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Original article

Relationship between early changes in cerebral blood volume and electrocortical activity after hypoxic–ischemic insult in newborn piglets ☆

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Abstract

Background: Early changes in cerebral hemodynamics and depressed electrocortical activity have been reported after a hypoxic–ischemic (HI) insult. However, the relationship between these two parameters is unclear. This study aimed to examine the relationship between changes in cerebral blood volume (CBV) and cerebral Hb oxygen saturation (ScO_2) after a HI insult and the low amplitude-integrated electroencephalography (aEEG) duration concomitantly observed. *Methods:* Sixteen newborn piglets obtained within 24 h of birth were used ($n = 3$ controls). Thirteen piglets were subjected to a HI insult of 20-min low-amplitude aEEG (<5 μV, LAEEG), after which a low mean arterial blood pressure (<70% of baseline) was maintained for 10 min. We measured changes in CBV and ScO_2 using near-infrared time-resolved spectroscopy (TRS) and cerebral electrocortical activities using aEEG until 6 h after the insult. *Results:* A positive correlation was observed between the LAEEG duration and CBV increase, but not ScO_2, after the insult. *Conclusion:* These results suggest that a larger increase in CBV reflected a more severe failure in cerebral circulation to maintain cell membrane action potentials, which induced a more extended recovery period of electrocortical activity after the insult. We conclude that an early increase in CBV and longer LAEEG indicate severe brain injury.

Keywords: Hypoxia–ischemia; Electroencephalography; Cerebral blood volume amplitude-integrated electroencephalography; Near-infrared time-resolved spectroscopy

Abbreviations: aEEG, amplitude-integrated electroencephalography; deoxyHb, deoxygenated hemoglobin; CBV, cerebral blood volume; HI, hypoxic–ischemic; HIE, hypoxic–ischemic encephalopathy; HR, heart rate; LAEEG, low-amplitude aEEG; MABP, mean arterial blood pressure; oxyHb, oxygenated hemoglobin; ScO_2, cerebral Hb oxygen saturation; TRS, near-infrared time-resolved spectroscopy.

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1. Introduction

Perinatal hypoxic–ischemic encephalopathy (HIE) remains a major cause of permanent neurodevelopmental disability and infant mortality [1–4]. It occurs in approximately 1 out of every 500 term births in developed nations, leading to long-term neurological and developmental disabilities. Recent clinical trials have demonstrated that the incidence of death and disability from hypoxia–ischemia in newborns can be significantly reduced by initiating hypothermia treatment strategies within 6 h after birth [5,6].

Owing to the brevity of the therapeutic window, the early detection of brain injury and correct estimation of the degree of severity are crucial [7]. The aEEG technique provides very useful information in real time regarding the severity of brain dysfunction in terms of the prognosis, and, given its ease of application at the bedside, aEEG can be an index for the induction of early hypothermia therapy after birth [8–11]. Previous animal studies reported that a longer duration of low-amplitude electroencephalography (LAEEG) after birth resulted in more severe neurological outcomes [12,13].

EEG activity can be influenced by substrate supply. Low cerebral blood flow has been associated with discontinuous EEG activity in preterm infants [14], and severe ischemia has consistently been associated with the prolonged suppression of EEG intensity in fetal sheep [15]. Although cerebral hemodynamics may markedly as a result of suppressed EEG activity after a hypoxic–ischemic (HI) insult, few studies have investigated the relationship between cerebral electrocortical activity and cerebral hemodynamics. Elucidating this relationship after a HI insult may advance understanding of the physiology of HIE and help detect brain injuries more precisely.

There are several limitations to examine this relationship after an insult in a clinical setting because changes in cerebral circulation and oxygen delivery need to be investigated together with the analysis of aEEG. We previously validated the measurement of CBV and cerebral Hb oxygen saturation (ScO_2) using near-infrared time-resolved spectroscopy (TRS) in a hypoxic piglet model [16,17], and reported that TRS was very useful for assessing cerebral hemodynamics and oxygen metabolism in infants [18,19]. We can use TRS to calculate the absolute value of CBV and ScO_2 using a light absorption coefficient, without the change in light absorption that occurs with materials such as oxygenated hemoglobin (oxyHb) or indocyanine green, and it can be easily and noninvasively used at the bedside for infants. This method makes it clinically possible to qualify the value of CBV using TRS continuously [17–19].

We hypothesized that changes in CBV after a HI insult would correlate with the duration of EEG depression after the insult. The purpose of the present study was to investigate the relationship between changes in CBV, ScO_2, and the length of LAEEG after a HI insult using a perinatal asphyxia model in newborn piglets.

2. Materials and methods

2.1. Animal procedures

The study protocol was approved by the Animal Care and Use Committee for Kagawa University and in accordance with the Animal Research: Reporting *In Vivo* Experiments guidelines. Sixteen newborn piglets obtained within 24 h of birth and weighting 1.63–2.10 g were used in this study.

2.2. Anesthesia, ventilation, and monitoring of physiological variables

Newborn piglets were initially anesthetized with 1–2% isoflurane (Forane® inhalant liquid; Abbott Co., Tokyo, Japan) in air using a facemask. Piglets were Camborough on breed (Daiwa Chikusan, Japan). Each piglet was then intubated and mechanically ventilated with an infant ventilator. The umbilical vein and artery were cannulated with a 3 or 4-FG neonatal umbilical catheter (Atom indwelling feeding tube for an infant; Atom Medical Co., Tokyo, Japan); the umbilical vein was at a site 5 cm in depth from the incision, and the umbilical artery was at a site 15 cm in depth from the incision for blood pressure monitoring and blood sampling, respectively. After cannulation, the piglets were anesthetized with fentanyl citrate at an initial dose of 10 μg/kg followed by infusion at 5 μg/kg/h, and were paralyzed with pancuronium bromide at an initial dose of 100 μg/kg followed by infusion at 100 μg/kg/h. Maintenance solution (electrolytes plus 2.7% glucose, KN3B; Otsuka Pharmaceutical Co., Tokyo, Japan) was infused continuously at a rate of 4 mL/kg/h via the umbilical vein (glucose was infused at a rate of 2 mg/kg/min). Arterial blood samples were taken at critical points and when clinically indicated throughout the experiment. Each piglet was then placed on a heated-water mattress. Rectal temperature was maintained at 38.0 ± 1.0 °C using an overhead radiant heater. Inspired gas was prepared by mixing O_2 and N_2 gases to obtain the oxygen concentrations required for the experiment. Ventilation was adjusted to maintain PaO_2 and $PaCO_2$ in their normal ranges.

2.3. TRS measurements

We used a portable three-wavelength near-infrared time-resolved spectroscopy system (TRS-10; Hamamatsu Photonics K.K., Hamamatsu, Japan) and attached a probe to the head of each piglet. Light emission and detection optodes were positioned on the parietal region