Exertional Heat Illness: Physiology, Pathology & Modifying Factors

Heat Related Illness - State of The Science Meeting

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OUTLINE

- Serious & Exertional Heat Illnesses
- Exercise Hyperthermia
- Physiology & Pathophysiology
- Heat Acclimation & Acquired Thermal Tolerance
- Conclusions

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Serious & Exertional Heat Illnesses

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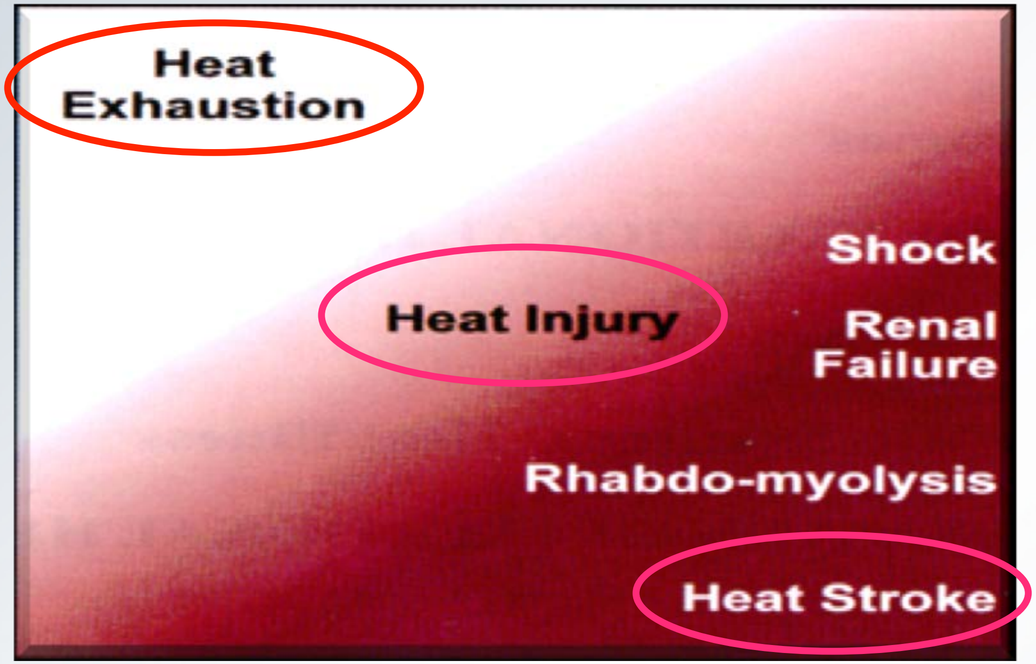
Serious Heat Illness: Spectrum of Severity



Moderate → **Severe**

<u>Heat Exhaustion</u>: Inability to Sustain Adequate Cardiac Output with Moderate to High Body Temperature.

<u>Heat Injury</u>: Organ (liver, renal) & Tissue (muscle, gut) Injury with High Body Temperature.

<u>Heat Stroke</u>: Central Nervous Dysfunction, Organ (liver, renal) & Tissue (muscle, gut) Injury with High Body Temperature (>40°C).

Gardner & Kark <u>Text. Mil. Med</u>. 2001

Sawka & O'Connor <u>Goldman-Cecil Med</u>. 2016

Exertional vs Classic Heat Stroke

- **<u>Classic</u>: Passive Heat Stress.** **(Overwhelming)**
- **<u>Exertional</u>: Physical Activity & Heat Stress.** **(Overwhelming or Routine)**

<u>Stroke-Like Symptoms</u>: Sudden Speech, Movement & Cognitive Impairments; but Extends Beyond Central Nervous System

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Comparison of Classic vs Exertional Heat Stroke

Patient Characteristics	Classic	Exertional
Age	Young & Elderly	15 – 55 years
Health	Chronic Illness	Usually Healthy
Weather	Heat Waves	Variable
Activity	Sedentary	Strenuous Activity
Drug Use	Diuretics, Antidepressants, Anticholinergics, Antipsychotics	Ergogenic Stimulants, Cocaine
Sweating	Often Absent	Common
Fever	Unusual	Common
Acute Renal Failure	Uncommon	Common (15%)
Rhabdomyolysis	Uncommon	Common (25%)
DIC	Mild	Marked

Sawka & O'Connor. Goldman-Cecil Medicine 2016

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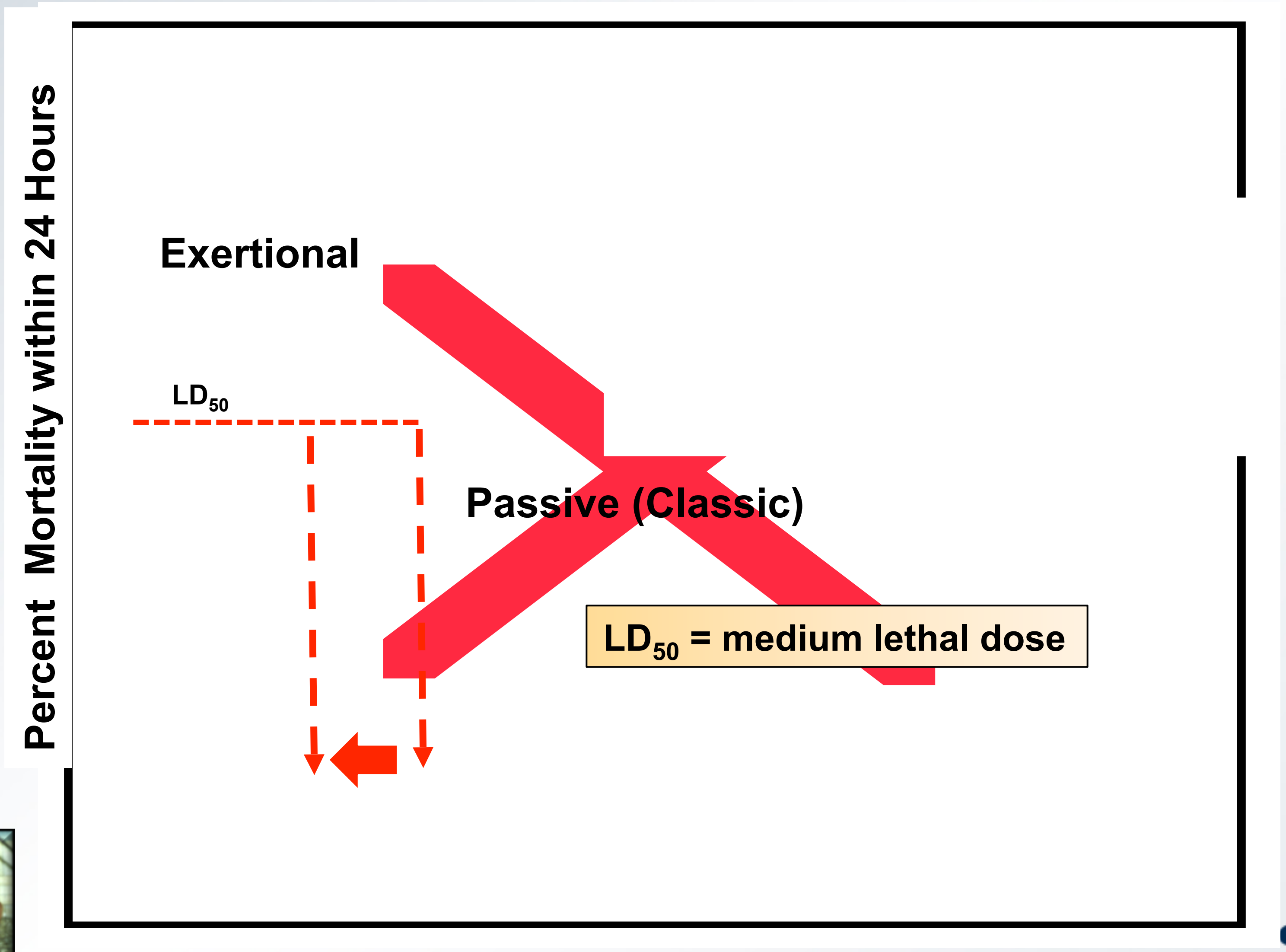
Exertional vs Classical Heat Stroke: Mortality in Rats



Hubbard et.al. JAPPL 1977

Hypotheses of Exertional Heat Stroke (EHS)

- **<u>Conventional</u>: Heat Stress Overwhelms Physiological Compensation.**

- **<u>Multiple-Hit Hypothesis</u>: Precedent Event Increases Risk During Subsequent Heat Stress Exposure.**
  - **Initial Exposure <u>Augments Exercise Hyperthermia</u>**
    (e.g., Fever)
  - **Initial Exposure <u>Sensitizes Tissues</u> to Injury**
    (e.g., Interferon Gamma / Alpha, Cytokine Storm)

Sonna et.al. <u>JAPPL</u> 2004
Sonna et.al. <u>Prog. Brain Res</u>. 2007

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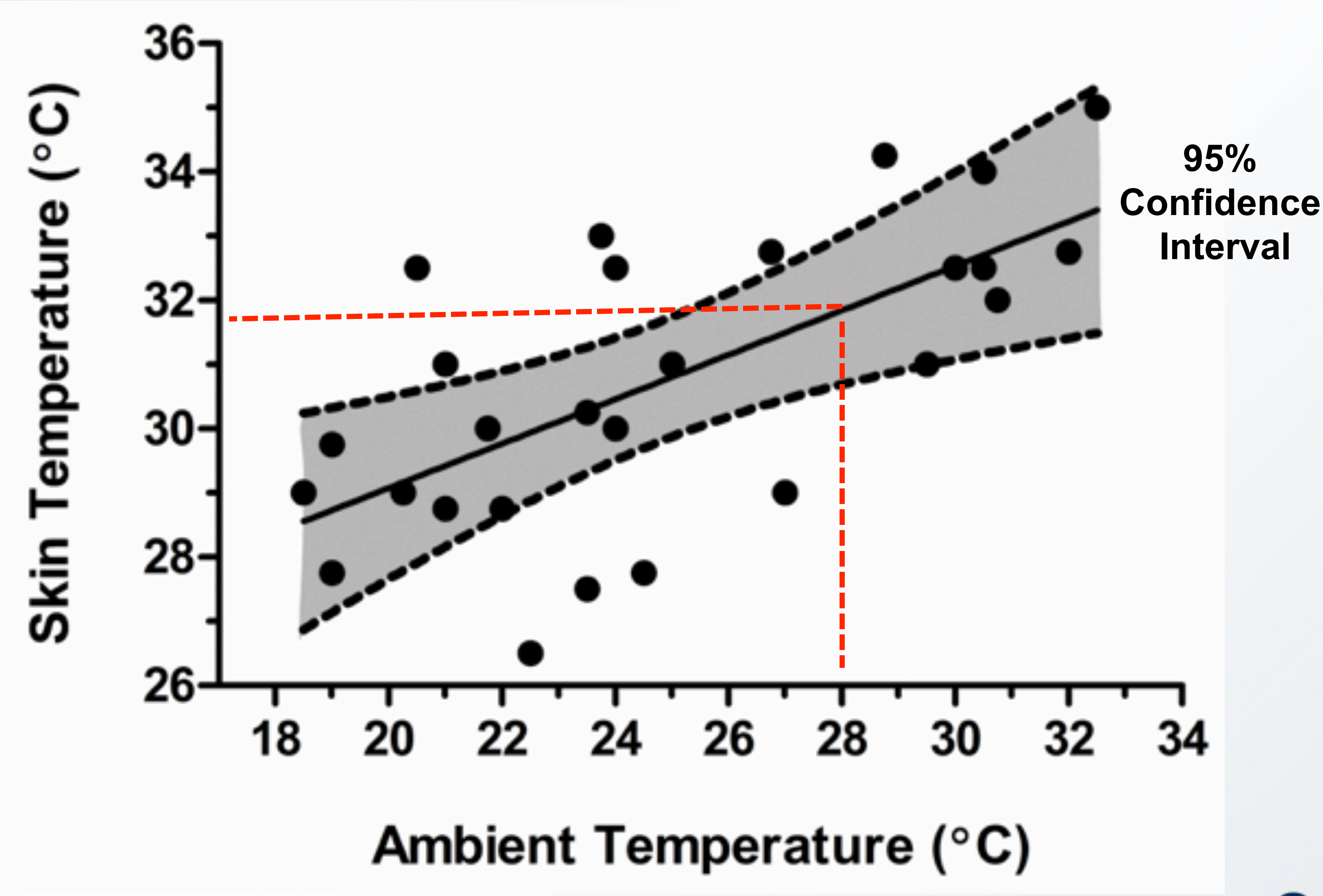
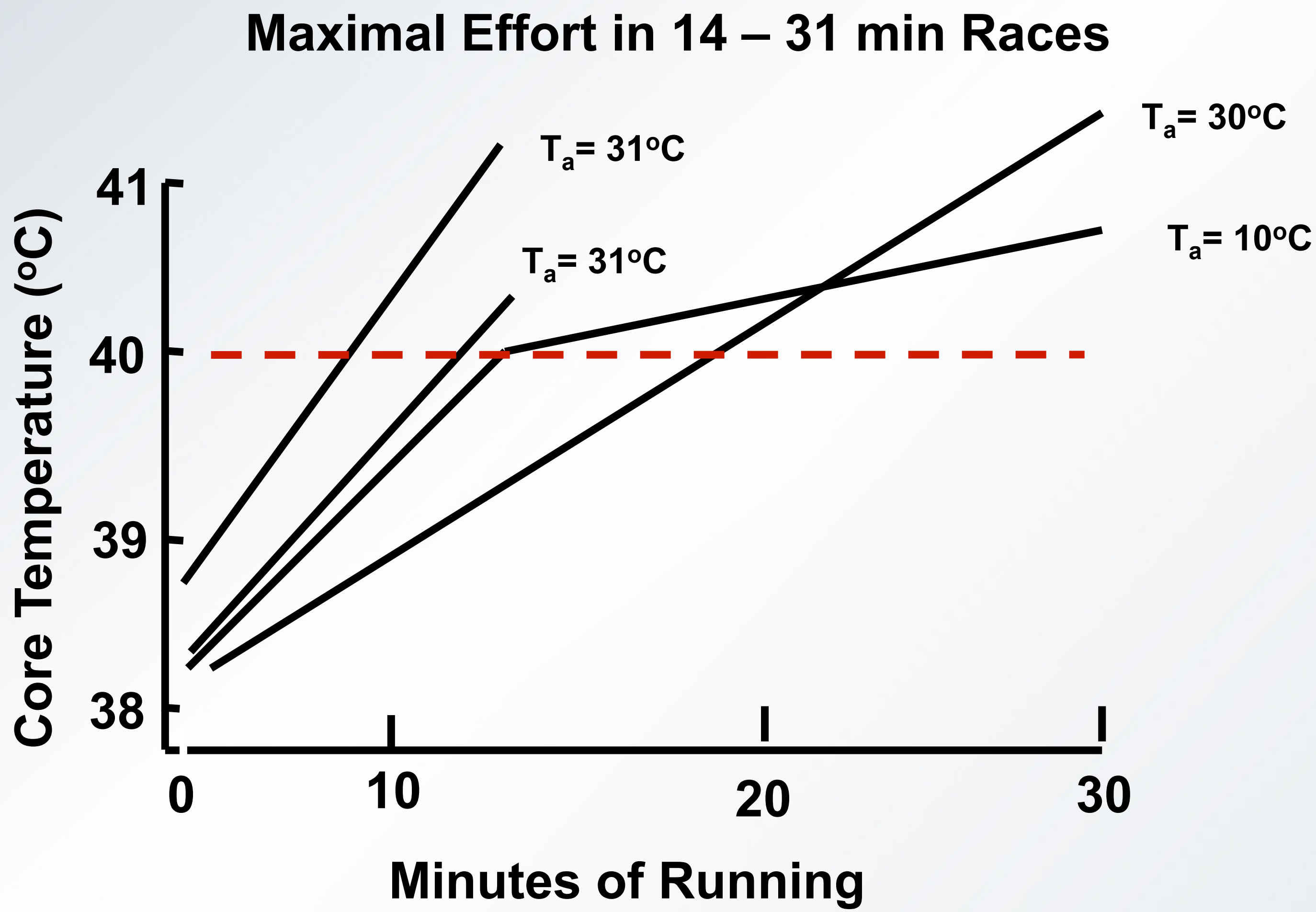
Exercise Hyperthermia

Skin Temperature Increases With Ambient Temperature (impact of Airflow, Sun & Forced Convection)



Adams, WC Ann. NY Acad. Sci. 1977

High Core Temperatures in Champion Runners



Robinson, Pediatrics 1963

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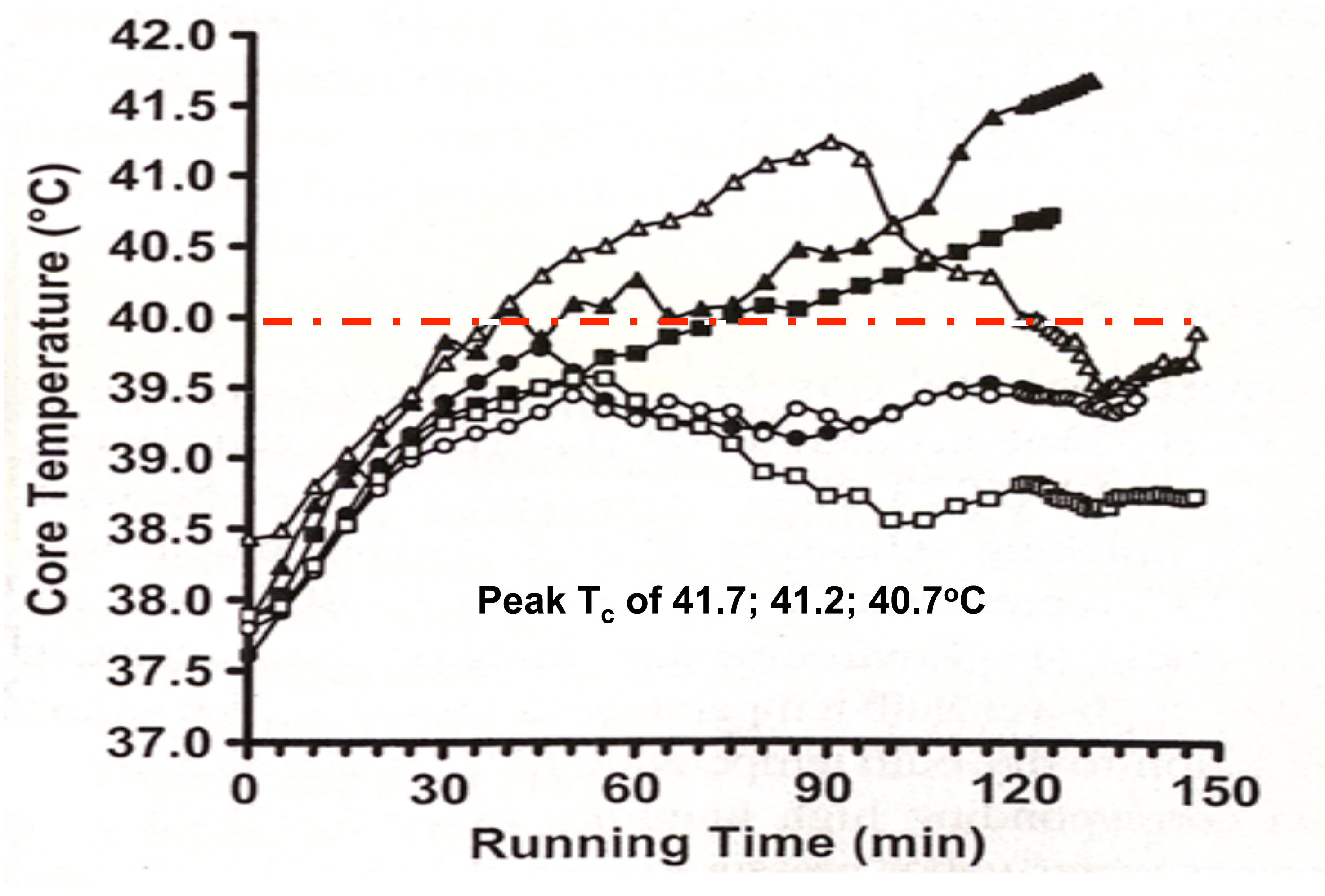
High (>40°C) Core Temperatures Common in Competitive Runners

21 Km Race in Warm – Humid Weather



Byrne et.al. MSSE 2006

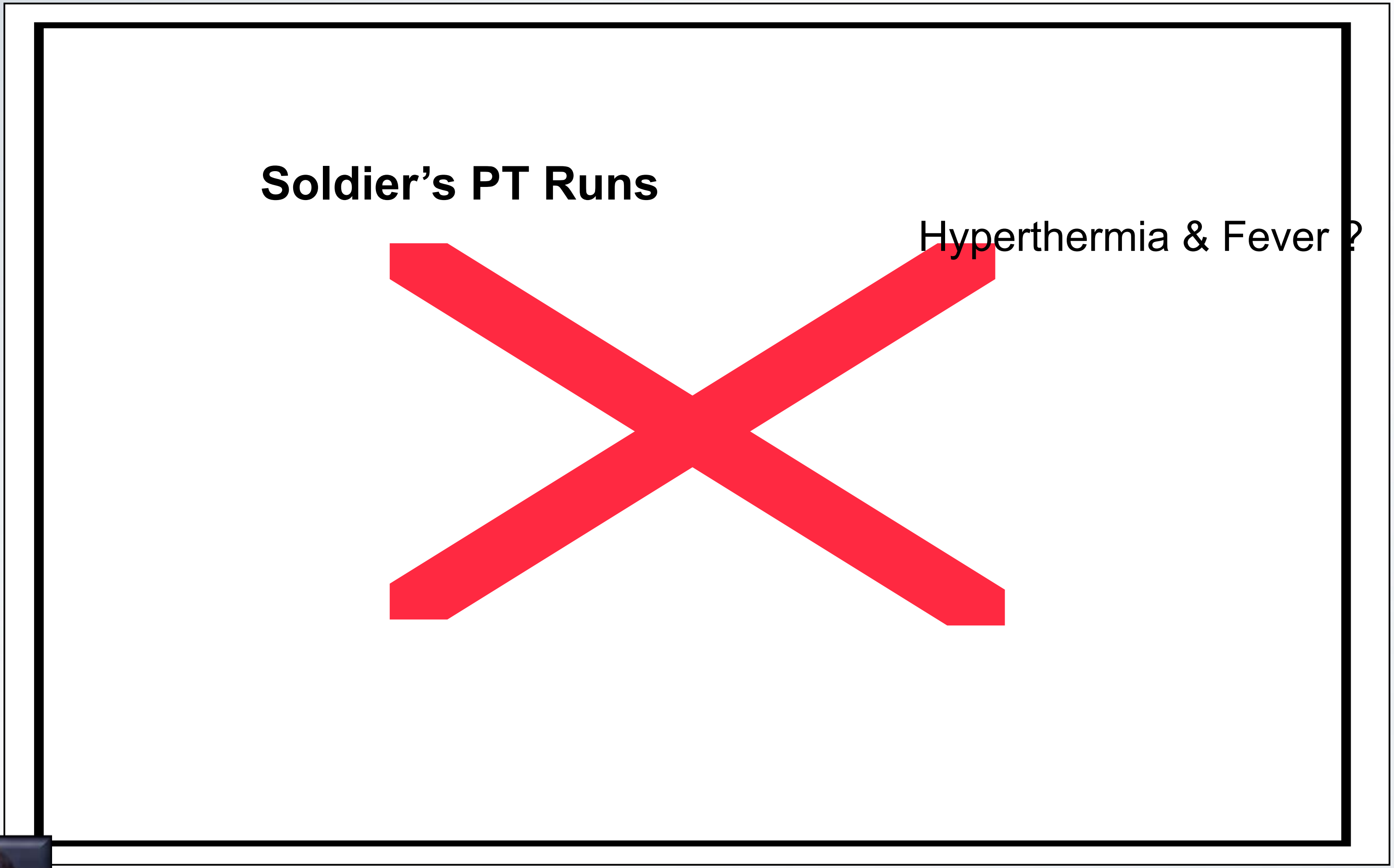
Epidemiologic Findings Suggest Acutely Altered Thermoregulation

EHS is Exertional Heat Stroke

- **Fatal EHS 71% (125 cases) Acute Without Warning** Malamud et.al. Mil. Surg. 1946
- **EHS 75% in First 10 km of March or Run** Shibolet et al. Q.J. Med. 1967
- **EHS 50-60% Occurred During Early Portions of March or Run** Epstein et al. MSSE 1999

"Explosive Increase in Body Temperature"- Common Observation

Idiosyncratic Hyperthermia with Exertional Heat Stroke , What is Different ?



C.B. Wenger, Unpublished (presented in Sawka et.al. Compr. Physiol. 2011)

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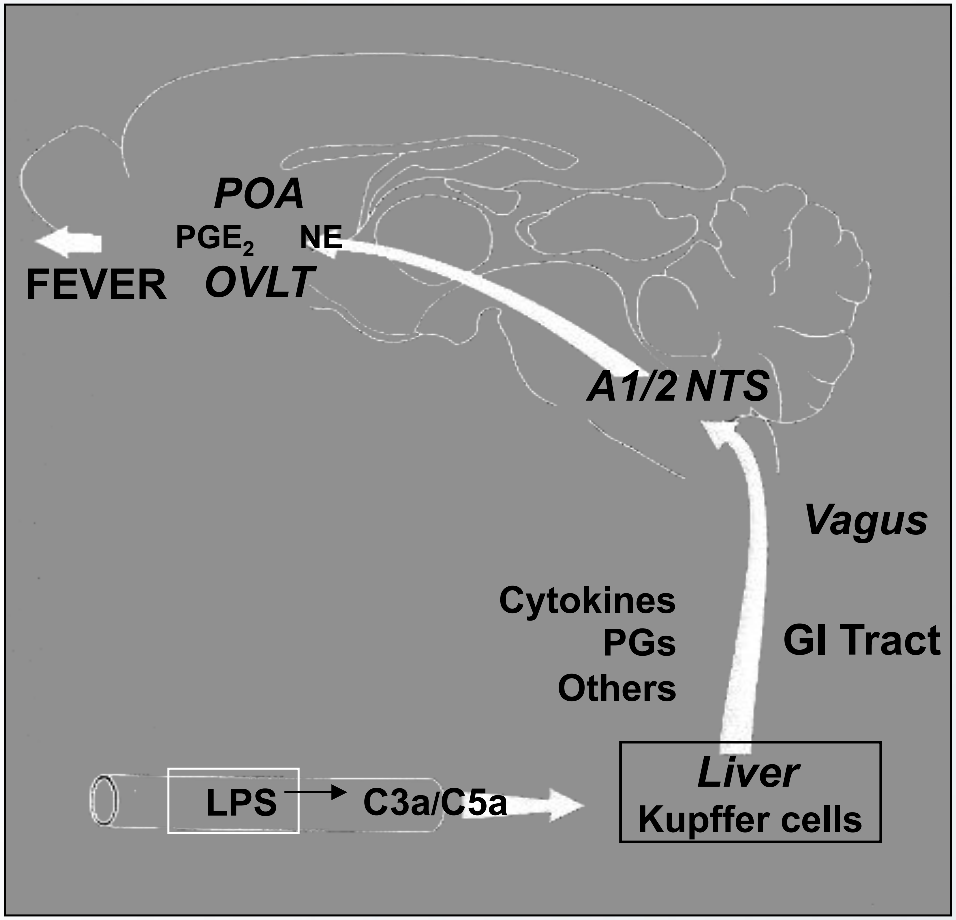
Rapid Fever: Endotoxin Mediated Neural Pathway
(Altered Thermoregulatory Control)

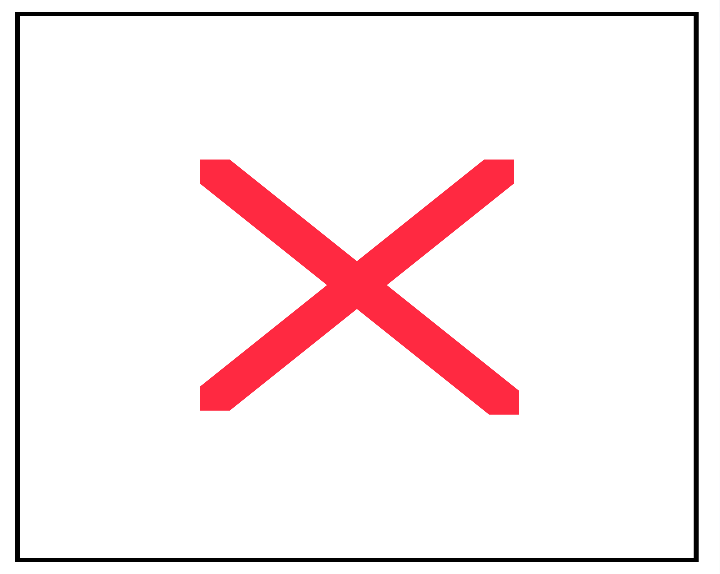
- Endotoxin Activates Peripheral Febrile Message
- Conveyed From Liver by Vagus Nerve Afferents
- Produces PGE_2 Fever

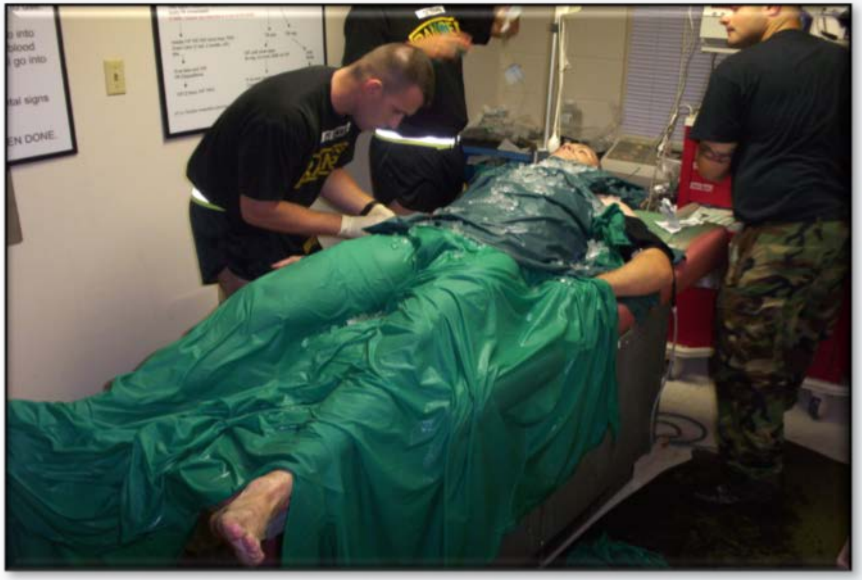


Blatteis Prog. Brain Res. 2007

LPS – Lipopolysacharide Endotoxin
OLVT – Organum Vasulosum Laminae Terminalis
PG - Prostaglandins
POA – Preoptic-Anterior Hypothalamus

Physiology & Pathophysiology

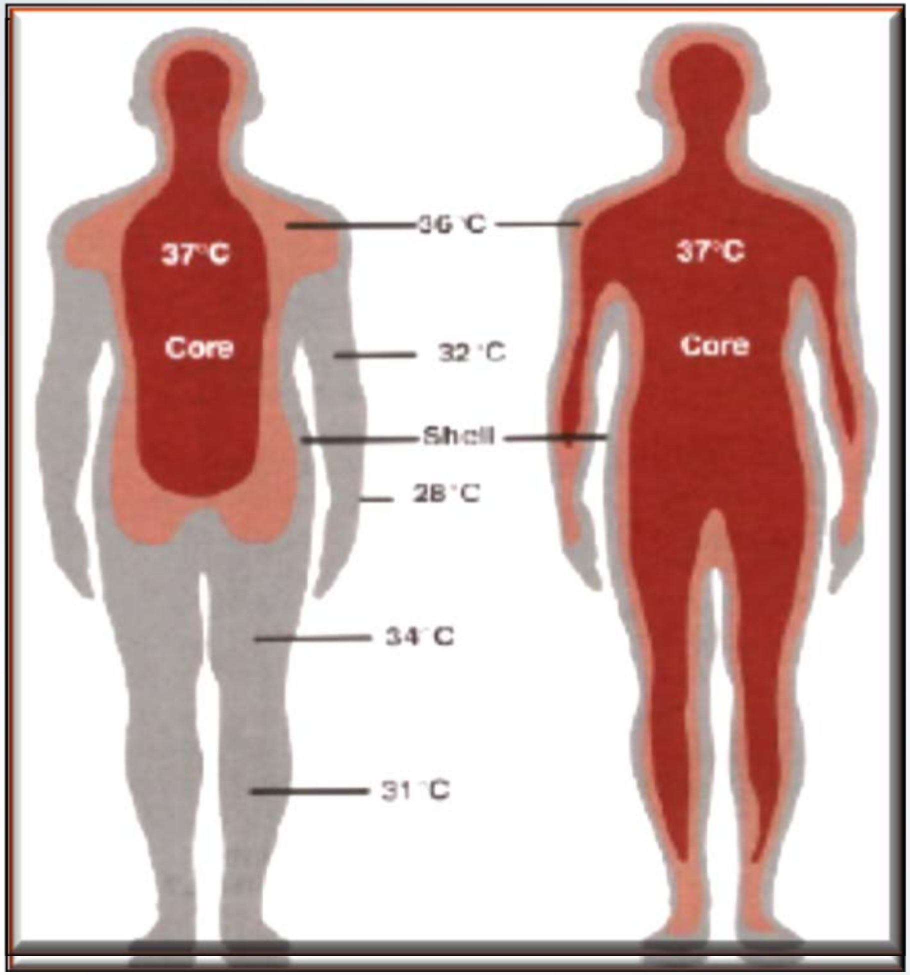




Heat Stress Redistributes Blood to Skin & Elevates Cardiovascular Strain

Relative Hypovolemia - ↓ Central Venous Pressure

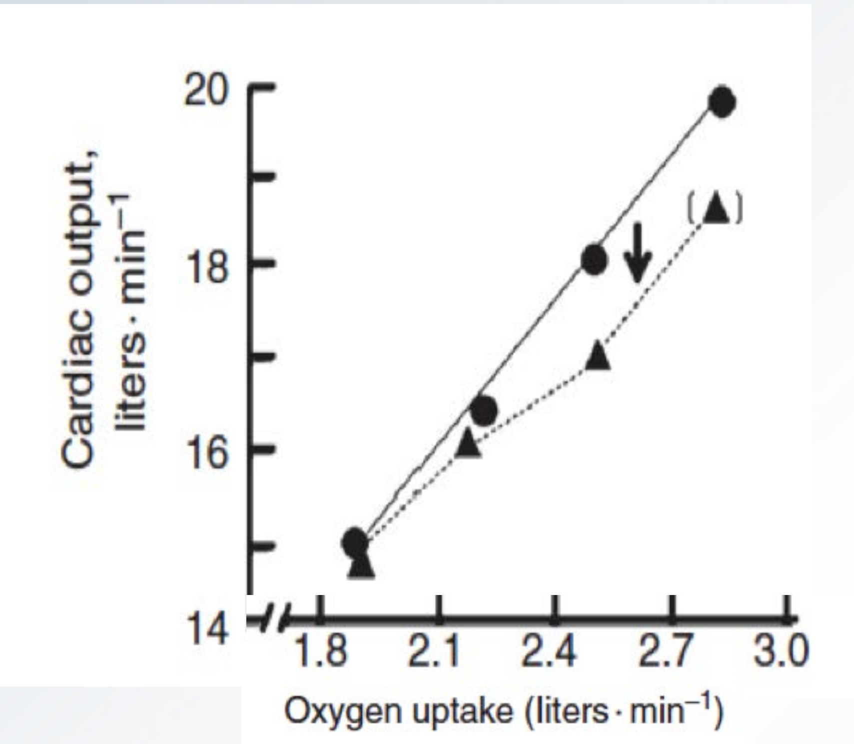
Tsk = 32ºC
SkBF = 0.5 L/min

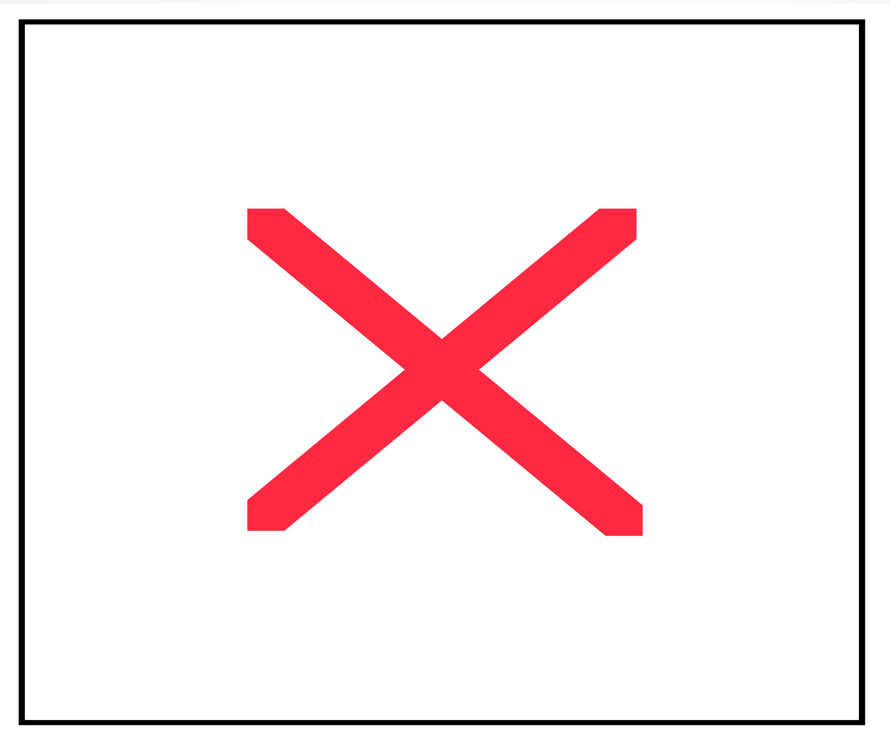


Tsk = 36ºC
SkBF = 5.0 L/min

C.B. Wenger <u>Human Physiology</u> 1989

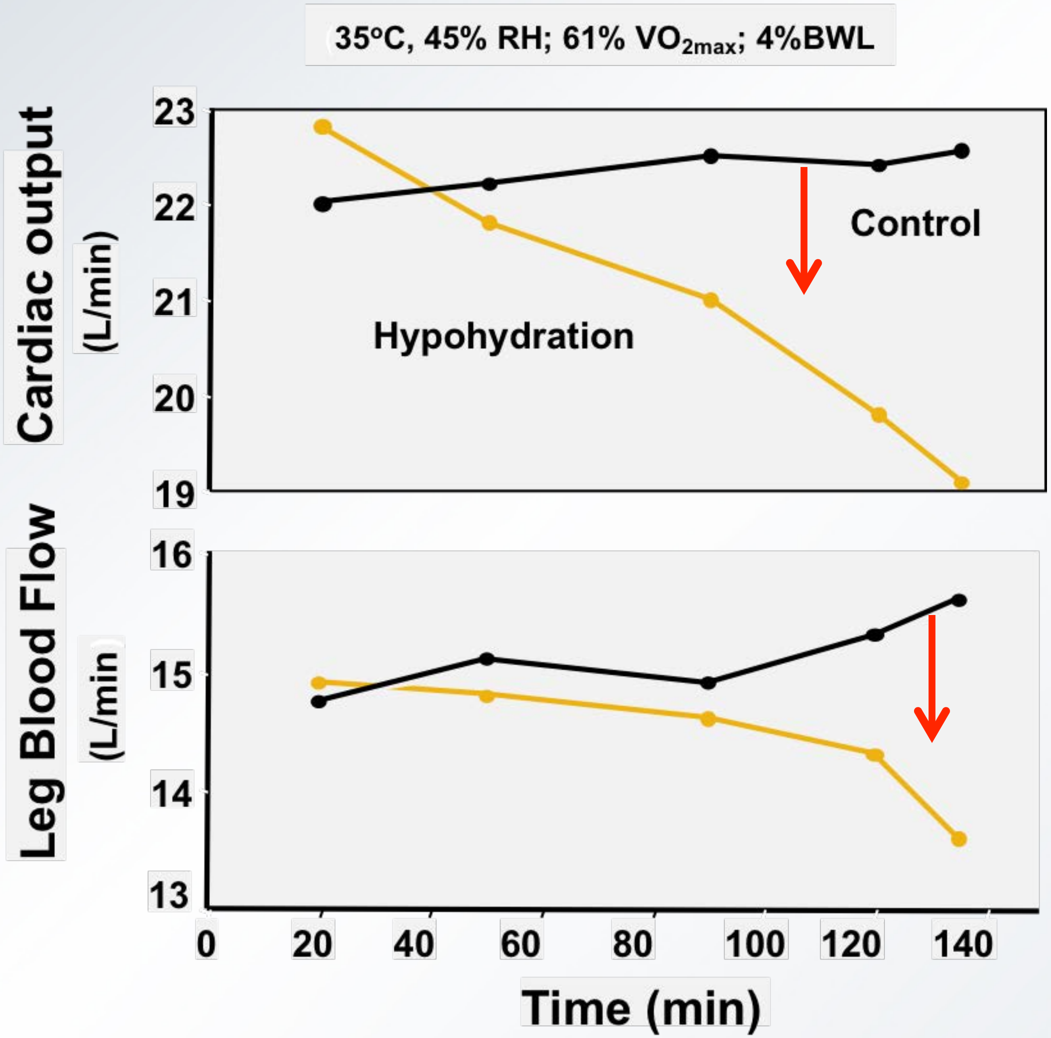
Exercise-Heat Stress Can Compromise Cardiac Output & Gut Blood Flow





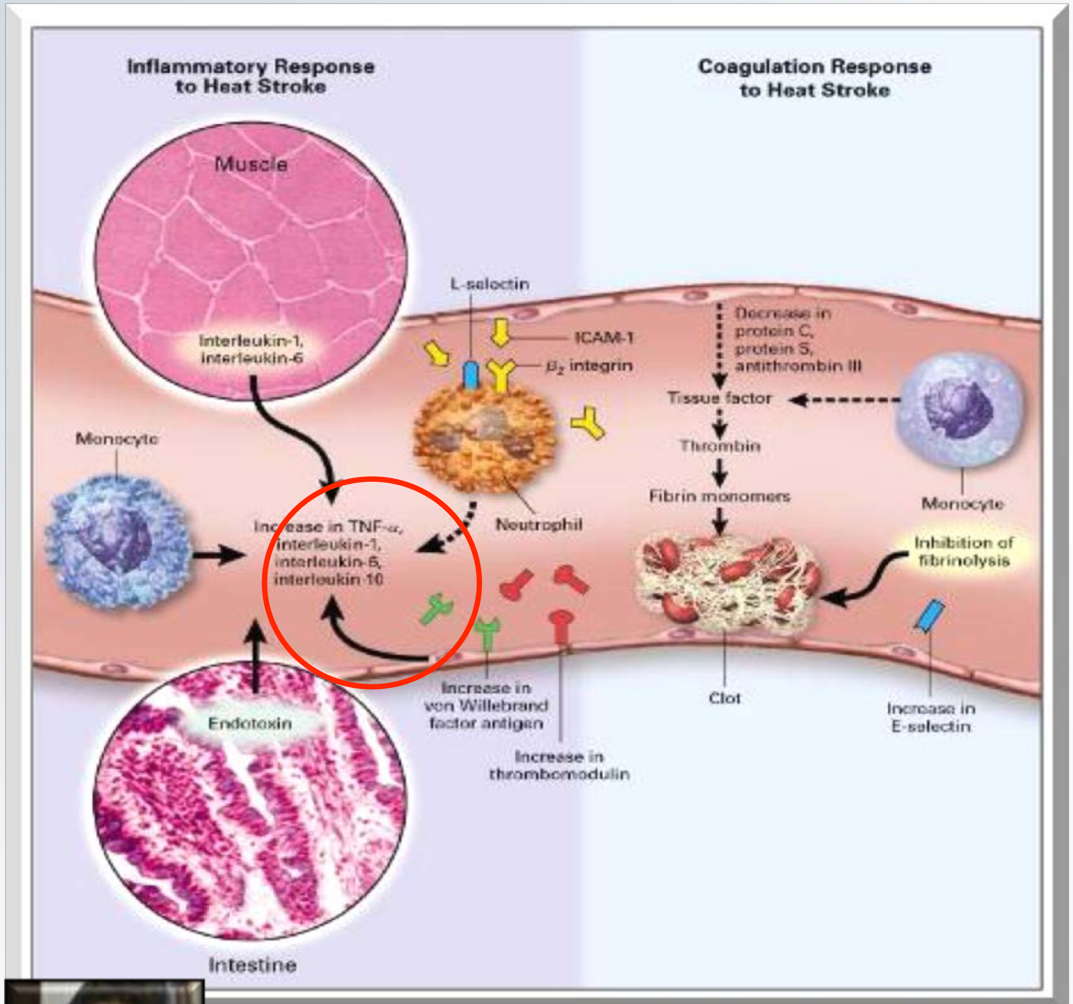
Rowell et.al. Clin. Invest. 1966
Rowell et.al. Handbook of Physiology 1983

Dehydration Reduce Muscle Blood Flow During Exercise-Heat Stress



Gonzalez-Alonso, et al, J. Physiol. 1998

Heat Stroke: Systemic Inflammatory Response Syndrome (SIRS) & Cytokine Storm



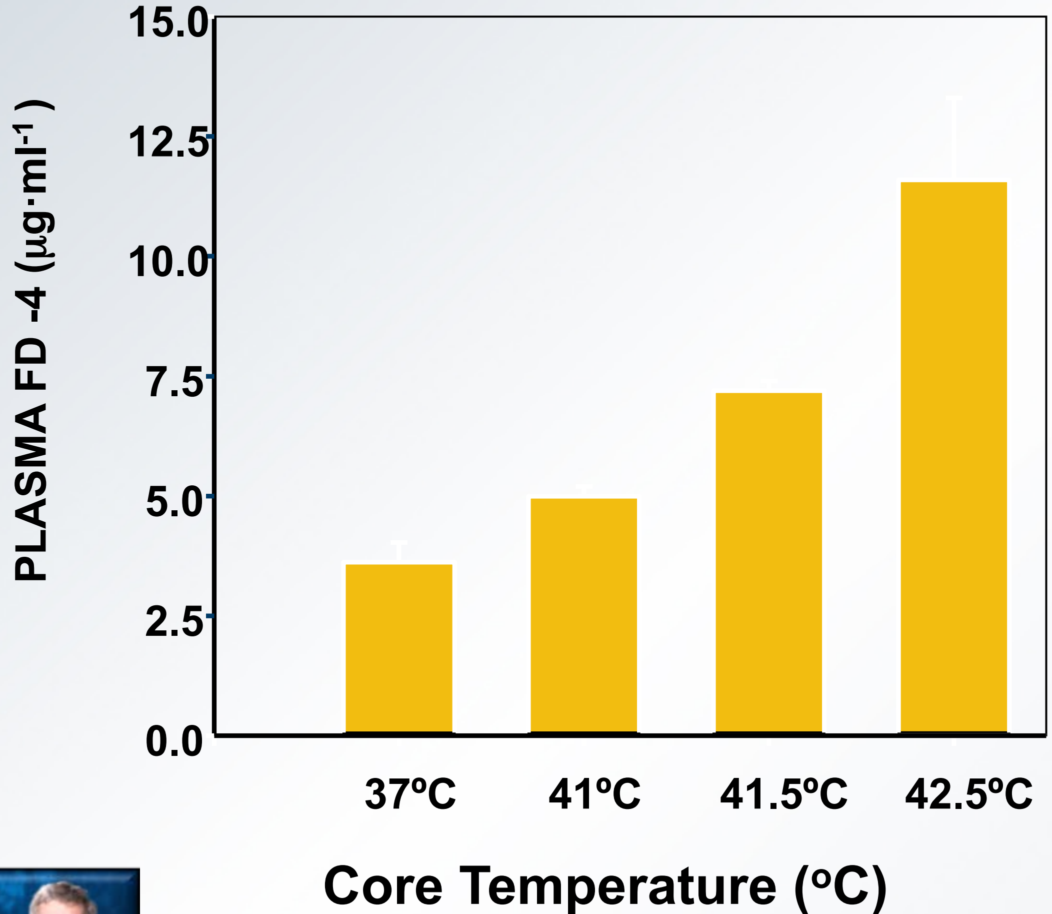
Under-Perfusion of Gut & Skeletal Muscle

"…form of hyperthermia associated with Systemic Inflammatory Response leading to syndrome of multi-organ dysfunction…"

Bouchama & Knochel. N. Eng. J. Med. 2002

Heating Increases Small Intestine Permeability

Rats; Passive Heat; Fluorescent Dextran



Dehydration Augments Gut Permeability During Exercise

Lambert et.al. IJSM, 2007

Lambert et.al, JAPPL 2002

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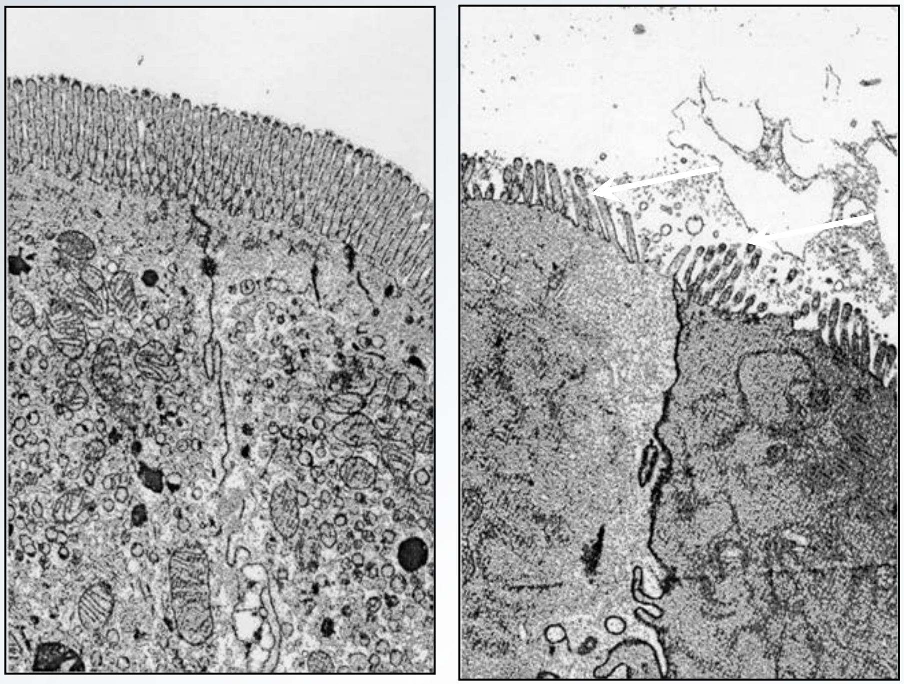
Heat Stroke: Intestinal Barrier Damage

Control **Hyperthermic**



(rats, Transmission electron micrographs of luminal area microvilli)

- Loss of Microvilli
- Precipitating Event for Endotoxin Leakage & Systemic Inflammatory Response Syndrome

Lambert et al., JAPPL 2002

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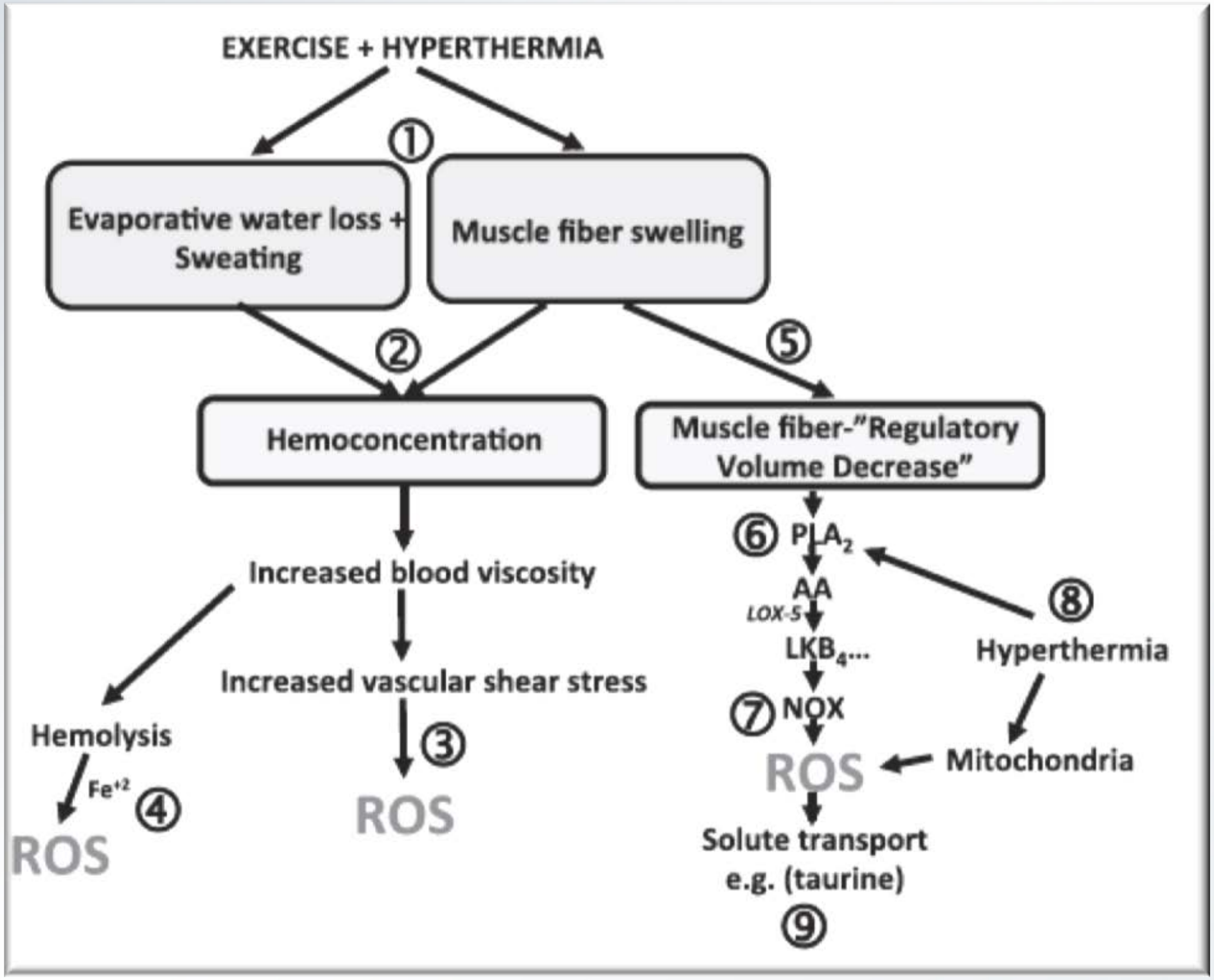
Exercise, Hyperthermia & Dehydration Independently Increase Reactive Oxygen Species (ROS) Stress



King et.al. AJP:Reg. 2015

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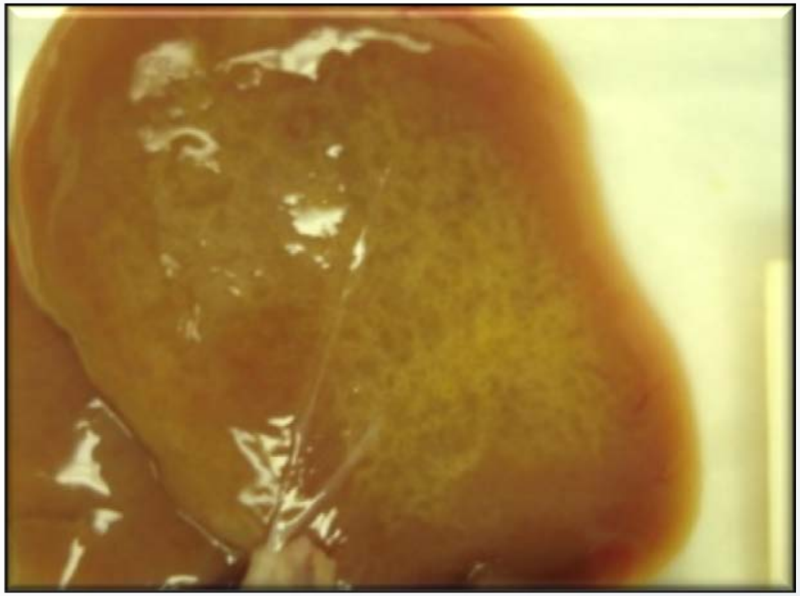
Heat Stroke: Liver Damage

Control

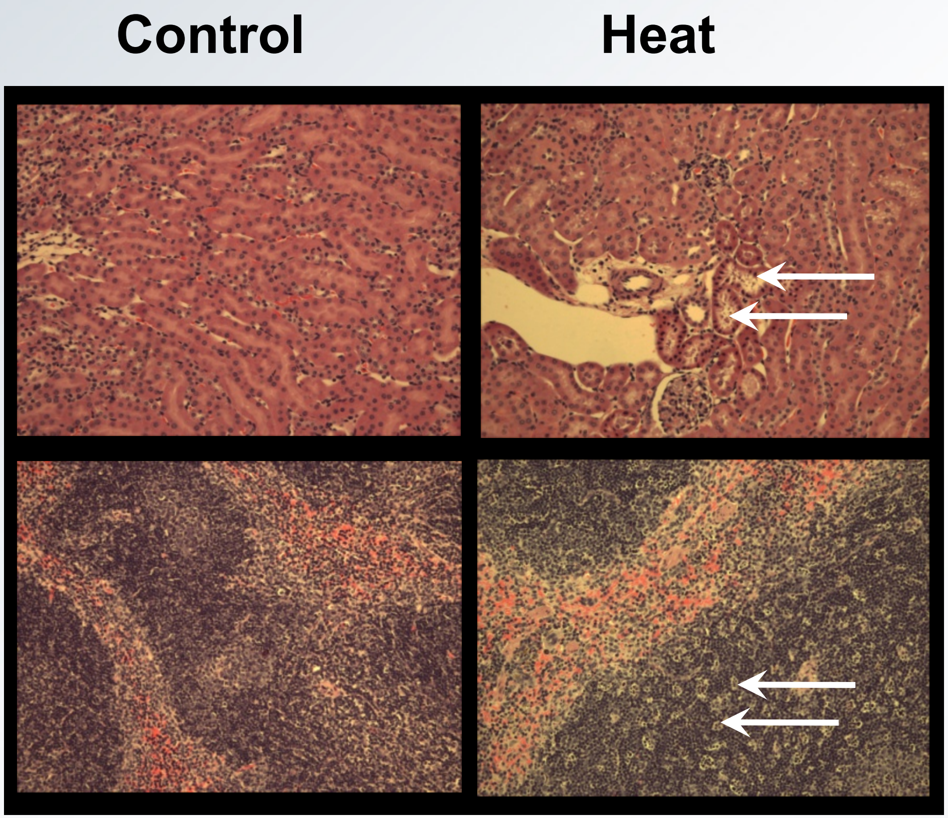
72h Post-Heat Stroke



"Fatty Liver Syndrome"

Leon Prog. Brain Res. 2007

Heat Stroke: Kidney & Spleen Damage



Kidney:
Tubular Ischemia / Necrosis
Proteinuria

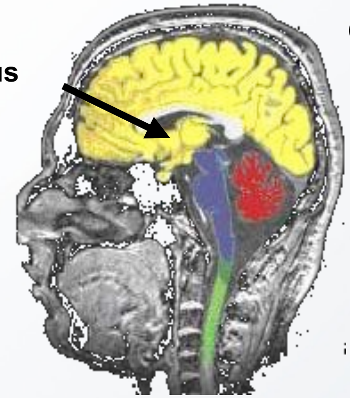
Spleen:
Nuclear / Cellular Debris
“cooked & coagulated”

(Photomicrographs of H & E staining)

Leon et.al. JAPPL 2006

Heat Stroke & Brain Damage

Autopsies of ~65 Brains from Heat Stroke Deaths



- **Cerebral Cortex:** Edema & Congestion
- **Cerebellum:** Atrophy “More striking than, more consistent than any other areas”; Purkinje layer severely degenerated”
- **Hypothalamus:** “Lack of demonstrable damage here contrasts with other portions of the brain”

Malamud et al. Mil Surg 1946

Hyperthermia Aggravates Brain Injury from Occlusion

Study	Species / T_c	Model	Outcome
Chen et.al. J Neurol. 1991	**Rat (39°C)**	**PMCAO**	**> Infarct Size**
Chen et.al. J. Cer. Bld. Flow. Met. 1993	**Rat (40°C)**	**TMCAO**	**> Infarct Size**
Kim et.al. Stroke 1996	**Rat (40°C, 24 h later)**	**TMCAO**	**> Infarct Size**
Morikawa et.al. J. Cer. Bld. Flow. Met. 1992	**Rat (39°C)**	**TMCAO & PMCAO**	**> Infarct Size**

PMCAO is permanent cerebral artery occlusion; **TMCAO** is transient middle cerebral artery occlusion

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Exertional Heat Stroke Impact on 30 Year Mortality - Military Victims

Cause of Death	Rate Ratio (AGE* as matching variable)
Ischemic Heart (IHD)	2.2
Cardiovascular (excluding IHD)	1.7
Liver	3.0
Digestive	2.7

Ratio of mortality rates for HI to Appendicitis patients. TAIHOD database

Wallace et al. Environ. Res. 2007

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Heat Acclimation & Acquired Thermal Tolerance

Heat Acclimation Is Induced By:

- Heat Exposure Over Many Days
- Heat Stress Sufficient to Elevate Body Temperature & Profuse Sweating
- Duration - 100 min / day
- Exposure - 4 to 14 days
- Specific to Heat Stress
  - Exercise / Rest
  - Intensity / Duration
  - Desert / Tropic

Periard et.l. Aut. Neu. Basic & Clinical 2016
Sawka et.al Compr. Physiol. 2011

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Physiology of Heat Acclimation

***Thermal Comfort** - Improved* | ***Aerobic Performance** – Improved*

Core Temperature – ***Reduced***
- **Tolerance** - ***Unchanged***

Sweating - ***Improved***
- **Earlier Onset**
- **Higher Rate**

Skin Temperature - ***Reduced***

Skin Blood Flow - ***Improved***
- **Earlier Onset**
- **Higher Rate (Tropic)**

Metabolic Rate – ***Lowered***
- **Lactate** – ***Lowered***
- ***Muscle Glycogen Use – Reduced***

Cardiovascular Stability - ***Improved***
- **Heart Rate** - ***Lowered***
- **Stroke Volume** – ***Increased***
- **Cardiac Reserve** - ***Increased***
- **Blood Pressure** - ***Better Defended***
- **Myocardial Compliance** – ***Increased***
- **Myocardial Efficiency** - ***Improved***

Fluid Balance- ***Improved***
- **Thirst**- ***Improved***
- **Electrolyte Loss** - ***Reduced***
- **Total Body Water** - ***Increased***
- **Plasma Volume** - ***Increased & Better Defended***

Sawka et.al. Compr. Physiol. 2011

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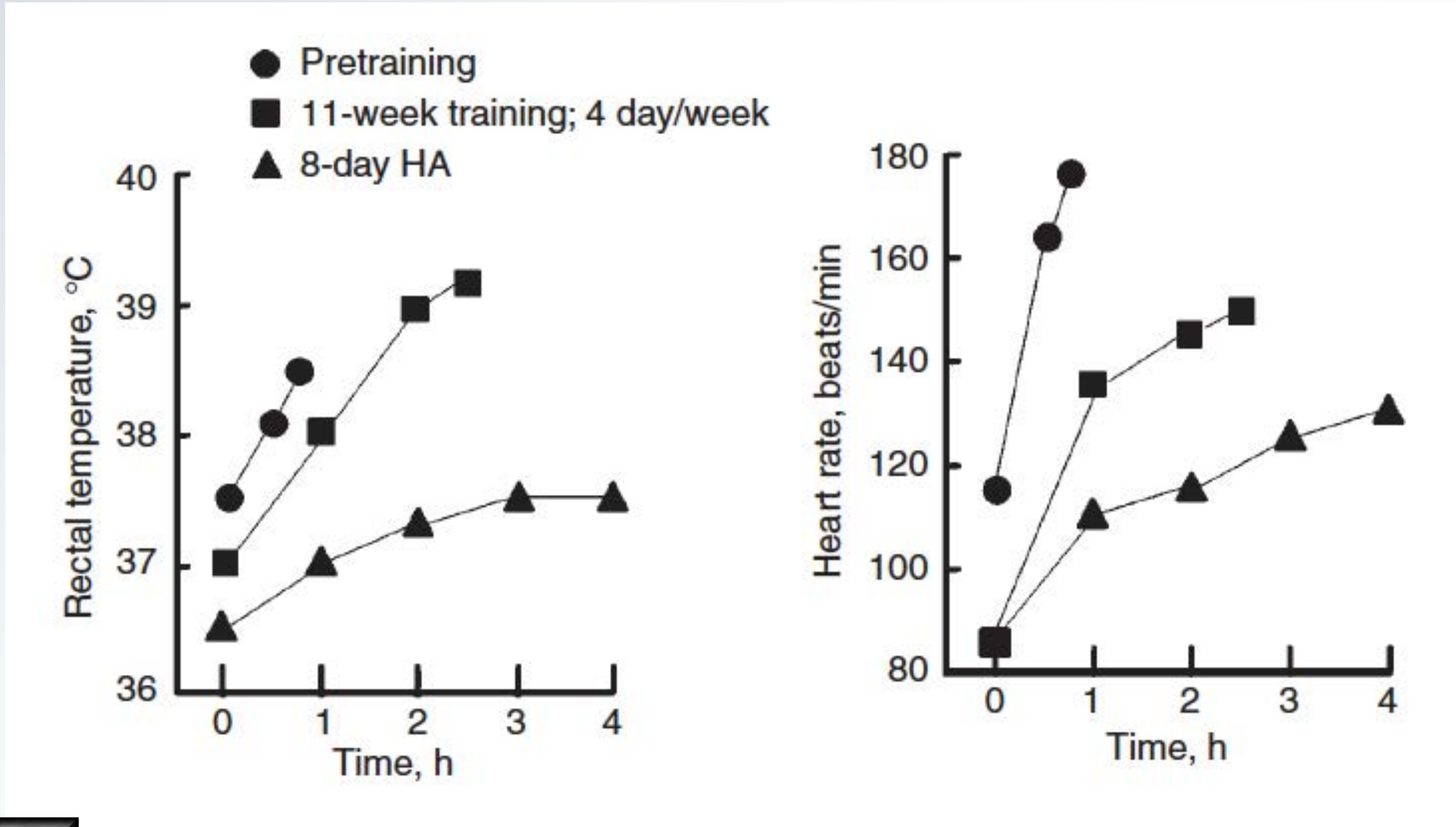
Aerobic Training Induces Partial Heat Acclimation



Cohen & Gisolfi, MSSE 1982

Acquired Thermal Tolerance

- Cellular Adaptations
- Caused by Single, Severe and Non-lethal Heat Stress
- Protect Cells from Heat / Exercise and Other Stress:
  - Ischemia, UV Irradiation, Monocyte Cytotoxicity
- Allows Organism to Survive Subsequent & Otherwise Lethal Heat Stress
- Heat Shock Protein Expression is An Important Contributor

Horowitz Compr. Physiol. 2014
Sawka et.al. Compr. Physiol. 2011

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Conclusions - Exertional Heat Illness: Physiology, Pathology & Modifying Factors

- **Serious Heat Illness Spectrum**
  - Exhaustion, Injury, Stroke
  - Exertional vs Classic
- **Physiology:**
  - High Skin Blood Flow & Sweat Loss
  - Cardiovascular Strain
  - Metabolism & Hyperthermia
- **Pathophysiology:**
  - Overwhelming vs Multiple Hit Hypothesis
  - Hyperthermia, Oxidative Stress, Under-Perfusion, SIRs
- **Modifying Factors (Mitigation):**
  - Hydration
  - Heat Acclimation
  - Acquired Thermal Tolerance