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Rewarming affects EEG background in term newborns with hypoxic–ischemic encephalopathy undergoing therapeutic hypothermia

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HIGHLIGHTS

- EEG background evolves during rewarming in neonates cooled for hypoxic–ischemic encephalopathy (HIE).
- Rewarming induced EEG discontinuity is worse in severe compared to moderate HIE.
- In moderate HIE, rewarming increases delta and decreases alpha/theta EEG activity.

ABSTRACT

Objective: To investigate how rewarming impacts the evolution of EEG background in neonates with hypoxic–ischemic encephalopathy (HIE) undergoing therapeutic hypothermia (TH).
Methods: We recruited a retrospective cohort of 15 consecutive newborns with moderate (9) and severe (6) HIE monitored with a continuous EEG during TH and at least 12 h after its end. EEG background was analyzed using conventional visual and quantitative EEG analysis methods including EEG discontinuity, absolute and relative spectral magnitudes. One patient with seizures on rewarming was excluded from analyses.
Results: Visual and quantitative analyses demonstrated significant changes in EEG background from pre- to post-rewarming, characterized by an increased EEG discontinuity, more pronounced in newborns with severe compared to moderate HIE. Neonates with moderate HIE also had an increase in the relative magnitude of slower delta and a decrease in higher frequency theta and alpha waves with rewarming.
Conclusions: Rewarming affects EEG background in HIE newborns undergoing TH, which may represent a transient adaptive response or reflect an evolving brain injury.
Significance: EEG background impairment induced by rewarming may represent a biomarker of evolving encephalopathy in HIE newborns undergoing TH and underscores the importance of continuously monitoring the brain health in critically ill neonates.

1. Introduction

Neonatal hypoxic–ischemic encephalopathy (HIE) is the leading cause of death in term newborns resulting in permanent neurodevelopmental disability in one to two thirds of survivors (Lawn et al., 2005; Dixon et al., 2002). Therapeutic hypothermia (TH) is currently the only proven neuroprotective intervention that improves survival and neurodevelopment in these newborns (Tagin et al., 2012; Jacobs et al., 2013).

Abbreviations: HIE, hypoxic–ischemic encephalopathy; TH, therapeutic hypothermia; cEEG, continuous EEG; qEEG, quantitative EEG; aEEG, amplitude-integrated EEG; MAP, mean arterial blood pressure; AIMS, Alberta infant motor scale; NIRS, near-infrared spectroscopy.

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The parameters of the currently accepted hypothermic protocols have been established based on animal experimental data (Shankaran et al., 2002; Gunn et al., 2005). These data suggest that, to achieve maximal neuroprotection, TH has to be initiated within six hours after birth, continued for around 72 h and followed by slow rewarming. However, no clinical trials have been conducted in humans to assess different rates of rewarming. Moreover, despite the encouraging results of TH trials, concerns have been raised as to the safety and tolerability of the rewarming period. Studies report recurrence or even *de novo* occurrence of seizures in HIE neonates on rewarming (Shah et al., 2014; Glass et al., 2014). Furthermore, animal studies have shown that rapid rewarming can abolish the beneficial effects of TH after cardiac arrest (Lu et al., 2014), exacerbate traumatically induced axonal injury (Suehiro and Povlishock, 2001) or reduce the neuroprotective effect of TH in acute ischemic stroke (Berger et al., 2007).

Remarkably, human studies have not systematically addressed the neurological tolerability of the current rewarming protocols. It is generally accepted that seizures, more particularly in context of HIE, are harmful to the developing brain (Glass et al., 2009; Miller et al., 2002; Shah et al., 2014; Wirrell et al., 2001). Yet, even in absence of seizures, rewarming may exacerbate brain injury induced by the anoxic event (Suehiro and Povlishock, 2001). To prevent this evolving brain injury, there is an urgent need to develop real-time monitoring tools and then evaluate whether rewarming-related brain damage has an impact on the long-term outcome.

Continuous EEG (cEEG) is a non-invasive and well-tolerated bedside tool that allows monitoring brain function over hours to days. cEEG is the gold standard for detecting seizure activity (Shellhaas, 2012). Moreover, it allows continuous evaluation of the EEG background, which is a reliable indicator of HIE severity and an excellent predictor of later neurodevelopmental outcome (Walsh et al., 2011; Tsuchida, 2013). EEG background patterns can be assessed by experienced neurophysiologists using conventional visual analysis. Various classification schemes have been proposed, but essentially all of them include features such as EEG continuity and amplitude as accurate markers of HIE severity (Glass et al., 2014; Holmes and Lombroso, 1993; Lamblin et al., 1999; Nash et al., 2011; Walsh et al., 2011; Tsuchida, 2013). Many studies have also assessed the frequency content of the background, with an increased amount of slow delta waves characterizing an abnormal trace and poor outcome (van Lieshout et al., 1995; Walsh et al., 2011; Zeinstra et al., 2001). User-independent quantitative EEG (qEEG) measures evaluating the same parameters have also been developed and shown to discriminate between HIE grades (Burnsed et al., 2011; West et al., 2006; Stevenson et al., 2013; Korotchikova et al., 2011; O'Reilly et al., 2012). Only one study evaluated the direct association between core body temperature and qEEG parameters in HIE neonates, but has not considered the possibility of more protracted effects of rewarming on cerebral activity (Burnsed et al., 2011).

The purpose of this study is to investigate how rewarming impacts the brain health of neonates with HIE by monitoring and analyzing cEEG background through TH, rewarming and early post-rewarming period. Our main hypothesis is that rewarming induces a deterioration of the cEEG background patterns and an increase in EEG discontinuity, as assessed using conventional visual and qEEG analysis tools, respectively. Additionally, we characterize the evolution of amplitude and frequency composition of the cEEG background in patients with moderate and severe HIE. Moreover, considering previous reports of impaired cardiovascular reactivity in response to rewarming (Thoresen and Whitelaw, 2000), we also explore the evolution of heart rate and systemic mean arterial blood pressure (MAP).

2. Methods

2.1. Patients

We recruited a retrospective cohort of 15 consecutive neonates with HIE that underwent TH at the CHU Sainte Justine tertiary level neonatal intensive care unit between June 2013 and April 2014. Patients were included if they (i) satisfied institutional criteria for TH ($\geqslant$36 weeks gestational age, $\geqslant$1800 grams at birth, <6 h of life, evidence of encephalopathy and severe metabolic acidosis with pH $\leqslant$ 7 or base deficit $\geqslant$16, or milder acidosis with pH 7.01–7.15 or base deficit 10–16, accompanied by Apgar score $\leqslant$5 or positive-pressure ventilation at 10 min and a sentinel perinatal event), (ii) had no evidence of malformation or congenital infection, (iii) had cEEG monitoring initiated within the 1st 24 h of life and maintained for at least 12 h after the end of TH. All patients' characteristics are presented in Table 1.

All neonates were treated with whole-body hypothermia (33–34 °C of core body temperature), initiated within six hours after birth, continued for 72 h and followed by gradual rewarming by 0.5 °C per hour over 6 h. Two patients had their TH discontinued earlier: (i) after 56.5 h due to difficulties managing persistent pulmonary hypertension, (ii) after 39 h as judged non encephalopathic (patients 12 and 8, respectively, in Supplementary Table S1, see also Section 2.3). Both patients were rewarmed at a standard rate.

Neonates had serial neurological examinations on admission and, subsequently, every 8 h until at least the end of the 4th day of life, quoted according to a modified Sarnat scale (Sarnat and Sarnat, 1976; Neonatal Encephalopathy Registry, 2012) of 0 (normal) to 3 (profoundly comatose), as part of standard clinical care in our institution (Supplementary Table S2). Patients with at least one evaluation quoted >2 were classified with severe HIE. All these patients remained at least moderately encephalopathic

Table 1
Demographic and clinical characteristics of the study population.

	Moderate HIE[a] (n = 9)	Severe HIE[a] (n = 6)	Overall (n = 15)
Gestational age, wks	39.5 ± 1.4	39.5 ± 2.0	39.5 ± 1.6
Birth weight, kg	3.4 ± 0.7	3.4 ± 0.2	3.4 ± 0.6
Sex, male	2 (22)	3 (50)	5 (33)
Emergent cesarean	5 (56)	4 (67)	9 (60)
Sentinel event[b]	4 (44)	3 (50)	7 (47)
Apgars[c]			
1 min	1 (0.8, 1.5)	1 (0, 2)	1 (0, 2)
5 min	2.5 (1.8, 3.3)	3 (1, 4)	3 (1, 4)
10 min	4.5 (3, 5.5)	3.5 (2.5, 4.5)	4 (3, 5.3)
Resuscitation score[d]	4 (4, 6)	5 (4.5, 6)	5 (4, 6)
Initial pH	6.91 ± 0.2	6.96 ± 0.1	6.93 ± 0.2
Age at therapeutic temperature, hours	5.6 ± 1.7	5.1 ± 1.7	5.4 ± 1.7
Inotropic support	2 (22)	3 (50)	5 (33)
Clinical seizures	4 (44)	5 (83)	9 (60)
Electrographic seizures	1 (11)	2 (33)	3 (20)
Status epilepticus	1 (11)	1 (17)	2 (13)
Initial EEG impairment[e]	2 (1.5, 2)	3 (2.3, 3)	2 (1.8, 2.8)
Sarnat score at the end of hypothermia[f]	0.9 (0.8, 1.5)	1.7 (1.5, 1.8)	1.4 (0.9, 1.8)
Deceased	0 (0)	1 (17)	1 (7)

Data are presented as n (%), mean ±SD, or median (interquartile range).
[a] HIE: hypoxic–ischemic encephalopathy.
[b] A sentinel event was defined as a placental abruption, uterine rupture, cord rupture, cord knot, or tight nuchal cord.
[c] Documented for 13/15 patients.
[d] The resuscitation score is based on interventions that are administered at birth, ranging from 1 (no intervention) to 6 (endotracheal intubation and epinephrine) (Miller et al., 2002).
[e] See methods, conventional visual EEG analysis.
[f] See Supplementary Table S2.