Renal Saturation and Acute Kidney Injury in Neonates with Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia

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Objective To investigate the range of renal near-infrared spectroscopy (NIRS) measures in neonates undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE) and to determine the association between renal NIRS measures and the development of acute kidney injury (AKI).

Study design A retrospective chart review was conducted of neonates with moderate to severe HIE who received therapeutic hypothermia at a tertiary care center from 2014 to 2016. Neonates had routine continuous NIRS monitoring of cerebral and renal saturation (Rsat) as part of their clinical care for 72 hours of cooling and until 24 hours after rewarming. The outcome of AKI was defined by an abnormal rate of decline of serum creatinine over the first 5 days of life. Mixed effects models determined the association between renal NIRS measures and AKI over time.

Results Of 38 neonates with HIE undergoing cooling, 15 (39%) developed AKI. Rsat was lower than cerebral saturation during cooling ($P < .01$), but Rsat increased over time after rewarming, while renal oxygen extraction levels decreased ($P < .0001$). Neonates with AKI had higher Rsat levels ($P < .01$) compared with those without AKI after 24 hours of life. Using receiver operating characteristic curves, Rsat >75% by 24-48 hours predicted AKI with a sensitivity of 79% and specificity of 82% (area under the receiver operating characteristic curve = 0.76).

Conclusions Throughout cooling, neonates with AKI had higher Rsat measures than those without AKI. These differences may reflect lower oxygen extraction by the injured kidney. NIRS monitoring of Rsat may identify neonates with HIE at risk of developing AKI. *(J Pediatr 2018;■■:■■-■■).*

Newborns with hypoxic ischemic encephalopathy (HIE) are at significant risk for acute kidney injury (AKI) from an antenatal insult impairing renal perfusion, followed by ongoing postnatal processes such as hypotension, nephrotoxic medication use, and/or hypoxia. Clinical studies have shown decreased renal blood flow velocities in asphyxiated neonates during the first 1-3 days of life,[1-3] and renal dysfunction as measured by serum creatinine or oliguria has been reported in up to 70% of neonates with HIE not receiving therapeutic hypothermia.[4,5]

AKI remains a complication in neonates with HIE receiving hypothermia. More recent studies in the era of therapeutic hypothermia have reported lower AKI rates, ranging from 19% to 40%.[6-8] This lower rate of AKI may reflect variation in AKI definitions, although there are hypothermic animal models demonstrating reduced renal blood flow, decreased creatinine synthesis, and reduced glomerular filtration rate.[9,10] The original randomized controlled trials of hypothermia for neonates with HIE have not demonstrated any significant difference in rates of oliguria or creatinine levels as a result of hypothermia itself.[11]

Regardless, AKI in the neonate with HIE is independently associated with worse outcomes including prolonged mechanical ventilation, longer duration of hospital stay, and injury on brain magnetic resonance imaging.[6,12] The ability to measure and follow kidney function during clinical care is needed in this high-risk population and may help identify AKI and allow for initiation of appropriate treatment.

Several studies have previously used near-infrared spectroscopy (NIRS) to measure cerebral saturation in neonates with HIE undergoing therapeutic hypothermia and have concluded that it is useful in the prediction of neonates at highest risk for mortality and neurodevelopmental impairment.[13-15] Similarly, renal saturation as measured by NIRS may provide insight into kidney function and risk of kidney injury in these children. We sought to investigate the range of renal NIRS measures in neonates with HIE during therapeutic hypothermia and through the rewarming period, with the goal of differentiating neonates who developed AKI based on renal NIRS measures. We hypothesized that lower renal saturation levels during therapeutic hypothermia would be associated with the development of AKI.

AKI	Acute kidney injury	NIRS	Near-infrared spectroscopy
$AKI_{DecSerCr}$	Acute kidney injury with abnormal rate of decline of serum creatinine	RCORs	Renal cerebral oxygenation ratios
AKIN	Acute Kidney Injury Network	RFTOE	Renal fractional tissue oxygen extraction
AUC	Area under the ROC curve	ROC	Receiver operating characteristic
Csats	Cerebral saturations	Rsats	Renal saturations
HIE	Hypoxic ischemic encephalopathy	SpO_2	Oxygen saturation

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Methods

This retrospective cohort study included a convenience sample of neonates who met *Eunice Kennedy Shriver* National Institute of Child Health and Human Development criteria for moderate to severe HIE[16] and underwent whole body hypothermia at a single tertiary care institution between January 2014 and December 2016. Neonates were excluded if they died prior to completion of full 72 hours of cooling, as serial serum creatinine measures to assess for AKI status were not available. Institutional Review Board approval with waiver of consent was obtained from the Stanford University Human Subjects in Medical Research Committee.

Therapeutic Hypothermia

Whole body cooling was initiated to maintain esophageal temperature at 33.5°C using a Cincinnati Sub-Zero Hyper-Hypothermia Blanketrol system (Cincinnati Sub-Zero, Cincinnati, Ohio). After 72 hours of hypothermia, rewarming to 37.0°C was achieved by increasing the rectal temperature by 0.5°C/hours.

NIRS Monitoring

All subjects undergoing whole body cooling had continuous NIRS monitoring of cerebral and renal saturation levels as part of their clinical care for the 72 hours of hypothermia and through the rewarming process using the INVOS 5100C (Medtronic, Minneapolis, Minnesota). Cerebral saturations (Csats) were monitored with a neonatal sensor on the lateral forehead. Renal saturations (Rsats) were monitored with a sensor on the right or left flank, lateral to the spine, below the costal margin and above the iliac crest at the T12-L2 level. Positioning changes to avoid prolonged pressure on the sensor and monitoring of the surrounding skin for erythema were done. Normal Rsat ranges are not specified, but a significant decline in Rsat from baseline would prompt notification of a provider to assess for adequate urine output and for conditions potentially impacting renal oxygenation including hypotension, systemic hypoxia, and anemia. Isolated oliguria may have been addressed per clinician discretion with the initiation of aminophylline (5 mg/kg IV loading dose followed by 1.8 mg/kg IV q6 hours to target serum aminophylline trough level of 5-7 mcg/mL and continued until resolution of oliguria).

Data Collection

NIRS data were recorded and saved every 30 seconds. Systemic oxygen saturation (SpO_2) data were simultaneously collected and time-synchronized with NIRS data. Renal fractional tissue oxygen extraction (RFTOE) was calculated as follows: $RFTOE = (SpO_2 - Rsat)/(SpO_2)$. The ratio of cerebral to renal saturation was calculated similarly. All saturation data were retrospectively analyzed by calculating the average value over 6 h time periods from birth until 24 hours after completion of rewarming. Time periods with missing NIRS data or physiologically inaccurate data were removed. Daily serum creatinine levels (mg/dL using isotope dilution mass spectrometry traceable enzymatic method) were acquired for the first 5 days of life. The primary outcome of AKI was defined by an abnormal rate of decline of serum creatinine over the first 5 days of life (AKI with an abnormal rate of decline of serum creatinine [$AKI_{DecSerCr}$]), which has been described as a more encompassing definition of AKI in the population of neonates with HIE[7] (rate of decline from serum creatinine at birth of <33%, <40%, and <46% on days 3, 5, and 7 of life, respectively). Subjects were secondarily identified for comparison using the modified neonatal Acute Kidney Injury Network (AKIN) criteria for AKI with rise in serum creatinine from baseline by 0.3 mg/dL, an increase of 150% from baseline, or any value ≥2.5 mg/dL.[17] This AKI_{AKIN} definition is similar to the neonatal AKI Kidney Disease: Improving Global Outcomes (KDIGO) classification developed in 2016 at the National Institute of Diabetes and Digestive and Kidney Diseases neonatal AKI workshop,[18] except that urine output is excluded as a criterion. Selection of this standard definition was made because anuria may occur in the first 24 hours of life for a healthy newborn during normal physiologic transition. Demographic and neonatal characteristics in addition to outcome data were acquired from the electronic medical record.

Statistical Analyses

Fisher exact, Kruskal-Wallis, and Student *t* tests were used to compare differences between categorical, ordinal, and continuous demographic and neonatal data between AKI and non-AKI groups. Mixed effects models determined the association between renal NIRS measures and $AKI_{DecSerCr}$ over time, and included potential confounders of gestational age, 1-minute Apgar, and aminophylline use. Analyses were conducted using SAS v 9.3 (SAS Institute, Cary, North Carolina) with statistical significance established for $P < .05$. Receiver operating characteristic (ROC) curve analyses including area under the ROC curve (AUC) were generated with Stata (StataCorp, College Station, Texas). Cut-off values that maximized the sensitivity and specificity of Rsat measures at 24 and 24-48 hours of age in terms of predicting $AKI_{DecSerCr}$ were chosen. Secondary ROC curve analyses after removal of subjects receiving aminophylline were also conducted.

Results

Forty neonates underwent therapeutic hypothermia for HIE with concurrent NIRS monitoring of renal saturation. Two died prior to completion of a full 72 hours of treatment and were excluded. Fifteen of the remaining 38 neonates (39%) developed $AKI_{DecSerCr}$. An additional 4 neonates died after withdrawal of intensive care support when severe brain MRI abnormalities were identified between 5 and 8 days of life. None of these 4 neonates developed AKI based on their serial creatinine levels.

Neonates with $AKI_{DecSerCr}$ had similar demographic, perinatal, and neonatal characteristics compared with those without $AKI_{DecSerCr}$ except for lower median 1-minute Apgar score (1 vs 2, $P = .01$) and significantly higher serum creatinine levels on days 2-4 of life ($P \leq .01$) (**Table**). More neonates in the $AKI_{DecSerCr}$ group received aminophylline (40% vs 9%) and had

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