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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INVOS infant-neonatal sensors and a 5100C oximeter (Covidien, Mansfield, Massachusetts). Fractional oxygen extraction (FOE) was calculated as FOE = (SpO_2 - $CrSO_2$)/SpO_2. The renal-cerebral oxygenation ratio was calculated by dividing $RrSO_2$ by $CrSO_2$. The foregoing clinical variables were captured for 11 hours, from 4 hours before to 7 hours after the start of rewarming, and time-synchronized every 30 seconds with a data integration and storage platform (Vital Sync; Medtronic, Minneapolis, Minnesota or Bernoulli One; Bernoulli Enterprise, Milford, Connecticut).

aEEG was monitored using an Olympic Brainz Monitor (Natus Medical, Pleasanton, California). The aEEG data were not synchronized with the data integration and storage platforms.

Magnetic Resonance Imaging Grading of HIE Severity

Noncontrast brain magnetic resonance imaging (MRI) was performed at a median age of 6 days (IQR, 5-9 days). A pediatric neuroradiologist blinded to the hemodynamic data and clinical outcome of the patients reviewed the images based on a previously described scoring system.[33] T1-, T2-, and diffusion-weighted MRI sequences were scored according to acute and subacute signal abnormalities in the basal ganglia/thalamus region (score 0-4) and watershed region (score 0-5). Injury severity was dichotomized to either normal-mild (normal imaging, basal ganglia/thalamus score ≤1, or watershed score ≤2), or moderate-severe (basal ganglia/thalamus score ≥2 or watershed score ≥3).

Statistical Analyses

All continuous data were averaged over 10 minutes at the time points T-3, T-1, T+2, T+4, and T+7. These 5 data points were collected during a quiet state immediately before echocardiography or ultrasound, to avoid analysis of data collected during patient movement or agitation. **Figure 1** (available at www.jpeds.com) illustrates the hemodynamic data captured before and during rewarming.

Datasets at each designated time point were tested for normality using the D'Agostino and Pearson omnibus normality test. For data that passed the normality test, results are presented as mean ± SD; otherwise, data are expressed as median and IQR. Baseline values (T-3 and T-1) were compared using a 2-way paired *t* test. Because the 2 baseline values were not different, data from T-1 served as the baseline values for comparison with the rewarming data. One-way repeated-measures ANOVA with Geisser-Greenhouse correction was used to identify any significant change in each hemodynamic measure from baseline to the end of rewarming (T-1 to T+7). Post hoc analysis using the Tukey multiple-comparisons test identified significant hemodynamic changes between time points. Statistical significance was defined as $P < .05$.

Results

The 20 patients (10 females) enrolled had a mean gestational age of 38.8 ± 2 weeks and a mean birth weight of 3345 ± 695 g. Based on the initial Sarnat staging, 17 infants had moderate encephalopathy and 3 had severe encephalopathy. Based on MRI grading, 16 infants had no or mild brain injury, and 4 had moderate or severe injury. Sarnat staging corresponded closely with MRI severity in all patients except 1 patient who had moderate Sarnat encephalopathy but severe brain injury on MRI. Median Apgar scores at 1 and 5 minutes were 2 (IQR, 1-4) and 4 (IQR, 3-6), respectively. pH and base deficit on umbilical cord blood sample or first-hour arterial blood gas were 6.99 ± 0.13 and 15 ± 5, respectively.

The antecedents of perinatal asphyxia included nonspecific nonreassuring fetal heart tone (n = 11), cephalo-pelvic disproportion (n = 2), abruptio placenta (n = 2), uterine rupture (n = 1), cord prolapse (n = 1), maternal urosepsis (n = 1), maternal cardiovascular collapse (n = 1), and maternal respiratory failure (n = 1). Seven patients had either clinical or aEEG-confirmed seizures and were treated with anticonvulsive drug(s). All patients were seizure-free during the 11 hours of hemodynamic monitoring. One patient received dopamine (7 μg/kg/min) throughout the rewarming period without dose titration. At the end of hemodynamic monitoring (T+7), the mean rectal temperature was 36.5 ± 0.3°C. Temperature-corrected arterial carbon dioxide during the period of data collection was 44.3 ± 6.7 mmHg.

Systemic and Cardiac Hemodynamic Changes

There was no significant difference between the baseline time points (T-3 and T-1) in terms of HR, systolic blood pressure, diastolic blood pressure, MBP, SVR, stroke volume, CO_{EV}, or CO_{echo}. During rewarming, there was an increase in HR ($P = .001$) and in fractional shortening ($P = .019$), but not in stroke volume ($P = .247$) (**Figure 2**, A; available at www.jpeds.com). There were stepwise increases in CO_{EV} and CO_{echo} over time ($P = .001$ for both) (**Figure 2**, B; available at www.jpeds.com). CO_{EV} increased from a baseline of 153 ± 43 mL/kg/min to 197 ± 42 mL/kg/min after rewarming was complete, for an overall CO increase of 29%. Similarly, CO_{echo} increased from a baseline of 149 ± 35 mL/kg/min to 179 ± 34 mL/kg/min, for an overall CO_{echo} increase of 20%. Conversely, both SVR and MBP decreased ($P < .0001$ and $P = .0203$, respectively) during rewarming (**Figure 2**, B). No significant changes in systolic blood pressure, diastolic blood pressure, or pulse pressure were detected.

MCA Doppler Velocity Indices

There was no significant difference between the baseline time points (T-3 and T-1) for peak systolic velocity, mean velocity, end diastolic velocity, and resistive index. We found a significant rise in peak systolic velocity ($P = .002$) over time, with post hoc multiple comparisons test revealing a significant difference between baseline (T-1) vs T+4 ($P = .023$) and T+7 ($P = .023$) (**Figure 3**). There were no significant changes in mean velocity, end diastolic velocity, or resistive index as core body temperature increased over time (data not shown).

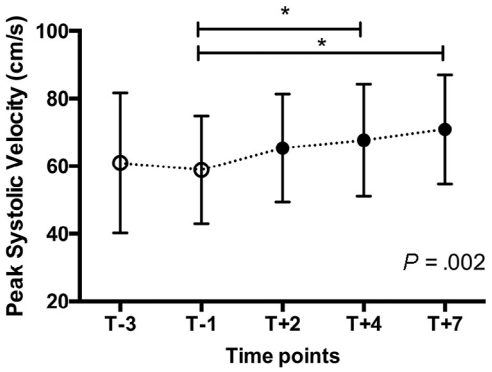

Figure 3. MCA peak systolic velocity during rewarming. Mean peak systolic velocity (± 1 SD) is shown for T-3, T-1 (baseline; open circles), T+2, T+4, and T+7 (rewarming; closed circles). *Significant differences ($P < .05$) between time points as denoted by the horizontal bars.

Regional Tissue Oxygen Saturation and FOE

There was no significant difference between the baseline time points (T-3 and T-1) for $CrSO_2$, $RrSO_2$, cerebral and renal FOE, and renal-cerebral tissue oxygenation ratio. There were no significant changes in $CrSO_2$ and cerebral FOE during the rewarming period. In contrast, $RrSO_2$ increased ($P = .01$) and renal FOE decreased ($P = .002$) (**Figure 4**, A and B). The renal-cerebral tissue oxygenation ratio increased during the rewarming period ($P = .006$) (**Figure 4**, C).

Discussion

In this prospective observational study of 20 neonates undergoing therapeutic hypothermia for HIE, we comprehensively and simultaneously assessed blood pressure, systemic and end-organ blood flow, and its determinants at time points set to correspond to a 1°C incremental increase in target core temperature (i.e. 33.5°C, 34.5°C, 35.5°C, and 36.5°C) during the rewarming process. The steady increase in core temperature to reverse therapeutic hypothermia initiates a dynamic metabolic process, likened to a "kickstart" to reestablish normothermic cerebral metabolism. Maladaptation to rapid rewarming may lead to a mismatch between or uncoupling of oxygen delivery and demand. Overall, we found a significant change in cardiovascular function as evidenced by increases in HR, fractional shortening, and CO_{EV} and CO_{echo} and decreases in SVR and MBP. As for the cerebral circulation, although there was an increase in MCA peak systolic velocity, $CrSO_2$ and cerebral FOE remained unchanged. Interestingly, $RrSO_2$ (in a "nonvital" organ) increased and renal FOE decreased during rewarming. The increase in cardiac output indicates an overall increase in systemic blood flow, and the increase in the renal-cerebral tissue oxygenation ratio suggests a redistribution of the increased systemic blood flow from a cephalic perfusion preference during hypothermia to all organs (vital and nonvital) during rewarming. The flow diagram in **Figure 5** illustrates the

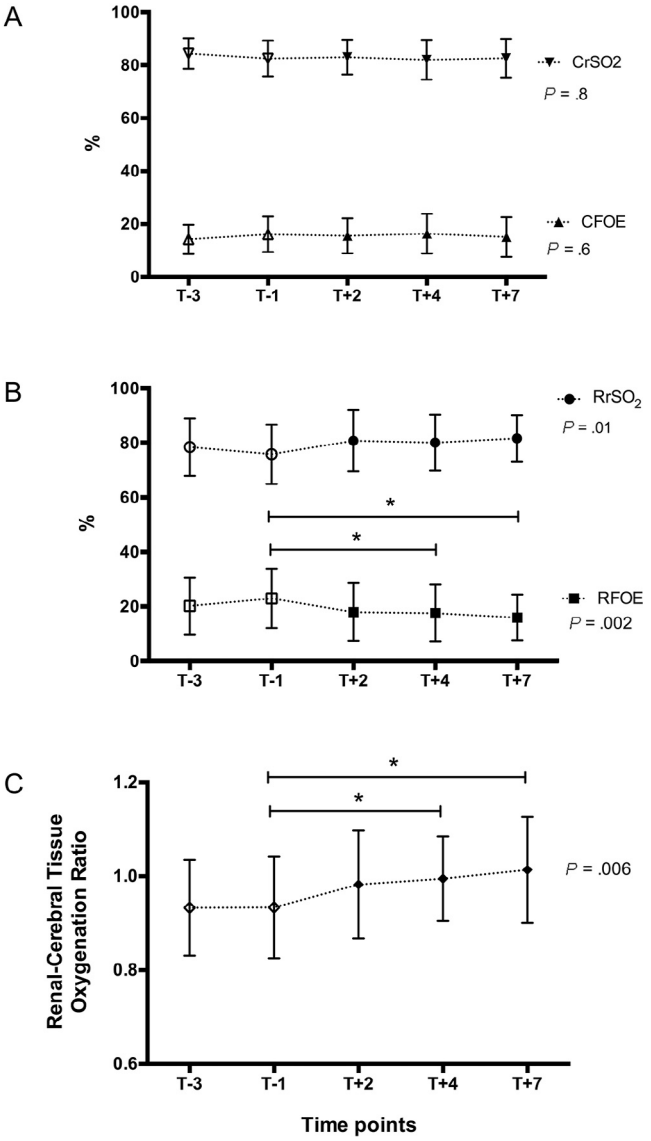

Figure 4. $CrSO_2$, $RrSO_2$, and FOE. **A.** $CrSO_2$ (down-pointing triangle) and cerebral FOE (up-pointing triangle) did not change during rewarming, suggesting intact flow-metabolism coupling. **B,** There was an increase in $RrSO_2$ (circle) (T-1 vs T+2 and T+4) and a decrease in renal FOE (square) during (T-1 vs T+4) and after (T-1 vs T+7) rewarming. **C,** The renal-cerebral tissue oxygenation ratio increased during rewarming (T-1 vs T+4) and after rewarming (T-1 vs T+7), suggesting a shift in blood flow (as a proportion of cardiac output) to nonvital organs while maintaining flow-metabolism coupling in the brain. Data (mean ±1 SD) are shown for T-3, T-1 (baseline; open circles), T+2, T+4, and T+7 (rewarming; closed circles). *Significant differences ($P < .05$) between time points as denoted by the horizontal bars.

complex interactions among the various hemodynamic measures.

It has long been established that HR increases during rewarming[22]; however, little is known about other changes in cardiovascular function. A small study (n = 7) found an increase

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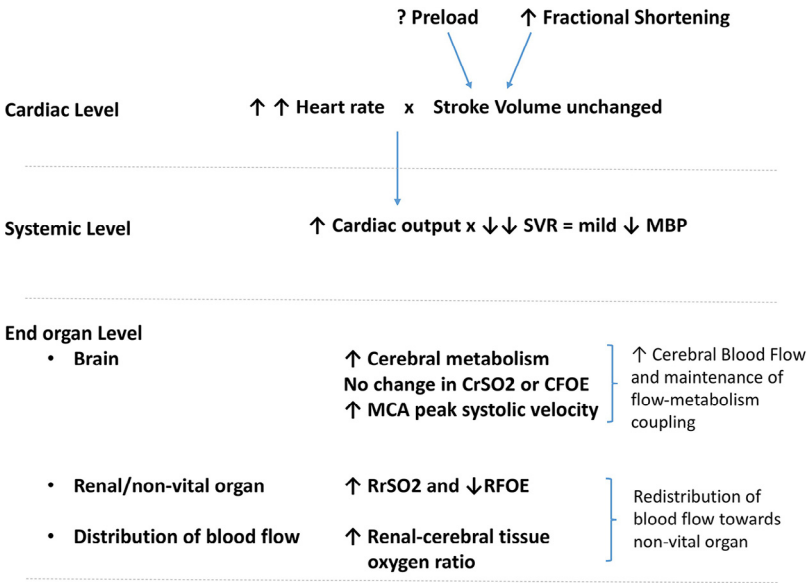

Figure 5. Flow diagram summarizing hemodynamic changes during rewarming. At the cardiac level, the increase in fractional shortening did not result in an increase in stroke volume. There is no information about potential changes in preload. The increase in heart rate led to an overall increase in cardiac output during rewarming. The difference between the magnitude of the decrease in SVR and that of the increase in systemic blood flow resulted in a mild decrease in MBP. Finally, at the end organ level in the brain and kidneys, our findings suggest that preferential cephalic blood flow distribution ceased in response to rewarming, and that despite the mild fall in MBP, vital and nonvital organ blood flow increased during rewarming, and cerebral flow-metabolism coupling was intact at the end of therapeutic hypothermia and remained so during rewarming. See the text for details.

in cardiac output during rewarming,[5] with more than one-half of the patients receiving dobutamine during the study. Similarly, approximately one-half of the patients in a recent study demonstrating an increase in cardiac output with rewarming were also receiving medications supporting cardiovascular function.[34] Except for 1 patient who received a dopamine infusion at a constant rate, our patients were not supported with vasopressors, and thus our finding of increased cardiac output can be attributed solely to the increase in core temperature. The observed increase in cardiac output was due to an increase in HR rather than to an increase in stroke volume, a finding consistent with a recent study.[34] Thus, the modest increase in fractional shortening seen in our cohort did not translate to a significant increase in stroke volume. This is also in agreement with the findings of a more recent study,[11] in which the post-rewarming increases in fractional shortening and stroke volume did not reach statistical significance. The decrease in SVR with rewarming also supports previously reported findings.[34] Of note, despite a 20%-30% increase in cardiac output, the decrease in SVR resulted in a decrease in MBP in our study population. However, although MBP was slightly lower than baseline (51 ± 7.8 vs 47 ± 6.7), it did not meet the accepted gestational age- and postnatal age- dependent definition of neonatal hypotension.[35] In other words, the increase in cardiac output mostly countered the significant fall in SVR, and despite the slight decrease in MBP, maintained perfusion pressure within the acceptable clinical range.

Because metabolic rate increases with increases in core body temperature, rewarming is assumed to be associated with increases in cerebral metabolic rate and oxygen demand. Accordingly, either cerebral blood flow or cerebral FOE (or both) must increase to meet the increased oxygen demand of the brain. In our study population, MCA peak systolic velocity increased and $CrSO_2$ and cerebral FOE remained unchanged, suggesting an increase in cerebral blood flow and intact cerebral flow-metabolism coupling, respectively, during and after rewarming. The finding that $CrSO_2$ and cerebral FOE remained unchanged also implies that flow-metabolism coupling was intact during therapeutic hypothermia, at least 3 hours before the start of the rewarming process.

Other indices of MCA flow (ie, mean velocity, end diastolic velocity, and resistive index) did not change. The reason for this observation is unknown; however, although changes in these indices reflect changes in flow, they represent different properties of the flow-vascular resistance interaction.[36] In addition, it is likely that MCA diameter also increases with rewarming,[37] which results in increased MCA flow even when velocity remains unchanged. Thus, it is possible that the complexity of the interaction between flow and vascular resistance combined with an increased MCA diameter explain the observation that among the indices of flow investigated, only peak systolic velocity increased.

As for renal tissue oxygen saturation, a relatively low baseline (77.3 ± 10.6%) was observed during therapeutic hypothermia compared with the $RrSO_2$ in term healthy newborns

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during the second to third postnatal days (86.8 ± 8.1%).[38] During and after rewarming, $RrSO_2$ rose and renal FOE fell. These findings suggest that, in addition to the increase in renal blood flow in response to rewarming, renal vasoconstriction and decreased renal perfusion had occurred during therapeutic hypothermia. In support of this assumption, the renal-cerebral tissue oxygenation ratio also increased from 0.93 ± 0.1 to 1.01 ± 0.1 after rewarming. Taken together, these findings suggest a progressive improvement in renal (nonvital organ) oxygenation comparable to that observed in the brain by the end of rewarming, and imply the presence of preferential cephalic distribution of left ventricular output during therapeutic hypothermia.[11] The notion of preferential cephalic distribution during therapeutic hypothermia is also supported by findings in the literature.[11,39] In one study, the superior vena cava flow-left ventricular output ratio decreased by 6-12 hours after rewarming,[11] and in another study, the relative proportion of descending aorta blood flow to left ventricular output increased after rewarming.[39]

Our observations add to our knowledge of the changes in vital and nonvital organ perfusion during rewarming from therapeutic hypothermia and they also raise some questions. Our findings indicate that despite a relatively lower systemic blood flow (cardiac output) during therapeutic hypothermia, cerebral blood flow and flow-metabolism remain intact. Cerebral blood flow (a vital organ blood flow) is maintained, at least in part, by the decrease in renal (a nonvital organ) perfusion, as suggested by the decrease in renal tissue oxygenation. However, whether therapeutic hypothermia is protective or detrimental for the kidneys in patients who exhibit the compensatory decrease in renal blood flow to preserve cerebral perfusion is unclear. This issue is especially important in patients in whom the initial hypoxemic-ischemic event also results in acute kidney injury. Indeed, available data show that 38%-56% of newborns treated with therapeutic hypothermia have evidence of acute kidney injury associated with, among other factors, longer duration of mechanical ventilation and longer length of stay.[40,41] Because fluid restriction is the mainstay of supportive therapy in these patients, the already low cardiac output might be further compromised in these patients when fluid administration is restricted. Future in-depth hemodynamic studies with a focus on patients with hemodynamic compromise and acute kidney injury are needed to address this clinically relevant question. Although therapeutic hypothermia is neuroprotective, it is important to investigate whether the effects of therapeutic hypothermia in patients with renal injury and compensatory renal hypoperfusion are detrimental or protective for the kidneys.

Although cerebral blood flow increases to match the increased oxygen demand secondary to the elevated metabolic activity during rewarming, a greater proportion of the increased cardiac output perfuses the kidneys after rewarming. This findings implies that therapeutic hypothermia is associated with vasoconstriction in nonvital organs to sustain cerebral perfusion so that cerebral flow-metabolism coupling remains intact.

The strength of our prospective observational study lies in the use of comprehensive, time-synchronized assessment of overall systemic blood flow, vascular resistance, end organ blood flow velocity, organ and tissue perfusion, and FOE, allowing us to gather reliable information on systemic perfusion and vital (brain) and nonvital (kidney) organ blood flow distribution before, during, and after rewarming in patients treated with therapeutic hypothermia for HIE. In addition, the majority of our cohort did not receive vasopressor-inotrope support during the rewarming process, enabling a more robust comparison of the hemodynamic measures in our patients.

This study has several limitations, however. First, we enrolled a relatively small number of patients, with the majority of the cohort (80%) having normal to mild injury on brain MRI. Although we used both NIRS and Doppler flow velocity indices for assessment of changes in organ blood flow, limitations of these techniques for assessing blood flow changes need to be kept in mind.

Significant cardiovascular changes occur during rewarming in neonates treated with therapeutic hypothermia for HIE. These changes include increases in HR, cardiac output, and vital (brain) and nonvital (renal) organ blood flow, with preservation of cerebral flow-metabolism coupling and cessation of preferential cephalic blood flow distribution that characterizes systemic hemodynamics during therapeutic hypothermia. ■

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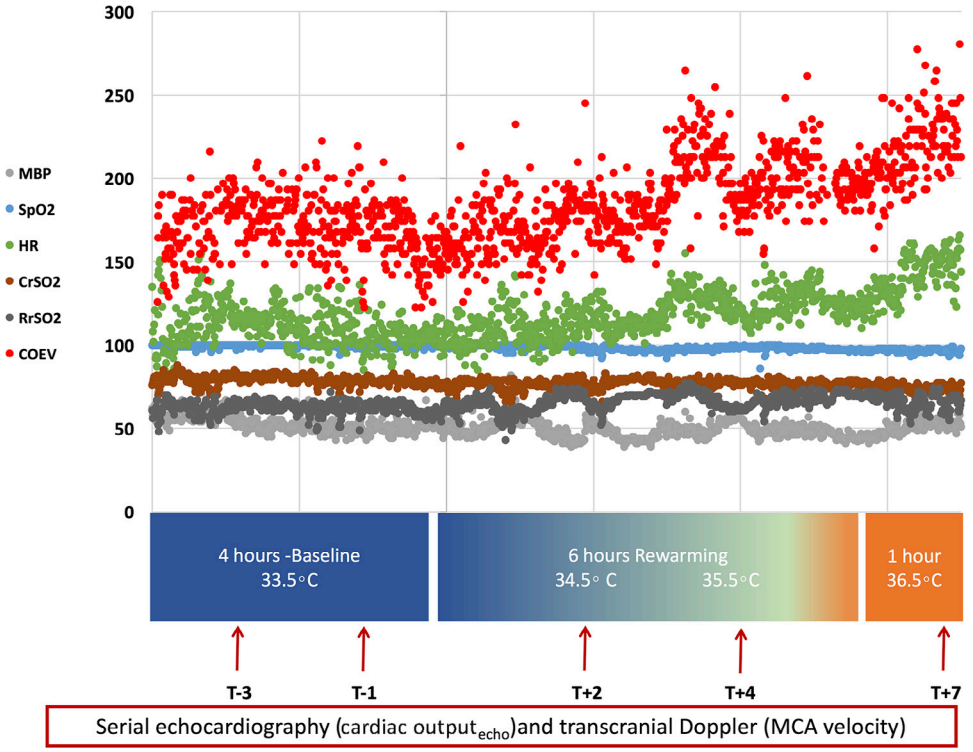

Figure 1. A sample of data collection for patient 5. Hemodynamic measures shown are HR, SpO_2, MBP, CO_{EV}, $CrSO_2$, and $RrSO_2$. Cardiac output (dark blue) closely follows HR (green). MBP (light gray) oscillations are mirrored by $RrSO_2$ (dark gray), suggesting lost autoregulation in the kidneys. For this individual patient, despite a steady increase in cardiac output and HR during rewarming, MBP and $CrSO_2$ remained largely unaffected.

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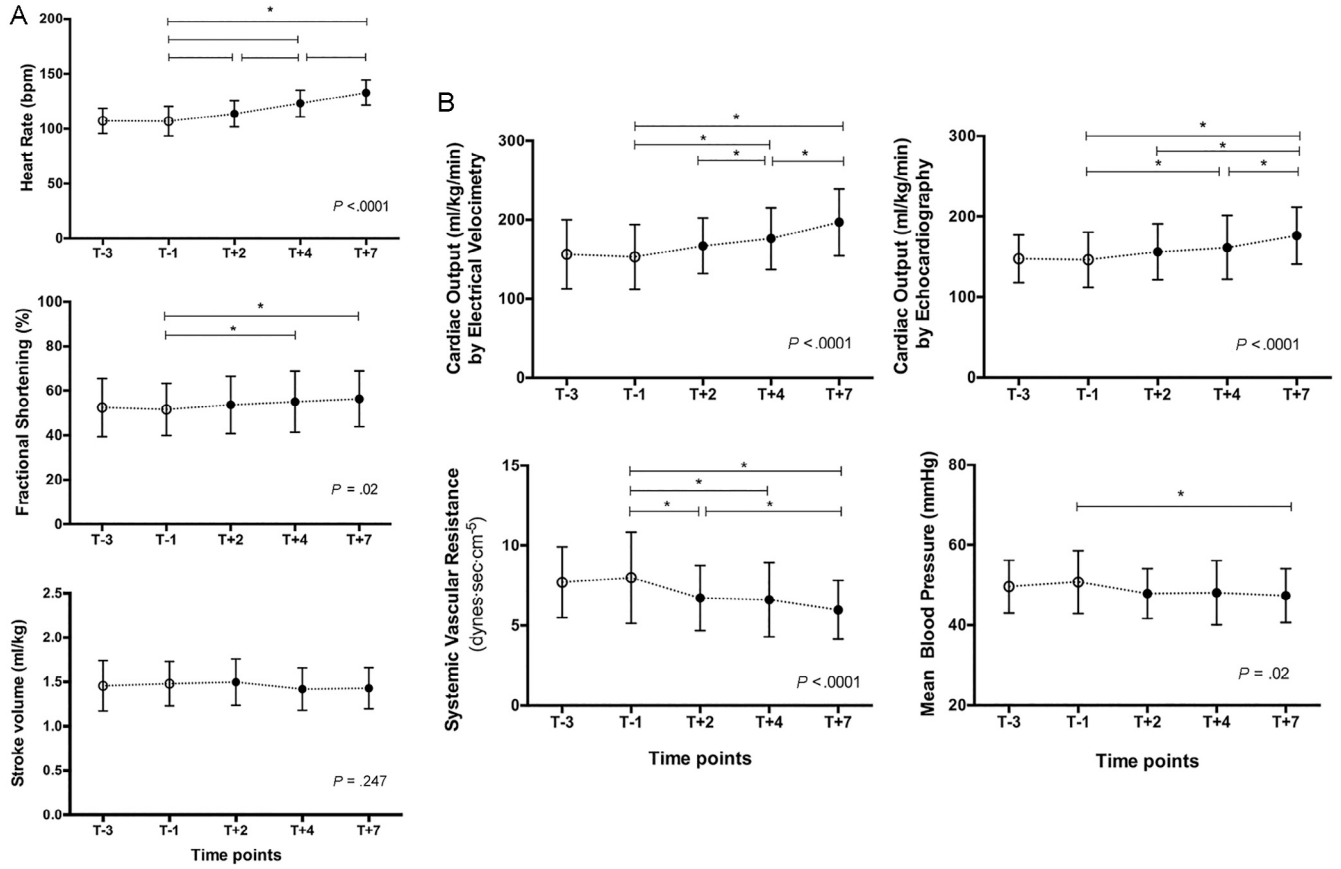

Figure 2. **A,** Changes in determinants of cardiac output, assessed by echocardiography. Mean hemodynamic data (± 1 SD) are shown for T-3, T-1 (baseline; open circles), T+2, T+4, and T+7 (rewarming; closed circles). *Significant differences ($P < .05$) between time points as denoted by the horizontal bars. **B,** Changes in cardiac output, systemic vascular resistance, and MBP during rewarming. Mean hemodynamic data (± 1 SD) are shown for T-3, T-1 (baseline; open circles), T+2, T+4, and T+7 (rewarming; closed circles). *Significant differences ($P < .05$) between time points as denoted by the horizontal bars.

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