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The Precision Between Transcutaneous Carbon Dioxide Versus P_{aCO_2} in Infants Undergoing Therapeutic Hypothermia

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BACKGROUND: Infants with hypoxic-ischemic encephalopathy are often treated with therapeutic hypothermia and high-frequency ventilation. Fluctuations in P_{aCO_2} during therapeutic hypothermia are associated with poor neurodevelopmental outcomes. Transcutaneous CO_2 monitors offer a noninvasive estimate of P_{aCO_2} represented by transcutaneously measured partial pressure of carbon dioxide (P_{tcCO_2}). We aimed to assess the precision between P_{tcCO_2} and P_{aCO_2} values in neonates undergoing therapeutic hypothermia. METHODS: This was a retrospective chart review of 10 neonates who underwent therapeutic hypothermia requiring respiratory support over 2 y. A range of 2–27 simultaneous P_{tcCO_2} and P_{aCO_2} pairs of measurements per neonate were analyzed via linear mixed models and a Bland-Altman plot for multiple observations per neonate. RESULTS: A linear mixed-effect model demonstrated that P_{tcCO_2} and P_{aCO_2} (controlling for sex) were similar. The 95% CI of the mean difference ranged from −2.3 to 5.7 mm Hg ($P = .41$). However, precision was poor as the P_{tcCO_2} ranged from > 18 mm Hg to < 13 mm Hg than P_{aCO_2} values for 95% of observations. CONCLUSIONS: The neonates' P_{tcCO_2} was as much as 18 mm Hg higher to 13 mm Hg lower than the P_{aCO_2} 95% of the time. Transcutaneous CO_2 monitoring may not be a good trending tool, nor is it appropriate for estimating P_{aCO_2} in patients undergoing therapeutic hypothermia.
Key words: statistics; blood gas analysis; blood gas monitoring; transcutaneous; hypothermia induced; infant; newborn. [Respir Care 2024;69(3):339–344.

Introduction

Perinatal asphyxia is a severe birth complication in neonates caused by inadequate blood flow and oxygen supply to the brain resulting in focal or diffuse brain injury. This condition is called hypoxic-ischemic encephalopathy. It can lead to debilitating long-term sequelae like cerebral palsy, a significant cause of disability in term and near-term infants. Hypoxic-ischemic encephalopathy occurs in approximately 1.5 cases/1,000 full-term live births in developed countries.[1] About 10–40% of these infants die, and 30% can show significant long-term neurodevelopmental disability.[2] Therapeutic hypothermia has become the standard of care to reduce morbidity and mortality related to hypoxic-ischemic encephalopathy.

Noninvasive methods of CO_2 monitoring for those with hypoxic-ischemic encephalopathy include end-tidal CO_2 pressure (P_{ETCO_2}) and transcutaneously measured partial pressure of carbon dioxide (P_{tcCO_2}) monitoring. P_{ETCO_2} is routinely used in operating rooms but has some limitations in patients receiving high-frequency oscillatory ventilation and non-intubated patients. As well, endotracheal tube leaks limit the utility of P_{ETCO_2} monitoring in neonatal ICUs (NICUs). Transcutaneous CO_2 devices provide another option for the continuous noninvasive estimation of P_{aCO_2} and, in several situations, are preferred over P_{ETCO_2} analysis.[3,4]

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The authors have disclosed no conflicts of interest.

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Reports of accuracy for transcutaneous CO_2 monitoring have been inconsistent. Whereas transcutaneous CO_2 monitors are often considered reliable and safe in low-birthweight premature infants,[5] Sorensen et al[6] highlighted the lack of precision at variable probe temperatures ranging from 39–44°C. Furthermore, Werther et al[7] reported poor precision of transcutaneous CO_2 reflecting P_{aCO_2} in neonates without severe lung disease. Thus, P_{ETCO_2} was more reliable and accurate as compared to the use of transcutaneous CO_2.

However, to this date, the effectiveness of transcutaneous CO_2 readings under hypothermic conditions in neonates has not been evaluated systematically. As such, this study aimed to examine the precision of transcutaneous CO_2 readings under hypothermic conditions compared to P_{aCO_2} in neonates with multiple observations.

QUICK LOOK

Current knowledge

Transcutaneous CO_2 devices provide an option for the continuous noninvasive estimation of P_{aCO_2}. However, the effectiveness of transcutaneous CO_2 (transcutaneously measured partial pressure of carbon dioxide [P_{tcCO_2}]) readings under hypothermic conditions in neonates has not been systematically evaluated against arterial blood.

What this paper contributes to our knowledge

This paper demonstrated that transcutaneous CO_2 monitoring was not precise when compared to P_{aCO_2}. The transcutaneous CO_2 device measured P_{CO_2} by as much as 18 mm Hg higher to 13 mm Hg lower than the actual P_{aCO_2} 95% of the time in neonates.

Methods

The study was approved by University of California, Davis (UC Davis) Institutional Review Board. A waiver of parental consent was approved due to the study's retrospective nature. This was a retrospective chart review from 2018–2021 in neonates who underwent therapeutic hyperthermia for hypoxic-ischemic encephalopathy that required respiratory support.

The study was conducted at the UC Davis NICU. Transcutaneous CO_2 monitors were introduced in the UC Davis NICU in August 2018. They have become the standard of care in the NICU, and all babies needing respiratory support via invasive and noninvasive routes routinely have a transcutaneous CO_2 device attached. We included all neonates undergoing therapeutic hypothermia requiring respiratory support who had a CO_2 sensor placed on their skin.

Transcutaneous CO_2 sensors were introduced for clinical use about 20 years ago. Transcutaneous measurement of P_{CO_2} uses the fact that CO_2 gas diffuses through body tissue and skin and can be detected by a sensor at the skin surface. By warming the sensor, local hyperemia is induced, which increases arterial blood supply to the dermal capillary bed below the sensor (Fig. 1). In general, this value correlates well with the corresponding P_{aCO_2} value. Because of the elevated temperature of the sensor, the P_{tcCO_2} is greater than arterial P_{CO_2}. It has become a common practice to apply a correction to the P_{tcCO_2} value to provide a reading that corresponds as close as possible to P_{aCO_2}, the accepted standard.

The shift of transcutaneous P_{CO_2} toward higher values is attributed to 2 main factors. First, the elevated temperature increases local blood and tissue P_{CO_2} by approximately 4.5%/°C (anaerobic element). Second, the living epidermal cells produce CO_2, which contributes to the capillary CO_2 level by a constant amount (metabolic constant). The skin metabolism increases the transcutaneous P_{CO_2} by approximately 5 mm Hg. The theoretical basis of the correction algorithm used by the manufacturers of transcutaneous CO_2 systems has been described explicitly by Hazinski and Severinghaus.[8]

A registered respiratory therapist calibrated all transcutaneous CO_2 devices (SenTec Digital Monitoring System, Sentec AG, Therwil, Switzerland) at least once daily. The sites where transcutaneous CO_2 sensors (V-Sign Sensor 2, sensor type VS-A/P/N, software version V04.17.0, Sentec AG) were placed include the upper chest, lateral chest, buttock, inside of the upper thigh, or forearm. The sensors were changed periodically and not always placed in the postductal region.

As a routine practice, the nursing staff at the UC Davis NICU documents the transcutaneous CO_2 value reported on the transcutaneous CO_2 monitor at every blood gas draw. We only collected transcutaneous CO_2 documented in the electronic medical record when there was a corresponding arterial blood gas draw. The arterial blood gas samples were sampled from an indwelling line, specifically an umbilical arterial catheter. These samples were analyzed immediately in the blood gas laboratory at the UC Davis Medical Center, near the NICU. The blood gas lab is accredited by the State of California Department of Public Health (Lab ID CDF0002547; CLIA number 05D0615654) and the College of American Pathologists (CAP number 2422006). The samples obtained were sent to the lab via a pneumatic tube system.

All samples were analyzed using the ABL90 FLEX blood gas analyzer (Radiometer Medical, Brønshøj, Denmark) at 37°C. The P_{tcCO_2} values were obtained from the Sentec transcutaneous CO_2 monitors (SMB software version V08.05.1; MPL software version MPL.V01.08.01; Sentec) with the skin probe sensor temperature set to 41°C per recommendations of Sorensen and colleagues.[6] The reading on the transcutaneous CO_2 monitor is a value corrected to 37°C.

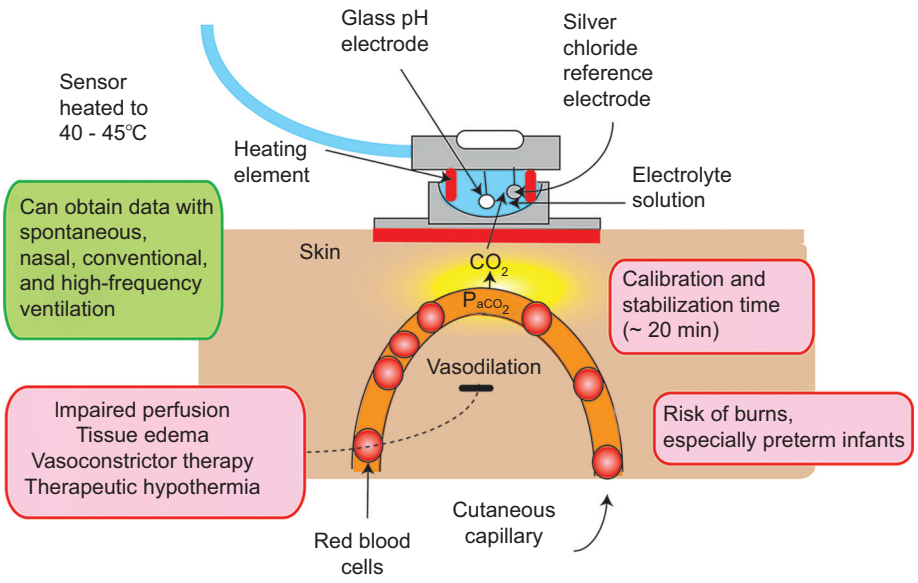

Fig. 1. Transcutaneous CO_2 monitoring. The structure, advantages (green box), and disadvantages (pink boxes) of transcutaneous CO_2 monitoring in neonates. From Sankaran et al.[24,25] Copyright Satyan Lakshminrusimha, used with permission.

Violin plots of the absolute differences between P_{tcCO_2} and P_{aCO_2} measurements (non-temperature corrected, ie, 37°C) were generated to examine the spread of the values between the 2 different measurements. A linear mixed-effects model was used to compare the mean differences between the 2 measurement devices. Linear mixed-effects models were used for both fixed and random effects, and the standard errors were corrected for the non-independence of the data.

Agreement between P_{tcCO_2} and P_{aCO_2} with multiple observations per individual was performed according to Bland and Altman.[9] The confidence interval estimates for the limits of agreement with multiple observations per individual were created from the mathematical formulas of Zhou.[10] The concordance correlation coefficient was also used to evaluate the agreement between the 2 methods.[11,12]

Analytical performance specifications from the Royal College of Pathologists of Australasia (RCPA)[13] benchmarked unacceptable differences in P_{aCO_2} between 2 measurements from the same specimen. The lower limit of acceptability defined by RCPA is ± 2 mm Hg when P_{aCO_2} ≤ 34 mm Hg and ± 6% when P_{aCO_2} > 34 mm Hg.[13] These acceptability limits were then applied for differences between P_{tcCO_2} and P_{aCO_2}.

Graphical displays of the results were achieved using a statistical software package (MedCalc software limited, version 20.110, MedCalc, Ostend, Belgium). A linear mixed-effect model using subjects as random effects and method and sex as fixed effects was performed using SPSS Statistics, version 28.0.0 (IBM, Armonk, New York). A P value < .05 was used to indicate statistical significance.

Results

We analyzed 90 paired measurements of P_{CO_2} between 2 methods from 10 neonates (3 females, 7 males) undergoing therapeutic hyperthermia from 2018–2021. Two–27 replicates were obtained from each subject, and the absolute differences between methods are shown per subject in Figure 2. Using analytical performance specifications from RCPA for blood gases,[13] any pair of measurements with an absolute difference between that > ± 2 mm Hg when ≤ 34 mm Hg or 6% for P_{aCO_2} > 34 mm Hg was considered unacceptable. For the 51 samples for which P_{aCO_2} > 34 mm Hg and the $P_{tcCO_2} - P_{aCO_2}$ difference > 6%, the mean P_{aCO_2} was 56 ± 11.5 mm Hg (range 35–94 mm Hg). This equates to a threshold of acceptability between the 2 methods that ranged from 2.1–5.6 mm Hg (depending on the P_{aCO_2}). The absolute mean difference in these 51 paired measurements was 8 ± 4 mm Hg (range 3–20 mm Hg). This equates to a mean difference of 14% (SD 7%, range 6–40%) between P_{tcCO_2} and P_{aCO_2}.

Birthweights ranged from 2,330–3,810 g, and their gestational age ranged from 36–40 weeks (Table 1). The P_{aCO_2} values range from 28–94 mm Hg at 37°C. The mean difference between methods was 1.7 (standard error = 2) mm Hg (95% CI 2–5.6) (P = .41). The mean difference between males and females was 5.5 (standard error 6.4) mm Hg (95% CI −9.1 to 20.1) (P = .42). Linear mixed-models analysis demonstrated that P_{tcCO_2}, on the whole, was similar to P_{aCO_2} and being male or female did not affect the results.

The absolute difference between P_{tcCO_2} and P_{aCO_2} was plotted against the mean of both.[14] The variability was

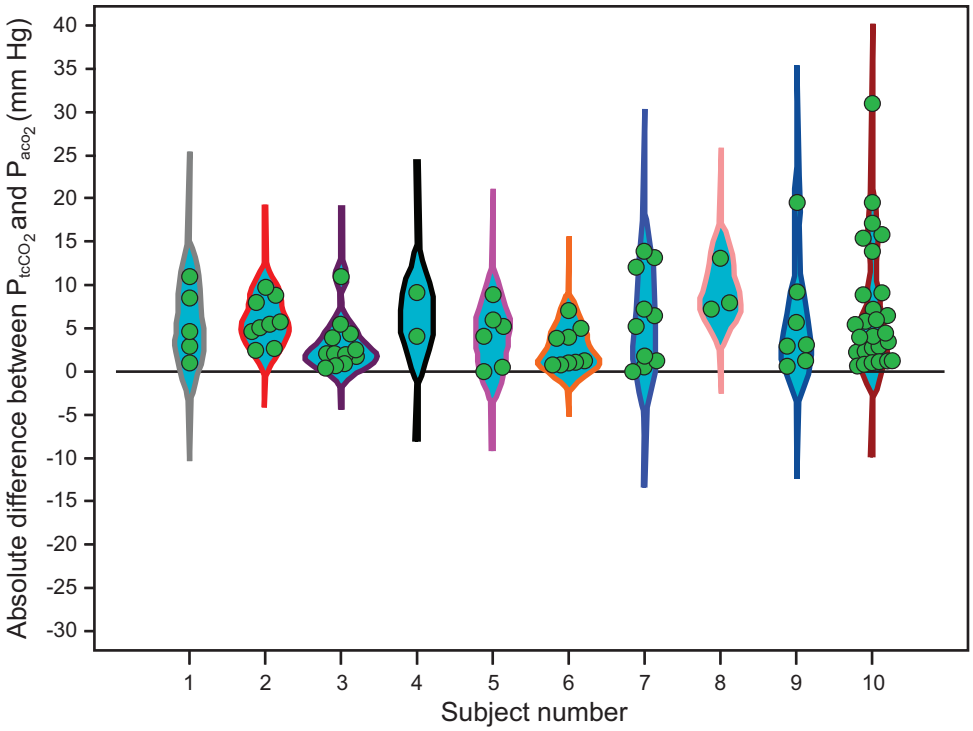

Fig. 2. Vertical violin plots of the absolute differences between P_{tcCO_2} and P_{aCO_2} (non-temperature corrected) with all observations in 10 subjects. The distribution shape of the data is displayed for each subject, with broader sections of the violin plot representing the higher probability that members of the population will take on the given value; the narrower sections represent a lower probability. The light-blue filling inside each violin plot is the kernel density estimation to show the data distribution. This plot combines the traditional box-and-whisker plot and a data density trace into one diagram.[26] The density trace supplements the traditional summary statistics.[26] Notice that subject 4 only has 2 replicated measurements (mean 7 ± 4 mm Hg), whereas subject 10 has 27 replicated measurements (mean 7 ± 7 mm Hg). About 55 paired observations (60% of the paired data) did not fall with Royal College of Pathologists of Australasia acceptability for a P_{CO_2}. P_{tcCO_2} = transcutaneously measured partial pressure of carbon dioxide.

Table 1. Clinical Characteristics of the 10 Neonates

Infant No.	Birthweight, g	Sex	Gestational Age, wk	No. Sample Pairs	Respiratory Support
1	3,260	M	38 1/7	5	Conventional ventilation
2	3,810	M	40 6/7	9	Conventional ventilation
3	3,150	M	39 3/7	12	High-frequency oscillatory ventilation
4	3,670	F	41	2	Conventional ventilation
5	2,330	F	36 6/7	6	High-frequency oscillatory ventilation
6	3,647	F	37 2/7	9	High-frequency oscillatory ventilation
7	3,100	M	40 3/7	10	High-frequency oscillatory ventilation
8	3,300	M	39	3	CPAP
9	3,532	M	37 2/7	7	CPAP
10	3,669	M	38 6/7	27	High-frequency oscillatory ventilation

independent of the magnitude of the measurement (Kendall τ b = 0.12, P = .10). Therefore, the difference between the 2 measurements with multiple observations per individual was plotted against the P_{aCO_2}[9] (Fig. 3). Even though the concordance correlation coefficient between P_{tcCO_2} and P_{aCO_2} was 0.86 (95% CI 0.55–0.96) (n = 10), Figure 3 demonstrates the poor precision of the transcutaneous CO_2 device compared to arterial blood gas measurements. The P_{tcCO_2} measurements vary from > 18 mm Hg than P_{aCO_2} to < 13 mm Hg than P_{aCO_2} for 95% of paired observations. The difference between a neonate's P_{tcCO_2} measurement and the actual P_{aCO_2} would be expected to be ≤ 15 mm Hg 95% of the time. Most of the paired observations fell outside the RCPA's performance specifications (see the 2 horizontal solid red lines in Fig. 3).

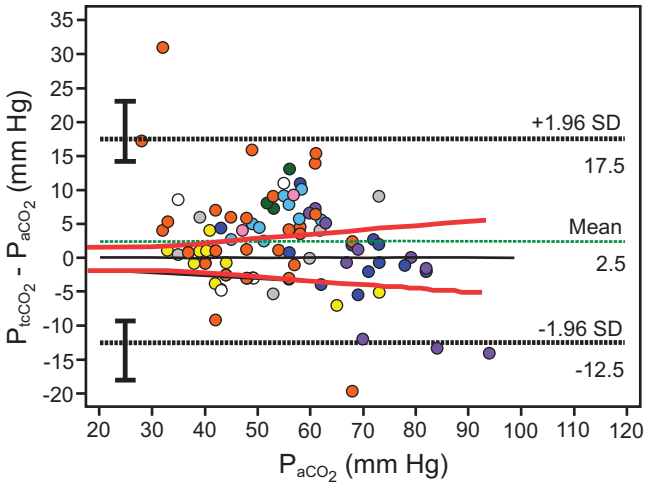

Fig. 3. Agreement between P_{tcCO_2} and P_{aCO_2} (at 37°C) was plotted against the P_{aCO_2} with multiple observations in each subject in which the actual values vary.[9] Each distinct solid color represents a subject. The data demonstrate that the mean P_{tcCO_2} measurements were about > 3 mm Hg than P_{aCO_2}. However, the precision was poor as the P_{tcCO_2} ranged from > 18 mm Hg to < 13 mm Hg than P_{aCO_2} 95% of the time over the P_{aCO_2} (range 28–94 mm Hg). The solid red line depicts the acceptable analytical performance specifications for P_{aCO_2},[13] which is ± 2 mm Hg when P_{aCO_2} is ≤ 34 mm Hg and ± 6% when P_{aCO_2} > 34.0 mm Hg. This acceptibility criterion was applied to the difference between P_{tcCO_2} and P_{aCO_2} (at 37°C). About 55 paired observations (60% of the paired data) did not fall with RCPA criteria for P_{CO_2}. P_{tcCO_2} = transcutaneously measured partial pressure of carbon dioxide.

Discussion

This retrospective chart review evaluated the precision between P_{tcCO_2} compared to P_{aCO_2} in neonates undergoing therapeutic hypothermia. This study demonstrated poor agreement between P_{tcCO_2} and P_{aCO_2} in neonates with 2–27 replicates observations. Specifically, the difference between the 2 measurements was ≤ 15 mm Hg in 95% of paired observations (Fig. 3). A difference of 15 mm Hg can represent a 16% or 54% difference, depending on whether the P_{aCO_2} is 28 mm Hg or 94 mm Hg. Hypothermia affects blood gas parameters such as pH, P_{O_2}, and P_{CO_2}. However, as the Sentec device reported P_{tcCO_2} values at 37°C, the P_{aCO_2} was also reported at 37°C for comparative purposes.

The literature has demonstrated similar results to this study. The weighted average of pooled data from 4 similar studies implies that P_{tcCO_2} can be as much as > 16 mm Hg to < 10 mm Hg than P_{aCO_2} for 95% of paired observations (n = 418 paired samples).[3,7,15,16] This indicates that P_{tcCO_2} measurements are not precise compared to P_{aCO_2}.

In a 2017 review that compared P_{tcCO_2} and P_{aCO_2} in adults,[17] the 95% limits of agreement were examined in 22 studies (2,317 samples). When we apply a weighted average of that data,[17] P_{tcCO_2} was > 7 mm Hg to < 5 mm Hg than P_{aCO_2} for 95% of paired observations. Thus, the range for the 95% limits of agreement is about 13 mm Hg,[17] which is half the range of the pooled data from 4 studies that included children and neonates (26 mm Hg).[3,7,15,16]

It is unknown why there is a tighter 95% limit of agreement between P_{tcCO_2} and P_{aCO_2} in adults compared to the pediatric population. Regardless, most of the paired differences in pediatric studies would not be acceptable when applying the RCPA acceptability standards for P_{aCO_2} to the difference between P_{tcCO_2} and P_{aCO_2} in neonates. When a clinician places a transcutaneous CO_2 sensor on an infant, it is not very assuring that a random P_{tcCO_2} measurement means that P_{aCO_2} can be < 16 mm Hg or > 10 mm Hg the P_{tcCO_2} measurement 95 times out of 100. And these limits are considering the pooled data from 4 other studies in children and neonates,[3,7,15,16] including the present study. Thus, the transcutaneous monitor is not suitable for trending, and we do not recommend that the device be used in neonates for clinical decision making. The transcutaneous CO_2 sensors were changed periodically and not always placed in the postductal region, which may have contributed to a lack of trending.

Most clinical trials evaluating therapeutic hypothermia in neonates have corrected blood gases for body temperature. Some studies have stated that there is no clinical advantage to temperature-correcting blood gases compared to leaving them at a standard temperature of 37°C.[18-20] However, animal studies comparing treatment with non-temperature–corrected blood gases versus treatment with temperature-corrected blood gases in deep hypothermia reported a significant increase in tissue oxygenation and cortical blood flow in studies using temperature correction.[21,22] Thus, the debate remains on whether to temperature correct or not.

In this study, we did not determine whether temperature-correcting blood gases altered the course of treatment in these neonates, nor was it the purpose to see if the outcomes were affected by temperature-correcting blood gases. We only examined the precision between P_{tcCO_2} and P_{aCO_2} values at 37°C. Temperature correcting the transcutaneous CO_2 device and arterial P_{CO_2} would not have affected the mean difference between the 2 measurements as both values would have been converted to the same extent. Thus, in this case, temperature correction does not make any difference in the outcome of this study.

Conclusions

This study shows that the mean P_{tcCO_2} is similar to the mean P_{aCO_2}, but the precision is poor. About 60% of the paired differences > ± 6%, which is RCPA's analytical performance specifications. In many NICUs, measuring one arterial blood gas and using the difference between P_{tcCO_2} and P_{aCO_2} to make management decisions is standard practice. Our findings do not support this practice. Since

capillary blood samples from the fingertip or earlobe accurately reflect arterial blood pH and P_{aCO_2},[23] this may be a better alternative than transcutaneous CO_2 monitoring when clinicians need to know the true P_{aCO_2}. We do not advocate transcutaneous CO_2 monitoring for clinical decision making in neonates.

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