# Noninvasive continuous cardiac output and cerebral perfusion monitoring in term infants with neonatal encephalopathy: assessment of feasibility and reliability

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**BACKGROUND:** Noninvasive hemodynamic monitoring of infants with neonatal encephalopathy (NE) undergoing therapeutic hypothermia (TH) would be a potentially useful clinical tool. We aimed to assess the feasibility and reliability of noninvasive cardiac output monitoring (NICOM) and near-infrared spectroscopy (NIRS) in this cohort.

**METHODS:** NICOM and NIRS were commenced to measure cardiac output (CO), systemic vascular resistance (SVR), blood pressure (BP), and cerebral regional oxygen saturations ($SctO_2$) during TH and rewarming. NICOM measures of CO were also compared with simultaneous echocardiography-derived CO (echo-CO).

**RESULTS:** Twenty infants with a median gestation of 40 weeks were enrolled. There was a strong correlation between NICOM- and echo-CO ($r^2 = 0.79$, $P < 0.001$). NICOM-CO was systematically lower than echo-CO with a bias of 27% (limits of agreement 3–51%). NICOM illustrated lower CO during TH, which increased during rewarming. $SctO_2$ increased over the first 30 h of TH and stayed high for the remainder of the study. There was a rise in SVR over the first 30 h of TH and a decrease during rewarming (all $P < 0.05$).

**CONCLUSIONS:** Noninvasive hemodynamic assessment of infants with NE is feasible and illustrates potentially important changes. Larger studies are needed to assess the clinical applicability of those methods in this cohort.

Term infants sustaining a hypoxic-ischemic perinatal insult resulting in neonatal encephalopathy (NE) are considered for therapeutic hypothermia (TH) as a neuroprotective measure (1). The effects of TH on cardiac output (CO), systemic vascular resistance (SVR), blood pressure (BP), and cerebral perfusion in this cohort is becoming an area of active research. Several studies have documented impaired myocardial performance (measured conventionally and by speckle tracking echocardiography) and a reduced CO measured by echocardiography in infants with NE undergoing TH when compared to healthy term counterparts (2,3). Animal data suggest that the fall in CO is secondary to a decreased heart rate and stroke volume (SV), accompanied by a concomitant increase in SVR (4–6). The decrease in metabolic demand associated with TH is thought to offset the potential detrimental effect of a low blood flow state in those infants. Near-infrared spectroscopy (NIRS) may also play a role in monitoring cerebral perfusion and oxygen extraction during TH. Recent studies have demonstrated good correlation between NIRS-measured cerebral mixed venous saturation values ($SctO_2$) and cerebral blood flow measured using magnetic resonance imaging (MRI) in infants undergoing TH (7). In addition, NIRS may have a prognostic role in this population (8,9).

However, studies to date assessing the hemodynamic status of infants undergoing TH have used echocardiography which produces discrete, isolated measurements of function and output. The ability to assess CO (including SV), SVR, BP, and heart rate in addition to $SctO_2$ in a continuous, noninvasive manner would enable a more detailed assessment of the interaction of all the above parameters in the setting of TH and NE in real time. Transthoracic bioreactance is a new technique of continuous noninvasive cardiac output monitoring (NICOM) that has demonstrated good reliability against invasive measures of CO in studies involving adults, children, and small animals (10–15). Our group has recently demonstrated the feasibility and reliability of NICOM (NICOM, Cheetah Medical, Portland, OR) compared with echocardiography in stable late-preterm and term neonates, and in premature infants following patent ductus arteriosus (PDA) ligation (16,17). Its application in neonates with NE however remains unexplored.

In this study, we aim to (i) perform continuous measurements of CO, SV, SVR, heart rate, BP, and $SctO_2$ using NICOM and NIRS in infants with NE undergoing TH throughout the cooling and rewarming period; and (ii) compare NICOM-measured CO with echocardiography-measured CO (echo-CO) over three time points. We hypothesized that NICOM use in infants with NE is feasible and can provide a reliable method of CO assessment in this population.

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## METHODS

### Study Setting, Patient Population, and Clinical Characteristics

This was a prospective observation study carried out in the neonatal intensive care units of the Rotunda Hospital and the Coombe Women and Infants University Hospital, Dublin, Ireland. Ethical approval was obtained from the local Research Ethics Committees and written informed consent was obtained from parents of all participants prior to enrollment. All infants were either passively or actively cooled within six hours following birth. Parents were given up to 12 h following the initiation of TH to consider the study. Infants greater than 35 weeks gestation with a diagnosis of NE who underwent TH were all eligible provided they fulfilled two of the following criteria based on the TOBY study (18): Apgar score of $\leq 5$ at 10 min after birth; continued need for endotracheal or mask ventilation at 10 min after birth; acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial, or capillary pH $<7.00$ or a base deficit $\geq 16$ mmol/l); and/or clinical seizures or moderate to severe encephalopathy using the Sarnat grading system (19). We excluded infants who were unlikely to survive beyond the cooling period.

All clinical care decisions including sedation and inotrope use were left to the discretion of the clinical team. Clinical characteristics including gestation, birth weight, mode of delivery, Apgar scores, first pH, base excess, and lactate, the need for resuscitation at birth, the use of sedation and inotropes during TH, the presence of seizures, and the use of antiepileptic medication were recorded. The clinical team was blinded to the NICOM and NIRS measurements.

### Continuous Hemodynamic Monitoring

We used the NICOM system (Cheetah Medical Inc, MA) which employs transthoracic bioreactance to obtain continuous hemodynamic readings during TH and rewarming (16,17). Bioreactance is the analysis of the variation in the frequency spectra of a delivered oscillating current when it traverses the thoracic cavity. This is obtained by placing four emitting and receiving electrodes in a manner that "boxes" the heart. Each electrode sensor strip consists of two contact points. Upper thoracic electrode strips were placed over the mid-clavicles and upper back bilaterally. The lower electrode sensors are placed between the sixth and seventh intercostal spaces at the mid-axillary line. NICOM measurements of SV and CO are obtained every minute. SVR is calculated by the NICOM system on an hourly basis as the mean BP is manually entered using the following formula: SVR = $(BP \times 80)/CO$ as per the entered algorithm; where BP is the mean arterial pressure.

NIRS monitoring of cerebral mixed venous saturations was performed using the INVOS Somanetics system (Medtronic, MN) and cerebral oximetry neonatal sensors. The sensors were applied to the skull over the frontal lobes at the center of the forehead and secured using clear bandages for the duration of TH and rewarming. NIRS provides continuous $SctO_2$ readings using spatially-resolved spectroscopy (20).

### MRI Findings

All enrolled infants underwent a brain MRI on day 5–10 after delivery. A pediatric radiologist who is blinded to NICOM and NIRS results reported and scored the MRI results using the Barkovich criteria (21). This employs a combination five-point score including components of both basal ganglia and watershed patterns of injury. Patients were divided into "normal" (score = 0) and "abnormal" (score = 1–4) neuroimaging groups for the purpose of data analysis.

### Echocardiography Measurements

Echocardiograms were performed using the Vivid S6 machine (GE Medical, Milwaukee, WI) and a 7 MHz cardiac multi-frequency probe on infants recruited from the Rotunda Hospital site. After TH initiation, infants underwent echocardiography assessments of CO on day 1 (10 h of TH), prior to rewarming (70 h of TH), and at the end of the rewarming period (100 h after commencement of TH). The 10-h time point was chosen to ensure that all the infants undergoing echocardiography also had NICOM monitoring. The delay in applying NICOM monitoring was to facilitate parental informed consent. The 70-h time point was chosen as the time of maximal cooling duration just prior to rewarming. The 100-h time point represented the completion of rewarming. At the time of the first echocardiogram, the NICOM and echocardiography internal clocks were synchronized. All echocardiograms were performed and analyzed by one investigator (CRB) to avoid inter-rater variability. The investigator was blinded to the NICOM readings during the echocardiogram. The echo-CO was calculated based on previously described methodology (22). At a later date, complete NICOM measurements for each infant were downloaded from the NICOM machine. The NICOM-CO measurements that exactly corresponded to the timed minute of acquisition of the echocardiography data were identified. These NICOM and echocardiography data were compared.

### Statistical Analysis

Continuous data were presented as median (interquartile range) or as means (SD) as appropriate. Categorical data were presented as absolute numbers and proportions. Two group analysis was conducted using the Mann-Whitney *U* test for continuous variables or the $\chi^2$ test for categorical variables. One-way repeated measures ANOVA was used to assess the change in the hemodynamic measurements with respect to time. Pairwise comparison carried out

**Table 1.** Hemodynamic measurements at three time points

| | During cooling (10 h) | Pre-rewarming (70 h) | Post-rewarming (100 h) | ANOVA *P* |
|---|---|---|---|---|
| Temperature (°) | 33.4 (0.4) | 33.5 (0.1) | 36.4 (0.8)[a] | <0.001 |
| NICOM-CO (ml/kg/min) | 82 (31) | 83 (38) | 120 (57)[a] | 0.003 |
| Echo-CO (ml/kg/min) | 91 (24) | 118 (38) | 153 (55)[a] | 0.001 |
| NICOM/Echo percentage bias (%) | 21 (14) | 29 (10) | 32 (9) | 0.14 |
| Cerebral regional O2 saturation (%) | 80 (9) | 85 (6)[a] | 85 (5)[a] | 0.005 |
| SVR × 1000 (dynes.sec.cm$^{-5}$) | 14.3 (10.1–18.0) | 16.0 (12.9–18.4) | 11.0 (8.3–14.1)[a] | <0.001 |
| SV (ml) | 3.0 (1.4) | 3.0 (0.8) | 3.5 (1.0) | 0.2 |
| Mean BP (mmHg) | 45 (5) | 50 (6) | 50 (5)[a] | 0.002 |
| Heart rate | 102 (13) | 97 (15) | 116 (16)[a] | <0.001 |

ANOVA, analysis of variance; Echo-CO, echocardiography-derived cardiac output; Mean BP, mean blood pressure; NICOM-CO, NICOM-derived cardiac output; SV, stroke volume; SVR, systemic vascular resistance.
Values are presented as means (SD) or medians (IQR). One was ANOVA with repeated measures was used to assess change over time.
[a]*P* value < 0.05 compared to baseline (Bonferroni adjustment).

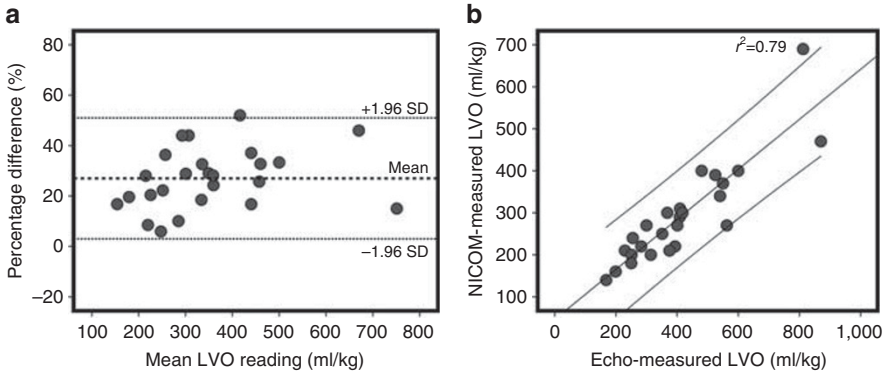


**Figure 1.** Bland-Altman Analysis (**a**) and Correlation (**b**) between echocardiography and noninvasive cardiac output monitoring (NICOM)-measured cardiac output. NICOM and Echo cardiac output (depicted as left ventricular output, LVO) was not indexed to weight for graphical representation.

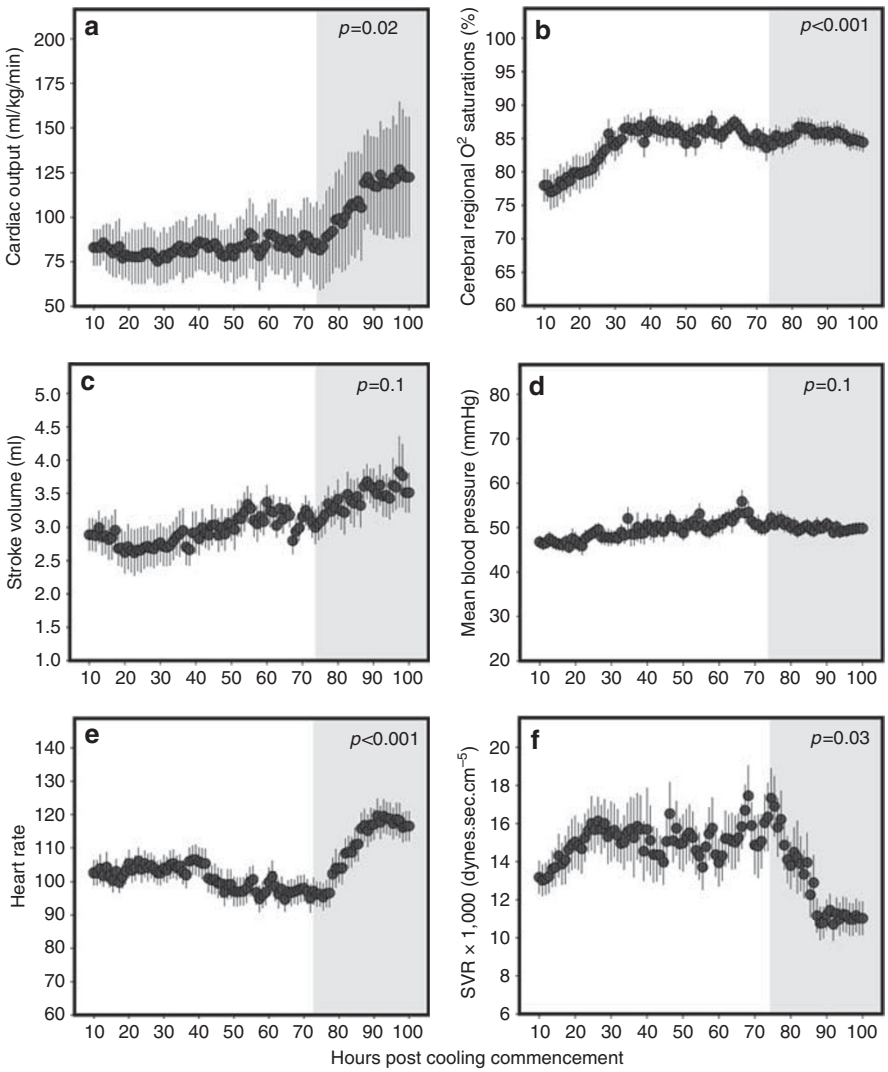


**Figure 2.** Continuous hemodynamic measurements in the cohort over the study period. Changes in cardiac output (**a**), cerebral regional oxygen saturation (**b**), stroke volume (**c**), mean blood pressure (**d**), heart rate (**e**), and systemic vascular resistance (**f**) are presented. The white area represents the hypothermia phase and the gray area represents the rewarming phase. Values are presented as means (dark gray circles) and the black lines represent the standard error. One-way ANOVA with repeated measures was used to assess the change over time. SVR, systemic vascular resistance.

**Table 2.** Clinical characteristics of infants with and without an abnormal MRI

| | Normal MRI ($n=10$) | Abnormal MRI ($n=10$) | $P$ |
|---|---|---|---|
| Gestation (weeks) | 38.7 (38.0–40.1) | 38.9 (38.0–39.1) | 0.42 |
| Birth weight (kg) | 3.53 (3.32–3.90) | 3.34 (2.50–4.23) | 0.83 |
| Cesarean section | 8 (80) | 5 (50) | 0.35 |
| Male gender | 8 (80) | 4 (40) | 0.17 |
| Outborn | 5 (50) | 7 (70) | 0.65 |
| Apgar Scores | | | |
| 1 min | 0 (0–1) | 3 (3–5) | <0.01 |
| 5 min | 4 (1–5) | 4 (2–7) | 0.19 |
| 10 min | 5 (3–9) | 7 (5–9) | 0.76 |
| Lowest first-hour pH | 6.96 (6.89–7.12) | 6.90 (6.82–7.01) | 0.74 |
| Base excess | −15.8 (−20.4–−12.3) | −14.8 (−19.8–−12.3) | 0.58 |
| First lactate (mmol/l) | 12.8 (10.4–14.4) | 10.9 (9.5–16.6) | 0.91 |
| Inotropes | 5 (50) | 4(40) | 1.0 |
| Seizure activity | 1 (10) | 4 (40) | 0.30 |

MRI, magnetic resonance imaging.
Data are presented as medians (interquartile range) or as count (%).

between two time points (70 and 100 h) and baseline (10 h) was conducted using the Bonferroni adjustment. Two-way repeated measures ANOVA was used to assess the difference in the hemodynamic measurements between two groups (normal vs. abnormal MRI) over time.

A systematic bias of 31 ± 8% between the two methods of CO assessment was demonstrated previously, with NICOM under-reading the echocardiography values (17). Therefore, differences in measurement between the two methods were expressed as a percentage ((echo-CO—NICOM-CO)/echo-CO). We compared the two methods using the Bland-Altman analysis, and assessed the correlation between the two methods using Pearson's correlation coefficient. A $P$ value < 0.05 was considered significant. SPSS (IBM House, Dublin, Ireland) (IBM version 22) was used to perform the statistical analysis.

## RESULTS

Over the study period, 27 infants were eligible for inclusion. Three were excluded due to the unavailability of the NICOM monitor, two were unlikely to survive (and subsequently had care redirected to palliation) and two families refused consent. Twenty infants with a median (IQR) gestation of 40.0 (38.7–41.1) weeks and a median birth weight of 3.6 (3.4–4.0) kg were enrolled over an eighteen-month period. Thirteen (65%) were delivered by cesarean section and twelve (60%) were male. Ten (50%) infants were outborn. Their 1, 5, and 10 min Apgar scores were 2 (0–4), 5 (2–7], and 6 (4–9) respectively. The cohort had an admission pH of 6.93 (6.85–7.07), a base excess of −14.9 (−19.3–−11.8), and an initial arterial lactate of 12.8 (9.0–14.8) mmol/l. TH was commenced within 6 h following birth in all infants. All infants were in receipt of either morphine ($n=11$), fentanyl ($n=11$) or midazolam ($n=5$) for sedation during TH. NICOM hemodynamic measurements (CO, SVR, BP, SV, and HR) and NIRS measurements ($SctO_2$) were all commenced within 10 h of TH initiation. During the cooling period, all infants were maintained at a temperature between 33° to 34° centigrade and were rewarmed following 72 h of TH over an 18 h period (Table 1).

NICOM and NIRS assessments were feasible in all enrolled infants. Eight infants underwent echocardiography assessments of CO over three time points. NICOM-CO were lower than echo-CO with a bias of 27% (limits of agreement 8–51%). There was a strong correlation between echo-CO and NICOM-CO ($r^2=0.79$, $P<0.001$) (Figure 1). The bias between the two methods remained constant throughout the study period with no difference noted between the cooling and rewarming phases. There was an increase in both NICOM-CO and echo-CO following the rewarming period (Table 1).

CO was lower during TH and significantly increased during rewarming. $SctO_2$ significantly increased over the first 30 h of TH and stayed higher for the remainder of the study period (Table 1, Figure 2). There was a significant rise in NICOM-measured SVR over the first 30 h of TH. SVR subsequently decreased during rewarming. There was no change in mean arterial BP or SV over the study period. Heart rate significantly increased during rewarming (Table 1, Figure 2).

Nine infants received inotropes during the study period. There was no difference in gestation, birth weight, Apgar scores, pH, base excess, or lactate between infants in receipt of inotropes and those without (data not shown). All infants received dopamine, with two infants receiving adrenaline and one infant receiving dobutamine as adjuvant therapy. The median time of commencement was 6 (2–18) h, with a total duration of 49 (23–83) h. The median BP at inotrope commencement was 44 (42–47). There was no significant change in any of the measurements in the 24 h period following the commencement of inotropes (data not shown).

All infants underwent a brain MRI between days 5–10 of age. Ten infants had an abnormal MRI. Table 2 summarizes the differences in characteristics between infants with and without a normal MRI. There were no significant differences between the two groups with the exception of the 1 min Apgar score which was higher in the abnormal MRI group (Table 2). Figure 3 illustrates the hemodynamic profiles in the two groups. Infants in the abnormal MRI group had lower CO, and SV and a higher SVR during TH. However those differences did not reach statistical significance (Figure 3).

## DISCUSSION

In this prospective study, we applied a relatively novel method of continuous hemodynamic assessment (NICOM) to infants with NE throughout the cooling and rewarming periods and compared CO measured using this method with that of echocardiography. The use of NICOM and NIRS in this population is feasible as measurements were obtainable in all recruited infants. We did not encounter difficulty in applying the sensors on the infants or maintaining the sensors in place throughout the study period. In addition, those sensors did not impede routine clinical monitoring or care provision to those infants.

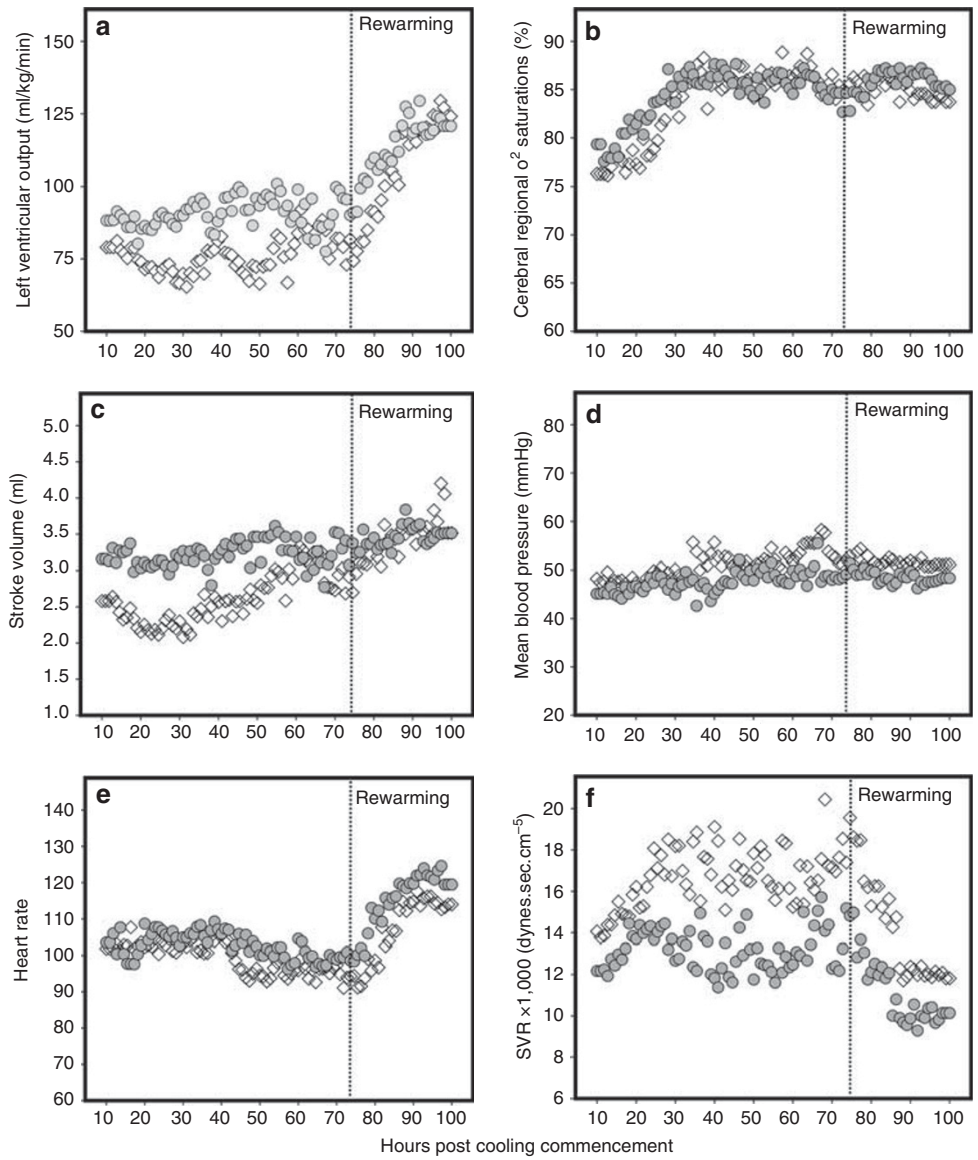


**Figure 3.** Change in the hemodynamic profile in infants with (white diamonds) and without (gray circles) an abnormal magnetic resonance imaging (MRI). Changes in cardiac output (**a**), cerebral regional oxygen saturation (**b**), stroke volume (**c**), mean blood pressure (**d**), heart rate (**e**), and systemic vascular resistance (**f**) are presented. One-way ANOVA with repeated measures was used to assess the change over time. There was no significant change in any of those measurements between the groups over time (all ANOVA $P > 0.05$). SVR, systemic vascular resistance.

We illustrated that NICOM under-reads echo-CO by an average of 27%; This systematic bias is similar to the bias illustrated by our group in two other patient populations: healthy term and late-preterm infants, and preterm infants following patent ductus arteriosus ligation (16,17). While acknowledging that neither method can be regarded as a gold-standard, we have previously provided a rationale for this systematic bias between the two methods (17). The NICOM algorithm used to estimate aortic diameter size in the neonatal population is extrapolated from adults which may have resulted in the lower NICOM values of CO (23). Conversely, echocardiography may overestimate CO readings as it uses the velocity of blood flowing through the central portion of the aortic root to estimate CO. This may significantly overestimate the true overall velocity of blood flowing through the aortic root as the higher velocity is found in the center of the vessel while flow along the periphery (not measured by echocardiography) is significantly lower (24). We also found that the bias appears to be constant throughout the cooling and rewarming phases with no significant differences between the three NICOM and echocardiography measurement time points. This has important implications as it suggests that body temperature changes do not appear to affect the bioreactance signal properties. Animal studies support these findings. In a study of nine open-chest pigs, where blood flow was controlled with cardiopulmonary bypass, NICOM-CO measurement correlated well with cardiopulmonary bypass measurements ($r = 0.84$) across two blood temperatures (36° and 38°C). Although this temperature

range is different to that in our study, the data suggest the relative lack of effect temperature has on NICOM-CO measurement (23).

We illustrated that NICOM monitoring of infants with NE during TH and rewarming reflects expected hemodynamic changes during this process, adding further support to its reliability in this patient cohort. Left ventricular output is lower during hypothermia and increased during rewarming. This change appears to be driven by changes in heart rate which mirrored the increased CO rather than SV, which increased at a lower rate. There was a rise in SVR during cooling which decreased with rewarming. There was no change in mean BP during the study period. Hypothermia is associated with a reduction in metabolic demand and a resultant fall in CO (25). Adult human data and animal models of TH have previously demonstrated this rise in SVR following the lowering of body temperature (26,27). The rise in SVR may be a contributing mechanism to the maintenance of cerebral perfusion in the cooled neonatal population (28). The early rise in $SctO_2$ seen in our cohort occurring in conjunction with the rising SVR supports this theory. $SctO_2$ remained elevated during rewarming despite a falling SVR. The increase in CO may have maintained cerebral perfusion.

We found that infants with evidence of brain injury seen on MRI had a higher SVR and a lower CO driven by a lower SV rather than heart rate (although none of those differences reached statistical significance, likely due to the small number of subjects). This finding suggests that the more severely affected infants may also have myocardial injury, with an inability to maintain adequate SV in the face of increasing afterload. This relationship warrants further study in a larger cohort to confirm those findings.

The effect of inotropes on the cardiovascular system during TH warrants further study. We found no demonstrable change in CO, mean BP or SVR following the introduction of inotropes in this population. The lack of change may highlight the lack of response to inotropes during TH (26), however, no meaningful conclusions can be drawn from this small sample size and the relatively diverse number of inotropes used in this study.

This study has several limitations: the relative small number of infants may have resulted in missing important differences in the measures between infants with and without brain injury. In addition, the relative delay in applying NICOM (done to facilitate obtaining consent) may have resulted in missing important hemodynamic changes during the early cooling phase. Although NICOM has been validated against echocardiography in neonates (16,17), further work is required to assess its precision and its ability to detect important changes over time. Our study was not powered to assess the effect of other important factors such as sedation, inotrope use, and the presence of seizures on the hemodynamic status of those infants.

## CONCLUSION

We have demonstrated that the assessment of the hemodynamic status of infants with NE undergoing TH in addition to cerebral perfusion in a continuous fashion is feasible and reflects the expected hemodynamic changes occurring as a result of TH and rewarming in infants with NE. Further studies are required to assess NICOM's clinical applicability in this condition in a larger cohort.

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