Tip of the Iceberg: Alterations of PK/PD in Patients Undergoing Targeted Temperature Management

A presentation for HealthTrust Members

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Speaker Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation.

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Learning objectives

- Compare pharmacokinetic parameters for normothermic and hypothermic patients
- Select monitoring parameters appropriate for targeted temperature management
- Identify medications likely to require adjustment due to targeted temperature management

Some Chilling Statistics

- 320,000 out-of-hospital cardiac arrests (OHCA) annually in the United States
  - 23% of these present with a shockable rhythm
  - Non-shockable rhythms have a poorer prognosis
- Remains a poor prognosis, survival to discharge in only ~7 – 11% of patients with OHCA and ~25% of patients arresting within the hospital

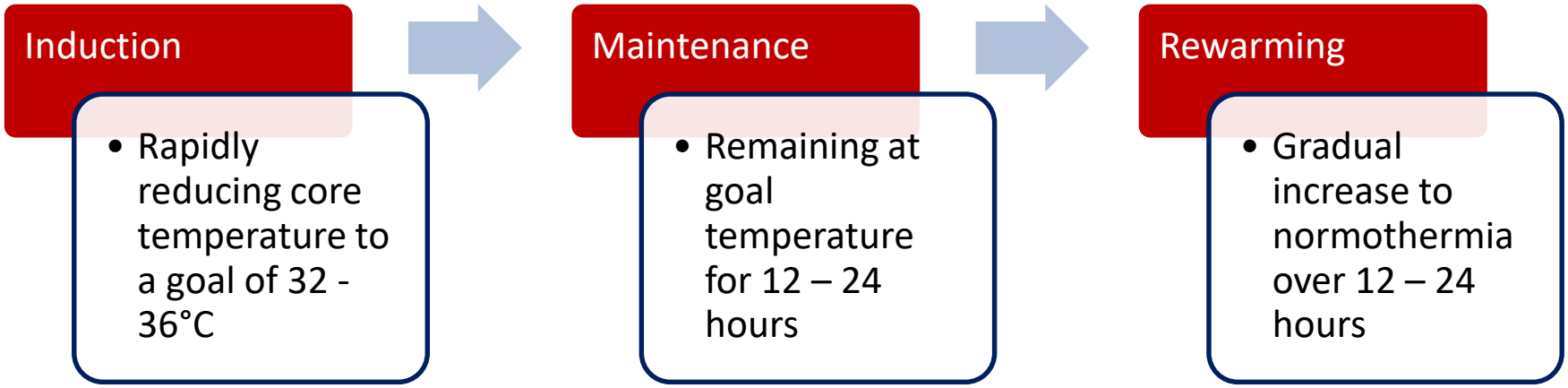
Source: Hunter BR, Ellender TJ. Open Access Emerg Med. 2015;7:69-77.

An icebreaker with targeted temperature management (TTM)

- Currently debated if the benefit is driven by therapeutic hypothermia (TH) vs. prevention of fever following cardiac arrest
  - Early trials showing benefits of TH allowed control group to become febrile
  - Terminology has shifted from TH to TTM
- Lack of reproducibility and conflicting evidence has led to an overall decline in the use of TTM
  - Clinicians overall unfamiliar with TTM
  - Opportunities for improvement in pharmacotherapy

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

TTM pathway and time course



Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Overview of TTM

- Hypothermic state decreases production of free radicals, preserving long-term neurologic function
- TTM has demonstrated improved neurological outcomes following cardiac arrest in patients cooled to a goal temperature of 32 - 36°C (89.6 – 96.8°F) for 12 – 24 hours
  - Best studied in patients remaining comatose, following return of spontaneous circulation (ROSC) following advanced cardiac life support (ACLS) interventions, initially presenting with a shockable rhythm (pulseless ventricular tachycardia or ventricular fibrillation)

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Pharmacokinetics & TTM

- Pharmacokinetics describes how drugs are absorbed, distributed, metabolized & excreted by the body
- Hypothermia has the potential to impact each of these phases, resulting in significant clinical effects
- An example of a drug-therapy interaction
- Overall lack of literature describing optimal medication changes in TTM

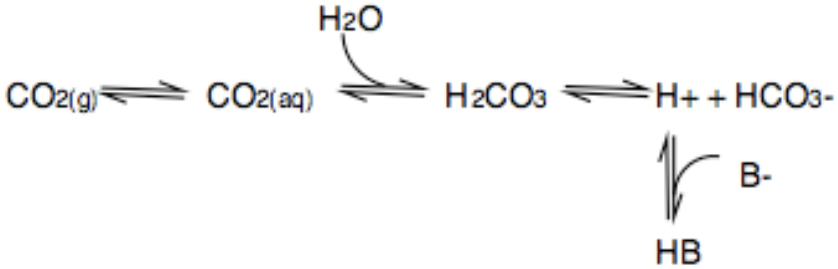
Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Absorption

- IV administration bypasses the absorption phase
  - May be considered the route of choice when possible for patients
- While not well characterized, it is expected that gut absorption is impaired during TTM secondary to increased transit times
  - Oral or rectal routes of administration are unreliable
- Little data exists examining alterations in subcutaneous, transdermal, and intramuscular routes of administration

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Distribution



- A variety of physiological changes alter drug distribution, making generalization of effect difficult
- Examples of physiologic changes that must be taken into consideration:
  - Altered blood flow, blood shunting to vital organs
  - Blood pH decreases at lower temperatures
    - CO2 partial pressure increases
  - Protein binding is altered
    - It may be increased, decreased, or unchanged depending on the drug
  - Lipophilic penetration and tissue binding is decreased

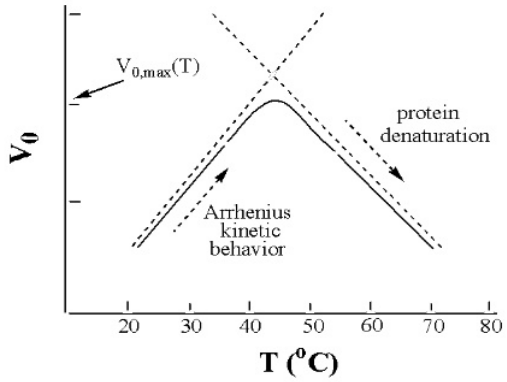
Sources: Wieruszewski, P. Pharmacy Times. 2016.
Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Distribution

- Changes in vasodilatation and decreases in cardiac output have not been consistently proven to decrease volume of distribution at temperatures of 32 - 36°C
- Active transporters such as ABCB1 (P –glycoprotein) have exhibited decreased activity at 32°C
  - Typically, these pumps efflux drugs out of the cell, into a biological lumen for elimination
  - In vitro digoxin clearance was decreased by 50% in a study conducted by Jin et al.

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Metabolism



- Decreased hepatic blood flow
- Decreased enzymatic activity
  - Prodrugs are less effective (decreased transformation)
  - Decreased breakdown of drugs to inactive metabolites
- Hepatic extraction ratio (E_H) describes drug concentration pre- and post- hepatically
  - $E_H=(C_a- C_v)/C_a$
    - C_a is the concentration in the hepatic arterial and mixed venous
    - C_v is the concentration in the hepatic venous blood
  - High extraction ratio (>0.7) are most altered by changes in blood flow
- **Favorable to avoid drugs with hepatic metabolism**

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Metabolism

Drug	Relevant Pharmacokinetic Properties				
	Elimination Half-Life	Hepatic Extraction Ratio	Cytochrome P450 Metabolism	Renal Elimination	Transporters
General anesthetics					
Propofol	30–60 min	High	2B	Yes	UDP-glucuronosyltransferase
Dexmedetomidine	2–2.67 hr	High	2A6	Yes	None
Midazolam	1.8–6.4 hr	Low/intermediate	3A4	Yes	None
Opioids					
Fentanyl	2.5–6.5 min	High	3A4	Yes	None
Remifentanil	3–10 min	n/a	n/a	Yes	n/a
Meperidine	2.5–4 hr	High	none	Yes	None
Nonopioids					
Acetaminophen	2 hr	Intermediate/high	2E1[a]	Yes	None
Buspirone	2–3 hr	High	3A4	Yes	None
Paralytics					
Vecuronium	51–80 min	Low	3A4	Yes	p-glycoprotein
Atracurium	20 min	n/a	n/a	n/a	None

[a]Cytochrome P4502E1 metabolizes acetaminophen to N-acetyl-p-benzoquinone imine, which is then inactivated by glutathione conjugation.
Antishivering activity qualification, as in reduction of shivering threshold: + (≤ 0.2°C), ++ (0.2–0.4°C), +++ (0.5–0.9°C), ++++ (≥ 0.9°C).

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Drugs Affected by P-glycoprotein

Substrates	Inducers	Inhibitors
Digoxin	Rifampin	**Amiodarone**
Loperamide	Carbamazepine	Ketoconazole
Colchicine	Phenytoin	Clarithromycin
Dabigatran	**Dexamethasone**	Cyclosporine
Morphine		Verapamil
		Quinidine
		Ritonavir

- This list is generalized and not specific to TTM, some studies report conflicting results about the effect of hypothermia on specific drugs such as quinidine
- Decreases in Pgp activity will cause higher uptake of drug into cells

Excretion

- Tubular secretion and reabsorption are enzyme-dependent processes
  - May be decreased in hypothermia
- Cold-induced diuresis has been described
  - Vasoconstriction from cold causes diuresis
- Decreases in renal clearance have not been consistently described
  - Creatinine synthesis is decreased
  - Cockcroft-Gault estimation may be unreliable

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Assessment question #1:

- Which of the following pharmacokinetic parameters are likely to be decreased in a patient undergoing targeted temperature management in an ICU setting? (Select all that apply)
  - A: Absorption
  - B: Distribution
  - C: Metabolism
  - D: Excretion

Assessment response #1:

- Which of the following pharmacokinetic parameters are likely to be decreased in a patient undergoing targeted temperature management in an ICU setting? (Select all that apply)
  - A: Absorption
  - B: Distribution
  - C: Metabolism
  - D: Excretion

General Goals of Pharmacotherapy in TTM

- Prevention of shivering
  - Managed with neuromuscular blockade & medications with anti-shivering effect
- Maintain deep level of analgosedation
  - Titrate sedatives to a goal Richmond Agitation-Sedation Scale (RASS) of -5
  - Use of validated pain scoring systems to prevent long-term complications of pain
    - Critical-Care Pain Observation Tool (CPOT)
    - Behavioral Pain Scale (BPS)

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Shivering

- Body's natural attempt to rewarm patient
  - Adaptive response to cold
    - Stimulated at 35.5°C, ceases at 33.5°C
    - May occur during induction or rewarming of patient
  - Shivering upon induction associated with better neurological outcomes
  - May undermine efforts to keep patient cool
- No single drug can be administered at safe, effective doses to reduce shivering threshold
  - Combinations must be used
  - Examination of individual drugs is warranted in TTM to determine a preferred standard

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Snow Day! Opioids for Shivering

- Decrease shivering threshold
- Dose often limited by respiratory depression
- Anti-shivering effect best characterized with meperidine
  - Reduces shivering threshold by ~ 2°C
  - Acts synergistically with buspirone
  - Active metabolite: normeperidine
    - Risk of neurotoxicity
- Remifentanil has potent anti-shivering effect
- Fentanyl has a minor anti-shivering effect
  - Class effect can not be assumed for opioids

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Non-opioids for Shivering

- Clonidine & dexmedetomidine (α2 agonists) both reduce shivering threshold
  - Dexmedetomidine clearance reduced by ~60% in hepatic impairment, unknown if this is seen in TTM
- Acetaminophen decreases the hypothalamic resting point for temperature homeostasis
  - Reductions of 0.2 – 0.4°C seen with 3g and 6g doses
- Buspirone
  - $5HT_{1A}$ partial agonism thought to provide anti-shivering effect
  - Typically given as 30mg po q8h
    - Studied in healthy male volunteers
    - Reduced shivering threshold by ~0.8°C

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Paralytics for Shivering

- A well characterized, prolonged duration of action regardless of metabolic route
- Initial dose reductions of 25 – 50% should be implemented to prevent a prolonged duration of action
- Train-of-four (TOF) monitoring is shown to be altered in TTM
  - During rewarming, patients exhibit resistance to paralytic effects
  - Ex: TOF 4/4 despite same dose of paralytic during maintenance

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Anti-shivering Efficacy

Drug	Anti-shivering activity
Paralytics	+++++
Meperidine	++++
Propofol	+++
Fentanyl, morphine	+++
Clonidine	+++
Doxapram, nefopam	+++
Midazolam	++
Magnesium	++
Dexmedetomidine	++
Ondansetron	+

Source: Polderman KH, et al. Crit Care Med. 2009;37:1101-1120.

Paralytics Monitoring

- TOF monitoring is unreliable in TTM
- Titrate paralytics to clinical endpoints
  - Reduction of shivering response
  - Improved ventilator synchrony
- Intermittent boluses of paralytics are appropriate during rewarming
  - Avoidance of supratherapeutic concentrations
  - Shivering less likely to occur during maintenance, continuous infusions may not be needed
  - Excessive blockade may delay neuroprognostication

Source: Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Bedside Shivering Assessment Scale (BSAS):

0 – None: No Shivering
1 – Mild: Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2 – Moderate: Intermittent involvement of the upper extremities +/- thorax
3 – Severe: Generalized shivering or sustained upper/lower extremity shivering

- Validated 4 point scale used to assess shivering
- Columbia anti-shivering protocol proposes maintaining BSAS $\leq$ 1 during induction

Source: Choi HA, et al. Neurocrit Care. 2011; 14(3):389-94.

Assessment question #2:

- Which of the following monitoring parameters is unreliable in a patient undergoing TTM?
  - A: Vancomycin trough level
  - B: TOF monitoring for paralytics
  - C: Blood glucose for patients receiving insulin
  - D: Serum creatinine

Assessment response #2:

- Which of the following monitoring parameters is unreliable in a patient undergoing TTM?
  - A: Vancomycin trough level
  - B: TOF monitoring for paralytics
  - C: Blood glucose for patients receiving insulin
  - D: Serum creatinine

Desirable Drug Qualities

- Short, predictable half life
  - Rapid onset & off-set
- Smaller volume of distribution
  - Less tissue penetration, more predictable kinetics
- Ease of monitoring
  - Monitoring for safety and efficacy of medication

Columbia Anti-Shivering Protocol

- Recommends baseline medications plus a stepwise approach to shivering management
- Baseline medications:
  - Acetaminophen 650 – 1000 mg q4-6h
  - Buspirone 30 mg q8h
  - Magnesium sulfate 0.5-1 mg/h IV
    - Goal magnesium level: 3 – 4 mg/dL
  - Skin counter warming at a maximum of 43 °C

Source: Choi HA, et al. Neurocrit Care. 2011; 14(3):389-94.

Columbia Anti-Shivering Protocol

- First line: dexmedetomidine or opioids
  - Dexmedetomidine preferred for patients with underlying agitation
    - Dexmedetomidine 0.2 – 1.5 mcg/kg/hr
  - Opioids preferred for bradycardia or hypotensive patients
    - Fentanyl 25 mcg/hr or meperidine 50 – 100 mg IM/IV
- Second line: dexmedetomidine + opioids
- Third line: deep sedation with propofol
- Fourth line: neuromuscular blockade
  - This protocol prefers vecuronium (0.15mg/kg IV bolus)

Source: Choi HA, et al. Neurocrit Care. 2011; 14(3):389-94.

Propofol vs. Midazolam

Outcome	Midazolam	Propofol	P value
Delayed awakening, n (%)	56 (29%)	5(6%)	<0.001
Ventilator free days at 28 days, n(IQR)	24 (22-26)	25 (22-26)	0.007
Pneumonia >48 hours post admission, n (%)	65 (20%)	28 (21%)	0.82
Duration of sedation, hours median (IQR)	34 (30-41)	40 (31 – 54)	0.0003
Renal replacement therapy, n(%)	151 (46%)	36 (27%)	<0.001

- Propofol/remifentanil (n=134) versus midazolam/fentanyl (n= 326) for sedation of patients during TTM following cardiac arrest
  - Retrospective study using prospectively collected data
  - Management protocol only differed in sedatives and neuromuscular blocker used
- Awakening: three consecutive RASS scores ≥ -2
- Delayed awakening: persistent unconsciousness ≥ 48 hours post sedative discontinuation

Source: Paul M, et al. Resuscitation. 2018; 128:204-210.

Propofol

- Studied in 2 women and 4 men on two different study visits with induced core hypothermia (to a targeted 34°C) on one of the two visits
- Blood was sampled from radial arterial catheter to determine propofol concentrations over 2 hours via HPLC
- Propofol concentrations were increased in hypothermic patients
  - Largely driven by a decreased intercompartmental clearance

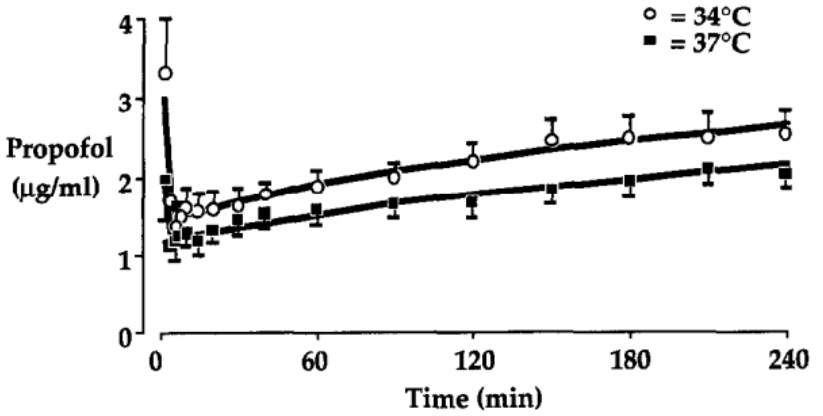


Figure 1. Actual propofol blood concentrations (μg/mL) were significantly more in hypothermic (34°C) volunteers than in normothermic (37°C) volunteers. Predicted concentrations from the final pharmacokinetic model are represented by the solid lines. Elapsed time zero indicates start of the propofol infusion. Error bars indicate SEM.

Source: Leslie K, et al. Anesthesia and Analgesia. 1995;80(5):1007-1014.

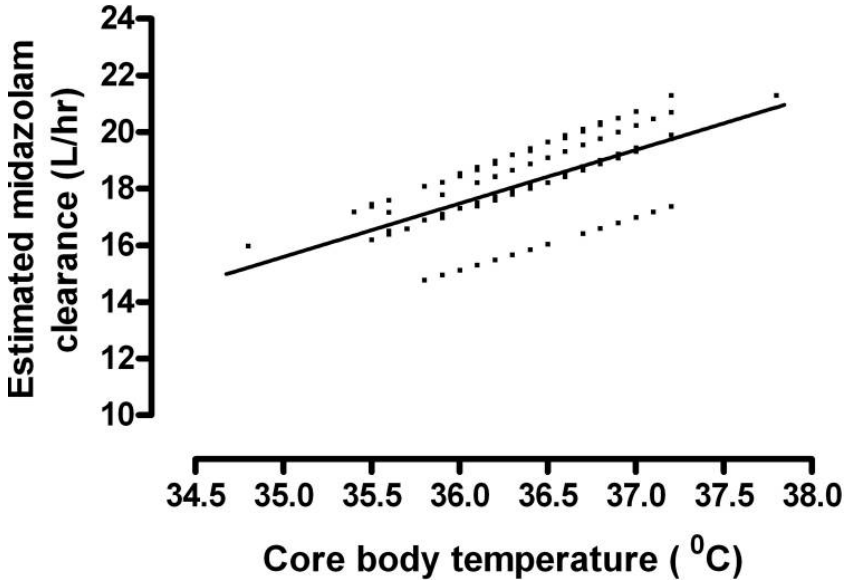
Propofol

- Propofol concentrations increased in hypothermic patients
- Anticipate decreases in the required doses to maintain sedation goals
- Largest differences observed in the first 5 minutes of drug administration
- Drug did not distribute as well in the hypothermic patients

Source: Leslie K, et al. Anesthesia and Analgesia. 1995;80(5):1007-1014.

Midazolam

- A dangerous kinetic recipe
  - Large volume of distribution
  - High hepatic extraction ratio
    - Active metabolite



- Hostler et al. modeled midazolam kinetics in 6 healthy subjects aged 19 – 39 with no known comorbidities infused with cold saline for 4 hours
  - Identified changes in midazolam clearance when hypothermia was induced
  - Predicted an 11% decrease in midazolam clearance for every 1°C decrease in core temperature from 35.5°C

Source: Hostler D, et al. Drug Metab Dispos. 2010; 38(5):781-788.

Fentanyl

- Commonly used in ICU settings to manage pain
  - Used in TTM to prevent shivering
- Extensively metabolized by CYP3A4
  - Well-stirred PK model predicts that decreased hepatic blood flow expected to cause a decrease in clearance, difficult to quantify changes
  - Bjelland et al. reported a 46% decrease in fentanyl clearance in 14 hypothermic patients matched to 8 normothermic controls
- Should be started at lower doses (25mcg/hr) to avoid overdosing & delayed awakening

Other TTM Considerations

- Cardiac output decreases
  - Initial rise in BP from vasoconstriction
  - Eventual decrease in output following cold diuresis
  - Oxygen demand and consumption also decreases
  - No effect on MAP
  - Heart rate slows
    - QTc prolongation is commonly observed (reports up to 670ms!)
    - Well documented safety of QTc prolongation during TTM
- Evidence supports the following hemodynamic parameters to improve neurologic outcomes:
  - MAP >65 mm Hg
  - CVP >15 mm Hg
  - permissive bradycardia (31 – 48 bpm)

Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

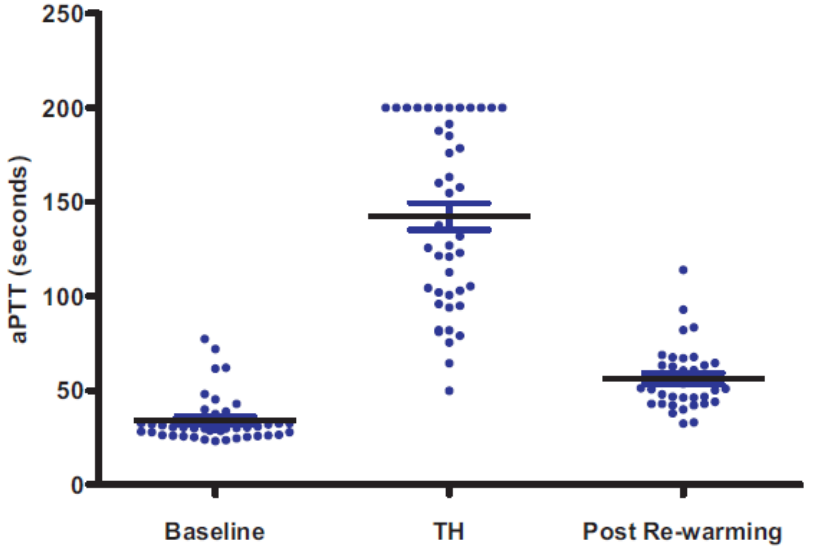
Vasopressor use in TTM

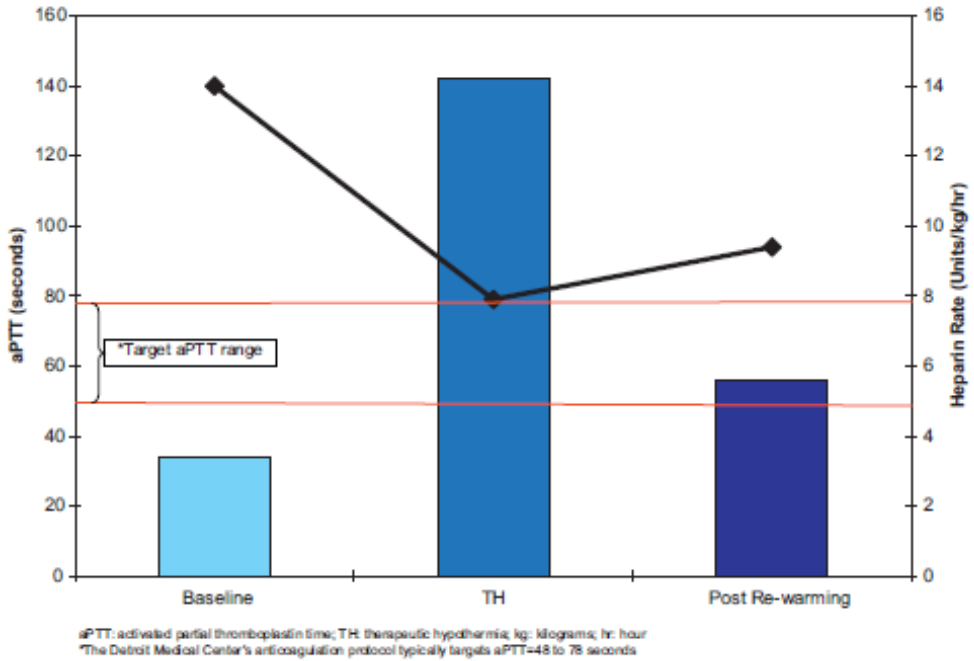
- 920 patients analyzed in multicenter study at 36 ICUs in 10 countries from the Target Temperature Management trial
  - ↑lactate, similar MAP, ↓HR observed in TTM group versus normothermic group
  - Lower MAPs were associated with increases in mortality
- Increased doses of vasopressors were observed in TTM group
  - Data regarding specific vasoactive agents used was not available
  - Higher doses of vasopressors was associated with increased mortality at 30 days, but difference was not statistically significant
- Vasoactive agents without chronotropic activity should be utilized to meet these goals (phenylephrine)
  - May avoid arrhythmia while maintaining MAP

Source: Bro-Jeppesen, et al. Critical Care Medicine. 2015; 43(2):318-327.

Bleeding Diathesis

- Hypothermia not recommended in actively bleeding patients
  - Relative contraindication
- Lower temperatures decrease activity of coagulation cascade
  - aPTT/PTT samples should be analyzed at 32 or 34 °C to reflect in vivo activity
- Bleeding is a enzymatic-dependent process effected by hypothermia
  - Elevated aPTTs are commonly observed





Sources: Wahby KA, et al. Resuscitation. 2014; 85(4):533-537.
Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Bleeding Diathesis

- Anticoagulation may be necessary depending on cause of cardiac arrest; ie: pulmonary embolism, myocardial infarction
  - Unfractionated heparin (UFH) preferred over low molecular weight heparins
  - UFH has a shorter half-life and is easily reversible with protamine
- Heparin has a saturable metabolism and clearance that is likely decreased in hypothermia
  - Wahby et al. found only 3/46 patients achieving goal aPTT following initial dosing of UFH
    - Dose was lower than standard dose for all 3 of these patients
    - Only 10/46 patients (22%) haf therapeutic aPTT at 24 hours
- Heparin rates expected to return to standard protocol ~24 hours after cessation of TTM

Sources: Wahby KA, et al. Resuscitation. 2014; 85(4):533-537.

Šunjić KM, et al. Critical Care Medicine. 2015; 43(10):2228-2238.

Bleeding Diathesis

- Antiplatelet agents are commonly given as part of ACS and PCI treatment algorithms
  - Clopidogrel is a prodrug requiring GI absorption and liver metabolism to become pharmacologically active
    - Both processes are decreased in TTM
    - Kaufmann et al. found a decrease in plasma concentration of clopidogrel and metabolites in TTM group versus normothermic group that were given 600mg as a loading dose for patients undergoing PCI
  - Aspirin is a highly protein bound drug that exhibited decreased effect (most pronounced at 72 hours) in a study conducted by Pruller et al.
    - Reduced GI absorption, accelerated platelet turnover in inflammatory states may explain decreased efficacy
- Patients may remain at significant risk for acute stent thrombosis due to decreased efficacy of antiplatelet therapies

Sources: Pruller F, et al. Ann Intensive Care. 2018;8:28.

Kaufmann J, et al. Resuscitation. 2016;102:63-69.

Electrolyte Disturbances

- Increase risk of arrhythmias if uncorrected
- Hypokalemia and hypomagnesemia are common complications of TTM that should be anticipated
  - Possibly due to increased renal excretion
- Beaulieu et al. found that 98% of patient experienced hypokalemia during TTM
  - Median of 45 mEq of potassium given each day
  - 30 % of patients remained hypokalemic despite repletion
  - 2% of patients became hyperkalemic
- Standard potassium repletion strategies may not be effective in TTM

Source: Beaulieu C, et al. Therapeutic Hypothermia and Temperature Management. 2018. https://www.liebertpub.com/doi/10.1089/ther.2018.0037. Accessed: Feb 17th, 2020.

Electrolyte Disturbances

- Some studies have observed hypokalemia is especially pronounced during induction phase
  - Effect is not consistent across all studies
- Hypomagnesemia may potentiate hypokalemia or prevent successful repletion
- Hypomagnesemia observed less frequently than hypokalemia
  - IV magnesium typically given as part of TTM protocol

Source: Beaulieu C, et al. Therapeutic Hypothermia and Temperature Management. 2018. https://www.liebertpub.com/doi/10.1089/ther.2018.0037. Accessed: Feb 17th, 2020.

Summary

- Use of IV administration bypasses GI absorption issues
  - GI absorption is decreased
- Distribution will likely be decreased
- Metabolism will likely be decreased
- Drugs with predictable kinetics are preferred
  - No hepatic clearance or metabolites
  - Low - intermediate volume of distribution
  - Short acting
- TOF, aPTT, PTT monitoring will be altered and potentially unreliable throughout TTM

Assessment question #3:

- Which of the following medications would likely require a dosage adjustment during TTM?
  - A: Fentanyl
  - B: Rosuvastatin
  - C: Famotidine
  - D: Trimethoprim/sulfamethoxazole

Assessment response #3:

- Which of the following medications would likely require a dosage adjustment during TTM?
  - A: Fentanyl
  - B: Rosuvastatin
  - C: Famotidine
  - D: Trimethoprim/sulfamethoxazole

References

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Thank you!!

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