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Clinical paper,

Heart rate response to therapeutic hypothermia in infants with hypoxic–ischaemic encephalopathy☆

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ABSTRACT

Aim of the study: Neonatal encephalopathy (NE) of hypoxic–ischaemic origin may cause death or life-long disability which is reduced by therapeutic hypothermia (TH). Our objective was to assess HR response in infants undergoing TH after perinatal asphyxia.
Methods: We performed a retrospective case series, from a single-centre tertiary care NICU. We included ninety-two infants with NE of likely hypoxic–ischaemic origin, moderate or severe, treated with TH ($n = 60$) or normothermia ($n = 32$) who had 18 month outcome data and at least 12 HR recordings the first 24 h after birth (1998–2010) Bristol, UK. Poor outcome was defined as death or severe disability. Data are reported as medians and 95% confidence intervals (CI).
Results: TH to 33.5 °C decreased HR by 30 bpm to 92 bpm (95% CI: 88, 96) 12 h after birth in infants with NE and good outcome as compared to infants treated at normothermia 118 bpm (95% CI: 110, 130). Despite constant low rectal temperature, HR increased gradually during cooling from 36 to 72 h to 97 bpm (89, 106) approaching the normothermia group, 117 bpm (96, 133). During TH, infants with poor outcome had higher HR at 12 h after birth (112 bpm, 95% CI: 92, 115) as compared to infants with good outcome ($p = 0.004$). Inotropic support increased HR by 17 bpm in infants with good outcome and by 22 bpm in infants with poor outcome.
Conclusions: In NE, TH decreases HR the first day of life. HR remained lower during TH, but increased during the last day of TH. Infants with poor outcome have higher HR.

Introduction

All neonates suffering from neonatal encephalopathy (NE) of assumed hypoxic–ischaemic origin are treated with therapeutic hypothermia (TH) within 6 h after birth as standard of care to reduce mortality and improve neurological outcome.[1] Even after the introduction of TH, NE results in death or disability in 47% of infants with moderate or severe perinatal asphyxia.[2]

Even a normal birth is a stressful event for the neonate, and immediately after birth heart rate (HR) is increased. In healthy neonates, HR stabilizes during the first day. The hypoxic-ischaemic insult that patients with perinatal asphyxia suffer from, has large impact on the cardiovascular system. In the present study we focused on HR.

Hypoxia per se reduce metabolism, reduce HR and decrease core temperature.[3] During TH, we reduce core temperature, with subsequent further reduction in HR. HR is decreased by 10 bpm in neonates when core temperature is reduced by 1 °C in response to reduced metabolism.[4] Neonates undergoing TH has a rapid decrease in HR, but it has not been reported whether this reduction is maintained throughout prolonged cooling. Previous physiological reports indicate that when unphysiological conditions are maintained, the human body has wide capacity of restoration of key variables. One example is the immediate reduction in cerebral blood flow seen during hypocapnia. During prolonged hypocapnia as well as hypercapnia in adults, cerebral blood flow is restored towards the baseline value and this is interpreted as a protective mechanism.[5]

There are few reports on variability in HR response to the induction of TH. Here we report variability in HR response, and that this variability represents important clinical differences due to severity of the underlying hypoxic–ischaemic insult and inotropic support.

In this retrospective study we describe the normal reduction and restoration of HR during TH in NE infants. The optimal HR response to TH is illustrated by the infants with NE, who had good outcome

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without inotropic support. We also describe the HR response in infants with and without inotropic support in relation to outcome. Lastly, we discuss whether HR could be used as an early predictor of neurological outcome.

The primary aim of this study was to determine the HR response during TH.

Methods

Infants were included if they were recruited into a registered pilot study of TH, two randomized trials of TH/normothemia or were cooled when TH became standard treatment in Bristol and included in the TOBY register.[4,6–8] All infants fulfilled the A, B and C entry criteria as defined for the CoolCap and TOBY trials[6,7]: gestational age ≥36weeks and A: having reduced consciousness and at least one of; Apgar score ≤5 at 10 min, needing assisted ventilation by 10 min, acidosis (pH < 7.0), or base deficit ≥16 mmol/L and B: moderate or severe clinical encephalopathy and C: moderately or severely abnormal aEEG or seizures. Patient records of the infants (1998–2010) Bristol, United Kingdom, were examined retrospectively to obtain cardiovascular variables and outcome and treatment (TH or normothermia).[9] All the above studies were approved by the local Research Ethics Committees including data collection after the trials (CH/2009/3091).

For both normothermia and TH infants, more than 90% of infants were ventilated during the first 3 days of life, and almost all of the infants had invasive blood pressure monitoring. Arterial blood gases were measured frequently according to clinical need. The infants were born between1998 and 2010. Two modes of cooling were used. Selective head cooling ($n = 4$) (Olympic Medical Cool Care System, Olympic Medical, Seattle, WA, USA) with the rectal temperature maintained at 34.5 ± 0.5 °C or whole body cooling (either a manually controlled cooling blanket (Tecotherm, TS Med 200M; Leister, UK ($n = 2$)) or a servo-controlled cooling wrap (CritiCool, MTRE, Yavne, Israel ($n = 54$)) was used with rectal temperature maintained at 33.5 ± 0.2 °C.[10] The rectal temperature was stable during the TH.

Inotropic support was left to the clinicians' decision guided by a clinical treatment protocol starting inotropic support treating hypotension when mean arterial blood pressure <45 mmHg. The first drug of choice was dopamine with addition of dobutamine and norepinephrine as supplement.

In the records of 97 identified infants, 60 and 32 eligible infants with recorded outcome were treated with TH and normothermia respectively (missing outcome in 3 normothermia infants), and had at least 12 hourly HR electronic recordings for the first 24 h (missing HR recordings in 1 TH and 1 normothermia infant). Poor outcome was defined as death or severe disability using the Bayley Scales of Infant Development II, Mental Development Index (MDI) <70 or Psychomotor Development Index (PDI) <70, deafness or blindness.[7,11] In infants without results from Bayley Scales of Infant Development II, the components of severe disability were used.[12] Severe disability was defined as any of the following: inability to walk, sit, use hands to feed, control head, speak, see or hear. Neurodevelopment was assessed by trained personnel not involved in the neonatal care or aware of treatment allocation. In 2 infants lost to follow up <18 months of age, a scoring system from MRI evidence of injury to the basal ganglia, thalami, internal capsule and white matter was used as a surrogate measure of poor outcome.[13]

Statistical analysis

Demographic and clinical characteristics were summarized at baseline as counts and percentages of the total numbers of infants for categorical variables, and as medians and interquartile ranges for other continuous variables. Tables of 2 × 2 were analysed with the 'N − 1' χ^2 test.[14] Hodges–Lehmann's estimates of 95% non-parametric confidence intervals (CI) of median were used to look for differences between groups.[15] p-values for comparisons of group data were found by two-tailed Mann–Whitney U-test. The area under the receiver operating curve (AUROC) was used for validity of HR as a predictor of neurological outcome. SPSS 20 (SPSS, Chicago, IL, USA), GraphPad Prism 6.0 for Windows (GraphPad Software, La Jolla, CA USA) and StatExact (Cytel Studio 7; Cytel Inc., Cambridge, MA, USA) were used for statistical calculations. The 95% CI of predictive values were calculated according to the efficient score method [http://faculty.vassar.edu/lowry/clin1.html].[16] $p < 0.05$ was considered significant.

Results

Demographic and clinical variables

Table 1 shows the characteristics of the infants. The initial markers of severity before 6 h of age were similar in the two treatment groups. The TH group received more inotropic support.

Effect of temperature on heart rate

The infants treated at normothermia started with HR at 139 bpm (95% CI: 119, 156) the first 3 h after birth and showed a trend towards decreasing HR during the first days of life (Fig. 1, red/grey line). At 24 h after birth HR was 118 bpm (110–130), at 48 h after birth 109 bpm (97–122) and at 72 h after birth 117 bpm (96, 133). In the present normothermia cohort few hourly HR values were documented after 48 h (7 infants with good outcome and reported HR).

To investigate whether TH had an effect on the HR response, we compared normothermia and TH infants with NE with good outcome and without inotropic support. The TH infants started with HR at 131 bpm (123, 140) the first three hours after birth before TH was initiated. After initiation of TH (range 1–6 h after birth), HR dropped rapidly to 89 bpm (85, 93) at 12 h after birth in the infants with good outcome without inotropic support. TH reduced HR by 30 bpm between 12 and 24 h after birth compared to normothermia treated infants ($p < 0.0001$, Wilcoxon matched-pairs signed rank test). HR stays low at 92 bpm until 36 h after birth (86, 98), HR then gradually increased to 97 bpm (89, 106) at 72 h after birth (during last day of TH). HR increases with rewarming, and stabilizes at 111 bpm (101–122) when rewarmed (84 h after birth).

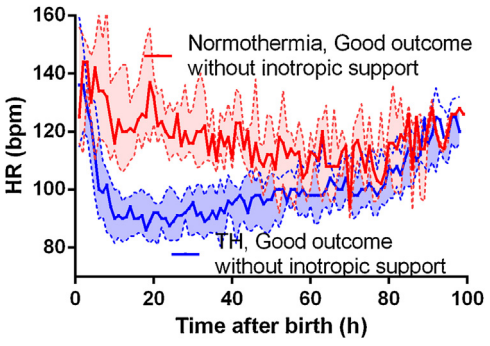

Fig. 1. Normal heart rate response after hypoxic-ischaemic encephalopathy in infants with good outcome. The two graphs represent the median heart rate response in infants treated for hypoxic–ischemic encephalopathy, grade II or III either at normothermia (red) or during 72 h of therapeutic hypothermia (blue) started within 6 h after birth. None of these infants received inotropic support. The shaded zones indicate the interquartile range between 25- and 75-percentiles. HR, heart rate; TH, therapeutic hypothermia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)