.616 p = 0.0849], trend over the last

Table 2 – Data for independent prediction of ROSC.

Independent comparison

Category	All patients		No ROSC		ROSC		
	N	Statistic	N	Statistic	N	Statistic	p-Value
Age	173	62.3 (14.4)	128	62.0 (13.0)	45	63.1 (17.7)	0.6520
Male sex	176	115 (65.3)	130	85 (65.4)	46	30 (65.2)	0.9837
EMS call to ED time (min)	108	39.0 (73.0)	85	31.9 (13.2)	23	65.3 (156)	0.0048[a]
Arrest location	176		130		46		
ED		19 (10.8)		3 (2.3)		16 (34.8)	<0.0001[b]
Out of hospital		157 (89.2)		127 (97.7)		30 (65.2)	
Arrest witnessed	176	116 (66.7)	130	78 (60.0)	46	38 (86.4)	0.0013
Immediate CPR performed	173	93 (53.8)	129	64 (49.6)	44	29 (65.9)	0.0612
Initial rhythm	176		130		46		
Asystole		56 (31.8)		47 (36.2)		9 (19.6)	0.0049
PEA		49 (27.8)		27 (20.8)		22 (47.4)	
No-shock advised		26 (14.8)		20 (15.4)		6 (13.0)	
VF/VT		45 (25.6)		36 (27.7)		9 (19.6)	
Rate of ROSC	176		130		46		

Direct Comparison

Category	All Patients		No ROSC		ROSC		
	N	Statistic	N	Statistic	N	Statistic	p-Value
Age	122	62.3 (14.9)	93	62.4 (12.9)	29	62.2 (20.5)	0.9688
Male sex	125	85 (68.0)	95	66 (69.5)	30	19 (63.3)	0.5297
EMS call to ED time (min)	90	41.6 (79.5)	72	31.9 (13.7)	18	80.8 (174)	0.0877[a]
Arrest location	125		95		30		<0.0001[b]
ED		13 (10.4)		3 (3.2)		10 (33.3)	
Out of hospital		112 (89.6)		92 (96.8)		20 (66.7)	
Arrest witnessed	124	85 (68.6)	95	59 (62.1)	29	26 (89.7)	0.0052
Immediate CPR performed	125	72 (57.6)	95	52 (54.7)	30	20 (66.7)	0.2490
Initial rhythm	125		95		30		0.1159
Asystole		39 (31.2)		32 (33.7)		7 (23.3)	
PEA		33 (26.4)		20 (21.1)		13 (43.3)	
No-shock advised		19 (15.2)		15 (15.8)		4 (13.3)	
VF/VT		34 (27.2)		28 (29.5)		6 (20.0)	
Rate of ROSC	125		95		30		

Parameter	$ETCO_2$				CerOx			
	N	AUC	OR	p-Value[c]	N	AUC	OR	p-Value[d]
Average value of the final minute during the resuscitation	113	0.77	1.056	0.0001	165	0.886	1.262	<0.0001
The delta first to last value	158	0.734	1.053	<0.0001	171	0.859	1.315	<0.0001
Average value of minute prior to the final minute during the resuscitation	123	0.759	1.051	0.0003	163	0.814	1.204	<0.0001
The trend over the last five minutes	150	0.744	1.00[d]	0.7354	171	0.821	1.055[d]	<0.0001
The maximum value	158	0.616	1.014	0.0849	171	0.778	1.094	<0.0001
The first value	158	0.533	0.99	0.3981	171	0.554	1.042	0.1143

Odds ratio for 5 unit change are: 1.311 final minute avg. ETCO2, 1.297 Delta ETCO2, 1.284 Next-to-last minute avg., 1.075 Max ETCO2, 0.953 First ETCO2. 3.206 final minute avg. CerOx, 3.930 Delta CerOx, 2.533 Next-to-last minute avg. CerOx, 1.569 max CerOx, 1.231 first CerOx.

[a] Wilcoxon Rank Sum — t-Test approximation.

[b] Fisher's Exact used due to insufficient cell counts.

[c] p-Values reported for odds ratios.

[d] Odds ratio for trend is based on a unit change of 0.001 in parameter slope. Rate of change for slopes is units (CerOx or ETCO2)/sec.

5 min [CerOx AUC = 0.821 $p < 0.0001$; $ETCO_2$ AUC = 0.744 p = 0.7354], delta from first to last value [CerOx AUC = 0.859 $p < 0.0001$; $ETCO_2$ AUC = 0.734 p = < 0.0001], average value of the penultimate minute of resuscitation [CerOx AUC = 0.814 $p < 0.0001$; ETCO2 AUC = 0.759 p = 0.0003], and average value of the final minute of the resuscitation [CerOx AUC = 0.886 $p < 0.0001$; ETCO2 AUC = 0.770 p = 0.0001]. CerOx had higher AUC values than $ETCO_2$ in all six parameters evaluated (Tables 1 and 2).

For the direct comparison of simultaneously collected data for the prediction of ROSC, (N = 125), the results were as follows: first value [CerOx AUC = 0.601 p = 0.0582; $ETCO_2$ AUC = 0.580 p = 0.1161], maximum value [CerOx AUC = 0.765 $p < 0.0001$; $ETCO_2$ AUC = 0.468 p = 0.9817], trend over the last 5 min [CerOx AUC = 0.802 $p < 0.0001$; $ETCO_2$ AUC = 0.787 p = 0.956], delta from first to last value [CerOx AUC = 0.830 $p < 0.0001$; $ETCO_2$ AUC = 0.754 p = 0.0002], average value of the penultimate minute of resuscitation [CerOx AUC = 0.830 $p < 0.0001$; $ETCO_2$ AUC = 0.783 p = 0.0040], and average value the final minute of the resuscitation [CerOx AUC = 0.887 $p < 0.0001$; $ETCO_2$ AUC = 0.747 p = 0.0015]. Simultaneous comparison results are summarized in Table 3. To assess whether one modality displayed superior discrimination (in the simultaneous comparison population), a direct comparison of AUCs was performed utilizing Chi-Squared. Although the AUCs differ markedly for CerOx and ETCO2 (as shown in Table 3), the direct AUC comparison requires the patient to have derived variables available in both modalities, as a result, the only variable with a significant difference in AUCs was maximum value, where CerOx displayed statistical superiority (p 0 0.0002).

Subsequently, we identified the average value of the penultimate minute of resuscitation and the delta from first to last values to be the most clinically useful variables. We proceeded to place each variable for both modalities into a Receiver Operating Characteristic (ROC) curve analysis (Fig. 2) as well as dot plots comparing the two variables for prediction of ROSC (Fig. 3).

Discussion

This is the first prospective cohort study to simultaneously compare the ability of $ETCO_2$ and CerOx to predict ROSC after out of hospital and emergency department cardiac arrest. With respect to the individual logistic models used to evaluate the simulatenously collected ETCO2 and CerOx data, CerOx was the overall better predictor. Five of the six derived parameters, Maximum, First-Last Delta, Final 5 min Trend, Penultimate Minute Average, and Final Minute Average showed significant predictive value in CerOx, while only the Final 5 min Trend, Penultimate Minute Average, and Final Minute Average showed significance in ETCO2. With respect to the direct comparison of AUCs, CerOx demonstrated a significantly greater AUC for Maximum value. All other AUCs showed no significance difference. However, the CerOx AUCs were larger for all parameters. Higher values and positive trends for both modalities were positive predictors of ROSC.

In regard to futility of resuscitation, the current literature demonstrates that $ETCO_2$ values of less than 10 mmHg and more recently less than 14 mmHg after 20 min of ACLS correctly identified those unlikely to achieve ROSC.[24,25] Recent data reveals a CerOx less than 25 at hospital arrival was predictive of poor neurologic outcome.[26] Additional studies were able to identify rSO_2 of 15%, (the lowest possible value on certain devices), within the first 3 min of hospital resuscitation to have a higher AUC for predicting futility than the ALS-TOR criteria.[27] It is obvious that values to predict futility require very high specificities to avoid missing possible survivors. $ETCO_2$ had acceptable and CerOx had excellent prediction of futility for trending data and average value over the last two minutes of resuscitation efforts.

Overall, static measurements like initial and maximum values were weaker predictors when compared to dynamic trending measurements. The import of dynamic values is further supported by Parnia et al., showing CerOx values increased 310% from baseline in patients with ROSC as compared to 150% in non-ROSC patients.[28] Additional data for $ETCO_2$ demonstrates that an initial $ETCO_2$ reading and the absence of a 25% reduction throughout a resuscitation was predictive of ROSC.[29]

Higher values in the last two minutes were generally more predictive of ROSC for both modalities. We found the trend over the last 5 min, the delta from initial to last value and the average values over the last 2 min of resuscitation was an acceptable predictor for $ETCO_2$ and excellent predictor for CerOx of ROSC.

We attempted to identify optimal cut-offs for the two parameters we believed to be the most clinically relevant; delta from first to the last value and the average value of the penultimate minute. Cut-offs were identified in the simultaneous comparison dataset. The cutoffs for the delta from the first to the last values were 1.5 for CerOx with a sensitivity of 76.7% and a specificity of 88.4% and 5.8 for $ETCO_2$ with a sensitivity of 80.0% and a specificity of 63.2. The cutoffs for the

Table 3 – Data for simultaneous comparison to predict ROSC.

Parameter	$ETCO_2$				CerOx			
	N	AUC	OR	p-Value[a]	N	AUC	OR	p-Value[a]
Average value of the final minute during the resuscitation	92	0.747	1.052	0.0015	123	0.887	1.246	<0.0001
The delta first to last value	125	0.754	1.058	0.0002	125	0.83	1.254	<0.0001
Average value of minute prior to the final minute during the resuscitation	101	0.738	1.045	0.004	119	0.83	1.194	<0.0001
The trend over the last five minutes	122	0.787	1.005[b]	0.956	125	0.802	1.047[b]	0.0002
The maximum value	125	0.468	1	0.9817	125	0.765	1.085	<0.0001
The first value	125	0.58	0.976	0.1161	125	0.601	1.055	0.0582

Odds ratio for 5 unit change are: 1.287 final minute avg. ETCO2, 1.323 Delta ETCO2, 1.247 Next-to-last minute avg., 0.999 Max ETCO2, 0.886 first ETCO2. 2.997 final minute avg. CerOx, 3.095 Delta CerOx, 2.427 Next-to-last minute avg. CerOx, 1.507 Max CerOx, 1.305 first CerOx.

[a] p-Values reported for odds ratios.

[b] Odds ratio for trend is based on a unit change of 0.001 in parameter slope. Rate of change for slopes is units (CerOx or ETCO2)/sec.

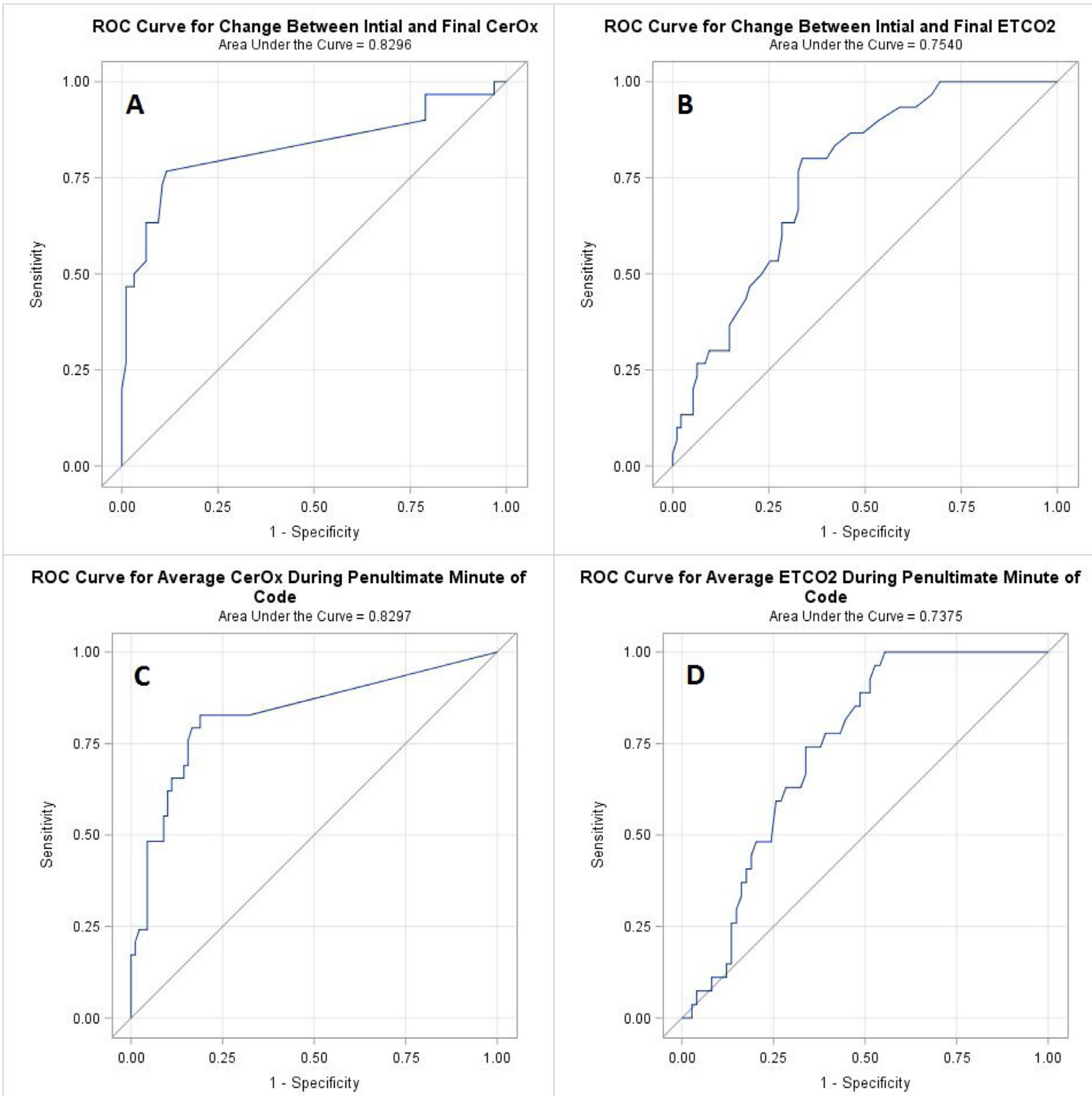

Fig. 2 – AUC Curve graphs for (A) change in CerOx value from initial to final value, (B) change in ETCO2 value from initial to final value, (C) average CerOx value for Penultimate minute, and (D) average ETCO2 value for penultimate minute.

average value of the penultimate minute were 19.1 for CerOx with a sensitivity of 79.3% and a specificity of 82.2%, and 26.5 for $ETCO_2$ with a sensitivity of 74.1% and a specificity of 59.5%. Of note, the AHA states that a value of 40 mmHg is predictive of ROSC based on previous research.[30] In our analysis 40 mmHg would only be 33.3% sensitive and 83.8% specific during the penultimate minute. This demonstrates that minor positive trends throughout the resuscitation improves the chance of ROSC and that lower values than previously reported near the end of a resuscitation are still associated with of ROSC. The dot plots (Fig. 3) graphically display the above comparisons and the overall greater spread and variability in $ETCO_2$ values as compared to CerOx.

The expanded use of these technologies could give real time feedback to improve resource utilization, compression quality, increase rates of ROSC, and possibly improve neurological outcomes. The feasibility of pre-hospital use of CerOx has been shown and the fact that an advanced airway is unnecessary expands its use to BLS providers.[31]

This manuscript reveals that in patients with suspected cardiac arrest that are resuscitated in the ED, cerebral oximetry provided a better predictor of outcome and therefore may better facilitate the decision to stop or continue resuscitation.

Limitations

Overall this is a relatively small sample size from a single institution. The start time of data collection for all patients varied due to arrest location, equipment availability, staff notification, and transport times. We had 102 and 153 patients dropped from analyses due to incomplete data sets. Additionally, we did not analyze other end points including hospital admission, hospital discharge, and most importantly neurological outcome of the patients. We did not track directly the adherence to AHA guidelines or quality of CPR, however for the direct comparison there were simultaneous recordings on the same patient.

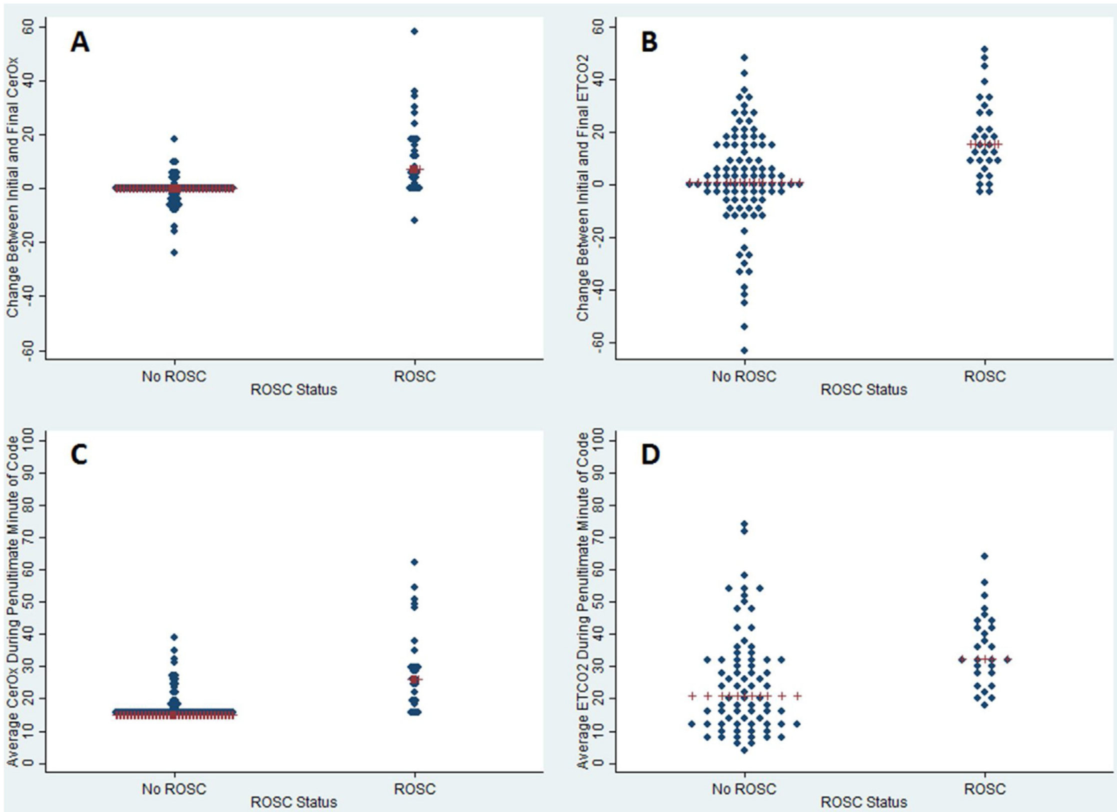

Fig. 3 – Dot Plot graphs for (A) delta in CerOx value from initial to final value, (B) delta in ETCO2 value from initial to final value, (C) average CerOx value for Penultimate minute, and (D) average ETCO2 value for penultimate minute.

Conclusion

Through simultaneous recording we found that CerOx was overall a better at predicting return of spontaneous circulation than $ETCO_2$. Higher values during resuscitation and positive temporal trends were associated with greater chances of return of spontaneous circulation.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.006.

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