Therapeutic Hypothermia

Curtis Dorn M.D.
Department of Neonatology
Wesley Medical Center

Dawn Gosnell, APRN
Clinical Nurse Specialist
Via Christi Hospitals Wichita, Inc.

Therapeutic Hypothermia
Declarations

- Curtis Dorn and Dawn Gosnell have no significant financial interests or other relationship with manufacturers of any of the products, processes or services that will be discussed.
- We will not present off-label use of any medication or medical device.

Therapeutic Hypothermia
Objectives

- Review the clinical findings and biochemical derangements in Hypoxic Ischemic Encephalopathy.
- Explain how therapeutic hypothermia blunts the secondary wave of damage after hypoxia/ischemia.
- Review the entry criteria and process of therapeutic hypothermia for infants and adults.
- Discuss complications and respiratory care issues related to therapeutic hypothermia.

Hypoxic-Ischemic Encephalopathy (HIE)

- HIE 3rd leading cause of neonatal death (23%) .
  Infection #1 (36%), Preterm birth #2 (28%)
- Brain insult from a lack of oxygen (hypoxia) and decreased blood flow (ischemia).
- Oxygen and glucose delivery is impaired, causing energy failure at the cellular level.

Volpe *Neurology of the Newborn*

Etiology of Neonatal HIE

Interruption of maternal-fetal exchange
(asphyxia - impaired oxygen / carbon dioxide exchange)

- Systemic (maternal): cardiopulmonary arrest, eclampsia, hypovolumic shock, trauma.
- Uterus: Uterine rupture
- Placenta: Abruption
- Cord: compression, rupture, knot

Cellular Energy Failure

- Poor perfusion → rapid depletion of ATP (adenosine tri-phosphate), our cellular gasoline.
- Krebs cycle: Glucose + oxygen = 36 ATP
  Glucose without 0_2 = 2 ATP + lactic acid.
- ATP – needed: for synthesis, transport, ion pumps
  - Sodium (Na), calcium (Ca) constantly leak into the cell.
  - Potassium (K) constantly leaks out of cell
  - ion pumps use ATP to pump Na & Ca out of cell, K into cell
  - No pump: Water follows Na into cell, cell swells and bursts.
- No ATP → cell death

Volpe *Neurology of the Newborn*

Necrosis vs. Apoptosis

Two types of cell death:

- Necrosis (early cell death): Brief / severe insult, ATP-dependent Na+/K+ pumps fail, Na then H_20 influx, cell swelling, membrane fragmentation, inflammation.
- Neuron is destroyed. Post-event cooling not helpful.
- Apoptosis (delayed cell death): longer / milder insult, membrane depolarization, glutamate release, calcium influx, cell shrinks, no inflammation.
- Cascade of Apoptosis: Starts 2-6hrs after event.
  Window of opportunity for body cooling therapy.

Volpe *Neurology of the Newborn*

Apoptosis

- Apoptosis - (G. *apo* – off, *ptosis* – falling) ie: falling leaves.
  Our body makes too many cells, so pruning is needed.
- Programmed cell death – critical to life, but
  Too much apoptosis → Atrophy
  Not enough apoptosis → Cancer
- Multiple triggers of apoptosis: hormones, cytokines, medications, heat, radiation, hypoxia, hypoglycemia.
- Trigger stimulates production of Caspase by the targeted cell → leads to cascade of cellular shrinkage and digestion of organelles.
- Common event in cascade is too much intracellular calcium ($[Ca^{+2}]^i$).

HIE – Power Failure at Cellular Level

- Intracellular calcium is critical intracellular second messenger.
- Tiny changes in intracellular calcium regulate cellular gene transduction, synthesis, transport and cell-to-cell signaling.
- Tiny changes in $[Ca^{+2}]^i$ are good.
- Triggers of Apoptosis cause large influx of calcium into the cell → with deadly effects.

Effects of High Intracellular Calcium

- Activates phospholipases (cell membrane injury)
- Activates proteases (disrupts cytoskeleton)
- Activates nucleases (nuclear injury)
- Disrupts ATP production (mitochondria)
- ↑ Excitatory neurotransmitter release (glutamate)
- Stimulates free radical production (membrane injury)
- All lead to cellular shrinkage and cellular death

→ Clinical Effects

Volpe *Neurology of the Newborn* 2008

Clinical Findings - 2 Stages

Early First Stage of HIE:

- Stuporous - Stunned
- Periodic breathing
- Hypotonia, minimal movement
- Voltage suppression or seizures on EEG (electroencephalogram)
- After the First Stage, a brief recovery of cerebral metabolism and alertness may follow.

Volpe *Neurology of the Newborn*

Clinical HIE - 2 Stages

Second Stage Delayed (re-perfusion) stage:

Starts 2-6 hrs after initial insult

Worsens over next 24-48 hrs, then slow recovery

Three levels of severity – Mild, Moderate, Severe (Sarnat's Stages of Encephalopathy)

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HIE – Clinical Findings

Mild HIE

- Mild hypertonia (increased tone).
- Brisk deep tendon reflexes.
- Sleepy, irritable, high-pitched cry.
- Poor feeding, sloppy, disorganized.
- CNS exam normal by day 3-4

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HIE – Clinical Findings

Moderate HIE

- Marked hypotonia and Lethargy
- Pausing or mild apnea
- May have onset of seizures in 1st 24 hrs.
- Full recovery within 1-2 weeks possible
- Quicker recovery → better long-term outcome.

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HIE – Clinical Findings

Severe HIE

- Minimal / no response to stimulus
- No gag reflex
- Pupils fixed/dilated
- Stuporous or comatose / floppy
- Irregular breathing / apnea → ventilator support
- Early seizures but often EEG goes flat

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HIE – Clinical Findings

Severe HIE – Other organs

- Renal failure: oliguria → high output ATN
  (acute tubular necrosis)
- Gut: ileus, poor gastric emptying, diarrhea
- Stunned heart: Poor contractility, hypotension
- Pulmonary hypertension

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HIE – Clinical Findings

Survivors of Severe HIE

- Level of alertness improves by day 4-5
- Spontaneous respiration by day 4-5
- Hypotonia / feeding difficulties persist
- Gastrostomy +/- fundoplication often needed

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Outcome of HIE

Severe HIE: 50-75% mortality by 1 month.
80% survivors significant mental retardation, cerebral palsy, seizures.

Moderate HIE:

30-50% significant long term problems,
10-20% minor neurologic abnormalities.

Mild HIE:

Most escape long-term complications

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HIE – Medical Care

Cardiovascular: Maintain normal BP
Fluids: Avoid hypoglycemia and hyperglycemia
Treat seizures: prevent additional damage
Ventilation: Keep carbon dioxide level normal (40-50)
Avoid Hyperoxia: 100% 0xygen toxic (goal 85-95% sat.)

In past, no effective treatment. Now →

Treatment: Therapeutic Hypothermia

HIE – Therapeutic Hypothermia

Mechanisms:

- Reduces metabolic rate (7-8 % lower / 1^{o} C)
- Reduces ion flux (calcium, sodium)
- Decreases excitatory transmitter release
- Reduces vascular permeability and edema
- Reduces apoptosis

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Therapeutic Hypothermia for Infants

Types: Whole body (cooling blanket) vs.
Selective head cooling (cool cap)

Timing: Within hour of injury ideal (up to 6hrs)
Maintain cooling for 72 hrs.
Re-warm over 6 – 8 hours

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Head Cooling

Coolcap RCT 2005

- 234 infants, mod-sev HIE
- 72hrs of head cooling (rectal 34-35° C).

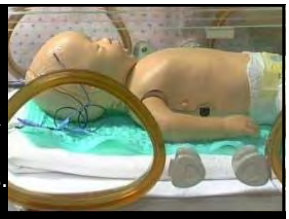
No difference in overall outcome.

(core of brain not adequately cooled?)

Subgroup analysis: Those with less severe aEEG had better neurologic outcome with head cooling.

Gluckman Lancet 2005

Whole Body Cooling Trial 2005



208 babies, mod-sev. HIE

Whole body cooling 72hrs. (rectal temperature 33.5° c)

Decreased death or moderate-severe disability
44% - hypothermia group vs. 62% - control
(RR- 0.72; 95% confidence interval 0.54-0.95; p=0.01)

Short-term side-effects decreased enthusiasm.
bleeding, acidosis, PHTN

Shankaran NEJM 2005

Whole Body Cooling for HIE

Whole Body Cooling: Follow-up Study 18-22 months

No adverse effects of hypothermia at 20 months

Rehospitalization: 27% hypothermia / 42% control

Death: 24 hypothermia / 38 control

Severe disabilities: 19 hypothermia / 25 control

Body Cooling: Declared "Standard of Care"

Shankaran S: Pediatrics 2008

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Wesley Medical Center
NICU Body Cooling Program

Started July 2009

- 1 - 2 infants per month
- 2 coolings stopped for bleeding, acidosis.
- Developmental Clinic: Much better than expected outcome - moderate-severe HIE.
- Not much improvement in Severe HIE
  (initial insult was devastating, cooling only helps decrease secondary/reperfusion injury)

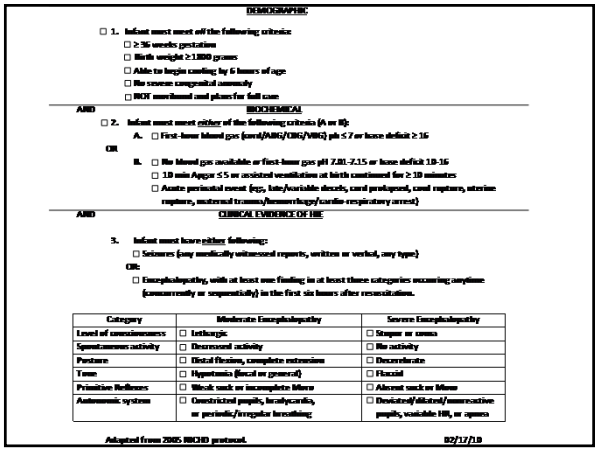
HIE: Neuro-resuscitation

Ongoing intervention trials:

- Allopurinol: free radical scavenger
- Xenon: NMDA antagonist, less apoptosis
- Erythropoietin: ↑ vasculogenesis / neurogenesis, ↓ inflammation, ↓ oxidant damage ↓ apoptosis
- Stem Cell Infusion (umbilical cord blood) migrate to damage area → helps repair.

Suspect you have candidate for therapeutic hypothermia for HIE?

- Turn off warmer (goal 34-35^{o}C for transport)
- Finish resuscitating and stabilizing infant
- Keep 02 saturations less than 95%
- Obtain cord gas or neonatal blood gas
- Call neonatologist to see if infant meets entry criteria, and arrange transfer or transport.



DEMOGRAPHIC

☐ 1. **Infant must meet *all* the following criteria:**
- ☐ **≥ 36 weeks gestation**
- ☐ **Birth weight ≥1800 grams**
- ☐ **Able to begin cooling by 6 hours of age**
- ☐ **No severe congenital anomaly**
- ☐ **NOT moribund and plans for full care**

AND

BIOCHEMICAL

☐ 2. **Infant must meet *either* of the following criteria (A or B):**

A. ☐ **First-hour blood gas (cord/ABG/CBG/VBG) ph ≤ 7 or base deficit ≥ 16**

OR

B. ☐ **No blood gas available or first-hour gas pH 7.01-7.15 or base deficit 10-16**
- ☐ **10 min Apgar ≤ 5 or assisted ventilation at birth continued for ≥ 10 minutes**
- ☐ **Acute perinatal event (eg., bradycardia, cord prolapsed, cord rupture, uterine rupture, maternal trauma/hemorrhage/cardio-respiratory arrest)**

AND

CLINICAL EVIDENCE OF HIE

3. **Infant must have *either* following:**
- ☐ **Seizures (any medically witnessed reports, written or verbal, any type)**

OR:
- ☐ **Encephalopathy, with at least one finding in at least three categories occurring anytime (concurrently or sequentially) in the first six hours after resuscitation.**

Category	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	☐ Lethargic	☐ Stupor or coma
Spontaneous activity	☐ Decreased activity	☐ No activity
Posture	☐ Distal flexion, complete extension	☐ Decerebrate
Tone	☐ Hypotonia (focal or general)	☐ Flaccid
Primitive Reflexes	☐ Weak suck or incomplete Moro	☐ Absent suck or Moro
Autonomic system	☐ Constricted pupils, bradycardia, or periodic/irregular breathing	☐ Dysiate/dilated/nonreactive pupils, variable HR, or apnea

Adapted from 2005 RICHD protocol. **02/17/10**

Body Cooling - Process

- Place UAC or UVC
- Cooling blanket – esophageal temp = 33.5 ^{o} C
- Cool for 72 hours
- Use morphine/nembutal – pain / sedation
- Increase temp by 0.5 C for complications: arrythmias / acidosis / bleeding / pulm. HPTN
- Rewarm over 6 hours.
- Reset blood gas machine for infant's temp.

Effect of Temperature: pH PCO_2 PO_2

- Decreased CO2 production with cooling (low metabolic rate) and more CO2 dissolved in cool blood (increased solubility)
- Partial pressure of a gas decreases as temperature decreases. (helium balloon → cold outside)
- So PO2 and PCO2 decrease with hypothermia (say 33° C) and as PCO2 decreases, pH increases.
- BUT measurement chamber in BG machine heated to 37° C.
- As sample drawn at a body temp of 33° C warms to 37° C, PO2 & PCO2 will increase and pH will drop.
- So the PaO2 and PCO2 will appear higher and the pH lower than it really is in the hypothermic patient.
- Does it matter? Two blood gas strategies.

Bacher Intensive Care Med 2005

Effect of Temperature: pH PCO_2 PO_2

Patient 33° C true BG = pH 7.47 PCO2 32 PO2 92
BG machine 37° C = pH 7.40 PCO2 40 PO2 117

- Alpha-stat method: No correction for patient's temperature. Argument: Intracellular pH doesn't change much during cooling due to protein buffering.
- Some adult literature: better neuro outcome w/ α-stat, (probably due to inadvertent decrease in cerebral blood flow)
- Many centers doing adult and pediatric cardiac surgery use the α-stat method/strategy.

Groenedaal Pediatrics 2009.

Effect of Temperature: pH PCO_2 PO_2

BG machine 37° C = pH 7.40 PCO2 40 PO2 117
Patient 33° C true BG = pH 7.47 PCO2 32 PO2 92

- pH-stat method: Correction for patient's temperature. Reason: low PCO2 decreases cerebral perfusion. If BG not corrected, you really don't know what PCO2 is.
- Low PCO2 in infants asso./with PVL and deafness.
- Low PCO2 infants after asphyxia → adverse outcome
- Improved cerebral recovery after hypothermic arrest in piglets using pH-stat method.
- NICHD neonatal cooling trials done w/ pH-stat method

Groenedaal Pediatrics 2009.

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Effect of Temperature: O2 saturation

- Oxy-hemoglobin Dissociation Curve shifted to the left with low temperature, low PCO2 and high pH
- At any pO2, saturation will be higher, especially when PO2 in the 30-50 range, BUT
- Leftward shift means Hb binds 02 more tightly and releases less O2 to the tissues. Additionally,
- Metabolism / O2 consumption decrease w/ cooling.
- Combined effect: low temperature on oxyhemoglobin and decreased O2 consumption (VO2) will lead to a large increase in mixed venous O2 saturation.

Bacher Intensive Care Med 2005

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Therapeutic Hypothermia for PICU Patients

- No fully developed guidelines for pediatric patients. Still being studied. Most PICUs have developed protocols adapted from neonatal or adult protocols.
- Most protocols target patients with non-traumatic cardiac arrest with ROSC who remain comatose (GCS < 8), no response to pain, are intubated and mechanically ventilated.
- They exclude patients with active bleeding, coagulopathy, intracranial hemorrhage, sickle cell patients, cardiovascular instability from cardiac dysrhythmias or refractory hypotension, sepsis, MODS as a cause for the cardiac arrest.

Therapeutic Hypothermia for PICU Patients

- Target core temperature of 33°C (+/- 1°) x 48 hours, instituted within 6 hours of ROSC, then gradual return to 36-37.5 C with avoidance of hyperthermia.
- Main issues: coagulopathy, hyperglycemia, arrhythmia, skin breakdown, hyperkalemia (upon rewarming).
- Neuromuscular blockade with sedation/analgesia for shivering.
- Typical respiratory issues include atelectasis, secretion clearance, and risk for VAP.

→ Therapeutic Hypothermia in adults

Dawn Gosnell, ARNP

HIE – Etiology in Adults

- Cardiac Arrest
  - Coronary artery disease, cardiomyopathy, Long QT syndrome
  - Respiratory failure – exacerbation, pneumonia
  - 265,100 out of hospital each year in the U.S.
  - 50% resuscitated
  - 14.6% survive
- Drownings
- Hangings
- Overdose

American Heart Association Guidelines - 2010

- **Post-cardiac arrest care**
  - Induced hypothermia generally recommended for adult survivors regardless of presenting rhythm.
    - Initiate as soon as possible after return of spontaneous circulation (ROSC) to a target temperature of 32^0-34^0C.
    - Ventricular Fib or Pulseless Ventricular Tach (Class I)
    - Pulseless Electrical Activity and Asystole (Class IIB)
  - Urgent cardiac catheterization and percutaneous coronary intervention are recommended for ST Elevation MI patients.
    - There is support for other acute coronary syndrome patients.

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Via Christi Exclusion Criteria

- Pulseless > 60 minutes
- > 12 hours since ROSC
- Uncontrolled GI bleeding, active bleeding, coagulopathy or bleeding diathesis
- Known terminal illness or pre-arrest impaired cognitive status
  - Unable to perform ADL independently, poor functional status
- Conflict with Advanced Directives or DNR status
- Follows commands
- Sepsis or multisystem organ failure as suspected cause of cardiac arrest
- Other reason for coma – intracranial pathology (intracranial hemorrhage, ischemic stroke, subarachnoid hemorrhage, sedation)
- Significant trauma, intra-abdominal such as splenic or liver laceration

Meaningful Neurological Response

Eye Opening	Verbal	Motor	Brainstem
Spontaneous	Oriented	Obeys	Pupils React
Voice	Confused	Localizes	Corneal
Pain	Inappropriate	Withdraws (to pain)	Spontaneous Respirations
None	Sounds	Decorticate	
	None	Decelerate	Doll's Eyes
	Intubated	None	

Orange shaded areas are considered purposeful and if purposeful, the patient is NOT ELIGIBLE for therapeutic hypothermia.

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Surface Cooling System

- There are many on the market, varying in price.
- Via Christi is utilizing the Gaymar wraps and blankets.

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Intravascular Cooling System

- Via Christi is utilizing ICY Cath with the Alsius CoolGard
- Triple lumen CVC with two teal colored ports that attach to the Alsius tubing.

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Cooling Process

- 2 liters of refrigerated (2-80C) saline @ 500 mL/hr
- Ice packs around head, neck, axillary areas and groin for 20-25 minutes.
- Initiate cooling system
  - Set target to of 33^0C (91.4^0F)
  - **Rapid cooling**
- Keep at 33-34^0C for 24 hours.
- No heated humidification on ventilator system

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Neurological Response

- Decreased cerebral metabolic rate
  - 5-10% for every 1^0C
- Reduced oxygen consumption in the ischemic brain
- Decreased intracranial pressure
- Decreased cerebral edema by maintaining integrity of the blood brain barrier
- Can decrease the frequency and amplitude of EEG studies

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Shivering

- Assess
  - Overt shivering
  - Feel for "humming" of jaw
  - Look for an isolated muscle twitch
- Treatment
  - Neuromuscular blockade – Vecuronium
    - Dilaudid (hydromorphone)

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Cardiovascular Response

- Decreased heart rate, contractility and cardiac output, increased systemic vascular resistance
  - 7% decrease in cardiac output for every 1^0C decrease
  - Hypotension
  - ECG changes
    - Prolonged PR Interval, Widened QRS, Prolonged QT Interval, ST elevation or depression, T Wave inversion
- Delayed depolarization in pacemaker tissue
  - Bradycardia
    - Infants 80-90, Adults 40-50
  - Atropine is ineffective.
    - Treat with dopamine or Isuprel

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Cardiovascular Response

- Decreased trans-membrane resting potential, fibrillation threshold, increased adrenergic stimulation secondary to catecholamine release
  - – Increase in atrial fibrillation and ventricular fibrillation.
    - Amiodarone is less effective. Treat with Lidocaine.
  - – For refractory or reoccurring arrhythmias or coding, must discontinue active cooling and begin re-warming.

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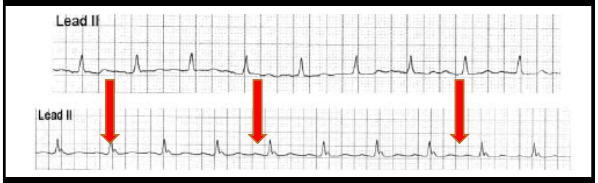
J Wave or Osborn Wave



- Secondary to delayed K+ transport
- As J wave increases, the T wave may flatten
- Reversible, but can persist for 12-24 hours after core temperature is restored.

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Pulmonary Response

- Blood gas values
  - pH increases 0.016 points for every 1^0C decrease
  - PCO2 decreased due to increased dissolved CO_2 and decreased CO_2 production
  - Spontaneously breathing patients have decreased minute ventilation
- Temperature adjustment
  - Respiratory alkalosis at actual patient temperature
  - Uncorrected would show a lower pH and increased CO_2

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Pulmonary Response

- Decreased oxygen consumption
  - – Shift to the left
    - O2 hangs onto the Hgb with less delivered to the tissues
- Increased pulmonary vascular resistance
- Bronchospasms
- Paralysis of mucociliary mechanism
  - – Increased airway secretions
  - – Impaired ciliary function
  - – Increased risk for aspiration and pneumonia
    - Aggressive pulmonary therapy

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Renal Response

- Impaired renal tubular transport and tubular dysfunction
  - Cold diuresis
    - Decreased sodium and water reabsorption
    - Significantly reduced levels of potassium, magnesium, calcium and phosphorus
  - Decreased antidiuretic hormone response
- Fluid shift into the interstitial spaces
- Shift in potassium intracellularly when cooled, shift out when re-warmed

Hematologic & Immunologic Response

- Increased blood viscosity
  - Hct increase 2% for every 1^0C decrease
- Delayed activation of the fibrinolytic system
  - Increased thrombus formation
- Leukocyte sequestration in the spleen
  - Increased bleeding risk
    - Delay in the clotting cascade
    - INR and PTT are prolonged
  - Platelet number and function decreases
- Decreased neutrophil function
  - Increased risk of infection

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Gastrointestinal & Metabolic Response

- Impaired bowel function
  - Hypomotility
  - Stress ulceration
- Decreased hepatic metabolism
  - Increase liver enzymes
- Hyperglycemia
  - Decreased insulin secretion
  - Decreased insulin sensitivity
- Pancreatitis has been reported.

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Hypothermia & Medication Effect

We don't really know on most medications.

Medication	Effect
Aspirin	No augmentation of platelet inhibition
Fentanyl	Plasma concentrations increased by 25%
GP IIb-IIIa Inhibitors	Augments eptifibatide (Integrilin) and tirofiban (Aggrastat) platelet inhibition
Nitroglycerin	Decreased metabolism by 66%, increased infusion rates
Phenytoin	AUC (Area under the concentration time curve) increased 180%, elimination rate constant decreased 50%
Propofol	Decreased clearance, increased serum level by 28%
Vecuronium	Decreased clearance by 11% per ^{0}C, doubled the duration of action

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(Arpino & Greer, 2008)

Re-warming Process

- Re-warm at 0.3^{0}C per hour to a target of 36^{0}C.
  - Slow over 12 hours
  - Thermoregulatory mechanisms will want to rebound or overcompensate.
  - Keep less than 37^{0}C for 24 hours

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Complications during Re-warming

- Seizures
- Ventricular fibrillation
- Hypovolemia
- Hypotension
  - Re-warming shock occurs when hypothermic vasoconstriction masks hypovolemia.
- Acidosis
- Hyperkalemia

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Cerebral Performance Categories Scale

CPC	
1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability: conscious,sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state; any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
5	Brain death: apnea, areflexia, EEG silence, etc

Safar (1981)

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Via Christi Statistics

- N= 65 since June 2010
- Twice as many men than women (2:1)
- Average age of 63 years
- More external than internal cooling (1.7:1)
- Survival
  - Asystole 29%
  - PEA 63%
  - V Fib 61%
  - V Tach 100%
- CPC Scores of 1 or 2 that go HOME 59%, Rehab/SNU 13%

Mia's Story

Maternal uterine rupture
Baby Mia had no heartbeat for 20 minutes
72 hours body cooling

Surprisingly good outcome
One year birthday follow-up

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