20 YEARS OF INNOVATION
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Cold Topic: Advanced Treatment Modalities in Acute Stroke

William M. Coplin, MD, FCCM

Associate Prof, Neurology & Neurosurgery

Wayne State University

Chief, Neurology

Medical Director, Neurotrauma & Critical Care

Detroit Receiving Hospital / Detroit Medical Center

wcoplin@med.wayne.edu

CARDIOVASCULAR RESEARCH FOUNDATION

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	EKR Therapeutics, Medivance Inc., Astellas Pharma US, Integra Neurosciences
Consulting Fees/Honoraria	EKR Therapeutics, Medivance Inc., Astellas Pharma US, Integra Neurosciences
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Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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Stroke: Impact

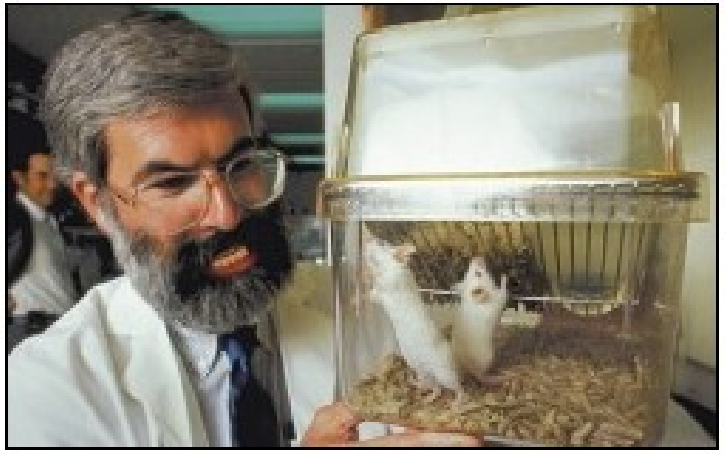
- Stroke is the #1 cause of disability
- Stroke is the #3 cause of death
- 700,000 strokes annually
  - Approximately 87% ischemic
    - 30-50% because of large vessel occlusions
- Every 45 secs someone in US has a stroke
- 10x greater risk of having a repeat stroke than the general population
- Stroke cost estimate at $62.7B in 2007

World's Scientists Admit They Just Don't Like Mice

DECEMBER 8, 2004 | ISSUE 40-49

ZURICH, SWITZERLAND—Nearly 700 scientists representing 27 countries convened at the University of Zurich Monday to formally announce that their experimentation on mice has been motivated not by a desire to advance human knowledge, but out of sheer distaste for the furry little rodents.

ENLARGE IMAGE



White examines detested specimens in his Oxford lab.

"As a man of science, I deal with facts, and the fact is that mice are gross," said Dr. Douglas White, chair of the Oxford biogenetics department and lifelong mouse-hater. "They're squirmy, scurrying little vermin, and they make my skin crawl. I speak for all of my assembled

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CHEF'S SPECIALS

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- Overpriced Happy Family 84.95
  Scallops, crabmeat and psychotropic mushrooms sauteed with fresh chef's thumbs and served on a Sealy Posturpedic.
- ★ Tienanmen Square Beef 17.75
  Oppressed young beef, severely battered, crushed with bamboo shoots and brutally smothered as you watch from your table on a big screen.
- Health Inspector's Seafood Delight ..... FREE!
  Fresh lobster, shrimp and prawns expertly prepared in the clean Mexican restaurant down the block, brought in through our back door and served with a crisp fifty dollar bill rolled in a napkin. (Must be ordered in advance.)

★ May Not be Edible

Waiter will change shirt at your request.

A MAD POSTER

Practical Questions

- Post-ischemic delay?
- Depth?
- Duration of therapy?
- How to rewarm?

Goals of Stroke Care

- Reverse the deficit
- Prevent progression of the deficit/death
- Reperfuse the brain
- Limit the extent of injury
- Prevent increased injury from ICP

Obstacles in Stroke

- Reperfusion injury
- Short therapeutic time window
- Intracranial hemorrhage

Temperature Control vs. Hypothermia in Stroke

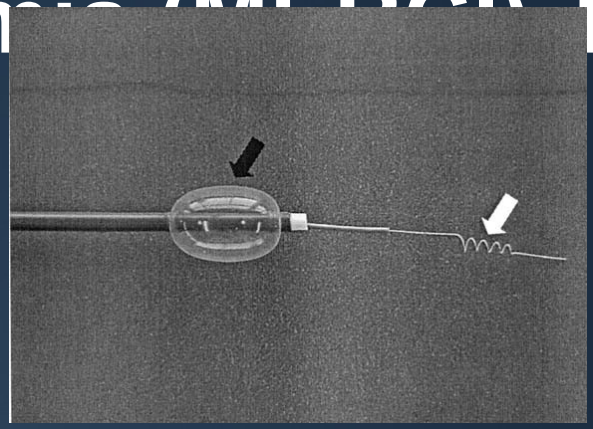
- Ischemic stroke during endovascular revascularization
- Aneurysmal SAH during microsurgical clipping
- Aneurysmal SAH during endovascular coiling
- EC-IC bypass revascularization
- Venous infarction paired with ICP reduction and hemicraniectomy

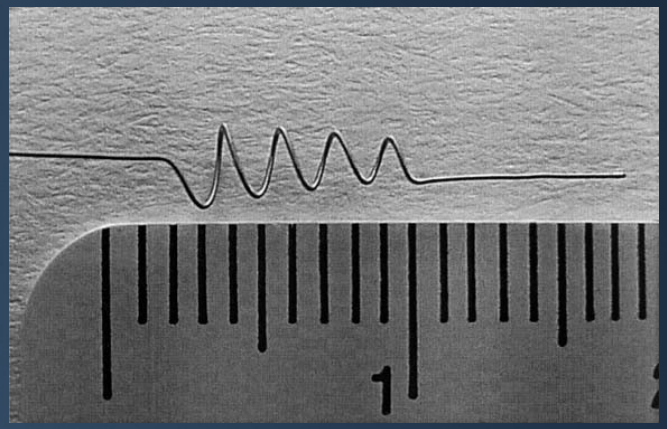
Large Vessel Stroke

- Carotid, MCA, vertebrobasilar arteries
- Poor natural history in large vessel stroke
- Mortality rates from published literature
  - Carotid-T 53% Jansen, 1995
  - MCA 30-35% Chambers, 1987
  - Basilar 89-92% Bruckman, H 1986 & Brandt, 1996

Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial

- Nonrandomized, multicenter trial of MERCI Retriever for large intracranial artery occlusion, ineligible for IV rt-PA and within 8 hrs of symptom onset (N=151)
- Recanalization in 46%
  - 18% in historical controls
  - Better neurological outcomes and lower mortality
- Clinically imprtant procedural complications: 7.1%
- Symptomatic intracranial hemorrhage: 7.8%





Used with permission from Higashida RT. Cerebrovasc Dis. 2005;20(suppl 2):140-147

Smith WS, et al. Stroke. 2005;36:1432-1438

Case Study

31 year old male
Baseline NIHSS score = 10
Symptom onset to treatment = 4 h 30 min

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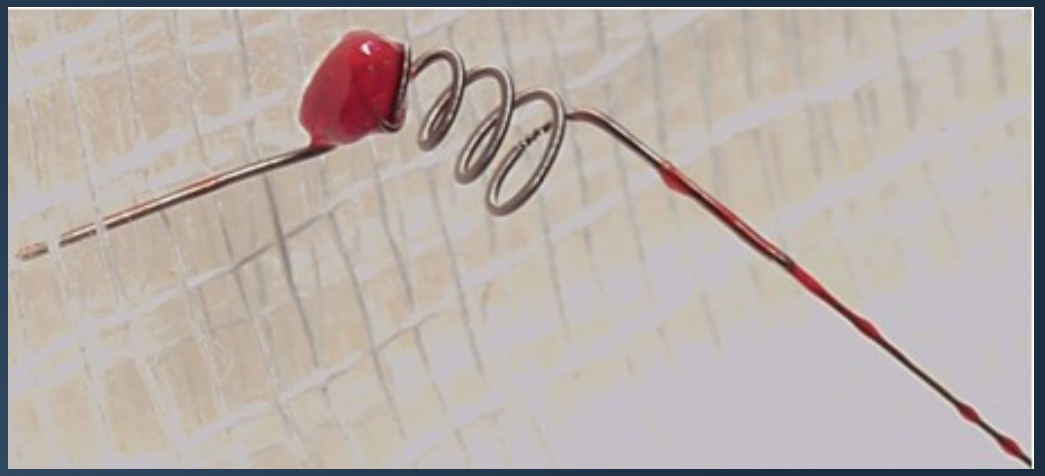
Case Study



NIHSS	24 hours	0
	30 days	0
mRS	90 days	0

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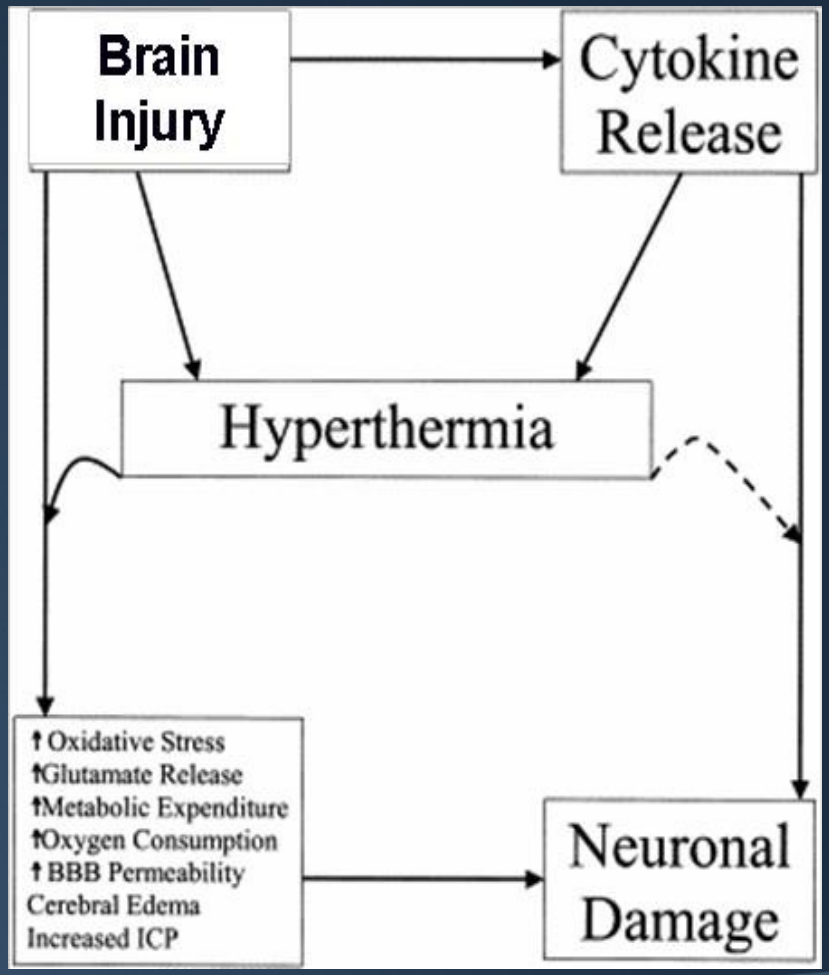
Rationale: Clinical Evidence: Cerebral Infarction

- Elevated temperature is associated with poor outcome after stroke
  - Meta-analysis: Hajat et al, Stroke 2000;31:410
  - Relative risk of poor outcome 2.2 for each 1° C increase in temperature on admission
    - Reith et al, Lancet 1996;347:422
  - Fever in first 24 hours associated with worse outcome
    - Castillo et al, Stroke 1998;29:2455
  - Fever on admission (>37.5 °C) associated with increased 1 year mortality
    - Wang et al, Stroke 2000;31:404

Fever and Brain Injury

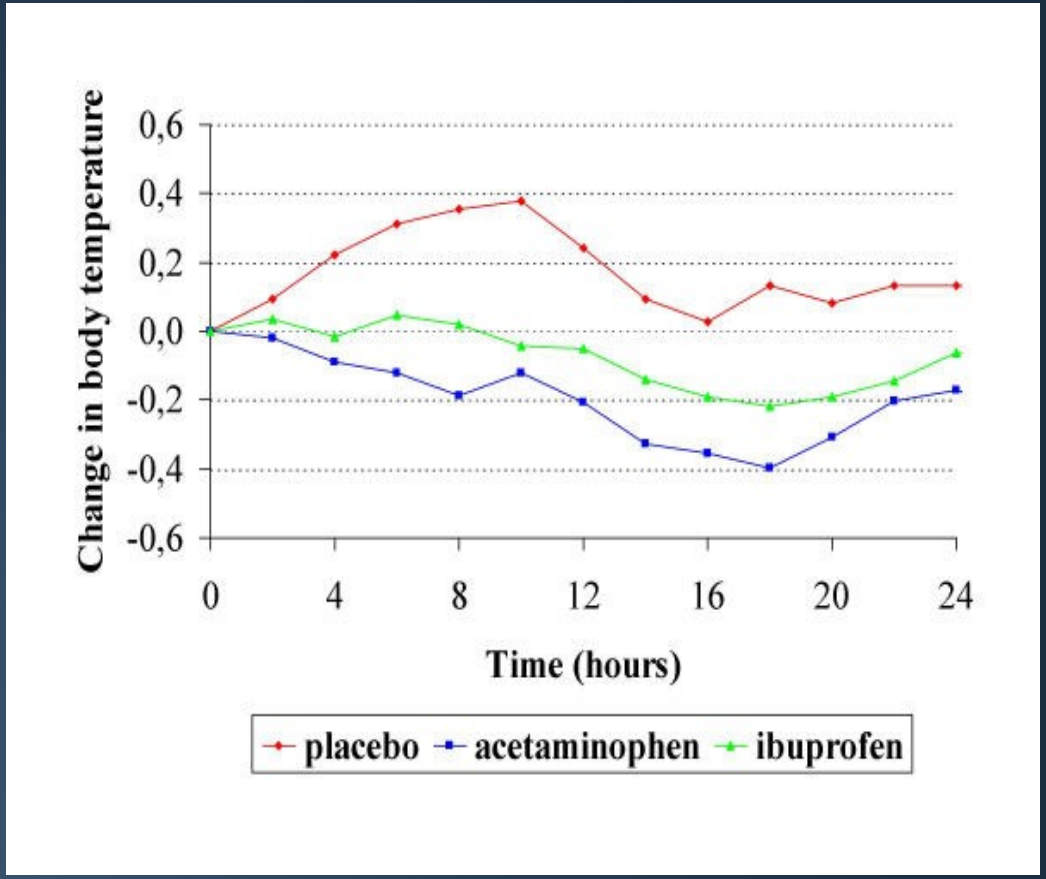
- Fever very common in neurocritical care setting
- Fever burden strongly associated with poor outcome
  - Secondary injury (neuronal damage)
  - Effects on level of consciousness
- Can eliminating fever improve outcomes?



What About NSAIDS?

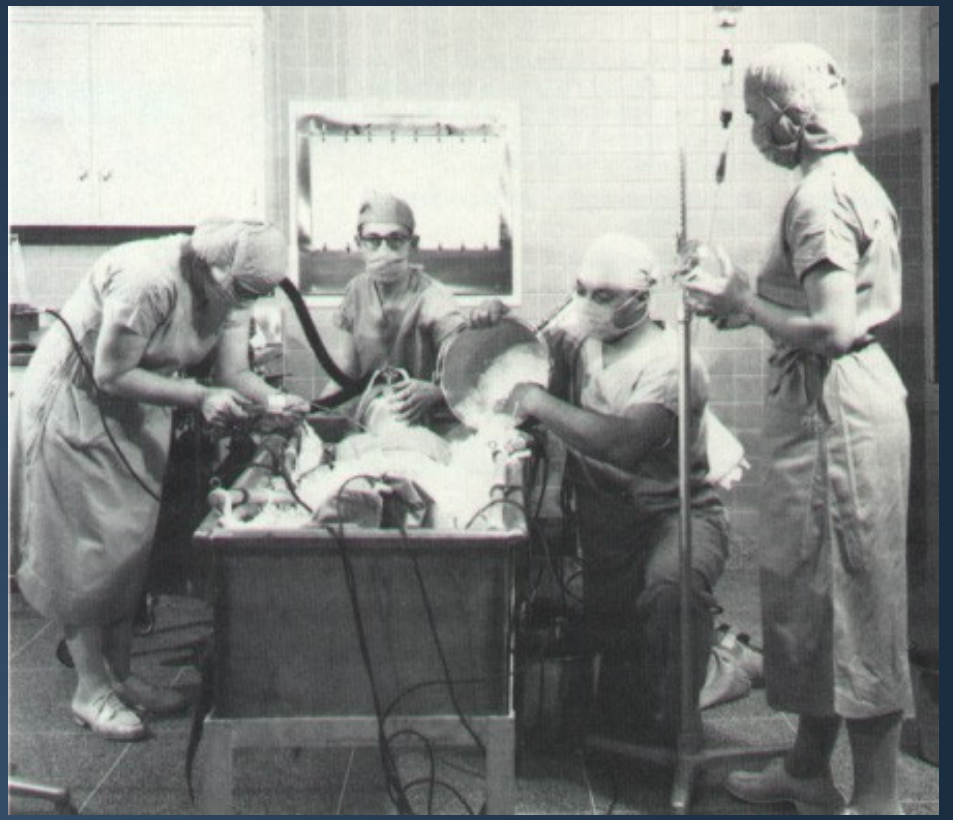
- Comparison of 3 fever Tx in 75 acute stroke patients:
- Acetaminophen (6gm/d)
- Ibuprofen (2400 mg/d)
- Placebo

- Acetaminophen reduced temp x 24 hr
- No better than placebo over 5 days Rx



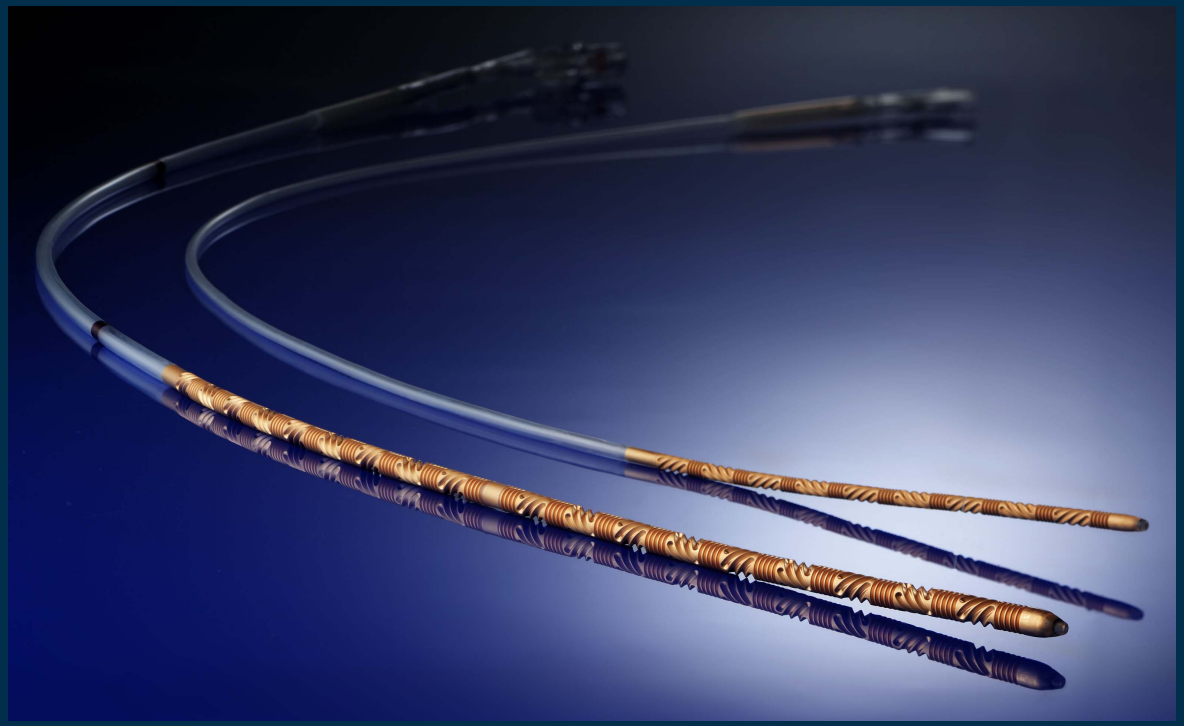
van Breda EJ. BMC Cardiovascular Disorders 2005, 5:24

Hypothermia: Techniques



Out-of-hospital cooling by Emergency Physician (Markus Födisch, Bonn)

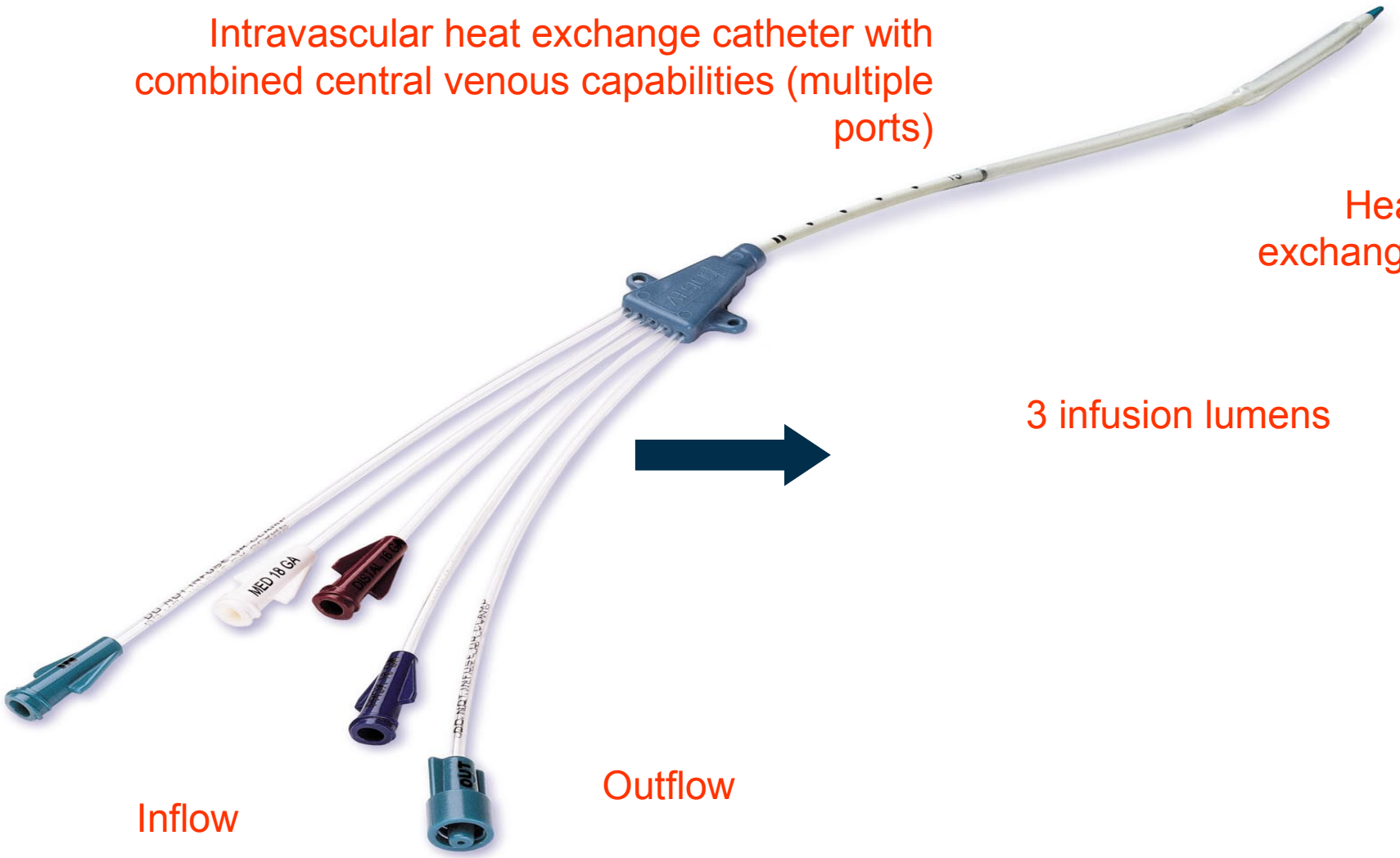
Medivance Arctic Sun



Innercool

Alsius

Intravascular heat exchange catheter with combined central venous capabilities (multiple ports)



Heat exchange

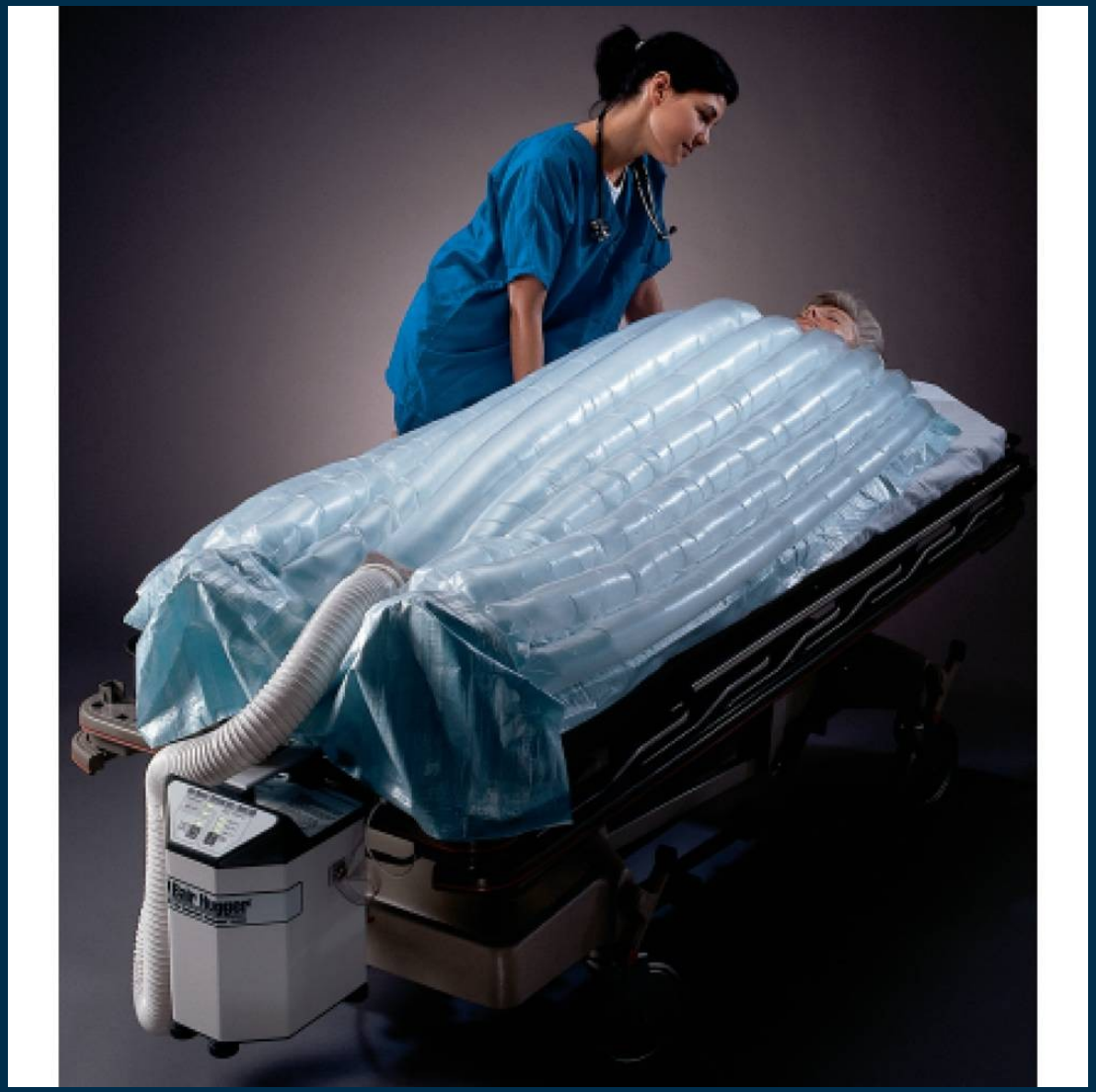
3 infusion lumens

Outflow

Inflow

Cincinnati Sub Zero

Bair Hugger



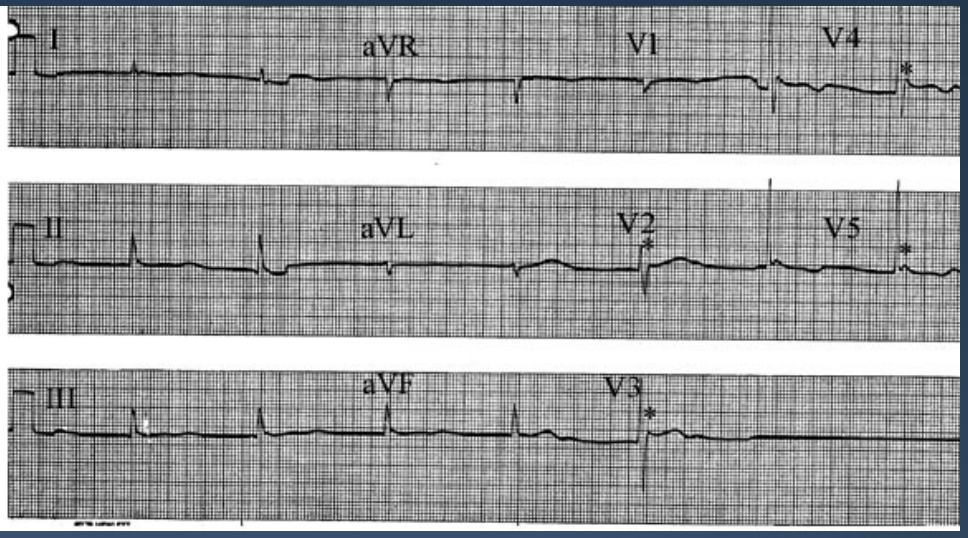
Head Cooling

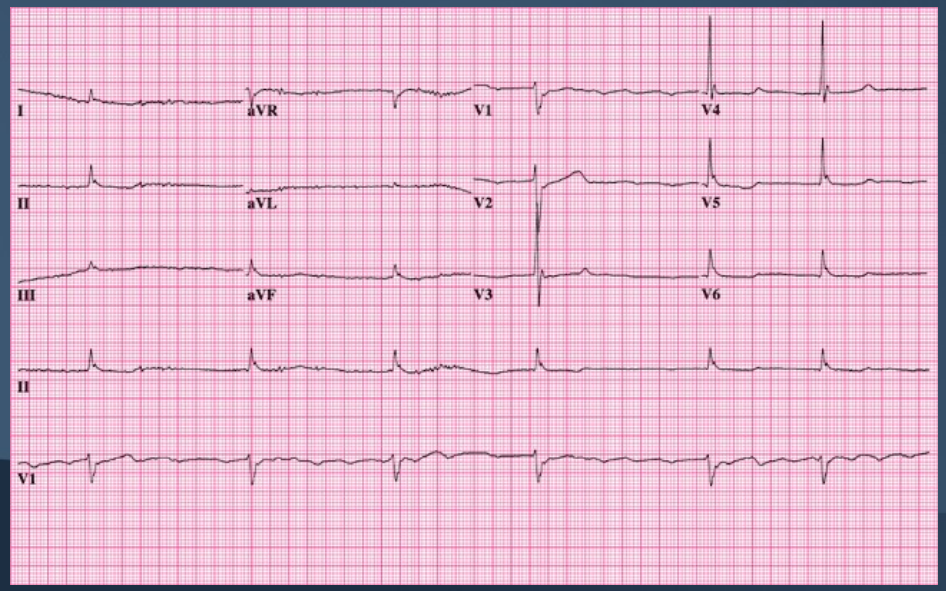
Infant with CoolCap

Effects of Hypothermia and Limits Below Which These Could Appear

T core (°C)	Effect of hypothermia
35	Shivering, peripheral vasoconstriction, ↓O_2 consumption, ↓metabolism
34	Tachycardia, bradycardia, ↓platelet count, impaired platelet function, impaired coagulation cascade
33	Electrocardiographic changes* Slight increase in blood pressure (average 10 mm Hg)
32	Mild dysrhythmias in some patients
31	Consciousness, lethargy, coma
30	“Hibernation”: shivering ceases, marked decrease in rate of metabolism
29	↑↑Risk of tachyarrhythmias, beginning with atrial fibrillation

Osbourne Waves





Shivering Control: Standing

Intervention	Application
Acetaminophen	650 mg every 4 hours PRN heat generation or active cooling, to minimize the pyrogenic response
Buspirone enterally	30 mg every 8 hours. Works synergistically with opioids to lower the shivering threshold.

PRN Shivering, Step 1

Intervention	Application
Skin counterwarming	e.g., Hands and feet; forced air convection warming blanket (Bair Hugger®) at 40-43° C
Face and neck air warming [OPTIONAL]	Standard face tent with 6-10 L/min of humidified air warmed to 40°C

PRN Shivering, Step 2

Intervention	Application
Meperidine	50-100 mg bolus followed by 12.5-50 mg q 30 minutes
Propofol infusion*	5-50 µg/kg/min
Dexmedetomidine infusion	Loading dose 1 µg/kg over 10 minutes followed by an infusion of 0.3 to 1.5 µg/kg/hour
Fentanyl infusion*	25-75 µg bolus dose followed by 50-200 µg/hour
Magnesium infusion	Start at 1g/hour and titrate to serum magnesium of 3-4 mEq/L

Besides size, what else can increase risk poor outcome after stroke?

- Poor clinical grade
- Volume depletion (dehydration)
- Bleeding
- Low cardiac output (LV dysfunction)
- Smoking
- Chronic hypertension
- Fever

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Strategies to Prevent and Treat Delayed Deterioration Form Stroke

- Isotonic crystalloids to maintain euvolemia
- Fever control
- Monitor/treat LV dysfunction
- Blood pressure monitoring and control

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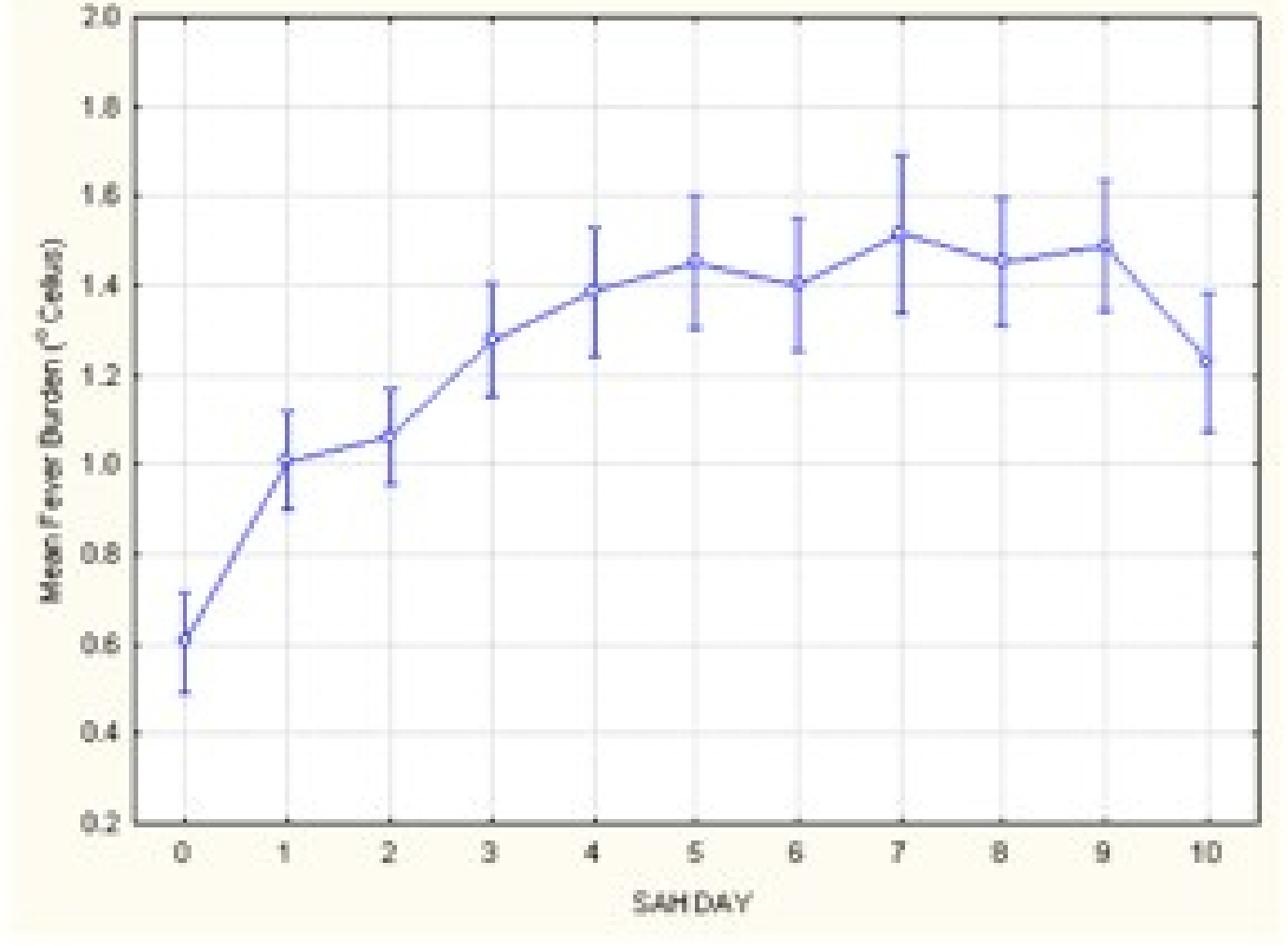
Time Course of Fever Burden after SAH



Therapeutic Temperature Modulation (TTM) in SAH or ICH

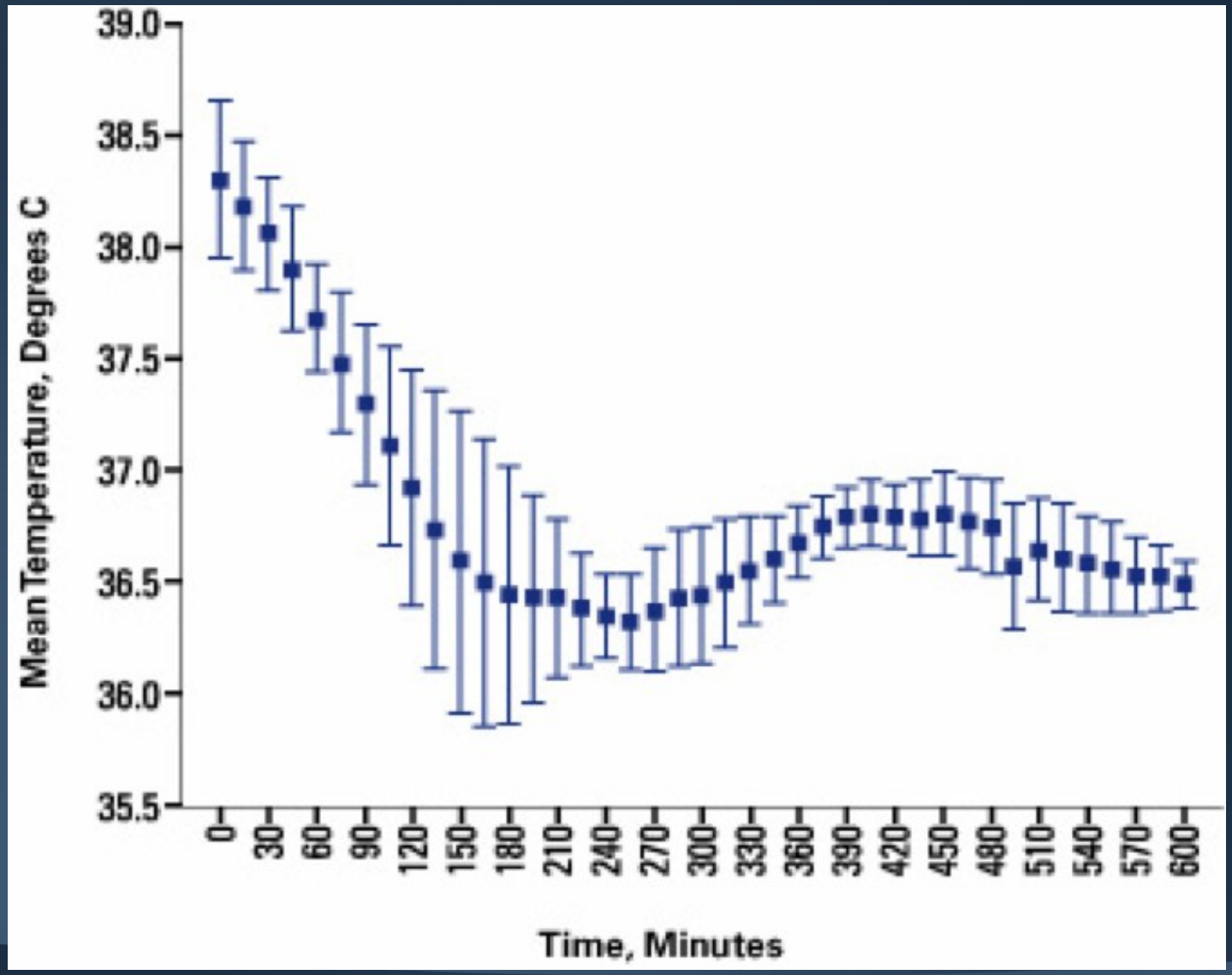
- One small uncontrolled single-center pilot
- N=9 SAH patients with refractory fever
- Innercool Celsius control system
- Target: Normothermia within 24 hours
  - Target attained in 78% (7/9)
- Complications
  - DVT in 22% (2/9)

Badjatia N et al. Neurocritical Care 2002;1:145

Therapeutic Temperature Modulation in AIS, SAH or ICH

- Uncontrolled single-center pilot (N=6)
- >38 C refractory to acetaminophen, ibuprofen
- Medivance Arctic Sun control system
- 38.4 → 36.9 C in 120 min
- Temperature "locked" at 36.55 °C for 600 min
- No complications
  - Skin integrity preserved

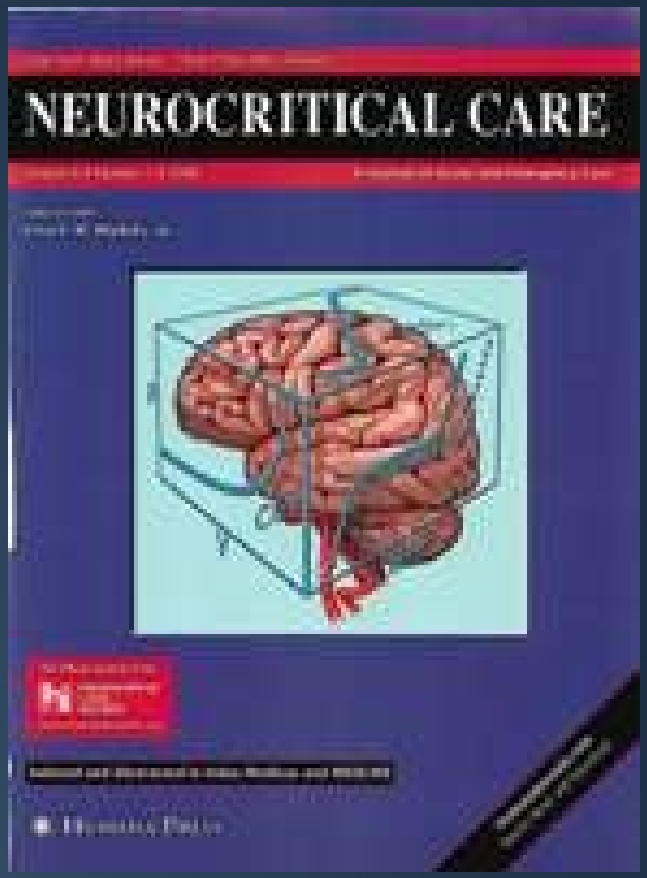
Carhuapoma, Gupta, Coplin et al. J Neurosurg Anesthesiol 2003;15:313


Mean Temperature, Degrees C
39.0
38.5
38.0
37.5
37.0
36.5
36.0
35.5
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
510
540
570
600
Time, Minutes

Is there a role for hypothermia in managing stroke?

- SAH
  - *Poor grade (Hunt-Hess 4-5)*
    - Acute hypothermia x 24 hours
    - ICU fever control for days 1-10
- ICH
  - *Comatose*
  - *IVH*
    - ICU fever control for days 1-10

Shameless Plug



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