Surgical Stress and the Heat Shock Response: Models of Stress Conditioning

G. Perdrizet MD, PhD, L. Hightower PhD, C. Godman PhD, and C. Giardina, PhD

Dept. of Molecular and Cell Biology
University of Connecticut, Storrs, CT
Overview

- Medical and Surgical Safety
  - Room for improvement
- Define Surgical Stress
- Introduce Stress Conditioning
- Hyperbaric Oxygen Therapy?
Health care in the United States is not as safe as it should be--and can be. At least 44,000 people, and perhaps as many as 98,000 people, die in hospitals each year as a result of medical errors that could have been prevented, according to estimates from two major studies. Even using
Risk Estimates of Stroke After Coronary Artery Bypass Graft and Carotid Endarterectomy

Rima M. Dafer, MD, MPH

Department of Neurology, Stritch School of Medicine, Loyola University Chicago,
2160 South First Avenue, Maywood, IL 60153, USA

CVA post-CABG ~ 1.1 - 3.2% (up to 25%)
CVA post-CEA ~ 0.5 - 7%
Surgical Stress

Examples:
- Ischemia-reperfusion
- Inflammation
- Hypoxia
- Wounds
- Radiation
- Drug toxicity
- Metabolic toxins
- Hyper/hypothermia

Clinical Settings:
- All surgery
- Cardiovascular
- Trauma
- Critical care
- Transplant
- Burns
Heat Shock Response: Birth of Molecular Biology

F. Ritossa, 1964 Italy
A. Tissieres, 1974 Switzerland
S. Lindquist, 1975 USA
Heat Shock Response-1960’s
Prevents Thermal Death in *Drosophila*
Thermotolerance
Yeast

Lindquist, S., unpublished
Thermotolerance: Rodent in Vivo

Recovery Time (hrs)

% necrosis

Con  4  24  72  1wk

Recovery Time (hrs)
Organ Preservation: A Model (1985)

TIME LIMITS (hrs):
Heart - 5
Lung - 6-8
Liver - 24
Kidney - 48
Experimental Design: Rodent Renal Isograft

SHAM

HEAT SHOCK (42.5 °C x 15 min)

RECOVERY (37 °C x hrs)
0  6-8  24

NEPHRECTOMY

PRESERVATION (4°C x 48hrs)

TRANSPLANTATION
SURVIVAL 45 DAYS
Sham SC
0/7 functioned

Stress/No recovery time
0/5 functioned

Stress Conditioned
4/5 normal function

Heat Shock Protects Renal Isografts During Cold Storage

<table>
<thead>
<tr>
<th>GROUP</th>
<th>KIDNEY GRAFTS (n)</th>
<th>EARLY FUNCTION (n)</th>
<th>SURVIVORS (n)</th>
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<td>7</td>
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<tr>
<td>HS/6-8hrs</td>
<td>5</td>
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<td>HS/24hrs</td>
<td>3</td>
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*p< 0.002 vs sham

Stress Conditioning
Definition

Exposure of living cells or tissues to a **sublethal** stressor, followed by a recovery period prior to exposure to a **lethal** stressor.
Skin Flap Survival

Groups: Sham vs Heat Shock
Rodent pedicle-skin flap
Day 5 viable length

Acute Spinal Cord Ischemia: Incidence of Paralysis


*p < 0.05  1 vs 2 or 3
Heat Shock Protein

Cell Biology

Basal cell functions:
Protein synthesis
Protein transport
Mitochondrial function

Welch, W. Sci Amer 1993;268:56
Stress Conditioning
Historical Support

- Hans Selye - G.A.S. - 1930
- Endotoxin tolerance - 1940
- Thermotolerance - 1970
- Heat-shock response - 1980
- Ischemic preconditioning - 1980
- Numerous - 1990-present
  - Cytokines, oxidants, metals, fasting
The Physiology and Pathology of Exposure to

STRESS

A treatise based on the concepts of the

GENERAL-ADAPTATION-SYNDROME

and the

DISEASES OF ADAPTATION

by

HANS SELYE

M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada)

Professor and Director

of the

Institut de Médecine et de Chirurgie expérimentales

Université de Montréal

1950

Hans Selye, MD 1907-1982
Universite de Montreal
All Stress Responses Are Triphasic

Selye, H. 1950, p55. The Physiology and Pathology of Exposure to Stress
Is it possible to induce this response using a non-stressful agent?

- Hyperthermia- 108°F (42.5°C)
- Ischemia or hypoxia
- Heavy metals
- Ethanol
- Oxygen?
Human Oxygen Toxicity
Dose-Response Curves

- **CNS**
- **Pulmonary**
- **Ambient**

Dose range for clinical HBO$_2$ therapy
HBO$_2$ Pretreatment Increases Ischemic Tolerance: Animal Models

- **Rodent brain**

- **Rodent heart**
  - Cabigas, B.P., Cardiovas Res. 2006;72:143.

- **Rabbit spinal cord**
  - Nie, H., J Cereb Bld Flow & Metabolism 2006;26:666.
Hypothesis

• Exposure of human micro-vascular endothelial cell line will:
  • Confer protection against thermal and oxidant injury.
  • Increase expression of cytoprotective genes.
Methods

• HMEC-1 cell line, immortalized; CDC

• Hyperbaric oxygen
  • 2.4 ATA ≈ 1,800 mmHg O₂
  • 60 minute exposure time

• Cytoprotection Assays
  • Thermal or oxidant challenge
  • PI or MTT cell viability

• Gene expression-Microarray
  • Illumina Bead – WG-6 chip
  • Analysis- PBC and Ingenuity Pway
  • rt-PCR confirmation
38,275 total genes on Microarray

Statistical Analysis

8,181 regulated genes

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<th>Official symbol</th>
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</table>
RT-qPCR: HBO$_2$ vs 100% O$_2$
HBO\textsubscript{2} Induces Oxidant Protection in HMEC-1 Cells

\[ t\text{-butyl hydroperoxide (mM)} \]

Relative Viability (%)

* \( p \leq 0.01 \)
HBO₂ Pre-treatments Decrease Post-CABG Cognitive Decline

Summary

• Surgery is stressful.
  • Prevent collateral tissue damage

• Stress Conditioning
  • Potent tissue protection
  • Preventative medicine

• HBO₂ as a safe pre-op stress conditioning agent?
“The Light”
Fritz Eichenberg (1901-1990)
Univ. Rhode Island

Questions??