

Hypothermia: Improving Neurologic Outcomes Following Cardiac Arrest and Stroke

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October 20, 2010**

- **Description of first hypothermic patient by Dr. Temple Fay**

“The patient was given avertin anesthesia, the trunk and legs were packed in cracked ice, and, with the assistance of the cold weather at that time of the year, the windows of the room were opened, permitting the patient’s body temperature to be rapidly lowered to 90°F. (rectal). The sedative effect of the avertin plus amytal maintained the patient throughout the first eighteen hours without discomfort or knowledge of the procedure. Within the first twelve hours the blood pressure gradually disappeared and the pulse disappeared from the periphery. Breathing, which remained slow, shallow and regular, was the only clinical finding that seemed to offer reassurance. Because of the prolonged absence of pulse and blood pressure and the fear of cerebral anoxia, it was decided to bring the patient back to normal temperature values again. Heat was applied to the body surfaces and a hot coffee enema was given. Within a few hours the patient had returned again to conscious levels and was not aware of the experience through which she had been taken.”

Fay T. Early Experiences with Local and Generalized Refrigeration of the Human Brain. J Neurosur 1959;16:239-260.

“...Extremely well-tolerated and clinical results were very satisfactory”

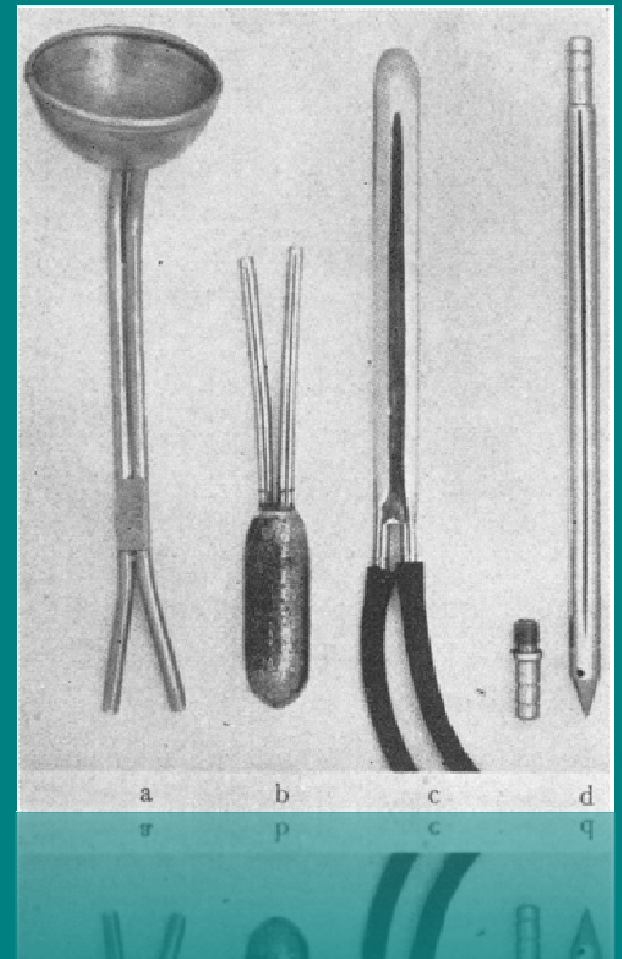


Fay T. Early
Experiences with Local
and Generalized
Refrigeration of the
Human Brain. J
Neurosurg 1959;16:239-
260.

“Observations on generalized refrigeration in cases of severe cerebral trauma”

- published by Fay in 1945
 - Failed attempt to publish in 1939
- first scientific report describing the clinical application of hypothermia in a case series of patients with severe head injury

Fay T. Observations of generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1945;24:611-619.



"In 1955, open-heart surgery was performed at the NIH Clinical Center using hypothermia. The patient was placed in a bed of ice to lower the total body temperature so that body tissues used very little oxygen. This permitted interruption of the blood flow for a brief period so that some procedures could be performed. This technique preceded the advent of the heart-lung machine, which today takes over the job of pumping blood during heart surgery."



History.nih.gov

Hypothermia After Cardiac Arrest Study Group

- European study, 275 pts
- Inclusion:
 - witnessed cardiac arrest, vfib or nonperfusing vtach as initial rhythm
 - cardiac origin of arrest
 - age 18-75
 - Interval of 5-15 min from collapse to first attempt at resuscitation by EMS
 - No more than 60 min from collapse to restoration of circulation

Hypothermia After Cardiac Arrest Study Group

- Exclusion:
 - Temp below 30C on admission
 - Comatose state before arrest 2/2 drugs that depress the CNS
 - Pregnancy
 - Response to verbal commands
 - Hypotension (MAP<60) for >30 min
 - Hypoxemia
 - Terminal illness that preceeded arrest
 - Preexisting coagulopathy

Hypothermia After Cardiac Arrest Study Group

- Randomized, controlled with blinded assessment of outcome
- Standard ICU care: sedation, paralysis
- Normothermia vs. hypothermia 32 °C-34 °C (bladder temp) by cooling blanket
- 24 hrs at target temp, passive rewarming over 8 hrs

Hypothermia After Cardiac Arrest Study Group

- Outcomes at 6 months:
 - Favorable neurologic outcome = Pittsburgh cerebral-performance category 1 (good) or 2 (moderate disability) on 5 category scale
 - Could live independently and work part-time
 - Secondary end-point: mortality at 6 months, complication rates

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	NORMOTHERMIA (N= 138)	HYPOTHERMIA (N= 137)
Age — yr		
Median	59	59
Interquartile range	49–67	51–69*
Female sex — no./total no. (%)	32/138 (23)	33/137 (24)
Medical history — no./total no. (%)		
Diabetes	26/138 (19)	11/135 (8)
Coronary heart disease	59/138 (43)	43/135 (32)
Cerebrovascular disease	11/138 (8)	10/135 (7)
NYHA class III or IV†	16/132 (12)	14/130 (11)
Location of cardiac arrest — no./total no. (%)		
Home	70/138 (51)	69/135 (51)
Public place	53/138 (38)	48/135 (36)
Other‡	15/138 (11)	18/135 (13)
Arrest witnessed — no./total no. (%)§	136/138 (99)	134/137 (98)
Presumed cardiac origin of arrest — no./total no. (%)§	135/138 (98)	135/137 (99)
Ventricular fibrillation or pulseless ventricular tachycardia — no./total no. (%)§	132/138 (96)	133/137 (97)
Basic life support provided by bystander — no./total no. (%)	68/138 (49)	59/137 (43)
Interval between collapse and restoration of spontaneous circulation — min¶		
Median	22	21
Interquartile range	17–33	15–28
Total epinephrine dose — mg		
Median	3	3
Interquartile range	1–6	1–5*
Hypotension after resuscitation — no./total no. (%)	68/138 (49)	75/137 (55)
Subsequent nonfatal arrest — no./total no. (%)	11/138 (8)	15/137 (11)
Thrombolysis after resuscitation — no./total no. (%)	24/133 (18)	27/135 (20)

Hypothermia After Cardiac Arrest Study Group

- 55% hypothermia group vs. 39% normothermia group had favorable neurologic outcomes; RR 1.40
- NNT= 6 to prevent one unfavorable neurologic outcome

TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA	RISK RATIO (95% CI)*	P VALUE†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

Treatment of Comatose Survivors of Out-Of-Hospital Cardiac Arrest with Induced Hypothermia

- Australian study, 77 pts
- Inclusion:
 - Vfib as initial rhythm
 - Successful return of circulation
 - Persistent coma after resuscitation
 - Transfer to participating hospital

Treatment of Comatose Survivors of Out-Of-Hospital Cardiac Arrest with Induced Hypothermia

- Exclusion:
 - Age less than 18
 - Age of less than 50 for women (pregnancy)
 - Cardiogenic shock
 - Other possible cause of coma

Treatment of Comatose Survivors of Out-Of-Hospital Cardiac Arrest with Induced Hypothermia

- Normothermia vs. hypothermia based upon day of month (odd-numbered = hypothermia)
- Standard ICU cardiac care
- Pulmonary artery catheter for temp
- Ice packs to maintain temp of 33°C for 12 hrs, **began out-of-hospital**
- Outcome: good = d/c home or Rehab
 - » Poor = death or d/c to SNF/ long-term care

Treatment of Comatose Survivors of Out-Of-Hospital Cardiac Arrest with Induced Hypothermia

TABLE 1. CLINICAL CHARACTERISTICS OF THE 77 PATIENTS WITH ANHYCIC BRAIN INJURY WHO WERE ELIGIBLE FOR RANDOMIZATION.*

CHARACTERISTIC	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)	P VALUE
Age (yr)			0.55
Median	66.8	65.0	
Range	49-89	41-85	
Male sex (%)	58	79	0.05
Arrest witnessed (%)	95	94	0.81
Bystander performed cardiopulmonary resuscitation (%)	49	71	0.05
Time from collapse to emergency-medical-services call (min)	2.1±1.9	2.7±3.0	0.32
Time from call to emergency-medical-services arrival (min)	7.9±3.1	8.3±2.8	0.60
Time from arrival to first DC shock (min)	2.5±2.2	2.0±1.2	0.22
Time from first shock to return of spontaneous circulation (min)	13.6±11.2	12.1±7.9	0.48
Time from collapse to return of spontaneous circulation (min)	26.5±12.9	25.0±8.9	0.54
Number of DC shocks	4.2±3.0	4.1±3.2	0.87
Dose of epinephrine (mg)	2.2±2.1	2.2±1.9	0.97

*Plus-minus values are means ±SD. DC denotes direct current.

Resuscitation initiated by a bystander was associated with a non-significant improvement in outcome

TABLE 5. OUTCOME OF PATIENTS AT DISCHARGE FROM THE HOSPITAL.

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

- **49% of hypothermia group vs. 26% normothermia had good outcomes (p=0.046)**

Criticisms

- Australian study:
 - Not blinded for treatment
- Small sample sizes
- Different treatment protocols: one starting out-of-hospital and one in-hospital
- Hypothermia group may not have been well matched with normothermic group
- VF pts are a small % of total cardiac arrests

Liu L, Yenari MA, Ding Y. Clinical application of therapeutic hypothermia in stroke. *Neurol Res* 2009;31(4): 331-335.

Efficacy and Safety of Endovascular Cooling After Cardiac Arrest

Cohort Study and Bayesian Approach

Michael Holzer, MD; Marcus Müllner, MD, MSc; Fritz Sterz, MD; Oliver Robak, MD; Andreas Kliegel, MD; Heidrun Losert, MD; Gottfried Sodeck, MD; Thomas Uray, MD; Andrea Zeiner, MD; Anton N. Laggner, MD

- Endovascular cooling
- Included non-VF cardiac arrest patients
- Retrospective cohort analysis
- Statistically improved mortality, improved favorable neurologic recovery at 30 days (not blinded for assessment of neurologic outcome)

Stroke 2006;37;1792-1797; e

International Liaison Committee on Resuscitation

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Therapeutic Hypothermia After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation

J.P. Nolan, P.T. Morley, T.L. Vanden Hoek, R.W. Hickey, W.G.J. Kloeck, J. Billi, B.W. Böttiger, P.T. Morley, J.P. Nolan, K. Okada, C. Reyes, M. Shuster, P.A. Steen, M.H. Weil, V. Wenzel, R.W. Hickey, P. Carli, T.L. Vanden Hoek and D. Atkins
Circulation 2003;108:118-121

Time is Brain – Quantified

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 hr

Time Is Brain--Quantified

Jeffrey L. Saver

Stroke 2006;37:263-266; originally published online Dec 8, 2005;

Hypothermia as a Neuroprotectant

- Reduces:
 - metabolic/enzymatic activity
 - Cerebral O₂ consumption decreases by 50% for every 10°C fall in temp
 - But, a barbiturate coma does that too...
 - Glutamate release and re-uptake
 - Inflammation
 - Production of reactive oxygen species

Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials, and patient care. *J Neurol Sci* 2007;261:118-126.

Benefits of Hypothermia: Animal Studies

- Prevents glutamate levels from rising beyond baseline
 - Decreases cell death via the apoptotic pathway
 - Decreases production of reactive oxygen species
- Permits better membrane regulation by allowing ionic perturbations, such as potassium gradients, to normalize more rapidly after ischemic injury



www.dogtopics.com

Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials, and patient care. J Neurol Sci 2007;261:118-126.

Hypothermia in Rats

- Decreases final infarct volume
- Extends the duration the brain can withstand ischemia before permanent damage occurs

Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effects of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke*. 1989;20:904-910.

Ginsberg MD, Sternau LL, Globus MY, Dietrich WD, Busto R. Therapeutic modulation of brain temperature: relevance to ischemic brain injury. *Cerebrovasc Brain Metab Rev*. 1992;4:189-225.

Karibe H, Chen J, Zarow GJ, Graham SH, Weinstein PR. Delayed induction of mild hypothermia to reduce infarct volume after temporary middle cerebral artery occlusion in rats. *J Neurosurg*. 1994;80:112-119.

Yanamoto H, Hong SC, Soleau S, Kassell NF, Lee KS. Mild postischemic hypothermia limits cerebral injury following transient focal ischemia in rat neocortex. *Brain Res*. 1996;718:207-211.

Huh PW, Belayev L, Zhao W, Koch S, Busto R, Ginsberg MD. Comparative neuroprotective efficacy of prolonged moderate intransischemic and postischemic hypothermia in focal cerebral ischemia. *J Neurosurg*. 2000;92:91-99.

How cold is cold enough?

- Mild: $> 32^{\circ}\text{C}$
- Moderate: $28 - 32^{\circ}\text{C}$
- Deep: $20 - 28^{\circ}\text{C}$
- Profound: $5 - 20^{\circ}\text{C}$
 - Deep to profound: too hard to do, too many complications (hypokalemia, arrhythmia, infection, heart failure)
- Most protective when applied during ischemia or before
- If postischemic period, likely need prolonged hypothermia

Methods of Cooling

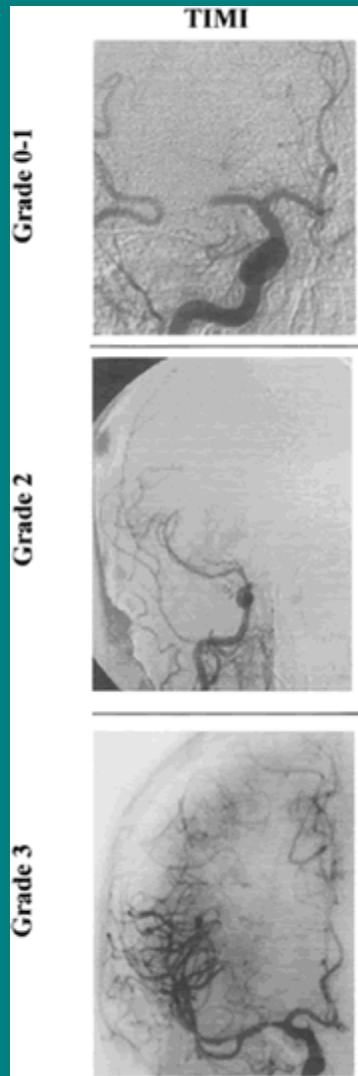
- **Surface cooling** – used in two cardiac arrest trials
 - Requires neuromuscular blockade and ventilatory support to combat shivering
 - Vasoconstriction, reduces heat exchange, makes temp control difficult
 - Lack of control during passive rewarming = reactive brain edema
- **Endovascular cooling** – via central line into femoral or subclavian veins
 - Exchange heat by temperature controlled circulation of cooled saline

Cooling for Acute Ischemic Brain Damage (COOL AID): An Open Pilot Study of Induced Hypothermia in Acute Ischemic Stroke

Derk W. Krieger, Michael A. De Georgia, Alex Abou-Chebl, John C. Andrefsky, Cathy A. Sila, Irene L. Katzan, Marc R. Mayberg and Anthony J. Furlan
Stroke 2001;32:1847-1854

- Open study design, **feasibility** and safety
- NIHSS > 15 w/i 6hrs of onset, MCA
- If NIHSS > 8 persisted, enrolled
- Surface cooling w/i 5hrs for IV tPA, w/i 8hrs for IA tPA (pts intubated, sedated)
- Limited to 12 hrs in pts with TIMI 3 or 3-equivalent
- Remaining pts, rewarming initiated 12hrs after repeat TCD showed TIMI 3-equivalent
- maximum of 72 hrs (32°C)
- 90 day outcomes

- Source: 2001 ACC Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes of Patients With Acute Coronary Syndromes.



- **Grade 0 (no perfusion):** There is no antegrade flow beyond the point of occlusion.
- **Grade 1 (penetration without perfusion):** The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.
- **Grade 2 (partial perfusion):** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (eg, the opposite coronary artery or the coronary bed proximal to the obstruction).
- **Grade 3 (complete perfusion):** Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed from the involved bed and is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

COOL AID

TABLE 2. Feasibility of Surface-Induced Moderate Hypothermia in Acute Ischemic Stroke Patients in Comparison to Nonhypothermia Patients

Patient	Thrombolytic Therapy	Time to Recanalization Therapy, h	Time to Hypothermia, h	Cooling Time, h	Duration of Hypothermia, h	Hospital Stay, d	Intensive Care Unit Stay, d	Intracerebral Hemorrhage
Hypothermia								
1	IA rtPA	1	4.5	5.0	40.0	11.0	2.0	None
2	IA rtPA	4.25	7	2.5	47.5	24.0	18.0	None
3	None	None	6.8	3.5	55.5	17.0	4.0	None
4	IA retevase	5	8	6.5	30.0	9.0	2.0	None
5	IA rtPA	3.25	7.5	3.5	23.5	7.0	4.0	None
6	None	None	6	2.3	37.0	6.0	4.0	None
7	None	None	6.5	3.5	96.0	4.0	4.0	None
8	IV rtPA	2.75	4.3	2.5	60.0	3.0	3.0	Parenchymal hemorrhage
9	IV rtPA	2.5	5	2.3	48.0	11.0	5.0	None
10	None	None	6.5	3.0	36.0	17.0	14.0	None
Mean		3.1	6.2	3.5	47.4	10.9	6.0	
SD		1.4	1.3	1.5	20.4	6.7	5.4	
Nonhypothermia								
1	IA retevase	6	5	2	Parenchymal hemorrhage
2	None	None	7	0	None
3	IA rtPA	5	24	13	Hemorrhagic transformation
4	IA rtPA	2	5	2	None
5	Angiojet	4.5	13	4	None
6	IA rtPA	5.5	8	1	None
7	IA retevase	4.25	11	6	None
8	None	None	13	7	None
9	IA rtPA	3.5	8	2	None
Mean		4.4	10.4	4.1	
SD		1.7	5.0	4.0	

COOL AID

- Moderate hypothermia is technically **feasible**
- Safe
- Can't say anything re: efficacy
- But...all outcome trends favor hypothermia

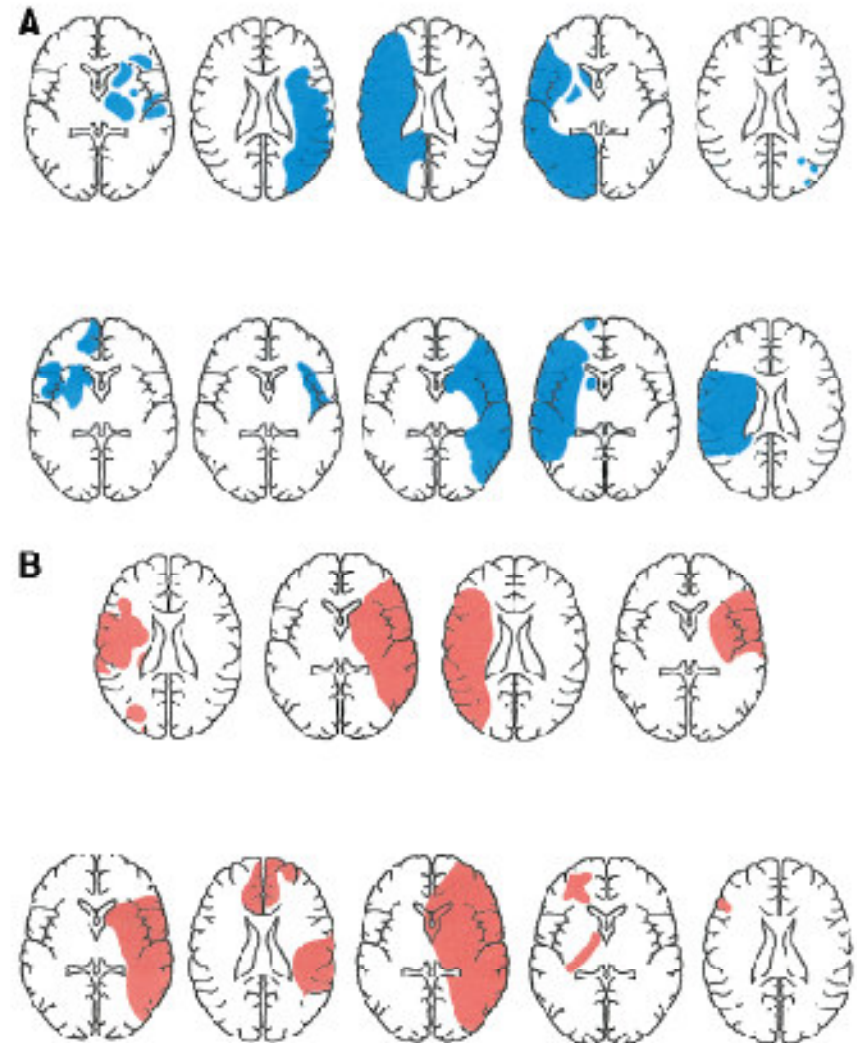


Figure 2. Representation of infarct pattern on 7 to 10 day CT or MRI in hypothermia patients (A) and normothermia patients (B).

Cooling for Acute Ischemic Brain Damage (COOL AID)

A feasibility trial of **endovascular** cooling

M.A. De Georgia, MD; D.W. Krieger, MD; A. Abou-Chebl, MD; T.G. Devlin, MD, PhD; M. Jauss, MD;
S.M. Davis, MD, FRACP; W.J. Koroshetz, MD; G. Rordorf, MD; and S. Warach, MD, PhD

- Clinical **feasibility** trial, randomized
- >18 yrs old, ant circulation stroke, NIHSS ≥ 8 and ≤ 25 , presented w/i 12 hrs
- mRS and NIHSS at 30 + 7 days
- tPA given if indicated
- 40 pts randomized
- Baseline MRI on all pts



Figure 1. The Reprive Endovascular Temperature Management System.

33 °C maintained for 24 hours; shivering suppressed using buspirone, IV meperidine, and surface warming via blanket

Outcomes

- **Feasible, safe**
- Mean time to target temp: 77 ± 44 min
(mean time 3.5 ± 1.5 hrs in previous)
- No overshoot of target temp
- No differences in clinical outcomes
- Infarct volume growth was less, but not significant

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L)

Final Results

- Prospective, randomized, endovascular cooling plus thrombolysis
- <6 hrs from onset, age 18-80, NIHSS ≥ 7
- Feasibility
- Safety

Table 1. Patient Group Randomization by Time of tPA Treatment From Stroke Onset

Hours From Stroke	Group	Patients (No.)	tPA	HY
0-3	1	22	+	-
	2	22	+	+
3-6	3	6	-	-
	4	2	+	-
	5	4	-	+
	6	2	+	+
total		58		

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L). Final Results

Thomas M. Hemmen, Rema Raman, Kama Z. Guluma, Brett C. Meyer, Joao A. Gomes, Salvador Cruz-Flores, Christine A. Wijman, Karen S. Rapp, James C. Grotta, Patrick D. Lyden and for the ICTuS-L Investigators
Stroke published online Aug 19, 2010;

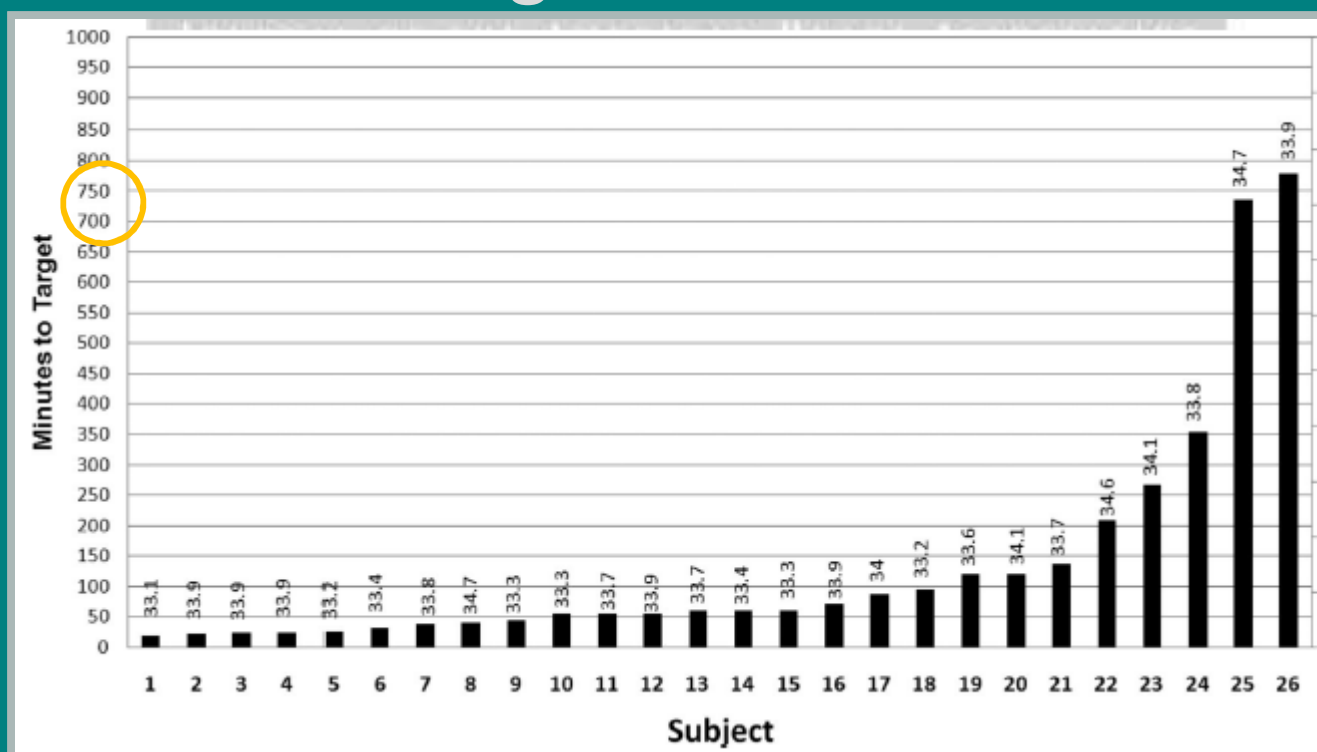
Outcome Measures

Table 3. Outcome Measures Between HY and NT Patients

	HY (Groups 2, 5, 6; n=28)	NT (Groups 1, 3, 4; n=30)	Fisher Exact Test P
mRS 0-1 at 90 days	5	7	0.747
NIHSS at 90 day (mean±SD)	6.3 (±6.6)	3.8 (±3.0)	0.355
At least one SAE (%)	75	43.3	0.018
Pneumonia (%)	50	10	0.001
All ICH (%)	28.6	20	0.752
Symptomatic ICH (%)	3.6	10	0.609
Mortality by 90 days (%)	21.4%	16.7	0.744

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

Time to cooling



Results

- 8/28 pts target temperature NOT reached
- Did NOT find a difference in mortality or mRS in treated pts vs. non-treated
- Serious adverse events more common in treated group (pneumonia)
 - Did NOT affect outcome at 90 days
- **Endovascular hypothermia can be combined with thrombolysis**
- **Antithivering protocol feasible in awake pts**