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Brain & Development xxx (2018) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Relationship between prolonged neural suppression and cerebral hemodynamic dysfunction during hypothermia in asphyxiated piglets

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Received 24 February 2017; received in revised form 9 February 2018; accepted 24 April 2018

Abstract

Objectives: Hypothermia (HT) improves the outcome of neonatal hypoxic-ischemic encephalopathy. Here, we investigated changes during HT in cortical electrical activity using amplitude-integrated electroencephalography (aEEG) and in cerebral blood volume (CBV) and cerebral hemoglobin oxygen saturation using near-infrared time-resolved spectroscopy (TRS) and compared the results with those obtained during normothermia (NT) after a hypoxic-ischemic (HI) insult in a piglet model of asphyxia. We previously reported that a greater increase in CBV can indicate greater pressure-passive cerebral perfusion due to more severe brain injury and correlates with prolonged neural suppression during NT. We hypothesized that when energy metabolism is suppressed during HT, the cerebral hemodynamics of brains with severe injury would be suppressed to a greater extent, resulting in a greater decrease in CBV during HT that would correlate with prolonged neural suppression after insult.

Methods: Twenty-six piglets were divided into four groups: control with NT (C-NT, $n = 3$), control with HT (C-HT, $n = 3$), HI insult with NT (HI-NT, $n = 10$), and HI insult with HT (HI-HT, $n = 10$). TRS and aEEG were performed in all groups until 24 h after the insult. Piglets in the HI-HT group were maintained in a hypothermic state for 24 h after the insult.

Results: There was a positive linear correlation between changes in CBV at 1, 3, 6, and 12 h after the insult and low-amplitude aEEG (<5 μV) duration after insult in the HI-NT group, but a negative linear correlation between these two parameters at 6 and 12 h after the insult in the HI-HT group. The aEEG background score and low-amplitude EEG duration after the insult did not differ between these two groups.

Abbreviations: aEEG, amplitude-integrated electroencephalography; CBF, cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, rate of cerebral metabolism of oxygen; HI, hypoxic-ischemic; HIE, hypoxic-ischemic encephalopathy; HR, heart rate; HT, hypothermia; LAEEG, low-amplitude electroencephalography; NIRS, near-infrared spectroscopy; NT, normothermia; PaO_2, arterial oxygen tension; ScO_2, cerebral hemoglobin oxygen saturation; TRS, time-resolved spectroscopy

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https://doi.org/10.1016/j.braindev.2018.04.010

Please cite this article in press as: Jinnai W et al. Relationship between prolonged neural suppression and cerebral hemodynamic dysfunction during hypothermia in asphyxiated piglets. Brain Dev (2018), https://doi.org/10.1016/j.braindev.2018.04.010

Discussion and conclusion: A longer low-amplitude EEG duration after insult was associated with a greater CBV decrease during HT in the HI-HT group, suggesting that brains with more severe neural suppression could be more prone to HT-induced suppression of cerebral metabolism and circulation.

Keywords: Animal model; Cerebral blood volume; Cerebral hemoglobin oxygen saturation; Electroencephalography; Hypothermic therapy; Hypoxia-ischemia; Hypoxic-ischemic encephalopathy; Near-infrared time-resolved spectroscopy; Piglet

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a notable cause of neonatal death and developmental psychomotor disorders. The incidence of neonatal HIE is 1.6–3.8 per 1000 newborns [1–4]. In Japan, the estimated incidence of moderate-to-severe HIE in neonates born from a gestational age of 37 weeks onward is 0.35 per 1000 live births [5]. Mild hypothermia (HT) therapy is recommended for neonates with HIE by current neonatal cardiopulmonary resuscitation guidelines [6,7]. However, in studies where HT was initiated within 6 h of birth and continued for 72 h, the incidence of death or disability decreased from 58% to 47%, representing a risk reduction of just 11% [8–10]. Hence, about 45–50% of these neonates who were given HT still had major disability, died due to global multi-organ injury, or died after redirection of care from life support due to severe brain injury. Therefore, many questions remain regarding the selection of candidates for HT and its optimal degree and duration [11], and other treatment strategies are still urgently needed. In this regard, the following should be considered: (1) the methods used to classify neonatal HIE severity during the 6 h after birth and to evaluate treatment strategies tailored to condition severity, and (2) the identification of patients with risk factors for poor prognosis during HT requiring additional treatment, such as cerebral circulatory support.

The most promising and clinically feasible early indicator of hypoxia-ischemia after birth is amplitude-integrated electroencephalography (aEEG) due to its ease of use, its noninvasiveness, and its high prognostic value as early as 6 h after birth [12]. However, some studies have questioned the sensitivity of aEEG for detecting such neonates because some infants may have "slowly" evolving injuries and these infants may have a normal early aEEG. In addition, the timing of the injury in the actual clinical situation is not known at the time of assessment using aEEG, and the primary cerebral energy failure from hypoxic-ischemia might already be improving, or the damage from delayed secondary energy failure might have already started [13]. This might explain why some infants have adverse short-term outcomes despite normal aEEG. Furthermore, hypothermia may alter the prognostic value of aEEG performed within 72 h of birth [14].

In contrast, near-infrared spectroscopy (NIRS) permits continuous bedside monitoring of cerebral hemodynamics and oxygen metabolism. Previous studies using NIRS in term neonates with severe HIE (treated with or without HT) revealed that changes in cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral hemoglobin oxygen saturation (ScO_2) could predict an adverse outcome [15–18]. These studies reported that an increase in ScO_2 in the 24 h after birth was a poor prognostic feature in neonates with HIE, even those receiving HT therapy. We previously evaluated CBV and ScO_2 by near-infrared time-resolved spectroscopy (TRS) in infants with neonatal HIE within 72 h of birth and found that an increase in CBV was associated with poor prognosis [18]. In addition, in a piglet model of HIE, we found a positive correlation between the length of the neural suppression and the CBV increase in the 6 h following the hypoxic-ischemic (HI) insult and a correlation between the CBV increase at this time and the severity of brain tissue injury when assessed 5 days later [19–20].

Thus, simultaneous evaluation of aEEG recordings and CBV would enable more accurate prognostication and possibly identify patients with risk factors for poor prognosis during HT requiring additional treatment. However, it is unclear how this relationship is altered by HT. We previously noted that increased CBV during NT after insult can indicate the severity of brain injury and correlates with prolonged neural suppression after insult, because CBF becomes pressure passive due to impaired cerebral circulatory autoregulation [20,21]. However, we hypothesized that, during HT, when the energy failure is more severe, cerebral hemodynamics would be more passive and suppressed, possibly resulting in a greater decrease in CBV that correlates with prolonged neural suppression after insult. This phenomenon could indicate more severe brain injury and correlate with prolonged neural suppression after insult.

We developed a piglet model of asphyxia using aEEG and CBV measurements to control the severity of the hypoxic insult [22]. This model provides a good supply of animals that not only survive a hypoxic insult, but

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