# Cooling Down Before It Heats Up: Rationale for Preservative (Intra-Arrest) Hypothermia

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# Preservative (Intra-Arrest) Cooling

Hypothermia – Not Just a Prehospital "Fad"

- 2005 = AHA / ILCOR recommendation
- multiple RCTs, comparative studies and case series
- NNT = 4-7
- OR for neurologically intact d/c = 2.5
- NNH = ???

Yet some would argue that this is not the standard of care. Often the same people who would defend other "standards."

# Preservative (Intra-Arrest) Cooling

**NYC Project Hypothermia**

**Intentional Two Phase Approach**

**Phase I – Selective Transport for Early Cooling**

**Phase II – Selective Transport with Prehospital (Preservative) Cooling**

# Preservative (Intra-Arrest) Cooling


**NYC Project Hypothermia**

Program began 1/5/09

Prehospital Inclusion

- age >18
- ROSC before tx
- no DNR/MOLST
- no traumatic etiology
- post-resus 12-lead for STEMI determination

Hospital Inclusion

- no DNR decision
- no refractory acidosis / hypoxia / hypotension
- no significant comorbidities
- ROSC within 30 minutes of resus initiation
- comatose but with brainstem reflexes

# Preservative (Intra-Arrest) Cooling

## Fire Department of New York City NEW YORK CITY

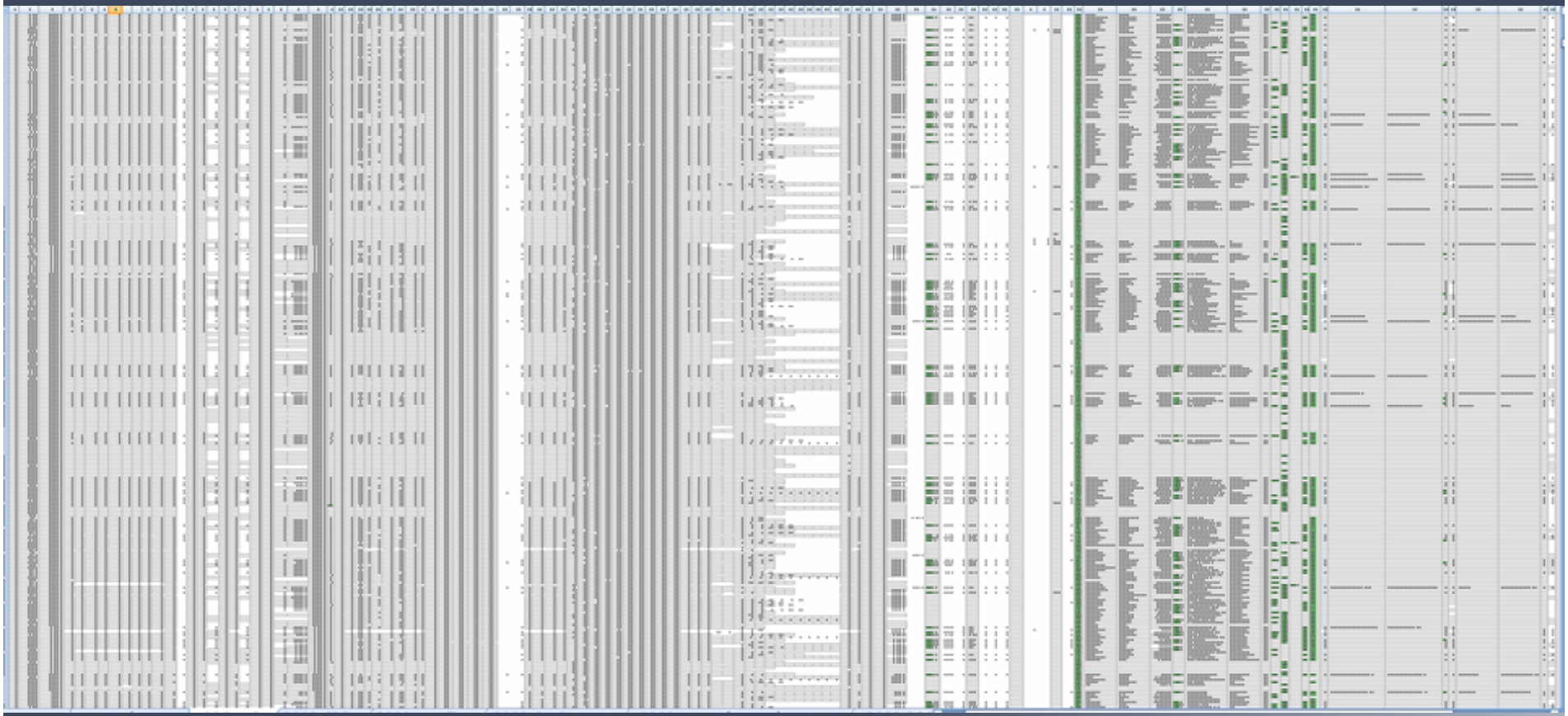
## PROJECT HYPOTHERMIA

**PROPOSED GUIDELINES FOR THE TREATMENT AND RESUSCITATTION OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST**

**PHASE 1: EMS TRANSPORT TO HOSPITAL CAPABLE OF STARTING HYPOTHERMIA IN 4 HOURS.**

**PHASE 2: EMS STARTS HYPOTHERMIA IN THE FIELD (INFUSION OF COLD NORMAL SALINE) AND TRANSPORTS TO HOSPITAL CAPABLE OF CONTINUING HYPOTHERMIA**

# Preservative (Intra-Arrest) Cooling



# Preservative (Intra-Arrest) Cooling

NYC Project Hypothermia

- began 1/5/09
- 2,108 post-ROSC transports to date
- 44 participating Cardiac Arrest Centers
- early data is strongly supportive

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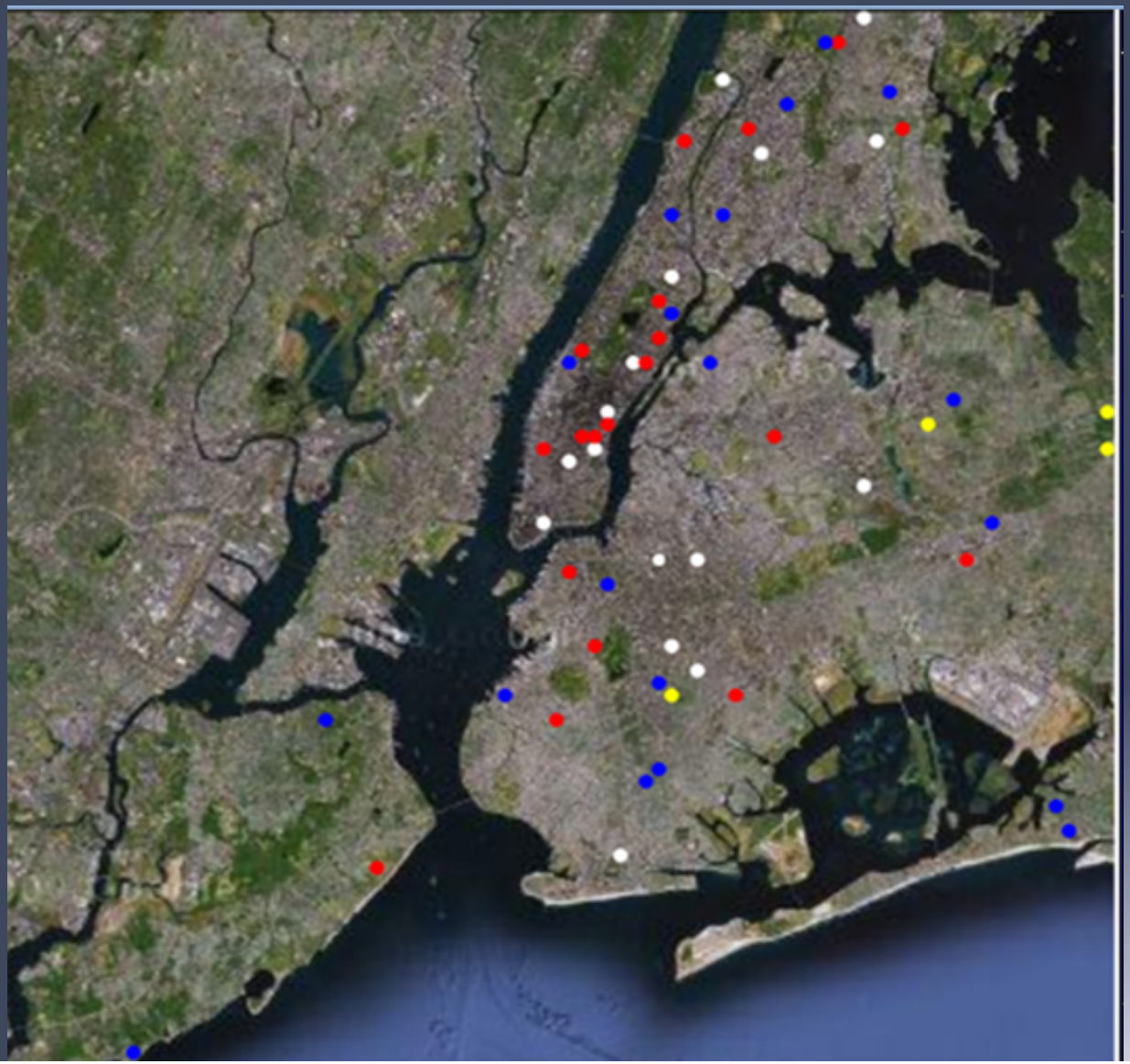

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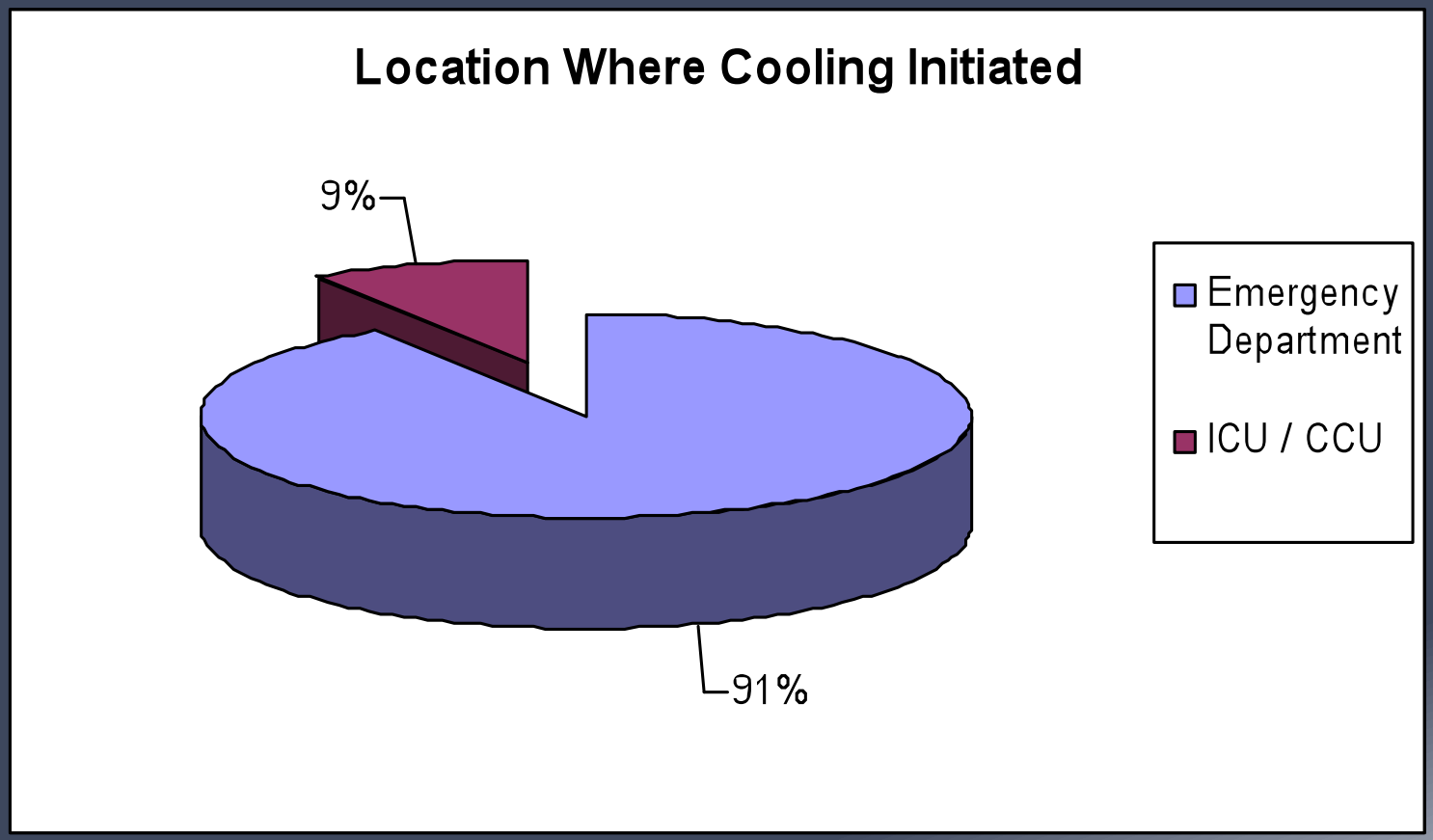

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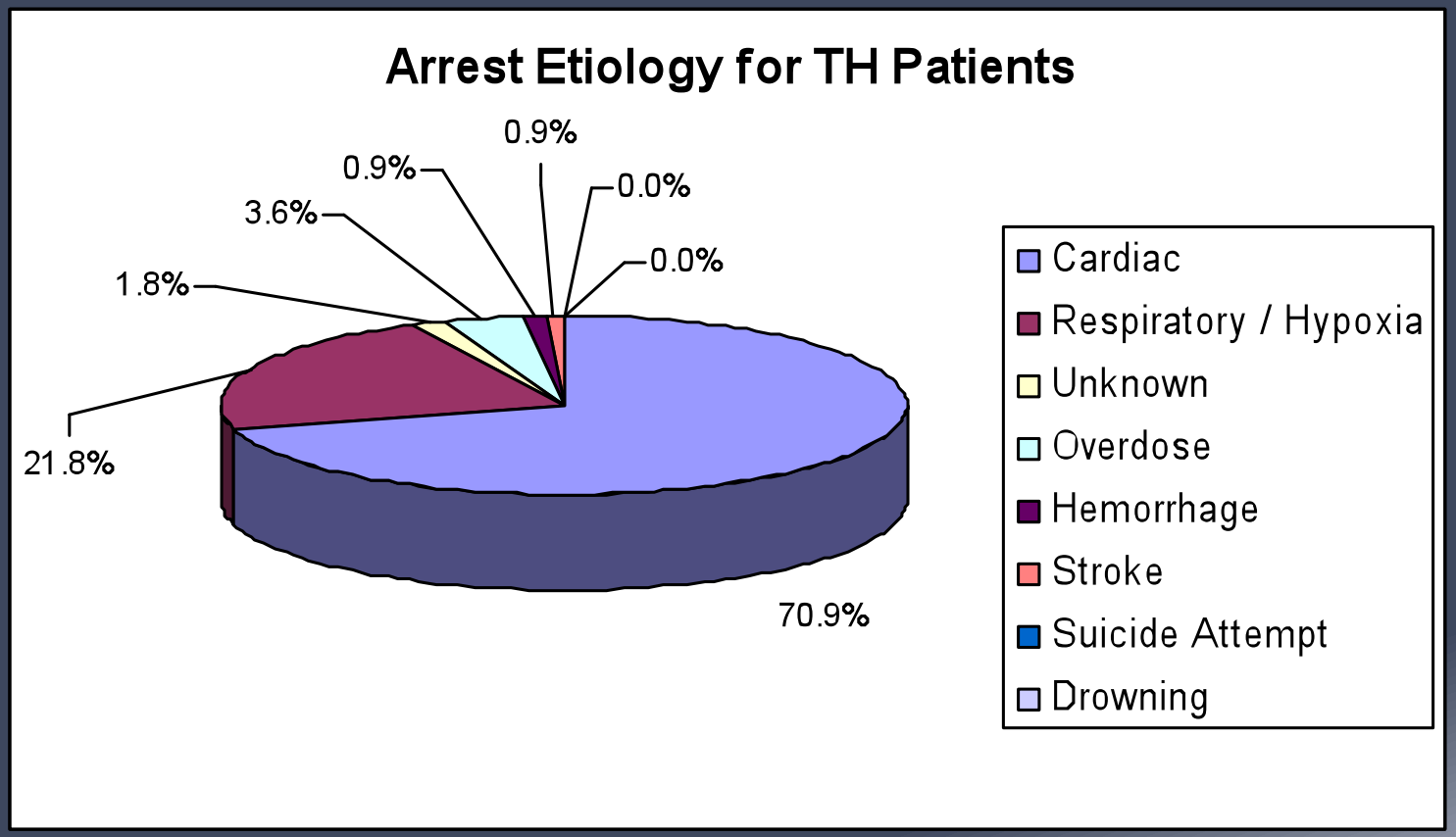

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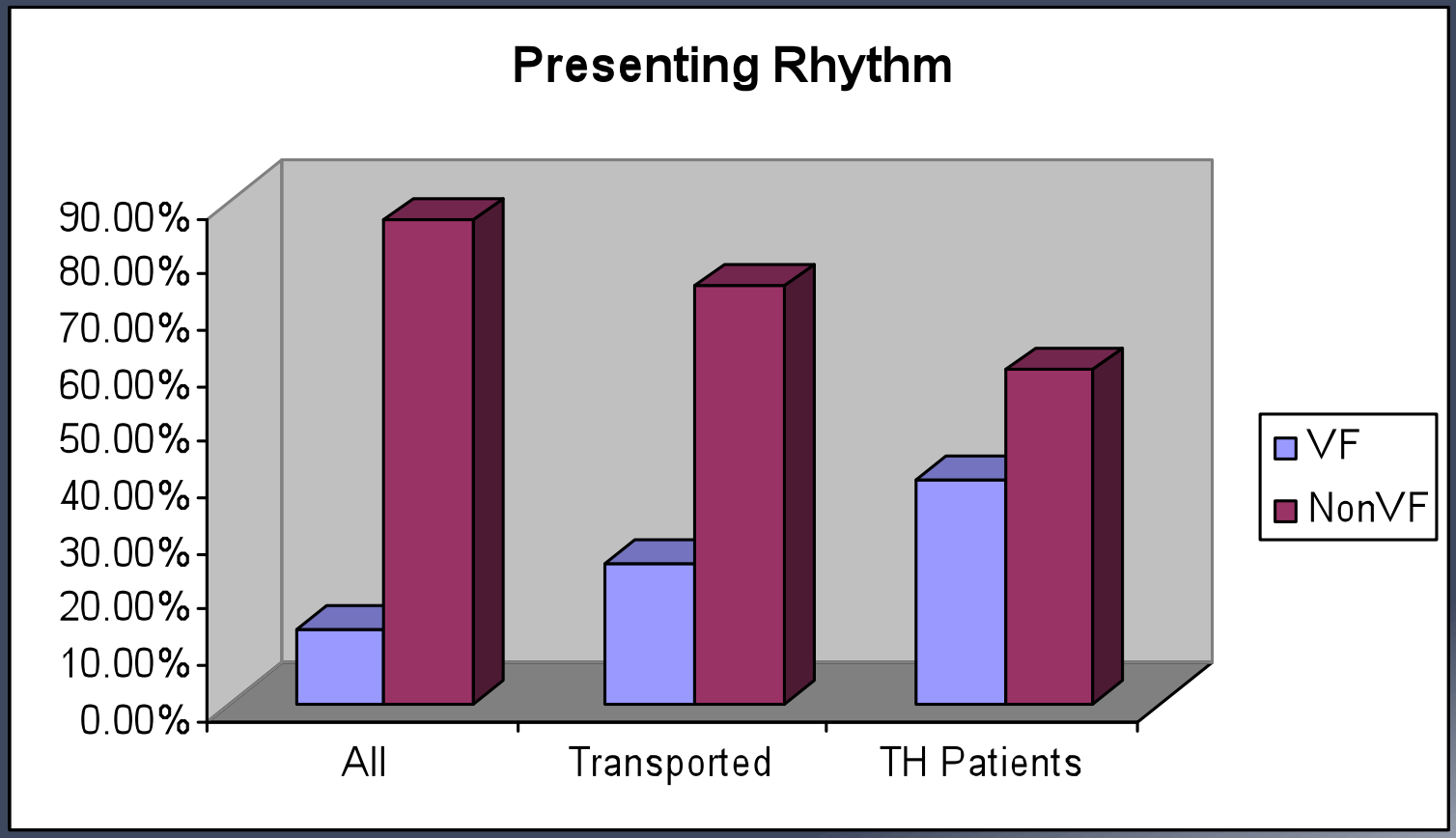

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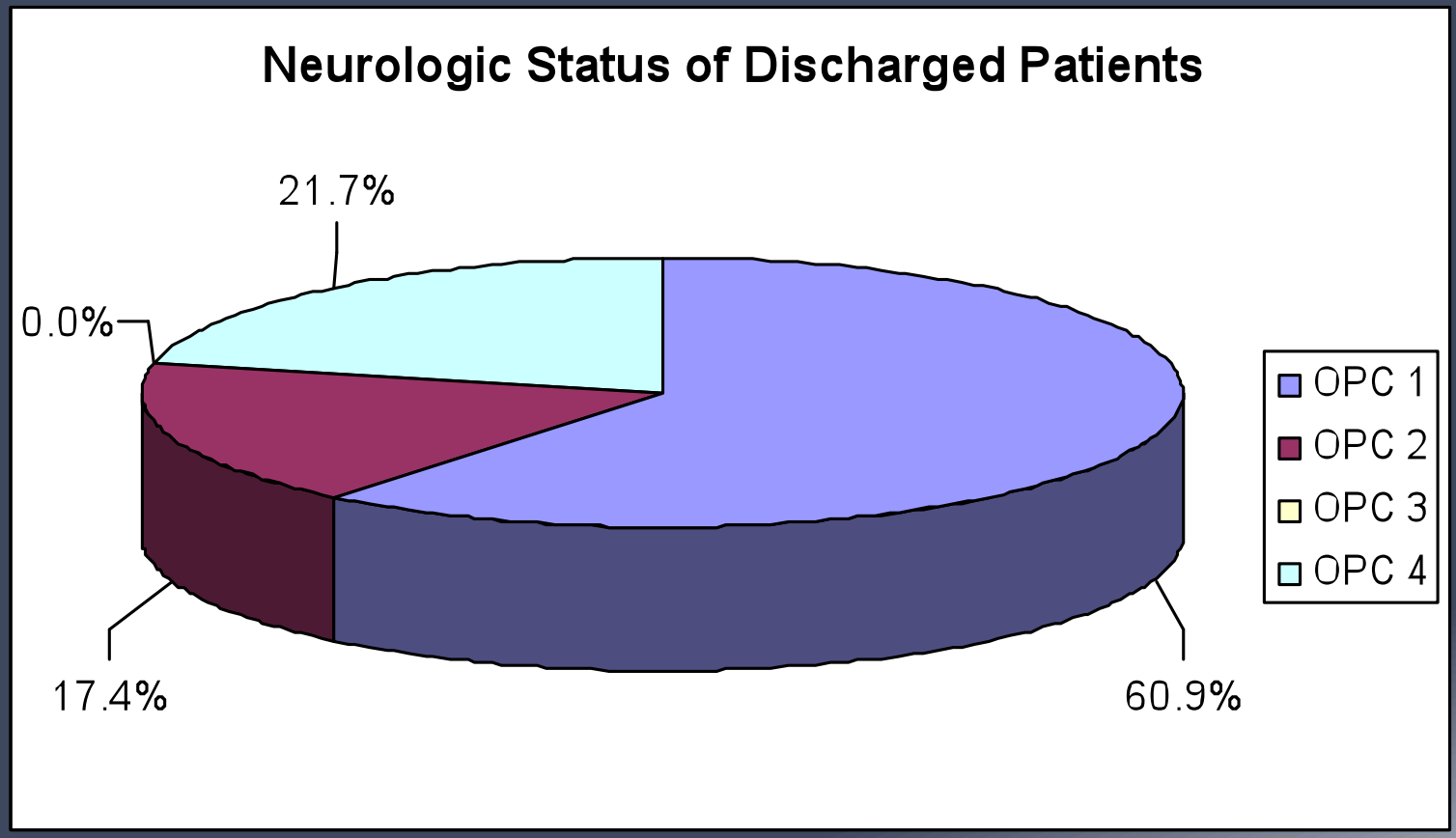

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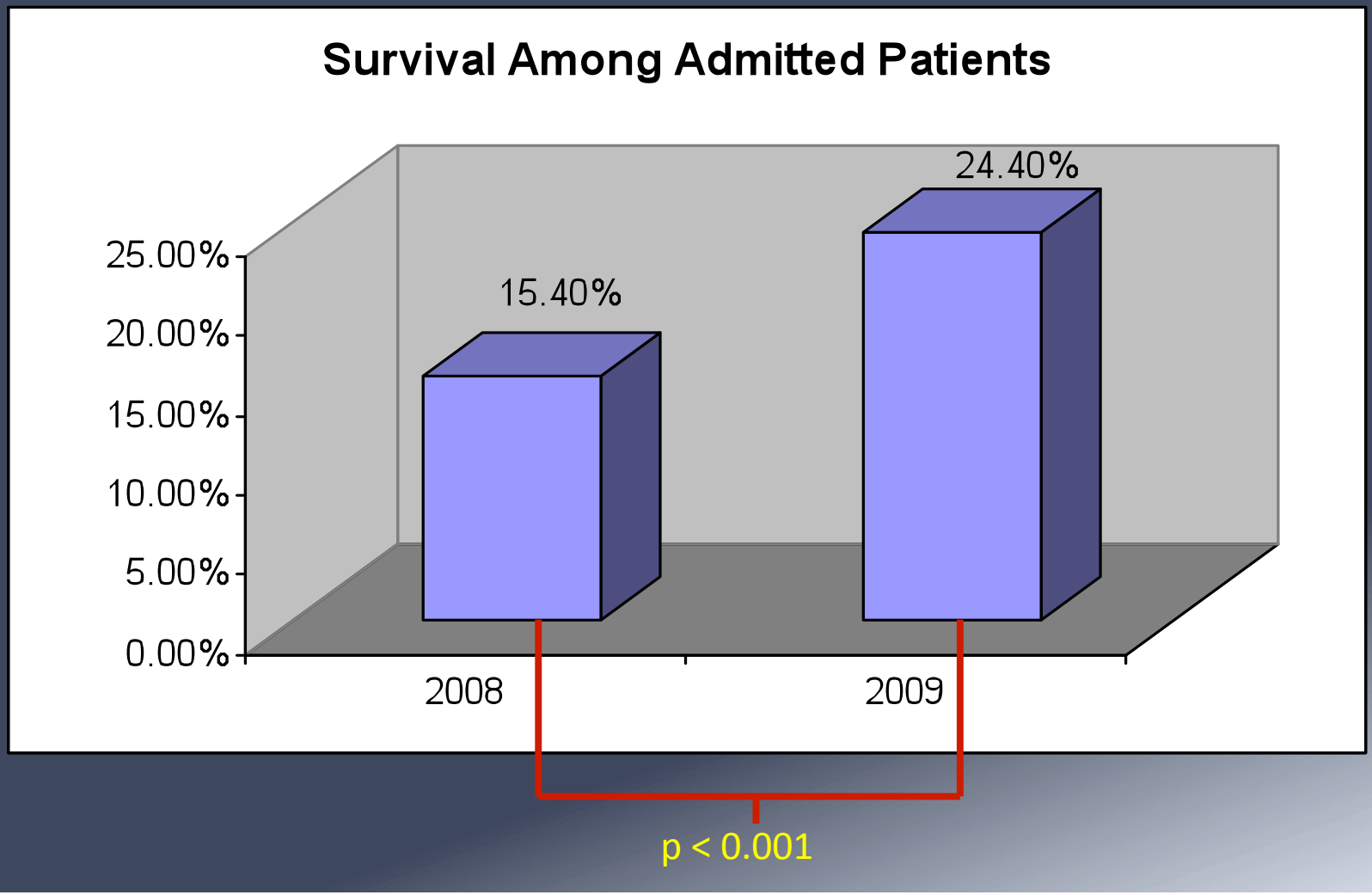

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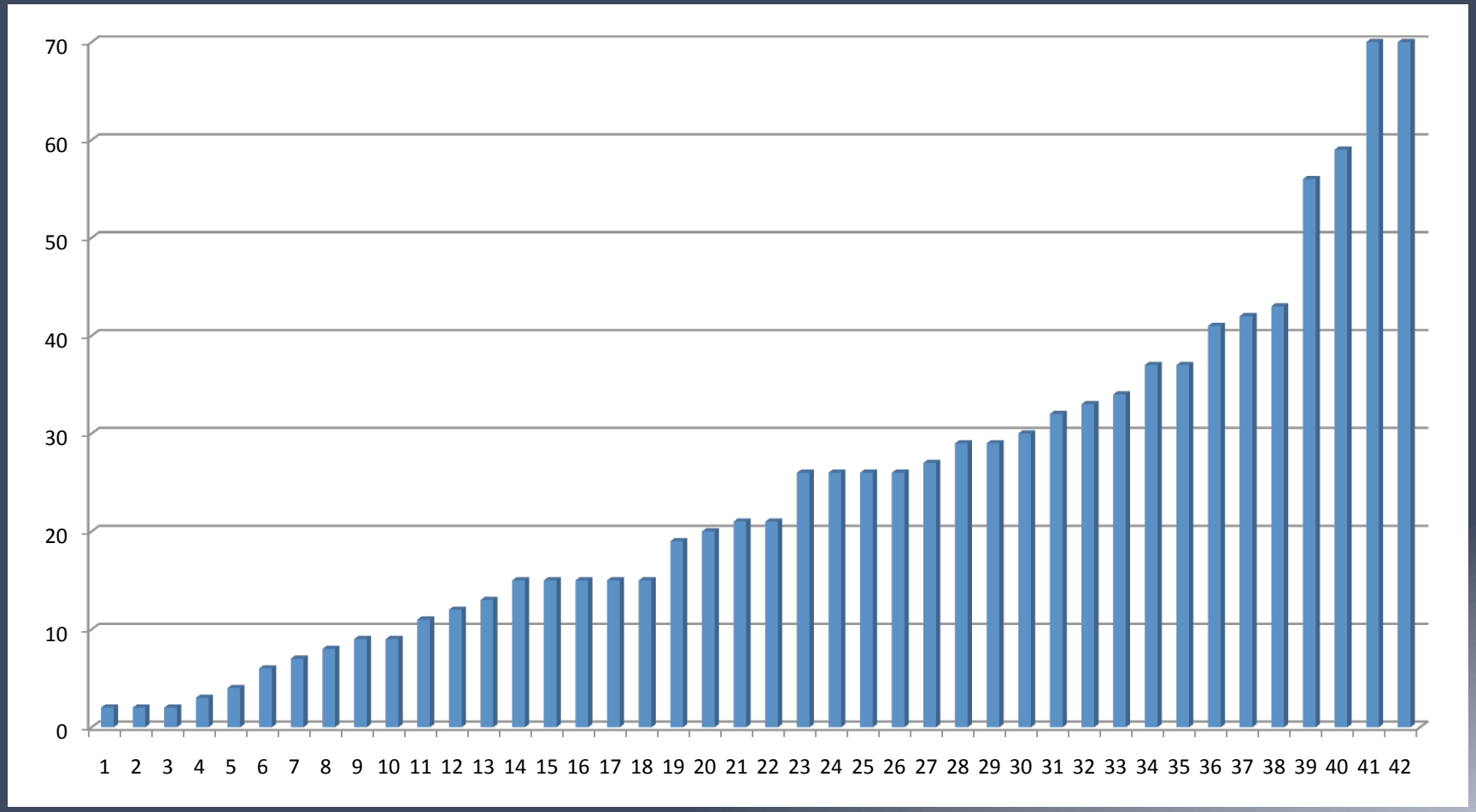


# Preservative (Intra-Arrest) Cooling

**And this brought us to an important point, one that made it safe to pursue Phase II…**

# Preservative (Intra-Arrest) Cooling

So now for Phase II…

# Preservative (Intra-Arrest) Cooling

"But why?"

"Where is the data?"

"So this has been shown to be successful in clinical trials?"

"How will cooling effect our treatment?"

"Will our drugs still work if given with cold saline?"

"Is it effective?"

"Is it safe?"

"This is going to cost a fortune!"

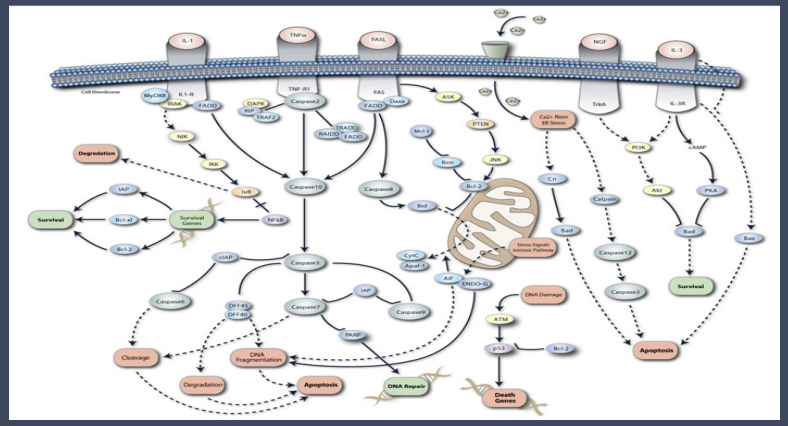
"Can you pronounce someone after you cool them?"

"You're forcing the hospitals to cool patients!"

# Where is the data?

**Physiologic Basis for Hypothermia**

- Slowed cellular metabolism
- Interruption of apoptotic pathway
- Attenuation of "excitotoxic arrest" processes
- Suppressed inflammatory response
- Reduced free radical production
- Reduction in ICP
- Maintenance of microvascular integrity
- Reduced accumulation of intracellular lactate
- Improved glucose metabolism
- Improved mitochondrial oxidative phosphorylation
- Combats hypercoaguable state that results from ischemic insult
- Reduced production of thomboxane A2 and prostaglandin $I_2$
- Improved tolerance for cerebral ischemia
- Reduced neurologic injury from convulsive and nonconvulsive seizures



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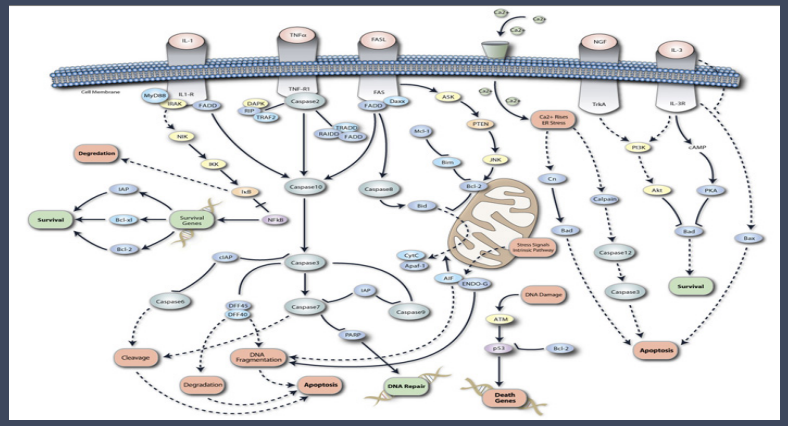

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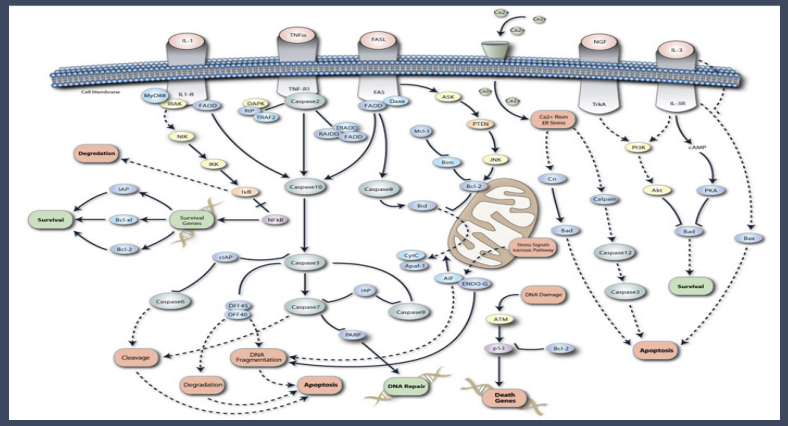

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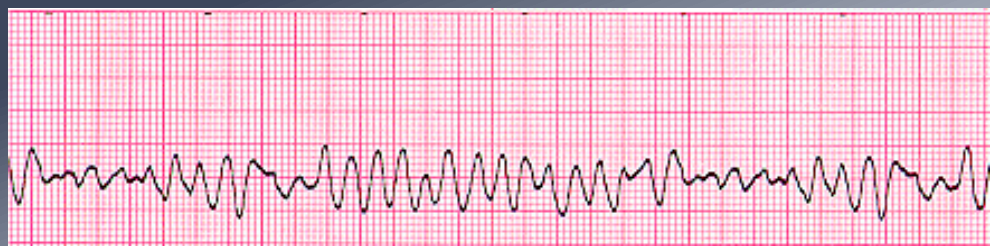
**Reduced neurologic injury from convulsive and nonconvulsive seizures**

# How will cooling affect our treatment?

Intra-Arrest Hypothermia:  Impact on Defibrillation

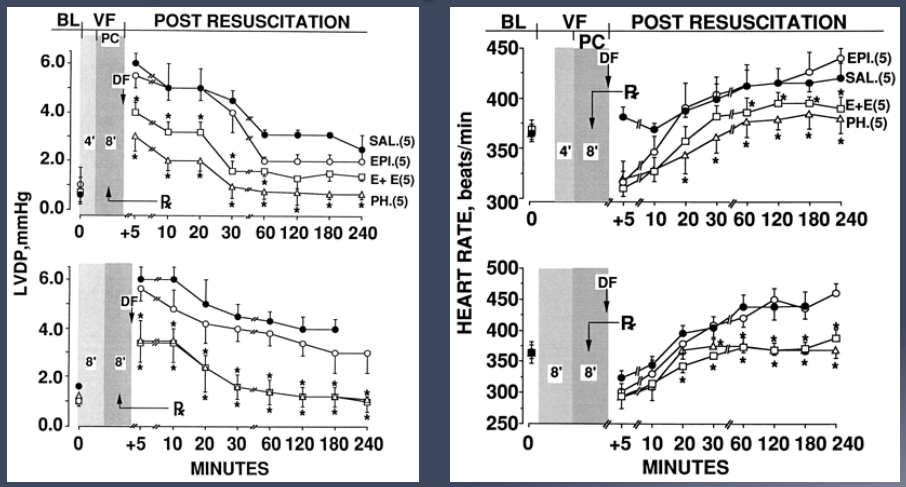
- limited efficacy during moderate / severe hypothermia
- but for mild hypothermia:
  - increased first shock efficacy
  - lower defibrillation threshold
  - lower number of defibrillatory shocks for later VF / VT



# How will cooling affect our treatment?

Intra-Arrest Hypothermia: Pharmacologic Impact

- current recommendations for vasopressor agents include epinephrine and/or vasopressin
- post-resuscitation myocardial dysfunction that results from β-agonism

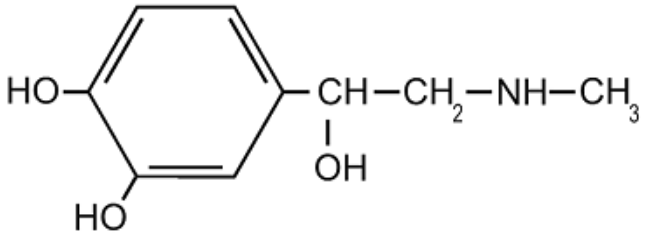



- ubiquitous distribution of V1 receptors via which vasopressin produces vasoconstriction

# How will cooling affect our treatment?

Intra-Arrest Hypothermia: Pharmacologic Impact

- mild hypothermia induces release of endogenous norepinephrine
- hypothermia-mediated vasoconstriction maintains core organ perfusion
- may reduce the degree of post-resuscitation myocardial dysfunction via less vasopressor administration
- greater sensitivity to administered vasopressor agents



# Will our drugs still work if given with cold saline?

## Intra-Arrest Hypothermia: Drug Efficacy

- Some limited data on implications for infusions (recommendation for boluses - Polderman)
- Clearance affected by hypothermia (Tortorici)
- Only data regarding drug efficacy is only for moderate to severe, accidental hypothermia (Reuler)

Table 1. Commonly used drugs in critical care patients

| Drug Class | Medication | Elimination Pathway |
|---|---|---|
| Antiarrythmics | Amiodarone | CYP3A4 |
| | Bretylium | Excreted unchanged |
| | Procainamide | N-acetyltransferase |
| | Lidocaine | CYP1A2 & CYP3A4 |
| | Sotalol | Renal excretion |
| β-blockers | Metoprolol | CYP2D6 & CYP2C9 |
| | Atenolol | Renal excretion |
| Inotropic agents | Digoxin | CYP3A4 |
| Calcium channel blockers | Verapamil | CYP3A4 |
| | Diltiazem | CYP3A4 |
| | Amlodipine | CYP3A4 |
| | Nifedipine | CYP3A4 |
| Benzodiazepines | Midazolam | CYP3A4 |
| | Alprazolam | CYP3A4 |
| Anesthetics | Propofol | CYP2B6 |
| Opioids | Morphine | CYP2C & CYP3A |
| | Codeine and derivatives | CYP2C & CYP3A |
| | Fentanyl | CYP3A4 |
| Anticonvulsants | Phenytoin | CYP2C9 & CYP2C19 |
| | Carbamezipine | CYP3A4 |
| Antimicrobials | Glycopeptides | Renal excretion |
| | Aminoglycosides | Renal excretion |
| | β-lactams | Renal excretion |
| | Macrolides | P450s |
| | Fluoroquinolones | P450s |
| | Rifampin | CYP3A4 |
| | Tetracyclines | P450s |
| Proton pump inhibitors | Pantoprazole | CYP3A4 & CYP2C19 |
| | Omeprazole | CYP3A4 & CYP2C20 |
| | Lansoprazole | CYP3A4 & CYP2C21 |
| H2-blockers | Famotidine | P450s |
| | Ranitidine | P450s |
| Corticosteriods | Methyprednisolone | P450s |
| | Prednisone | P450s |
| | Dexamethasone | P450s |
| Neuromuscular blockers | Vecuronium | P450s |
| | Atracurium | Renal excretion |

# Is it effective?

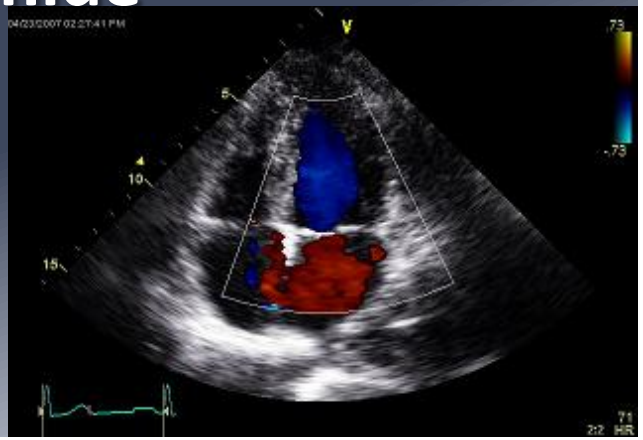
Large Volume Infused Cold Saline - Efficacy

- 24-40cc/kg boluses
- reduction in core temperature by 1.4 – 1.8°C
- when used prehospital, 1.8°C reduction possible from onset of infusion to ED arrival

# Is it safe?

Large Volume Infused Cold Saline – Safety

- no significant risk identified
- two patients with radiographic (but no clinical) evidence of pulmonary edema
- one patient with clinical pulmonary edema (SaO2 = 85%); responded to single dose of IV furosemide
- study specifically to look at CV function found no change in vitals, LVEF, PAP, CVP, or LAFP



# This is going to cost a fortune!

Equipment

- coolers capable of 4°C storage (~$250)
- sliding tray to place the cooler on (~$70)
- pressure infusion sleeves (~$10) x2
- saline (already have it)
- fentanyl (already have it)
- versed (already have it)

(multiply by 65 ALS ambulances)

==========

Total Cost = $22,100

# This is going to cost a fortune!

**Equipment to begin preservative cooling = $22,100**

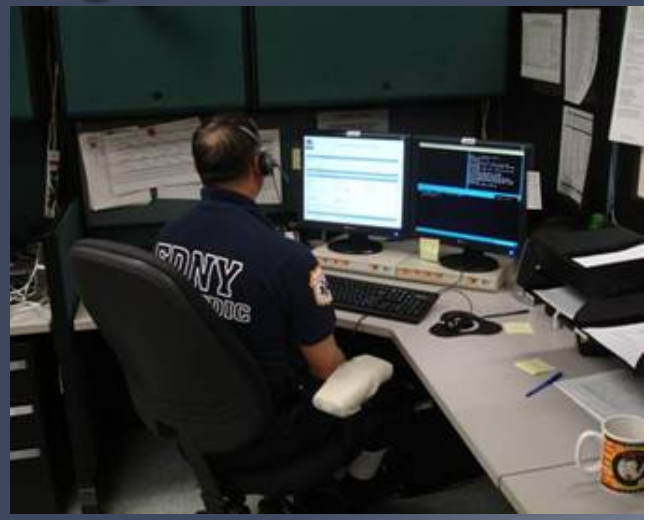
**Money FDNY spend on epinephrine, atropine, vasopressin, and amiodarone in 2009 = $27,524**

**Saving a life = PRICELESS**


# Can you pronounce a cooled patient?

On-Scene Termination Decisions

- no effect based on induced cooling
- no need to rewarm
  - loss of prognostic value of PEA / asystole / lack of response only <30°C




- OLMC contact and termination decision as for any other case

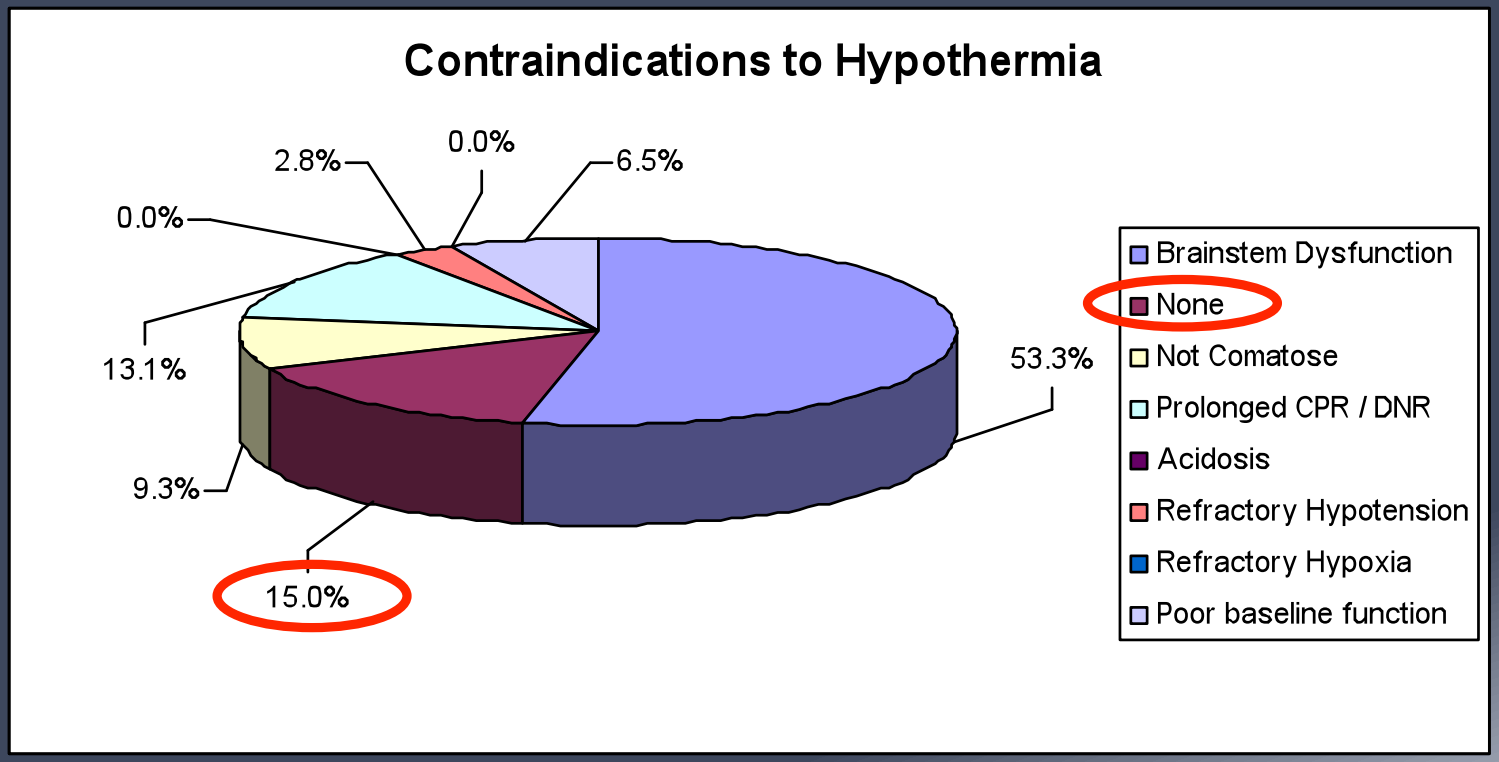
# You're forcing the hospitals to cool patients!

ED / In-Patient Decisions

- Continuation / termination of resuscitation no different than in field
- Post-resuscitation protocols, including exclusion criteria, still apply
- Continuation of cooling / maintenance of cooling easy after ED arrival, including during cardiac cath

# You're forcing the hospitals to cool patients!

## That said…



# Preservative (Intra-Arrest) Cooling

THE REGIONAL EMERGENCY MEDICAL SERVICES COUNCIL OF NEW YORK CITY

ADVANCED EMERGENCY MEDICAL TECHNICIAN (PARAMEDIC) PROTOCOLS

DRAFT DRAFT DRAFT DRAFT DRAFT DRAFT DRAFT

503 - C

POST-RESUSCITATION MANAGEMENT FOR NON-TRAUMATIC CARDIAC ARRESTS

APPROVED

1. Perform, record, and evaluate a 12-lead EKG.
2. If the patient is intubated, ensure adequate ventilation to maintain a waveform capnography values between 35-45 mmHg.
3. Administer Dopamine 5 ug/kg/min, IV/Saline Lock drip to maintain a systolic blood pressure >90mmHg. If there is insufficient improvement in hemodynamic status, the infusion rate may be increased until the desired therapeutic effects are achieved or adverse effects appear. (Maximum dose 20 ug/kg/min, IV/Saline Lock drip.)
4. If the patient is not awake and able to follow commands:
   a) Continue the infusion of ice cold (4o Calcium Chloride saline via IV / IO to a total of 30cc/kg (maximum total volume = 2 liters).
   b) Administer Midazolam 0.1mg/kg IV / IO (maximum dose 10mg).
5. Initiate transport.
6. If the nearest 911 receiving facility is not a Cardiac Arrest Center, contact OLMC to request selective transport to the nearest Cardiac Arrest Center.
   a. If the 12-lead EKG performed meets STEMI criteria, contact OLMC to request selective transport to a Cardiac Arrest Center that is also capable of performing PCI.

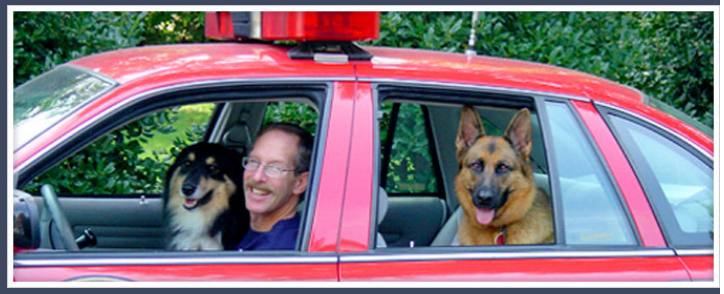
NOTE: OLMC APPROVAL IS REQUIRED FOR ALL STEMI TRANSPORTS, EVEN WHEN THE NEAREST 911 RECEIVING FACILITY IS ALSO A STEMI CENTER, INCLUDING 12-LEAD EKG TRANSMISSION.

MEDICAL CONTROL OPTIONS

A. For shivering prophylaxis or treatment, administer Fentanyl 1mcg/kg IV/IO (maximum dose 100mcg) to suppress shivering.

# Preservative (Intra-Arrest) Cooling

Take Home Points (five of them)



- therapeutic hypothermia saves lives and improves neurologic status
- regionalization may improve baseline survival for all patients
- the physiology of hypothermia suggests benefits of preservative cooling
- intra-arrest cooling may be safely and effectively implemented in a cost-efficient manner via LVICS
- prehospital cooling (pre- or post-ROSC) requires a functional environment into which the patient care may be transferred

## NYC Project Hypothermia – Phase II: Rationale for Preservative Hypothermia

**Background:** As a result of a large volume of basic science and clinical data, including two randomized controlled trials that were published in 2002 [1,2], the use of therapeutic hypothermia is now recommended and even considered to be the standard of care in the post-resuscitation management of out-of-hospital cardiac arrest, particularly for patients whose presenting rhythm was ventricular fibrillation.[3,4] And more recent studies have suggested a role for therapeutic hypothermia in the post-resuscitation management of a wider population of out-of-hospital cardiac arrest patients.[5]

In New York City, the FDNY partnered with the Greater New York Hospital Association, the Health and Hospitals Corporation, the New York City Regional Emergency Medical Advisory Committee (REMAC), local and international experts, and the local ambulance services and hospitals to develop a regional approach to resuscitation management called New York City Project Hypothermia. Phase I of this project centered around the transport of post-arrest patients to Cardiac Arrest Centers, hospitals that had agreed to participate in this effort to ensure the use of therapeutic hypothermia, when appropriate, for all patients who survived to hospital admission following out-of-hospital cardiac arrest. There, under a suggested regional protocol developed in consensus with other subject matter experts, patients not meeting exclusion criteria would be treated with therapeutic hypothermia as part of their post-resuscitation care (resuscitative hypothermia) without concern for their presenting rhythm or the etiology of their non-traumatic cardiopulmonary arrest.

In the first year of this project, nearly one thousand nine hundred patients were successfully resuscitated in the pre-hospital setting following non-traumatic cardiac arrest and were transported to Cardiac Arrest Centers for post-resuscitation management. Among those whose post-resuscitation care included therapeutic hypothermia, over 90% had their cooling process initiated in the emergency department, more than one in four survived to hospital discharge (irrespective of etiology or presenting rhythm), and nearly 80% of those discharged were noted to be functionally intact (OPC 1 or 2). And among those neurologically intact survivors were patients whose initial rhythm was PEA or asystole as well as patients whose arrests were of non-cardiac etiology (i.e. respiratory, overdose).

In Phase II of NYC Project Hypothermia, we will seek to initiate hypothermia during the resuscitation (preservative hypothermia) in an effort to maximize the timing and effects of the induced hypothermic state, including those effects that may positively impact upon the resuscitation effort itself. This document is meant to provide supporting evidence for this extension of hypothermia to the pre-hospital setting.

**Physiology of Hypothermia:** The mechanisms by which hypothermia improves clinical outcomes have been attributed to a wide range of cellular and metabolic pathways, suggesting an advantage over pharmacologic treatments that often target just one pathway or process. Early work with hypothermia was based upon the protective effects that were believed to result from the slowing of overall cellular metabolism, but those effects alone were not sufficient to explain the protective effects of hypothermia.[6,7]

One specific cellular process that is interrupted by induced hypothermia is the intracellular pathway leading to cellular apoptosis. Several studies have found that hypothermia mitigates or prevents apoptosis by influencing the initiation of this self-destructive pathway, inhibiting caspases and other enzymes that are involved in the pathway, reducing the degree of mitochondrial dysfunction (a powerful trigger of apoptosis) that results from the ischemic insult, decreasing production of excitatory neurotransmitters, and alteration of intracellular ion concentrations.[8-11]

Another pathway, sometimes referred to as "excitotoxic arrest", results from the significant increases in intracellular calcium that are brought about by excessive glutamate receptor stimulation, anaerobic metabolism and resulting intracellular acidosis (leading to calcium influx), and ion channel and electrolyte pump dysfunction that follow the rapid depletion of intracellular ATP stores. All of these factors, and a related glycine-mediated stimulation of glutamate receptors, have been shown to be reduced by the induction of therapeutic hypothermia.[12-15]

Cellular injury and death is also a product of the inflammatory response that results from the ischemic insult. The release of pro-inflammatory mediators (IL-1, TNF-α, and other cytokines) and adhesion molecules, activation of the complement system, and the migration of leukocytes into the affected area all contribute to cell destruction and tissue infarction. Hypothermia has been shown to suppress these inflammatory responses and to prevent or reduce DNA injury, decrease leukotriene and nitric oxide production, and diminish lipid peroxidation.[12,13,16-20]

It is well known that free radical production ($O_2^-$, $H_2O_2$, $No_2^-$, $OH^-$) is another of the responsible agents that leads to cell death following ischemia and reperfusion. While hypothermia does not prevent free radical production, it does significantly reduce resulting free radical levels and allows endogenous antioxidants to more adequately protect cells from secondary injury.[14,17]

One of the markers of on-going neuronal injury is the measurement of intracranial pressure which rises due to increased permeability of the blood-brain barrier, decreased fluidity of cerebral capillary endothelial cells, and resulting increased permeability of the microvascular capillary endothelium (which results from nitric oxide release). The impact of hypothermia on nitric oxide production has already been mentioned, but it has also been shown to attenuate blood-brain barrier injury, extravasation of large molecules from the vascular space and other hypoxia-mediated changes in vascular permeability, as well as causing a reduction in ICP. [18-27]

The conversion of intracellular metabolism from aerobic to anaerobic metabolism that results in the accumulation of intracellular lactate, the reduced glucose metabolism, and the long-term changes in cerebral metabolism and mitochondrial oxidative phosphorylation all contribute to cerebral injury following an ischemic injury. But hypothermia has been shown to reduce the degree of all three processes and the resulting accumulation of toxic metabolic byproducts. [28-21]

Though somewhat speculative, and not yet demonstrated in any clinical study, a mild bleeding diathesis resulting from reduced platelet count, altered platelet function, and direct effects on the coagulation cascade are known consequences of a hypothermic state an may play a role in combating the intravascular fibrin formation and platelet activation that result from an ischemic event and contribute to secondary ischemic injury. [22-27]

A portion of the demand-delivery imbalance that occurs during ischemia and reperfusion results from the altered production of vasoactive substances such as endothelin, thromboxane A2, and prostaglandin $I_2$. A shift in equilibrium that favors the production of thromboxane A2, a potent vasoconstrictor, particularly when combined with its platelet activating properties, results in a reduction in local (cerebral) blood flow, worsening


Thank you!

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Prepared by: John Freese, M.D., FAAEM, FDNY Office of Medical Affairs

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**Physiology of Hypothermia**: The mechanisms by which hypothermia improves clinical outcomes have been attributed to a wide range of cellular and metabolic pathways, suggesting an advantage over pharmacologic treatments that often target just one pathway or process. Early work with hypothermia was based upon the protective effects that were believed to result from the slowing of overall cellular metabolism, but those effects alone were not sufficient to explain the protective effects of hypothermia.[6, 7]

One specific cellular process that is interrupted by induced hypothermia is the intracellular pathway leading to cellular apoptosis. Several studies have found that hypothermia mitigates or prevents apoptosis by influencing the initiation of this self-destructive pathway, inhibiting caspases and other enzymes that are involved in the pathway, reducing the degree of mitochondrial dysfunction (a powerful trigger of apoptosis) that results from the ischemic insult, decreasing production of excitatory neurotransmitters, and alteration of intracellular ion concentrations.[8-11]

Another pathway, sometimes referred to as "excitotoxic arrest", results from the significant increases in intracellular calcium that are brought about by excessive glutamate receptor stimulation, anaerobic metabolism and resulting intracellular acidosis (leading to calcium influx), and ion channel and electrolyte pump dysfunction that follow the rapid depletion of intracellular ATP stores. All of these factors, and a related glycine-mediated stimulation of glutamate receptors, have been shown to be reduced by the induction of therapeutic hypothermia.[12-15]

Cellular injury and death is also a product of the inflammatory response that results from the ischemic insult. The release of pro-inflammatory mediators (IL-1, TNF-α, and other cytokines) and adhesion molecules, activation of the complement system, and the migration of leukocytes into the affected area all contribute to cell destruction and tissue infarction. Hypothermia has been shown to suppress these inflammatory responses and to prevent or reduce DNA injury, decrease leukotriene and nitric oxide production, and diminish lipid peroxidation.[12, 13, 16-20]

It is well known that free radical production ($O_2^-$, $H_2O_2$, $No_2^-$, $OH^-$) is another of the responsible agents that leads to cell death following ischemia and reperfusion. While hypothermia does not prevent free radical production, it does significantly reduce resulting free radical levels and allows endogenous antioxidants to more adequately protect cells from secondary injury.[14,17]

One of the markers of on-going neuronal injury is the measurement of intracranial pressure which rises due to increased permeability of the blood-brain barrier, decreased fluidity of cerebral capillary endothelial cells, and resulting increased permeability of the microvascular capillary endothelium (which results from nitric oxide release). The impact of hypothermia on nitric oxide production has already been mentioned, but it has also been shown to attenuate blood-brain barrier injury, extravasation of large molecules from the vascular space and other hypoxia-mediated changes in vascular permeability, as well as causing a reduction in ICP. [18-27]

The conversion of intracellular metabolism from aerobic to anaerobic metabolism that results in the accumulation of intracellular lactate, the reduced glucose metabolism, and the long-term changes in cerebral metabolism and mitochondrial oxidative phosphorylation all contribute to cerebral injury following an ischemic injury. But hypothermia has been shown to reduce the degree of all three processes and the resulting accumulation of toxic metabolic byproducts. [28-31]

Though somewhat speculative, and not yet demonstrated in any clinical study, a mild bleeding diathesis resulting from reduced platelet count, altered platelet function, and direct effects on the coagulation cascade are known consequences of a hypothermic state an may play a role in combating the intravascular fibrin formation and platelet activation that result from an ischemic event and contribute to secondary ischemic injury. [32-37]

A portion of the demand-delivery imbalance that occurs during ischemia and reperfusion results from the altered production of vaosactive substances such as endothelin, thromboxane A2, and prostaglandin $I_2$. A shift in equilibrium that favors the production of thromboxane A2, a potent vasoconstrictor, particularly when combined with its platelet activating properties, results in a reduction in local (cerebral) blood flow, worsening the ischemic insult. Hypothermia has been shown to attenuate this imbalance and to reduce the production of prostaglandin $I_2$, another vasoconstricting agent. [38-39]

Hypothermia has also been shown, independent of the above mechanisms, to improve cerebral tolerance for ischemia. Although some of this literature was related to the perioperative setting, this effect has been shown to extend long after the initial insult, a finding that is particularly relevant following CPR when intracellular cerebral ischemia may persist long after arterial oxygenation has been restored. [40-43]

Finally, while nonconvulsive status epilepticus has been associated with additional brain injury in trauma patients, both convulsive (often at onset) and nonconvulsive status epilepticus in the setting on anoxic injury may be responsible for further brain injury. Hypothermia has been successfully used in the treatment of grand mal seizures and to prevent seizure-induced brain injury.[44-49]

**Early Versus Late Induction of Therapeutic Hypothermia**: The reason that it is so important to consider and understand the physiologic effects of hypothermia is that a familiarity with these effects allows us to understand and discuss the implications related to the timing of hypothermia induction – specifically, to address the question of whether there may be a benefit to the early induction of hypothermia.

The concept of resuscitative hypothermia (that induced after successful resuscitation / ROSC) is predicated on the thought that there exists an hours-long interval from the onset of the ischemic insult until the time at which therapeutic hypothermia must be initiated. This is consistent with the protocol utilized in the largest hypothermia studies to date.[1-2] And it is in keeping with the realization that many of the physiologic effects of hypothermia are delayed sequelae of the ischemic insult (i.e. initiation of apoptosis, free radical production, abnormalities of glucose utilization) and are therefore still able to be suppressed or altered when there is a delay in the initiation of cooling.

Yet the earliest descriptions of the protective effects of therapeutic hypothermia were reported following the unintentional introduction of hypothermia prior to experimental ischemia or arrest in which the subjects benefited from the effects of hypothermia induced prior to or at the time of their ischemic insult. [50-51] And other studies have found that the ability of hypothermia to influence the neuroexcitatory arrest may be limited, with a window of up to 120 minutes but potentially as little as ten minutes. [52] And were we to look at the aforementioned physiologic bases for therapeutic hypothermia, we may find more evidence for the same.

For example, the disruptions in calcium homeostatis on which hypothermia acts (see above) begin within minutes of the ischemic insult and may be one reason for the evidence suggesting that these effects of hypothermia are most prominent or perhaps only important when cooling is initiated in the early phases of this process.[6, 52-55] The initiation of the immune responses (production of pro-inflammatory mediators / cytokines) also occurs early, often within one hour of reperfusion and may therefore be suitable for early intervention via induced hypothermia.[6,56] Similar temporal relationships have been suggested for other physiologic effects and may help to explain the temporally-related association for resuscitative hypothermia and preservative effects of intra-ischemic hypothermia as demonstrated in clinical models.[54, 57-59] And these may help to explain the functional benefits that are derived from intra-arrest hypothermia as demonstrated in other studies.[60-61]

These early physiologic advantages, when combined with the potential impact of hypothermia on the resuscitation effort itself, would argue for the implementation of preservative hypothermia (pre-ROSC or intra-arrest) rather than the current utilization of resuscitative hypothermia (post-ROSC).

**Impact of Hypothermia on On-Going Resuscitation Efforts**: The induction of hypothermia during the resuscitation effort is likely to have effects on not only the early post-resuscitation physiology, but also the resuscitation effort itself. And if one were to consider the resuscitative implications of accidental hypothermia (lower myocardial fibrillation threshold, possible deleterious effects of CPR, limited defibrillation success), there may be concern as to the harm that could be incurred by cooling the patient during the arrest. In discussing these implications, it is important to consider that accidental hypothermia often involves moderate (28-32$^{o}$C) or severe (<28$^{o}$C) hypothermia, where mild hypothermia (32-34$^{o}$C) is the goal of therapeutic hypothermia.

One concern with respect to the on-going resuscitation effort is the impact of the lowered body temperature on defibrillation attempts. In accidental hypothermia, the success of defibrillation is often limited when the core temperature is less than 30$^{o}$C.[62] But it has been demonstrated that mild hypothermia results in a higher first-shock efficacy, lower defibrillation threshold, and lower number of defibrillatory shocks necessary to terminate late ventricular fibrillation as compared to normothermic controls.[63] Therefore, the induction of hypothermia during the early phases of the resuscitation effort may serve to augment the success of subsequent defibrillation attempts.

With respect to pharmacologic management, the literature and recommendations for the management of accidental hypothermia may also suggest a deleterious effect of hypothermia.[62,64] Yet in the setting of mild hypothermia, the need for pharmacologic support may actually be lessened.

In the setting of mild hypothermia, there is an upregulation of sympathetic activity including the release of endogenous norepinephrine and selective peripheral vasoconstriction / arteriovenous shunting in conjunction with central vasodilation in order to maintain perfusion of core organs.[65,66] These vasoactive effects are more appropriate to maintaining core organ perfusion during an arrest than any of the currently available pharmacologic adjuncts. The deleterious β-agonist effects that result from the use of epinephrine (or dopamine) lead to increased myocardial oxygen demand and have been associated with progressive post-resuscitation myocardial dysfunction. [67-70] And while vasopressin may seemingly avoid these β-agonist effects though its V1 receptor-mediated vasoconstriction, the ubiquitous distribution of these receptors (including the coronary arteries) may help to explain the lack of any significant benefit for this agent when compared to epinephrine in studies to date.[71-76]

This role of preservative hypothermia and its ability to limit the need for additional vasopressor support are admittedly hypothetical but are based upon the available literature. What is clear is that hypothermia induces a response within the vasculature that may be beneficial to the resuscitation effort and that the induction of mild hypothermia is expected to increase the responsiveness of the vasculature to other vasopressor agents, when administered. If these two effects are able to reduce or eliminate the need for vasopressor support, the resulting impact on post-resuscitation myocardial dysfunction may allow for a yet unmeasured survival benefit.

With respect to antidysrhythmics, although their use in accidental hypothermia is limited due to the lack of clinical effects when the core temperature is less than 30°C, there is no data to suggest that these effects are lost during mild hypothermia.[66] And given the increased efficacy of defibrillation, the need for such agents would be expected to lessen during mild hypothermia.

Finally, in the past, hypothermia protocols relied on the use of paralytics to prevent shivering and this requirement provided potential training and implementation barriers for the use of such hypothermia protocols in the pre-hospital setting. With time and experience, hypothermia protocols have shifted away from the early or even common use of paralytics and therefore, this potential barrier to pre-hospital initiation has been removed.

**Utility of Large Volume Infused Cold Fluids for Induction of Hypothermia**: The induction of hypothermia via infusion of ice-cold saline has been shown to be an effective means to achieving a lowered core temperature. Bernard et al demonstrated the ability of a 30cc/kg bolus of ice-cold (4o Celcius) saline to induce hypothermia, with a 30cc/kg bolus resulting in an average core temperature reduction of 1.6oC.[77] Similarly, Kliegel and colleages found that the infusion of 24±7 cc/kg of cold fluid resulted in a reduction of core temperature from 36.5°C to 33.8°C.[78] And this ability to rapidly infused large volume, ice-cold intravenous fluid has been shown to be possible in the prehospital setting as well with an average core temperature reduction of 1.8°C – a change that was produced in the interval from the initiation of the infusion to hospital arrival in the first of those studies.[79,80]

**Safety of Large Volume Infused Cold Fluids for Induction of Hypothermia**: The infusion of large volumes (30cc/kg, up to two liters) of intravenous fluids is not without concern either, something that was addressed in the aforementioned studies on the utility of this method. In studies to date utilizing large volume cold intravenous fluid infusion, the rate of complications (specifically "fluid overload" manifesting as pulmonary edema) was exceedingly low.[77-80] Among those studies, two patients developed radiographic signs of pulmonary edema without clinical evidence of the same, and one patient developed clinical evidence of pulmonary edema with oxygen desaturation to 85%. But even that one patient returned to baseline after the administration of a single dose of intravenous furosemide.

This concern for "fluid overload" was further studied by Kim et al following large volume infusions for the induction of mild therapeutic hypothermia. They found that the average core temperature decreased by 1.4°C and that there were no associated changes in other vital signs, coagulation indices, blood gas results, or electrolytes. On echocardiographic examination, the infusions did not induce any change in ejection fraction, left atrial filling pressures, central venous pressure, or pulmonary artery pressures.[81]

**Impact of Pre-hospital Resucitation with Induced Hypothermia on ED workload:** One of the reasons why therapeutic hypothermia has been implemented in a two-phase manner is to allow time for ED and ICU staff to become familiar with its use and to setup interdisciplinary teams for implementation. While a variety of cooling methods are used throughout the ICUs in the NYC 911 system, nearly all of the hospitals have utilized ice cold saline as the primary modality for cooling in the ED. As this method is identical to what we plan for the pre-hospital setting and as all of the participating EDs are familiar with it s use, our survey of our system's ED departments have found that they are now ready to participate with EMS as full partners in phase II.

**Discontinuation of Pre-hospital Resuscitation Efforts (Including Induced Hypothermia) in the in the Field or in the Emergency Department**: The adage that "they are not dead until they are warm and dead" is directed at the management of accidental hypothermia, a condition in which moderate or often severe hypothermia has been induced and in which resulting dysrhythmias (including asystole) are not reliable indicators of prognosis. In such cases, passive or active rewarming is recommended prior to terminating a resuscitation effort because of the lack of any such reliable indicators of outcome.[66]

Because mild therapeutic hypothermia seeks to reduce core temperature only to the range of 32-34°C, far above the 20-30°C range in which ventricular dysrhythmias and asystole are both common and survivable, and even above the 30-32°C range in which atrial arrhythmias are possible,[66] the infusion of large volumes of ice-cold saline would not necessitate rewarming prior to decisions / discussions with EMS On-line Medical Control (OLMC) regarding the termination of resuscitation. As this project moves forward, we will continue to monitor the outcomes of patients who are not successfully resuscitated in the prehospital setting and, should evidence arise of neurologically intact survival without successful field resuscitation, the protocol will immediately be altered to account for this effect.

Among patients who are transported to the hospital, the decision to terminate resuscitation efforts and with regard to the continuation or termination of cooling efforts among survivors will also be unaffected by the prehospital initiation of hypothermia. Patients requiring on-going resuscitation while en route to the hospital will undergo the same evaluation and decision process regarding termination as would occur today.

Patients who survive to hospital admission will need to be assessed as to the appropriateness of continued therapeutic hypothermia as part of their post-resuscitation management. These decisions will utilize the same inclusion and exclusion criteria that are in place today, and will primarily be based on assessment of pre-arrest functional status and post-arrest metabolic status. All of these factors are best done in the hospital and as with any therapy initiated in the prehospital setting, those for whom continued hypothermia is not appropriate may either have the cooling discontinued or be actively rewarmed, just as we would do for a patient today whose temperature was found to be less than 37°C and for whom therapeutic hypothermia was not to be provided.

**Quality Assurance and Oversight**: While some protocol changes are designed with the intent of providing quality assurance measures to measure the impact of those changes, others are of such a potentially important nature that the results derived from those activities may have value to others and be thought worthy of publication. In the latter case, that intent to review the impact of a protocol change and publish the results requires oversight and approval by an institutional review board (IRB). In 2008, the FDNY sought and received IRB oversight from the New York City Department of Health's IRB for NYC Project Hypothermia. In addition, a robust data collection system and data sharing agreements with all participating Cardiac Arrest Centers will allow the FDNY and the New York City EMS system to provide 100% quality assurance review within the 9-1-1 system, to rapidly accumulate data with regard to the impact of this protocol change, and to report back to the REMAC and SEMAC regarding those findings.

**Conclusion**: The use of therapeutic hypothermia is considered the standard of care for the post-resuscitation management of out-of-hospital cardiac arrest patients, particularly those presenting with ventricular fibrillation, and emerging data suggests a much more broad role for this treatment in post-arrest management. In New York City, efforts to ensure the utilization of this treatment as part of a standardized post-resuscitation management protocol have resulted in improved survival for all patients and a high percentage of neurologically intact survivors among those who receive therapeutic hypothermia. Phase II of this project, which is firmly based upon our current understanding of the physiology of therapeutic hypothermia, as well as the implications of mild hypothermia for on-going resuscitation and the safety of induced cooling via cold intravenous fluid infusion, will seek to expand the benefits of this therapy to the intra-arrest management for out-of-hospital cardiac arrest. This shift from resuscitative hypothermia (post-ROSC) to preservative (intra-arrest) hypothermia is anticipated to result in further improvements in overall out-of-hospital cardiac arrest survival and neurologically intact status among those survivors.

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