The Role of Inducing Hypothermia as a Neuroprotective Strategy in the ICU

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March 15, 2019 - Neurosciences Symposium
Outline

1. Definitions
2. Theoretical Basis for HT
3. How HT is achieved
4. History of HT
5. Landmark Studies
6. Clinical Scenarios in which to consider HT, including indications, contraindications… and times when the beneficial use of HT is currently unclear
7. End Organ Effects of HT
8. What we do “know”
9. Questions we still have
Definitions

HT: hypothermia (TH: therapeutic hypothermia) TTM: targeted temperature management

- **Mild** hypothermia: 32-35°C
- **Moderate** Hypothermia: 28-32°C
- **Severe** Hypothermia: 17-28°C
- **Profound** Hypothermia: <17°C

Gruber A, Behringer W, Knosp E. Hypothermia in the operating theatre. *Critical Care* 2012, 16(Suppl2):A17
Temperature: Brain versus Body

- **Normal**: Brain temp 0.5-1°C higher than core temperature

- **Brain injury**: Brain lesion up to 2°C higher than core temp
  
  Suspected to be due to transient cellular hyperactivity
  
  Local brain edema → cerebral thermopooling

With endovascular cooling, able to cool brain almost to core temperature, even when T<36.5(1)

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Stages to HT

- **Induction**
  - Conventional (no device)
    - Ice: high availability, ↓cost
  - Non-invasive (surface)
    - Arctic Sun
  - Invasive (endovascular)
    - Zoll

- **Maintenance**
- **Rewarming**

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<table>
<thead>
<tr>
<th>Company</th>
<th>Device</th>
<th>Type of cooling</th>
<th>Cooling rate (°C/hour)</th>
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<th>Reusable</th>
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<td>1.5</td>
<td>Yes</td>
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</table>

The table gives the most common cooling devices with no claim to be complete. Cooling rates provided either by the company or at the company’s Internet homepage. CSZ, Cincinnati Sub-Zero; MTRE, Medical ThermoRegulation Expertise.

Devices for Attaining HT

Figure 1. Arctic Sun® 5000 Temperature Management System

The Arctic Sun® 5000 Temperature Management System is a non-invasive medical device utilized for therapeutic hypothermia by circulating chilled water in pads directly attached to the patient's skin.

Arctic Sun® Temperature Management System and ArcticGel™ Pad are trademarks and/or registered trademarks of C.R. Bard, Inc.
How HT is attained

- ice packs / cold IVF / surface cooling / endovascular cooling
Theoretical Basis

◊ ↓cerebral metabolic rate —> ↓demand for O2, glucose
  ◊ T32°C: metabolic rate (including O2 consumption, CO2 production) = 50-65% normal
  ◊ ↓temp ➔ ↓metabolism ➔ ↓glucose utilization ➔ ↓lactate accumulation ➔ ↓acidosis
  ◊ ↓cerebral oxygenation —> depletion of ATP —> dysfunction of ATP-dependent membrane pumps —> anoxic depolarization
  ◊ ↓10°C —> 2-4x↓: ATP consumption, cerebral metabolic rate of O2, glucose, and lactate (1)

Gruber A, Behringer W, Knosp E. Hypothermia in the operating theatre. Critical Care 2012, 16(Suppl2):A17
Theoretical Basis

HT inhibits:

🔹 Excitotoxicity
  ✷ ↑↑glutamate released from intracellular space -> extracellular space —> excitotoxic injury by stimulating NMDA R —> Ca2+ influx

🔹 Neuroinflammation
  ✷ HT inhibits leukocyte migration and phagocytosis, and decreases synthesis of proinflammatory cytokines: neuroprotective, BUT increases infection risk

🔹 Apoptosis

🔹 Free radical production
  ✷ ↑ free radical production —> ↑ protein oxidation, lipid membrane disintegration, BBB disruption —> ischemic necrosis

🔹 Seizure activity

🔹 BBB disruption
  ✷ ↓ temp stabilizes the BBB, ↓ vascular permeability —> ↓ brain edema —> ↓ brain injury

🔹 Blood vessel leakage

🔹 Cerebral thermopooling

and ↓ ICP and ↓ edema

🔹 ↓ metabolism —> ↓ energy consumption —> ↓ oxygen utilization (↓ demand, ↓ consumption) —> ↓ CO2 production
  —> ↓ vasodilation (or ↑ vasoconstriction) —> ↓ ICP

Theoretical Basis: Timing

- Brain edema: 72h
- Leukocytosis/Proinflammatory state: 5d

Window for TTM?

History

- 5000 years ago: **Egyptian** times: Edwin Smith Papyrus on medicine and surgery
- **Hippocrates**: snow and ice packing to reduce hemorrhage in the wounded
- 4th, 5th century BC: total body cooling for **tetanus** treatment
- 1650: Woman **hung** on a cold day in December —> brought down 1/2 hr later, with full neurologic recovery
- Late 1700s: James Currie: **first systematic experiments** on human via cold water
- 1803: Russians covered people with **snow** in an effort to **resuscitate** them
- 1812: Baron de Larry, Napoleon’s chief surgeon during the war of 1812, **packed limbs in ice** prior to **amputation** to decrease pain; realized that hypothermic soldiers placed closer to a fire died faster than those who remained hypothermic
- 1892 Sir William Osler (John Hopkins) reported a decline in mortality (24.2 —> 7.1%) in **typhoid** patients who underwent hypothermia
- 1938 Dr. Temple Fay cooled patients with **intractable pain 2/2 malignancy** - cooling blankets. Also implanted metal capsule intracranially to deliver localized hypothermia
- 1950s: Bigelow et al: positive effects on the brain during cardiac surgery in animals; Rosomoff et all: HT —> dec CBF, O2 consumption, ICP in dogs in TBI; used during intracranial aneurysm repair
- 1958: increased survival in comatose pts s/p cardiac arrest treated with HT (50% survival) versus normothermia (14% survival)
- Decreased interested 2/2 associated S/E (arrhythmias, coagulopathy, infection) a/w moderate (28-32°C) HT was used
- 1980s: benefits with even mild cooling —> 1990s: extensive research on animals (neuroprotection s/p CA, cerebral ischemia, bacterial meningitis) —>
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE NEW ENGLAND JOURNAL OF MEDICINE

VOLUME 346
FEBRUARY 21, 2002
NUMBER 8

ABSTRACT

Background Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation.

Methods In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32°C to 34°C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary:

AN estimated 375,000 people in Europe undergo sudden cardiac arrest yearly.1 Recovery without residual neurologic damage after cardiac arrest with global cerebral ischemia is rare. After cardiac arrest with no blood flow for more than five minutes, the generation of free radicals, together with other mediators, during reperfusion creates chemical cascades that result in cerebral injury.2 Until recently, there was no therapy with documented efficacy in preventing brain damage after cardiac arrest.

Several studies have shown that moderate systemic hypothermia (30°C)3 or mild hypothermia (34°C)4-8 markedly mitigates brain damage after cardiac arrest in dogs. The exact mechanism for this cerebral resuscita-
HACA

- HACA: Hypothermia After Cardiac Arrest
- Mild systemic therapeutic hypothermia increases the rate of neurologic recovery and decreases mortality in patients who have been successfully resuscitated after cardiac arrest due to vfib
- HT (32-34°C x24h with surface [mattress] cooling +/- ice packs → passive rewarming) versus normothermia
- 1° outcome: favorable outcome 6mo s/p CA: 75/136 (55%) HT vs 54/137 (39%) NT: P0.009
  - measured by CPC
  - NNT 6 - to prevent one unfavorable outcome
- Mortality at 6 mo: 41% HT vs 55% NT: P0.02
  - NNT 7 - to prevent one death
- No change in 7d complication rate
Landmark Studies

INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA


ABSTRACT

Background Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest.

Methods The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33°C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good

Currently, the treatment of patients with coma after resuscitation from out-of-hospital cardiac arrest is largely supportive. Because cerebral ischemia may persist for some hours after resuscitation, the use of induced hypothermia to decrease cerebral oxygen demand has been proposed as a treatment option. Although this suggestion has been supported by studies in animal models, the studies in humans that have been reported to date have been uncontrolled or retrospective.

After a pilot study that suggested the feasibility, safety, and possible efficacy of this treatment, we conducted a prospective, controlled trial comparing moderate induced hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest.

METHODS
77 patients vfib cardiac arrest with persistent coma s/p successful ROSC

43 HT: 33°C x12h, started within 2h of ROSC; 34 NT

- HT started in the field on odd days: removing pt’s clothing, applying cold packs
- HT maintained for 12h after arrival at hospital; anti-shivering meds; actively rewarmed starting at 18h with heated-air blanket to target 37°C

1° outcome: good outcome: DC home/IPR vs death/LTAC

- 49% HT, 26% NT reached 1° outcome (p0.046)
- Adjusted OR good outcome 5.25 with HT
  - Adjusted for age and length of time between collapse and ROSC; unadjusted OR 2.65 in favor of HT

- No outcome of severe disability in HT, despite total #patients
- ↓ mortality in HT (not significant): 22/43 (51%) HT, 23/34 (68%) NT
Scenarios in Which to Consider HT

- Cardiac arrest – vfib
- Cardiac arrest, other
- SAH
- ICH
- AIS
- SCI
- SE
- Infection
- TBI
- Other (CABG, aneurysm repair, hepatic failure)
Cardiac Arrest - vfib

- Improved mortality, functional outcome with HT s/p vfib with ROSC

- See HACA, Bernard et al
Cardiac Arrest, other

- Conflicting results; poor data

- Majority: trend towards lower mortality, increased neurological outcome with HT, but not convincing

SAH

- IHAST: Intraoperative Hypothermia for Aneurysm Surgery Trial
  - 1,001 patients with good-grade SAH (WFNS1-3*): 33°C vs 36.5°C
  - No improvement in neurological outcome at 3mo (1)
  - No difference in cognitive impairment (2)
  - Duration of intraoperative clipping most important determinant of outcome (3)
  - No evidence of benefit of intraop HT for temporary clipping (3)
  - May be worthwhile to consider HT as a treatment of last resort in complex aneurysms which would otherwise be untreatable

Gruber A, Behringer W, Knosp E. Hypothermia in the operating theatre. Critical Care 2012, 16(Suppl2):A17
Seule M, Keller E. Hypothermia after aneurysmal subarachnoid hemorrhage. Critical Care 2012, 16(Suppl2):A16
ICH

- Limited data
- Case series (proof of concept) shows that HT $\rightarrow$ ↓ perihemorrhagic edema (PHE)
  - ICH: perihemorrhagic edema $\rightarrow$ ↑ ICP $\rightarrow$ risk of herniation
  - PHE volume ↑ over the first few days; correlates with ICH volume
- 35˚C over 10d(!) vs historical controls
  - 20 HT pts (ICH volume 57+/-25mL) versus (59+/-31mL) control group
    - No significant difference in PHE on days 1 and 2, but
    - Significantly lower volumes of PHE in HT on days 3, 6, 11, 14, with
    - No rebound PHE after rewarming, as checked on days 11 and 14
    - No ICP crisis in HT group; 44% ICP crisis in control group

Kollmar R, Scwab S, Staykov D. Therapeutic hypothermia decreased growth of perihemorrhagic edema and prevents critical increase of intracranial pressure in large intracerebral haemorrhage. *Critical Care* 2012, 16(Suppl2):A14
AIS

**ICTuS**
- Whether hypothermia reduces post-ischemic edema; using CTH baseline, 36-48h, and 30d
- 18 patients with AIS “underwent hypothermia:” target 33°C x24h —> 12h controlled re-warm using endovascular system
  - 7 patients effectively cooled; 11 patients cooled partially/not at all
  - “effective:” cooled to a temperature nadir of ≤34.5°C within 8h
- Their conclusion: “therapeutic hypothermia results in a significant reduction in **acute** post-ischemic cerebral swelling”, using “CSF volume as a surrogate of brain swelling”.

- CSF (surrogate for edema) @36-48h significantly lower in NT patients (more edema) compared to HT / baseline; difference “resolved” by 30d (non-statistically significant ↓ in CSF in NT compared to HT)
- **NIHSS improved** in NT patients, and **worsened** in cooled patients (not stat sig)
- **AIS volume** (not statistically significant):
  - @36-48h: ↓AIS vol in HT (54 +/- 59mL AIS in HT vs 73 +/- 73 mL in NT)
  - @30d: ↑AIS vol in HT (84 +/- 102mL AIS in HT vs 73 +/- 71 mL in NT)

AIS

- **ICTuS-L**  L: longer tPA window
  - tPA and hypothermia (33°C x24h → 12h controlled rewarming) in awake AIS patients with NIH≥7:
    - Sx hrs 0-3: received tPA, and then randomized to HT vs NT
    - Sx hrs 3-6: randomized to receive tPA or not, and then randomized a second time for HT vs NT
    - 58 pts: 44 pts tPA h 0-3 → 22HT, 22NT; 14pts hr 0-3, of whom 4 got tPA (2HT, 2NT), 10 0tPA (4HT, 6NT)
- safety + feasibility trial
  - placed endovascular cooling catheter 30-180min from completion of tPA
    - delay time of treatment
    - No difference in AE
- 3 mo **mRS 0-1**: 18% HT, 24% NT (no stat sig diff)
- **PNA**: 14pts HT, 3pt NT  p0.001
- **Trend towards worse mRS, worse NIHSS, more death, higher volume AIS with HT**
  - Although pre stroke mRS >1 present in 14.3% HT and 3.3%NT (P 0.214)
  - **NIHSS**: 24h: 17HT, 11.1 NT (sedated with meperidine); **30d 8HT, 5NT** from baseline preTx 14.3 / 13.7
  - 6 HT died, 5NT died
    - **PNA**: 7/28HT vs 2/30NT, P<0.05
- Meperidine → ↓ RR → ↑ aspiration risk → ↑ PNA;  stroke → transient immune depression → ↑ PNA risk

AIS

♦ ICTuS2
  ♦ Added 2L NS bolus (4°C NS vs room temp) to help achieve target temp faster
    ♦ Also added protocols to attempt to reduce PNA rate (HOB, permissive hypothermia), thought likely to be 2/2 meperidine —> respiratory depression —> ↑ aspiration risk
  ♦ 1° outcome: mRS 0-1 at 90d: 38% NT vs 33%HT ITT, with OR 0.62(0.226-1.51)
    ♦ PP (per protocol): OR 0.29 (0.10-0.85) HT vs NT- significant
  ♦ Trend towards ↑mortality (15.9% vs 8.8%), ↑serious adverse effects (41% vs 35%), ↑PNA (19% vs 10.5%)
  ♦ “No increase in signs of volume overload” - comparing HT vs NT, both of whom got 2L NS bolus
  ♦ Stopped early 2/2 approval of endovascular thrombectomy (not included in trial) and end of 1° funding

Lyden P, Hemmen T et al. Results of the ICTuS2 Trial (Intravascular Cooling in the Treatment of Stroke 2). Stroke DOI:1.1161/STROKEAHA.116.014200
SCI

- 2014: no RCTs, but case series showing trend towards improvement in AIS grade with HT s/p complete (ASIA A) cervical spine injuries
  - 5/14 HT converted to ASIA B/C vs 2/14 control (1)
  - 43% improvement by at least one grade at 1 year followup in cervical SCI treated with HT, which was better than historical controls (12.5-20%) (2)

- Case report: High profile NFL player (Kevin Everett) with a complete AIS A cervical spine injury was treated immediately with moderate hypothermia, and had a much better than expected outcome.
- Of note, consider that fever may represent an infection, but may be a sequela of SCI; SCI has a high incidence of thermoregulatory problems

Guadalupe A. Hypothermia in spinal cord injury. Critical Care 2012, 16(suppl2):A12
HYBERNATUS: Hypothermia for Neuroprotection in Convulsive Status Epilepticus

- 270 critically ill, intubated patients “with convulsive status epilepticus”: 138 HT (32-34°C x24h) vs 130 standard care
- Trend toward improvement with HT, but not statistically significant
  - Fewer cases of refractory status on day 1 and of super-refractory status on d1-3 with HT
  - 90d GOS5 ↑ in HT (49% vs 43%, not sig)
- Trend toward ↑ seizure recurrence in HT
  - Also seen in other studies when pts rewarmed to normothermia (Rosetti)
  - Thus, HT may be used to gain some time, rather than in and of itself to control seizures
- Refractory SE (persisting despite adequate doses of benzodiazepines and >/=1AED) develops in 23-43% SE, and is a/w encephalitis, large AIS, rapidly progressive brain tumors… all etiologies for which HT has been considered on their own merits
- Consider avoidance of barbiturates, as they may further ↑ the risk of paralytic ileus


Rosetti A. Hypothermia in refractory status epileptics. Critical Care 2012, 16(suppl2):A26
EEGs in HT/NT

- **SE during TH**: mostly seen as a seizure suppression EEG pattern - reflects extremely severe brain damage, and patients are extremely unlikely to survive

- **SE arriving after rewarming** (normothermia), in the presence of a reactive EEG background, with preservation of brainstem reflexes and early cortical somatosensory evoked potentials may be successfully treated with traditional treatment; good outcome may be reached — only 10% represent post anoxic SE

Rosetti A. Hypothermia in refractory status epileptics. Critical Care 2012, 16(suppl2):A26
Infection

- Viral encephalitis, severe bacterial meningitis, brain abscesses → ↑ ICP; HT ↓ ICP → theoretically improved outcomes
  - May be particularly helpful in HSV, which has limited conventional ICP-lowering therapies

- HT may → ↓ cerebral infarction, which can be a sequelae of bacterial meningitis → theoretically improved outcomes

- HT → ↓ excitotoxic cascade → ↓ SE?

- Dr. Roland Burkitt: ↓ core T in pts with ↑ fevers (cerebral malaria, meningitis, encephalitis) → improved outcome

- Zdravev: ↑ body T a/w ↑ ICP → poor outcomes

- RCT HT (32-34Cx48h) in severe bacterial meningitis (comatose) → increased mortality (unadjusted RR 1.99 vs NT; p0.04; adjusted NS/trend)

- Case reports/case series:
  - Japanese group: adults with influenza type A virus-associated encephalopathy, Tx w oseltamivir and methylprednisone pulse therapy; severe brain swelling → HT → full recovery without neurologic sequelae (1)
  - 27/43 children with acute inflammatory encephalopathy and/or encephalitis treated with mild HT; effect appeared to be dependent on timing of HT initiation: early (<12h from onset of neurological Sx) improved outcome, vs delayed (>12h) appeared harmful (2)

- Numerous others

Hypothermia for Intracranial Hypertension after Traumatic Brain Injury


BACKGROUND
In patients with traumatic brain injury, hypothermia can reduce intracranial hypertension. The benefit of hypothermia on functional outcome is unclear.

METHODS
We randomly assigned adults with an intracranial pressure of more than 20 mm Hg despite stage 1 treatments (including mechanical ventilation and sedation management) to standard care (control group) or hypothermia (32 to 35°C) plus standard care. In the

ABSTRACT
TBI

- EuroTherm3235
- TBI: HT → ↓ ICP;
  - → improved neurological outcome?
  - Pts with ICP>20mmHg despite stage 1 treatments (ventilation, sedation) within 10d of ictus
  - HT: core temp reduced by the minimum needed to maintain an ICP ≤ 20mmHg, within the limits of 32-35°C.
  - Maintained for ≥ 24h, or as long as was necessary to control ICP. → rewarming considered starting at 48h; rewarmed at 0.25°C/hr.
- ICP control:
  - st1: vent, sed
  - st2: osmotic Tx, HT (osmotic only if later needed)
  - st3: barbituates, decompressive hemicrania
- HT effective at controlling ICP
  - but pts had worse outcome
  - **GOS-E score 5-8 (favorable)**
    - 25.7% HT and 36.5% control, P 0.03
  - **Risk of death** (hazard ratio 1.45; 95%CI 1.01-2.10) favored control group
- Trial stopped early given concerns for harm in treatment group
BHYPO: 32-34C vs fever control (35.5-37C) >72h for patients with GCS 4-8 and initiation of cooling within 2h TBI

Concluded: TH does not improve the neurologic outcome or risk of mortality

in fact, trend toward improved outcome of DAI II, III with fever control (for all patients; more significant for pts<50yo)

However, subgroup analysis showed:

significantly ↑ favorable outcomes with (77.8% HT vs 33.3% fever control) for young patients (<50yo) with surgically evacuated mass lesions, p0.015: 18HT vs12NT pts

Type of evacuated mass lesion (SDH, contusion+SDH, epidural hematoma) did not seem to matter

Patients with diffuse injury III —> significantly increased mortality with HT
Other

❖ CABG
  ❖ Mild, moderate HT protective against operative mortality vs NT. Mod HT protective against stroke vs mild HT

❖ Aneurysm repair

❖ Hepatic failure/hepatic encephalopathy
  ❖ → ↑ ICP → ↑ mortality
  ❖ High ICP occurs in 80-95% pts with stage III-IV hepatic encephalopathy → ↑ mortality, neurocognitive complications in survivors
  ❖ No RCTs, but case reports of acute liver failure successfully bridged to OLT following initiation of HT (32-33˚C) with subsequent complete neurologic recovery
    ❖ HT → significant ↑ in MAP, CPP, with ↓ need for inotropes
    ❖ HT → sig ↓ arterial [ammonia], ↓ brain metabolism, ↓ CBF, ↓ brain cytokine production, and ↓ markers of oxidative stress

❖ Neonatal Resuscitation
  ❖ 2010 Guidelines recommend inducing HT (33.5-34.5˚C) within 6h for birth asphyxia in term or near-term infants.
  ❖ HT → fewer neurodevelopment deficits, fewer signs of perinatal distress, and ↓ mortality

❖ Severe burns +/− → refractory hyperthermia: hypermetabolic state

End Organ Effects

- rewarming injury
- shivering
- electrolyte dysbalance
- pharmacological and pharmacodynamic alterations
- cardiovascular effects (arrhythmia, bradycardia)
- insulin resistance
- infections
dose-dependent fashion with HT


- Neuro → Metabolism
  - shivering
- Pulm
  - PNA (AIS). ?pulmonary edema (most commonly a/w cardiogenic shock)
- Cards
  - Bradycardia
- GI
  - No ↑ in GIB, but when GIB, more likely to have ↑ pRBC requirements
  - Delayed gastric emptying
  - Increased risk of ileus
- Endocrine
  - ↓ insulin sensitivity
- Renal
  - Electrolyte imbalances
- Heme
  - Once formulated, clots stable at all temps, but ↓ clot formation at lower temps → control bleeding first
- ID
  - ↑ infection risk (a/w ↑ glucose)
  - ↑ bed sores, 2/2 peripheral vasoconstriction
  - Can be difficult to accurately assess fever → look at RATE of cooling, or how hard the machine is working to maintain desired temperature
  - Consideration of empiric initiation of BSAB and/or daily routing BCx
Changed Pharmacokinetics, Pharmacodynamics

- **Speed** of most enzyme-mediated reactions are **temperature-dependent**: much slowed by HT
  - ↓ **drug metabolism** by the liver
  - ↓ **clearance**
    - vasoactive drugs (epi, NE), opiates (fentanyl, morphine), sedatives (propofol, barbiturates, midazolam, volatile anesthetics), neuromuscular blocking agents (rocuronium, atracurium, vecuronium), phenytoin, nitrates, some beta blockers
- Body reacts differently to drugs at different temperatures
  - ↓ effect of vasoactive drugs (epi, NE) seen at lower temperatures
- Usually, ↑ **drug potency** and ↑ **duration of effect** seen with HT
- HT changes volume of distribution, affects renal function, and may alter how drugs work

- **Consider bolus > gtt**
  - Drugs with long t1/2, e.g. amiodarone, less affected by periods of HT
    - amount eliminated within 24h would be low anyway; no significant change in amount remaining

Rewarming

- Recommended rewarming speed: 0.1 - 0.4 °C/hr
  - 0.1°C/hr → >/=24h to reach normothermia
  - 0.4°C/hr → 6-8h to reach normothermia
- Too rapid rewarming → vasoDILation → ↑ ICP → ↓ CPP → worse neurological outcomes
  - Rapid rewarming not only reverses the neuroprotection conferred by hypothermia, but may further exacerbate the underlying pathology (e.g. ↑ axonal damage in TBI patients) and its associated functional consequences
- Passive rewarming → ↑ insulin sensitivity, but
  - active rewarming (e.g. from cardiopulmonary bypass) ↓ insulin sensitivity
- Rewarming may → ↑ ICP, excitotocity, ↑ metabolic demand, and derangement of cerebrovascular reactivity
  - Slow, controlled rewarmin may prevent ICP increase, glutamate release
- Rewarming → ↑ insulin sensitivity → potential for hypoglycemia (which correlates with poor neurological outcome)
- Rewarming → electrolyte disturbances

Normothermia, Decreasing the Depth of Cooling, and Avoidance of Fever

◊ Greer et al: fever alone is a significant and independent predictor of morbidity and mortality in AIS, ICH, TBI (1)

◊ TTM Trial: 32-33˚C vs 36˚C: no significant differences in mortality, neurological function (CPC), or mRS.
  ◊ Concluded no benefit conferred from 33˚C vs 36˚C

◊ Retrospective studies have found ↓ active cooling, ↓ time at target T, ↑ fever, ↓ DC alive/home, ↓ favorable neurologic outcomes, and trend towards ↓ survival

Questions that Remain

- Timing of initiation
- Degree of cooling
- Duration of cooling
- Rate of rewarming

- Other potential uses? MS?
Summary

- HT improves neurologic outcome and decreases mortality in comatose survivors of VF cardiac arrest
- HT worsens neurologic injury, and increases mortality, in severe TBI patients
- Most other severe neurologic insults have conflicting or inconclusive data, based primarily on case reports and case series, which do not clearly denote benefit or harm of HT in improving neurological outcome

- If HT chosen:
  - Rapidly induce HT
  - Carefully maintain temperature control during maintenance period: minimize fluctuations
  - Rewarm very slowly
  - Control shivering
  - Address electrolytes - and other S/E - as they occur

- More research needs to be done
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