RESUSCITATION 169 (2021) 189–197

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Pulse oximetry waveform: A non-invasive physiological predictor for the return of spontaneous circulation in cardiac arrest patients —— A multicenter, prospective observational study

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https://doi.org/10.1016/j.resuscitation.2021.09.032
Received 28 February 2021; Received in Revised form 26 September 2021; Accepted 27 September 2021
0300-9572/

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Abstract

Objective: This study aimed to investigate the predictive value of pulse oximetry plethysmography (POP) for the return of spontaneous circulation (ROSC) in cardiac arrest (CA) patients.

Methods: This was a multicenter, observational, prospective cohort study of patients hospitalized with cardiac arrest at 14 teaching hospitals cross China from December 2013 through November 2014. The study endpoint was ROSC, defined as the restoration of a palpable pulse and an autonomous cardiac rhythm lasting for at least 20 minutes after the completion or cessation of CPR.

Results: 150 out-of-hospital cardiac arrest (OHCA) patients and 291 in-hospital cardiac arrest (IHCA) patients were enrolled prospectively. ROSC was achieved in 20 (13.3%) and 64 (22.0%) patients in these cohorts, respectively. In patients with complete end-tidal carbon dioxide ($ETCO_2$) and POP data, patients with ROSC had significantly higher levels of POP area under the curve (AUCp), wave amplitude (Amp) and $ETCO_2$ level during CPR than those without ROSC (all $p < 0.05$). Pairwise comparison of receiver operating characteristic (ROC) curve analysis indicated no significant dierence was observed between $ETCO_2$ and Amp (p = 0.204) or AUCp (p = 0.588) during the first two minutes of resuscitation.

Conclusion: POP may be a novel and eective method for predicting ROSC during resuscitation, with a prognostic value similar to $ETCO_2$ at early stage.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation, Oximetry, Plethysmography, Return of spontaneous circulation

Introduction

Despite great advances in developing guidelines for resuscitation, cardiac arrest (CA) continues to have a high mortality and leads to enomourous economic costs worldwide[1–3]. Many studies have reported monitoring physiologic values during cardiopulmonary resuscitation (CPR) and relating them to clinical outcomes for cardiac arrest patients[4–7]. Some have even used physiologic indicators to guide CPR actions to improve the quality of chest compressions. Previously reported objective indicators include end-tidal carbon dioxide ($ETCO_2$)[5,8,9], invasive arterial pressure[10,11], and near-infrared spectroscopy[12]. However, these methods are inapplicable to some pre-hospital situations and many emergency department (ED) initial resuscitations due to their dependence on a secured airway, arterial lines or expensive hardware. Pulse oximetry, which is easy-to-use and non-invasive, is already widely used in patient monitoring worldwide and can provide peripheral circulatory information in addition to hemoglobin oxygen saturation[13,14]. The concept of how the waveform of pulse oximetry relates to a patient's blood pressure and microcirculation status during resuscitation has been proposed for more than 20 years[15,16], but to date there have been no rigorous prospective trials of its clinical effectiveness.

Our previous study in porcine models found that the area under the curve (AUCp) and the amplitude (Amp) of the pulse oximetry plethysmography (POP) waveform were positively correlated with the depth of chest compressions, coronary perfusion pressure (CPP) and $ETCO_2$[17–19]. However, data on the utility of POP waveform analysis in clinical settings has been lacking. Therefore, we conducted this multicenter clinical study to assess the application of POP waveform analysis for predicting return of spontaneous circulation (ROSC) during chest compressions for cardiac arrest patients.

Methods

Study design and setting

This was a multicenter, prospective, observational study conducted from December 1, 2013 through November 30, 2014 in the EDs of 14 teaching hospitals in seven provinces located throughout China (Fig. 1A. The inclusion criteria included adults with cardiac arrest who received advanced cardiac life support (ACLS) with intubation according to American Heart Association (AHA) guidelines[20] monitored by trained study staff. Exclusion criteria were those patients with a written advance directive to not resuscitate, no POP measurement available, age younger than 18 years, and clinical comorbidities that might influence the accuracy of capnography or pulse oximetry including rib fractures, hemorrhagic shock, pulmonary embolism, pericardial tamponade, anemia with hemoglobin less than 7 g/dl and tension pneumothorax without drainage[5,21,22]. Patients with completed $ETCO_2$ and POP records were analyzed to compare the discriminative ability for detecting ROSC in CA patients.

The study protocol was approved by the ethics committee of the Chinese Academy of Medical Sciences - Peking Union Medical College Hospital and was registered on the ClinicalTrials.gov website, number NCT 01987245. Written informed consent was obtained from the patient's next of kin, when feasible, before resuscitation procedures.

Resuscitation procedures

All rescuers were trained to provide care according to the AHA's current ACLS guidelines[20]. Electrocardiogram and pulse oximetry were monitored at the initiation of CPR. $ETCO_2$ was continuously monitored starting immediately after performing endotracheal intubation. All procedural decisions including termination of CPR were made at the discretion of the attending physicians for each patient (Fig. 1B).

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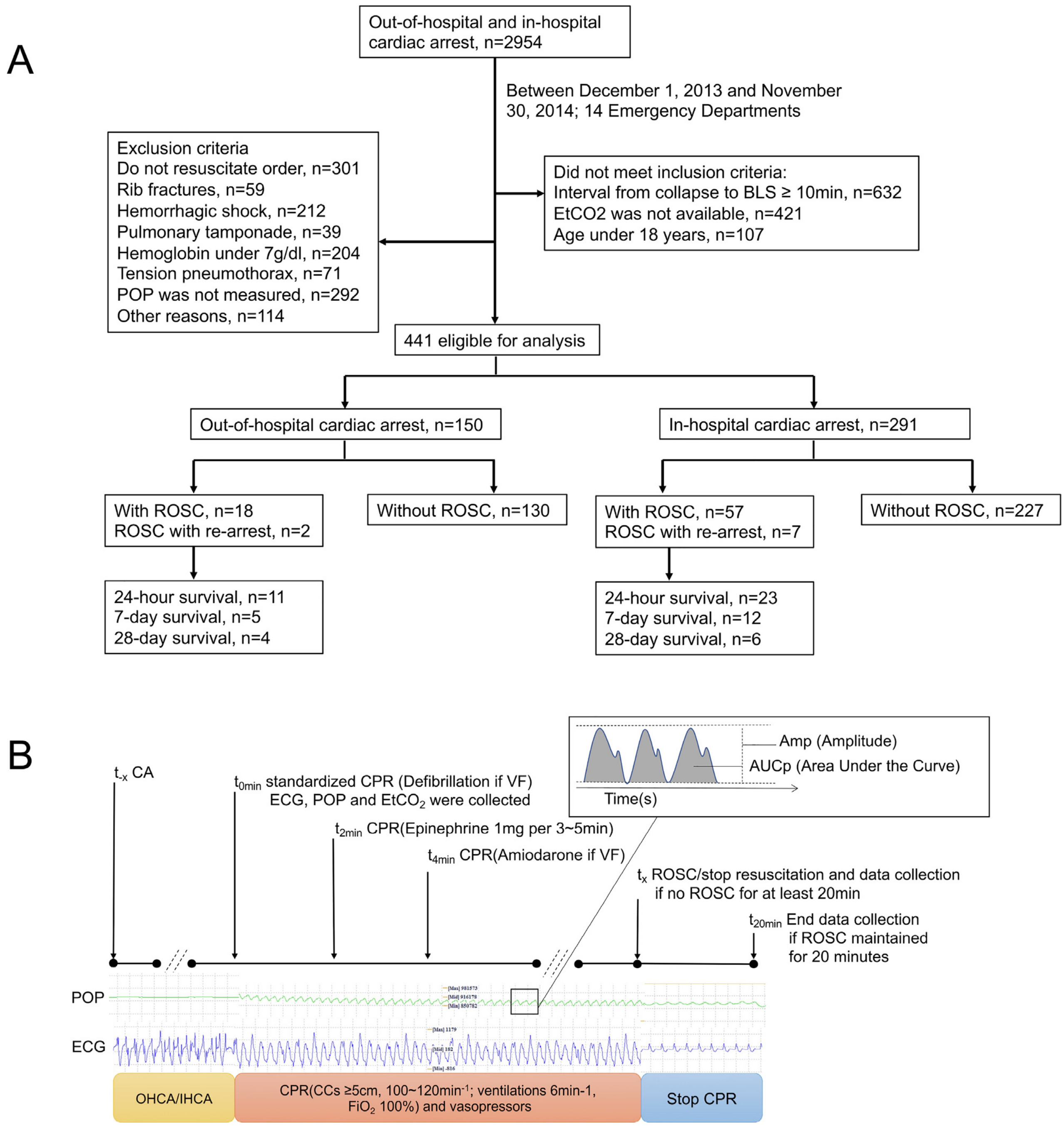


Fig. 1 – (A) Enrollment of study patients and outcomes. Out of all 2954 cardiac arrest patients, 441 were enrolled in this study with 150 out-of-hospital cardiac arrest patients and 291 in-hospital-cardiac arrest patients. BLS = basic life support. POP = pulse oximetry plethysmographic. $ETCO_2$ = end-tidal carbon dioxide. ROSC = return of spontaneous circulation. (B) Protocol design. During the resuscitation period, a standardized resuscitation protocol was used for cardiac arrest patients. Data including electrocardiogram (ECG) and pulse oximetry plethysmography (POP) were collected at the same time. For patients with no ROSC, resuscitation continued for at least 20 minutes and all data were collected throughout CPR. For patients with ROSC, data were extracted from the resuscitation progress and an extra 20 minutes was recorded to make sure ROSC was stable (ending at t_{20min}, as shown). All rescuers were trained to provide care aligned with the AHA's ACLS guidelines. CA = cardiac arrest, CPR = cardiopulmonary resuscitation, VF = ventricular fibrillation, ROSC = return of spontaneous circulation.

POP parameters and $ETCO_2$

A pulse oximetry probe was connected to a T8 cardiac monitor (Mindray Biological Medical Electronic Co, Ltd, Shenzhen, China) which was fixed to the patient's right finger (forefinger was preferred) to continuously obtain raw red (660 nm) and near-infrared (900 nm) POP signals when CPR was in-progress.

The data was stored on Compact Flash cards and analyzed by Mindray POP viewer V8.0 (Mindray Research Center for Monitoring and Life Support) using MATLAB software V7.10.0 (MathWorks, Natick, Massachusetts, USA). We acquired the values for Amp, AUCp and frequency of the POP waveform from the near-infrared signals of POP, as has been previously described[17]. In brief, Amp was derived as the mean square root of each single pulse wave and AUCp was calculated using the point-by-point integral of the absolute area under the waveform (Fig. 1B). The mean value of $ETCO_2$ during the first two minutes, last two minutes and overall resuscitation process were calculated.

Data collection and quality control

Data were collected prospectively using an Utstein-style form that included: victim identifier, age, sex, incident date, known precipitating event, preexisting illnesses, bystander details, the presence and type of any bystander CPR, the cause of cardiac arrest (if known), location of cardiac arrest, initial documented cardiac rhythm, the time from collapse to first resuscitation attempt, and, finally, details of ACLS procedures (including endotracheal intubation, any vasopressors used, and defibrillation attempts).

The following parameters were monitored: electrocardiogram, rates of pulse and breathing, the AUCp, Amp and frequency of the POP waveform, and $ETCO_2$ levels. When all devices were available, the data of POP and $ETCO_2$ were collected continuously as soon as possible. The time-synchronized data (averaged data from stabilization to the first two minutes, last two minutes before the end of CPR, and the total process) of Amp, AUCp and $ETCO_2$ were calculated afterward (Fig. 1B). For patients with no ROSC, resuscitation continued for at least 20 minutes and all data were collected throughout CPR. The first, last and total values were extracted from the whole resuscitation process (which may be longer than 20 minutes). For patients with ROSC, the first and the last two minutes were extracted from the overall resuscitation. Data collection was maintained for an extra 20 minutes to make sure ROSC was stable (and ended at t_{20min}, as shown). Pauses in chest compressions were not included in the calculations. The data form was completed by the attending ED physicians in charge of the patients, and then the collected data were recorded into an online REDCap database server. Forms were checked for logical consistency by the computer system and were confirmed by the research study team.

Study endpoints

The primary study endpoint was ROSC, defined as the restoration of a palpable pulse and an autonomous cardiac rhythm lasting for at least 20 minutes after the completion or cessation of CPR. Other outcome data including 24-hour and 28-day survival were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA) and MedCalc software version 12.3.0 (MedCalc Software, Gent, Belgium). F-test, Student's *t*-test or Mann-Whitney tests were applied to determine differences between the two groups, depending on the distribution of the variables. Categorical variables were compared using chi-squared or Fisher Exact tests to determine correlation between two parameters. $p < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the accuracy of predicted ROSC. Area under the curve (AUC) between potential predictors was compared using a nonparametric test, and the optimal cutoff point was determined by estimating Youden's index.

Results

In total, 2954 adult patients with CA were screened in the participating EDs. 292 patients were excluded because POP was not recorded by research monitors and another 421 patients were excluded because capnography was not available. After exclusions, 150 out-of-hospital cardiac arrest (OHCA) patients and 291 in-hosptial cardiac arrest (IHCA) patients were included in our analysis (Fig. 1A). Among these, 20 (13.3%) OHCA patients and 64 (22.0%) IHCA patients developed ROSC (Table 1). The 24-hour and 28-day survival rates of all enrolled patients were 34 (7.7%) and 10 (2.2%), respectively. 142 patients had capnography applied but did not have stable $ETCO_2$ values suitable for extraction. These were excluded in further analyses comparing the discriminative ability of $ETCO_2$ to POP to minimize potential confounders.

In 299 patients with complete POP and $ETCO_2$ records, we found that patients with ROSC had significantly higher levels of Amp than those without ROSC (median[IQR] 108.9[64.9–269.0] versus 82.2 [32.0–224.9] pulse oximeter voltage amplitude (PVA), p = 0.042 in the first two minutes, 105.5[47.3–181.4] versus 50.7[18.3–140.7] PVA, p = 0.001 in the last two minutes, 142.6[80.6–264.2] versus 93.5[49.9–218.4] PVA, p = 0.010 in total process) . The AUCp level was also higher in ROSC patients (median[IQR] 2889.0[2191.3–3256.6] versus 2312.8[1568.4–3009.3] pulse oximeter voltage plethysmography (PVPG), p = 0.003 in the first two minutes, 2882.6[2173.6–3381.5] versus 2129.1[1332.6–3087.9] PVPG, p = 0.001 in the last two minutes, 2903.2[2327.2–3194.1] versus 2303.1[1775.4–2963.8] PVPG, p = 0.001 in total process) (Table 2).

Area under the ROC curve for Amp and AUCp for predicting ROSC were 0.588 (95 %CI 0.509–0.666), 0.627(0.551–0.702) in the first two minutes, 0.637(0.562–0.712), 0.656(0.582–0.730) in the last two minutes, and 0.611(0.529–0.692), 0.646(0.571–0.721) overall (Fig. 2). Pairwise comparison of the ROC curves for Amp, AUCp and $ETCO_2$ in the first two minutes found no statistical differences. However, ROC curves of $ETCO_2$ were superior to POP parameters in the final two minutes (p = 0.007 for Amp and p = 0.018 for AUCp) and in the overall resuscitation (p = 0.023 for Amp and p = 0.106 for AUCp).

According to the ROC analysis, the optimal cutoff of Amp in the first two minutes to predict ROSC was 85 PVA, with sensitivity, specificity, PPV and NPV of 69.1%. 51.6%, 58.8%, 62.5%, respectively. And the optimal cutoff for AUCp in the first two minutes to predict ROSC was 2046 PVPG, with a sensitivity, specificity, PPV and NPV of 70.9%, 55.7%, 61.5%, and 65.7%, respectively. In the last two minutes, with an optimal cutoff Amp of 43 PVA, the sensitivity, specificity, PPV and NPV were 83.0%, 44.1%, 59.7% and 72.2%; with an optimal cutoff for AUCp of 2095 PVPG, with a sensitivity, specificity, PPV and NPV of 81.1%, 46.7%, 60.3%, and 71.1%, respectively (Table 3).

Discussion

This prospective observational study demonstrated that POP parameters are associated with ROSC in resuscitation, providing evidence

Table 1 – Characteristics of patients with out-of-hospital and in-hospital cardiac arrest (comparison between patients with ROSC and those without ROSC).

Characteristics	Total	With ROSC	Without ROSC	p
Total, n(%)	441	84(19.0%)	357(81.0%)	/
OHCA	150	20(13.3%)	130(86.7%)	/
IHCA	291	64(22.0%)	227(78.0%)	/
Male, n(%)	285(64.6)	51(60.7%)	234(65.5%)	0.695
Age (mean (SD))	59.2(18.4)	58.3(20.9)	59.4(17.7)	
Origin (%)				
Cardiac	175(39.7)	32(38.1)	143(40.0)	
Respiratory	143(32.4)	20(23.8)	123(34.5)	
Neurologic	32(7.3)	3(3.6)	29(8.1)	
Trauma	47(10.6)	10(11.9)	37(10.4)	
Unknown	44(10.0)	19(22.6)	25(7.0)	
Physiologic indicators, median (IQR)				
First_2min				
OHCA patients				
Amp (PVA), n = 150	95.8 (34.9–246.8)	151.7 (86.4–288.2)	92.7 (32.2–235.9)	0.157
AUCp (PVPG), n = 150	2435.2 (1531.0–3174.0)	2941.5 (2136.7–3442.6)	2366.1 (1480.1–3136.2)	0.071
$ETCO_2$ (mmHg), n = 99	12.6(7.5–18.2)	18.1 (14.1–26.0)	10.9 (7.1–17.1)	0.004
IHCA patients				
Amp (PVA), n = 291	76.8 (30.9–240.1)	94.3 (41.3–268.9)	66.4 (27.5–234.9)	0.114
AUCp (PVPG), n = 291	2306.6(1566.9–3021.1)	2690.9 (1783.1–3062.0)	2238.9 (1519.7–2995.5)	0.041
$ETCO_2$ (mmHg), n = 200	11.4 (7.2–21.5)	15.4 (9.4–29.0)	10.0 (6.9–19.1)	0.009
Last_2min				
OHCA patients				
Amp (PVA), n = 150	56.6 (20.6–140.8)	81.3 (30.6–192.7)	41.3 (18.3–139.2)	0.176
AUCp (PVPG), n = 150	2123.3 (1353.7–3169.2)	2554.3 (1751.5–3242.2)	2115.1 (1331.1–3147.9)	0.363
$ETCO_2$ (mmHg), n = 99	12.2 (8.0–21.9)	29.0 (22.9–43.0)	10.7 (7.0–17.3)	<0.001
IHCA patients				
Amp (PVA), n = 291	56.2 (20.1–140.7)	82.3 (38.9–161.6)	50.9 (17.5–128.6)	0.013
AUCp (PVPG), n = 291	2195.0(1433.5–3042.6)	2726.2 (1854.5–3318.5)	2056.5 (1327.8–2923.9)	0.002
$ETCO_2$ (mmHg), n = 200	12.1 (6.0–24.5)	22.5 (13.6–34.8)	9.3 (5.2–17.5)	<0.001
Total				
OHCA patients				
Amp (PVA), n = 150	109.7 (56.9–238.6)	143.5 (97.9–218.6)	106.1 (55.1–242.0)	0.391
AUCp (PVPG), n = 150	2411.7 (1820.2–3021.9)	2675.7 (2090.2–3027.3)	2379.4 (1814.5–3022.0)	0.490
$ETCO_2$ (mmHg), n = 99	12.5 (7.9–19.4)	23.0 (18.2–42.1)	11.0 (7.1–17.0)	<0.001
IHCA patients				
Amp (PVA), n = 291	97.3 (48.5–210.1)	137.4 (65.6–295.5)	87.4 (45.8–178.8)	0.004
AUCp (PVPG), n = 291	2304.5(1748.9–2948.4)	2772.9 (2071.9–3138.8)	2213.5 (1715.8–2805.9)	0.002
$ETCO_2$ (mmHg), n = 200	13.1 (7.6–21.9)	13.2 (21.0–32.9)	11.2 (7.1–18.3)	<0.001

Data are n (%) or median (interquartile range). ROSC = return of spontaneous circulation. VF = ventricular fibrillation. VT = ventricular tachycardia. PEA = pulseless electrical activity. EMS = emergency medical services. CPR = cardiopulmonary resuscitation. Amp = amplitude of the pulse oximetry plethysmographic waveform. AUCp = area under the curve of the pulse oximetry plethysmographic waveform. $ETCO_2$ = end-tidal carbon dioxide.

that monitoring POP waveform could be an effective alternative to $ETCO_2$ during CPR. Compared to $ETCO_2$ in CA patients, POP during early CPR had similar predictive ability for ROSC.

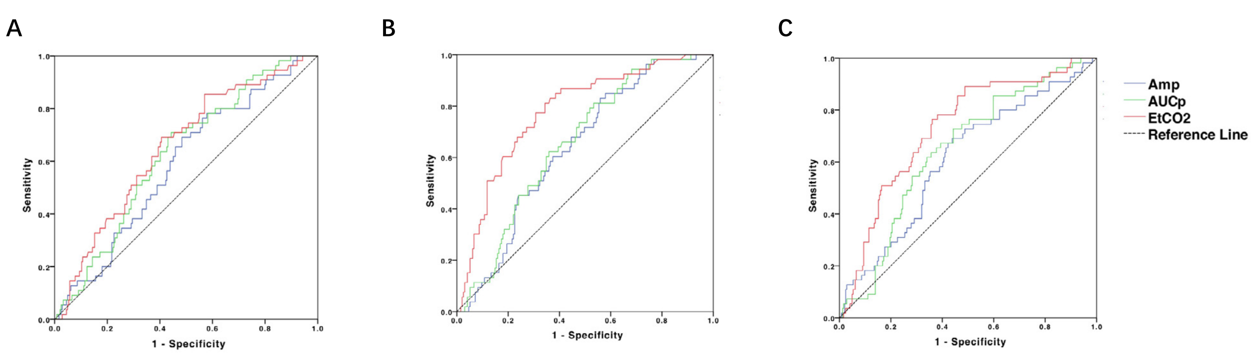
The goal of CPR is to promote adequate tissue perfusion in order to achieve ROSC. In our study, IHCA patients who developed ROSC had significantly higher POP AUCp and Amp values than those without ROSC (Table 1). A previous study by our group showed that the AUCp and Amp of the POP waveform not only reflect CPR metrics including the depth and frequency of chest compressions, but are also positively correlated with coronary perfusion pressure (CPP) and $ETCO_2$[17–19]. Thus higher Amp values and AUCp might indicate improved microcirculation and perfusion during resuscitation and lead to better prognosis. For OHCA patients, observed differences in Amp and AUCp levels between patients with and without ROSC did not reach statistical significance. This might be caused by a limited OHCA patient population. Another possible cause might be that POP waveforms in OHCA patients were more likely to be influenced by cold whether or other environmental factors outside of the hospital[23–25].

Generally speaking, in this study $ETCO_2$ performed slightly better than POP parameters for predicting ROSC. $ETCO_2$ levels were significantly higher in patients with ROSC at every time point we analyzed, while no differences were observed for POP parameters at some time points as shown in Table 1. There are several possible explanations. POP waveforms were confirmed to be related to CPR metrics and do seem to reflect the depth and frequency of CPR[17]. Still, compared to $ETCO_2$, POP amplitude appears to be closely related to the status of the peripheral microcirculation, regardless of central circulation status. A patient with good microcirculation does not always turn out to achieve ROSC. $ETCO_2$ reflects metabolism and macrocirculatory (i.e. pulmonary) blood flow during CPR, and is thus more physiologically related to ROSC. Sec-

Table 2 – Characteristics of patients with completed POP and $ETCO_2$ records.

	With ROSC	Without ROSC	p
No. Patients	55	244	
Gender (%)			
Male	37 (67.3)	160 (65.6)	0.876
Female	18 (32.7)	84 (34.4)	
Age (mean (SD))	58.3 (19.4)	58.3 (18.4)	0.786
Origin (%)			
Cardiac	24 (42.9)	94 (38.5)	0.542
Respiratory	13 (23.6)	65 (26.6)	
Neurologic	2 (3.6)	21 (8.6)	
Trauma	7 (12.7)	26 (10.7)	
Unknown	11 (20.0)	38 (15.6)	
Location (%)			
Out-hospital	13 (23.6)	86 (35.2)	0.114
In-hospital	42 (76.4)	158 (64.8)	
Physiologic indicators*, median (IQR)			
First_2min			
Amp (PVA)	108.9(64.9, 269.0)	82.2(32.0, 224.9)	0.042
AUCp (PVPG)	2889.0(2191.3, 3256.6)	2312.8(1568.4, 3009.3)	0.003
$ETCO_2$ (mmHg)	16.4(10.0, 28.6)	10.5(7.0, 18.2)	<0.001
Last_2min			
Amp (PVA)	105.5(47.3, 181.4)	50.7(18.3, 140.7)	0.001
AUCp (PVPG)	2882.6(2173.6, 3381.5)	2129.1(1332.6, 3087.9)	0.001
$ETCO_2$ (mmHg)	28.0(16.0, 37.2)	10.6(5.7, 18.4)	<0.001
Total			
Amp (PVA)	142.6(80.6, 264.2)	93.5(49.9, 218.4)	0.010
AUCp (PVPG)	2903.2(2327.2, 3194.1)	2303.1(1775.4, 2963.8)	0.001
$ETCO_2$ (mmHg)	22.4(15.0, 33.1)	11.3(7.3, 18.3)	<0.001

Data are medians (interqurtile rage). CPR = cardiopulmonary resuscitation. Amp = amplitude of the pulse oximetry plethysmographic waveform. AUCp = area under the curve of the pulse oximetry plethysmographic waveform. $ETCO_2$ = end-tidal carbon dioxide. *Data missed in five (Amp and AUCp) and 23 ($ETCO_2$) patients. # Data missing in one (Amp and AUCp) and in 151 ($ETCO_2$) patients.



	AUC(95%CI)	ΔAUC*	Z-statistic	P value
Amp_pre2	0.588 (0.509-0.666)	0.067	1.271	0.204
AUCp_pre2	0.627(0.551-0.702)	0.026	0.542	0.588
EtCO2_pre2	0.653(0.577-0.730)	/	/	/
Amp_last2	0.637 (0.562-0.712)	0.141	2.704	0.007
AUCp_last2	0.656(0.582-0.730)	0.122	2.357	0.018
EtCO2_last2	0.778(0.710-0.846)	/	/	/
Amp_total	0.611 (0.529-0.692)	0.117	2.278	0.023
AUCp_total	0.646(0.571-0.721)	0.082	0.023	0.106
EtCO2_total	0.728(0.657-0.799)	/	/	/

Fig. 2 – Receiver operating characteristic curve analysis of Amp, AUCp and $ETCO_2$ as predictors of return of spontaneous circulation. (A) Pre_2min, (B) Last_2min, (C) Total. The AUC of the blue, green and red lines refer to Amp, AUCp and $ETCO_2$, repectively. AUCs with 95% confidence intervals are listed below. To predict ROSC in the first two minutes of CPR, Amp and AUCp showed comparable AUC with $ETCO_2$. Amp = amplitude of pulse oximetry plethysmographic. AUCp = area under the curve of pulse oximetry plethysmographic. $ETCO_2$ = end-tidal carbon dioxide.

ond, POP waveform detection is dependent on a patient's anatomy for detection (e.g. size of finger tips, etc.), which may not be fully consistent with their circulation in other essential organs. Third, we hypothesize that the detection of ROSC is often delayed and that an early ROSC circulation may happen concurrently with continuing chest compressions, leading to decreased Amp and AUCp in early

Table 3 – Logistic analysis of odds ratio (OR) values for different factors contributing to ROSC.

Characteristics	Cut-off value	Youden's index	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
First_2min						
Amp	85 PVA	0.21	69.1	51.6	58.8	62.5
AUCp	2046 PVPG	0.27	70.9	55.7	61.5	65.7
$ETCO_2$	9 mmHg	0.29	85.5	43.0	60.0	74.8
Last_2min						
Amp	43 PVA	0.27	83.0	44.1	59.7	72.2
AUCp	2095 PVPG	0.28	81.1	46.7	60.3	71.1
$ETCO_2$	14 mmHg	0.47	81.1	65.6	70.2	77.6
Total						
Amp	107 PVA	0.25	69.1	43.9	61.1	64.5
AUCp	2437 PVPG	0.28	72.7	55.7	62.1	67.1
$ETCO_2$	11 mmHg	0.40	89.1	51.2	64.6	82.4

Data are n (%). OR = odds ratio. ROSC = return of spontaneous circulation. AUCp = area under the curve of the pulse oximetry plethysmographic waveform. $ETCO_2$ = end-tidal carbon dioxide. PPV = positive predictive value, NPV = negative predictive value.

ROSC patients[26]. This may explains the results: in the ROC curve analysis the predictive ability for ROSC with POP was similar to $ETCO_2$ during the first two minutes and overall resuscitation, while that of POP was worse than $ETCO_2$ during the last two minutes. This hypothesis needs to be confirmed in further animal and clinical studies.

For decades, pulse oximetry has been a standard of care for the continuous non-invasive monitoring of arterial blood oxygen saturation. More recently, patients with different pathological statuses have been shown to display unique plethysmographic waveforms[27]. Respiratory variation in POP has been proposed to predict volume responsiveness in mechanically ventilated patients[28–30]. POP was reported to be correlated with arterial blood pressure and indicated a spontaneous pulse in animals undergoing automated CPR[16]. This study established that the POP waveform provides effective physiological parameters for predicting CPR prognosis in CA. Significantly higher Amp and AUCp were observed in patients who developed ROSC in IHCA, indicating that POP may be a reliable tool to evaluate the prognosis of CA patients. ROC analysis revealed that the optimal Amp and AUCp cutoff values have relatively high sensitivity, high NPV and low PPV, which means detecting levels lower than the optimal cutoff values of POP physiological indicators implies a low probability of successful CPR. This could help physicians identify patients with a low probability of ROSC, who may need either more aggressive management (such as extracorporeal membrane oxygenation), or to have CPR efforts cease earlier (to save on stress and costs). Persistently low Amp and AUCp suggests poor peripheral circulation that may serve as predictor for poor prognosis. Furthermore, POP waveform appears beat by beat, which contains information about both heart rate and stroke volume. The former is related to the frequency of chest compressions, while the latter is affected by the intensity of chest compressions. Our group found that pulse rate could provide real-time feedback for the chest compression rate, which infers a potential application of POP to quality control in CPR[19].

$ETCO_2$ has been extensively studied and is now recommended as an indicator of ROSC in resuscitation. Similar to many previous studies[8,31,32], $ETCO_2$ measurements during CPR in this study were significantly higher in patients who later achieved ROSC compared to those who did not. However, elevated $ETCO_2$ might be a result of ROSC instead of a predictor of ROSC, and an accurate cut-off value during CPR has not been fully established[8,31,33]. $ETCO_2$ is variable depending on numerous factors including vasopressor administration, air leaks around an artificial airway, airspace disease with pulmonary shunts, cardiac shunts and PEEP[4,8], all of which might cause difficulty in $ETCO_2$ measurement, as demonstrated by the relatively high rate of failed $ETCO_2$ measurement in this study as well as in actual clinical settings[9]. POP is much more accessible than $ETCO_2$ and can be applied without endotracheal intubation. In this study, of the 441 enrolled patients, $ETCO_2$ values were successfully recorded in only 299 participants (67.8%), even though $ETCO_2$ capnography was applied in these patients. CPR and intubation secretions during resuscitation are believed to have caused the unreliable $ETCO_2$ data. When comparing patients with completed data (those with both POP and $ETCO_2$ data available) and those without completed data ($ETCO_2$ data unavailable), their baseline characteristics were comparable without significant differences (Supplementary Table 1). We conclude that POP may have better prospects for "real-world" application during CPR. Moreover, since $ETCO_2$ measurement depends on advanced airway management, the initial period of chest compressions prior to intubation may need a tool such as POP to help guide CPR. While useful for monitoring metabolic and macrocirculatory activity, $ETCO_2$ is not a direct parameter reflecting hemodynamics and tissue perfusion, and may delay clinical decisions. POP may provide an alternative to $ETCO_2$ during the early stage of CPR.

There are some important limitations to our study. First, quantitative parameters and waveform features of POP cannot yet be observed real-time using currently available monitors; we had to develop custom software to analyze the data after CPR was complete. However, this is easily solvable with future software updates to monitor systems as monitor processor power is currently sufficient to provide real-time POP parameter values. Second, we used traditional finger probes for POP detection in this study. Central POP measurement has been advocated by some researchers, because a peripheral site is more susceptible to confounding factors such as hypoperfusion and movement of the testing part[34]. It is important to note that multiple resuscitation attempts may potentially influence POP during cardiac arrest with concurrent hypoxia and hypovolemia[21,35]. Epinephrine is the most commonly used drug in resuscitations and can decrease the reliability of POP for detecting peripheral circulation. Nevertheless, we were attempting to test "real-world" conditions in this study, so standard peripheral detectors and ACLS protocols with epinephrine were used. Third, $ETCO_2$ values of 142 (32.2%) patients were unable to be recorded even though capnography was available. This was most likely due to difficulties with setting up and using the equipment than to any problem with $ETCO_2$ itself, but this does speak to the relative challenges of using $ETCO_2$ in typical clinical practice. Fourth, the ROSC rates were relatively low in this study which might decrease the power of this study. Further investigation with larger populations is needed.

Conclusion

This study showed that POP had a discriminative ablitity between CA patients with and without ROSC during CPR process in clinical settings, with a prognostic value similar to $ETCO_2$ during the early stage of resuscitation. POP may thus be a novel and effective real-time predictor of ROSC during CPR.

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Declaration of Competing Interest

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

Acknowledgments

Financial support was received from the Special Scientific Research Funds of the Public Welfare Program of the National Health and Family Planning Commission of China (Grant Reference Number 201502019) and from the Chinese Academy of Medical Sciences Fundamental Research Fund for the Central Public Welfare Research Institute [2017PT31009]. We would like to thank Fei Han, Cheng Wang, Xiaocui Zhang, Jie Qin, Jian Cen, Xinsheng Li, the engineers from Mindray Corporation for their support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.09.032.

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