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

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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

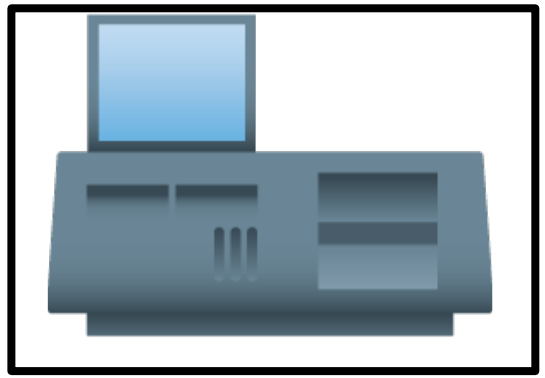
1) To describe the pathophysiology of newborn hypoxic ischemic encephalopathy (HIE)
2) To discuss why therapeutic hypothermia is an effective treatment for HIE.
3) To review the alpha-stat versus the pH- stat strategies (and limitations of each) for measuring and reporting blood gas results during therapeutic 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^{o}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

NICU Body Cooling Therapy Manage My Version

Add Order

Version: 20-Aug-2014 (3042061021)

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.

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.

LABORATORY

Before Initiation of Cooling Therapy

- ☑ Basic metabolic panel
  STAT First occurrence Today at 1330, Blood
- ☑ 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
  Last Lab Result: HEMOGLOBIN (g/dL) Date Value 05/12/2016 9.7* ----------
- ☑ 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

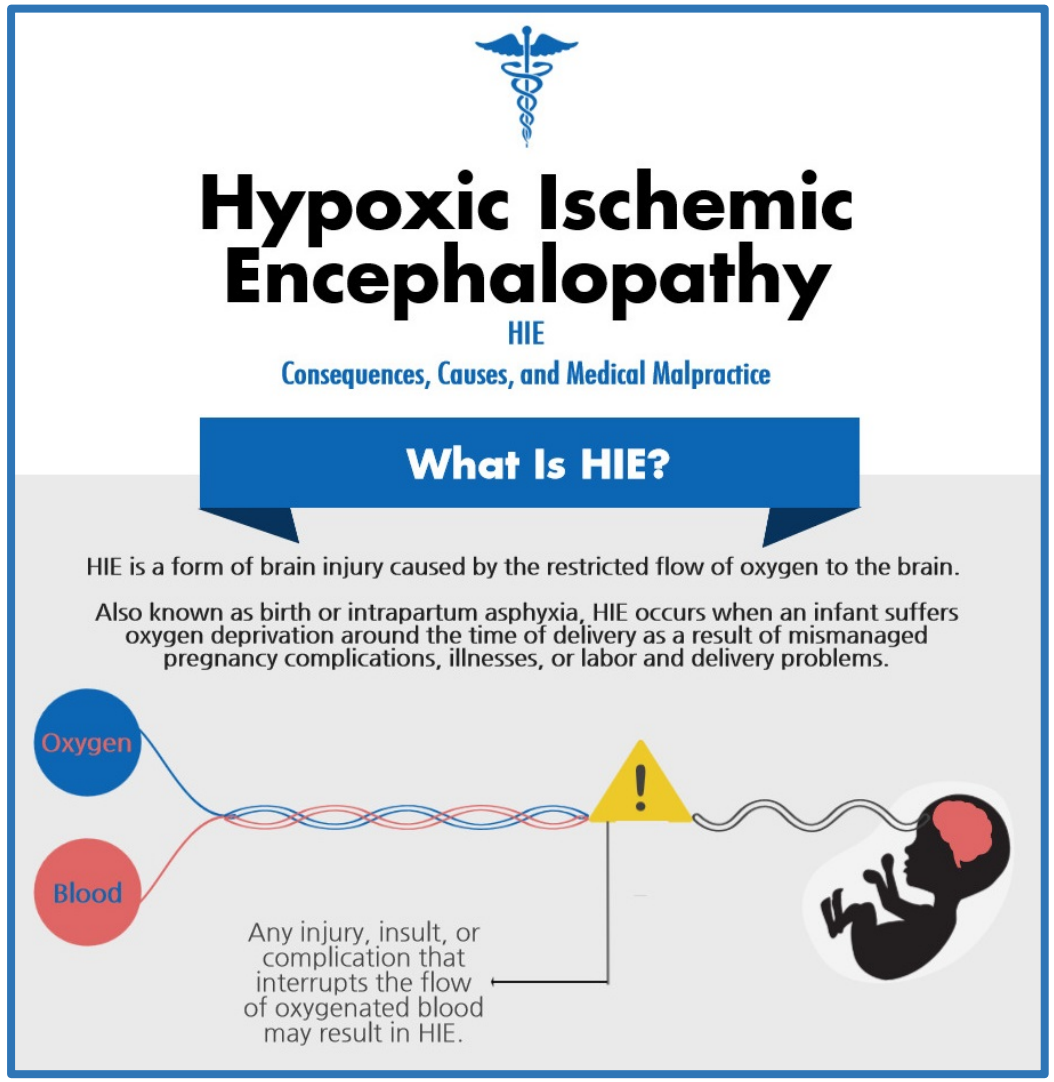
Repeat Q12H During Cooling Therapy

- ☑ 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
  Last Lab Result: CREATININE (mg/dL) Date Value 05/12/2016 0.22 ----------
- ☑ Urea nitrogen

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

Hypothermia for newborns with hypoxic ischemic encephalopathy

Abraham Peliowski-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee

Canadian Paediatric Society

Français en page 44

A Peliowski-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee. Hypothermia for newborns with hypoxic ischemic encephalopathy. Paediatr Child Health 2012;17(1):41-43.

Hypoxic ischemic encephalopathy (HIE) remains a significant cause of mortality and long-term disability in late preterm and term infants. Mild therapeutic hypothermia to a rectal temperature of 34±0.5°C initiated as soon as possible within the first 6 h of life decreases mortality and severe long-term neurodevelopmental disabilities in infants with moderate HIE who are ≥36 weeks' gestational age. There are minimal side effects, and the incidence of disability in survivors is not increased. Infants with severe encephalopathy are less likely to benefit from treatment. Cooling may be achieved by either total body or selective head cooling. As cooling is now considered a standard of care, infants ≥36 weeks' gestational age who are depressed at birth should be assessed to determine whether they meet the criteria for cooling. There is currently no evidence that therapeutic hypothermia offers any benefit to infants <36 weeks' gestational age.

Key Words: *Asphyxia, Cooling, Hypothermia, Hypoxic ischemic encephalopathy, Outcome*

L'hypothermie chez les nouveau-nés présentant une encéphalopathie hypoxique-ischémique

L'encéphalopathie hypoxique-ischémique (EHI) demeure une cause importante de mortalité et d'invalidité à long terme chez les nourrissons peu prématurés et à terme. L'hypothermie thérapeutique bénigne à une température rectale de 34 °C±0,5 °C amorcée le plus rapidement possible dans les six premières heures de vie réduit la mortalité et les graves invalidités neurodéveloppementales à long terme chez les nourrissons d'au moins 36 semaines d'âge gestationnel ayant une EHI modérée. Les effets secondaires sont minimes, et l'incidence d'incapacité chez les survivants n'est pas plus élevée. Les nourrissons ayant une grave encéphalopathie sont moins susceptibles de profiter du traitement. On peut opter pour le refroidissement du corps entier ou de la tête seulement. Puisque le refroidissement est désormais considéré comme une norme de soins, les nourrissons d'au moins 36 semaines d'âge gestationnel qui sont en détresse neurologique à la naissance devraient faire l'objet d'une évaluation afin de déterminer s'ils respectent les critères de refroidissement. Pour l'instant, il n'existe aucunes données probantes indiquant que l'hypothermie thérapeutique apporte des bienfaits aux nourrissons de moins de 36 semaines d'âge gestationnel.

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 experi-

6 h to 12 h, which is the therapeutic window for neuroprotective interventions. The secondary phase of energy failure develops at 12 h to 36 h, and may last seven to 14 days with initiation of apoptosis, mitochondrial failure, cytotoxic edema, accumulation of excitatory amino acids and release of free radicals terminating in cell death (1,2,10). This secondary phase is associated with worsening of HIE and correlates with poor outcomes (1,2).

Therapeutic mild hypothermia's mechanism of protection is multifactorial and is attributed to a broad inhibitory activity against a variety of harmful cell processes. The beneficial effects of

- 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

Which babies are eligible for therapeutic hypothermia?

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- Based on inclusion criteria published in clinical trials

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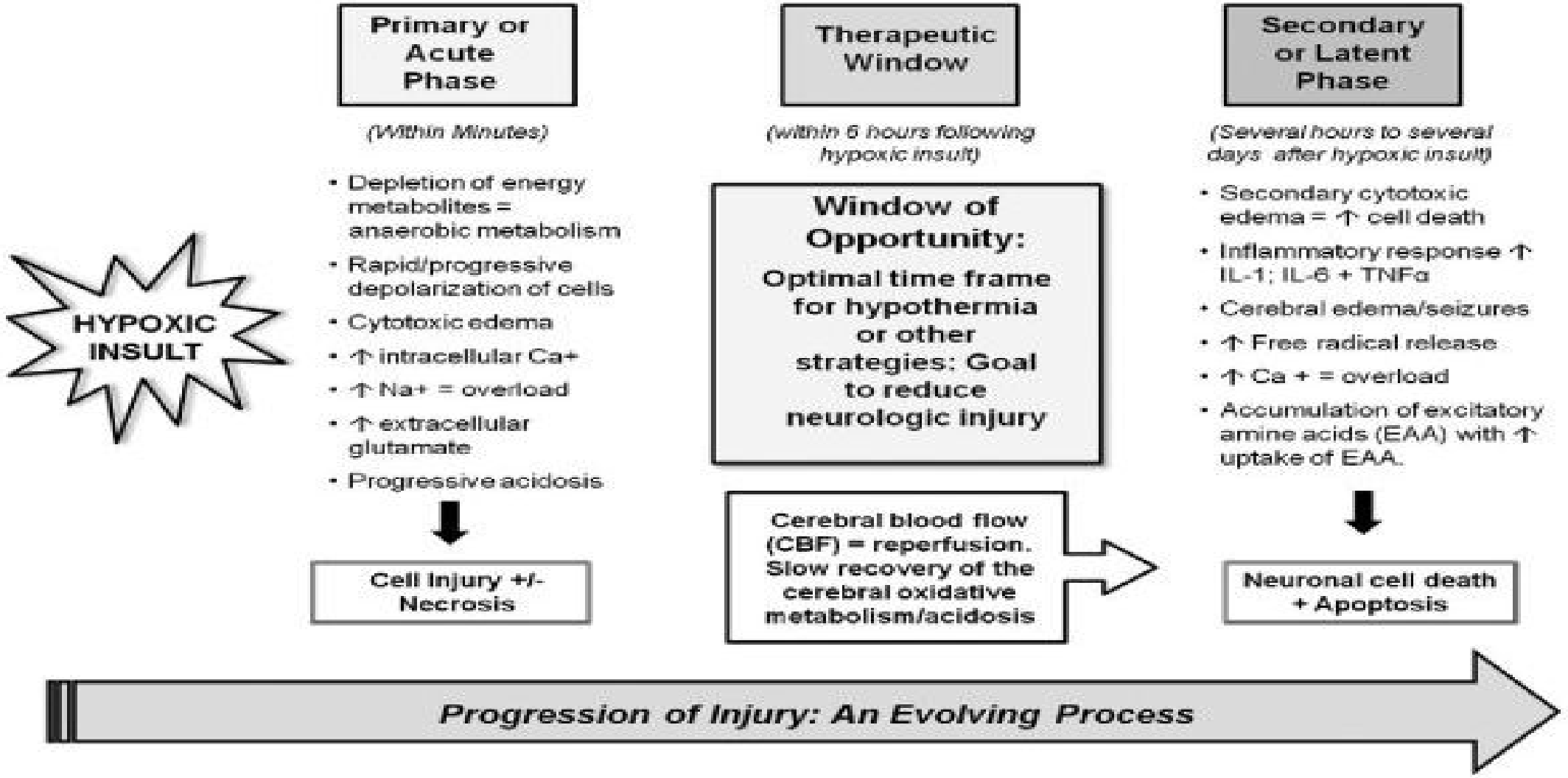
- 10 minute APGAR score < 5
- Assisted ventilation initiated at birth and continued for at least 10 minutes
- Neurologic examination demonstrating moderate to severe encephalopathy is essential

Pathophysiology of HIE

Pathophysiology of HIE

Medscape



How/Why is Hypothermia Neuroprotective?

- Reducing brain perfusion and metabolism

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- Reducing brain perfusion and metabolism
  - Decrease of cellular oxygen and glucose requirements by 5-8% per ^{o}C decrease in temperature
  - This leads to a decrease in CO_2 production
  - Hypocapnia with normoxemia induces cerebral vasoconstriction and decreases cerebral blood flow
  - Mitigate reperfusion injury

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- Decrease free radical production

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- Reducing brain perfusion and metabolism
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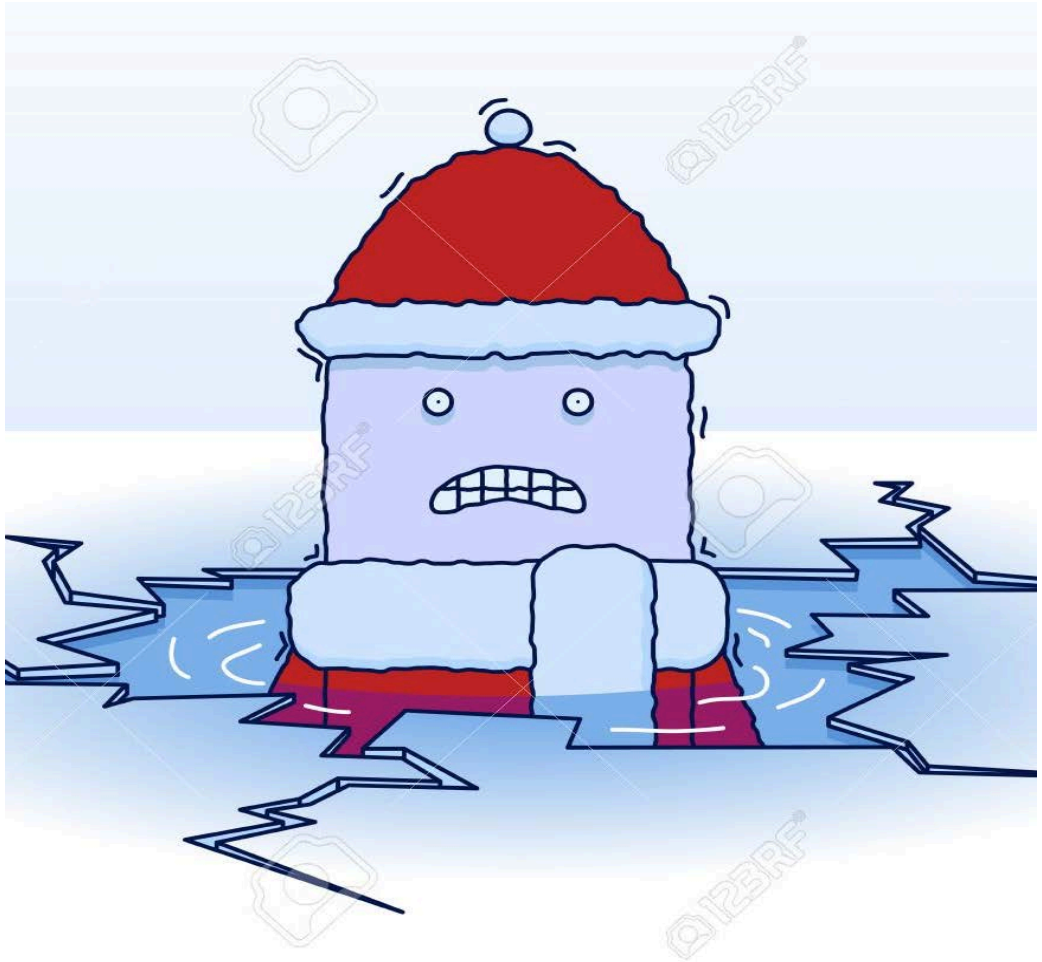
- Decrease the immune response

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

Arctic Sun Device

Will hypothermia affect blood gas parameters?

Henry's Law

William Henry
December 12, 1774 – September 2, 1836

- 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

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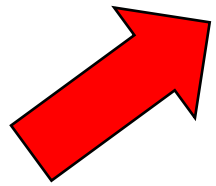
$$C = K/P_{gas}$$



Mass of a gas dissolved in a solution

Henry's Law

Solvent and temperature dependent

Henry's Law Constant

$$C = K/P_{gas}$$

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Partial Pressure of the gas

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Abraham Peliowski-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee

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Français en page 44

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- Mild therapeutic hypothermia to a rectal temperature of 34 ± 0.5°C initiated as soon as possible within the first 6 hours of life

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

Saskatoon Health Region

☐ RUH ☐ SCH ☐ SPH

☐ OTHER _____

Patient Identification

Hypoxic Ischemic Encephalopathy (HIE) Admission Order Set

ACTION			
MAR	ICP	REQ	RN

Lab Investigations

Lab Investigations on admission

☐ CBC ☐ APTT ☐ INR ☐ Fibrinogen ☐ d-dimer
☐ Lyte 6: Na, K, Cl, Creatinine, BUN, Bicarb ☐ Ca, Mg
☐ Blood Gas & Metabolites
☐ Arterial ☐ Venous ☐ Capillary
☐ ALT ☐ AST ☐ Bili PRN ☐ Albumin
☐ Blood C+S ☐ Tracheal C + S
☐ Stool for frank and occult blood

Additional Lab Investigations

☐ CBC q12h
☐ Lyte 6: Na, K, Cl, Creatinine, BUN, Bicarb q12h ☐ Ca, Mg q12h
☐ Blood Gas & Metabolites q6h
☐ Arterial ☐ Venous ☐ Capillary
☐ APTT q24h ☐ INR q24h ☐ Fibrignogen q24h ☐ d-dimer q24h
☐ ALT q24h ☐ AST q24h ☐ Albumin q24h
☐ Bili PRN

Diagnostics

Investigations on admission

☐ 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:

_____

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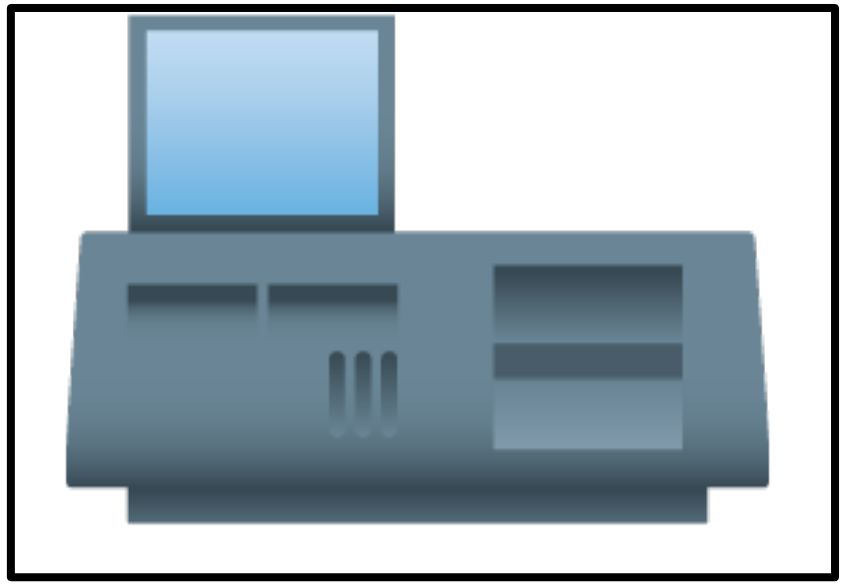
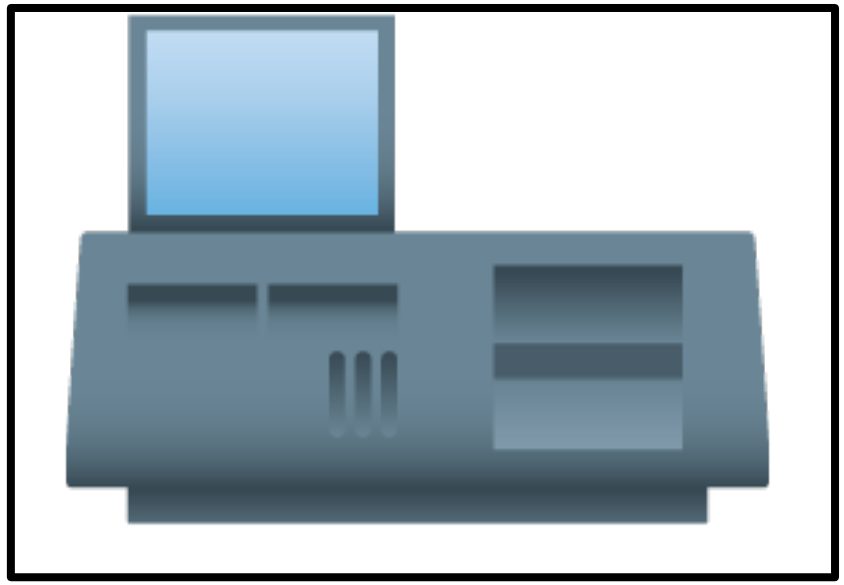
Blood gas measurement in the clinical laboratory



- Blood gas instruments commonly conduct their analysis of blood gas parameters by warming the blood gas specimen to 37^{o}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^{o}C
- Most instruments can calculate temperature corrected values

$$pCO_2\,(T) = pCO_2\,(37)\ X\ 10^{\,[0.021X(t-37)]}$$

CLIN. CHEM. 29/11, 1877–1885 (1983)

review

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

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 moeities 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

pH

1. $pH = pH_m + [-0.0146 + 0.0065(7.4 - pH_m)]\,(t - 37)$
2. $pH = pH_m - 0.015(t - 37)$
3. $pH = pH_m + [-0.0147 + 0.0065(7.4 - pH_m)]\,(37 - t)$
4. $pH = pH_m - 0.0146(t - 37)$

HIE Neonate – Which pCO_2 is truth?

DATE	pCO2 (37)	pCO2 (33.5)	pCO2 (34.5)
Day 1 4:20:00 PM	51	43	45
Day 1 10:05:00 PM	43	36	38
Day 2 4:00:00 AM	44	37	39
Day 2 10:05:00 AM	76	64	67
Day 2 12:20:00 PM	38	32	34
Day 2 3:10:00 PM	43	36	38
Day 2 6:00:00 PM	39	33	35
Day 2 10:30:00 PM	35	30	31
Day 2 11:55:00 PM	40	34	35
Day 3 4:00:00 AM	50	42	44
Day 3 10:00:00 AM	45	38	40
Day 3 4:00:00 PM	36	30	32
Day 3 10:00:00 PM	43	36	38
Day 4 4:00:00 AM	37	31	33
Day 4 6:05:00 PM	33	28	29

HIE Neonate – Which pCO_2 is truth?

DATE	pCO2 (37)	pCO2 (33.5)	pCO2 (34.5)
Day 1 4:20:00 PM	51	43	45
Day 1 10:05:00 PM	43	36	38
Day 2 4:00:00 AM	44	37	39
Day 2 10:05:00 AM	76	64	67
Day 2 12:20:00 PM	38	32	34
Day 2 3:10:00 PM	43	36	38
Day 2 6:00:00 PM	39	33	35
Day 2 10:30:00 PM	35	30	31
Day 2 11:55:00 PM	40	34	35
Day 3 4:00:00 AM	50	42	44
Day 3 10:00:00 AM	45	38	40
Day 3 4:00:00 PM	36	30	32
Day 3 10:00:00 PM	43	36	38
Day 4 4:00:00 AM	37	31	33
Day 4 6:05:00 PM	33	28	29

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 pCO_2 of 40 mm Hg (alpha stat) or adjusted to achieve a temperature corrected pCO_2 of 40 mm Hg (pH stat)"

  - Chris Higgins, Jan 2016

  Temperature Correction of Blood gas and pH measurement- an unresolved controversy

Alpha Stat

- Do not correct to body temperature

Alpha Stat

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- Initially based on the publications:
  - Davis BD. On the importance of being ionized. **Archives of Biochemistry and Biophysics** 78:497-509, 1958
  - 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

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- 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^{o}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)

CARBON DIOXIDE, PARTIAL PRESSURE (pCO_2)

Male and Female				
Test	**Age**	**n**	**mmHg**	**kPa**
1	Newborn	*	27–40	3.6–5.3
	Infant		27–41	3.6–5.5
	Thereafter		32–48	4.3–6.4
2	Premature neonates	248	39–68	5.2–9.1

Specimen Type(s)	1	Arterial whole blood
	2	Capillary blood
Reference(s)	1	Behrman RE, ed. Nelson textbook of pediatrics, 14th ed. Philadelphia, PA: WB Saunders Company, 1992:1818.
	2	Soldin SJ. Children's National Medical Center. Unpublished data.
Method(s)	1	Not given.
	2	I-Stat (Abbott Laboratories, Abbott Park, IL).
Comment(s)	1	*Numbers not provided.
	2	Study used hospitalized patients and a computerized approach adapted from the Hoffmann technique.

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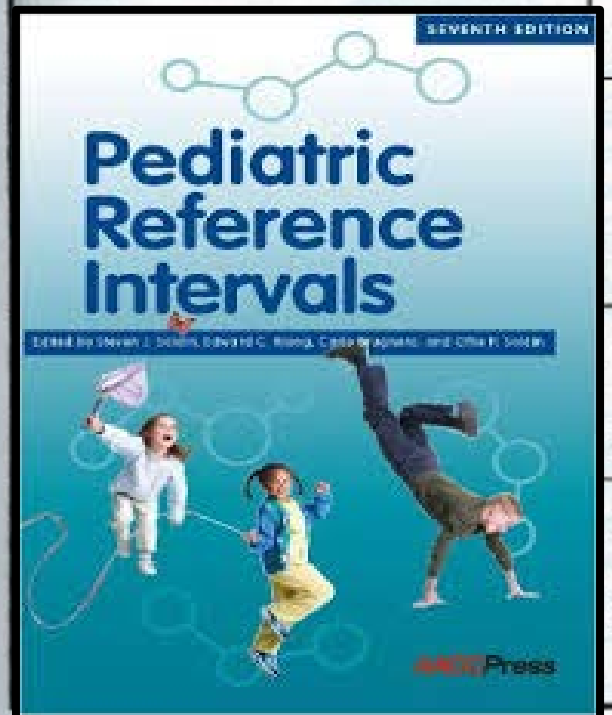

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Clinical Biochemistry 38 (2005) 905–907

CLINICAL BIOCHEMISTRY

Neonate capillary blood gas reference values

Jocelyne Cousineau[a], Suzanne Anctil[b], Ana Carceller[b], Monique Gonthier[b], Edgard E. Delvin[a,b,*]

[a]*Department of Clinical Biochemistry, CHU Ste-Justine, Université de Montréal, Québec, Canada*
[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

Table 1

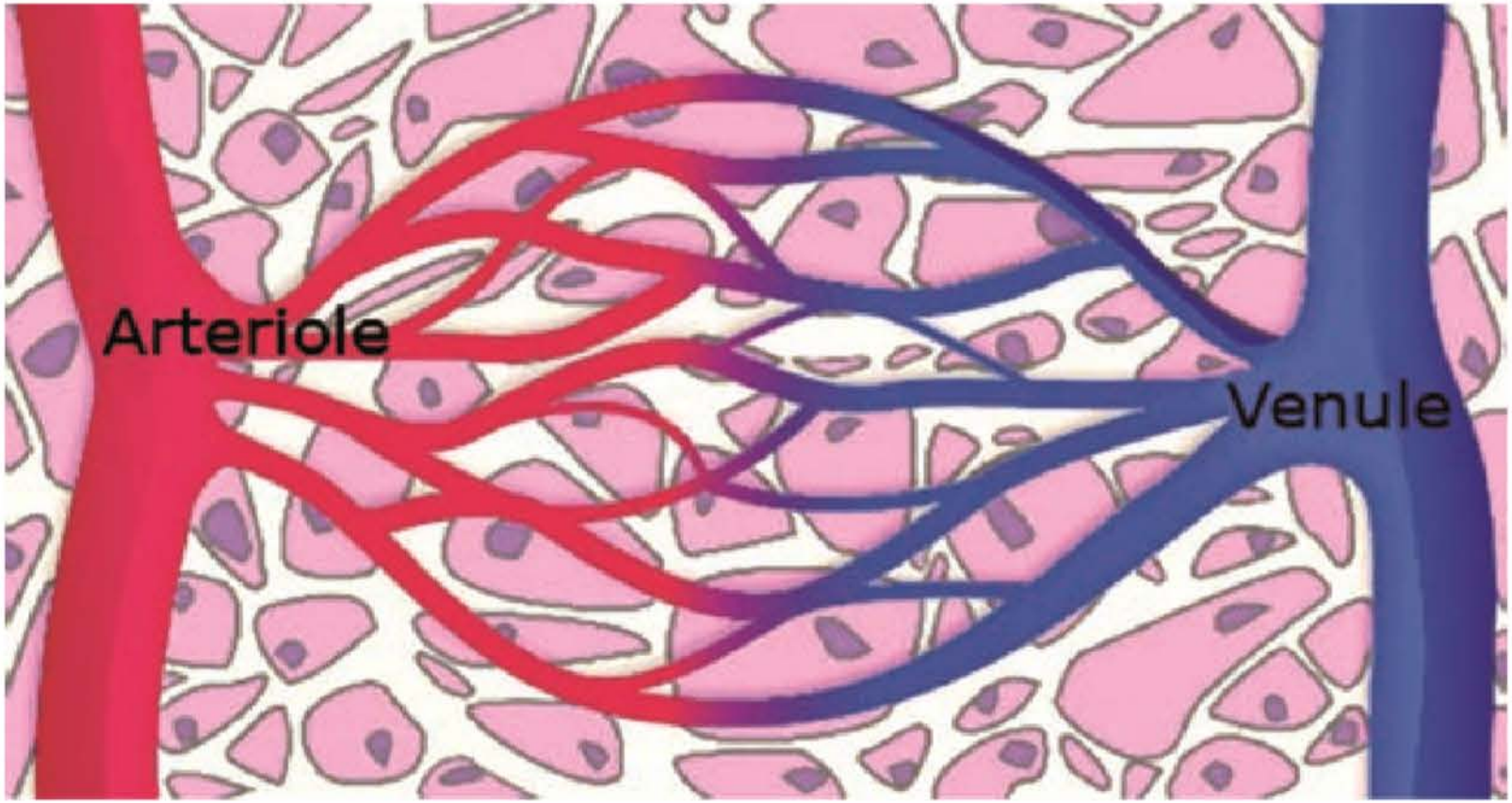
Pediatric references for blood capillary pH, pCO_2, pO_2, hemoglobin, lactate, glucose and ionized calcium

Variables	N	Mean	1 SD	2.5%ile	97.5%ile
pH	119	7.395	0.037	7.312	7.473
pCO_2 (mm Hg)	119	38.7	5.1	28.5	48.7
pO_2 (mm Hg)	119	45.3	7.5	32.8	61.2
Lactate (mmol/L)	114	2.6	0.7	1.4	4.1
Hb (G/L)	122	204	116	145	239
Glucose (mmol/L)	122	3.8	0.8	2.1	5.3
iCa (mmol/L)	118	1.21	0.07	1.06	1.34

N: number of samples analyzed.

What differences can be expected between pCO_2 values in different specimen types?

Figure 1: Capillary network



Arterial blood		AV Difference		Venous Blood	
pH	7.40	pH	0.02	pH	7.38
pCO_2	5.3 kPa	pCO_2	0.7	pCO_2	6.0
pO_2	13.0 kPa	pO_2	8.0	pO_2	5.0

Higgins C. Capillary-blood gases: To arterialize or not. MLO. November 2008:42-47

ORIGINAL ARTICLE

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

Arch Dis Child 2004;**89**:176–180. doi: 10.1136/adc.2004.016261

See end of article for authors' affiliations

Correspondence to: Dr D Yıldızdas, Çukurova

Aims: To investigate the correlation of pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), base excess (BE), and bicarbonate (HCO_3) 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, PCO_2, BE, and HCO_3 were all significantly correlated in ABG, VBG, and CBG. Correlation in PO_2 was also significant, but less so. Correlation between pH, PCO_2, PO_2, BE, and HCO_3 was similar in the presence of hypothermia, hyperthermia, and prolonged capillary refilling time. In hypotension, correlation in PO_2 between VBG and CBG was similar but disappeared in ABG–VBG and

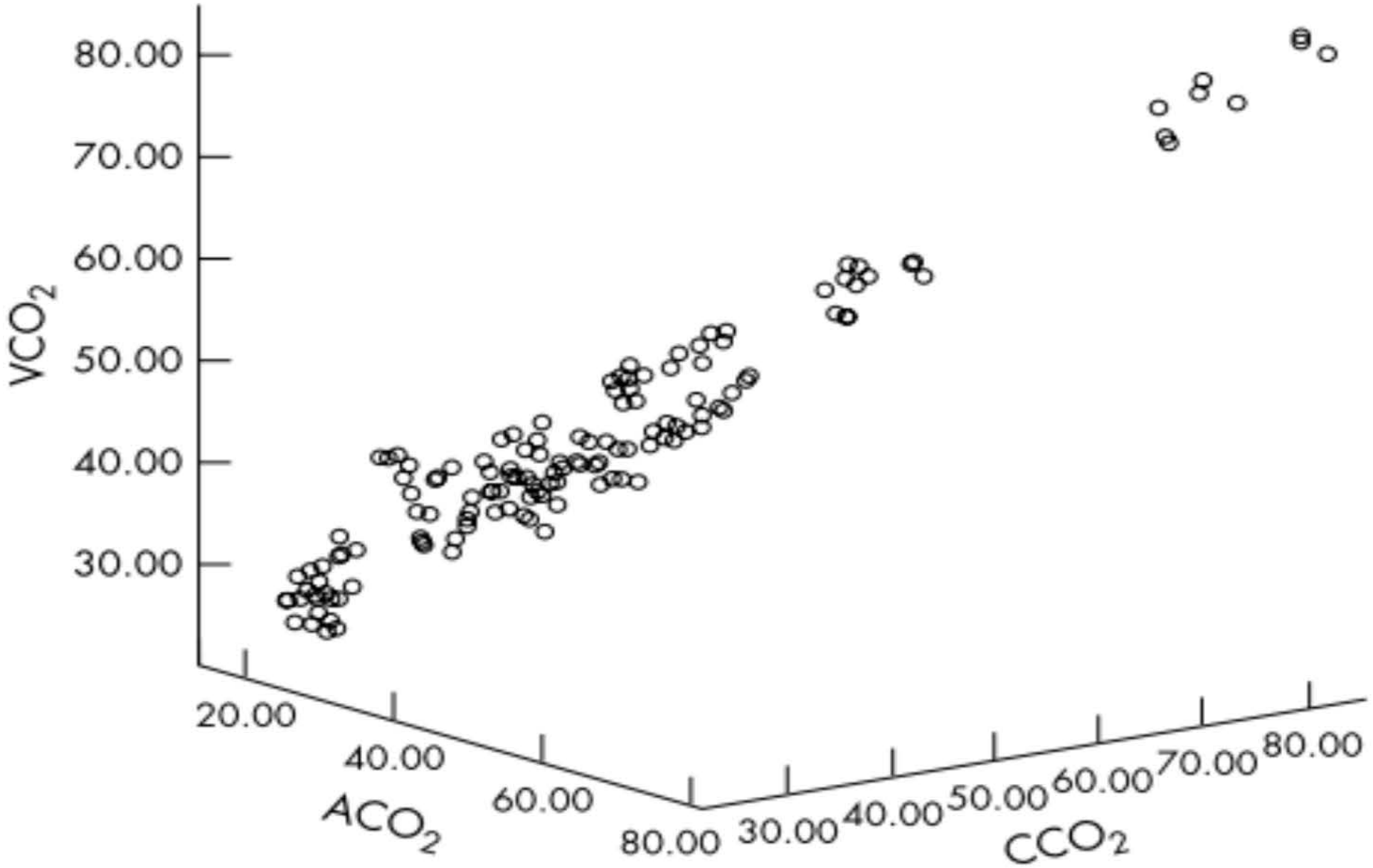


Figure 2 Correlation of arterial, venous, and capillary blood gases for PCO_2.

Table 4 Regression of arterial blood gas values on venous and capillary blood gas values

	Venous				Capillary			
Arterial	Constant (SE)	β (SE)	R^2	SE of estimate	Constant (SE)	β (SE)	R^2	SE of estimate
pH	0	1.005 (0.001)	0.994	0.0397	0	1.004 (0.001)	0.995	0.0535
PCO_2	−5.752 (1.22)	0.976 (0.025)	0.957	3.171	−7.143 (0.945)	1.037 (0.020)	0.975	2.41
PO_2	0	2.006 (0.092)	0.869	37.486	28.45 (11.57)	1.151 (0.163)	0.669	31.3
BE	−0.495 (0.226)	1.105 (0.032)	0.945	1.758	0.611 (0.125)	1.058 (0.017)	0.981	1.02
HCO_3	0	0.975 (0.007)	0.996	1.676	0	1.001 (0.005)	0.990	1.07

many years, clinicians have been looking for alternatives to ABG sampling in both children and adults, and studies have

poor correlation when hypothermia, hypoperfusion, or shock were present.[9 15] However, patients with these kinds of

showed pH, PCO_2, BE, HCO_3 were all correlated in arterial, venous, and capillary blood gases in normotensive, hyperten-

the present study we showed that neither temperature nor peripheral perfusion altered the correlation of pH, PO_2, PCO_2,

Arterial Venous pCO_2 Difference ~ 7 mmHg

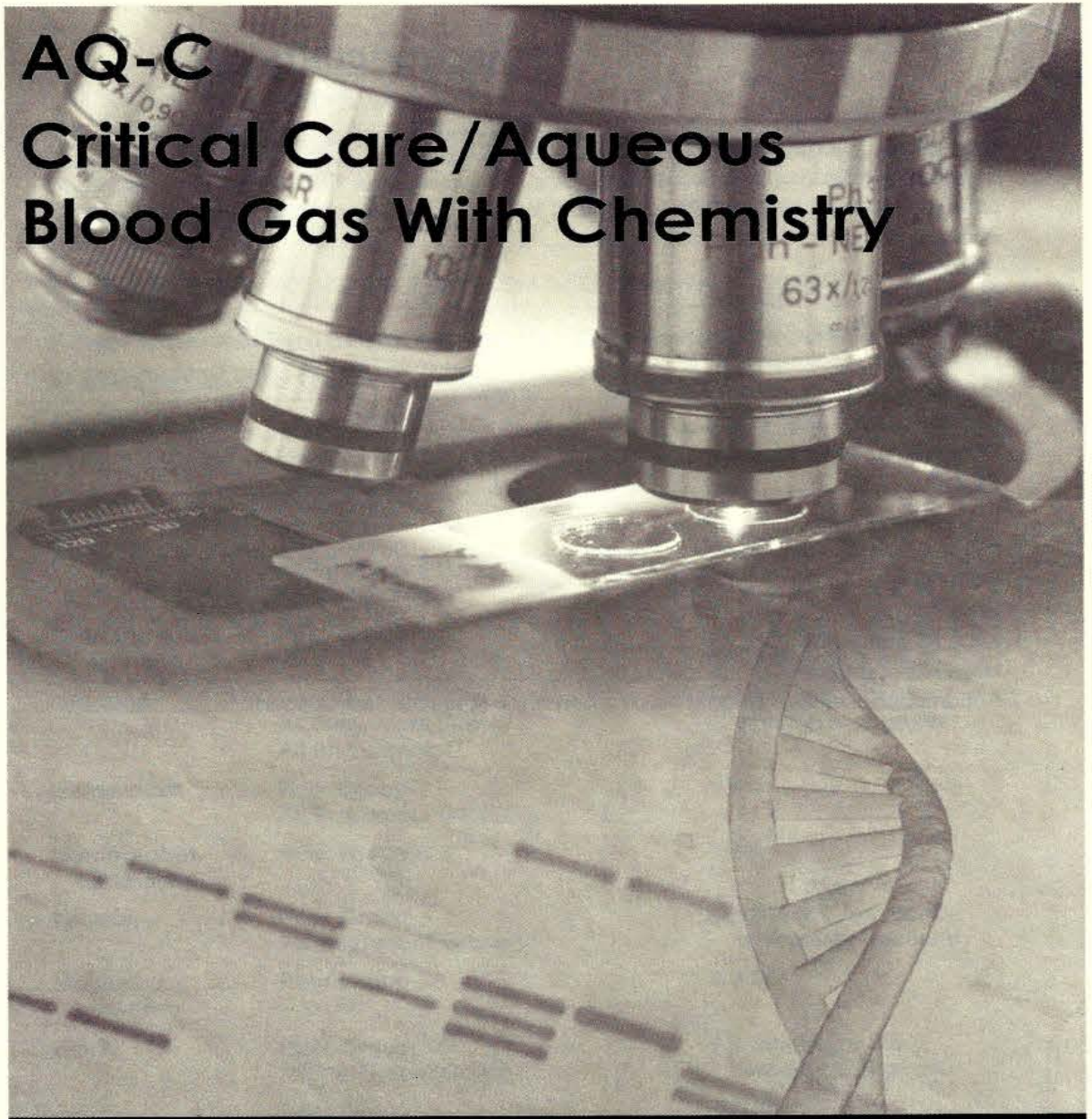
Arterial Capillary pCO_2 Difference ~ 6 mmHg

Will these pCO_2 reference ranges be dependent upon the blood gas instrument used to measure the specimens?

cap

SURVEYS 2013

LABORATORY ACCREDITATION PROGRAM



AQ-C
Critical Care/Aqueous Blood Gas With Chemistry

PARTICIPANT SUMMARY

AQ-11

INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
EPOCAL EPOC SYSTEM	266	60.3	2.3	3.8	60	53	65
IL GEM PREMIER 3000	370	62.2	2.1	3.4	62	56	67
IL GEM PREMIER 3500	273	62.2	2.0	3.2	62	57	67
IL GEM PREMIER 4000	1008	59.3	2.4	4.0	59	53	66
ALL IL GEM BLOOD GAS INST	1653	60.4	2.7	4.4	60	53	67
i-STAT (EXC CHEM8-P, EC8)	2829	53.5	1.4	2.7	54	49	58
i-STAT - W (EXC CHEM8-P)	15	53.4	2.2	4.2	54	48	57
i-STAT EC8+	46	61.4	2.4	4.0	61	57	67
ITC IRMA TRUPT CC,BG,H3	50	61.5	1.4	2.3	62	59	65
ALL ITC BLOOD GAS INST	50	61.5	1.4	2.3	62	59	65
NOVA STAT PROFILE CCX	151	56.2	2.5	4.4	56	49	63
NOVA STP pHOx	13	[illegible]	2.7	5.1	54	47	58
NOVA STP pHOx PLUS	11	51.3	2.4	4.7	51	46	55
NOVA STP pHOx ULTRA	26	55.4	2.5	4.5	56	50	61
ALL NOVA BLOOD GAS INST	201	55.7	2.8	5.0	56	46	63
OPTI CCA	171	59.7	1.3	2.2	60	56	63
OPTI R	27	57.6	2.3	4.0	58	53	62
ALL OPTI BLOOD GAS INST	198	59.4	1.6	2.8	60	53	63
RADIOMETER ABL 5	27	58.8	1.2	2.0	59	56	61
RADIOMETER ABL 80	64	59.6	2.8	4.7	60	52	66
RADIOMETER ABL 80 w/Co-ox	415	63.2	1.9	2.9	63	58	68
RADIOMETER ABL 90 w/Co-ox	260	57.2	1.0	1.8	57	54	59
RADIOMETER ABL 700 SER	87	58.3	1.5	2.6	58	54	62
RADIOMETER ABL 800 SER	1287	58.2	1.3	2.3	58	54	63
RADIOMETER NPT7	28	59.9	1.7	2.9	60	57	63
ALL RADIOMETER BLOOD GAS INST	2172	59.1	2.5	4.2	59	52	68
ROCHE COBAS b123	27	58.2	1.1	1.9	58	57	61
ROCHE OMNI S/COBAS b221	274	60.6	1.3	2.1	61	57	64
ALL ROCHE BLOOD GAS INST	311	60.4	1.4	2.4	60	57	64
SIEMENS RAPIDLAB 248	21	59.6	1.5	2.5	60	56	62
SIEMENS RAPIDLAB 1240	15	59.7	2.3	3.9	60	55	63
SIEMENS RAPIDLAB 1245	78	58.6	1.8	3.0	59	55	63
SIEMENS RAPIDLAB 1265	335	[illegible]	1.6	2.6	60	55	64
SIEMENS RAPIDPOINT 400	31	67.6	2.8	4.2	68	62	73
SIEMENS RAPIDPOINT 405	975	65.1	2.6	4.1	65	57	73
SIEMENS RAPIDPOINT 500	344	64.7	2.5	3.8	65	58	72
ALL SIEMENS BLOOD GAS INST	1820	63.6	3.5	5.5	64	55	73
ALL INSTRUMENTS	9581	58.6	4.4	7.5	58	46	73

AQ-11

INSTRUMENT	NO. LABS	MEAN	S.D.				
EPOCAL EPOC SYSTEM	266	60.3	2.3				
IL GEM PREMIER 3000	370	62.2	2.1				
IL GEM PREMIER 3500	273	62.2	2.0				
IL GEM PREMIER 4000	1008	59.3	2.4				
ALL IL GEM BLOOD GAS INST	1653	60.4	2.7				
i-STAT (EXC CHEM8-P, EC8)	2829	53.5	1.4				
i-STAT - W (EXC CHEM8-P)	15	53.4	2.2				
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ITC IRMA TRUPT CC,BG,H3	50	61.5	1.4				
ALL ITC BLOOD GAS INST	50	61.5	1.4				
NOVA STAT PROFILE CCX	151	56.2	2.5				
NOVA STP pHOx	13	[illegible]	2.7				
NOVA STP pHOx PLUS	11	51.3	2.4				
NOVA STP pHOx ULTRA	26	55.4	2.5				
ALL NOVA BLOOD GAS INST	201	55.7	2.8				
OPTI CCA	171	59.7	1.3				
OPTI R	27	57.6	2.3				
ALL OPTI BLOOD GAS INST	198	59.4	1.6				
RADIOMETER ABL 5	27	58.8	1.2				
RADIOMETER ABL 80	64	59.6	2.8				
RADIOMETER ABL 80 w/Co-ox	415	63.2	1.9	2.9	63	58	68
RADIOMETER ABL 90 w/Co-ox	260	57.2	1.0	1.8	57	54	59
RADIOMETER ABL 700 SER	87	58.3	1.5	2.6	58	54	62
RADIOMETER ABL 800 SER	1287	58.2	1.3	2.3	58	54	63
RADIOMETER NPT7	28	59.9	1.7	2.9	60	57	63
ALL RADIOMETER BLOOD GAS INST	2172	59.1	2.5	4.2	59	52	68
ROCHE COBAS b123	27	58.2	1.1	1.9	58	57	61
ROCHE OMNI S/COBAS b221	274	60.6	1.3	2.1	61	57	64
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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

AQ-11

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ALL NOVA BLOOD GAS INST	201	55.7	2.8				
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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?

AQ-11

ITC IRMA TRUPT CC,BG,H3	50	61.5	1.4	2.3	62	59	65
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RADIOMETER NPT7	28	59.9	1.7	2.9	60	57	63
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SIEMENS RAPIDLAB 1265	335	59.5	1.6	2.6	60	55	64
SIEMENS RAPIDPOINT 400	31	67.6	2.8	4.2	68	62	73
SIEMENS RAPIDPOINT 405	975	65.1	2.6	4.1	65	57	73
SIEMENS RAPIDPOINT 500	344	64.7	2.5	3.8	65	58	72
ALL SIEMENS BLOOD GAS INST	1820	63.6	3.5	5.5	64	55	73
ALL INSTRUMENTS	9581	58.6	4.4	7.5	58	46	73

AQ-11

ITC IRMA TRUPT CC,BG,H3	50	61.5	1.4	2.3	62	59	65
ALL ITC BLOOD GAS INST	50	61.5	1.4	2.3	62	59	65
NOVA STAT PROFILE CCX	151	56.2	2.5	4.4	56	49	63
NOVA STP pHOx	13	53.8	2.7	5.1	54	47	58
NOVA STP pHOx PLUS	11	51.3	2.4	4.7	51	46	55
NOVA STP pHOx ULTRA	26	55.4	2.5	4.5	56	50	61
ALL NOVA BLOOD GAS INST	201	55.7	2.8	5.0	56	46	63
OPTI CCA	171	59.7	1.3	2.2	60	56	63
OPTI R	27	57.6	2.3	4.0	58	53	62
ALL OPTI BLOOD GAS INST	198	59.4	1.6	2.8	60	53	63
RADIOMETER ABL 5	27	58.8	1.2	2.0	59	56	61
RADIOMETER ABL 80	64	59.6	2.8	4.7	60	52	66
RADIOMETER ABL 80 w/Co-ox	415	63.2	1.9	2.9	63	58	68
RADIOMETER ABL 90 w/Co-ox	260	57.2	1.0	1.8	57	54	59
RADIOMETER ABL 700 SER							62
RADIOMETER ABL 800 SER							63
RADIOMETER NPT7							63
ALL RADIOMETER BLOOD GAS INST							68
ROCHE COBAS b123							61
ROCHE OMNI S/COBAS b221							64
ALL ROCHE BLOOD GAS INST							64
SIEMENS RAPIDLAB 248	21	59.6	1.5	2.5	60	56	62
SIEMENS RAPIDLAB 1240	15	59.7	2.3	3.9	60	55	63
SIEMENS RAPIDLAB 1245	78	58.6	1.8	3.0	59	55	63
SIEMENS RAPIDLAB 1265	335	59.5	1.6	2.6	60	55	64
SIEMENS RAPIDPOINT 400	31	67.6	2.8	4.2	68	62	73
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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

- Azzopardi D, Brocklehurst P, Edwards D. et al., **The TOBY study. Whole body hypothermia for the treatment of perinatal asphyxia encephalopathy: a randomized control trial.** *BMC. Pediatr.* 2008; 8:17
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- 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?

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Hypocarbia and Adverse Outcome in Neonatal Hypoxic-Ischemic Encephalopathy

Athina Pappas, MD[1], Seetha Shankaran, MD[1], Abbot R. Laptook, MD[2], John C. Langer, MS[3], Rebecca Bara, RN[1], Richard A. Ehrenkranz, MD[4], Ronald N. Goldberg, MD[5], Abhik Das, PhD[3], Rosemary D. Higgins, MD[6], Jon E. Tyson, MD MPH[7], and Michele C. Walsh, MD MS[8] for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network*

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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 PCO_2 and cumulative exposure to PCO_2 <35 mmHg. The relationship between cumulative PCO_2 <35 mmHg (calculated as the difference between 35mmHg and the sampled PCO_2 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 (±

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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 pCO_2 < 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 trails conducted between 2005 and 2012, demonstrated that mild hypothermia (33.5^{o}C – 34.5^{o}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 pCO_2 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 CO_2
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^{o}C