Exertional Heat Illness: Physiology, Pathology & Modifying Factors

Heat Related Illness - State of The Science Meeting

Michael N. Sawka, Ph.D., FAPS, FACSM
School of Biological Sciences
College of Sciences

Georgia Institute of Technology
• Serious & Exertional Heat Illnesses
• Exercise Hyperthermia
• Physiology & Pathophysiology
• Heat Acclimation & Acquired Thermal Tolerance
• Conclusions
Serious Heat Illness: Spectrum of Severity

Heat Exhaustion: Inability to Sustain Adequate Cardiac Output with Moderate to High Body Temperature.

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

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

Moderate → Severe

Gardner & Kark Text. Mil. Med. 2001
Exertional vs Classic Heat Stroke

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

  Stroke-Like Symptoms: Sudden Speech, Movement & Cognitive Impairments; but Extends Beyond Central Nervous System
## Comparison of Classic vs Exertional Heat Stroke

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

Exertional vs Classical Heat Stroke: Mortality in Rats

Exertional

Passive (Classic)

LD_{50} = medium lethal dose

Percent Mortality within 24 Hours

Hubbard et.al. JAPPL 1977
Hypotheses of Exertional Heat Stroke (EHS)

- **Conventional**: Heat Stress Overwhelms Physiological Compensation.

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

Sonna et.al. JAPPL 2004
Sonna et.al. Prog. Brain Res. 2007
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

Maximal Effort in 14 – 31 min Races

Core Temperature ($^\circ$C)

$T_a = 31^\circ$C

$T_a = 30^\circ$C

$T_a = 10^\circ$C

Minutes of Running

Robinson, Pediatrics 1963
High (>40°C) Core Temperatures Common in Competitive Runners

21 Km Race in Warm – Humid Weather

Peak $T_c$ of 41.7; 41.2; 40.7°C

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?

Soldier’s PT Runs

Hyperthermia & Fever?

**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

LPS – Lipopolysaccharide Endotoxin
OLVT – Organum Vasculosum Laminae Terminalis
PG - Prostaglandins
POA – Preoptic-Anterior Hypothalamus
Heat Stress Redistributes Blood to Skin & Elevates Cardiovascular Strain

Relative Hypovolemia - ↓ Central Venous Pressure

Tsk = 32°C
SkBF = 0.5 L/min

Tsk = 36°C
SkBF = 5.0 L/min

C.B. Wenger *Human Physiology* 1989
Exercise-Heat Stress Can Compromise Cardiac Output & Gut Blood Flow

Rowell et.al. *Handbook of Physiology* 1983
Dehydration Reduce Muscle Blood Flow During Exercise-Heat Stress

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

“...form of hyperthermia associated with Systemic Inflammatory Response leading to syndrome of multi-organ dysfunction...”

Under-Perfusion of Gut & Skeletal Muscle

Heating Increases Small Intestine Permeability

Rats; Passive Heat; Fluorescent Dextran

Core Temperature (°C)

PLASMA FD-4 (µg·ml⁻¹)

0.0
2.5
5.0
7.5
10.0
12.5
15.0

37°C
41°C
41.5°C
42.5°C

Dehydration Augments Gut Permeability During Exercise
Lambert et al. IJSM, 2007

Lambert et al., JAPPL 2002
Heat Stroke: Intestinal Barrier Damage

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

Control

Hyperthermic

(rats, Transmission electron micrographs of luminal area microvilli)

Lambert et al., JAPPL 2002
Exercise, Hyperthermia & Dehydration Independently Increase Reactive Oxygen Species (ROS) Stress

King et.al. AJP:Reg. 2015
Heat Stroke: Liver Damage

Control vs. 72h Post-Heat Stroke

“Fatty Liver Syndrome”

Leon Prog. Brain Res. 2007
Heat Stroke: Kidney & Spleen Damage

Control

Heat

Kidney:
- Tubular Ischemia / Necrosis
- Proteinuria

Spleen:
- Nuclear / Cellular Debris
  “cooked & coagulated”

(Photomicrographs of H & E staining)

Leon et.al. JAPPL 2006
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Species / $T_c$</th>
<th>Model</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Chen et. al. J Neurol. 1991</td>
<td>Rat (39°C)</td>
<td>PMCAO</td>
<td>&gt; Infarct Size</td>
</tr>
<tr>
<td>Kim et. al. Stroke 1996</td>
<td>Rat (40°C, 24 h later)</td>
<td>TMCAO</td>
<td>&gt; Infarct Size</td>
</tr>
</tbody>
</table>

PMCAO is permanent cerebral artery occlusion; TMCAO is transient middle cerebral artery occlusion
### Exertional Heat Stroke Impact on 30 Year Mortality - Military Victims

<table>
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<tr>
<th>Cause of Death</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Heart (IHD)</td>
<td>2.2</td>
</tr>
<tr>
<td>Cardiovascular (excluding IHD)</td>
<td>1.7</td>
</tr>
<tr>
<td>Liver</td>
<td>3.0</td>
</tr>
<tr>
<td>Digestive</td>
<td>2.7</td>
</tr>
</tbody>
</table>

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

Wallace et al. Environ. Res. 2007
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

Sawka et al. Compr. Physiol. 2011
Physiology of Heat Acclimation

Thermal Comfort - 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

Aerobic Performance – Improved

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
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
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