The myocardial function during and after whole-body therapeutic hypothermia for hypoxic–ischemic encephalopathy, a cohort study

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ABSTRACT

Background: Therapeutic hypothermia has become standard treatment for moderate and severe neonatal hypoxic–ischemic encephalopathy (HIE) to reduce cerebral morbidity and mortality. The effect on the heart is incompletely explored.

Aim: To assess the myocardial function during and after whole-body therapeutic hypothermia for HIE.

Study design: Observational cohort study.

Subjects: Forty-four infants with HIE cooled for 72 hours were compared with 48 healthy term infants and 20 normothermic infants with HIE.

Outcome measures: Tissue Doppler deformation indices of myocardial function (peak systolic strain, peak systolic strain-rate, early diastolic strain-rate and strain-rate in atrial systole) during (days 1 and 3) and after (day 4) therapeutic hypothermia.

Results: On days one and three all indices in both HIE groups were lower than the corresponding indices in the healthy infants. The two HIE groups had similar indices, except peak systolic strain-rate on days 1 and 3 and strain-rate in atrial systole on day 1. All strain-rate indices improved from day 3 to 4 (after rewarming) in the cooled group and achieved similar values to those in healthy infants on day 3. All indices were higher in the cooling-group after rewarming than in the normothermic infants with HIE on day 3, except early diastolic strain-rate.

Conclusions: Infants with HIE had similarly impaired myocardial function during days 1–3 whether normothermic or hypothermic. The myocardial function improved significantly at day 4 (after rewarming), approaching the day 3 levels in the healthy neonates.

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1. Introduction

Perinatal asphyxia affects many organ systems, of which the irreversible cerebral injury is of most concern. Therapeutic hypothermia (HT) for neonatal hypoxic–ischemic encephalopathy (HIE) has become standard treatment to reduce disability and mortality [1]. The myocardial function may be impaired after hypoxia [2,3] and this may exacerbate organ damage [4]. Little is known on the effect of hypothermia on myocardial function.

Assessment of the myocardial function by cardiac ultrasound has traditionally been based on the radial shortening of left ventricle cavity as fractional shortening [5–8]. A reduced fractional shortening after perinatal asphyxia has been found in some studies [6–9], but not in others [4,10–12]. Newer indices for myocardial function have been introduced in newborn infants, such as tissue Doppler derived atrioventricular (AV)-plane velocities [13–16] and tissue Doppler derived strain and strain-rate [16–21]. Both AV-plane velocities [12,22] and strain and strain-rate [20,21] have proven more sensitive than conventional measures for assessing reduced myocardial function after perinatal asphyxia. Among these new indices, strain and strain-rate have the advantage that they are normalised for heart size. We have shown that the reproducibility in strain and strain-rate analyses can be significantly improved by analysing one large segment from each wall instead of smaller segments [21]. To our knowledge, there are no published data comparing the myocardial function between infants with HIE receiving HT and those at normal temperature. Recently, two articles with strain and strain rate measurements by B-mode speckle tracking of the left ventricle in respectively eight [23] and twenty-four [24] cooled infants...
with HIE have been published, one without control groups [23], the other with only healthy controls [24]. Assessment of deformation by B-mode speckle tracking is hampered by each vendor having its own variant of the technology that might yield different values in the same images [25].

The objective of the present study was to compare the myocardial function during and after therapeutic hypothermia for moderate and severe HIE using strain and strain rate indices by tissue Doppler from the left-, septum and right-side of the heart. Our hypothesis was that therapeutic hypothermia has an impact on the myocardial function.

2. Methods

2.1. Study design

This prospective observational cohort study was performed between March 2010 and December 2011 at Oslo University Hospital, Ullevål. Entry criteria were the Norwegian National Guidelines for Therapeutic Hypothermia (Table 1). Infants in the HT-group received whole-body cooling with a target rectal temperature of 33.5 °C for 72 h and were then rewarmed to 37 °C at a rate of 0.5 °C/h. Measurements in the HT-group were compared with measurements on days 1 and 3 in two historical control groups of 20 term infants with HIE treated at normal temperature (NT-group) and 48 healthy term infants previously examined by the same cardiac ultrasound protocol [21]. The NT infants were recruited among infants diagnosed with HIE and admitted to the Department of Neonatal Intensive Care at Oslo University Hospital, Ullevål, before therapeutic hypothermia became standard treatment [20,21]. The healthy controls were recruited from the Postnatal Ward at Oslo University Hospital, Ullevål [19,21]. Based on power calculations in the control groups, inclusion of 30 infants in the HT-group would provide the study with 80% statistical power to assess differences of 10% in the myocardial function indices with a two-sided p-value of 5%.

2.2. Ethics

The study was approved by the South-East Norwegian Regional Committee for Research Ethics (REK Helse Sør-Øst) and by the Scientific Committee at Oslo University Hospital, Ullevål. Written informed parental consent was obtained for collecting and publishing data from the additional examinations during and after the cooling process.

2.3. Echocardiographic study

Congenital heart defects were ruled out at the first examination. Four different operators performed the scans. Tissue Doppler images of nine myocardial walls were recorded from five different apical views [19–21] during cooling (days 1 and 3) and after rewarming (day 4) on a Vivid S6 scanner (GE Vingmed, Horten, Norway). Probe type (SS) and tissue Doppler frame-rate (default, typically 130–200/s) and frequency (2.4 MHz) were equal to settings used for acquisition of the tissue Doppler images in the control groups [21], and were chosen based on an earlier study [26] where it has been shown that less disturbance in the analyses was obtained by using a relatively low frequency during image acquisition. One researcher (EN) assessed the peak systolic strain (PSS), peak systolic strain-rate (PSSR), early diastolic strain-rate (ESR) and strain-rate in atrial systole (ASR) from tissue Doppler images with sinus rhythm and using equal settings as had been used in the control groups. One large segment (length 21 mm, width 3 mm) were set stationary in the ultrasound sector within each wall, ensuring that the whole segment was within the myocardium throughout the cardiac cycles [21]. The segment was defined by a strain length of 20 mm and a length of the region of interest of 1 mm and a width of the region of interest of 3 mm. Indices for each examination were assessed by averaging measurements from all walls eligible for analysis. The fractional shortening (FS) was assessed at each examination [5]. At normal states, PSS and PSSR are negative values while ESR and ASR are positive. Higher absolute values indicate better myocardial function. PSS and PSSR are used as systolic function indices, with PSSR probably less dependent on load than PSS and hence more feasible as a measure of changes in contractility [27–31]. ESR and ASR mainly assess diastolic function [32].

2.4. Patient data

Patient data were obtained prospectively from medical records, including gestational age, Apgar score at 1, 5 and 10 minutes, peak measured cardiac Troponin T (cTnT) (Roche Diagnostics, GmbH, Mannheim, Germany), initial blood gas values, and use of mechanical ventilation, inotropic medication and sedatives, blood gas values and mean arterial blood pressure (MAP) at each day echocardiography was performed. MAP was mainly measured invasively by umbilical arterial catheters. Data for the control groups had been collected previously for other studies [19–21].

2.5. Statistical Analysis

Continuous unrelated variables were compared by t-tests, One-Way Analysis-Of-Variance (ANOVA) tests with Fisher’s Least Significant Difference (LSD) for post-hoc pair-wise comparisons and independent samples Kruskal–Wallis tests with pair-wise post-hoc tests. Categorical data were compared by Chi-square tests. Variance analyses, paired-sample t-tests and Fridman test for repeated measurements were used for related variables. Missing data were handled by omitting the missing values. Two-sided p-values and 95% confidence intervals were used. Repeatability was assessed by intraclass correlation coefficients by analysing seven images from each of the three groups, twice by the same researcher (EN) several months apart and once by another researcher (AS).

3. Results

3.1. Study population and demographic data

Fifty-one infants were cooled during the study period. Seven cases were excluded from the final analyses; one refused participation, one had postnatal asphyxia, one was later diagnosed with Dystrophia Myotonica, in one case the treatment was aborted due to severe
There were no changes over time in pH or PCO₂. MAP varied between 3.2. Myocardial deformation indices are shown in Table 3. Base de and both control groups. Data at each examination in the HT-group controls than in the HT-group, FS was similar between the HT-group in any of the groups. Except for a lower FS at day three in the healthy HT-group than in the NT-group. The FS did not change between days among infants not receiving inotropic medication with the highest value on day 3, while there were no changes in MAP in infants receiving inotropic medication. Details on the use of sedatives and inotropic medications could be performed due to lack of personnel. Forty-one of the 44 included survived to discharge.

Demographic, clinical and conventional echocardiographic data are shown in Table 2. Gestational age, birth weight and Apgar score at 1 and 5 min were lower in the HT-group than in the healthy controls. That some indices were lower in the HT-group than in the NT-group, the HT-group had probably a more severe hypoxic–ischemic encephalopathy. All strain-rate indices in the HT-group improved significantly after rewarming on day 4 while there were no changes in PSS. No indices after rewarming on day 4 were different from the healthy controls on day 3. All indices after rewarming were higher than in the NT-group on day 3, except for the ESR.

There were no variations in any indices with gestational age, age in hours at examination within each day, or between indices from images acquired by each of the four different operators performing the scans. Impacts on the indices in the treatment group from the use of sedatives, inotropic medication and mechanical ventilation, and from the MAP, pH, Lactate and Base Deficit at each examination were seldom present; significant impacts were found from lactate (mmol/L) on the PSSR \((B = 0.051, SE = 0.023, p = 0.035 \text{ (B: regression factor, SE: standard error for the regression factor, p = p-value)}) and on the ASR \((B = 0.097, SE = 0.038, p = 0.015)\) and the ASR was significantly lower \((0.69 (0.22)/s \text{ (mean (SE) (p = 0.003)})\) in ventilated that in non-ventilated neonates. Further, there were no impacts from the maximal cTnT or the presence of convulsions on any indices in the treatment group.

3.3. Repeatability

The PSS intra-class correlation coefficients were 0.98 for the intra-observer and 0.89 for the inter-observer analyses, and the corresponding strain-rate coefficients ranged 0.93–0.96 and 0.84–0.95.

4. Discussion

All indices on days 1 and 3 were lower in both the HT-group and the NT-group than in the healthy controls and thus confirm that the reduced myocardial function following perinatal asphyxia can be assessed by echocardiography[6–9,12,20–23,33]. Although the Apgar score at 1 and 5 min were similar in the HT-group and the NT-group, the HT-group had probably a more severe hypoxic–ischemic insult than the NT-group, as the initial pH, Apgar score at 10 min, Base Deficit and peak cTnT were significantly worse in the HT-group. That some indices were lower in the HT-group than in the NT-group on day one and three could either be due to a more pulmonary hypertension and in three cases no tissue Doppler examinations could be performed due to lack of personnel. Forty-one of the 44 included survived to discharge.

Demographic, clinical and conventional echocardiographic data are shown in Table 2. Gestational age, birth weight and Apgar score at 1 and 5 min were lower in the HT-group than in the healthy controls. As expected, the heart rate at days 1 and 3 were lower in the HT-group than in both control groups. Apgar score at 10 min and initial pH were lower and the first PCO₂ and Base Deficit were higher in the HT-group than in the NT-group. The FS did not change between days among infants not receiving inotropic medication with the highest value on day 3, while there were no changes in MAP in infants receiving inotropic medication. Details on the use of sedatives and inotropic medication are shown in Table 4.

3.2. Myocardial deformation indices

The absolute values of the deformation indices are shown in Fig. 1. On days 1 and 3, all indices were lower in absolute value in both the HT-group and the NT-group than in the healthy controls. The days 1 and 3 PSSR and the day 1 ASR were significantly lower in the HT-group than in the NT-group. The PSS and ASR in the HT-group and the PSS in the healthy controls improved from day 1 to day 3. There were no changes over time in pH or PCO₂, MAP varied between 3.2.

The absolute values of the deformation indices are shown in Fig. 1. On days 1 and 3, all indices were lower in absolute value in both the HT-group and the NT-group than in the healthy controls. The days 1 and 3 PSSR and the day 1 ASR were significantly lower in the HT-group than in the NT-group. The PSS and ASR in the HT-group and the PSS in the healthy controls improved from day 1 to day 3.

All strain-rate indices in the HT-group improved significantly after rewarming on day 4 while there was no change in PSS. No indices after rewarming on day 4 were different from the healthy controls on day 3. All indices after rewarming were higher than in the NT-group on day 3, except for the ESR.

Table 2
Demographic, clinical and conventional echocardiographic data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonates with HIE treated with therapeutic hypothermia (HT-group)</th>
<th>Neonates with HIE treated with normothermia (NT-group)</th>
<th>Healthy neonates</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (examinations)</td>
<td>44 (118)</td>
<td>20 (34)</td>
<td>48 (92)</td>
<td>0.003b</td>
</tr>
<tr>
<td>GA (weeks) (median[quartiles])</td>
<td>39.5 (38, 41)</td>
<td>40 (39, 41)</td>
<td>41 (40, 41)</td>
<td>*</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.38 (0.09)</td>
<td>3.35 (0.15)</td>
<td>3.68 (0.07)</td>
<td>0.014f</td>
</tr>
<tr>
<td>Apgar score (median[quartiles])</td>
<td>3.5 (3.5)</td>
<td>5 (4.6)</td>
<td>9 (9, 9)</td>
<td>*</td>
</tr>
<tr>
<td>First pH</td>
<td>7.07 (0.02)</td>
<td>7.21 (0.04)</td>
<td>9 (9, 9)</td>
<td>*</td>
</tr>
<tr>
<td>First PCO₂ (kPa)</td>
<td>7.2 (0.6)</td>
<td>5.7 (0.5)</td>
<td>0.2f</td>
<td></td>
</tr>
<tr>
<td>First Base Deficit (mmol/L)</td>
<td>16.3 (0.9)</td>
<td>9.3 (1.7)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Peak cardiac troponin T (mmol/L) (median[quartiles])</td>
<td>0.29 (0.19, 0.57)</td>
<td>0.11 (0.06, 0.20)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Age at examination (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>11.9 (0.7)</td>
<td>8.4 (1.2)</td>
<td>12.2 (0.7)</td>
<td>*</td>
</tr>
<tr>
<td>Day 3</td>
<td>60.7 (1.0)</td>
<td>56.1 (1.6)</td>
<td>58.6 (0.7)</td>
<td>0.026f</td>
</tr>
<tr>
<td>Day 4</td>
<td>88.1 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>98 (2)</td>
<td>127 (3)</td>
<td>124 (2)</td>
<td>*</td>
</tr>
<tr>
<td>Day 3</td>
<td>96 (2)</td>
<td>123 (4)</td>
<td>118 (2)</td>
<td>*</td>
</tr>
<tr>
<td>Day 4</td>
<td>124 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional Shortening (per cent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>29.5 (1.3)</td>
<td>30.0 (1.9)</td>
<td>29.3 (0.7)</td>
<td>0.9f</td>
</tr>
<tr>
<td>Day 3</td>
<td>31.5 (1.0)</td>
<td>29.2 (1.7)</td>
<td>28.0 (0.8)</td>
<td>*</td>
</tr>
<tr>
<td>Day 4</td>
<td>33.1 (0.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival to discharge (per cent)</td>
<td>41/44 (93%)</td>
<td>19/20 (95%)</td>
<td>48/48 (100%)</td>
<td>0.2f</td>
</tr>
</tbody>
</table>

Results are mean (SEM) unless otherwise indicated. P-values are for overall group differences. (SEM: standard error of the mean.) HIE: hypoxic–ischemic encephalopathy.

- a Different from the asphyxiated neonates treated with therapeutic hypothermia.
- b Independent sample Kruskal–Wallis test.
- c One-way ANOVA test.
- d T-test.
- e Different from the healthy controls.
- f Chi square test.
severe insult in the HT-group or the cooling itself. One-segment strain-rate indices can be regarded as AV-plane velocities normalised for heart size, and Wei and colleagues [22] have shown lower AV-plane systolic velocities in severe than less severe asphyxia. Czernik and colleagues found a decreased peak systolic strain rate and no decrease in peak systolic strain in the left heart during therapeutic hypothermia by use of B-mode speckle tracking [23], while Sehgal and colleagues found a decrease in peak systolic strain in the left heart during hypothermia [24], in accordance with the decreased peak systolic strain found in our study. An increase in circumferential function indices concomitant with a reduction in longitudinal function indices has been described [34], and we observed the same phenomenon at day 3, where the FS was higher in the cooled infants than in the healthy controls.

Echocardiographic data in our study were obtained during the first four days of life when profound changes in the neonatal circulation occur. There are few longitudinal data on the normal circulatory changes directly comparing the myocardial function on day 3 and day 4. However, the major changes take place during the first day, with little or no changes on the following days [13,35–38]. The impact from perinatal asphyxia on the heart has been shown to be more pronounced on the first days of life as compared to subsequent examinations [20,22,39], but studies of the impact after day 3 of life in non-cooled infants are scarce. Given the present evidence for the effect of therapeutic hypothermia [1,40], novel longitudinal data on the myocardial function in infants with HIE treated at normal temperature might not become available. Left heart strain and strain rate indices by B-mode speckle tracking have been shown similar in cooled infants immediately after rewarming and at days 5–7 [22].

Significant haemodynamic changes occur during rewarming [33,41]. The profound differences between days 3 and 4 in the HT-group could have been influenced not only by the rewarming but also by the longer time interval since the hypoxic–ischemic insult. As there were no change within the NT-group and only minor changes in the HT-group between days 1 and 3, we suggest that the changes were mainly related to the rewarming. Kishkurno and colleagues have suggested that neonatal hearts work at a maximal level of contractility [35]. Changes in peak systolic strain-rate have been suggested to reflect changes in contractility, being less influenced by the loading conditions than conventional indices of myocardial function (FS) and peak systolic strain [27–31]. The differences between the HT-group and NT-group could reflect differences in the maximal capacity for cardiac work, and the increase within the HT-group from day 3 to 4 along with the lack of difference between the HT-group at day 4 and the healthy controls at day 3 could indicate that therapeutic hypothermia preserved the ability of the heart to work at a high level of contractility.

The high lactate at day 1 probably reflects the insult. As the lactate levels normalised on the following days and were normal also when the myocardial function was low on day 3, tissue perfusion was probably adequate during cooling. Because the reductions in the myocardial function in the HT-group and NT-group were similar, the myocardial function might have been insufficient in the NT-group, as a higher myocardial function would have been expected due to the higher metabolic demands when kept normothermic.

From this study, the impact from use of inotropic medication, MAP and sedatives on the myocardial function could not be assessed, as inotropic medication was probably used more often in infants in an impaired haemodynamic state. Inotropic medication (Dopamine) was used only in one infant in the NT-group. The effect of mechanical ventilation on the ASR was probably caused by changes in the loading conditions.

The finding of similar reduced myocardial function in the two asphyxiated groups might suggest that the cooling added little extra depression of myocardial function in infants with HIE. One possible

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical data at each day of echocardiography in the infants with HIE treated with therapeutic hypothermia (HT-group).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td>During hypothermia</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td>Neonates examined (n)</td>
<td>40 (73%)</td>
</tr>
<tr>
<td>Mechanical ventilation n (%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Inotropic medication n (%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Dobutamine n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Adrenaline n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Sedation (morphine) n (%)</td>
<td>40 (100%)</td>
</tr>
<tr>
<td>MAP (mm Hg) (mean (SEM))</td>
<td>44.5 (1.3)</td>
</tr>
<tr>
<td>With inotropic medication</td>
<td>46.0 (0.8)</td>
</tr>
<tr>
<td>Without inotropic medication</td>
<td>46.0 (0.8)</td>
</tr>
<tr>
<td>Arterial blood sample (median (quartiles))</td>
<td>7.27 (7.15, 7.31)</td>
</tr>
<tr>
<td>pH</td>
<td>4.8 (2.8, 6.5)</td>
</tr>
<tr>
<td>Base deficit (mmol/L)</td>
<td>1.4 (0.8, 2.4)</td>
</tr>
<tr>
<td>PCO2 (kPa)</td>
<td>8.1 (5.3, 13.4)</td>
</tr>
</tbody>
</table>

P-values are for overall differences by Friedman test for repeated measurement unless otherwise indicated. (SEM: Standard error of the mean.)

HIE: hypoxic–ischemic encephalopathy.

* Different from day 3 and day 4.

Table 4 Details on use of sedatives and inotropic medication in the infants treated with therapeutic hypothermia for HIE (HT-group).

| Morphone treatment n (%) | 44 (100%) | 19 (50%) | 9 (24%) |
| Age at start of treatment (h) | 4 (1–12) | 14 (2–83) | 30 (19–35) |
| Duration of treatment (h) | 84 (39–182) | 14 (2–83) | 14 (2–83) |
| Peak dose (μg/kg/min) | 40 (12–70) | 40 (12–70) | 10 (4–20) |
| Dobutamine treatment n (%) | 23 (52%) | 3 (7%) | 1 (2%) |
| Age at start of treatment (h) | 28 (13–55) | 14 (2–83) | 28 (13–55) |
| Duration of treatment (h) | 76 (7–115) | 76 (7–115) | 76 (7–115) |
| Peak dose (μg/kg/min) | 9 (4–30) | 9 (4–30) | 9 (4–30) |

Results are median (range) unless otherwise indicated.
mechanism for the significant increase in indices from day 3 to 4 in the cooled infants could be that the cooling had two opposite effects on the myocardial function, a depressive effect imposed during cooling and a preservative effect on the myocardial function. However, our study was not designed to study these effects separately.

4.1. Limitations

This study has several limitations. Great care must always be taken when interpreting results based on historical control groups. Even though there is little evidence of changes in myocardial function between days 3 and 4 after birth, the control groups were not examined at day 4, and hence the natural history of myocardial function in the control groups beyond day 3 was not documented. Historical control groups were used, but a prospective trial with inclusion of non-cooled infants with HIE is at present ethically disputable. The NT-group were less severely asphyxiated than the HT-group, a problem probably of even more concern if the results had not shown a better myocardial function in the HT-group after rewarming than in the NT controls. The myocardial injury was compared biochemically between the asphyxiated groups by the peak cTnT value, since only the peak cTnT values were available for the asphyxiated controls. MAP measurements were not available for the control groups. Measurements of stroke volume and cardiac output were not available in the study group. As measurements from historical controls were used, the analyses could not be blinded between the protocol group and the control groups. To assess the impact from the myocardial function on the outcome further long-term evaluation of treated infants is required.

5. Conclusion

Infants cooled for 72 h for HIE had impaired myocardial function during hypothermia as compared to healthy term infants, but at the same level as in non-cooled infants with HIE. The myocardial function improved significantly from the examination during cooling on days 1 and 3 to the examination after rewarming on day 4. The myocardial function at day 4 was higher than at day 3 in non-cooled infants with HIE, and similar to the function at day 3 in healthy infants.

Conflicts of interest statement

There are no conflicts of interest.

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