Brain-targeted hypothermia for ischemic brain injury

MedTech Frontiers
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Ischemic brain injury

- surgery
- shock
- arrest
- stroke
- trauma
Both scheduled and unpredictable

- Cardiac surgery
- TAVI
- Cardiac ablation
- Carotid interventions
- Cerebral aneurism interventions
- Orthopedic surgery
- Surgery in elderly

- Stroke
- Cardiac arrest
- TBI
- Severe hemorrhage - knife, gun, car, battle
- Ruptured cerebral aneurism
Cardiac surgery

100% Debris delivered to brain

61% Strokes diagnosed by MRI

53% Loss of mental ability

17% Strokes diagnosed by clinical exam

Infarcts are common during procedures.
Stroke is the #2 cause of death in the world
15 million annually …… “1 in 6” lifetime risk

- **Death**: 18%
- **Recovery**: 35%
- **Disability**: 47%

#1 cause in US

> $140k per stroke

- 87% after 30 days
- 13% first 30 days

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Age is a major, unalterable risk factor

Source: Statistics Bureau, MIC; Ministry of Health, Labour and Welfare.
Reestablishing blood flow is often not enough

In addition to causing direct cell injury, reactive oxygen species (ROS) thus increase leukocyte activation, chemotaxis, and leukocyte–endothelial adherence after ischemia–reperfusion (I-R).

### Role of Complement

Ischemia–reperfusion results in complement activation and the formation of several proinflammatory mediators that alter vascular homeostasis. Particularly important are the anaphylatoxins, C3a and C5a, and complement components, iC3b and C5b-9. The most potent of these proinflammatory mediators is C5a, which is approximately 20 times more potent than C3a. In addition to stimulating leukocyte activation and chemotaxis, C5a may further amplify the inflammatory response by inducing production of the cytokines monocyte chemoattractant protein 1, tumor necrosis factor (TNF-α), interleukin-1, and interleukin-6. C5b-9 and iC3b may also alter vascular homeostasis. iC3b is formed after C3b cleavage and is a specific ligand for leukocyte adhesion to the vascular endothelium via the integrin, CD11b–CD18 (Mac-1). In addition, C5b-9 may activate endothelial nuclear factor-κB to increase leukocyte adhesion molecule transcription and expression.

### Role of Leukocytes

Ischemia–reperfusion results in leukocyte activation, chemotaxis, leukocyte–endothelial cell adhesion, and transmigration. Leukocytes interact with the vascular endothelium via a series of distinct steps characterized by leukocyte “rolling” on the endothelium, firm adherence of leukocytes to the endothelium, and endothelial transmigration (fig. 1). The first step is initiated by I-R–induced increases in endothelial P-selectin surface expression, which interacts with its leukocyte counterreceptor, P-selectin glycoprotein 1. This initial low affinity interaction results in intermittent leukocyte–endothelial binding characterized as leukocyte “rolling.” Subsequent interaction of leukocyte integrins, such as CD11a/CD18 (leukocyte function–associated antigen-1) or Mac-1, with endothelial intercellular adhesion molecule 1 (ICAM-1) results in firm leukocyte adherence and aggregation. Leukocyte transmigration into the interstitial compartment is facilitated by platelet-endothelial cell adhesion molecule 1 (PECAM-1) within the endothelial cell junctions.

### Reperfusion injury mechanisms

- Inflammation
- Oxidative stress
- Excitotoxicity
- Apoptosis
- Disruption of blood-brain barrier
Humans are still waiting for an effective drug solution

~1000 rat stroke cures

~200 trials

~0 results
“Hypothermia is the current mainstay of cerebral protection”

Julie Swain, MD
Professor of Cardiothoracic Surgery
Director of the Center for Medical Devices, Mount Sinai Heart
Former Chair of FDA Cardiovascular Advisory Panel
Former FDA Lead clinical reviewer for medical devices for embolic protection, therapeutic hypothermia and cardiopulmonary resuscitation
Hypothermia consistently reduces infarct size in all species

REVIEW ARTICLE

Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis

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1Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre, Utrecht, The Netherlands, 2Department of Clinical Neurosciences, University of Edinburgh, UK and 3National Stroke Research Institute and University of Melbourne Department of Medicine, Melbourne, Australia

• >40% reduction in infarct overall
• 101 trials
• 3,353 animals – all species and all models
Pre-ischemia hypothermia can prevent infarction (in rats)

Brain temperature during 80 minutes of ischemia

Total infarct volume (% of hemisphere)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Infarct Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.7°C</td>
<td>15</td>
</tr>
<tr>
<td>35.7°C</td>
<td>10</td>
</tr>
<tr>
<td>34.4°C</td>
<td>5</td>
</tr>
<tr>
<td>29.2°C</td>
<td>0</td>
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</tbody>
</table>

100% reduction @ 29°C

Brain cooling during transient focal ischemia offers complete neuroprotection.
Barone, Neuroscience and Biobehavioral Reviews 21(1997) 31-44.
Cardiac surgery, 1955

ice applied to patient
Post-infarct cooling prevents reperfusion injury (baboons)

36°C 35% infarct

26°C 0.5% infarct

Cooling started after 2.5 hours. 1.5 hours of warm reperfusion.

Brain temperature, initiated 2.5 hrs after stroke onset

Post-infarct cooling effect is dose dependent (baboons)

98% reduction @ 25.5°C

Total infarct volume (% of hemisphere)

37°C  32°C  25.5°C

Multifaceted benefits of cooling

- Crosses the blood-brain barrier
- Crosses into non-perfused and poorly perfused regions
- Effects many biochemical pathways
- Is a physical process with well understood side effects
- Cooling is available now, an effective drug has yet to be identified
> $300 M of investment in cooling technology

MediVance

BeneChill

Zoll

QuickCool
A delivery problem – **delay** and **toxicity** need to be overcome
Key variables in cooling

**Timing of Hypothermia**
- pre- and intra-ischaemic
- pre-, intra-, and postischaemic
- intra-ischaemic
- intra- and post-ischaemic
- post-ischaemic

**Depth of Hypothermia**
- 24 to 29°C
- 30°C
- 31°C
- 32°C
- 33°C
- 34°C
- 35°C

**Summary**
- Reduction in infarct volume

![Graph showing the impact of hypothermia on infarct volume reduction](image)
Faster is better after arrest

Delayed goal temp increases risk of poor outcome

31% per 1 hour

Delayed initiation increases risk of poor outcome

8% per 5 minutes
20% per 1 hour

Slow cooling increases risk of poor outcome

17% per 30 minutes

Recent trials allowed dramatic delays in injury, therapeutic hypothermia plus standard care to reduce intracranial pressure did not significantly improve outcomes compared to standard care alone. The study concluded that while therapeutic hypothermia may be beneficial in certain cases, further evidence is needed to support its routine use in the management of traumatic brain injury.

**Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest**

10 hours to goal

**Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children**

12 hours to goal

**Hypothermia for Intracranial Hypertension after Traumatic Brain Injury**

>16 hours to goal
Serious complications caused by body cooling

Death
Hypotension
Arrhythmia
Myocardial infarction
Surgical site infections
Bleeding – 2C can increase blood loss by 500ml
Transfusion – cardiac surgery is the primary use for blood
Shivering
Altered drug metabolism
Increased stay in ICU, hospital

Medicare and hospital accrediting agencies mandate normal core temperature during all surgeries that do not induce cooling for neuroprotection
Cold body during surgery - expensive & unsafe

Cold body increases cost and systemic complications

$2,500 – $7,000+

1.5°C difference

¹Mahoney, AANA Journal 1999 Vol. 67 No. 2 155-164 [meta-analysis]
Cold body during surgery - expensive & unsafe

Cold body increases cost and systemic complications\(^1\)

$2,500 – $7,000+

1.5°C difference

Single center analysis (>45,000 patients)

Increases

XX% Death
XX% M.I.
25% Length of Stay

1.1°C difference

\(^1\)Mahoney, AANA Journal 1999 Vol. 67 No. 2 155-164 [meta-analysis]
During cardiac surgery

colder = fewer strokes, but more deaths

warmer = fewer deaths, but more strokes

3°C (5.4°F)
Avoided complications save money in cardiac surgery

$4,500
Reduced costs from colder brain

$4,700
Reduced costs from warmer body

3°C $9,200 per surgery
Our solution
Cool the brain, not the body

- fast
- deeper/safer
- better when sicker
- anywhere
One must cool the blood before it enters the brain

- The brain generates 20% of body heat
- The skull traps heat
- The vasculature functions as a radiator
- Brain gets colder as brain perfusion decreases
The closest surface to the arteries is easily accessed
Long column brain-targeted cooling

1. Arteries closely track mucosa
2. Easy access to cooling surfaces
3. Free fluid sweeps irregular surfaces
4. Low pressure prevents aspiration and barotrauma
2 paths of circulating fluid

To esophagus

From mouth

To nose

To ventilator
Free-flowing fluid cools tissue around arteries
Familiar, intuitive components

base unit

disposable kit
Counter-warming can be added
Clinical data
NeuroSave clinical feasibility trial

- 5 patients having cardiac surgery
- 3 patients with chiller set at 12C, 1 patient at 6C and 1 patient at 2C
- Brain temperature via jugular bulb
- Body temperature via bladder
- No device related safety issues
- No hemodynamic or respiratory effects
To goal brain temperature in 15 min

brain temperature depends on cooling-fluid temperature

Patient 1 not displayed due to limited duration of device use

Patient 2

Patient 3

12°C

Patient 5

2°C

Patient 4

6°C
Body maintained warmer than the brain

Body-brain temp difference (maximum, °C)

Pt 1  Pt 2  Pt 3  Pt 4  Pt 5

* with concurrent cooling/warming via cardiopulmonary bypass circuit
# lower during hypotension (to ~ 27°C)
^ limited duration of device use
Depth of brain cooling

* with concurrent cooling/warming via cardiopulmonary bypass circuit
# lower during hypotension (to ~ 27°C)
^ limited duration of device use
More targeted brain cooling during hypotension

3 min episode of hypotension (MAP ~45mmHg)

NeuroSave stopped when temp <30°C, per protocol

Patient 5, cooling fluid temperature set at 2°C
Fastest cooling

Time required to decrease brain temperature by 3°C

- **Catheters**: 2 hours
- **Skin pads**: 3 hours
- **MedCool** (BeneChill): not demonstrated

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3. Abou-Chebl, Stroke; 42:2164-2169
Greatest selectivity

**Brain–body temperature difference**

- **MedCool**: 0.6°C
- **BeneChill**: 0.5°C
- **Catheters**, **Skin pads**, **Bypass machine**: 0°C

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2 Abou-Chebl, Stroke; 42:2164-2169
3 Crit Care 2007;11(4):R91
NeuroSave cooling is:

1. fast – time is brain
2. deep – colder brain is better
3. targeted – warmer body is better
4. non-vascular, mobile
5. enhanced by hypotension
Our Team
## Proven team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Experience/Company</th>
</tr>
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<tbody>
<tr>
<td>CEO</td>
<td>Seth Rodgers, PhD</td>
<td>PhD Chemical Engineering (MIT); Bioprocessors, McKinsey</td>
</tr>
<tr>
<td>Chief Medical Officer</td>
<td>Tom Kreck, MD</td>
<td>Pulmonary/critical care; Kaiser-Permanente, U of Washington</td>
</tr>
<tr>
<td>Regulatory, Quality</td>
<td>Zachary Woodson</td>
<td>Medtronic, Conor Medsystems</td>
</tr>
<tr>
<td>Engineering</td>
<td>Kelly Hoofer</td>
<td>Medtronic, Volcano</td>
</tr>
<tr>
<td>Clinical Affairs</td>
<td>Amy Steig, PhD</td>
<td>Medtronic, J&amp;J</td>
</tr>
<tr>
<td>Program Mgmt.</td>
<td>Shadi Haag, MBA</td>
<td>ALZA, Conor, J&amp;J, Genentech</td>
</tr>
<tr>
<td>Business Dev.</td>
<td>Drew Scott, MBA</td>
<td>ARCH, ALZA, J&amp;J</td>
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</table>
Advisors

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Medtronic
In conclusion
A better delivery system

- fast
- deeper/safer
- better when sicker
- anywhere
A platform technology for:

- surgery
- shock
- arrest
- stroke
- trauma

NEUROSSAVE®
Thank you