Preferential Cephalic Redistribution of Left Ventricular Cardiac Output during Therapeutic Hypothermia for Perinatal Hypoxic-Ischemic Encephalopathy

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Objective To determine the relationship between left ventricular cardiac output (LVCO), superior vena cava (SVC) flow, and brain injury during whole-body therapeutic hypothermia.

Study design Sixteen newborns with moderate or severe hypoxic-ischemic encephalopathy were studied using echocardiography during and immediately after therapeutic hypothermia. Measures were also compared with 12 healthy newborns of similar postnatal age. Newborns undergoing therapeutic hypothermia also had cerebral magnetic resonance imaging as part of routine clinical care on postnatal day 3-4.

Results LVCO was markedly reduced (mean ± SD 126 ± 38 mL/kg/min) during therapeutic hypothermia, whereas SVC flow was maintained within expected normal values (88 ± 27 mL/kg/min) such that SVC flow represented 70% of the LVCO. The reduction in LVCO during therapeutic hypothermia was mainly accounted by a reduction in heart rate (99 ± 13 vs 123 ± 17 beats/min; $P < .001$) compared with immediately postwarming in the context of myocardial dysfunction. Neonates with brain injury on magnetic resonance imaging had higher SVC flow prerewarming, compared with newborns without brain injury ($P = .013$).

Conclusion Newborns with perinatal hypoxic-ischemic encephalopathy showed a preferential systemic-to-cerebral redistribution of cardiac blood flow during whole-body therapeutic hypothermia, which may reflect a lack of cerebral vascular adaptation in newborns with more severe brain injury. *(J Pediatr 2014;164:999-1004)*.

Neonatal hypoxic-ischemic encephalopathy (HIE) is an important cause of neurodevelopment morbidity and of mortality in term and preterm infants, with an estimated 1.2 million deaths every year worldwide.[1-3] Newborns with HIE often have multiple organ failure as a result of the hypoxic-ischemic insult, including myocardial dysfunction.[4] In the past few years, therapeutic hypothermia has become standard of care for newborns with moderate-to-severe HIE, as this treatment has been shown to improve survival and long-term neurodevelopment.[5,6] Based on animal experimental models, the clinical benefit of therapeutic hypothermia in HIE presumably occurs through a reduction in secondary neuronal damage following reperfusion of the primary insulted brain.[7] Studies conducted before the use of therapeutic hypothermia became standard demonstrated that cerebral autoregulation is impaired in newborns who develop more severe brain injury.[8] Since the introduction of therapeutic hypothermia as a treatment, studies have showed a reduction in cerebral blood flow in newborns receiving therapeutic hypothermia, suggesting that this may help prevent secondary neuronal damage.[9] However, the extent of systemic-to-cerebral blood flow redistribution that occurs during the period of therapeutic hypothermia has not been documented.

Newborns are generally able to maintain adequate blood pressure at the low temperature achieved during therapeutic hypothermia.[10,11] In a recent study examining the cardiac hemodynamic effect of whole-body therapeutic hypothermia in newborns with HIE, using echocardiography, the authors concluded that left ventricular cardiac output (LVCO) is reduced by about 67% during therapeutic hypothermia compared with values after rewarming. This suggests that therapeutic hypothermia may limit the extent of systemic blood flow available to vital organs, including the brain.[10] However, a limitation of the study by Gebauer et al is the absence of measures of cerebral blood flow. As commented by the authors, it is unclear what degree of systemic-to-cerebral blood flow redistribution occurs in newborns with HIE treated with therapeutic hypothermia.[10] It is also unclear how such mechanisms of blood flow redistribution may influence the subsequent risk of cerebral

HIE	Hypoxic-ischemic encephalopathy
HR	Heart rate
LVCO	Left ventricular cardiac output
MRI	Magnetic resonance imaging
SV	Stroke volume
SVC	Superior vena cava

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injury due to secondary neuronal damage.[12] Echocardiography is a valid, noninvasive method of measuring superior vena cava (SVC) flow, which is largely a reflection of cerebral blood flow in newborns.[13] Therefore, we prospectively determined LVCO and SVC blood flow immediately before and after rewarming, and validated our findings using a reference group of healthy newborns.

Methods

Newborns admitted to the Neonatal Intensive Care Unit of the Children's & Women's Health Centre of British Columbia (Canada) and treated with whole-body therapeutic hypothermia for moderate or severe HIE (based on the Sarnat staging system[14]) were prospectively enrolled between January 2009 and June 2010, following parental informed consent. Newborns were started on therapeutic hypothermia within 6 hours of life according to our institutional standards of presentation with moderate or severe HIE (based on the Sarnat staging system), were of gestational age ≥35 weeks, and met ≥2 of the following criteria: Apgar score ≤5 at 10 minutes, mechanical ventilation or resuscitation at 10 minutes, and cord or early arterial/venous blood gas pH <7.00 or base deficit ≥12 within 60 minutes of birth. Therapeutic hypothermia was administered according to the published Infant Cooling Evaluation trial method of cooling, at ambient environmental temperature, by applying refrigerated gel packs as necessary to reach a target core body temperature of 33°-34°C measured using a rectal temperature probe, for 72 hours.[15] In all infants, rewarming was initiated exactly at 72 ± 1 hour and proceeded at a rate not exceeding 0.5°C every 2 hours. After rewarming, core temperature was strictly maintained between 36.0°C and 36.5°C for 96 hours after initiation of therapeutic hypothermia. A comparison group of healthy term-born newborns with no clinical evidence of HIE or cardiovascular dysfunction (usually admitted for transient feeding difficulties or for unrelated investigation) were also assessed using echocardiography. The study was approved by the University of British Columbia Clinical Research Ethics Board.

Echocardiography

In newborns treated with hypothermia, 2 echocardiographic assessments were performed before initiation of rewarming and within 6-12 hours after the end of the progressive rewarming process. Healthy comparison newborns were assessed at a similar postnatal age between 72 and 96 hours after birth. Echocardiographic assessments were performed by 2 neonatologists (O.H. or P.L.) experienced in echocardiography, using a 7S-RS phased array transducer on a Vivid i BT09 Ultra-Portable High-End echocardiography instrument (GE Healthcare, Calgary, Alberta, Canada). LVCO was calculated by multiplying the stroke volume (SV) using the aortic valve diameter in a mid-parasternal long-axis 2-dimensional view, the velocity-time interval measured by pulsed Doppler in an apical 5-chamber view, and the heart rate (HR). SVC flow was calculated by multiplying the averaged minimal and maximal excursion of the SVC diameter in a high parasternal view 2-dimensional view, the velocity-time interval measured by pulsed Doppler over a ≥3 representative heartbeat in low subcostal view, and HR. Fractional shortening was calculated from a parasternal long-axis view using M-mode. All flow measures were indexed on weight. The left ventricular myocardial performance (Tei) index was calculated from an M-mode view as described previously.[16,17] The patency of and flow direction across the ductus arteriosus and atrial septum were also assessed, as described previously.[18]

Brain Imaging

Newborns treated with hypothermia also underwent cerebral magnetic resonance imaging (MRI) as part of clinical care on postnatal day 3-4, after rewarming. MRI findings that were considered positive for brain injury were restricted water diffusion on diffusion-weighted images, with or without accompanying T1-weighted imaging signal intensity changes, and categorized by predominant pattern of injury as previously described: basal nuclei, watershed, total (both basal nuclei and watershed), and multifocal (stroke or white matter injury).[19] All MRI studies were scored by an experienced clinical pediatric neuroradiologist.

Statistical Analyses

Based on measures in healthy term neonates, we estimated that between 10 and 19 newborns would provide 80% power ($P < .05$) to detect a 15%-20% difference in SVC or LVCO in nonpaired analyses (calculated with: http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). Differences in echocardiographic measurements: LVCO, HR, and SV, before and after rewarming, or between newborns with or without MRI evidence of brain injury were assessed using a Wilcoxon matched-pairs signed-ranks test. Differences in echocardiographic measurements between newborns receiving therapeutic hypothermia and healthy comparison newborns were assessed using a Student *t*-test. A *P* value <.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 20 (IBM, Chicago, Illinois).

Results

Newborns treated with therapeutic hypothermia were comparable with the healthy term-born newborns with regard to their birth weight (mean ± SD 3.49 ± 0.52 vs 3.54 ± 0.43 kg; $P = .78$). The clinical markers of severity of the HIE in newborns are detailed in **Table I**. Moderate (n = 15) or severe HIE (n = 1) was diagnosed in all 16 newborns, of whom 13 had seizures (diagnosed by combination of clinical signs and cerebral function monitor changes). None of the newborns died before the rewarming was completed. The median duration of ventilator support with an endotracheal tube in newborns with perinatal HIE was 3 days (range 0-6 days). Nine of the newborns (56%) were ventilated at the time of the prerewarming echocardiographic assessment; of these, 8 remained ventilated during the postrewarming echocardiographic