Temperature Correction of Blood Gas Measurements during Therapeutic Hypothermia: Is it Time to Chill Out?

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Dr. Gwenyth Fischer
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Disclosures (ML)

• Speaking Honoraria
  – Radiometer
  – Nova Biomedical
  – Draeger

• Research Support (Reagents, Instrumentation, Travel)
  – Nova Biomedical
  – Roche Diagnostics (Canada)
  – Radiometer
  – Instrumentation Laboratories (Canada)

• ALOL Biomedical Inc
  • Clinical Laboratory Consulting Business
Disclosures (EZ)

• Nothing to disclose
Disclosures (GF)

• Nothing to disclose
Objectives

1) To describe the pathophysiology of newborn hypoxic ischemic encephalopathy (HIE)
2) To discuss why therapeutic hypothermia is an effective treatment for HIE.
3) To review the alpha-stat versus the pH-stat strategies (and limitations of each) for measuring and reporting blood gas results during therapeutic hypothermia.
4) To outline the inconsistency in the measurement and reporting of blood gas parameters in the published clinical trials that demonstrated the efficacy of therapeutic hypothermia.
5) To present clinical cases and discuss how the inconsistency in reporting blood gas results could influence the care of the neonate.
Clinical Case Example

- An outside hospital calls to request transport for a newborn
- 39w5d gestation female infant, birth weight 3050 g
- Mother presented to hospital with spontaneous rupture of membranes, meconium-stained fluid
- During fetal monitoring, noted to have “down tones” so stat C section was performed
Clinical Case Example

• At delivery, infant is limp, blue, and pulseless
• Immediately intubated, received chest compressions, epinephrine, bicarb, and calcium
• Required chest compressions for 20 minutes, multiple doses of epinephrine
• APGARs were 0, 1, 1, 1, 1 at 1, 5, 10, 15, and 20 minutes of age
• Arterial blood gas: pH 6.75, CO2 123, O2 108, HCO3 17
Clinical Case Example

- When our transport team arrived, infant was noted to be intubated and unresponsive
- Passive cooling initiated during transport to our facility
- Upon arrival, examination showed an unresponsive infant with no purposeful movements, minimal pupillary reaction to light, and intermittent lip-smacking and upper extremity jerking
- Admission temperature 32.7°C
- Seizure activity confirmed on a EEG
Clinical Case Example

• Admission laboratory data:
  • Na 143, K 3.6, Cl 102, CO2 12, BUN 8, Creatinine 0.78, Glucose 165
  • ALT 142, AST 312
  • Lactate 19
  • ABG 7.11/38/87/12/-16
  • WBC 35.9, hgb 14.6, plt 142
  • INR 2.4, PTT 88, fibrinogen 98
Clinical Case Example

Plan:

- Neuro: Initiate therapeutic hypothermia (33.5°C for 72 hours). Loaded with phenobarbital x2 and keppra for seizures.
- FEN: TPN with total fluids written for 40 ml/kg/day due to anuria.
- Respiratory: Conventional mechanical ventilation
- CV: Dopamine and hydrocortisone started for hypotension
- ID: Started on ampicillin, gentamycin, and acyclovir (mother with HSV but treated during pregnancy and infant delivered via c-section)
- Heme: Coagulopathy treated with FFP and cryoprecipitate, continue to monitor coags
- Sedation: Fentanyl prn
PATIENT CARE

Cooling Phase

☑ Initiate: Neonatal Body Cooling Protocol
  Routine, EFFECTIVE NOW starting Today at 1330 Until Specified
  COOLING PHASE: Neonatal Body Cooling Protocol

☑ Cooling phase
  Routine, EFFECTIVE NOW starting Today at 1330 Until Specified
  COOLING PHASE: Begin body cooling therapy with cooling blanket unit (Blanketrol®) to achieve and maintain an esophageal temp of 33.5 °C. Cooling therapy is to last 72 hours from initiation.

☑ Vital signs & BP per NICU protocol
  Routine, PER UNIT ROUTINE starting Today at 1330 Until Specified
  COOLING PHASE: Vital signs & BP per NICU protocol During Body Cooling Therapy

☑ Cooling phase: Temperature
  Routine, EFFECTIVE NOW starting Today at 1330 Until Specified
  COOLING PHASE: Obtain esophageal, skin, and cooling blanket water and set temps: 1. Q 15 mins x 2 hrs after initiating cooling, then 2. Q 1H x 4 hrs, then 3. Q 2H until 72 hrs of cooling are complete

☑ NO external heat source
  Routine, EFFECTIVE NOW starting Today at 1330 Until Specified
  COOLING PHASE: No external heat source is to be used during body cooling

☑ Amplitude-integrated EEG (aEEG)
  Routine, Qty-1, ONE TIME First occurrence Today at 1330

Rewarming Phase

☑ Assess temperature: Re-Warming Phase
  Routine, EVERY HOUR First occurrence on Sun 6/12 at 0000 for 6 hours
  REWARMING PHASE: After 72 hrs of cooling, begin to re-warm by increasing blanket set-point 0.5 °C Q1H x 6 hrs. At end of 6 hour re-warming period, discontinue cooling blanket unit (Blanketrol®).

☑ Assess temperature: Temperature
  Routine, EVERY HOUR First occurrence on Sun 6/12 at 0000 for 6 hours
  REWARMING PHASE: Q1H Obtain esophageal, skin, and cooling blanket water temps

Thermoregulation Post Cooling Therapy

☑ Radiant warmer
  Routine, EFFECTIVE NOW starting Today at 1330 Until Specified
  POST COOLING THERAPY: Continue thermoregulation by radiant warmer servo-control *Initial set-point at 0.5 °C higher than infant’s current skin temp *Increase set-point by 0.5 °C Q1H until warmer set-point of 36.5 °C is reached OR until the infant has achieved an axillary temp of 36.5 °C *Maintain infant thermoregulation per NICU protocol.
Before Initiation of Cooling Therapy

- **Basic metabolic panel**
  - Magnesium: STAT First occurrence Today at 1330, Blood
  - Phosphorus: STAT First occurrence Today at 1330, Blood
  - Lactic acid whole blood: STAT First occurrence Today at 1330, Blood
  - CBC with platelets differential: STAT First occurrence Today at 1330, Blood
  - INR: STAT First occurrence Today at 1330, Blood
  - Partial thromboplastin time: STAT First occurrence Today at 1330, Blood
  - D dimer quantitative: STAT First occurrence Today at 1330, Blood
  - Baby type and screen: STAT First occurrence Today at 1330, Blood
  - Blood gas arterial: STAT First occurrence Today at 1330, Blood

Repeat Q12H During Cooling Therapy

- **Sodium whole blood**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood
- **Potassium whole blood**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood
- **Calcium ionized whole blood**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood
- **Glucose whole blood**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood
- **Blood gas arterial**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood
- **Lactic acid whole blood**
  - EVERY 12 HOURS First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 1200 for 6 occurrences, Blood

Repeat Q24H During Cooling Therapy

- **INR**
  - DAILY First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 0000 for 3 occurrences, Blood
- **Partial thromboplastin time**
  - DAILY First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 0000 for 3 occurrences, Blood
- **D dimer quantitative**
  - DAILY First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 0000 for 3 occurrences, Blood
- **Creatinine**
  - DAILY First occurrence Tomorrow at 0000 Last occurrence on Sun 6/12 at 0000 for 3 occurrences, Blood
- **Urea nitrogen**
  - Last Lab Result: CREATINE (mg/dL) Date Value 05/12/2018 0.22
Neonate – Hypoxic Ischemic Encephalopathy (HIE)

- Lack of oxygen in the brain around the time of birth (perinatal asphyxia) affects 3-5 infants/1000 live births
  - 0.5-1 infants per 1000 live births develop brain damage in the form of HIE
- Up to 60% of infants with HIE will die and 25% of survivors will have long term neurodevelopmental sequelae
Therapeutic mild hypothermia (33.5°C) is currently the only neuroprotective treatment to have been clinically tested in large trials to minimize brain injury in term newborns.

Prior to the hypothermia clinical trials, supportive measures (no specific therapies) were only available for HIE.
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- ≥ 36 weeks gestation and ≤6 hours of age
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- pH ≤ 7.0 or a base deficit of ≥ 16 mmol/L (cord blood or blood collected within the first hour of birth)
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  - 10 minute APGAR score < 5
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- Assisted ventilation initiated at birth and continued for at least 10 minutes
- Neurologic examination demonstrating moderate to severe encephalopathy is essential
Pathophysiology of HIE
Pathophysiology of HIE

Primary or Acute Phase
- Depletion of energy metabolites = anaerobic metabolism
- Rapid/progressive depolarization of cells
- Cytotoxic edema
- ↑ intracellular Ca+
- ↑ Na+ = overload
- ↑ extracellular glutamate
- Progressive acidosis

Cell Injury + Necrosis

Therapeutic Window
- (within 6 hours following hypoxic insult)
- Window of Opportunity:
  - Optimal time frame for hypothermia or other strategies: Goal to reduce neurologic injury
- Cerebral blood flow (CBF) = reperfusion. Slow recovery of the cerebral oxidative metabolism/acidosis

Secondary or Latent Phase
- (Several hours to several days after hypoxic insult)
- Secondary cytotoxic edema = ↑ cell death
- Inflammatory response ↑ IL-1; IL-6 + TNFα
- Cerebral edema/seizures
- ↑ Free radical release
- ↑ Ca+ = overload
- Accumulation of excitatory amino acids (EAA) with ↑ uptake of EAA.

Neuronal cell death + Apoptosis

Progression of Injury: An Evolving Process

Source: © 2011 Elsevier Inc.
How/Why is Hypothermia Neuroprotective?

• Reducing brain perfusion and metabolism
How/Why is Hypothermia Neuroprotective?

• Reducing brain perfusion and metabolism
  • Decrease of cellular oxygen and glucose requirements by 5-8% per ⁰C decrease in temperature
  • This leads to a decrease in CO₂ production
  • Hypocapnia with normoxemia induces cerebral vasoconstriction and decreases cerebral blood flow
  • Mitigate reperfusion injury
How/Why is Hypothermia Neuroprotective?

- Reducing brain perfusion and metabolism
- Decrease free radical production
How/Why is Hypothermia Neuroprotective?

• Reducing brain perfusion and metabolism
• Decrease free radical production
• Decrease the immune response
How/Why is Hypothermia Neuroprotective?

- Reducing brain perfusion and metabolism
- Decrease free radical production
- Decrease the immune response
- Suppression of epileptic activity
Other Clinical Situations With Hypothermic Patients

• Cooling for head trauma in older children and adults

• Near drowning events

• Weather exposure

• Use of extracorporeal machines such as dialysis and ecmo
Cooling Older Patients

- **External Cooling**
  - Ice Packs
  - Water Immersion
  - Cooling Blankets
  - Conductive Pads

- **Internal Cooling**
  - Ice Lavage
  - Cooled IV Fluids
  - Catheter Based Cooling Technologies
Will hypothermia affect blood gas parameters?
Henry’s Law

- At a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid.
Henry’s Law

William Henry
December 12, 1774 – September 2, 1836

\[ C = \frac{K}{P_{\text{gas}}} \]

Mass of a gas dissolved in a solution
Henry’s Law

C = K/P_{gas}

Mass of a gas dissolved in a solution

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Henry’s Law Constant

Solvent and temperature dependent
Henry’s Law

C = \frac{K}{P_{\text{gas}}}

- Mass of a gas dissolved in a solution
- Henry’s Law Constant
- Partial Pressure of the gas

William Henry
December 12, 1774 – September 2, 1836
Hypothermia for newborns with hypoxic ischemic encephalopathy

A Pelioiws-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee


Mild therapeutic hypothermia to a rectal temperature of 34 ± 0.5⁰C initiated as soon as possible within the first 6 hours of life.

Cooling can be achieved by either total body or selective head cooling.

Key Words: Apoplexy, Cooling, Hypothermia, Hypoxic ischemic encephalopathy, Outcome

Despite advances in perinatal care, moderate to severe acute perinatal hypoxic ischemic encephalopathy (HIE) in late preterm and term infants remains an important cause of mortality and acute neurological injury with subsequent long-term neurodevelopmental disabilities (1). The risk of disability and impaired cognitive development correlates with the severity of HIE (1,2). A mild reduction in brain temperature, of 2°C to 4°C, initiated within 6 h after birth, was the first therapy to demonstrate neuroprotection in newborn animals. Subsequently, in large randomized clinical studies, infants treated with cooling experienc...
Hypoxic Ischemic Encephalopathy (HIE) Admission Order Set

Page 2 of 2

Lab Investigations

- CBC
- APTT
- Lyte 6: Na, K, Cl, Creatinine, BUN, Bicarb
- Blood Gas & Metabolites
  - Arterial
  - Venous
  - ALT
  - AST
  - Blood C+S
  - Tracheal C + S
- Stool for frank and occult blood

- INR
- Fibrinogen
- d-dimer
- Ca, Mg

Additional Lab Investigations

- CBC q12h
- Lyte 6: Na, K, Cl, Creatinine, BUN, Bicarb q12h
- Blood Gas & Metabolites q6h
  - Arterial
  - Venous
- APTT q24h
- INR q24h
- ALT q24h
- AST q24h
- Bill PRN

Diagnostics

- ECG (to be done as soon as possible) - Reason: ____________________________
- ECHO (to be done as soon as possible) - Reason: ____________________________
- Head Ultrasound (to be done as soon as possible) - Reason: __________________

Glycemic Management

- Glucose strip testing q2h

Additional Orders:
## Hypoxic Ischemic Encephalopathy (HIE) Admission Order Set

### Lab Investigations

- CBC
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- INR
- Ca, Mg
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- d-dimer
- Venous
- AST
- Tracheal C+S
- Capillary
- Albumin
- PRN

### Additional Lab Investigations

- CBC q12h
- Lyte 6: Na, K, Cl, Creatinine, BUN, CR q12h
- Blood Gas & Metabolites q6h
- APTT q24h
- ALT q24h
- AST q24h

### Diagnostics

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### Glycemic Management

- Glucose strip testing q2h
Blood gas measurement in the clinical laboratory

• Blood gas instruments commonly conduct their analysis of blood gas parameters by warming the blood gas specimen to 37°C

• Most instruments can calculate and present temperature corrected values
Blood gas measurement in the clinical laboratory

• Blood gas instruments commonly conduct their analysis of blood gas parameters by warming the blood gas specimen to 37°C

• Most instruments can calculate temperature corrected values

\[ p\text{CO}_2 (T) = p\text{CO}_2 (37) \times 10^{0.021 \times (t-37)} \]
Temperature Correction of Blood-Gas and pH Measurements

Edward R. Ashwood, Gerald Kost, and Margaret Kenny

We critically review formulas for temperature correction of pH, $p_{CO_2}$, and $p_{O_2}$ measurements in whole blood and the clinical usefulness of these formulas. We discuss both the theoretical derivation and experimental verification of temperature-induced changes. We recommend when to use and when not to use these formulas, based upon the clinical interpretation of these assays.

Modern blood-gas analyzers measure pH, $p_{CO_2}$, and $p_{O_2}$ in a sample of whole blood. Usually, the instrument then calculates the bicarbonate concentration and the oxygen saturation. Newer instruments allow the primary measurements to be automatically corrected to the patient's actual body temperature, by use of various correction formulas (Table 1). Although standard textbooks (1–3) used in clinical laboratories recommend correction of pH, $p_{CO_2}$, and $p_{O_2}$ to the patient's temperature (or measurement at the patient's temperature), we believe that such recommendations are inappropriate for many clinical situations.

**Temperature-Induced Changes**

**pH Change in a Closed System**

The "anaerobic" change of blood pH with respect to temperature is a change that occurs within a closed system at constant pressure. By definition, a closed system permits no mass exchange with the environment. Energy exchange, however, is possible. Stadie and Martin (5) used these assumptions when they predicted $dpH/dT$ in 1924. By determining the total titration curves of whole blood at 15 °C and 38 °C, they calculated the heat of ionization, $-\Delta H$, of hemoglobin acid to be 42 kJ/mol ($-10$ kcal/mol). From equations 2 and 3, the calculated value of $dpH/dT$ is $-0.0224/°C$. Whole blood contains many buffers with pK values between 6 and 8, the most important of which are bicarbonate and the imidazole moieties of proteins. Given the heats of ionization of bicarbonate and plasma protein, Hastings and Sendroy (6) concluded that $dpH/dT$ would be between $-0.007$ and $-0.024/°C$. Stadie et al. (7) derived a theoretical equation based on the heats of ionization of bicarbonate, phosphate, and protein and the buffering power of blood. $dpH/dT$ calculated from this equation is a function of the carbon dioxide content, protein concentration, initial pH, buffering capacity of bicarbonate, and temperature.

**Table 1. Temperature-Correction Formulas Used by Blood-Gas Analyzers**

<table>
<thead>
<tr>
<th>Formula</th>
<th>pH Change Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. $pH = pH_m + [-0.0146 + 0.0065(7.4 - pH_m)] (t - 37)$</td>
<td>$pH$ change in a closed system</td>
</tr>
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<td>2. $pH = pH_m - 0.015(t - 37)$</td>
<td>$pH$ change in an open system</td>
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HIE Neonate – Which pCO₂ is truth?

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<tr>
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<tr>
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<td>Day 1 10:05:00 PM</td>
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Two Schools of Thought

• Alpha stat school
  • Do not correct to body temperature

• pH stat school
  • Do correct to body temperature
Two Schools of Thought

• Alpha stat versus pH stat controversy
  “Should ventilation be adjusted to achieve a temperature uncorrected pCO₂ of 40 mm Hg (alpha stat) or adjusted to achieve a temperature corrected pCO₂ of 40 mm Hg (pH stat)”
  - Chris Higgins, Jan 2016

  *Temperature Correction of Blood gas and pH measurement - an unresolved controversy*
• Do not correct to body temperature
Alpha Stat

- Do not correct to body temperature
- Initially based on the publications:
  - Davis BD. On the importance of being ionized. *Archives of Biochemistry and Biophysics* 78:497-509, 1958
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  - Reeves RB. An imidazole alphastat hypothesis for vertebrate acid base regulation: Tissue carbon dioxide content and body temperature in bullfrogs *Respiration Physiology* 14:219-236, 1972

- Intracellular pH remains at or close to neutrality (with temperature) largely due to protein buffering (phosphate and bicarbonate buffers also functional)

- Established reference ranges for interpretation of blood gas values have been determined at 37°C
**pH Stat**

- Do correct to body temperature
- Level of CO$_2$ is externally controlled to maintain normal pH and CO$_2$ of the temperature corrected values
- It best represents what is happening in the patient
- Concerned about the application of Henry’s law
A closer look at blood gases reference ranges as it relates to HIE and therapeutic hypothermia
A closer look at blood gases reference ranges as it relates to HIE and therapeutic hypothermia

- ≥ 36 weeks gestation and ≤6 hours of age
- duration of the hypothermia is 72 hours (3 days post natal)
<table>
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<td>Premature neonates</td>
<td>248</td>
<td>39–68</td>
<td>5.2–9.1</td>
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</table>

**Specimen Type(s)**

1. Arterial whole blood
2. Capillary blood

**Reference(s)**


**Method(s)**

1. Not given.

**Comment(s)**

1. *Numbers not provided.
2. Study used hospitalized patients and a computerized approach adapted from the Hoffmann technique.
# CARBON DIOXIDE, PARTIAL PRESSURE (pCO₂)

## Male and Female

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<th>kPa</th>
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### Specimen Type(s)

- 1. Arterial whole blood
- 2. Capillary blood


1. Not given.

1. *Numbers not provided.
2. Study used hospitalized patients and a computerized approach adapted from the Hoffmann technique.
Neonate capillary blood gas reference values

Jocelyne Cousineau\textsuperscript{a}, Suzanne Anctil\textsuperscript{b}, Ana Carceller\textsuperscript{b}, Monique Gonthier\textsuperscript{b}, Edgard E. Delvin\textsuperscript{a,b,*}

\textsuperscript{a}Department of Clinical Biochemistry, CHU Ste-Justine, Université de Montréal, Québec, Canada
\textsuperscript{b}Department of Pediatrics, CHU Ste-Justine, Université de Montréal, Québec, Canada

Received 27 April 2005; received in revised form 7 June 2005; accepted 6 July 2005
Available online 16 August 2005

Abstract

Objectives: Because biological data are instrument-dependent and because technology has evolved over the last two decades, the published capillary blood reference values for blood gases, lactate, ionized calcium (iCa) and glucose may not reflect the present day situation. Hence, we report such values for healthy term neonates at 48 ± 12 h of life.

Design and methods: The Institution Ethics Review Board for Research on Human Subjects has accepted the protocol. Extra blood sample was obtained at the time heel-pricks were performed in the frame of the Quebec genetic screening program. One hundred twenty-six term neonates (39.6 ± 1.2 weeks of gestation) were included in the study. pH, $pO_2$, $pCO_2$, lactate, ionized calcium and glucose were measured in the ABL800 blood gas analyzer (Radiometer®).
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N: number of samples analyzed.
What differences can be expected between pCO$_2$ values in different specimen types?
Figure 1: Capillary network

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Higgins C. Capillary-blood gases: To arterialize or not. MLO. November 2008:42-47
Correlation of simultaneously obtained capillary, venous, and arterial blood gases of patients in a paediatric intensive care unit

D Yıldızdaş, H Yapıcıoğlu, H L Yılmaz, Y Sertdemir

Aims: To investigate the correlation of pH, partial pressure of oxygen (PO₂), partial pressure of carbon dioxide (PCO₂), base excess (BE), and bicarbonate (HCO₃⁻) between arterial (ABG), venous (VBG), and capillary (CBG) blood gases.

Methods: Patients admitted to the paediatric intensive care unit (PICU) in Çukurova University between August 2000 and February 2002 were enrolled.

Results: A total of 116 simultaneous venous, arterial, and capillary blood samples were obtained from 116 patients (mean age 56.91 months, range 15 days to 160 months). Eight (7%) were neonates. Sixty six (57%) were males. pH, PCO₂, BE, and HCO₃⁻ were all significantly correlated in ABG, VBG, and CBG. Correlation in PO₂ was also significant, but less so. Correlation between pH, PCO₂, PO₂, BE, and HCO₃⁻ was similar in the presence of hypothermia, hyperthermia, and prolonged capillary refill time. In hypotension, correlation in PO₂ between VBG and CBG was similar but disappeared in ABG–VBG and ABG–CBG data.
Figure 2  Correlation of arterial, venous, and capillary blood gases for PCO₂.
Arterial Venous pCO₂ Difference ~ 7 mmHg

Arterial Capillary pCO₂ Difference ~ 6 mmHg
Will these pCO$_2$ reference ranges be dependent upon the blood gas instrument used to measure the specimens?
AQ-C
Critical Care/Aqueous
Blood Gas With Chemistry

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**All method mean (SD)**

58.6 (4.4) mm Hg

**Lowest method mean (SD)**

51.3 (2.4) mm Hg

**Highest method mean (SD)**

67.6 (2.8) mm Hg
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All method mean (SD) 58.6 (4.4) mm Hg

Lowest method mean (SD) 51.3 (2.4) mm Hg

Highest method mean (SD) 67.6 (2.8) mm Hg

Can we use the same reference ranges for use with all blood gas instruments?

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Can we use the same reference ranges for use with all blood gas instruments?
Clinical Trials

- Address the safety and efficacy of induced hypothermia in perinatal HIE


- Simbruner G, Mittal RA, Rohlmann F, Muche R. neo.nEURO. Network Trial Participants. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. Pediatrics 2010; 126(4); e771-778
Clinical Trials

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**pH Stat: Corrected for body temperature**
Is there an association between hypocarbia and 18-22 month outcome among neonates with HIE?
Hypocarbia and Adverse Outcome in Neonatal Hypoxic-Ischemic Encephalopathy

Athina Pappas, MD, Seetha Shankaran, MD, Abbot R. Laptok, MD, John C. Langer, MS, Rebecca Bara, RN, Richard A. Ehrenkranz, MD, Ronald N. Goldberg, MD, Abhik Das, PhD, Rosemary D. Higgins, MD, Jon E. Tyson, MD MPH, and Michele C. Walsh, MD MS for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

1Department of Pediatrics, Wayne State University School of Medicine, Detroit MI
2Department of Pediatrics, Women and Infants’ Hospital, Brown University, Providence RI
3Statistics and Epidemiology, RTI International, Research Triangle Park, NC
4Department of Pediatrics, Yale University School of Medicine, New Haven CT
5Department of Pediatrics, Duke University, Durham, NC
6Pregnancy and Perinatology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
7Department of Pediatrics, University of Texas Medical School at Houston
8Department of Pediatrics, Rainbow Babies & Children’s Hospital, Case Western Reserve University, Cleveland OH

Abstract

Objective—To evaluate the association between early hypocarbia and 18-22 month outcome among neonates with hypoxic-ischemic encephalopathy (HIE).

Study design—Data from the NICHD NRN randomized controlled trial of whole body hypothermia for neonatal HIE were used for this secondary observational study. Infants (n=204) had multiple blood gases recorded from birth-12h of study intervention (hypothermia vs. intensive care alone). The relationship between hypocarbia and outcome (death/disability at 18-22 months) was evaluated by unadjusted and adjusted analyses examining minimum PCO2 and cumulative exposure to PCO2 <35 mmHg. The relationship between cumulative PCO2 <35 mmHg (calculated as the difference between 35 mmHg and the sampled PCO2) multiplied by the duration of time spent <35 mmHg) and outcome was evaluated by level of exposure (none-high) using a multiple logistic regression analysis with adjustments for pH, level of encephalopathy, treatment group (± hypothermia), race, gender, and gestational age.
Evaluated the relationship between hypocarbia ( < 35 mm Hg) and outcome (disability/death at 18-22 months).

Blood gases were corrected for body temperature.

Poor outcomes and death/disability increased with greater cumulative exposure to pCO₂ < 35 mmHg.
Clinical Case Wrap-up

• Patient underwent therapeutic hypothermia for 72 hours.
• No further seizures noted, Keppra stopped prior to discharge.
• Brain MRI consistent with profound hypoxic ischemic injury.
• Patient was successfully extubated after 6 days.
• Some difficulty handling secretions, managed with glycopyrrolate.
• Unable to orally feed. Mother elected not to pursue G tube and patient was discharged on NG feeds.
• Neurologic exam at discharge was notable for hypertonicity in upper extremities and a weak suck reflex.
• Discharged from NICU at 5 weeks of age.
Clinical Case Wrap-up

• After discharge, patient had recurrent aspiration and stridor, at least one episode of aspiration pneumonia
• Tracheostomy and g tube were placed at 4 months of age
• Currently 5 months old, continues to have increased tone and spasticity in upper and lower extremities but does show good visual tracking and interaction with caregivers
Conclusions

1) Six clinical trials conducted between 2005 and 2012, demonstrated that mild hypothermia (33.5°C – 34.5°C) for 72 hours is an effective treatment to help reduce morbidity and mortality associated with hypoxic ischemic encephalopathy (HIE).

2) During therapeutic hypothermia, it is critical to closely monitor pCO₂ and pH to confirm adequate cerebral blood flow in the neonate.

3) Interpretation of blood gas results during therapeutic hypothermia is complicated because hypothermia can affect the solubility of CO₂.

4) A controversy exists as to whether blood gas measurement should be corrected to the patient’s actual body temperature or be consistently measured at 37°C.