Importance of normothermia

• Silverman et al. 1958
  ▫ Poor temperature control correlated with increased neonatal morbidity and mortality
• If admission temperature <35º C
  ▫ EGA 23 weeks = 58% mortality
  ▫ EGA 24 weeks = 43% mortality
  ▫ EGA 25 weeks = 30% mortality
Newborns are prone to heat loss

- Increased ratio of surface area to body mass
  - Term infants: 3x adult ratio
  - Preterm/SGA: 4x adult ratio
- Thin skin with little subcutaneous fat
- Superficial blood vessels
Physiology of thermoregulation
Fetal Heat Production

- Thermogenesis suppressed in utero
  - Intrauterine inhibition
- Most heat production from chemical reactions relating to growth/function
  - Last trimester: 3-4 W/kg heat generated (2x adult)
    - Fetal temp 0.5° greater than mother
Fetal Heat Production

• Mechanisms of heat dissipation
  ▫ 15%: **Conduction** through skin into amniotic fluid
  ▫ 85%: **Convection** through venous blood in placenta
Perinatal thermoregulation

• Governed by preoptic chiasma/anterior hypothalamic nuclei (POAH)
  ▫ Receives central sensory input and info from cutaneous temperature receptors
• Nonshivering thermogenesis
  ▫ Activated by sympathetic NE secreting nerve fibers
  ▫ Innervate brown adipose tissue (BAT)
• Shivering thermogenesis
  ▫ Activated by posterior hypothalamic nucleus
Cold Sensation (Internal)

- Thermosensors in POAH
  - Cooling evokes heat production and vasoconstriction
- Receptors also found in lower brainstem
  - Midbrain and medulla oblongata
  - Less sensitive than POAH
- Spinal cord
  - Extremely sensitive
  - Change of > 0.02° C sufficient to elicit shivering
Cold sensation (External)

- Fine unmyelinated nerve endings in basal layer of epidermis
- Have mitochondria connected to temp-sensitive Na/K pump
  - Converts cold stimulus to electrical signal
  - Exaggerated response to sudden change in temp
- Travel within spinothalamic tract in anterolateral spinal cord
- Change of 0.01°C sufficient to evoke sensation
Shivering

• Small, random muscle contractions
• Hydrolyzes ATP, + respiration, dissipates free energy as heat
• Primary motor center in posterior hypothalamus
  ▫ When hyper/euthermic, inhibited by POAH
• In adults, increases heat production 4-5x
Shivering

• 2nd line of defense for infant
  ▫ Higher surface to mass ratio
  ▫ Poorer thermal insulation
  ▫ Increases convective heat loss because of body oscillations

• Shivering ability not absent in neonates
  ▫ Observed with severe hypothermia
  ▫ Threshold is displaced to lower body temp
Nonshivering thermogenesis

- Brown adipose tissue (BAT)
  - 0.5-1.5% of total infant body weight in 3rd TM, 2-7% at term
  - Begins differentiation at 26-30 weeks
    - Continues development until 5 weeks after delivery
  - Near highly perfused organs or adjacent to vessels
    - Predominantly near kidneys and intrascapular area of back extending up dorsal neck
  - $O_2$ consumption increased 10x on exposure to NE
    - Effect mediated by $\beta_3$ and $\alpha_1$ receptors
Nonshivering thermogenesis

- Thermogenic properties due to action of uncoupling protein (UCP1)
  - Found only in BAT
  - Allows protons into mitochondrial matrix
  - Uncouples oxidative phosphorylation from the production of ATP
- Preterm infants have lower amounts of BAT and decreased UCP1 expression
Mechanisms to control heat loss

- **Vasomotor**
  - Noradrenergic sympathetic stimulation causes:
    - Vasoconstriction in acral areas (fingers, hands, ears, lips, nose)
    - Vasodilation in trunk and proximal limbs
    - Minimal vasoconstriction on head and brow
Mechanisms to control heat loss

• Behavioral Regulation
  ▫ Postural reactions against overheating
  ▫ Flexion of extremities
    • Decreases surface area available for heat loss
  ▫ Cry to signal thermal discomfort and alert caregiver
Effect of hypothermia on metabolic rate

• MR increases initially with decrease in body temperature
  ▫ Can be prevented with deep general anesthesia
• Van’t Hoff’s law – rate of chemical reactions ↑ 2-3x for every 10°C ↑ in temperature
Effect of hypoxia on thermogenesis

- In animal studies, exposure to cold increases $O_2$ consumption by 100% or more
- Increase is attenuated if hypoxic
  - Conserves oxygen that would be used to generate heat
  - May reduce or override sympathetic activation of BAT in response to cold
Effect of hypoxia on thermogenesis

- Anaerobic metabolism insufficient to produce enough heat for thermoregulation
- Shivering thermogenesis not affected
- Infants with chronic hypoxia (CHD) are still able to manifest thermogenic response
Response to heat

- Term newborns able to sweat at birth
  - Greater density of sweat glands than adult
  - Primarily on forehead, temple, occiput
- Sweating absent in infants <36 weeks EGA
  - Appears by 2 weeks of age
- Vasodilation occurs in term and preterm infants
  - Skin warm/red when overheated
- Will decrease activity, sleep more, lie in extended position
Fever

- Neonates are capable of temperature elevations above 38-39°C with septicemia, purulent meningitis, and pneumonia
- Nonshivering thermogenesis is prevailing response
Fever

- Set-point displacement
  - Organism attempts to set and sustain a higher body temperature
- Activation of normal cold defense reactions at an elevated temperature
  - Begins with peripheral vasoconstriction, central vasodilation
  - Followed by enhanced thermogenesis
    - Adult = shivering
    - Infant = nonshivering thermogenesis
Fever

- Triggered by exogenous pyrogen (LPS)
  - Stimulates granulocytes and macrophages to produce endogenous pyrogen (IL-1)
  - IL-1 activates PLA2
    - Cell membrane phospholipids $\rightarrow$ arachidonic acid
    - $\rightarrow$ converted to PG
- $\text{PGE}_2$ produces set point shift in hypothalamus
- Antipyretics (ASA) inhibit COX activity and PG formation
Environmental factors affecting temperature
Mechanisms of heat loss

- **Conduction**
  - Transfer of heat from warm to cool surface
  - Objects in direct contact
  - 3% of body heat loss
  - Increased with wet clothing or immersion

- **Convection**
  - Heat loss by air or fluid circulating around the skin
  - 12-15% of body heat loss
Mechanisms of heat loss

- **Radiation**
  - Infrared heat emission into surrounding air
  - Primarily from head and non-insulated areas
  - 55-65% of heat loss
  - Heat loss is proportional to temperature difference between adjacent surfaces
    - Independent of speed and temperature of intervening air
Mechanisms of heat loss

- **Evaporation**
  - 560 calories of heat lost/mL evaporated water
  - 25% of heat loss
    - ¼ respiratory, ¾ transepidermal water loss (TEWL)
  - Affects term infants at delivery (amniotic fluid)
  - Preterm infants have increased TEWL
    - Thin, poorly keratinized stratum corneum
    - TEWL approaches that of newborn by 2-3 weeks
  - Use of radiant warmer increases TEWL 0.5-2x
Measures to prevent heat loss

• Conduction
  ▫ Pre-warm objects coming to contact with infant
    • Bed, stethoscope, blankets
  ▫ Chemical thermal mattresses can be placed under preterm infants for rewarming
Measures to prevent heat loss

• Convection
  ▫ Cover with plastic prior to transport
  ▫ Keep sides of radiant warmer up/port holes in incubator closed
  ▫ Heat/humidify O2
  ▫ Minimize skin exposure to environment
Measures to prevent heat loss

• Evaporation
  ▫ No bathing if infant hypothermic or unstable
  ▫ Dry infant thoroughly after delivery
  ▫ Increase ambient humidity
  ▫ Plastic blanket/film – decreases H₂O loss 75%
  ▫ Aquaphor/vegetable oil
    • Increased risk of coag negative staph infection
Measures to prevent heat loss

• Radiation
  ▫ Keep bed/incubator away from windows and outside walls

• Overheating can occur with radiant warmer or direct sunlight
Perioperative hypothermia

• Normal OR maintained at 23° C or below
• Multiple cold surfaces increase radiant heat loss
• Temperature gradient increases convective and evaporative heat loss
• Induction of anesthesia induces core to peripheral heat distribution
• Increased complications in infants
  ▫ Apnea, hypoxemia, hypercarbia, acidosis, impaired oxygen delivery
Perioperative Hypothermia

- 108 NICU patients who underwent surgical procedures in OR vs NICU
  - OR group had increased perioperative hypothermia (65% vs 13%)
  - Hypothermic patients
    - 3x higher rate of respiratory support interventions
    - 6x higher rate of cardiac support interventions

- Hypothermia in adults results in increased wound infections, EBL, adverse cardiac events
  - Vasoconstriction decreases oxygen delivery to wound
  - Starvation and anesthesia blunt response to cold stress
  - Increased evaporative losses by exposed organs
Effect of hypothermia on metabolic rate with anesthesia

Compensation lost at 30°C
Management of the operating room

- OR temperature 28-30° C (82-86° F)
- Use of forced air warming systems or radiant heater
- Insulate infant during transport
- Minimize area of exposure
Therapeutic hypothermia
Hypoxic ischemic encephalopathy

- Intrapartum asphyxia resulting in diminished supply of oxygen and blood to the brain, resulting in neuronal injury
- Incidence 1-8/1000 live births worldwide
  - Higher in areas without access to obstetric/perinatal care
- Extent of injury does not follow a wholly reproducible pattern
Hypoxic ischemic encephalopathy

- Precipitating conditions:
  - Prolapsed umbilical cord
  - Uterine rupture
  - Placental abruption
  - Amniotic fluid embolism
  - Acute maternal hemorrhage
  - Any condition with ↓ maternal cardiac output and fetal blood flow (anaphylaxis)
  - Acute neonatal hemorrhage
    - Vasa previa, bleeding from cord, fetal-maternal hemorrhage
Classification

- **Stage 1 (mild)**
  - Transient irritability, hypertonia, poor feeding
  - ~100% normal functional outcome
- **Stage 2 (moderate)**
  - Lethargy, hypotonia, hyporeflexia, seizure
  - 30-40% normal, 30-50% epilepsy
- **Stage 3 (severe)**
  - Profound stupor, coma, isoelectric EEG, flaccid, decerebrate posturing
  - 50-75% mortality, 80-100% disability
Hypoxic ischemic encephalopathy

- Acute phase: 0-6 hrs
  - Insufficiency delivery of O2 and substrates (glucose and lactate)
  - Neurons and glia unable to maintain homeostasis
  - ATP exhausted $\rightarrow$ Na/K pump fails $\rightarrow$ cell depolarizes
  - Cl and H2O enter cell $\rightarrow$ cytotoxic edema $\rightarrow$ lysis
Primary Phase: Hypoxia-ischemia

↓ Oxygen  +  ↓ Blood flow

Anoxic depolarization

↓ EAA

NaCl + H₂O entry

Ca²⁺ influx

Death receptors (FAS)

Intracellular events after reperfusion

Cell swelling

Biophysical damage

Acute cell lysis
Hypoxic ischemic encephalopathy

- Reperfusion
  - Oxidative metabolism recovers in 30-60 min
  - Resolution of acute cell swelling
  - Burst of superoxide and NO formation
  - Breakdown of blood-brain barrier
    - Increased brain swelling
    - Degradation of basement membrane by MMPs
Hypoxic ischemic encephalopathy

- Latent phase (6-15 hrs)
  - Activation of cell death pathways activated by:
    - Calcium influx – depolarization of mitochondria
    - Abnormal excitatory receptor signalling - ↑Ca influx
    - Loss of trophic support from astrocytic growth factors
    - Cytokine release
    - Activation of cell surface death receptors (Fas)
Reperfusion

- Tissue oxygenation
- Inflammatory cells
- Reactive oxygen species, NO
- Cell death pathways

Secondary Phase

- Failure of oxidative metabolism
- Intranuclear stage of programmed cell death
- Epiphenomena
  - Seizures
  - Local metabolism
- Hyperperfusion
- Cell swelling
- Cell Death
Effect of Cooling

- Suppression of programmed cell death
- Depression of metabolic activity
  - Reduced oxygen demand
- Inhibits induction of proinflammatory cytokines
  - IL-10, TNF α, IFN γ
- Reduced cytotoxic edema
- Reduced secondary injury (seizures)
Inclusion criteria:

- <6 hours since birth
- >36 weeks gestation
- >1800 grams
- Cord or neonatal blood gas pH <7.0 or BD >16
- Abnormal neurologic exam
  - APGAR <3 after 5 minutes
- Experimental
  - >6 hours since birth
  - 34-36 weeks
Results

- 8 RCTs – 630 infants with moderate/severe HIE
  - Decreased risk of major death/disability (RR 0.75)
    - Death RR 0.74, Disability RR 0.92
  - Benefits seen with whole body cooling (vs. head)
  - Adverse effects
    - Decreased baseline HR (RR 5.96)
    - Increased need for BP support (RR 1.17)
    - Platelet count <150 (RR 1.55)
    - No difference in arrhythmia, transfusion, bleeding, hypoglycemia, sepsis
References

Questions?