

## Changes in the PQRST Intervals and Heart Rate Variability Associated with Rewarming in Two Newborns Undergoing Hypothermia Therapy

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### Key Words

Hypoxic-ischemic encephalopathy · Hypothermia therapy · Electrocardiogram · QT interval · Heart rate variability

### Abstract

**Background:** Little is known about the effects of hypothermia therapy and subsequent rewarming on the PQRST intervals and heart rate variability (HRV) in term newborns with hypoxic-ischemic encephalopathy (HIE). **Objectives:** This study describes the changes in the PQRST intervals and HRV during rewarming to normal core body temperature of 2 newborns with HIE after hypothermia therapy. **Methods:** Within 6 h after birth, 2 newborns with HIE were cooled to a core body temperature of 33.5°C for 72 h using a cooling blanket, followed by gradual rewarming (0.5°C per hour) until the body temperature reached 36.5°C. Custom instrumentation recorded the electrocardiogram from the leads used for clinical monitoring of vital signs. Generalized linear mixed models were calculated to estimate temperature-related changes in PQRST intervals and HRV. **Results:** For every 1°C increase in body temperature, the heart rate increased by 9.2 bpm (95% CI 6.8–11.6), the QTc interval decreased by 21.6 ms (95% CI 17.3–25.9), and low and high frequency HRV decreased by 0.480 dB (95% CI 0.052–0.907) and 0.938 dB (95% CI 0.460–1.416), respectively. **Conclusions:** Hypothermia-induced changes in the electrocardiogram should be monitored carefully in future studies.

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Recent randomized controlled trials suggest that head cooling and whole-body hypothermia may reduce the high rates of mortality and neurodevelopmental morbidity associated with neonatal hypoxic-ischemic encephalopathy (HIE) [1–3]. Hypothermia has well-documented effects on the adult cardiovascular system [4–6]. The cited randomized controlled trials [1–3] involving newborns with moderate to severe HIE report a reversible slowing of the heart rate with cooling. Sinus bradycardia and hypotension requiring inotropic support increase in neonates undergoing cooling for HIE [7]. Gunn et al. [8] reported that the heart rate of an HIE newborn cooled (head cooling) to 34°C slowed to 85 bpm with an abnormally prolonged QT interval (570 ms in lead V5). No arrhythmias were detected. One day after rewarming, the heart rate and QT interval were within the normal range. Horan et al. [9] have recently reported much more modest effects of cooling on the QTc (corrected) interval. The QTc interval of infants receiving extracorporeal membrane oxygenation therapy increased by 3.12 ms (95% CI 0.84–6.17) for each degree drop (from 37 to 34°C) in body temperature during the first 48 h of cooling. ‘During rewarming, there was no significant relationship between QTc and temperature change’ (p. 217). The data analysis by Horan et al. [9] compared QTc intervals of different infants at different temperatures. Therefore, the reported differences in QTc may be influenced by factors that vary between infants other than temperature. Large between-patient variability

**Table 1.** Temperature-related changes in the PQRST intervals during rewarming

ECG interval	Change associated with a 1°C increase in temperature	Lower bound of the 95% CI	Upper bound of the 95% CI	p value
PR, ms	-1.0	-3.4	1.5	0.435
QRS, ms	-1.1	-2.5	0.4	0.139
QT, ms	-27.1	-31.3	-22.9	<0.001
QTc, ms	-21.6	-25.9	-17.3	<0.001
RR, ms	-36.0	-44.9	-27.2	<0.001
Heart rate, bpm	9.2	6.8	11.6	<0.001

**Table 2.** Temperature-related changes in the HRV during rewarming

Frequency band	Change in power associated with a 1°C increase in temperature	Lower bound of the 95% CI	Upper bound of the 95% CI	p value
VLF, dB	-0.249	-0.905	0.409	0.459
LF, dB	-0.480	-0.907	-0.052	0.028
HF, dB	-0.938	-1.416	-0.460	<0.001
LF/HF	0.024	0.013	0.035	<0.001

VLF = Very low frequency; LF = low frequency; HF = high frequency.

may obscure within-patient changes in QTc. In contrast, within-subject designs evaluate changes in QTc associated with changes in temperature within the same newborn.

We report hypothermia-induced changes in the electrocardiograms (ECGs) of 2 newborns after being cooled and gradually rewarmed. We also analyzed temperature-induced changes in heart rate variability (HRV), hypothesized to be an indicator of stress in newborns and a predictor of a wide range of adverse health outcomes [10–12]. To our knowledge, there are no reports of the effects of cooling and rewarming on HRV in newborns.

## Methods

This substudy was reviewed and approved by our Institutional Review Board, and consent was obtained for 2 newborns undergoing hypothermia therapy as participants in the National Institutes of Child Health and Human Development whole-body hypothermia trial [3]. Within 6 h after birth, the newborns were

cooled to a core body temperature of 33.5°C for 72 h using a cooling blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero Products, Inc., Cincinnati, Ohio, USA) followed by gradual rewarming (0.5°C per hour) until body temperature reached 36.5°C.

Custom LabView (National Instruments Inc., Austin, Tex., USA) instrumentation recorded the ECG (digitized at 1 kHz) from the leads used for clinical monitoring of vital signs. The latencies of the start of the P wave, the peak of the P wave, the start of the Q wave, the Q, R and S peaks, the end of the S wave, the T peak, the end of the T wave, and the peak of the U wave (if present) were measured for 10 consecutive heart beats from segments of stable and artifact-free ECG. No Osborn waves (positive deflections in the ECG at the junction of the S wave that are associated with hypothermia) were detected.

The PR interval reflecting the duration of atrial activation, the QRS complex reflecting the duration of ventricular activation, the QT interval reflecting ventricular activation and repolarization/recovery, Bazett's correction (QTc = QT divided by the square root of the preceding RR interval), and the RR interval (the reciprocal of the heart rate) were calculated from the measured values. The means of these measures for 10 consecutive beats were used in all subsequent analyses.

In addition, the R waves of QRS complexes were identified and a vector of interbeat intervals was generated to analyze HRV. After cubic polynomial detrending of each segment of 720 consecutive heart periods, the Kolmogorov-Smirnov test was used to assess stationarity (constant statistical properties over time). The power spectra of the HRV measurements were computed using Lomb's algorithm. The resulting power spectrum was integrated within a very low-frequency power band (0.003–0.03 Hz), a low-frequency (LF) power band (0.04–0.25 Hz) and a high-frequency (HF, respiratory sinus arrhythmia) power band (0.25–1.00 Hz). The band powers  $P_i$  were averaged on all stationary segments after conversion to decibels using a reference value of 0.02 Hz ms<sup>2</sup>:  $10 \log_{10} (P_i/0.02)$ . The LF/HF ratio was calculated as a measure of sympathetic modulation of the heart rate.

Generalized linear mixed models were calculated using STATA (version 10.0, Stata Corp., College Station, Tex., USA) to estimate temperature-related changes in the ECG. The repeated measurements during rewarming were clustered within each of the 2 newborns (a 2-level hierarchical model) to account for the correlations among measurements. Temperature was estimated from an esophageal probe. The esophageal probe was removed when the esophageal temperature reached 36.5°C. Thereafter, the axillary temperature was measured.

## Results

One of the newborns studied was a 3,850-gram, 40-week gestational age white female, with a venous umbilical cord blood gas pH of 6.57, and 1-, 5- and 10-min Apgar scores of 3 or less. The other newborn was a 2,910-gram, 37-week gestational age Hispanic female, with an arterial umbilical cord blood gas pH of 6.98, and 1-, 5- and 10-min Apgar scores of 4 or less. Both newborns were clas-

sified as having moderate encephalopathy based on a modified Sarnat exam [3].

Table 1 indicates that the decrease in the RR interval (increase in heart rate) with rewarming reported in other studies was replicated. The decrease in the RR interval was associated with a significant reduction in QT, but not in PR or QRS. Neither newborn experienced bradycardia, arrhythmias or hypotension during the recording session.

The HRV results are presented in table 2. Allowing separate slopes (random coefficients) for each newborn improved model fit for the LF model but not the very low-frequency or HF models. LF and HF powers decreased with rewarming. Including the heart rate in the model increased the magnitude of the significant decrease in HF power associated with rewarming (-2.658, 95% CI -4.108 to -1.209).

## Discussion

Most of the observed cooling effects responsible for the dramatic slowing of the heart rate are associated with events after the activation of the atria and ventricles. Our study indicates that cooling induces QTc prolongations in hypoxic term newborns that become normal with rewarming. A prolonged QTc is associated with ventricular

arrhythmias in adult patients. Ventricular arrhythmias have been reported to be more frequent in accidental hypothermia [13] and in patients cooled (35°C) during surgery [14].

Critically ill preterm newborns have depressed HRV at normal body temperature [15]. Increased LF and HF HRV power during cooling in term newborns replicate the results in adult hypothermia-treated patients [16]. Tiainen [16] concluded that 'hypothermia may preserve autonomic regulation of the heart' and that 'HRV was associated with a more favorable outcome in hypothermia-treated (adult) patients' (pp. 80–81). Given the similarity of results for Tiainen's adult patients and the newborns in this study, Tiainen's conclusions may also apply to term newborns. Testing that hypothesis deserves research attention. Hypothermia-induced changes in the heart rate, PQRST intervals and HRV should be evaluated carefully in future trials involving newborn patients, especially if the depth and duration of hypothermia are increased.

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