

Therapeutic Hypothermia Post Cardiac Arrest

WWW.RN.ORG®

Reviewed December, 2020 Expires December, 2022
Provider Information and Specifics available on our Website
Unauthorized Distribution Prohibited

©2020 RN.ORG®, S.A., RN.ORG®, LLC

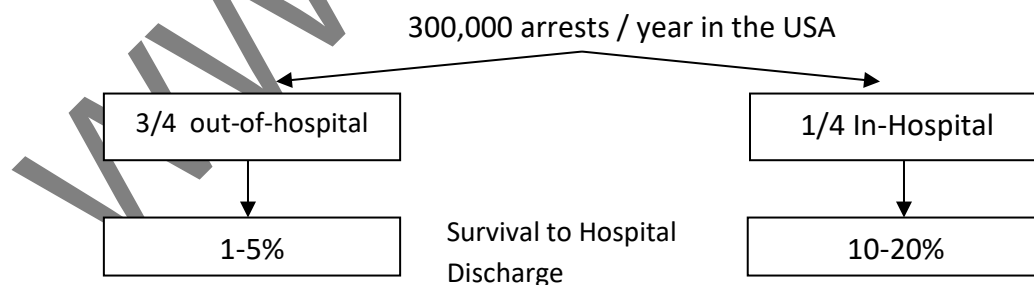
By Cynthia R. Bascara, APN, MSN, CCRN

Objectives:

At the end of the learning session, the participant will be able to:

1. Discuss definition of Therapeutic Hypothermia and its benefits after cardiac arrest
2. State the inclusion and exclusion criteria for Therapeutic Hypothermia
3. State the different phases of the Therapeutic Hypothermia and the collaborative activities in each phase.
4. Discuss the common adverse events of Therapeutic Hypothermia and the practical approaches for these adverse events
5. State some pediatric considerations related to Therapeutic Hypothermia
6. State the newest evidence on stroke and Therapeutic Hypothermia
7. State the newest research studies on traumatic brain injury and Therapeutic Hypothermia.

Cardiac Arrest: Epidemiology



Becker et al, 1993

Peberdy et al, 2003

What Happens After Cardiac Arrest?

After cardiac arrest, health care providers and patients loved ones feel excited about patients survival. Unfortunately, there's usually cerebral ischemia and hypoxia that may occur after the cardiac arrest. Why do these changes happen? There is what is called reperfusion injury. Reperfusion injury is the damage observed after restoration of blood flow to ischemic tissues leading to reactive oxygen species, inflammatory cascades, and mitochondrial dysfunction. Reactive oxygen species are chemically reactive molecules containing oxygen. When reactive oxygen species are produced during stress, they may damage cell structure. Mitochondrial dysfunction is the impairment of ability of mitochondria (parts of cell) to convert nutrient into energy due to reactive oxygen species causing oxidative damage. These pathophysiological changes may lead to vascular dysfunction and hypotension. Apoptosis or organ dysfunction may follow which leads to cerebral edema. Neurologic Injury is the most common cause of death in patients with out-of-hospital cardiac arrest. Neurological injury contributes to the mortality of in-patients post cardiac arrest in addition to multiple organ failure.

Definition

Therapeutic Hypothermia is the process of cooling the body by reducing body temperature to 32°C to 34°C within 6-8 hours after return of spontaneous circulation (pulse) and continuing to cool the body for 12 to 24 hours. Therapeutic Hypothermia is also called Induced Hypothermia.

Therapeutic Hypothermia hypothesized benefits include:

- Decrease production of excitotoxins and free radicals; suppression of apoptosis; and other inflammatory reactions reducing cerebral edema
- Decrease in metabolic activity leading to a reduction in oxygen consumption therefore decreasing ongoing cerebral ischemia

American Heart Association (AHA) Guidelines supporting hypothermia was published on November, 2005 stated:

- Comatose out-of-hospital VF: Class IIa recommendation
- In-hospital arrest, other rhythms: Class IIb recommendation

Cochrane for Clinicians: Putting Evidence into Practice stated:

- Compared with standard of care, therapeutic hypothermia with conventional cooling methods improve the rate of survival to hospital discharge and neurological outcomes in patients successfully resuscitated after cardiac arrest (Strength of Recommendation=A)

Inclusion Criteria for Therapeutic Hypothermia

- post cardiac arrest

- with return of spontaneous circulation (ROSC)
- ROSC is within past six hours
- persistent coma (less than 10 on the Glasgow Coma Scale.)

Exclusion Criteria for Therapeutic Hypothermia

- Prolonged resuscitation (greater than 90 minutes of arrest time)
- Improving neurological status
- Preexisting Coma (stroke, sepsis, overdose, etc.)
- Intracranial hemorrhage
- Respiratory insufficiency (unable to maintain pulse oximetry of greater than 85%)
- Active bleeding
- Known Allow Natural Death (AND) or Do Not Resuscitate (DNR) or Do Not Intubate (DNI)

Relative Exclusion for Therapeutic Hypothermia

- Patients under 18 years old. Depending on the hospital policy or case by case basis, patients may be transferred to another facility providing higher level of care.
- Major surgery within last 3 days. Laparoscopic surgeries are not exclusions which means patients should receive the intervention if meeting criteria.
- Pregnancy. If patient is pregnant, emergency consult for maternal-fetal medicine is necessary.

Therapeutic Hypothermia: Not a New Concept

- 450 BC-Hippocrates packed injured patients in snow with apparent improved survival
- 1800 century- Snow was used to attempt to revive patients by Russians
- 1959 – Study on therapeutic hypothermia in cardiac arrest patients was published, with mixed results. Some of the patients were cooled at very low temperature and not on controlled settings.
- 1990's- Peter Safar pioneered concept of induced hypothermia as treatment of cardiac arrest with extensive animal modeling . After several decades of animal research, then the hypothermia landmark studies or trials came.

Hypothermia Landmark Studies						
Trial	Multicenter?	Main site	Patient rhythm	Patient location	Method	N
HACA, 2002	Yes	Austria	VF	Out-of-Hospital (OOH)	Cool air	275
Bernard, 2002	Yes	Australia	VF	Out-of-hospital	Ice packs	77
Idrissi, 2001	No	Belgium	PEA/asystole	Out-of-hospital	Helmet	30

Hypothermia Trials Outcomes: Alive at Hospital Discharge with Favorable Neurological Recovery				
Trial	Hypothermia (%)	Normothermia (%)	RR (95% CI)	P value
HACA, 2002	72/136 (53%)	50/137 (36%)	1.51 (1.14-1.89)	0.006
Bernard, 2002	21/43 (49%)	9/34 (26%)	1.75 (0.99-2.43)	0.052
Idrissi, 2001	4/16 (25%)	1/17 (6%)	4.25 (0.70-53.83)	0.16

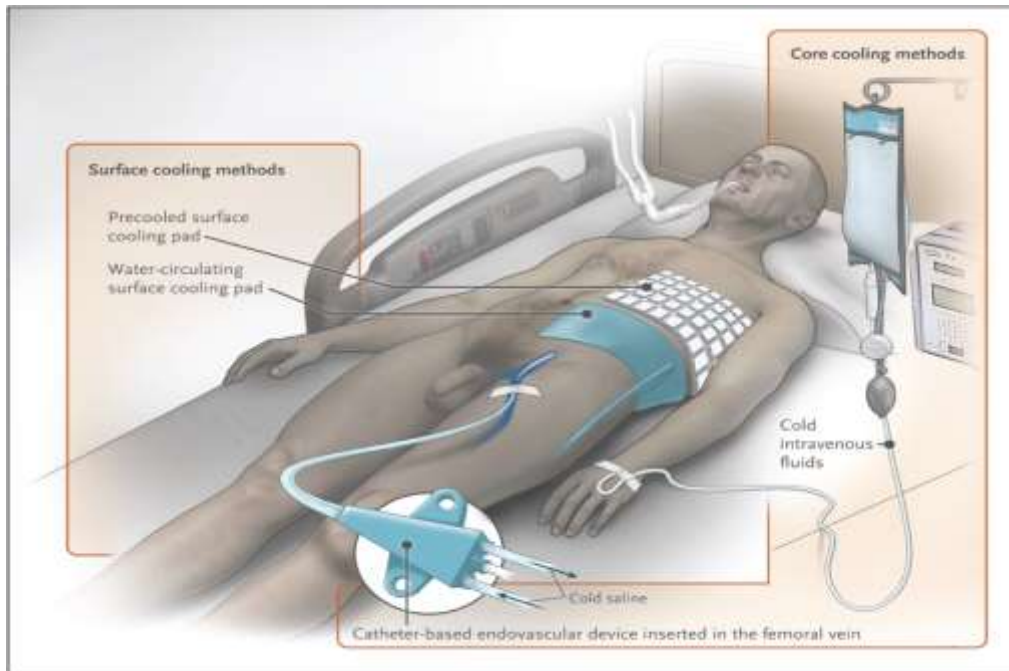
Hypothermia Trial Outcomes: Alive at 6 Months with Favorable Neurological Recovery				
Trial	Hypothermia (%)	Normothermia (%)	RR (95% CI)	P value
HACA, 2002	71/136 (52%)	50/137 (36%)	1.44 (1.11-1.76)	0.009

Adverse Events: HACA trial		
Adverse Events	Normothermia (%)	Hypothermia (%)
Bleeding	19%	26%
Arrhythmia	32%	36%
Pneumonia	29%	37%
Sepsis	7%	13%
Pancreatitis	2%	1%
Renal Failure	10%	10%
Pressure sores	0%	0%

Therapeutic Hypothermia Techniques

- External Methods
 - Cooling blankets
 - Ice packs
 - Wet towels and fanning
 - Cooling helmet
- Internal Methods
 - IV infusion of cold NS (4°C)
 - Peritoneal and pleural lavage
 - Extracorporeal method
 - Intravascular exchange device

Some Examples of Therapeutic Hypothermia Techniques







Therapeutic Hypothermia (“Code Chill”) Phases

- Initiation or induction or cooling (Goal temp: 33°C *within 4 hours* from initiation of protocol)
- Maintenance (Goal temp 33°C *for 24 hours*)
- Re-warming (Goal temp 36°C *within 24 hours*)
- Post-treatment (Goal temp 37°C to 38°C *48 hours after end of rewarming*)

Induction Phase Collaborative Activities

Goal: Achieve target temperature of 33°C (range 32°-34°C) within 4 hours and maintain for 24 hours

- On-going communication with family and support is essential during all phases and whole trajectory of patient stay
- Get pastoral care involved from the beginning
- Admit to ICU
- Stat Consults: Intensivist, Cardiologist, Neurologist
- Insert arterial line (needed for intensive blood pressure monitoring and frequent blood draws)
- Secure airway with endotracheal tube and place on ventilator
- Insert central venous access (internal jugular or subclavian site)
- Stat PCXR then daily for 72 hours
- Stat head CT without contrast (if ST elevated myocardial infarction (STEMI), may do head CT after going to cardiac catheterization lab before going to ICU to prevent delay in door-to-balloon time)

- Stat serum pregnancy (childbearing age)
- CBC with differential, PT/PTT every 8 hours for 48 hours
- Comprehensive Metabolic Profile , Phosphorus, Magnesium, Calcium, and lactate every 8 hours for 48 hours. Hypokalemia (also hypophosphotemia/hypomagnesemia/hypocalcemia) usually occurs during cooling period of Therapeutic Hypothermia due to the shift of potassium into the cells during cooling. This shift reverses during rewarming causing hyperkalemia.
- CPK and troponin every 8 hours for 3 times
- ABG stat then every 8 hours for 48 hours, temperature corrected
- Check blood sugar every 2 hours for 48 hours (consider insulin drip if blood sugar > 150 mg/dl for 2 times)
- Blood cultures, 2 sets 12 hours after initiation of protocol
- Continuous cardiac monitoring
- VS, CVP, water temperature, Bedside Shivering Assessment Scale (BSAS) monitoring every 15minutes for 1hour, then every 30minutes for 2 hours, then every 1 hour for 4 hours then ICU protocol
- Urinary catheter or esophageal temperature probe (if urinary output \leq 10ml/hr, use rectal probe). Urinary catheter or esophageal temperature probe is more accurate method of monitoring body's core temperature than the rectal probe.
- Gastric tube to low intermittent suction
- I & O every hour
- HOB 30° unless contraindicated
- Neurological checks every 2 hours
- Skin assessment and repositioning every 2 hours
- Neurological evaluation: baseline, during and post treatment
- Sedation and analgesia; neuromuscular blocker (NMB) if needed
- Shivering agent before cooling; titrate per BSAS
- Avoid NMB for shivering if patient's initial temp < 34°C before cooling
- Infuse 2 L (or 30ml/kg) of cold NSS over 30 minutes (may infuse longer time period if known dialysis patient or patient known with low ejection fraction)

- Ice packs to groin, axillae, behind neck
- Initiate external cooling using cooling wraps (or per protocol)

Maintenance Phase Collaborative Activities

Goal: Maintain target temperature of 33°C for 24 hours

- Continue sedation, analgesia
- Continue shivering agent until rewarming phase when temperature reaches 36°C
- Maintain patient NPO until the end of rewarming phase
- Notify Critical Care physician if:
 - Target temperature not obtained within 4 hrs
 - Urine output < 0.5 ml/kg/hr
 - MAP < 65 mmHg
 - Heart rate < 50/min or > 110/min
 - SpO₂ < 92% by temperature corrected ABG
 - Water temperature drops < 20°C or drops by more than 10° after target temperature obtained
 - BSAS of 2-3. Goal is 0-1.
 - Cardiac arrhythmias
 - abnormal laboratory test results

Rewarming Phase Collaborative Activities

Goal: Achieve temperature of 36°C within 24 hours after the end of maintenance phase

- Discontinue all potassium containing fluids prior to rewarming but always correct hypokalemia and other electrolytes . Potassium shift to extracellular compartment during rewarming so there is a tendency for hyperkalemia.
- Volume load aggressively with NS to compensate for reductions in blood pressure/ScvO₂/CVP. As cooler blood shifts from core to extremities, there is decreased venous return and cardiac output causing hypotension.

- No neuroprognostication should occur for at least 72 hours after ROSC or longer because all systems “slowed down” during cooling.
- VS, CVP and BSAS q 15min for 1hour, then every 30minutes for 2 hours, then every hour for 4 hours, then ICU protocol
- Remove cooling pads when temperature reaches 36°C.
- Maintain shivering agent until temperature reaches 36°C.

Post treatment Phase Collaborative Activities

Goal: Maintain temperature between 37°-38°C for 48 hours after end of rewarming

- Monitor for rebound hyperthermia. Use cooling unit and/or antipyretic if needed.
- Obtain orders to reduce sedation/analgesic/NMBA (if ordered) as appropriate.
- Consider nutrition.
- Continue to monitor for hemodynamic instability and neurological changes.
- Initiate Physical Therapy.
- After extubation, Occupational Therapy, swallowing evaluation, cognitive evaluations should be performed when appropriate.

Sedation and Analgesia

Sedation Goals: ventilator synchrony; Modified Ramsey Scale (MRS): 3; Bispectral Index Scale (BIS): 50

Some of the commonly used agents for sedation:

- Propofol (Deprivan)
- Midazolam (Versed)

Analgesia Goals: non-verbal/behaviorial and physiological pain parameters

Some of the commonly used agents for analgesia:

- Morphine
- Fentanyl

Shivering Agent from Induction to Rewarming Phases

Bedside Shivering Assessment Scale Goal: Score 0-1

Some of the commonly used agents for shivering

- Demerol (use with caution with elderly patients or patients with history of renal insufficiency or seizures)
- Others: Fentanyl; Magnesium; propofol, acetaminophen, buspirone, surface warming or skin counter-warming measures (e.g. Bair-hugger) and/or neuromuscular blocking agent (NMBA). Fentanyl or propofol drip may be titrated to control shivering if tolerated. Magnesium infusion is usually between 1-2 Gms/hour and titrated to maintain serum level of 3-4 mg/dl. Acetaminophen dose is 500 mg liquid/gastric tube every 6 hours. Buspirone is given at 30 mg/gastric tube every 8 hours.
- Neuromuscular blocking agents if above drugs are not effective to control shivering. Avoid if NMBA in patients with seizures. Intermittent dosing of NMBA is preferred to continuous drip because seizure activity can be masked with NMBA use. If seizure is detected, it can be treated right away. Avoid NMBA if patient's temperature is already < 34 °C before the intervention. Post cardiac arrest patients' temperature usually range between 35°C-35.5 °C to begin with. Most commonly used NMBA are Vecuronium and Cisatracurium (Nimbex)

NOTE: If continuous NMBA drip is used, continuous EEG or BIS monitoring is important since the use of Train-of-Four (TOF) peripheral nerve stimulator testing is challenging due to peripheral vasoconstriction or due to slowing of peripheral nerve conduction. If TOF is being used, the goal is 2/4.

Bedside Shivering Assessment Scale (BSAS)	
SCORE	DEFINITION
0	None: no shivering noted on palpation of the masseter muscle, neck, or chest walls
1	Mild: Shivering localized to the head, neck, and/or thorax only
2	Moderate: Shivering involves gross movement of the upper extremities
3	Severe: Shivering involves gross movements of upper and lower extremities

Seizure

Monitor closely during rewarming where seizures most likely to occur!

Most commonly used agents for seizures are:

- Phenytoin
- Keppra

Other Aspects of Care

- Treat acute coronary syndrome
 - ASA 300mg per rectum stat unless contraindicated
 - If STEMI or new LBBB and no prolonged arrest time, cardiology may perform early cath./PCI or thrombolysis
- Treat hypoglycemia-Insulin drip for blood sugar > 150 mg/dl twice
- Respiratory
 - If ALI/ARDS-use low stretch protocol
 - Goals: arterial pH: 7.30-7.45; FIO2 60%; wean O2 for SaO2 >92%-95%; PaCO2 40-45 mmHg; PaO2 65mmHg-80mmHg
- VTE prophylaxis
- PUD prophylaxis
- Cardiovascular support-vasoactive drugs and/or IABP if necessary

NOTE: If Therapeutic Hypothermia needs to be discontinued, rewarm the patient as per hospital procedure

Potential Laboratory Abnormalities after Cardiac Arrest

Leukocytosis of 10, 000-20,000 due to acute demargination of WBCs and inflammation

Lactic acidosis (lactate up to 15 mmol/L). Higher levels suggest ongoing intra-abdominal or muscle compartment ischemia. Lactate should clear over time after adequate perfusion.

Mild ↑ troponin (0-5 ng/ml)- due to CPR and defibrillation. Higher levels- suggest ACS

Physiologic/Pathophysiologic Effects of Hypothermia: Cardiovascular

Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Vasoconstriction (due to activation of sympathetic nervous system) 	<ul style="list-style-type: none"> • Use of sedatives, opiates, neuromuscular blocking agents (NMBAs)

<ul style="list-style-type: none"> • Shivering (due to activation of sympathetic nervous system) <ul style="list-style-type: none"> ➤ ↑ heat production ➤ ↑ O₂ consumption (VO₂) by 40-100% • Tachycardia (due to vasoconstriction; ↑ level of adrenaline and noradrenaline)→ bradycardia (due to vasodilation when pt. cool; ↓metabolism; also due to slowing of cardiac conduction) • QT interval prolongation- due to slowing of cardiac conduction (when patient is cold) • Ventricular arrhythmias-may be due to electrolyte disorder or myocardial ischemia • ↓ cardiac output (due to ↓HR) • ↑ SVR (due to vasoconstriction) • ↑ BP (initially)-due to vasoconstriction→↓BP (“cold diuresis”) • ↑CVP despite hypovolemia- due to venoconstriction; ↑SVR 	<ul style="list-style-type: none"> ➤ counteract these responses ➤ enhance cooling effectiveness ➤ Sedation increases peripheral blood flow → ↑ transfer of heat from core to periphery <ul style="list-style-type: none"> • Avoid NMBA's if temperature already < 34°C- may result in precipitous drop in core temp. • Note that elderly patients will cool more quickly than younger and obese patients • For bradycardia <ul style="list-style-type: none"> ➤ If MAP > 65 mmHg (or per protocol), observe unless symptomatic ➤ If MAP < 65 mmHg or unstable bradycardia, consider: <ul style="list-style-type: none"> ❑ Fluids until CVP goal per protocol (usually 12-15 mmHg) ❑ Pressors if persistent ↓ MAP and/or ↑CVP; clinical and radiologic signs of HF or ❑ ↑ set point to 34°C-35°C or ❑ Pacing instead of atropine because atropine is not effective in a “cold” heart ➤ Usually not treated unless symptomatic- follow MAP, lactate, SCVO₂, CVP trends ➤ Keep temp > 30°C <ul style="list-style-type: none"> ❑ < 30°C: ↑risk for arrhythmias ❑ < 28°C: ↑risk for Vfib • Avoid rewarming with arrhythmias unless absolutely necessary-may exacerbate arrhythmias • ACLS for Vfib or life threatening arrhythmias • Initiation: 2 L of cold NSS x 30 min.(for ↓ejection fraction (EF) and known dialysis patient, may infuse slower) • CVP goal 12 mmHg-15 mmHg (or as per protocol) • If CVP <15 mmHg and MAP< 65mmHg, fluid bolus (NSS)
---	--

- Conduction system: J wave (Osborn wave-notch on downstroke of QRS complex)- due to delayed closing of transient outward potassium current channel of the heart's epicardium



- Other EKG changes: widened QRS; ST elevation or depression; T-wave inversion- due to ischemia or acidosis

Note: mild ↑ troponin (1-5 ng/ml)-due to cardiac arrest, CPR and defibrillation and not from hypothermia. Rising and higher levels may suggest acute coronary artery occlusion

- If MAP still <65 mmHg but with clinical or radiologic signs of heart failure, consider vasopressors
- Look at global picture of perfusion (check labs and patient) and fluid balance!
- Volume load aggressively using CVP goal especially. within 6-8 hours. prior to rewarming
- Vigilance for hypovolemia in face of ↑ CVP related to venoconstriction- may conceal hypovolemia especially during rewarming
- J wave just confirms patient is hypothermic. No intervention needed for J wave
- Treat acute coronary syndrome accordingly. Patient with STEMI and new LBB may need emergent cardiac cath and percutaneous coronary intervention while Therapeutic Hypothermia on. These procedures can be done simultaneously.
- Handle hypothermic patient gently to prevent stimulation of an irritable myocardium which may lead to ventricular arrhythmias
- Maintain horizontal position to avoid aggravating hypotension and prevent orthostasis (may elevate HOB 30° and turn q 2 hours)

Physiologic/Pathophysiologic Effects of Hypothermia (Central Nervous System)

Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Seizures- due to hypoxia or anoxia during cardiac arrest <p>Note:</p> <ul style="list-style-type: none"> ➤ Seizures may be concealed by use of continuous NMBAs ➤ Seizures may likely to occur during rewarming ➤ Seizures occur in up to 40% of cardiac arrest patients; in about 44% receiving Therapeutic Hypothermia 	<ul style="list-style-type: none"> • Avoid use of NMBAs if patient exhibiting seizures • If decision to start Therapeutic Hypothermia is not clear and GCS was <10 but improving, follow improvements for 1-2 hours • EEG is the most reliable way to detect seizures • No neuro prognostication while patient is cold; wait at least 72 hours after ROSC. • Gradual rewarming to reduce seizure and other adverse events

Physiologic/Pathophysiologic Effects of Hypothermia (Pulmonary)

Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • ↓ O₂ delivery-due to shift of the oxyhemoglobin curve to the left • ↓ O₂ consumption and ↓ CO₂ production-due to ↓ metabolic rate • Reduction in airway protective mechanism- due to impairment of ciliary function predisposing patient for aspiration and pneumonia • Bronchospasm and bronchorrhea- not clinically significant 	<ul style="list-style-type: none"> • Adjust ventilator settings using temperature-corrected ABGs • Maintain PaCO₂ no lower than 40-45 mmHg (or end-tidal CO₂ 35-40 mmHg)- prevent hypocapnia-induced cerebral vasoconstriction • HOB 30° • Ventilator bundle • Oral care • Standard precautions • Hold nutrition until end of rewarming <p>Note: When a patient's core temp is 33°C, the patient's actual PaCO₂ may be 6-7 mmHg lower than the value reported by the blood gas machine. However there is no evidence whether it is better to use corrected or uncorrected values to adjust ventilation.</p>

Physiologic/Pathophysiologic Effects of Hypothermia (Hematologic)

Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Coagulopathy or bleeding-due to ↓ number and function of platelets • PT/PTT may be prolonged- clotting enzymes operate slowly • Pneumonia-due to impaired leukocyte migration/function; macrophage function and hyperglycemia which ↑ risk for infection • Risk for sepsis-due to ↓ number and function of WBCs 	<ul style="list-style-type: none"> • If no bleeding, leave alone! • If bleeding present, treat coagulopathy with platelets and FFP • If TH has begun, ↑ set point to 35°C as platelets and coagulation effects reverse at this temp. • Monitor CBC diff, lactate, CXR • Inspect lines • Blood cultures x2 in 12 hours after protocol initiation • Consider prophylactic antibiotic • Monitor water temp during cooling; if water temp drops <20°C or >10°C drop from previous one (cooling machine is trying to counteract patient's temperature spike; there is ↑ heat production and ↑VO₂; suspect fever), consider: <ul style="list-style-type: none"> ➤ cultures to rule out source ➤ Broad-spectrum antibiotics ➤ Infectious Disease consult ➤ Follow up MAP, CBC with differential, lactate, SCVO₂ trends <p>Note: Some of the pneumonia post cardiac arrest may actually be chemical or acid-induced pneumonitis, since aspiration of the gastric fluid is almost constant after cardiac arrest. Unfortunately, procalcitonin level is elevated after cardiac arrest.</p>

Physiologic/Pathophysiologic Effects of Hypothermia (Metabolic)

Effects/Rationale	Practical Approaches

<ul style="list-style-type: none"> • Hypokalemia/hypophostemia (also hypomagnesemia, hypocalcemia)-due to shift into the cells during cooling. This shift reverses during rewarming, causing hyperkalemia. <p>Note: Hyperkalemia during rewarming may be aggravated by rapid rewarming</p> <ul style="list-style-type: none"> • Hyperglycemia- due to <ul style="list-style-type: none"> ↓ insulin secretion and sensitivity • ↓ ph- due to increased levels of lactic acid, glycerol, free fatty acids and ketonic acids • ↑ drug level effects-due to <ul style="list-style-type: none"> ↓ hepatic clearance due to slow metabolism by 30-40% <p>Note: Magnesium should be corrected whenever it is low because of mageneium role in mitigating neurological injuries.</p> <ul style="list-style-type: none"> • Intracellular free magnesium in brain declines by up to 60% following moderate traumatic injury in rats • Magnesium also may play a role in the prevention of reperfusion injury and reduces the role the loss of cortical cells. • Loss of magnesium is associated with vasoconstriction of cerebral and coronary arteries. <p>Serum magnesium levels do not always accurately reflect magnesium status and so should be maintained in the high or high-normal levels in all patients with neurological injury.</p>	<ul style="list-style-type: none"> • Monitor lytes during protocol • NSS preferred than RL if hyperkalemic or with hepatic insufficiency • Switch RL to NSS prior to rewarming to avoid rebound hyperkalemia • Disc. All K+ containing fluids before rewarming (abt. 6-8 hours) but always correct electrolytes abnormality (keep K+ on low normal before and during rewarming) • Gradual rewarming better (0.2°C-0.5 °C per hour increase of temp) • Consider insulin drip if blood sugar > 150mg/dl (x2) • Avoid drop in blood sugar < 90 mg/dl • Watch closely for drug accumulations
---	--

Physiologic/Pathophysiologic Effects of Hypothermia (Gastro Intestinal)	
Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Ileus-bowel motility suppressed • Gastric stress ulcer • Hepatic dysfunction-↑LFTs • Pancreatic dysfunction- <ul style="list-style-type: none"> ↑ amylase, but no clinical pancreatitis 	<ul style="list-style-type: none"> • Hold off on feeding • PUD prophylaxis • Monitor LFTs/amylase but no need for work-up unless clinical finding or progressive or persistent after rewarming

Physiologic/Pathophysiologic Effects of Hypothermia (Renal)	
Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Cold-diuresis-due to <ul style="list-style-type: none"> ➢ Decrease in reabsorption of solute in the ascending limb loop of Henle ➢ Resistance to the action of vasopressin or ADH 	<ul style="list-style-type: none"> • Watch for and treat volume depletion during cooling • During rewarming, hypovolemia may manifest as hypotension/shock-volume load (w/o K+) pre and during rewarming unless presence of HF • Follow Mg, phos, K+ and Ca closely during cooling and rewarming <ul style="list-style-type: none"> ➢ Replace lytes if low ➢ If K+ high, treat before rewarming including hemodialysis patients

Physiologic/Pathophysiologic Effects of Hypothermia (Musculoskeletal)	
Effects/Rationale	Practical Approaches
<ul style="list-style-type: none"> • Shivering- raises body temp; \uparrow VO_2 (40-100%), \uparrow work of breathing (WOB), \uparrow HR, \uparrow MVO_2 • Risk for skin breakdown due to moisture from cooling wrap 	<ul style="list-style-type: none"> • Extremely important to prevent and treat shivering with sedation or NMBs if needed • Watch skin under the wraps for breakdown and signs of infection • Reposition gently q 2 hours

Hypothermia Registry

Background: The Hypothermia Registry was founded to monitor outcome, performance and complications of Therapeutic Hypothermia. Data on out-of-hospital cardiac arrest (OHCA) patients admitted to intensive care for Therapeutic Hypothermia were registered. Hospital survival and long-term outcome (6–12 months) were documented using the Cerebral Performance Category (CPC) scale, CPC 1–2 representing a good outcome and 3–5 a bad outcome.

Results: From October 2004 to October 2008, 986 TH-treated OHCA patients of all causes were included in the registry. Long-term outcome was reported in 975 patients. The median time from arrest to initiation of TH was 90 min (interquartile range, 60–165 min) and time to achieving the target temperature ($\leq 34^{\circ}\text{C}$) was 260 min (178–400 min). Half of the patients underwent coronary angiography and one-third underwent percutaneous coronary intervention (PCI). Higher age, longer time to return of spontaneous circulation, lower Glasgow Coma Scale at admission, unwitnessed arrest and initial rhythm asystole were all predictors of bad outcome, whereas time to initiation of TH and time to reach the goal temperature had no significant association. Bleeding requiring transfusion occurred in 4% of patients, with a significantly higher risk if angiography/PCI was performed (2.8% vs. 6.2% $P=0.02$).

Conclusions: Half of the patients survived, with >90% having a good neurological function at long-term follow-up. Factors related to the timing of TH had no apparent association to outcome. The incidence of adverse events was acceptable but the risk of bleeding was increased if angiography/PCI was performed.

Do we stop active cooling?

There are many occasions when clinicians are tempted to discontinue Therapeutic Hypothermia protocol when adverse events occur. Only when patients remain symptomatic despite practical approaches discussed above that Therapeutic Hypothermia should be discontinued. Only if the risks outweigh the benefits that the intervention should be discontinued. To discontinue active cooling, do not turn off cooling unit or cooling method but rewarm the patient to temperature $> 35^{\circ}\text{C}$ as per hospital protocol.

Monitoring the Nervous System

Continuous assessment of nervous system is extremely important. Pre intervention, nervous system monitoring is necessary to determine criteria eligibility and to assess for primary neurological catastrophe. During the Therapeutic Hypothermia protocol, nervous system assessment is used to detect ongoing (secondary) neurological injury since cardiac arrest patients are prone to seizures. Post Therapeutic Hypothermia protocol, it is used to determine prognosis.

Upon Discharge

Care of the patient who had the Therapeutic Hypothermia post cardiac arrest does not end at the post treatment phase. The cause for the cardiac arrest must be completely explored. Some cardiac arrest survivors who received Therapeutic Hypothermia stated that while they had physical and cognitive

recovery from the cardiac arrest and Therapeutic Hypothermia, few things are “still not the same” even though they may look “normal” and able to resume work and social function. These patients stated that cognitive rehabilitation helped them regain their full cognitive function. Some patients also stated that sometimes they feel “weird” that they were almost dead and now they’re back to society.

Some recommended activities that may further help patients after discharge:

- Consider
 - Electrophysio Studies (EPS) Consult if appropriate
 - Psychologist/Psychiatrist follow up
 - Support Group referral
- Glasgow Coma Scale for neurological assessment (before, end of rewarming, during hospitalization, and prior to discharge)
- CPC (Cerebral Performance Category) may be used for neurological assessment
- 6 month follow-up is essential to determine neurological outcome

Glasgow Coma Scale

Eye Opening (E)	Verbal Response (V)	Best Motor Response (M)
-----------------	---------------------	-------------------------

<p>4= Spontaneous-eyes open without verbal or noxious stimuli 3= To speech-eyes open with verbal stimuli but not necessarily to command 2= To pain-eyes open with various forms of noxious stimuli 1= None-no eye opening with any type of stimulation</p>	<p>5= Oriented-aware of person, place, time, reason for hospitalization and personal data 4= Confused-answers not appropriate to question but correct use of language 3= Inappropriate words-disorganized, random speech, no sustained conversation 2=Incomprehensible sounds-moans, groans, mumbles incomprehensibly 1=None-no verbalization, even to noxious stimuli</p>	<p>6= Obeys command-performs simple tasks on command and able to repeat task on command 5= Localizes pain-organized attempt to localize and remove painful stimuli 4=Withdraws from pain-withdraws extremity from source of painful stimuli 3= Abnormal flexion-decorticate posturing that occurs spontaneously or in response to noxious stimuli 2= Extension-decerebrate posturing that occurs spontaneously or in response to noxious stimuli 1= None- no response to noxious stimuli</p>
---	--	---

GCS= E + V + M

Barker, E. (2008)

Cerebral Performance Category

<p>CPC 1</p>	<p>A return to normal cerebral function and normal living</p>
--------------	---

CPC 2	Cerebral disability but sufficient function for independent activities of daily living
CPC 3	Severe disability, limited cognition, inability to carry out independent existence
CPC 4	Coma
CPC 5	Brain death

Jennett, B. & Bond, M. (1975)

Recommended Quality Improvement Activities

Continuous process and quality improvement activities must be in effect to improve patient outcomes and to have consistency and efficiency in the delivery of care and implementation of the Therapeutic Hypothermia protocol. Multidisciplinary approach with direct care nurses involvement and engagement and reviews of research literatures play important roles to the successful Therapeutic Hypothermia implementation.

- Regular Therapeutic Hypothermia Task Force meetings
- Emergency Therapeutic Hypothermia meeting as needed (small group)
- Therapeutic Hypothermia case reviews
- Therapeutic Hypothermia data presentations
- Revision of Therapeutic Hypothermia protocol and order set as needed
- On-going education
- Hands-on trainings

Case Study 1

A 33 year old male arrived in ED without palpable BP, tachycardic, cyanotic, SPO₂ was 64%. He had fractured leg 10 days ago which was immobilized with splint. One day before admission, he had flown while returning from business. Within a minute of ED arrival, he got intubated and was given fluids. He had a pulseless arrest for 6 minutes with ROSC after CPR. Pulmonary embolism was suspected and was given systemic TPA. He remained hypotensive while on vasopressors. ABG: pH 6.97; PaCO₂ 70; PaO₂ 72.

Wife arrived and stated that patient had DVT in lower extremity and was treated with warfarin 3 years ago for short time. According to the wife, two of patient's family members had history of hypercoagulable protein abnormalities.

Patient was taken to Interventional Radiology department and had pulmonary angiogram. A large ilio-femoral thrombosis and large bilateral pulmonary embolism were found. Pulse-spray TPA was given directly to pulmonary artery. Patient had another asystolic arrest lasting for 14 minutes. Upon ROSC, patient remained unresponsive with extensor posturing.

Therapeutic Hypothermia (33°C) was implemented 60 minutes after ROSC and goal temperature was achieved within 4 hours. Temperature of 33°C was maintained for 18 hours (another protocol). Rewarming occurred during the 24 hour. Patient had recovery complications such as pulmonary infarcts, prolonged mechanical ventilation, mediastinal and rectus sheath hematomas requiring blood transfusions.

Three weeks later, patient was discharged with no neurological impairment.

Six weeks later, patient returned to work full time with no apparent neurological deficits.

Case Study 2

A 60 year old man in good health had sudden shortness of breath and chest pain at the Newark airport-collapsed before boarding airplane. Bystander CPR was initiated. AED was placed and defibrillation was performed. Patient was transported to ED where a recurrent arrest occurred. Presenting cardiac rhythm was VF on arrival. Patient was defibrillated twice and intubated in ED. ROSC noted. ECG was done and showed STEMI.

Therapeutic Hypothermia was initiated. Patient was immediately transported to cardiac cath lab. Percutaneous coronary intervention (PCI) was performed with stent to LAD.

Two months later, patient had intact neurologic function. Echocardiogram revealed left ventricular ejection fraction (LVEF) to be 55%. Threadmill stress test showed no ischemia in 9 minutes.

Summary Points

- Randomized trials strongly support hypothermia use for OOH VF arrest
- Benefit doesn't seem dependent on method of cooling

- Evidence-based medicine supports basic protocol of 32°C-34°C for 12-24 hours
- Adverse effects of cooling are mild from clinical trials and institutional experience
- Watch out for occult hypovolemia (during rewarming particularly)
- Watch out for electrolyte depletion when cooling but hyperkalemia when rewarming
- Cardiac arrest is a morbid neurological disease
- Therapeutic Hypothermia is an effective strategy to reduce secondary injury and to improve outcome
- Nervous system monitoring should occur before, during and after Therapeutic Hypothermia
- There are many tools for neurological monitoring-clinical exam and EEG have most utility
- Determination of prognosis should occur at least 72 hours after ROSC or longer.
- Therapeutic Hypothermia is not a complete science yet because there are still many research studies going on to answer some of its components such as duration of maintenance or rewarming phase, method of cooling, scientific approaches to adverse events, etc.
- Adverse events largely depend on the degree of hypothermia
- Hypothermia adverse events depend on patient's age, underlying disease, co-morbidity, etc.
- Rigorous hemodynamic monitoring, assessment, surveillance of labs and medications may help prevent or suppress adverse events

Post-Resuscitation Bundle

Goal of post resuscitation bundle: systemic delivery of post-resuscitation care

Elements of post-resuscitation bundle

- Therapeutic hypothermia (if appropriate)
- Early percutaneous coronary intervention (if candidate)
- Hemodynamic optimization
- Other adjuncts to intensive care

Therapeutic Hypothermia and Children

Therapeutic Hypothermia has deep roots in the area of pediatric resuscitation. Early case reports of dramatic recovery from prolonged cardiac arrest and resuscitation after cold-water drowning represented some of the groundwork for the ultimate clinical application of this important therapy. In that era, Rye syndrome was also a relatively common condition in pediatric critical care and the response of these patients to therapies directed at intracranial hypertension, such as hypothermia, could be dramatic with normal recovery despite prolonged deep coma and even fixed and dilated pupils.

There are two important factors that merit discussion to put the current status of Therapeutic Hypothermia after cardiac arrest in infants and children: (1) the unique pathophysiology of the asphyxial cardiac arrest and (2) the developmental differences in the response of infants and children to central nervous system (CNS) insults. Cardiac arrest in children often results from asphyxia rather than ventricular fibrillation. Most children suffer cardiac arrest from a respiratory etiology such as drowning or choking. The consequences of asphyxia cardiac arrest appear to be particularly detrimental.

Hypothermia for birth asphyxia has become more accepted over the past decade, based on two breakthrough clinical studies, and is poised as the only therapy that improves long-term neurological outcome and mortality. It is likely that the large surface area of the infant's head allows for the potential utilization of the cool cap as a method of inducing systemic hypothermia. Continued studies on the mechanisms of neuroprotection and the various devices that may be useful need to be completed, and refinement of study design and patient selection will be required. Formation of national and international registries should be formed so that scientific progress in the field can be assessed continuously for developing, refining and optimizing therapies.

Extrapolating from the adult randomized controlled studies, the 2005 American Heart Association's Pediatric Life Support guidelines recommended the consideration of hypothermia for 12-24 hours in comatose children after cardiac arrest, acknowledging that the optimal duration of cooling and rewarming is unknown, and cautioning about hypothermia's side effects (American Heart Association Guidelines for Cardiopulmonary Resuscitation, 2006). Arguments against the adoption of Therapeutic Hypothermia in children include the fact that the primary etiology of cardiac arrest in children is asphyxia, which has a unique pathophysiology from the arrhythmia-induced cardiac arrest.

There is still no prospective data in the pediatric population in the 2010 guidelines but planning is underway for a multi-center randomized controlled trial. While results of the randomized controlled trial is awaited to determine the efficacy of hypothermia for neuroprotection in children after cardiac arrest, other questions remain regarding the optimal duration of hypothermia therapy and rewarming, methods of initiation and maintenance of cooling, and contemporary monitoring modalities. Although more work is needed, particularly in the use of Therapeutic Hypothermia in children, there is a strong possibility that this important therapy will ultimately have broad applications after cardiac arrest and CNS insults in the pediatric population.

Since there is currently insufficient evidence to make a recommendation on the use of therapeutic hypothermia in children resuscitated from cardiac arrest, use of Therapeutic Hypothermia on children after cardiac arrest should be considered on case by case basis. Stat pediatric consultation should be

done during decision process. If the pediatric patient is in a community hospital, transfer to a facility with higher level of expertise on Therapeutic Hypothermia on children should occur if decision is made to initiate the protocol

Therapeutic Hypothermia and Stroke

Experimental evidence and clinical experience show that hypothermia protects brain damage during ischemia. There is a growing hope that the prevention of fever in stroke will improve outcome and that hypothermia may be a therapeutic option for the treatment of stroke. Body temperature is directly related to stroke severity and outcome, and fever after stroke is associated with substantial increases in morbidity and mortality .

Normalization of temp after in acute stroke by antipyretics is generally recommended, although there is no direct evidence to support the treatment.

TH in stroke has been investigated in only few very small studies. In addition due to serious side effects (hypotension, cardiac arrhythmias, and pneumonia) TH is still thought of as experimental, and more evidence of efficacy from clinical trials is needed.

Therapeutic Hypothermia and Traumatic Brain Injury (TBI)

Many posttraumatic adverse events that occur in traumatic brain injury at a cellular and molecular level are highly temperature-sensitive and are thus a good target for Therapeutic or Induced Hypothermia. The basic mechanisms through which the hypothermia protects the brain are clearly multifactorial and include at least the following: reduction in brain metabolic rate, effects on cerebral blood flow, reduction of the critical threshold for oxygen delivery, blockade of excitotoxic mechanisms, calcium antagonism, preservation of protein synthesis, reduction of brain thermopooling, a decrease in edema formation, modulation of the inflammatory response, neuroprotection of the white matter and modulation of apoptotic cell death.

The new developments in the research studies on Therapeutic Hypothermia and traumatic brain injury indicate that, by targeting many of the abnormal neurochemical cascades initiated after TBI, Therapeutic Hypothermia may modulate neurotoxicity and, consequently, may play a unique role in opening up new therapeutic avenues for treating severe TBI and improving its devastating effects. Furthermore, greater understanding of the pathophysiology of TBI, new data from both basic and clinical research. The good clinical results obtained in randomized clinical trials in cardiac arrest and better and more reliable cooling methods have given hypothermia a second chance in treating TBI patients. It should be mandatory to do further studies to critically evaluate reasons for previous failures with regards to induced hypothermia in TBI. Furthermore, multicenter randomized clinical trials need to be designed to

confirm or refute the potential benefits of Therapeutic Hypothermia in the management of severe traumatic brain injuries.

References

Abella, BS, Rhee JW, Huang, KN, Vanden Hoek TL, Becker LB (2005). Induced hypothermia is undersued after resuscitation from cardiac arrest: a current practice survey. *Resuscitation*, 64: 181-186.

Bader, MK, et al (2007). Keeping cool: a case for hypothermia after cardiopulmonary resuscitation, *American Journal of Critical Care*, 16(6): 632-636.

Badjeatia, N & Mayer, S. (2007). Assessment of the metabolic impact of shivering: The bedside shivering assessment scale (BSAS). *Neurocritical Care*,6:213.

Badjatia, N, Strongilis, E, Gordon, E, et al (2008). Metabolic impact of shivering during therapeutic temperature modulation; the bedside shivering assessment scale. *Stroke* 39: 3242-3247

Bahrt, G (2009, July) "Cooler heart, better odds: Induced Hypothermia" *Nursing Management*.

Barker, E. (2008). *Neuroscience Nursing: A Spectrum of Care*

Becker, L, Smith, D & Rhodes, K (1993). Incidence of cardiac arrest: A neglected factor in evaluating survival rates
Annals of Emergency Medicine, 22 (1): 86-91

Bernard, SA., Gray, TW., Buist, MD, et al (2002). Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *New England Journal of Medicine*, 346 (8):557-563.

Chen, Y., Lin, J., Yu, H., Ko, W., Chang, W., & Chen, W. et al. (2008, August 16). Cardiopulmonary resuscitation with cooling versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: An observational study and propensity analysis. *The Lancet*, 372:554-561.

Clumper, M., & Mobley, J. (2008, September). Raising the dead. *EMS: Emergency Medical Service*, 37(9):52-61.

Combes, A. (2011). Early-onset pneumonia after cardiac arrest: an unintended consequence of therapeutic hypothermia? *American Journal of Respiratory and Critical Care Medicine*, 184 (9): 993-994.

Cushman, L., Warren, M., & Livesay, S. (2007, April/June). Bringing research to the bedside: The role of induced hypothermia in cardiac arrest. *Critical Care Nurse Quarterly*, 30(2):143-153.

Gaeski, DF, Band RA, Abella BS (2009). Early-goal directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation*, 80: 418.

Green, Robert S., & Howes, Daniel William. (2007). Stock your emergency room with ice packs: a practical guide to therapeutic hypothermia for survivors of cardiac arrest. *Canadian Medical Association Journal*, 176(6)

Hassani, H & Meyer, S (Sept 1, 2010). Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *American Family Physician*, 82 (5): 477-478.

Holzer, M (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest (The hypothermia after cardiac arrest study group) *New England Journal of Medicine* 346 (8) 549-556.

Idrissi, SH (2001). Mild hypothermia induced by a helmet device: A clinical feasibility study. *Resuscitation*, 51(3): 275-281.

Khot et al (2006). *Neurology*, 26:422-431

Kochanek, P.M., Fink, E.R., Bell, M.J., Bayir, H., & Clark, R.S.B.(2009). Therapeutic Hypothermia: Applications in Pediatric Cardiac Arrest. *Journal of Neurotrauma*, 26: 421-627.

Koran, Zeb. (2008). Therapeutic hypothermia in the post resuscitation patient. *Advanced Emergency Nursing Journal*, 30(4), 319-330.

Laver, S., Farrow, C., Turner, D., Nolan, J. (2004). Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Medicine*, 30: 2126.

McCoy, J., Trzeciak, S., Parrillo, J. E., Dellinger, R. P., Abate, N., Shapiro, N. et al. (2008, December). Increased microcirculatory flow during early resuscitation is associated with reduced organ failure. *Intensive Care Medicine*, 34(12).

Melnyk, B., & Fineout-Overholt, E. (2005). Evidence-based practice in nursing and healthcare: A guide to best practice. Philadelphia: Lippincott, Williams, & Wilkins

Meyers, B., & Hinchey, P. (2008, July 1). Simple innovations radically improve cardiac arrest survival rates. *Journal of Emergency Medical Services*, 33(7).

Neumar, RW., Nolan, JP., Adrie, C (2008). Post Cardiac Arrest Syndrome: Epidemiology, Pathophysiology, Treatment and Prognostications: A Consensus Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative and Critical Care the Council on Clinical Cardiology and the Stroke Council. *Circulation*, 118: 2452-2483.

Neumar, R, Fuchs, B, Maguire, C, Munish, G, Kolansky, D, & Gaeski, D (2006). Post-Cardiac Arrest Early Goal-Directed Therapy. Hospital of the University of Pennsylvania Clinical Center for Resuscitation. Hospital of the University of Pennsylvania. Philadelphia, PA.

Nielson, N, et al (2009). Hypothermia Registry. *Acta Anaesthesia Scandinavia*, 53: 926-34

Nolan, JP, Morley, PT., Vanden Hoek, TL, et al (2003) Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation*; 108: 118-121.

Oddo, M., Ribordy, V., Feihl, F., Rossetti, A., Schaller, M. D., & Chiolerio, R. et al. (2008, August). Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: A prospective study. *Critical Care Medicine*, 36(8): 2296-2301.

Olse, TS, Weber, UJ, Kammersgaard, LP. (2003, July). Therapeutic Hypothermia for acute stroke. *The Lancet neurology*, 2 (7): 410-416.

Part 7.5: Post resuscitation Support (2005). *Circulation*.

Peberdy, W Kaye, JP Ornato, GL, et al 2003 - Elsevier
Cardiopulmonary resuscitation of adults in the hospital: A report of 14 720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation
Resuscitation, 58(3): 297.

Polderman, KH. (2004). Application of therapeutic hypothermia in the intensive care unit: Opportunities and pitfalls of a promising treatment modality-Part 2: Practical aspects and side effects. *Intensive Care Medicine*, 30: 757-769.

Polit, D., Beck, C., & Hungler, B. (2001). *Essential of nursing research: Methods, Appraisals, and Utilization* (5th ed.). Philadelphia: Lippincott, Williams & Wilkins.

Rosetti et al (2009). *Neurology*, 72 (8): 744-749.

Rundgren, M., Rosen, I., & Friberg, H. (2006, April 29). Amplitude-integrated EEG predicts outcome after cardiac arrest and induced hypothermia. *Critical Care Medicine*, 32, 836-842.

Safar P: Resuscitation after Brain Ischemia, in: Grenvik A. and Safar P, Eds: *Brain Failure and Resuscitation*, Churchill Livingstone, New York, 1981; 155-184.

Safar, P, Kbayama, K, Radovsky, A, et al (1993). Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

Sahuquillo, J., Vilalta, A. (2007). Cooling the injured brain: How does moderate hypothermia influence the pathophysiology of traumatic brain injury. *Current Pharmaceutical Design*, 13(22): 2310-2322.

6abc.com. (2010) *Therapeutic hypothermia* helping cardiac arrest patients.

Sunde, K, Pytte M, & Jacobson, D, et al (2007). Implementation of a standardized treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*, 73: 29-39.

The Hypothermia after Cardiac Arrest Study Group (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New England Journal of Medicine*, 346: 549-556

Wolfrum, S., Pierre, C., Radke, P., Schunkert, H., & Kurowski, V. (2008, June). Mild hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Critical Care Medicine*, 36(6), 1780-1786.

WWW.RN.ORG®