Neuroprotezione:
Implicazioni cliniche dell'ipertermia,
evidenze scientifiche sperimentali e cliniche

Dichiarazione conflitto di interessi

In qualità di docente/relatore/tutor, ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012, per conto del Provider SIAARTI ID 205

dichiaro

che negli ultimi due anni non ho avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Learning outcome

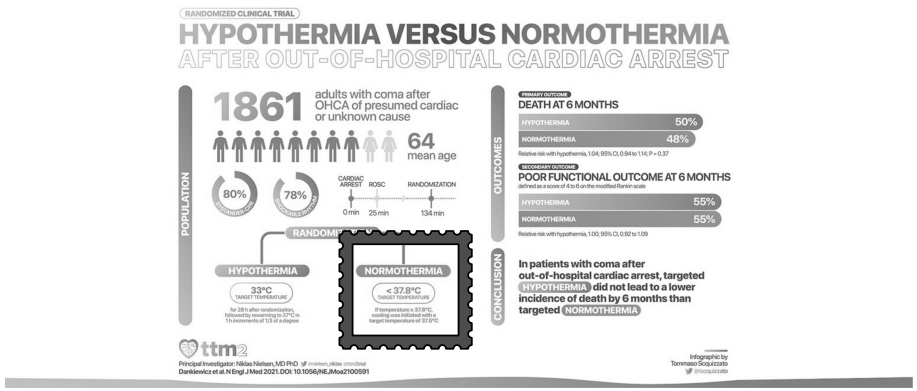
- Definition of fever
- What is normothermia?
- Mechanism of cellular damage
- Fever in injured brain
- Recommendations
- Neuro-protection after cardiac arrest
- Limitation and a sneak peek of future

What's fever?

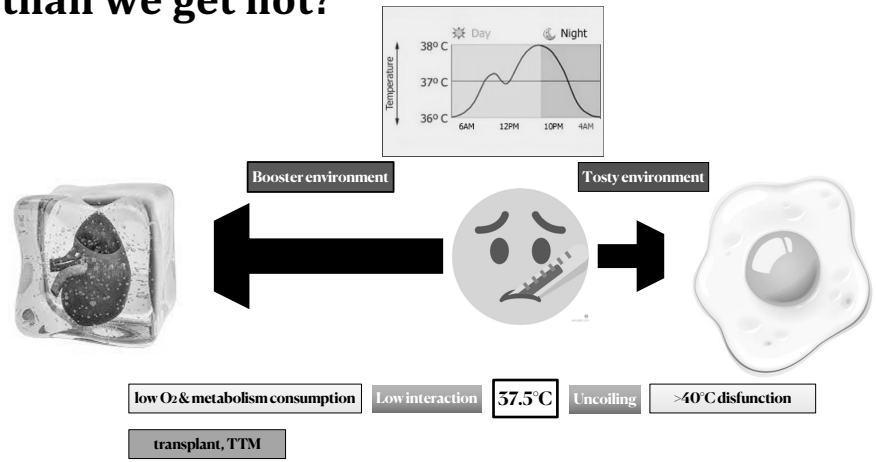
"a state of elevated core temperature, which is often, but not necessarily, part of the defensive response"

no universally accepted thermal definition of fever exists to this day.

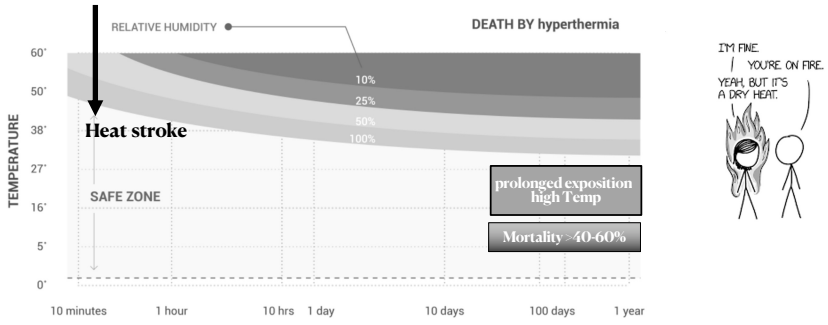
What's normothermia?



Why can we get much cooler than we get hot?

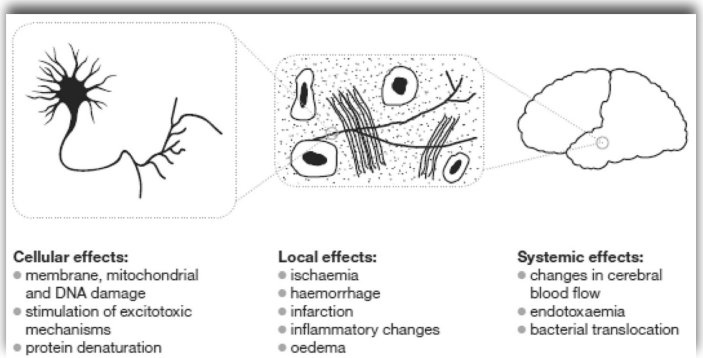


EXTREME HEATWAVES: SURPRISING LESSONS FROM THE RECORD WARMTH

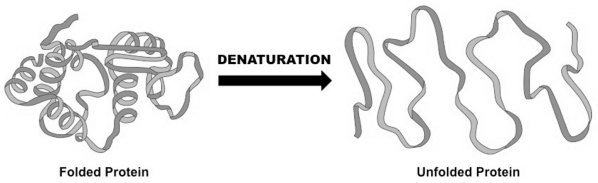


Nature | Vol 608 | 18 August 2022

Mechanism of cerebral damage

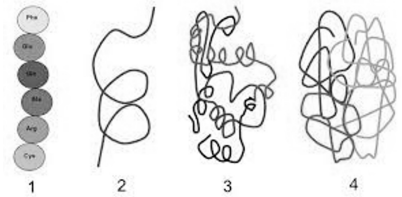


Cellular effects of hyperthermia



Cellular denaturing

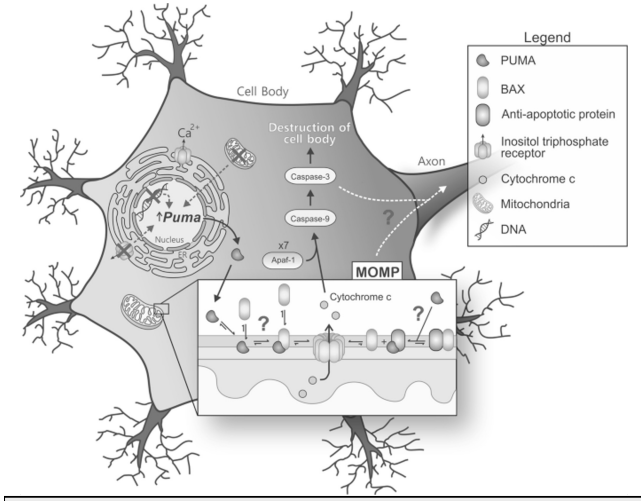
↑ ionic flux
mitocondrial dysfunction



>40°C Aggregates

HT potentiates damage caused by toxic insults like hypoxia and ischaemia

Neuronal death



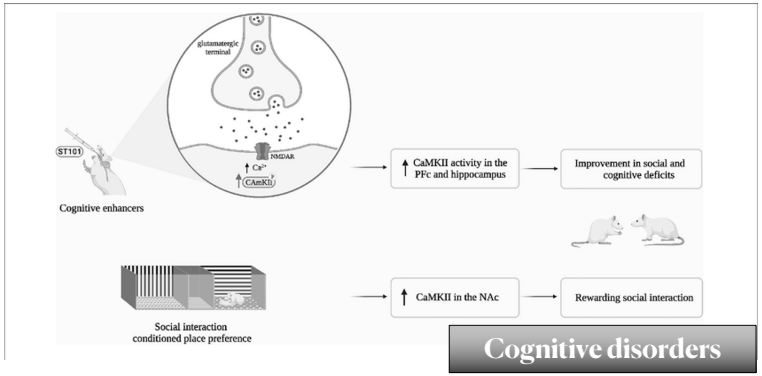
Caspase
Apoptosi

Cell death ↑
glutamate e glycine

Heat shock proteins

AD, SM, TBI

Changes in channel signaling



Cognitive disorders

Fever in injured brain

Clinical paper

Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest☆

John Bro-Jeppesen[a,*], Christian Hassager[a], Michael Wanscher[b], Helle Søholm[a], Jakob H. Thomsen[a], Freddy K. Lippert[c], Jacob E. Møller[a], Lars Køber[a], Jesper Kjaergaard[a]

Similar PFC vs No fever

CrossMark

>39°C for >7h

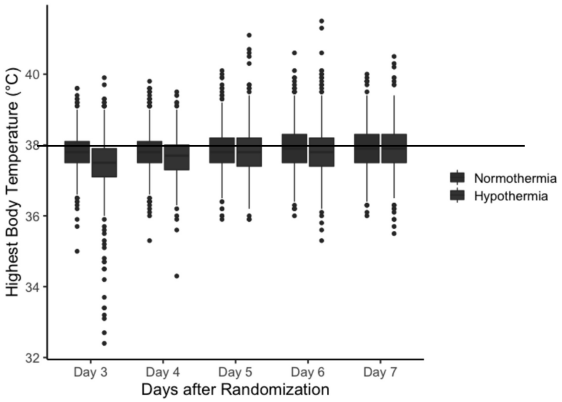
Question?

marker or secondary damage?

Should we actively treat or prevent PCF?

Protocols include a post cooling TH period..
is this improving the neurological outcome?

TTM2 trial fever



ERC-ESICM Recommendations

GOOD PRACTICE
We **recommend** continuous monitoring of core temperature in patients who remain comatose after ROSC from cardiac arrest.

LOW
We **recommend** actively preventing fever (defined as a temperature > 37.7°C) in post-cardiac arrest patients who remain comatose.

GOOD PRACTICE
We **recommend** actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose.

GOOD PRACTICE
There is currently insufficient evidence to recommend for or against temperature control at 32-36°C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this. We **recommend not** actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia.

MODERATE
We **recommend not** using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC.

Hyperthermia after brain damage

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Department of Anesthesia, Carver College of Medicine, University of Iowa, Iowa City, Iowa

CLINICAL STUDIES

Perioperative Fever and Outcome in Surgical Patients with Aneurysmal

> Lancet. 1996 Feb 17;347(8999):422-5. doi: 10.1016/s0140-6736(96)90008-2.

70%
1/3 non infctive

Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome

mortality >1°C

J Reith [1], H S Jørgensen, P M Pedersen, H Nakayama, H O Raaschou, L L Jeppesen, T S Olsen

Stroke
Volume 26, Issue 11, November 1995; Pages 2040-2043
https://doi.org/10.1161/01.STR.26.11.2040

American Heart Association.

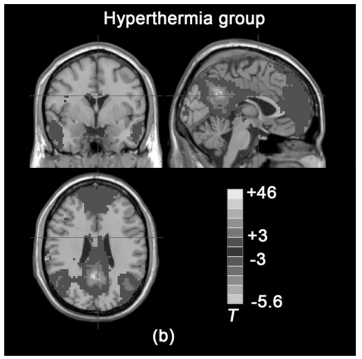
ARTICLE

Fever in Acute Stroke Worsens Prognosis

A Prospective Study

>37.9°C

Neurocognitive disorders



> Intensive Care Med. 2009 Aug;35(8):1454-8. doi: 10.1007/s00134-009-1500-x. Epub 2009 Apr 29.

Early organ dysfunction course, cooling time and outcome in classic heatstroke

Sebastian Pease [1], Lila Bouadma, Nathalie Kermarrec, Frédérique Schortgen, Bernard Régnier,

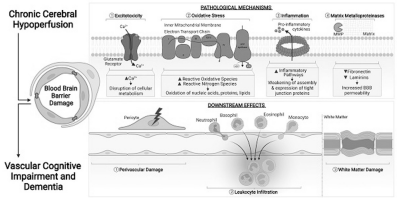
Controlled Clinical Trial > Int J Hyperthermia. 2012;28(7):621-6.
doi: 10.3109/02656736.2012.705217. Epub 2012 Sep 4.

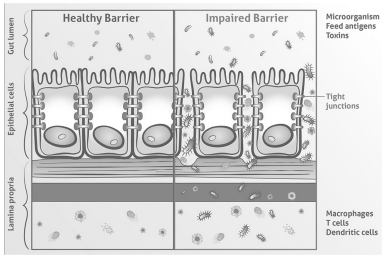
Hyperthermia impairs the executive function using the Attention Network Test

Gang Sun [1], Xiao Yang, Qingjun Jiang, Kai Liu, Bo Li, Li Li, Lun Zhao, Min Li

limbic system: memory and learning ability
prefrontal cortex: executive functions
intraparietal sulcus: processing and memory

Systemic effects of Hyperthermia





> Neuroscience. 2009 Jul 7;161(3):926-39. doi: 10.1016/j.neuroscience.2009.04.004. Epub 2009 Apr 9.

Permeability of the blood-brain barrier depends on brain temperature

start >38°C

E A Kiyatkin [1], H S Sharma

Review > Prog Brain Res. 2007;162:153-69. doi: 10.1016/S0079-6123(06)62009-8.

Cerebral pathophysiology and clinical neurology of hyperthermia in humans

Olaf L Cremer [1], Cor J Kalkman

CBF, Oxigen and glucose consumption

> Aviat Space Environ Med. 1979 Aug;50(8):816-9.

Increased survival in experimental dog heatstroke after reduction of gut flora

G Bynum, J Brown, D Dubose, M Marsili, I Leav, T G Pistole, M Hamlet, M LeMaire, B Caleb

Treatment

Farmacologic

Active cooling

Rebound hyperthermia

ORIGINAL INVESTIGATION

Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome

Andrea Zeiner, MD; Michael Holzer, MD; Fritz Sterz, MD; Waltraud Schörkhuber, MD; Philip Eisenburger, MD; Christof Havel, MD; Andreas Kliegel, MD; Anton N. Laggner, MD

Therapeutic Hypothermia and Temperature Management > Vol. 7, No. 4 > Original Articles

Clinical Effect of Rebound Hyperthermia After Cooling Postcardiac Arrest: A Meta-Analysis

Parth Makker, Yumiko Kanei, and Deepkia Misra

Published Online: 1 Dec 2017 | https://doi.org/10.1089/ther.2017.0009

systemic inflammatory response, infection and neurogenic

Recap

Common insult to the CNS.
Neurocognitive effects, in some cases, may persist after the acute insult

Histopathological and neuroradiological changes are reported

A core temperature of 40 °C is associated long-term or permanent neurological damage, consistent with the cellular changes and cell death

The mechanism of the cerebral damage is unclear (combination of direct cytotoxic damage and indirect systemic effects inhibiting neuronal function)

Current treatment is essentially limited to cooling

Bacterial and endotoxin translocation from the GI tract. A novel targets for future treatments to minimise neurological complications