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ORIGINAL RESEARCH

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Monitoring tissue oxygenation index using near-infrared spectroscopy during pre-hospital resuscitation among out-of-hospital cardiac arrest patients: a pilot study

Jumpei Tsukuda[1,2], Shigeki Fujitani[1*], Mahbubur Rahman[3], Kenichiro Morisawa[1], Takeshi Kawaguchi[1] and Yasuhiko Taira[1]

Abstract

Background: Tissue oxygenation index (TOI) using the near infrared spectroscopy (NIRS) has been demonstrated as a useful indicator to predict return of spontaneous circulation (ROSC) among out-of-hospital cardiac arrest (OHCA) patients in hospital setting. However, it has not been widely examined based on pre-hospital setting.

Methods: In this prospective observational study, we measured TOI in pre-hospital setting among OHCA patients receiving cardio-pulmonary resuscitation (CPR) during ambulance transportation between 2017 and 2018. Throughout the pre-hospital CPR procedure, TOI was continuously measured. The study population was divided into two subgroups: ROSC group and non-ROSC group.

Results: Of the 81 patients included in the final analysis, 26 achieved ROSC and 55 did not achieve ROSC. Patients in the ROSC group were significantly younger, had higher ΔTOI (changes in TOI) (5.8 % vs. 1.3 %; $p < 0.01$), and were more likely to have shockable rhythms and event witnessed than patients in the non-ROSC group. ΔTOI cut-off value of 5 % had highest sensitivity (65.4 %) and specificity (89.3 %) for ROSC. Patients with a cut-off value ≤-2.0 % did not achieve ROSC and while all OHCA patient with a cut-off value ≥ 8.0 % achieved ROSC. In addition, ROSC group had stronger positive correlation between mean chest compression rate and ΔTOI ($r = 0.82$) than non-ROSC group ($r = 0.50$).

Conclusions: This study suggests that Δ TOI could be a useful indicator to predict ROSC in a pre-hospital setting.

Keywords: Cardiopulmonary resuscitation, Out-of-hospital cardiac arrest

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Background

More than 100,000 people die from out-of-hospital cardiac arrest (OHCA) each year in Japan [1]. Although American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) are regularly updated and the survival rate has been improved, the overall mortality of admitted OHCA patients still remain poor [2]. Survival rate after 1 month varied from 5.6 to 7.4 % regardless of the initial cardiac rhythm in Japan [1]. Brain is a vital organ with high metabolic activity and low energy storages and vulnerable to circulatory arrest [3, 4]. High-quality CPR according to the AHA guidelines for cardiopulmonary arrest (CPA) (with proper rate of 100–120 /min, proper depth of 5–6 cm, complete chest recoil and minimizing interruption of chest compressions measured by chest compression fraction and so on) can maintain cerebral blood flow only by 30–40 % of normal flow [5, 6]. Even if return of spontaneous circulation (ROSC) is obtained, brain injury remains as the leading cause of death after ROSC [7]. Some markers using neurological findings, imaging techniques and serum biomarkers, are known to evaluate the extent of brain injury and are only useful after ROSC [8]. However, there are no specific and reliable indicators to assess the cerebral blood flow directly to the response of CPR quality [9].

Near-infrared spectroscopy (NIRS) can provide information on oxygen saturation of brain tissue (StO_2) non-invasively and continuously during CPR without a pulsating rhythm [10]. NIRS can measure StO_2 from the ratio of oxygenated hemoglobin (O_2Hb) to oxygenated and deoxygenated hemoglobin (HHb) in blood flow within venous, arterial and cerebral cortical tissue [7]. Several studies examined the correlation between StO_2 and ROSC or neurological outcomes based on hospitalized patients [11, 12]. In our previous study which included 117 OHCA patients, we observed that ROSC patients had significantly higher initial StO_2 than non-ROSC patients [13]. Other studies have also demonstrated that increase in StO_2 (ΔStO_2) were associated with ROSC [12, 14]. In addition, usefulness of StO_2 as a dynamic value rather than a single static value has also been emphasized [15]. Our previous study also showed that ΔStO_2 could be more useful and accurate than a single initial StO_2 when predicting ROSC [16]. Furthermore, in a recent meta-analysis, ΔStO_2 demonstrated excellent predictive value for ROSC [15]. However, there is a dearth of well-designed studies which examined the association between high-quality CPR and level of StO_2 during CPR, although a recent study based on small sample size demonstrated that high-quality CPR improved StO_2 values [12].

In Japan, the average time from emergency medical service (EMS) call to hospital arrival was 39.4 minutes in 2016 and the time has been increasing every year [1]. Brain can reserve only limited energy, and inadequate cerebral blood flow within 5 minutes can lead to hypoxic brain injury [17]. For every minute without CPR and defibrillation, the chance of survival decreases by 7–10 % [18]. In order to improve the quality of pre-hospital CPR, evaluation of direct cerebral blood flow is necessary. Portable NIRS device equipped in ambulance, where only limited devices can be equipped, can help evaluate the cerebral blood perfusion [19, 20], especially oxygen delivery to the brain. Effective CPR might increase O_2Hb and StO_2 and through these mechanism ROSC rate can be improved. However, based on pre-hospital setting, the association between various types of StO_2 and, ROSC and CPR according to the latest CPR guidelines has not been examined yet.

The objective of this study was to examine the association between ΔStO_2 and ROSC as well as between ΔStO_2 and the CPR quality.

Methods

Study design and setting

This single-center prospective and observational study was conducted at St. Marianna University School of Medicine, a 1200-bed tertiary hospital in Kawasaki, Japan. Enrollment for this study started from May 2017 and continued till March 2019. The research protocol received ethics committee Institutional Review Board (IRB) approval. In Japan, paramedic's Advanced Life Support (ALS) team consists of three persons, under the direction of a physician while they are permitted to administer epinephrine and perform intubation. Additional devices are allowed to use only in the five EMS teams in northern Kawasaki medical area as all of these teams completed required training sessions before this study started.

Study intervention

All ≥ 18 years old OHCA patients with non-traumatic cardiac arrest transferred to our emergency department (ED) were included. Excluded patients were as follows: patients with traumatic cause, patients with core body temperature less than 30°Celsius and patients who had achieved ROSC before the placement of the device probe. When the patients met inclusion criteria, the probe was placed onto the patient's forehead left-laterally above the eyebrow immediately after transportation to the ambulance. One of the 3 paramedics placed the probe to minimize interruption of CPR procedure according to the AHA guidelines 2015 [21]. Although the paramedics were not blinded, they have not received the explanation about the meaning of the values, and followed the latest AHA guidelines without considering the StO_2 values. They were instructed to administer epinephrine and perform tracheal intubation. They did not use mechanical chest compressions but did only manual chest compressions.

We used CCR-1® (Hamamatsu Photonics, Hamamatsu-City, Shizuoka, Japan) which can non-invasively and continuously measures StO_2, so called tissue oxygenation index (TOI) in CCR-1®. This device is portable and can be operated by battery for 2 hours which make it suitable for use in an ambulance. TOI monitoring continued throughout ambulance transportation. Initial ROSC was defined as the presence of a palpable carotid pulse after CPR discontinuation, and successful ROSC was defined as ROSC > 20 minutes after CPR [22].

Measurements and statistical analysis

The study population was divided into 2 groups according to outcome: ROSC group and non-ROSC group. We defined initial TOI as the TOI measured at the moment the probe was attached inside the ambulance and final TOI as the last recorded TOI value at the arrival of the patient to our ED. We evaluated the change of TOI, namely the ΔTOI (ΔTOI = final TOI - initial TOI). In addition to these values, mean, maximum and minimum TOI during ambulance transportation were also assessed. This device can also calculate the chest compression (CC) rate per minute using the waveform of O_2Hb and HHb. Additional data were extracted from pre-hospital and hospital records according to Utstein style [23]. Pre-hospital records included the information about sex, age, the initial cardiac rhythm of cardiopulmonary arrest (CPA), witness, bystander CPR and the time from the EMS call to the scene arrival and hospital arrival. The hospital records included the causes of CPA, the amount of epinephrine received during CPR procedure, laboratory data and the outcomes in ED.

Primary aim of the statistical analysis was to examine the association between ΔTOI and ROSC. Secondary aims were to examine the association between other TOI values such as initial, final, mean, maximum and minimum and ROSC. In addition, different cut-off values of ΔTOI were examined as predictors of ROSC. We also examined the correlation between mean CC rate and ΔTOI using spearman's rank correlation coefficient (r).

Continuous variables were summarized as median with interquartile range (IQR) or mean with standard deviation (SD). Distribution of continuous variables was examined using Shapiro-Wilk test. When the variables were normally distributed, unpaired t-tests were conducted. On the other hand, when the variables were positively or negatively skewed, we used Mann-Whitney U-tests. Categorical variables were summarized using counts and percentages, compared using chi-square test. Multiple regression analysis was conducted to examine the association between ΔTOI and Utstein variables after controlling for the potential confounding effects. Receiver Operating Characteristic (ROC) analysis was also conducted to determine the specific cut-off values predictive of ROSC. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 25 (SPSS Inc., Chicago, IL, USA) and R statistical software (V.1.0.143, R Foundation for Statistical Computing).

Results

Of 104 patients that were transported to our ED, TOI was measured in 81 (77.8 %) patients and 23 were excluded. The reasons for exclusion were; 19 patients were due to apparatus dysfunction during initial CPR procedure (i.e.: attachment failure of probes and start-up delay), 3 patients achieved ROSC before arrival at ED and one patient had CPA due to trauma. Among those who were included in this study (n = 81), 26 (32.1 %) achieved ROSC (ROSC group) and 55 (67.9 %) did not achieve ROSC (non-ROSC group) (Fig. 1).

Patients' demographics and key characteristics according to Utstein style were compared between ROSC and non-ROSC group (Table 1). Patients in ROSC group were younger and were more likely to have their cardiac event witnessed. Furthermore, patients in this group exhibited higher shockable initial rhythm and suspected cardiac cause of CPA. Blood gas analysis showed that patients in ROSC group had significantly lower lactate concentration and higher PaO_2 than patients in non-ROSC group.

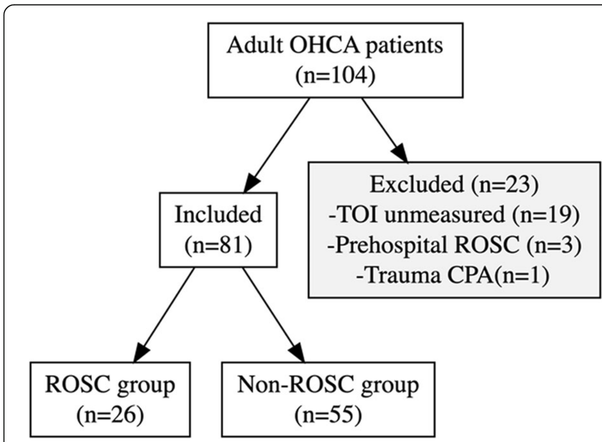

Fig. 1 Flow chart of patient inclusion. Abbreviations: OHCA Out-of-hospital cardiac arrest, TOI Tissue oxygenation index, ROSC Return of spontaneous circulation, CPA Cardiopulmonary arrest.

Table 1 Patient characteristics

	ROSC group ($n = 26$)	Non-ROSC group ($n = 55$)	
Male, n (%)	19 (73.1)	32 (57.1)	0.166
Age (years), mean (SD)	72.4 (13.9)	80.8 (11.8)	0.006
Shockable rhythm, n (%)	7 (26.9)	1 (1.8)	< 0.01
Witness, n (%)	16 (61.5)	9 (16.4)	< 0.01
Bystander CPR, n (%)	10 (38.5)	24 (42.9)	0.707
Time from EMS call to the scene (min), median [IQR]	9 [8-10]	8 [6-10]	0.099
Time from EMS call to the hospital (min), median [IQR]	32 [27–36]	34 [29–40]	0.245
Time during ambulance (min), median [IQR]	8.5 [6-10]	9 [7-12]	0.089
Epinephrine dose during ambulance (mg), median [IQR]	1 [0–2]	1 [0–3]	0.48
Suspected cardiac cause, n (%)	11 (42.3)	3 (5.4)	< 0.01
Blood gas analysis	ROSC group	Non-ROSC group	
pH, mean (SD) [a]	6.94 (0.19)	6.75 (0.22)	< 0.01
$PaCO_2$ (Torr), median [IQR] [a]	65.3 [44.2–90.0]	90.5 [67.4122.3]	0.012
PaO_2 (Torr), median [IQR] [a]	96.2 [31.0-274.9]	38.7 [22.5–77.9]	0.007
HCO_3^- (mmol/L), mean (SD) [a]	13.8 (6.2)	12.7 (5.2)	0.427
Blood sugar (mg/dl), median [IQR] [b]	265 [209–388]	173 [102–268]	0.013
Lactate (mmol/L), mean (SD) [c]	9.7 (4.6)	13.4 (4.4)	0.002
Potassium (mmol/L), mean (SD) [d]	5.5 (1.5)	7.2 (1.7)	< 0.01

[a]The number of non-ROSC group was 44
[b]The number of non-ROSC group was 33
[c]The number of non-ROSC group was 38
[d]The number of non-ROSC group was 30
Abbreviations: *CPA* cardiopulmonary arrest, *CPR* cardiopulmonary resuscitation, *EMS* emergency medical services, *ROSC* return of spontaneous circulation, *TOI* tissue oxygenation index

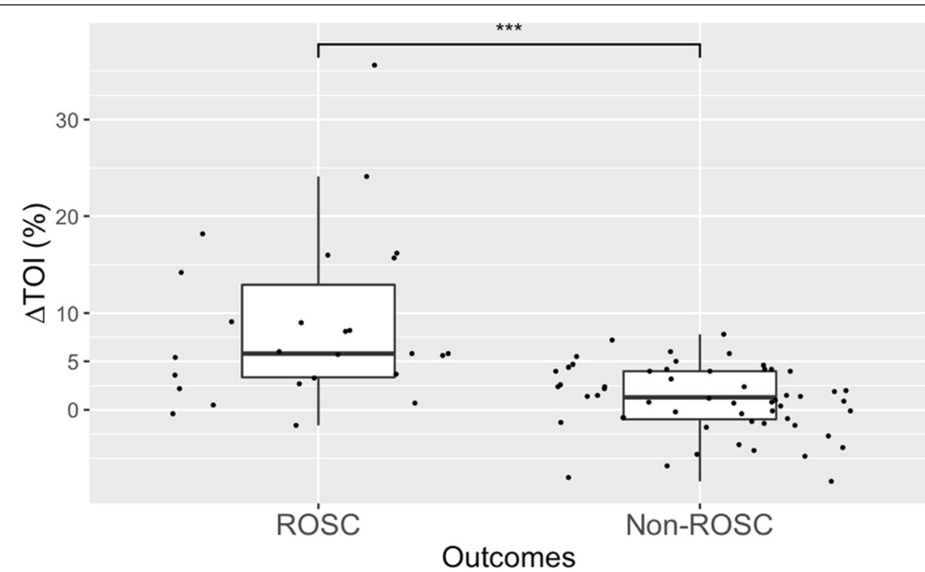

Fig. 2 Distributions of ΔTOI for patients with out-of-hospital cardiac arrest (OHCA) by ROSC status***: $p < 0.01$. Abbreviations: ROSC Return of spontaneous circulation, TOI Tissue oxygenation index

Table 2 Various type of tissue oxygenation index (TOI) and outcomes

	ROSC group (*n* = 26)	Non-ROSC group (*n* = 55)	*p*-value
ΔTOI (%), median [IQR]	5.8 [3.2–14.6]	1.3 [-1.1-1.3]	< 0.01
Initial TOI (%), mean (SD)	33.6 (8.5)	29.6 (7.6)	0.034
Final TOI (%), mean (SD)	42.2 (10.4)	30.6 (8.2)	< 0.01
Maximum TOI (%), mean (SD)	52.8 (14.0)	42.8 (10.5)	< 0.01
Minimum TOI (%), mean (SD)	26.8 (9.2)	19.2 (9.6)	< 0.01
Mean TOI (%), mean (SD)	37.9 (9.0)	30.3 (8.0)	< 0.01

Abbreviations: *TOI* tissue oxygenation index, *ROSC* return of spontaneous circulation

Primary outcome measurement

ΔTOI was significantly higher in ROSC group (median 5.8 % [IQR3.2 to14.6 %]) than non-ROSC group (median 1.3 % [IQR-1.1 to -1.3 %]) ($p < 0.01$) (Fig. 2).

Secondary outcome measurement

Initial, final, minimum, maximum and mean TOI values were also significantly higher in ROSC group than that in non-ROSC group (Table 2).

Table 3 shows crude and adjusted odds ratio of achieving ROSC based on logistic regression analysis. Among different TOI values, ΔTOI had highest odds ratio for predicting ROSC based on bivariate logistic regression analysis. Even after adjusted by witness status and shockable rhythm, the association between ΔTOI and ROSC was statistically significant, although other TOI values were not. (Table 3).

Figure 3 shows correlation between CC rate and ΔTOI during ambulance transportation. Overall, there was statistically significant positive correlation between CC rate and ΔTOI ($r = 0.65$). ROSC group had stronger positive correlation between CC rate and ΔTOI ($r = 0.82$) than non-ROSC group ($r = 0.50$).

ROC analysis showed that ΔTOI cut-off value 5 % had the highest sensitivity and specificity to predict ROSC (65.4 and 89.3 %, respectively). The area under the ROC curve (AUC) was 0.82 (95 % confidence interval, 0.72–0.93) (Fig. 4). Patients with OHCA whose ΔTOI was ≤-2.0 % did not achieve ROSC, whereas patients with OHCA whose ΔTOI was ≥ 8.0 % achieved ROSC (Fig. 5).

Table 3 Odd ratio of ROSC prediction for each TOI and Δ TOI after adjustment for baseline variables

	Crude OR (95 % CI)	Adjusted OR ratio (95 % CI)
Δ TOI	1.42 (1.18–1.71)	
Initial TOI	1.07 (1.00-1.15)	
Final TOI	1.21 (1.10–1.34)	
Maximum TOI	1.08 (1.03–1.13)	
Minimal TOI	1.09 (1.03–1.16)	
Mean TOI	1.17 (1.03–1.29)	
Adjusted-ΔTOI		1.46 (1.16–1.8)

Adjusted for shockable rhythm and witness which were best 2 predictive indicators for ROSC
Abbreviations: *ROSC* return of spontaneous circulation, *TOI* tissue oxygenation index, *OR* odds ratio

Discussion

To the best of our knowledge, this is the first study conducted in Japan which demonstrated that ΔTOI is a significant predictor of ROSC even after adjusting for Utstein variables in a pre-hospital setting. Several other studies also reported regional cerebral oxygen saturation (rSO_2) as a correlate of ROSC status in a hospital setting [24]. Together, these studies emphasize that initial rSO_2 as well as increase in rSO_2 (ΔrSO_2) could be regarded as a useful parameter to assess ROSC in hospital and pre-hospital settings [19, 20].

Utstein variables are widely used to determine the predictive indicators associated with ROSC [23]. Among these variables, initial cardiac rhythm, witness, bystander CPR, time from EMS call to scene arrival and cardiac cause are especially known as core Utstein variables [24]. Similar to our previous study based on hospital setting, we also observed in this study that adding witness status and initial shockable rhythm to ΔTOI in pre-hospital setting increased the accuracy of ROSC prediction [13]. Other study with larger sample size also demonstrated that witness and shockable rhythm had significant association with ROSC [20]. We also observed stronger correlation between CC rate and ΔTOI among patients in the ROSC group than in non-ROSC group. Thus, ΔTOI might also be considered as an indicator of high-quality CPR in addition to its effectiveness as a ROSC predictor.

Determining the cut-off values might suggest that TOI could potentially replace pulse checks during CPR, which could reduce hands-off time. TOI increases when CPR delivers O_2Hb to the brain. ΔTOI as a dynamic value might reflect the quality of CPR. $\Delta rSO_2 \geq 15\,\%$ during CPR procedure showed higher chance of achieving ROSC in a previous study[20]. In our study, we observed that ΔTOI cut-off value 5.0 % could predict

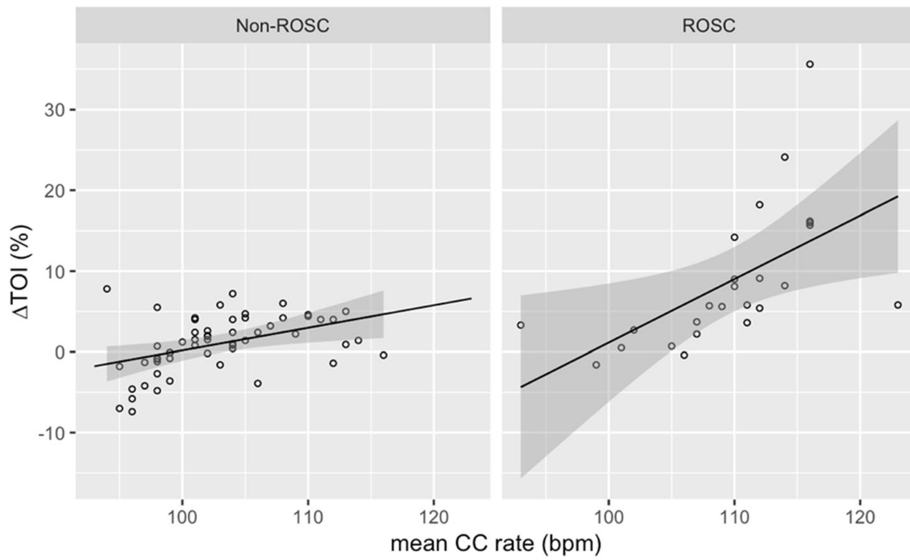

Fig. 3 Correlation between ΔTOI and mean CC rateThe shaded region indicated 95 % CI. Abbreviations: ROSC Return of spontaneous circulation, TOI Tissue oxygenation index, CC Chest compression, CI Confident interval

ROSC. This discrepancy was due to difference in using the parameter as predictors in the respective study (ΔrSO_2 v.s. ΔTOI) as well as differences in the calculation method[13]. Different cut-off values of ΔTOI generated in this study to predict the probability of ROSC (ΔTOI ≤-2 % did not achieve ROSC ≥ 8 % achieved ROSC) are study-specific values only. Although these values are based on the findings of our study, future studies might shed more light on appropriate cut-off values.

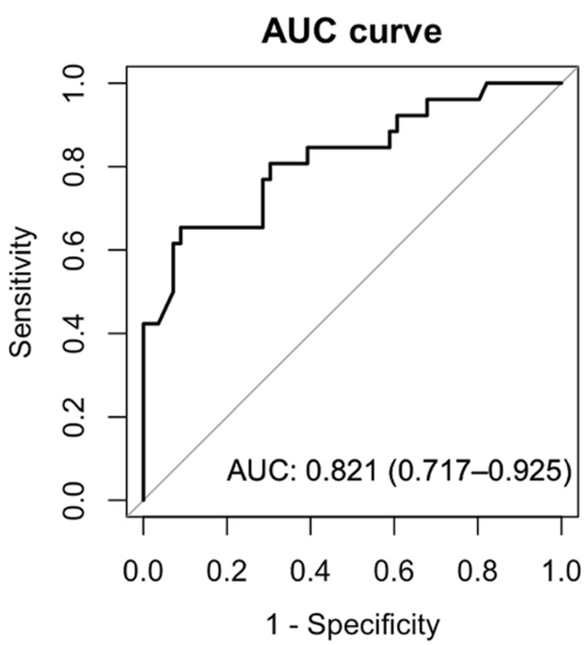

Fig. 4 ROC curve with ΔTOI as a predictor of ROSC. Abbreviation: AUC Area under the curve

CCR-1® can measure mean CC rate from the waveform of O_2Hb and HHb. ΔTOI and CC rate showed significant positive correlation in this study with stronger correlation in ROSC group than non-ROSC group. Appropriate CC rate based on CPR guidelines is 100–120 per minute [5]. Surprisingly, 23 out of 81 people (28.4 %) could not comply with the latest CPR guidelines in this study. As in the narrow space of the ambulance, chest compressions are not always performed according to the guidelines, visual NIRS monitoring might replace the evaluation of CPR quality.

ΔTOI as a dynamic value was more specific indicator to predict ROSC than other static TOI values. These results are similar to other studies based on NIRS monitoring in pre-hospital setting [19, 20]. TOI is expressed as the ratio of O_2Hb and HHb, and it increases with O_2Hb level. Blood gas analysis showed that ROSC group had higher PaO_2 and lower $PaCO_2$ than non-ROSC group. Experimental animal CPR model also showed that rSO_2 was lower with 50 % oxygen than 100 % oxygen [25]. Together, these studies support the use of TOI as a dynamic value to predict ROSC in both pre-hospital and hospital settings.

Our study has several limitations. This study was conducted in a single center, and the sample size was small because only 5 EMS teams could be equipped with portable NIRS device. There were many date errors attached to probe performance. Also, we had only a few subjects with neurological event, therefore we could not evaluate the association between TOI values and neurological

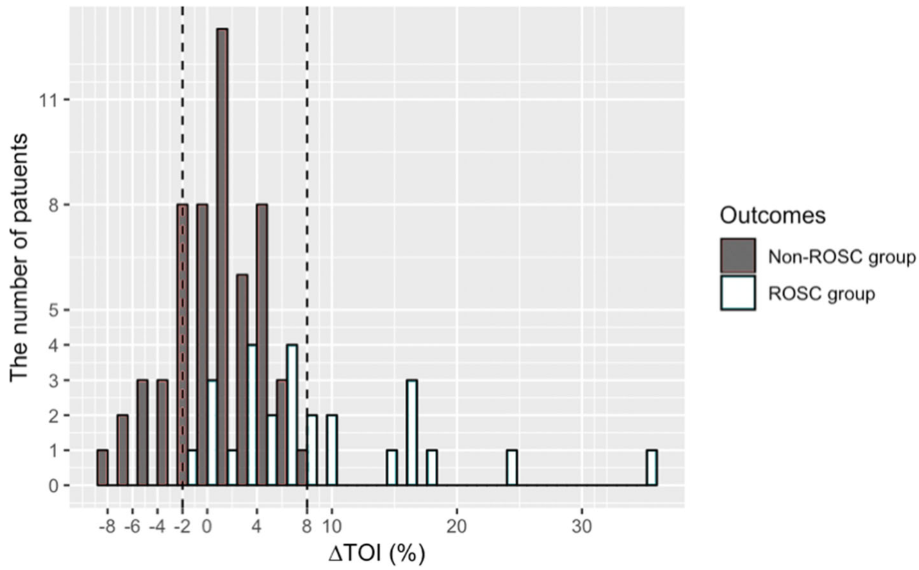

Fig. 5 Δ tissue oxygenation index (TOI) of each patient. Abbreviation: ROSC Return of spontaneous circulation

outcomes. Portable NIRS device could not measure the depth of CC during CPR and we could only evaluate the correlation between mean CC rate and ΔTOI. Finally, we did not have laboratory data and, therefore, could not evaluate the change in PaO_2 during ambulance transportation.

Conclusions

In this pilot study, we demonstrated the feasibility of ΔTOI as a dynamic value rather than single static value among OHCA patients in a pre-hospital setting. ΔTOI can be considered as a predictor of ROSC and can guide CC rate. Other findings, such as, an absolute increase of 8 % or higher in TOI during pre-hospital CPR procedure is associated with ROSC and absolute decrease of 2 % or lower from the baseline is associated with non-ROSC, would be helpful to generate future cut-off values in this regard.

Abbreviations

TOI: Tissue oxygenation index; NIRS: Near infrared spectroscopy; ROSC: Return of spontaneous circulation; OHCA: Out-of-hospital cardiac arrest; CPR: Cardio-pulmonary resuscitation; AHA: American Heart Association; CPA: Cardiopulmonary arrest; StO_2: Oxygen saturation of brain tissue; O_2Hb: Oxygenated hemoglobin; HHb: Deoxygenated hemoglobin; ΔStO_2: Increase in StO_2; EMS: Emergency medical service; IRB: Institutional Review Board; ALS: Advanced Life Support; ED: Emergency department; TOI: Tissue oxygenation index; CC: Chest compression; IQR: Interquartile range; SD: Standard deviation; ROC: Receiver Operating Characteristic; rSO2: Regional cerebral oxygen saturation

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Authors' contributions

JT, SF and YT conceived the research idea and designed the study. JT, KM and TK supervised the study and collected the data. JT and MR provided statistical advice on study design and analyzed the data. SF chaired the data oversight committee. JT, SF and MR drafted the first version of the manuscript, and all authors contributed substantially to the subsequent version and revisions. SF takes public responsibility of the contents of this paper. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of St. Marianna University School of Medicine (IRB: 3022). Informed consent from the patients was waived because this study contains de-identified information, which does not affect the rights and welfare of the patients.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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