Hypothermia for Stroke
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Past-President, Neurocritical Care Society
Director, Division of Neurocritical Care and Stroke
University of Southern California
FEVER
Harmful Inflammatory processes
Calcium influx into cell, Excitotoxic cascade
Decrease metabolism/Energy production; in later stages increase metabolic demands
Membrane leakage, Edema formation, Intracellular acidosis
Free radical production
Reperfusion Injury
Others??
Epileptic activity And seizures?
Coagulation activation, Formation of microthrombi
Increased blood-Brain barrier Permeability, Edema formation
Mitochondrial Injury and Dysfunction.
Apoptosis, Calpain-mediated Proteolysis, DNA injury
Local brain Hyperthermia, “cerebral Thermo-pooling”
Increased vascular Permeability, Edema formation

are all stimulated by
FEVER
# Fever and Stroke Outcome

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Infarct Volume</th>
<th>Greater Deficit</th>
<th>Poor Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.99–1.05)</td>
<td>1.04 (1.01–1.07)</td>
<td>1.08 (1.05–1.12)</td>
</tr>
<tr>
<td>Infection</td>
<td>0.72 (0.32–1.62)</td>
<td>0.92 (0.43–2.01)</td>
<td>1.49 (0.65–3.39)</td>
</tr>
<tr>
<td>Highest temp</td>
<td>2.81 (1.34–5.89)</td>
<td>1.68 (0.84–3.40)</td>
<td>1.85 (0.88–3.88)</td>
</tr>
<tr>
<td>Time at which hyperthermia was observed:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>3.23 (1.63–6.43)</td>
<td>3.06 (1.70–5.53)</td>
<td>3.41 (1.69–6.88)</td>
</tr>
<tr>
<td></td>
<td>1.14 (0.52–2.51)</td>
<td>1.47 (0.78–2.80)</td>
<td>1.41 (0.66–3.05)</td>
</tr>
<tr>
<td></td>
<td>0.23 (0.05–1.09)</td>
<td>0.33 (0.10–1.03)</td>
<td>0.20 (0.04–0.96)</td>
</tr>
</tbody>
</table>

Fever and ICH
(Schwarz S, Hafner K)

• 251 patient series
• Fever at admission 19%
• Fever <24 (34%), 24-48 (36%), >48(21%)
• Duration of fever independent prognostic variable (GOS 3-5)

(Neurology 2000;54:354)
Fever and SAH
(Oliveira-Filho J, Ezzedine MA, et al)

• 92 patient series
• Poor Outcome OR 1.4 (1.1 - 1.88) for each 24 hour period of fever
• Predictors of fever: ventriculostomy, vasospasm, age

Neurology 2001;56:1304
Elevated Body Temperature and Outcomes

- Prospectively collected data that were retrospectively reviewed.
- Reviewed 6,759 admissions to a 20-bed neurology/neurosurgery ICU over a period of 6 years.
- Measurements included APACHE scores, GCS scores, daily maximum temperature, complications, length of stay, mortality rate and discharge disposition.
- Controlled for age, diagnosis, severity of illness and complications.

Diringer et al, CCM 2004
Results

• Elevated body temperature was independently associated with increased ICU and hospital LOS, higher mortality rate and worse outcome

• 3.2 additional ICU days and 4.3 additional hospital days
• Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I; Level of Evidence C).

SAH Guidelines 2012:

- Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH (Class IIa). (New recommendation)

ICH Guidelines 2010:

• The duration of fever is related to outcome and appears to be an independent prognostic factor in these patients.

• These data provide a rationale for **aggressive** treatment to maintain normothermia in patients with ICH.

Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke. 2010*
Hyperthermia is BAD!

Is Hypothermia GOOD?
History of Hypothermia
History of Hypothermia

Sarah Parks . . . gave still-birth to a baby boy . . . A tub of ice was ordered and the young doctor plunged the baby into it. Out came the screaming little Parks and he was named Gordon after the doctor who prodded him to life.

Sir John Floyer, 1697
History of Hypothermia

Baron de Larrey
1766-1842
History of Hypothermia

Sir William Osler
(1849 – 1919)
History of Hypothermia
Temple Fay, pioneered ‘human refrigeration’. In November 28, 1938, he first introduced whole body hypothermia as a treatment for malignancies and head injuries.
History of Hypothermia
History of Hypothermia
History of Hypothermia

Although Fay’s data were presented at the Third International Cancer Congress in 1939, the manuscript forwarded to Belgium for publication was confiscated by the Nazis. In Nazi concentration camps, especially Dachau, these techniques were brutally applied without any benefit of anesthesia. Such atrocities were exposed in part at the Nuremberg Trials.

The results of the Dachau ‘experiments’ were discredited on multiple levels. The “methods” used for torturing of the prisoners were condemned in Western literature. A close analysis of “data” showed falsification of the results by Nazi “scientists” and lack of scientific significance.

# History of Hypothermia

## EXPERIENCES WITH REFRIGERATION OF HUMAN BRAIN

### TABLE 1

*Survey of refrigeration material (126 cases)*  
*July 9, 1936 to October 1, 1940*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>112</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4</td>
</tr>
<tr>
<td>Brain tumor (glioblastoma)</td>
<td>5</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>3</td>
</tr>
<tr>
<td>Filarialias</td>
<td>1</td>
</tr>
<tr>
<td>Syphilis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>126</strong></td>
</tr>
</tbody>
</table>

- Patients receiving local refrigeration: 88
- Total period of applied local refrigeration: 2807 days
- Patients receiving general refrigeration: 66
- Episodes of general refrigeration: 169
- Biopsies: 189
- Autopsies: 72 (57.1%)
History of Hypothermia

EARLY EXPERIENCES WITH LOCAL AND GENERALIZED REFRIGERATION OF THE HUMAN BRAIN*

TEMPLE FAY, M.D.†
Philadelphia, Pennsylvania

(Received for publication April 25, 1938‡)

The clinical benefits from the use of local cold applications to the cutaneous surfaces of the body and head have been known to the profession for many centuries.

As far as I am aware, capsules housing refrigerated solutions were first introduced into the tissues of the human skull and brain in 1936 at Temple University Hospital in Philadelphia, on the author’s Neurosurgical Service.

The original apparatus devised for local refrigeration of an area was crude (Fig. 1). Ice water was circulated by the method of gravity. An old

Fig. 1. Closed irrigation unit with constant thermal control used with metal capsules for clinical observations of the effect of local refrigeration. (Reproduced from Surgery, Gynecology and Obstetrics.16)
History of Hypothermia
History of Hypothermia
Some Physiopathologic Regularities in the Process of Dying and Resuscitation
V. A. NEGROVSKY
*Circulation* 1961;23:452-457
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539
It seemed most tempting to try to use artificial hypothermia and hibernation with the aim of inhibiting the destructive processes in the living tissues, which develop during the dying period and in clinical death. Artificial hypothermia (26 to 20° C) obtained with the aid of general cooling and pentothal anesthesia enables one to obtain complete and sustained restoration of the vital functions in animals after clinical death has lasted up to 1 hour. With the aid of deep hypothermia (12 to 10° C) we obtained recently complete and sustained restoration of the vital functions of the organism in animals after 2 hours duration of clinical death.”

V. Negovsky
History of Hypothermia

- **Busto et al.** Mild hypothermia in rat global brain ischemia
- **Rosomoff & Safar.** Comatose patients
- **Safar.** Hypothermia as part of the first CPR ABCs
- **Conn.** Hypothermia for pediatric drowning
- **Tisherman et al.** Early work on emergency preservation for exsanguination cardiac arrest
- **Leonov et al.** Mild hypothermia improves outcome after VF cardiac arrest in dogs

![Bar chart showing the number of articles on cardiac arrest and hypothermia over the years from 1960 to 2000.](chart.png)
Hypothermia after Cardiac Arrest

*Two studies reported in NEJM 21 Feb 02*

- European Study: 24-hours @ 32-34° C
- Australian Study: 12-hours @ 33° C
- 1° endpoint: neurological function, 5-point scale
- 2° endpoint: mortality & complications
Cardiac Arrest
European Study

6-mo neurological outcome: 41% relative improvement

Cardiac Arrest
European Study

6-mo mortality: 26% relative reduction

Cardiac Arrest
Australian Study

30-day neurological outcome: 88% relative improvement

Hypothermia: Side effects

- Decreased cardiac output
- Increased systemic vascular resistance
- Thrombocytopenia
- Bradycardia
- Pneumonia
Is hypothermia an answer?

- Moderate hypothermia 33.5 °C, applied for 72 h, decreases mortality in newborn with moderate to severe hypoxic encephalopathy (Shankaran, NEJM, 2005).
Neuroprotection is Based on Supply and Demand
Neuroprotection is Based on Supply and Demand

Decrease Demand (Cerebral Metabolism)

Increase Supply (Cerebral Blood Flow)

Demand

Hypothermia

Supply
Ischemic Brain Injury

- EAA release
- Opening of EAA-coupled ion channels
  - Massive ionic fluxes
- Activation of energy-dependent ion pumps
  - Increase in energy demand
  - Activation of glycolysis
- Metabolic Depression
<table>
<thead>
<tr>
<th>Temperature</th>
<th>Infarcted Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermia 38°C</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Hyperthermia 39°C</td>
<td>![Diagram]</td>
</tr>
<tr>
<td>Hyperthermia 40°C</td>
<td>![Diagram]</td>
</tr>
</tbody>
</table>

Kim, Y. et al. Stroke 1996;27:2274-2281
Neurologic function

![Graph showing % Neurologic Function vs Temperature (°C)]

- 37°C
- 38°C
- 39°C

Brain tissue -25%

Brain tissue -4%
Use of hypothermia in *ischemic stroke*:

- Some experiments suggest that the available time window may be somewhat shorter than in global ischemia and TBI (1-2 hours, compared to 2-6 hours in global ischemia and TBI).

- However, other animal studies in focal ischemia have reported much longer therapeutic windows (up to 5 hours).

- Depending on the type of animal model, whether full or only partial reperfusion was achieved, and other injury-related factors.

- At times spectacular protective effects, especially if reperfusion was achieved.

## Use of hypothermia in *ischemic stroke*:

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of pts (H/C)</th>
<th>Target temp</th>
<th>Time from injury to start of cooling</th>
<th>Time to target temp</th>
<th>Duration</th>
<th>Re-warming rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe stroke, mostly sedated patients in ICU setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naritomi H et al. 1996</td>
<td>4 (4 / 0)</td>
<td>33°C</td>
<td>&lt; 5 hrs</td>
<td></td>
<td>72-96 hrs</td>
<td></td>
</tr>
<tr>
<td>Schwab et al. 1998</td>
<td>20 (20 / 0)</td>
<td>33°C</td>
<td>Patient data included in subsequent study (Schwab et al. 1998, see below).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwab et al. 1998</td>
<td>25 (25 / 0)</td>
<td>33°C</td>
<td>14 ± 7 hrs, range 4-24</td>
<td>3.5-6.2 hrs</td>
<td>48-72 hrs</td>
<td>7-24 hrs median 18</td>
</tr>
<tr>
<td>Steiner T et al. 2001</td>
<td>15 (15 / 0)</td>
<td>32-33°C</td>
<td>4-84 hrs, median 17</td>
<td>2-7 hrs</td>
<td>72 hrs</td>
<td>26-88 hrs</td>
</tr>
<tr>
<td>Schwab et al. 2001</td>
<td>50 (50 / 0)</td>
<td>33°C</td>
<td>22 ± 9 hrs</td>
<td>3.5-11 hrs</td>
<td>48-72 hrs</td>
<td>Passive 17 hrs</td>
</tr>
<tr>
<td>Jian S et al. 2003</td>
<td>50 (50 / 0)</td>
<td>33°C</td>
<td>Patient data included in subsequent study (Schwab et al. 2001, see above).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georgiadis et al. 2001</td>
<td>6 (6 / 0)</td>
<td>33°C</td>
<td>28 ± 17 hrs</td>
<td>3 ± 1 hrs, range 2-4.5</td>
<td>48-72 hrs</td>
<td>0.12-0.2°C/hr</td>
</tr>
<tr>
<td>Georgiadis et al. 2002</td>
<td>36 (19 / 17)</td>
<td>33°C</td>
<td>24 (range 18-24)</td>
<td>4 ± 1 hrs, range 2-6</td>
<td>48-72 hrs</td>
<td>Not stated</td>
</tr>
<tr>
<td>De Georgia et al. 2004*</td>
<td>40 (18 / 22)</td>
<td>33°C</td>
<td>8’59” ± 2’52”</td>
<td>Variable;</td>
<td>24 hrs</td>
<td>0.2°C/hr</td>
</tr>
<tr>
<td><strong>Moderate Stroke (awake patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kammersgaard et al. 2000</td>
<td>73 (17 / 56)</td>
<td>35.5°C</td>
<td>3.25 ± 4.5 hrs</td>
<td>6 hrs</td>
<td>6 hrs</td>
<td>4 hrs</td>
</tr>
<tr>
<td>Krieger et al. 2001*</td>
<td>19 (10 / 9)</td>
<td>32±1°C</td>
<td>6.2 ± 1.3 hrs</td>
<td>3.5 ± 1.5</td>
<td>48 (range 24-96) hrs</td>
<td>0.25-0.5°CCh</td>
</tr>
<tr>
<td>Knoll et al. 2002</td>
<td>18 (18 / 0)</td>
<td>36-37°C</td>
<td>3.3 hrs</td>
<td>24 hrs</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Els et al. 2006</td>
<td>25 (12 / 13)</td>
<td>35°C</td>
<td>15 ± 6 hrs</td>
<td>2 ± 1 (range 1.5-3.5) hrs</td>
<td>48 hrs</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lyden et al. 2006*</td>
<td>18 (18 / 0)</td>
<td>33°C</td>
<td>7.7 ± 3.1 hrs</td>
<td>7 hrs</td>
<td>12-24 hrs</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Guluma et al. 2006</td>
<td>10 (10 / 0)</td>
<td>33°C</td>
<td>&lt;6 hrs</td>
<td>1.7±0.7 hrs</td>
<td>24 hrs</td>
<td>0.3°C/hr</td>
</tr>
<tr>
<td>Hemmen et al. 2010 ICTuS-L*</td>
<td>58 (28 / 30)</td>
<td>33°C</td>
<td>&lt;6 hrs</td>
<td>1.1 hrs (median)</td>
<td>24 hrs</td>
<td>0.33°C/hr</td>
</tr>
</tbody>
</table>

*Cooling combined with thrombolytics/reperfusion.

Total number of cooled patients reported so far: 270.


Less severe/moderate stroke: 113.
## Ventilated patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Goal temperature °C</th>
<th>Time to Treatment (hour±SD)</th>
<th>Duration of hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwab, 1998</td>
<td>25</td>
<td>33°C</td>
<td>14±7</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Schwab, 2001</td>
<td>50</td>
<td>33°C</td>
<td>22±9</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Georgiadis, 2001</td>
<td>6</td>
<td>33°C</td>
<td>28±17</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Georgiadis, 2002</td>
<td>19</td>
<td>33°C</td>
<td>24 (18-14)</td>
<td>2-3 days</td>
</tr>
</tbody>
</table>

Kollmar, Schwab, 2010
# Awake patients

<table>
<thead>
<tr>
<th></th>
<th>N hypothermia</th>
<th>Goal temperature in °C</th>
<th>Time to Treatment (hours+/−SD)</th>
<th>Hypothermia duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kammersgaard, 2000</td>
<td>17</td>
<td>35.5°C</td>
<td>3±4</td>
<td>6 h</td>
</tr>
<tr>
<td>Krieger, 2001</td>
<td>10</td>
<td>32±1°C</td>
<td>6±1</td>
<td>1-4 days</td>
</tr>
<tr>
<td>DeGeorgia, 2004</td>
<td>18</td>
<td>33°C</td>
<td>9±3</td>
<td>24h</td>
</tr>
<tr>
<td>Lyden, 2005</td>
<td>18</td>
<td>33°C</td>
<td>8±3</td>
<td>24h</td>
</tr>
<tr>
<td>Guluma, 2006</td>
<td>10</td>
<td>33°C</td>
<td>6±1</td>
<td>24h</td>
</tr>
<tr>
<td>Kollmar, 2009</td>
<td>10</td>
<td>35.5°C</td>
<td>1,5</td>
<td>-</td>
</tr>
<tr>
<td>Hemmen, 2010</td>
<td>28</td>
<td>33°C</td>
<td></td>
<td>24h</td>
</tr>
</tbody>
</table>

Kollmar, Schwab, 2010
CHILI - Controlled Hypothermia in Large Infarction

- U.S.C.
- Columbia University
- U.M.D.N.J.
- Case Western
- Lehigh Valley
- Wayne State University
- Via Christi Regional Medical Center
CHILI

• Large hemispheric stroke
• Within 72 hours of onset
  – no herniation
• Immediate cooling to 35.0 for 3 days
• 0.5 C q12 hr rewarming
• Uniform shivering prophylaxis
• Measure: GCS, NIHSS, CT, Rankin, Barthel, Mortality, discharge location, LOS/costs
CHILI - Trial Hypotheses

• Pts within 72 hrs of symptom onset can be safely treated with moderate hypothermia
• Moderate hypothermia reduces morbidity/mortality
• Reduction of infarct volume is a reliable surrogate marker of treatment effect
Patient with large MCA stroke:

24 hrs after 1st symptoms
Core temperature 37.0° C

38 hrs after 1st symptoms
Core temperature 33.0° C

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

Final Results

Thomas M. Hemmen, MD, PhD; Rema Raman, PhD; Kama Z. Guluma, MD; Brett C. Meyer, MD; Joao A. Gomes, MD; Salvador Cruz-Flores, MD; Christine A. Wijman, MD, PhD; Karen S. Rapp, RN; James C. Grotta, MD; Patrick D. Lyden, MD; for the ICTuS-L Investigators

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

<table>
<thead>
<tr>
<th>Hours From Stroke</th>
<th>Group</th>
<th>Patients (No.)</th>
<th>tPA</th>
<th>HY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>1</td>
<td>22</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3–6</td>
<td>3</td>
<td>6</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Outcome Measures Between HY and NT Patients

<table>
<thead>
<tr>
<th></th>
<th>HY (Groups 2, 5, 6; n=28)</th>
<th>NT (Groups 1, 3, 4; n=30)</th>
<th>Fisher Exact Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>5</td>
<td>7</td>
<td>0.747</td>
</tr>
<tr>
<td>NIHSS at 90 day (mean±SD)</td>
<td>6.3 (±6.6)</td>
<td>3.8 (±3.0)</td>
<td>0.355</td>
</tr>
<tr>
<td>At least one SAE (%)</td>
<td>75</td>
<td>43.3</td>
<td>0.0118</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>50</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>All ICH (%)</td>
<td>28.6</td>
<td>20</td>
<td>0.752</td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>3.6</td>
<td>10</td>
<td>0.609</td>
</tr>
<tr>
<td>Mortality by 90 days (%)</td>
<td>21.4%</td>
<td>16.7</td>
<td>0.744</td>
</tr>
</tbody>
</table>

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.
<table>
<thead>
<tr>
<th></th>
<th>Eurohyp-1</th>
<th>ICTUS 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Europe</td>
<td>US&amp;Europe</td>
</tr>
<tr>
<td><strong>Investigator</strong></td>
<td>Eurohyp (ER)</td>
<td>UCSD-Lyden</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>EU</td>
<td>NIH</td>
</tr>
<tr>
<td><strong>Devices</strong></td>
<td>Endovasc.</td>
<td>Endovascular</td>
</tr>
<tr>
<td><strong>Target Pop</strong></td>
<td>Rt-PA Patients</td>
<td>Rt-PA patients</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>Saline (4° C)</td>
<td>Saline (4° C)</td>
</tr>
<tr>
<td><strong>Target Temp.</strong></td>
<td>34-35° C</td>
<td>33° C</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>24 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

EU-Applikation by Eurohyp, networking through unrestricted grant of Werner Hacke
Hypothermia Possible Indications

• Too many to count!
• All variables open to question:
  – Depth, timing, duration, rewarming, shivering management, complication avoidance
Absence of Proof is NOT Proof of Absence!
PFC Intranasal Cooling Schematic

O₂ → PFC
Hypothermia Possible
Indications

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