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## Accepted Manuscript

Title: Heart rate response to therapeutic hypothermia in infants with hypoxic-ischaemic encephalopathy

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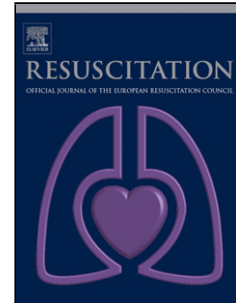
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Heart rate response to therapeutic hypothermia in infants with hypoxic-ischaemic encephalopathy

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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 24h 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) 12h 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 72h to 97 bpm (89,106) approaching the normothermia group, 117 bpm (96,133). During TH, infants with poor outcome had higher HR at 12h 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 6h after birth as standard of care to reduce mortality and improve neurological outcome.<sup>1</sup> Even after the introduction of TH, NE results in death or disability in 47% of infants with moderate or severe perinatal asphyxia.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup>

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 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.

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## METHODS

Infants were included if they were recruited into a registered pilot study of TH, two randomized trials of TH/normothermia or were cooled when TH became standard treatment in Bristol and included in the TOBY register.<sup>4,6,7,8</sup> All infants fulfilled the A, B and C entry criteria as defined for the CoolCap and TOBY trials:<sup>6,7</sup> gestational age  $\geq$  36weeks and A: having reduced consciousness and at least one of; Apgar score  $\leq$  5 at 10 min, needing assisted ventilation by 10min, acidosis (pH  $<$  7.0), or base deficit  $\geq$ 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).<sup>9</sup> 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 between 1998 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  $34.5 \pm 0.5^{\circ}\text{C}$  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  $33.5 \pm 0.2^{\circ}\text{C}$ .<sup>10</sup> 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 24h (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.<sup>7,11</sup> In infants without results from Bayley Scales of Infant Development II, the components of severe disability were used.<sup>12</sup> 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.<sup>13</sup>

#### 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 x 2 were analysed with the 'N-1'  $\chi^2$  test.<sup>14</sup> Hodges–Lehmann's estimates of 95% non-parametric confidence intervals (CI) of median were used to look for differences between groups.<sup>15</sup> 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 California 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>].<sup>16</sup> 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 6h 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 three hours after birth and showed a trend towards decreasing HR during the first days of life (figure 1, red/grey line). At 24h after birth HR was 118 bpm (110-130), at 48h after birth 109 bpm (97-122) and at 72h after birth 117 bpm (96, 133). In the present normothermia cohort few hourly HR values were documented after 48h (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 1-6h after birth), HR dropped rapidly to 89 bpm (85, 93) at 12h after birth in the infants with good outcome without inotropic support. TH reduced HR by 30 bpm between 12 and 24h after birth compared to normothermia treated infants ( $p < 0.0001$ , Wilcoxon matched-pairs signed rank test). HR stays low at 92 bpm until 36h after birth (86,98), HR then gradually increased to 97 bpm (89,106) at 72h after birth (during last day of TH). HR increases with rewarming, and stabilizes at 111 bpm (101-122) when rewarmed (84h after birth).

### Effect of inotropic drugs on heart rate

In the normothermia group, 31% of the infants received inotropic support, while 70% of the infants received inotropic support during TH ( $p = 0.0004$ , table 1). Inotropic support increased the HR

at 12h after birth during TH (122 bpm vs 95 bpm,  $p=0.0002$  Mann-Whitney test, figure 2).

Normothermia infants received inotropic support from 8h (95%CI: 4, 12) after birth, while TH infants received inotropic support from 12h (95%CI: 9, 14).

During TH, relatively more infants with good outcome received inotropic support than normothermia infants with good outcome ( $p=0.001$ ,  $n-1 \chi^2$ ). In the normothermia and TH groups with good outcome 1 of 13 and 25 of 40, respectively, received inotropic support. In the groups with poor outcome, 9 out of 19 normothermia treated infants and 17 of 20 TH infants received inotropic support. In normothermia, inotropic support was related to poor outcome ( $p=0.02$ ,  $n-1 \chi^2$ ), while during TH inotropic support was not statistically related to poor outcome ( $p=0.08$ ).

The mean arterial blood pressure during TH did not differ between the infants with and without inotropic support (54 mmHg ( $n=9$ ) vs 51 mmHg ( $n=29$ ) at 12h after birth, respectively). Few infants in each group had several observations of mean arterial blood pressure.

Heart rate response to TH with good or poor outcome

The initial drop in HR differed according to inotropic support and outcome (figure 2). At the initiation of TH (<6h after birth), the HR drop in infants with good outcome and without inotropic support was rapid and substantial (~30 bpm). Poor outcome delayed the HR drop (no difference in time to start TH) and the decrease was smaller. Inotropic support delayed and reduced the HR drop in infants with good outcome, while in infants with poor outcome and inotropic support, the HR drop was abolished.

Nadir of the HR response after TH was reached at 12h after birth. Both during normothermia and TH, HR is higher in the groups with poor outcome than good outcome ( $p=0.005$  and  $p<0.0001$  respectively, Mann-Whitney test, figure 3). HR at 12h during TH and normothermia had an AUROC of 0.81 and 0.65 respectively on prediction of neurological outcome.

During TH, without inotropic support, the median HR at 12h was higher in infants with poor outcome compared to those with good outcome (112 bpm vs. 92 bpm,  $p=0.004$  Mann-Whitney test, two-sided, table 2, figure 3).  $HR \leq 100$  bpm significantly differentiated between good and poor outcome for TH infants without inotropic support ( $p = 0.001$ , 'N-1'  $\chi^2$  test). During TH without inotropic support,  $HR \leq 100$  bpm already at 12h, was predictive of good outcome in 27 out of 31. The accuracy of HR as a single early predictor for death or severe disability in the infants during TH was 82% (95% CI: 65%, 92%) in infants without inotropic support.

Also during TH with inotropic support the median HR at 12h was higher in infants with poor outcome compared to those with good outcome (134 bpm vs. 109 bpm,  $p=0.02$  Mann-Whitney test, two-sided, table 2). However, the accuracy of HR as a single early predictor for death or severe disability in the infants during TH with inotropic support was lower, 68 % (95% CI: 45%, 85%).

## DISCUSSION

We found that HR decreases initially with 30 bpm during TH compared to during normothermia in NE infants. HR increased during TH and was higher at last day of hypothermia compared to the first day. Infants with poor outcome have higher HR the first day after birth compared to HR in infants with good outcome. Inotropic support reduces the HR drop during TH.

Normal HR response to therapeutic hypothermia in HIE infants

In healthy normothermic newborns, HR is 112 bpm on the first postnatal day and 118 bpm on the fifth postnatal day during quiet rest.<sup>17</sup> We found that normothermic NE infants have higher HR on the first postnatal day. TH elicits rapid cardiovascular changes. HR drops to 90 bpm at 12h after birth (6h after start of TH) in the infants with good outcome without inotropic support, followed by a gradual increase at the last day of TH. HR was restored after rewarming, to the level similar to normothermia treated HIE infants, and similar to the HR observed in healthy newborns.<sup>17</sup>

We found that HR dropped 9 bpm per °C reduction in core temperature, similar to our previous findings in a small clinical study and in piglets.<sup>4,18</sup> This drop in HR is a physiological response to the decreased metabolism during TH, and a reduction in HR during TH has been associated with improved neurological outcome after cardiac arrest in adults.<sup>19</sup>

There is a debate whether TH is cardioprotective or cardiodepressive. Cardioprotective properties are suggested in the resuscitated neonatal heart.<sup>20</sup> On the other hand, reduced core temperature may stiffen the heart, making its relaxation, filling and contraction less efficient, with reduction in cardiac output in adults.<sup>21</sup> In infants the changes in cardiac output during TH are not clear.<sup>22</sup>

Hypothermia treated infants receive more inotropic support than normothermia treated infants

In our material, significantly more infants with good outcome received inotropic support during TH compared to during normothermia, but this material is not a randomized control trial. A large meta-analysis report that TH did not change the use of inotropic support, while a small study concluded that TH infants receives more inotropic support than during normothermia treatment.<sup>23,24</sup> The physiological decrease in HR during TH was counteracted by inotropic support in neonates, similar to previous findings in pigs.<sup>25</sup>

The mean arterial blood pressure level for infants during TH did not differ between the infants with and without inotropic support, and it seems as clinicians aim for the same blood pressure at the two temperatures.<sup>22</sup> However, the optimal mean arterial blood pressure during TH is yet to be defined.<sup>22</sup>

Could heart rate on the first postnatal day predict neurological outcome?

Recently, lower heart rate (HR) during TH in adults after cardiac arrest was found to be associated with favourable outcome.<sup>19</sup> To the best of our knowledge, this has not been investigated in NE patients receiving TH. In our study, HR $\leq$ 100 bpm at 12h after birth predicted good outcome in 87% during TH without inotropic support. During TH, the accuracy of HR as a single early predictor for death or severe disability was 82% (95% CI: 65%, 92%) in infants without inotropic support. This is comparable to prediction from MRI findings at day 8. The accuracy of prediction of death or severe disability from MRI was 84% (95%CI: 74%, 94%).<sup>13</sup>

HR is extremely easy to measure and independent on subjective scoring. In our current study, the predictability was lower during inotropic support and in view of the observation that 70% of the TH infants receive inotropic support which blunts the HR response during TH, makes HR a difficult predictor on neurological outcome. Other factors like pain or discomfort from being ventilated and cooled, sedation level and previous atropine boluses also influence HR.<sup>26</sup> We have previously found that premedication with atropine prior to intubation, increases HR lasting more than 8h after birth.<sup>26</sup>

HR is an important factor in stress scores of infants, and the clinician may be alert to the factors that may interfere with HR. As our study suggests, postnatal age will also influence HR.

#### Limitations

Our retrospective study has several weaknesses. We evaluated the use of inotropic support as a dichotomous variable, while inotrope score with dose of medication, type of medication and number of medication, could improve the study. In addition, the time varying degree of base deficit may influence the HR response to TH. Other clinical information such as anti-convulsion medication, cardiac function and any severe infection should ideally have been included. A future prospective multi-centre study should include the bedside information listed above and assess cardiac function at different time points during TH and after rewarming. Until our current results are confirmed from a larger prospective study testing the suggested hypothesis, this knowledge should not be used in outcome prediction or counselling parents.

**CONCLUSIONS**

Heart rate drops fast during therapeutic hypothermia in infants who do well. The initial drop in heart rate is reduced and delayed in infants who receive inotropic support and develop poor outcome. Heart rate increases during the last day of therapeutic hypothermia and is restored when rewarmed. Heart rate  $\leq 100$  bpm at 12h after birth without inotropic support during therapeutic hypothermia is predictive of favourable neurological outcome.

**CONFLICTS OF INTEREST**

We have no conflicts of interest.

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**Figure legends**

Figure 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 72h of therapeutic hypothermia (blue) started within 6 hours 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.

Figure 2 Median heart rate during therapeutic hypothermia divided by outcome and inotropic support

The four graphs represent the median heart rate response during therapeutic hypothermia for infants with poor outcome (grey) with (dotted line) and without inotropic support (solid line) and for infants with good outcome (black) with (dotted line) and without inotropic support (solid line). Infants with good outcome had lower median heart rate regardless of inotropic support. HR, Heart rate; TH, therapeutic hypothermia.

Figure 3 Heart rate at 12h after birth during normothermia and therapeutic hypothermia.

Each symbol represents one infant's heart rate at 12h after birth during therapeutic hypothermia or normothermia. The horizontal lines indicate median and interquartile range. Therapeutic hypothermia decreases heart rate. The infants with poor outcome had higher heart rate compared to

infants with good outcome, both during normothermia and therapeutic hypothermia. HR, Heart rate;  
TH, therapeutic hypothermia.

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Table 1 Patient characteristics in normothermia and therapeutic hypothermia infants

	<b>Normothermia (n=32)</b>	<b>Therapeutic Hypothermia (n=60)</b>	<b>P-value</b>
<b>Female</b>	56%	48%	>0.5
<b>Gestational age (weeks)</b>	40 (38-41)	40 (39-41)	0.67
<b>Birth weight (g)</b>	3428 (3101-3798)	3240 (3015-3665)	0.5
<b>Apgar@10 min</b>	6 (4-8)	6 (4-8)	0.87
<b>Worst pH by ≤1hr</b>	6.90 (6.86-7.02)	6.90 (6.83-7.09)	0.82
<b>Inotropic support during NICU</b>	31%	70%	0.0004
<b>Seizures</b>	56%	65%	0.4
<b>Poor outcome (death or severe disability<sup>1</sup>)</b>	59%	33%	0.02

Median and interquartile range. NICU, neonatal intensive care unit. P-values calculated by Mann-

Whitney or N-1 X<sup>2</sup>. Severe disability is described in methods.

Table 2 Heart rate and neurological outcome during therapeutic hypothermia

<b>HR at 12h after birth during therapeutic hypothermia</b>	<b>Without inotropic support</b>	<b>With inotropic support</b>
<b>Good outcome</b>	92 bpm  (88, 96)  n=30	109  (85, 110)  n=10
<b>Poor outcome</b>	112 bpm  (92, 115)  n=8	134  (111, 145)  n=12

95% confidence interval calculated by Hodges-Lehmann's estimate.<sup>15</sup>

Conflicts of interest statements

Maja Elstad has no conflict of interest.

Xun Liu has no conflict of interest.

Marianne Thoresen has no conflict of interest.

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