Hemodynamic Changes During Rewarming Phase of Whole-Body Hypothermia Therapy in Neonates with Hypoxic-Ischemic Encephalopathy

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Objective To delineate the systemic and cerebral hemodynamic response to incremental increases in core temperature during the rewarming phase of therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy (HIE).

Study design Continuous hemodynamic data, including heart rate (HR), mean arterial blood pressure (MBP), cardiac output by electrical velocimetry (CO_{EV}), arterial oxygen saturation, and renal ($RrSO_2$) and cerebral ($CrSO_2$) regional tissue oxygen saturation, were collected from 4 hours before the start of rewarming to 1 hour after the completion of rewarming. Serial echocardiography and transcranial Doppler were performed at 3 hours and 1 hour before the start of rewarming (T-3 and T-1; "baseline") and at 2, 4, and 7 hours after the start of rewarming (T+2, T+4, and T+7; "rewarming") to determine Cardiac output by echocardiography (CO_{echo}), stroke volume, fractional shortening, and middle cerebral artery (MCA) flow velocity indices. Repeated-measures analysis of variance was used for statistical analysis.

Results Twenty infants with HIE were enrolled (mean gestational age, 38.8 ± 2 weeks; mean birth weight, 3346 ± 695 g). During rewarming, HR, CO_{echo}, and CO_{EV} increased from baseline to T+7, and MBP decreased. Despite an increase in fractional shortening, stroke volume remained unchanged. $RrSO_2$ increased, and renal fractional oxygen extraction (FOE) decreased. MCA peak systolic flow velocity increased. There were no changes in $CrSO_2$ or cerebral FOE.

Conclusions In neonates with HIE, CO significantly increases throughout rewarming. This is due to an increase in HR rather than stroke volume and is associated with an increase in renal blood flow. The lack of change in cerebral tissue oxygen saturation and extraction, in conjunction with an increase in MCA peak systolic velocity, suggests that cerebral flow metabolism coupling remained intact during rewarming. *(J Pediatr 2018;■■:■■-■■).*

Neonatal hypoxic-ischemic encephalopathy (HIE) is estimated to affect more than 1 million newborn infants annually worldwide.[1] Over the past decade, therapeutic hypothermia has emerged as standard of care for neonatal HIE.[2]

During whole-body therapeutic hypothermia, the lowering of core temperature induces a myriad of physiological changes.[3] These include, but are not limited to, lower heart rate (HR) from slowing of the firing of the sinoatrial node,[4] decreased cardiac output and mild to no hypotension,[5] centralization of blood flow via peripheral vasoconstriction, increased metabolic heat production,[6] decreased cerebral and systemic metabolic rate, mild hyperglycemia, mild coagulopathy, and diminished immunoreactivity.[3] At the target organ, decreased cerebral oxygen consumption is coupled to a relative decrease in cerebral blood flow.[7-10] However, despite an overall lower cerebral blood flow, a higher percentage of left ventricular output is directed to the injured brain.[11]

Because neuroapoptosis is mitigated by lowering the core temperature, rewarming may reinitiate or hasten the destructive process.[12-15] Generally, the rewarming phase at the end of therapeutic hypothermia in neonates with HIE proceeds at a

aEEG	Amplitude-integrated electroencephalography
CO_{echo}	Cardiac output by echocardiography
CO_{EV}	Cardiac output by electrical velocimetry
$CrSO_2$	Regional cerebral oxygen saturation
FOE	Fractional oxygen extraction
HIE	Hypoxic-ischemic encephalopathy
LVEDA	Left ventricular end-diastolic area
LVESA	Left ventricular end-systolic area
MBP	Mean arterial blood pressure
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
$RrSO_2$	Regional renal oxygen saturation
SpO_2	Arterial oxygen saturation
SVR	Systemic vascular resistance

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recommended incremental rate of 0.5°C/hour. Slower rewarming rates have been advocated for patients with postcardiac arrest (0.25°C/hour) and severe traumatic brain injury (0.1°C/hour).[16] In animal studies, rapid rewarming results in temporary flow-metabolism uncoupling,[17] worsening of traumatically induced axonal injury,[18] loss of neuroprotective effects of therapeutic hypothermia,[19,20] and increased mortality.[21] In neonates, unwanted effects of rewarming from hypothermia include systemic hypotension,[22] seizures,[23] and even intraventricular hemorrhage.[24]

Hemodynamic changes have been described during the rewarming phase of therapeutic hypothermia, including increases in cardiac output and systolic blood pressure and a decrease in systemic vascular resistance (SVR) and diastolic blood pressure.[25] However, these studies had small numbers of patients[5,22] or focused on the use of a single monitoring tool, such as echocardiography,[11,26,27] transcranial Doppler, or near-infrared spectroscopy (NIRS).[28,29] Time-synced, comprehensive hemodynamic data collection encompassing the rewarming period is necessary to understand the hemodynamic interplay at both the systemic and organ-specific levels. In this prospective observational study, we characterized a wide range of acute systemic and regional hemodynamic changes using a comprehensive hemodynamic monitoring and data acquisition system and echocardiography during the rewarming phase of therapeutic hypothermia.

Methods

Newborn infants with HIE admitted for therapeutic hypothermia to the Newborn and Infant Critical Care Unit at Children's Hospital Los Angeles between May 2012 and May 2017 were prospectively enrolled in this study. The criteria for initiation of therapeutic hypothermia were similar to those of the National Institute of Child Health and Human Development's whole-body hypothermia trial[30]: gestational age of at least 36 weeks, admitted within 6 hours, cord blood gas or first-hour blood gas pH of ≤7.0 or a base deficit of ≥16 mmol/L. If the pH was 7.01-7.15 or the base deficit was 10-15.9 mmol/L, additional criteria were required, including history of an acute perinatal event and a 10-minute Apgar score ≤5 or the need for assisted ventilation at birth for >10 minutes. For these patients, therapeutic hypothermia was initiated in the presence of moderate to severe encephalopathy based on the Sarnat examination or clinical seizures. Patients with a birth weight <1800 g, a congenital heart defect, no direct arterial blood pressure monitoring data, higher doses of vasopressors-inotropes (eg, dopamine >10 μg/kg/min), or extracorporeal membrane oxygenation were excluded from the study. The hospital's Institutional Review Board approved the study. Written consent from parents was obtained before enrollment.

Whole-body therapeutic hypothermia maintained at target rectal temperature of 33.5°C for 72 hours was achieved using a cooling device and disposable blanket (Blanketrol III; Cincinnati Sub-Zero, Cincinnati, Ohio). HIE severity was assessed by Sarnat staging on admission. Patients were monitored for seizures using amplitude-integrated EEG (aEEG) until rewarming was complete. No patient experienced a clinically evident or aEEG-detected seizure during the rewarming period. Rewarming was accomplished over 6 hours by manually raising the target rectal temperature from 33.5°C to 36.5°C in increments of 0.5°C/hour.

Echocardiography and Doppler Measurements

Interval measurements of left ventricular output by echocardiography (CO_{echo}), fractional area shortening by echocardiography, and middle cerebral artery (MCA) velocity indices by transcranial Doppler (Philips iE33 ultrasound machine; Philips, Andover, Massachusetts) were performed at 5 different time points by a single operator. Baseline measurements were obtained at 3 hours and 1 hour before the initiation of rewarming (T-minus hours: T-3 and T-1), and 3 rewarming measurements were obtained at 2, 4, and 7 hours after the initiation of rewarming (T-plus hours: T+2, T+4, and T+7). Data collection at T-3, T-1, T+2, T+4, and T+7 corresponded to 1 hour of steady state at target temperatures of 33.5°C, 34.5°C, 35.5°C, and 36.5°C, respectively. All patients had a closed or constricting ductus arteriosus at time of the echocardiography examinations. From the apical view, pulsed wave Doppler was performed to measure blood velocity at the aortic valve. Fully enveloped Doppler waveforms that were similar in shape and size were used to measure the velocity time integral and then averaged over 4 consecutive cardiac cycles. Aortic valve annulus diameter (D) was measured from the parasternal long-axis view during the first examination. CO_{echo} (in mL/kg/minute) was calculated as $[(\pi D^2/4) \times$ average velocity time integral $\times$ HR] and normalized for body weight (in kg). From the parasternal short-axis view, left ventricular end-diastolic area (LVEDA) and end-systolic area (LVESA) were calculated by endocardial contour tracing at the level of the midpapillary muscle. Left ventricular fractional shortening (%) was calculated as $[(\text{LVEDA} - \text{LVESA})/\text{LVEDA}] \times 100$.[31]

Flow velocity indices in the left MCA were measured using pulse-wave Doppler. The left MCA was identified in the axial plane through the temporal window by color Doppler, and a Doppler sample gate was placed at the proximal portion (M1) of the MCA. Common velocity indices (peak systolic, end diastolic, and mean velocity) were obtained by outlining the waveform envelope manually and averaging over 3-4 consecutive cardiac cycles. Resistive index was calculated as (peak systolic velocity - end diastolic velocity)/peak systolic velocity.

Data Collection and Synchronization

HR, arterial oxygen saturation (SpO_2), and systolic, diastolic and mean arterial blood pressure (from an indwelling arterial catheter) were recorded with a Philips Intellivue MP70 ECG monitor (Philips). Cardiac output measured by electrical velocimetry (CO_{EV}) was averaged over 10 cardiac cycles with an ICON monitor (Osypka Cardiotronic, La Jolla, California).[32] SVR was calculated as SVR = 80 × (MBP - right atrial pressure)/CO_{echo}, with right atrial pressure assumed to be 5 mmHg for all patients. Frontal cerebral regional tissue oxygen saturation ($CrSO_2$) and left renal regional tissue oxygen saturation ($RrSO_2$) values were acquired every 30 seconds by NIRS using

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