Abstract

correlation with ETCO₂.

Keywords

ORIGINAL RESEARCH



Correlation of EEG-based brain resuscitation index and end-tidal carbon dioxide in porcine cardiac arrest model

Dong Sun Choi^{1,2,3,†}, Heejin Kim^{4,†}, Ki Jeong Hong^{2,5,6,}*, Sang Do Shin^{2,6}, Hee Chan Kim^{3,7}, Yong Joo Park⁸, Tae Han Kim^{2,9}, Young Sun Ro², Kyoung Jun Song^{2,10}, Ki Hong Kim^{2,10}

Evaluation and monitoring perfusion of vital organs is important during resuscitation

from cardiac arrest. We developed a non-invasive electroencephalogram (EEG) based

brain resuscitation index (EBRI) as a physiologic indicator measuring organ perfusion

during cardiopulmonary resuscitation (CPR) and evaluated the correlation of EBRI and

end-tidal carbon dioxide (ETCO₂). A randomized crossover experimental study using

a porcine cardiac arrest model was designed. After 1 minute of untreated ventricular

fibrillation, 10 periods of higher-quality CPR (compression depth 5 cm and compression

rate 100/min) for 50 seconds and lower-quality CPR (compression depth 3 cm and

compression rate 60/min) for 50 seconds were performed in alternation. EBRI was

calculated from the single EEG channel with the lowest noise. Mixed-model analysis

was conducted to compare the differences of hemodynamic parameters, $ETCO_2$, and

EBRI between higher-quality CPR periods and lower-quality CPR periods. Pearson's

correlation coefficient was calculated to assess correlation between EBRI and ETCO₂.

The experiment was performed on 5 female swine (44.6 \pm 2.8 kg). Higher-quality CPR

showed significantly higher delta EBRI (median [IQR] 0.1 [0.0–0.2]) than did lower-

quality CPR (median [IQR] -0.1 [-0.2-0.0], p < 0.01). EBRI had a statistically moderate

positive correlation with $ETCO_2$ (r = 0.51). In this porcine cardiac arrest model,

EBRI was successfully obtained during resuscitation and had a statistically moderate

Cardiopulmonary resuscitation; Electroencephalogram; End-tidal CO₂

¹Department of Emergency Medicine, Uijeongbu Eulji Medical Center, 11759 Uijeongbu, Republic of Korea ²Laboratory of Emergency Medical Services, Biomedical Research Institute, Seoul National University Hospital, 03080 Seoul, Republic of Korea ³Department of Emergency Medicine, College of Medicine, Eulji University, 34824 Daejeon, Republic of Korea ⁴Clinical Trial Center, Seoul National University Hospital, 03080 Seoul, Republic of Korea

⁵Department of Emergency Medicine, Seoul National University Hospital, 03080 Seoul, Republic of Korea ⁶Department of Emergency Medicine, College of Medicine, Seoul National University, 03080 Seoul, Republic of Korea

⁷Department of Biomedical Engineering, College of Medicine, Seoul National University, 03080 Seoul, Republic of Korea

⁸Department of Emergency Medicine, Gyeongsang National University Changwon Hospital, 51472 Changwon, Republic of Korea

⁹Department of Emergency Medicine, Seoul National University Boramae Medical Center, 07061 Seoul, Republic of Korea

¹⁰Seoul National University Hospital Biomedical Research Institute, 03080 Seoul, Republic of Korea

*Correspondence

emkjhong@gmail.com; ssberg@snu.ac.kr (Ki Jeong Hong) [†] These authors contributed equally.

1. Introduction

Out-of-hospital cardiac arrests (OHCA) occur in more than 74 per 100,000 people annually, and only 8% of all cardiac arrest patients show good neurological recovery in the United States [1–3]. Although the survival rate for cardiac arrests is steadily rising, the rate of good neurological recovery remains low [2–5]. To improve clinical outcomes of cardiac arrest, it is important to deliver high-quality cardiopulmonary resuscitation (CPR) [6, 7]. Immediate and high-quality chest compression is a core of the chain of survival [6, 8, 9].

To achieve high-quality CPR, it is recommended to measure the quality of chest compressions and provide real-time feedback. Thus, diverse CPR feedback devices have been developed which commonly assess the depth, frequency, and chest recoil of chest compressions [10–12]. However, measurement of the depth and rate of chest compressions cannot directly measure the current status of organ perfusion during CPR. Recently, physiologic parameters, including end-tidal carbon dioxide (ETCO₂), diastolic arterial pressure (DBP), and coronary perfusion pressure (CoPP), have been recommended as indicators of assess systemic perfusion of cardiac arrest victims [13]. However, vascular access is required to achieve DBP or CoPP. During CPR, ETCO₂ can be monitored using bag mask ventilation or advanced airway, including supraglottic airways and endotracheal intubation. However, current guidelines recommend use of ETCO₂ obtained under endotracheal intubation as an outcome predictor [14]. It is difficult to implement endotracheal intubation or vascular access for basic life support by laypersons or prehospital care by lower-level emergency medical technicians (EMTs).

Electroencephalography (EEG), including somatosensoryevoked potential (SSEP) and amplitude-integrated EEG (aEEG), reflects brain activity and has been used for predicting prognosis in post-cardiac arrest care [15–17]. However, a few case reports have reported about EEG application during cardiac arrest [18, 19]. They showed that cerebral electrical activity in EEG is associated with spontaneous circulation. In shock status, experimental studies have shown that EEG and bi-spectral index (BIS) are associated with cerebral hypoperfusion [20]. They attempted to compare BIS and CPR quality, although significant association was not identified due to external artifacts.

In a previous study, we developed an EEG-based brain index (EBRI) derived from EEG signals by machine learning techniques, which could estimate cerebral perfusion pressure (CePP) accurately in a porcine cardiac arrest model [21]. In this study, we showed that EBRI correlates with ETCO₂, which is known as indicator of CPR quality using EEG signals in cardiac arrest swine models. EBRI could reflect the quality of chest compressions as ETCO₂ does. The objective of this study was to evaluate whether EBRI and ETCO₂ are correlated in a swine cardiac arrest model. The hypothesis of this study was that EBRI is correlated with ETCO₂ during CPR in a swine cardiac arrest model.

2. Methods

2.1 Study design and setting

We designed a crossover animal experimental study using a porcine ventricular fibrillation (VF) cardiac arrest model. The experimental protocol is shown in Fig. 1. Surgical procedures to induce VF were performed under general anesthesia. After 1 minute of untreated VF, 10 2-minute cycles of chest compressions were delivered and physiologic indicators including EBRI were measured. Each 2-minute chest compression cycle was composed of a higher-quality CPR (HQ-CPR) phase for 1 minute and a lower-quality CPR (LQ-CPR) phase for 1 minute. During HQ-CPR phase, an emergency medical technician (EMT) delivered manual chest compressions at the rate of 100 times per minute with a depth of 5 cm. Compression at the rate of 60 times per minute with a depth of 3 cm was conducted during LQ-CPR phase. During each CPR phase, a real-time CPR feedback device (X-Series, Zoll Medical Corporation, Chelmsford, MA, USA) was used and an EMT received realtime feedback information and adjusted the quality of CPR according to HQ-CPR and LQ-CPR parameters. Each HQ-CPR and LQ-CPR session lasted for 50 seconds. A 10-second pause was included for transitions between sessions. After a total of 20 minutes of the experimental period, 1 mg of epinephrine was administered via IV and defibrillation was performed with a 200J biphasic shock. Return of spontaneous circulation (ROSC) was attempted and 2 minutes of HQ-CPR. If ROSC was not achieved, a second 200J defibrillation and 2 minutes of CPR were performed, and then ROSC was checked. Upon completion of the experimental protocol, pigs were sacrificed by injection of 20 mL of saturated potassium chloride.

2.2 Experimental animals and housing

Domestic pigs aged approximately 3 months were studied in this research. The animals were maintained in an accredited AAALAC International (#001169) facility in accordance with the Guide for the Care and Use of Laboratory Animals, 8th Edition, NRC (2010). After 24 hours of fasting, the pigs were initially sedated with an intramuscular injection of 5 mg/kg of tiletamin/zolazepamhypochloride (Zoletil®, Virbac laboratories, France) and 2 mg/kg of xylazine (Rompun®, Bayer Korea, South Korea), followed by inhaled isoflurane at a dose of 1–1.5%.

2.3 Surgical preparation and experimental procedure

While the pigs were sedated with spontaneous ventilation, endotracheal intubation was performed using a 7.5 mm internal diameter endotracheal tube. The pigs were ventilated with a volume-control ventilator adjusted for a tidal volume of 12 mL/kg with 12 breath cycles per minute. The tidal volume was adjusted so that the partial pressure of carbon dioxide in arterial blood (PaCO₂) remained approximately 40 mmHg and partial oxygen tension in arterial blood (PaO₂) was maintained above 80 mmHg.

With the pigs in the supine position, a 2 mm ultrasonic flow probe (MA2PSB, Transonic Systems Inc., Ithaca, NY, USA) was placed around a surgically dissected internal carotid artery to measure carotid blood flow (CBF). CBF was measured by a one-channel perivascular flowmeter (T420, Transonic Systems Inc., Ithaca, NY, USA). A Mikro-tip® Transducer was inserted through the left femoral artery under ultrasonic guidance and placed in the descending thoracic aorta to measure the aortic blood pressure (ABP). Another Mikro-tip® Transducer was inserted in the right atrium via the right external jugular vein to record the right atrial pressure (RAP). We used PowerLab (PowerLab 16/35, AD Instruments, Dunedin, New Zealand) data acquisition hardware to obtain other bio-signals simultaneously. During the experiments, the device acquired and displayed biological signals including ETCO2, CBF, ABP, and RAP. $ETCO_2$ was measured with a CO_2 analyser (CapStar-100, CWE Inc., Ardmore, PA, USA) pre-calibrated with a single calibrated CO₂ gas at 5% and with room air. The depth of anesthesia of the experimental animals was monitored by attaching a BIS monitor. The concentration of isoflurane before induction of VF was adjusted to maintain light sedation status (BIS 70-90).

VF was induced by delivering direct current via a pacing wire placed in the right ventricle. VF was confirmed by the electrocardiogram (ECG) change in lead II and the abrupt drop in the aortic blood pressure (ABP) wave. The ventilator



FIGURE 1. Experimental protocol. Abbreviations: VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; HQ, higher-quality; LQ, lower-quality.

was disconnected and the animal was left untreated VF for 1 minute. Then, in the supine position, 10 cycles of chest compression including HQ-CPR and LQ-CPR were performed in alternation. Manual ventilation with 100% oxygen using a self-inflation bag was provided with a ventilation rate 10/min while collecting physiologic parameters including EBRI. After completion of the experiment protocol, the pigs were sacrificed with a 20 mL injection of saturated potassium chloride.

2.4 EEG signal measurementss

A four-channel digital EEG monitor was developed inhouse to measure the scalp EEG using a micro-controller (ATmega168A, Microchip Technology, USA) and an analogue-to-digital converter (ADC) specialised for biopotential measurement (ADS1294, Texas Instruments, USA). The analogue front-end circuit comprised amplifiers with a gain of 2400 V/V, a noise level under $\pm 3 \mu$ Vp-p, and a band-pass filter with a frequency range of 0.5 Hz to 47 Hz. The ADC operated at a sampling frequency of 250 Hz and sent digitised EEG data to the microcontroller. The microcontroller transmitted the received data to a laptop computer via a Bluetooth module (FB155C, Firmtech, Korea). In the laptop computer, data-acquisition software based on the LabVIEW platform (NI LabVIEW 2013, National Instruments, USA) displayed and stored the EEG data in real time.

To calculate EBRI, we measured EEG signals in real time during the experiment. With the pigs in the prone position, silver/silver chloride electrodes (2223H, 3M Health Care Limited, Bracknell, UK) were attached to collect four-channel EEG signals under unipolar montage and secured by surgical tape to prevent detachment during CPR. The reference and ground electrodes were attached on the mastoid area and four active electrodes were attached on the frontal area of the scalp (**Supplementary Fig. 1**). A single EEG channel with the lowest noise was used.

2.5 EBRI calculation

EEG and ETCO₂ data measured during CPR were analyzed to establish the EBRI formula. EEG was processed to derive four parameters every 0.5 seconds; burst suppression ratio (BSR), relative beta ratio (BetaR), relative delta ratio (DeltaR), and relative synchrony of fast and slow wave (SFS). All four EEG parameters are summarized in **Supplementary Table 1**.

Mean ETCO₂ data were also obtained within the same time interval. Thereafter, linear regression was applied to find the relationship between EEG parameters as independent parameter and the mean ETCO₂ as dependent parameter. Fivefold cross-validated linear regression models were derived to obtain EBRI for each particular animal. To obtain EBRI for animal #1, for example, all the EEG and ETCO₂ data from the other 4 animals were used together. The final EBRI formula was established from the data of all 5 animals. Specific coefficients and y-intercept were denoted on the formula.

$$\begin{split} \text{EBRI} &= a + b_1 * \text{BSR} + b_2 * \text{ BetaR } + b_3 * \text{ SynchFastSlow } + b_4 * \text{ DeltaR} \\ & (a = 26.047, b_1 = -0.141, b_2 = 4.481, b_3 = 2.821, b_4 = 5.452) \end{split}$$

Delta EBRI calculated the amount of change in EBRI for each 0.5 seconds.

2.6 Statistical analysis

EBRI was calculated using MATLAB (MATLAB R2015b, The Mathworks, Natick, MA, USA). Systolic blood pressure (SBP) was measured at a point immediately preceding the release phase and DBP was measured at a point immediately preceding the compression phase during closed chest compressions [22]. The mean arterial pressure (MAP) was calculated as the mean value of ABP during each compression cycle. Systolic right atrial pressure (sRAP), diastolic atrial pressure (dRAP), and mean right atrial pressure (mRAP) were measured at the highest, the lowest, and mean points of the RAP curve from each cardiac cycle. Coronary perfusion pressure (CoPP) was calculated by subtracting dRAP from DBP [22].

All statistical analysis was performed using SAS version 9.4

Parameters	Baseline		Higher-quality CPR		Lower-quality CPR		<i>p</i> -value ^{<i>a</i>}
	Median	(IQR)	Median	(IQR)	Median	(IQR)	
SBP, mmHg	105	(101–116)	89	(76–104)	42	(34–54)	< 0.01
DBP, mmHg	75	(74–84)	24	(15–30)	22	(17–27)	$< 0.01^{b}$
MAP, mmHg	90	(87–94)	38	(31–48)	25	(19–31)	$< 0.01^{b}$
sRAP, mmHg	7	(7–8)	181	(112–212)	44	(33–68)	< 0.01
dRAP, mmHg	3	(2–3)	7	(6–8)	9	(7–11)	$< 0.01^{b}$
mRAP, mmHg	5	(5–5)	47	(34–56)	20	(16–23)	$< 0.01^{b}$
ETCO ₂ , mmHg	46	(43–46)	23	(17–26)	18	(14–22)	$< 0.01^{b}$
CBF, mL/min	323	(243–374)	207	(160–352)	53	(16–119)	< 0.01
CoPP, mmHg	80	(75–84)	16	(8–22)	13	(9–17)	$< 0.01^{b}$
BIS	81	(78–84)	16	(8–28)	30	(11–54)	$< 0.01^{b}$

TABLE 1. Hemodynamic parameters according to CPR quality.

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; sRAP, systolic right atrial pressure; dRAP, diastolic right atrial pressure; mRAP, mean right atrial pressure; ETCO₂, end-tidal CO₂; CBF, carotid blood volume over 2seconds; CoPP, coronary perfusion pressure.

^a p-value for the fixed effect of CPR quality between the high and low CPR groups in linear mixed model.
^b p-value for interaction of the time within CPR period and CPR quality <0.05.

(SAS Institute Inc., Cary, NC, USA). Data were expressed as median with interquartile range (IQR). We used a linear mixed model to test the fixed effect of CPR quality on physiologic parameters including SBP, DBP, MAP, sRAP, dRAP, mRAP, ETCO₂, CoPP, CBF and EBRI, adjusted for the interaction of the time within CPR period and CPR quality. Pearson's correlation coefficient was calculated to assess correlation between EBRI and ETCO₂.

3. Results

Five female domestic pigs weighing mean 44.6 (SD: 2.7) kg were included in the analysis. EBRI was calculated every 0.5 seconds and a total of 100 values were derived for each 50 second epoch of each HQ-CPR or LQ-CPR. In animal #4, EBRI was not obtained due to excess of EEG noise after the 16th CPR segment. EBRI and hemodynamic parameters were measured every 0.5 seconds. A total of 9520 data points was used for analysis. None of the 5 pigs achieved ROSC.

The hemodynamic parameters at baseline and during CPR shown in Table 1. HQ-CPR showed significantly higher DBP than did LQ-CPR (median [IQR] HQ-CPR: 24 [15–30] mmHg, LQ-CPR: 22 [17–27] mmHg, p < 0.01). HQ-CPR showed higher ETCO₂ than did LQ-CPR (median [IQR] HQ-CPR: 23 [17–26] mmHg, LQ-CPR: 18 [14–22] mmHg) and higher CoPP than did LQ-CPR (median [IQR] HQ-CPR: 16 [8–22] mmHg, LQ-CPR: 13 [9–17] mmHg). HQ-CPR also showed higher CBF than did LQ-CPR (median [IQR] HQ-CPR: 207.6 [160–352] mL/min, LQ-CPR: 53 (16–119) mL/min).

According to CPR quality, HQ-CPR showed significantly lower EBRI than did LQ-CPR (median [IQR] HQ-CPR: 14.1 [11.5–19.1], LQ-CPR: 15.0 [12.0–18.9]). However, HQ-CPR showed higher values of delta EBRI than did LQ-CPR (median [IQR] HQ 0.1 [0.0–0.2], LQ –0.1 [–0.2–0.0]) (Table 2). EBRI and ETCO₂ over time for each animal are shown in Fig. 2. In HQ-CPR, EBRI value was increased, while EBRI value was decreased during the period of LQ-CPR.

The correlations between ETCO₂ and EBRI in all experimental animals are shown in Fig. 3. In all experimental animals, there was a moderate positive correlation between ETCO₂ and EBRI (Pearson r = 0.51, adjusted R-squared = 0.24). However, no significant correlation was observed between EBRI and CoPP (Pearson r = -0.02, adjusted R-squared = 0.005).

4. Discussion

This study was conducted to evaluate whether EBRI during CPR is correlated with $ETCO_2$. EBRI was correlated with $ETCO_2$ with a Pearson correlation coefficient of 0.51. Delta EBRI was significantly higher in HQ-CPR than in LQ-CPR. These findings suggest that EBRI during CPR may be changed according to systemic perfusion that changes according to CPR quality.

In this study, DBP, ETCO₂, and CoPP were significantly higher in HQ-CPR than in LQ-CPR, although the differences between HQ-CPR and LQ-CPR were small. The small differences might be because median values of the indicators were compared during CPR. There was an interaction effect of CPR quality and elapsed time within CPR in the changes of DBP, ETCO₂, and CoPP (p < 0.05). Among the CPR parameters, ETCO₂, DBP, and CoPP gradually increased during HQ-CPR and decreased during LQ-CPR (Supplementary Fig. 2). The median value of EBRI during HQ-CPR was lower than that of LQ-CPR. EBRI responded promptly to changes in CPR quality. It was continuously elevated during HQ-CPR (Supplementary Fig. 2D). This elevation might be attributable to the change of average EEG parameters. To reduce variations, each EEG parameter was smoothed with a moving average over 15-seconds. This method might result

The best of the stimuting brook a containing to of it quantify										
Parameters	Higher-	quality CPR	Lower-	p-value ^{b}						
	Median	(IQR)	Median	(IQR)						
EBRI	14.1	(11.5–19.1)	15.0	(12.0–18.9)	< 0.0 c					
delta EBRI a	0.1	(0.0–0.2)	-0.1	(-0.2-0.0)	< 0.01					

TABLE 2. EBRI estimating ETCO₂ according to CPR quality.

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range; EBRI, EEG-based brain resuscitation index.

^{*a*} delta EBRI calculated the amount of change in EBRI for 0.5 seconds.

^b *p*-value for the fixed effect of CPR quality between the high and low CPR groups in linear mixed model.

 c p-value for interaction of the time within CPR period and CPR quality < 0.05.



FIGURE 2. Trend of ETCO₂ and EBRI over time. Abbreviations: ETCO₂, end-tidal CO₂; ETCO₂-EBRI, ETCO₂ based EEG-based brain resuscitation index.

in a time-lag effect. EBRI was increased consistently during HQ-CPR, but was not decreased immediately during pauses or at the beginning of LQ-CPR. However, delta EBRI, defined as the time differential of EBRI, showed negative values during LQ-CPR. This means that EBRI was decreased on the whole of the periods. Thus, delta EBRI, rather than EBRI, could be a better CPR quality indicator.

In this study, sRAP was excessively high during HQ-CPR

(median 181 mmHg). The mid-sternal area was compressed during CPR, but it is possible that this position was deviated toward the right heart. In addition, as the ablation catheter for VF induction was inserted into the right internal jugular vein, the right atrial catheter might be displaced.

In this study, EEG components including BSR, SFS, BetaR, and DeltaR were used to calculate EBRI. Their changes during the experiment are shown in **Supplementary Fig. 3**. These



FIGURE 3. Correlation between $ETCO_2$ and EBRI (Pearson correlation coefficient = 0.51). Abbreviations: $ETCO_2$, end-tidal CO_2 ; EBRI, EEG-based brain resuscitation index.

parameters have been reported to reflect the level of consciousness. BSR, which is related to the degree of unconsciousness, is defined as the percentage of continuous periods in which EEG is suppressed below $\pm 5 \ \mu$ V. BSR has been reported to be elevated in cerebral perfusion disturbance under general anesthesia [23, 24]. In patients comatose due to post cardiac arrest or stroke, BSR has been reported as a predictor of poor outcome [25, 26]. In this study, it was observed that BSR was not detected until VF induction, increased rapidly from about 20 seconds after VF induction, decreased in HQ-CPR, and increased in LQ-CPR. In the derived EBRI formulation, BSR has a negative coefficient. BetaR and SFS are used as frequency domain-based sub-parameters of BIS. In the combination algorithm that determines BIS, BSR is most prevalent when EEG has the characteristics of light sedation. SFS predominates during EEG activation (excitement phase) and during surgical level of hypnosis [27]. BetaR is the ratio of cumulative spectral power from 30-47 Hz to that from 11-20 Hz. It shows the changes of beta band and gamma

band resulting from the neural activity associated with the cognitive process [28, 29]. BetaR had range from -1.1 to -0.8 before VF induction, then increased over 20 seconds to -0.5 in VF induction, then decreased during HQ-CPR, and increased during LQ-CPR. SFS was computed to reveal the level of non-linear phase coupling [30]. SFS showed large volatility during the VF period, then increased during HQ-CPR and decreased during LQ-CPR. Relative delta ratio (DeltaR), defined as the ratio of the cumulative spectral power from 8–20 Hz to that from 1–4 Hz, was considered because a sudden power decrease in the delta band was followed by conscious recovery [31]. DeltaR was decreased during HQ-CPR and it was increased during LQ-CPR, but overall tended to be decreased over time.

Most studies on using EEG signals in cardiac arrest are focused on the change of EEG profiles at return of spontaneous circulation [18, 19, 32]. In a previous study, BIS was used to predict prognosis of cardiac arrest. However, the effect of artifacts caused by chest compression obscured any relationship between BIS and prognosis [20]. BIS was developed and optimized to use in operation rooms for measuring depth of anaesthesiology, so direct application of BIS on CPR could be affected by chest compression noise. In this study, a fourthorder Butterworth band-reject filter was applied to eliminate fundamental and harmonic noises from EEG signals caused by compression. During HQ-CPR sessions, for example, the fundamental noise of approximately 1.66 Hz and its harmonics could have contaminated the EEG signal, so we filtered out these unwanted artifacts. Therefore, the EBRI model developed in this study could be easily implemented and showed good correlation with CPR quality.

EBRI was developed as a linear regression model that regressed EEG components to ETCO₂. In an animal experiment, Gudipati *et al.* [33] showed that ETCO₂ change paralleled those of cardiac index during cardiac arrest. Also, Lewis et al. [34] showed that ETCO₂ was secondarily correlated with cerebral blood flow during CPR. Cerebral blood flow is known to affect EEG. As cerebral blood flow decreases, EEG proceeds to loss of faster frequency (8-14 Hz), increase of slower frequency (4-7 Hz), increase of slower frequency (1-4 Hz), and suppression [16]. Therefore, the change of EEG according to cerebral perfusion may be related to ETCO₂ during cardiac arrest. In this study, we found that EBRI responded promptly to changes in CPR quality. EBRI was continuously elevated during HQ-CPR (Fig. 2). Use of EBRI derived from EEG signals of brain viability could be a sensitive way to predict the quality of CPR. In the protocol of this study, the CPR interval was only 50 seconds, so the plateau of EBRI of HQ-CPR and LQ-CPR was not confirmed. Because basic life support guidelines recommend 2 minutes of the duration of chest-compression cycle, we designed each HQ-CPR and LQ-CPR coupled session as a 2-minute session in the experiment protocol.

To improve the outcome of cardiac arrest, it is important to measure the quality of CPR. A physiologic indicator is better than using surrogate indicators like accelerometer sensors of chest compression pads or defibrillator patches. Current guidelines recommend to use ETCO2 obtained via endotracheal intubation as an outcome predictor [14], Utilization of ETCO2 obtained with a bag-valve mask state has a low level of evidence [35]. The ETCO₂ sensor may not be measured due to the patient's secretion, water vapor, mucosal plug or kinking of endotracheal tube [13, 36]. Previous studies to use indicators of brain function or brain perfusion such as pupillography and near-infra-red spectroscopy (NIRS) during resuscitation has been attempted [37-39]. As an extension of these attempts, this study was conducted to use EEG as an indicator of brain function during resuscitation. Although the scope of this study did not include prognosis of cardiac arrest, this study showed that EBRI, which is derived from EEG, has significant correlation with CPR quality and a moderate correlation with ETCO₂, an indicator of systemic perfusion during resuscitation. Meanwhile, portable low-cost EEG sensors and acquisition systems have been developed which could be easily applicable to cardiac arrest patients [40]. It is relatively easy to acquire EEG signals as it requires only attaching electrodes to the forehead. Also, EBRI could be calculated automatically and give feedback in real time. It can be used as a candidate for physiologic indicators to measure organ perfusion during

CPR.

This study had several limitations. First, this study was an animal experimental study. The EEG signals and craniocerebral anatomy of pigs are different from those of humans. Second, to remove chest compression-related noise of the EEG raw signal, we used a method to exclude the signal with the corresponding frequency of chest compressions. During this process, loss of EEG signals could have been occurred. Third, each CPR quality interval was only 50 seconds. We collected short periods of data for each level of CPR quality, and the plateau of EBRI information could not be obtained. Fourth, epinephrine was not used during the experiment. Epinephrine is known to elevate CoPP and have a temporary cerebral vasoconstriction effect [41]. Epinephrine was not used to minimize its effect on EEG. However, epinephrine is an essential drug for advanced cardiac life support (ACLS) [14]. Therefore, the results of this study reflect only the situation of basic life support (BLS). Thus, further studies involving the administration of epinephrine are needed for use in ACLS. Fifth, no-flow time of the experiment is 1 minute. As the no flow time increases, irreversible brain injury may be caused, so the no-flow time was limited to 1 minute to obtain a clear EEG. It is difficult to apply to an OHCA situation with a long no-flow time, as this scenario corresponds to a witnessed arrest scenario. Further trials with no flow time of 5 minutes or more are required to be applied to other clinical scenarios. Sixth, sedative medications may have affected EEG. In this study, tiletamin/zolazepam hydrochloride was used for induction of anesthesia. These drugs are an NMDA antagonist and a benzodiazepine, which are widely used for anesthesia of animals. The duration is known to be effective for 20 to 60 minutes and to significantly lower the most band power of EEG [42]. Isoflurane, used as an inhalation anesthetic, is known to suppress EEG [43]. In order to minimize this effect, the experiment was conducted by monitoring BIS before the experiment and adjusting the isoflurane concentration for light sedation (BIS 70-90). Last, the sample size is insufficient. In order to increase the effect size using 5 animals, HQ-CPR and LQ-CPR were performed for each animal by 10 sections, and a total of 48 sets of CPR period were obtained. A linear mixed model was used to analyze repeated measured variables. Thus, the difference between animals was adjusted as a random effect.

5. Conclusions

We derived EBRI from EEG signals during CPR in a swine VF cardiac arrest model. EBRI was correlated with $ETCO_2$ values measured via endotracheal tube. Delta EBRI was significantly higher in high quality CPR period than in low quality CPR period. These findings suggest that EBRI is associated with CPR quality and organ perfusion status. Therefore, EBRI has the potential to be used as an indicator of CPR quality. Further research about EBRI and the prognosis of cardiac arrest are required.

AUTHOR CONTRIBUTIONS

DSC and HK drafted the manuscript and contributed this study equally as the first author. KJH organized and super-

vised the article and taking the responsibility. SDS and HCK designed the concept of the EBRI model. YJP, THK and KHK developed experimental protocol and participated in the experiments. YSR and KJS analyzed the dataset and consult interpretation of the result.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Animal Care and Use Committee of the study institution (IACUC Number: 15-0288-C1A0[1]). All animal care was compliant with the Laboratory Animal Act of the Korean Ministry of Food and Drug Safety. A certified and licensed veterinarian assured the protocols were performed in accordance with the aforementioned guideline.

ACKNOWLEDGMENT

The authors would like to thank Hyun-Jung Kang and Sora Song, the members of the preclinical division of SNUH LEMS, for the help with the animal experiments.

FUNDING

This study was financially supported by the Encouragement Program for the Industries of Economics Cooperation Region (R&D) funded by Korea's Ministry of Trade, Industry and Energy (R0004491).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae. com/mre-signavitae/article/1458343041347534848/ attachment/Supplement%20materials.docx.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

REFERENCES

- [1] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020; 141: e139– e596.
- [2] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke Statistics-2019 update a report from the American Heart Association. Circulation. 2019: 139: e56–e528.
- [3] Sawyer KN, Camp-Rogers TR, Kotini-Shah P, Del Rios M, Gossip MR, Moitra VK, *et al.* Sudden Cardiac Arrest Survivorship: a Scientific Statement from the American Heart Association. Circulation. 2020; 141: e654–e685.

- [4] Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, et al. Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). Resuscitation. 2015; 91: 108–115.
- [5] Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). Circulation. 2004; 110: 3385–3397.
- [6] Cummins RO, Ornato JP, Thies WH, Pepe PE. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. Circulation. 1991; 83: 1832–1847.
- [7] Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K, et al. Continuous Improvements in "Chain of Survival" Increased Survival after out-of-Hospital Cardiac Arrests. Circulation. 2009; 119: 728–734.
- [8] Kleinman ME, Brennan EE, Goldberger ZD, Swor RA, Terry M, Bobrow BJ, et al. Part 5: Adult Basic Life Support and Cardiopulmonary Resuscitation Quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132: S414–S435.
- [9] Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. Resuscitation. 2015; 95: 81–99.
- [10] Cheng A, Brown LL, Duff JP, Davidson J, Overly F, Tofil NM, et al. Improving cardiopulmonary resuscitation with a CPR feedback device and refresher simulations (CPR CARES Study): a randomized clinical trial. Journal of the American Medical Association pediatrics. 2015; 169: 137–144.
- [11] Kirkbright S, Finn J, Tohira H, Bremner A, Jacobs I, Celenza A. Audiovisual feedback device use by health care professionals during CPR: a systematic review and meta-analysis of randomised and nonrandomised trials. Resuscitation. 2014; 85: 460–471.
- [12] Yeung J, Meeks R, Edelson D, Gao F, Soar J, Perkins GD. The use of CPR feedback/prompt devices during training and CPR performance: a systematic review. Resuscitation. 2009; 80: 743–751.
- [13] Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132: S444–S464.
- [14] Callaway CW, Soar J, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, et al. Part 4: Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015; 132: S84– S145.
- [15] Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132: S465–S482.
- [16] Sharbrough FW, Messick JM, Sundt TM. Correlation of Continuous Electroencephalograms with Cerebral Blood Flow Measurements during Carotid Endarterectomy. Stroke. 1973; 4: 674–683.
- [17] Tiainen M, Kovala TT, Takkunen OS, Roine RO. Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. Critical Care Medicine. 2005; 33: 1736–1740.
- [18] England M. The Changes in Bispectral Index during a Hypovolemic Cardiac Arrest. Anesthesiology. 1999; 91: 1947–1947.
- [19] Moss J, Rockoff M. EEG monitoring during cardiac arrest and resuscitation. The Journal of the American Medical Association. 1980; 244: 2750–2751.
- ^[20] Fatovich DM, Jacobs IG, Celenza A, Paech MJ. An observational study of bispectral index monitoring for out of hospital cardiac arrest. Resuscitation. 2006; 69: 207–212.

- [21] Kim TH, Kim H, Hong KJ, Shin SD, Kim HC, Park YJ, et al. Prediction of cerebral perfusion pressure during CPR using electroencephalogram in a swine model of ventricular fibrillation. The American Journal of Emergency Medicine. 2021; 45: 137–143.
- [22] Idris AH, Becker LB, Ornato JP, Hedges JR, Bircher NG, Chandra NC, et al. Utstein-style guidelines for uniform reporting of laboratory CPR research: a statement for healthcare professionals from a task force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine. Circulation. 1996; 94: 2324–2336.
- [23] Momeni M, Gaudin A. Intraoperative cerebral hypoperfusion and electroencephalogram suppression resulting in neurological complications after cardiac surgery: the need for an in depth investigation. Acta Anæsthesiologica Belgica. 2016; 67: 73–79.
- [24] Morimoto Y, Monden Y, Ohtake K, Sakabe T, Hagihira S. The Detection of Cerebral Hypoperfusion with Bispectral Index Monitoring during General Anesthesia. Anesthesia and Analgesia. 2005; 100: 158–161.
- [25] Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JJ, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Medicine. 2015; 41: 1264–1272.
- [26] Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJ. Burstsuppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. Clinical Neurophysiology. 2014; 125: 947– 954.
- [27] Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology. 1998; 89: 980–1002.
- ^[28] Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. Journal of clinical monitoring and computing. 2000; 16: 593–596.
- ^[29] Thenayan EA, Savard M, Sharpe MD, Norton L, Young B. Electroencephalogram for prognosis after cardiac arrest. Journal of Critical Care. 2010; 25: 300–304.
- [30] Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. Journal of clinical monitoring. 1994; 10: 392– 404.
- [31] Sheth BR, Sandkühler S, Bhattacharya J. Posterior beta and anterior gamma oscillations predict cognitive insight. Journal of Cognitive Neuroscience. 2009; 21: 1269–1279.
- [32] Azim N, Wang C. The use of bispectral index during a cardiopulmonary arrest: a potential predictor of cerebral perfusion. Anaesthesia. 2004; 59: 610–612.
- ^[33] Gudipati CV, Weil MH, Bisera J, Deshmukh HG, Rackow EC. Expired

carbon dioxide: a noninvasive monitor of cardiopulmonary resuscitation. Circulation. 1988; 77: 234–239.

- [34] Lewis LM, Stothert J, Standeven J, Chandel B, Kurtz M, Fortney J. Correlation of end-tidal CO_2 to cerebral perfusion during CPR. Annals of Emergency Medicine. 1992; 21: 1131–1134.
- [35] Cereceda-Sánchez FJ, Molina-Mula J. Systematic Review of Capnography with Mask Ventilation during Cardiopulmonary Resuscitation Maneuvers. Journal of Clinical Medicine. 2019; 8: 358.
- [36] Kodali BS, Urman RD. Capnography during cardiopulmonary resuscitation: Current evidence and future directions. Journal of Emergencies, Trauma, and Shock. 2014; 7: 332–340.
- [37] Lee HJ, Shin J, Hong KJ, Jung JH, Lee SJ, Jung E, et al. A feasibility study for the continuous measurement of pupillary response using the pupillography during CPR in out-of-hospital cardiac arrest patients. Resuscitation. 2019; 135: 80–87.
- [38] Cournoyer A, Iseppon M, Chauny J, Denault A, Cossette S, Notebaert É. Near-infrared Spectroscopy Monitoring during Cardiac Arrest: a Systematic Review and Meta-analysis. Academic Emergency Medicine. 2016; 23: 851–862.
- [39] Yagi T, Kawamorita T, Kuronuma K, Tachibana E, Watanabe K, Chiba N, *et al.* Usefulness of a New Device to Monitor Cerebral Blood Oxygenation Using NIRS during Cardiopulmonary Resuscitation in Patients with Cardiac Arrest: a Pilot Study. Advances in Experimental Medicine and Biology. 2020; 128: 323–329.
- [40] Berka C, Levendowski DJ, Cvetinovic MM, Petrovic MM, Davis G, Lumicao MN, et al. Real-Time Analysis of EEG Indexes of Alertness, Cognition, and Memory Acquired with a Wireless EEG Headset. International Journal of Human-Computer Interaction. 2004; 17: 151– 170.
- [41] Gervais HW, Schleien CL, Koehler RC, Berkowitz ID, Shaffner DH, Traystman RJ. Effect of adrenergic drugs on cerebral blood flow, metabolism, and evoked potentials after delayed cardiopulmonary resuscitation in dogs. Stroke. 1991; 22: 1554–1561.
- [42] Jang HS, Kwon YS, Lee MG, Jang KH. The Effect of Tiletamine/Zolazepam (Zoletile) Combination with Xylazine or Medetomidine on Electroencephalograms in Dogs. Journal of Veterinary Medical Science. 2004; 66: 501–507.
- [43] Martín-Cancho MF, Lima JR, Luis L, Crisóstomo V, Ezquerra LJ, Carrasco MS, et al. Bispectral index, spectral edge frequency 95

How to cite this article: Dong Sun Choi, Heejin Kim, Ki Jeong Hong, Sang Do Shin, Hee Chan Kim, Yong Joo Park, *et al.* Correlation of EEG-based brain resuscitation index and end-tidal carbon dioxide in porcine cardiac arrest model. Signa Vitae. 2022; 18(3): 128-136. doi:10.22514/sv.2021.226.