The Future of Critical Care Medicine

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The Future...

- Targeted Temperature Therapy
- Understanding & manipulating the microcirculation
- Endotoxin adsorption
- Point-of-care ultrasound
- Telemedicine
Therapeutic Hypothermia
Hippocrates (460 BC - 377 BC)

• “Extreme Remedies are very appropriate for Extreme diseases.”
The Facts

• 250,000 Americans die every year from SCA occurring outside of the hospital

• Out-of-hospital cardiac arrest only has an average survival rate of 6% worldwide

• Approximately 20% of patients who survive and are comatose during the post resuscitation period will awaken with a good neurological outcome

Circulation 2005. IV-206
Reperfusion Injury

• Global ischemia occurs during periods of circulatory collapse

• During reperfusion, free radicals and mediators are released causing cerebral ischemia, which may persist for several hours after return of spontaneous circulation (ROSC)
Post–Cardiac Arrest Brain Injury:

- Patients who survived to ICU admission but subsequently died in the hospital, brain injury was the cause of death in 68% after out-of-hospital cardiac arrest and in 23% after in-hospital cardiac arrest.
Post-Cardiac Arrest Syndrome: Epidemiology, Pathophysiology, Treatment, and Prognostication

A Scientific Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, Resuscitation Council of Southern Africa, and the New Zealand Resuscitation Council); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke

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Post–cardiac arrest syndrome  ILCOR

• 1-Post–cardiac arrest brain injury.

• 2-Post—cardiac arrest myocardial dysfunction.

• 3-Systemic ischemia/Reperfusion response.

• 4-Persistent precipitating pathology
Hypothermia
Hypothermia

• Definitions of hypothermia:
  – Mild: 33-36 degrees Celsius
  – Moderate: 26-32 degrees Celsius
  – Deep: 20-25 degrees Celsius
  – Profound: < 20 degrees Celsius
Physiologic Effects on CNS:

• Hypothermia decreases Intracranial Pressure.


| TABLE 3. MEAN DAILY ARTERIAL PRESSURE, INTRACRANIAL PRESSURE, AND CEREBRAL PERFUSION PRESSURE IN PATIENTS WITH BRAIN INJURY ASSIGNED TO INDUCTION OF HYPOTHERMIA OR TO NORMOTHERMIA. * |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| VARIABLE                                         | DAY 1                                          |        | DAY 2                                          |        | DAY 3                                          |        | DAY 4                                          |        | DAYS 1-4                                      |        |
| Mean arterial pressure                           | HYPOTHERMIA (mm Hg)                           | 95.5  | NORMOTHERMIA (mm Hg)                          | 92.6  | HYPOTHERMIA (mm Hg)                           | 93.4  | NORMOTHERMIA (mm Hg)                          | 95.2  | HYPOTHERMIA (mm Hg)                           | 92.4  | NORMOTHERMIA (mm Hg)                          | 95.8  | <0.001                                         |
| Patients in whom pressure was ever <70 mm Hg (%)| 31                                             |        | 18                                            |        | 11                                            |        | 15                                            |        | 8                                             |        | 0.07                                           |        | 0.01                                           |
| Intracranial pressure                           | HYPOTHERMIA (mm Hg)                           | 15.7  | NORMOTHERMIA (mm Hg)                          | 17.1  | HYPOTHERMIA (mm Hg)                           | 15.6  | NORMOTHERMIA (mm Hg)                          | 17.7  | HYPOTHERMIA (mm Hg)                           | 16.2  | NORMOTHERMIA (mm Hg)                          | 16.1  | 0.91                                           |
| Patients in whom pressure was ever >30 mm Hg (%)| 23                                             |        | 14                                            |        | 28                                            |        | 16                                            |        | 26                                            |        | 0.03                                           |        | 0.06                                           |
| Therapy Intensity Level†                        | HYPOTHERMIA (mm Hg)                           | 4.9   | NORMOTHERMIA (mm Hg)                          | 5.3   | HYPOTHERMIA (mm Hg)                           | 5.2   | NORMOTHERMIA (mm Hg)                          | 5.0   | HYPOTHERMIA (mm Hg)                           | 5.3   | NORMOTHERMIA (mm Hg)                          | 4.3   | 0.005                                          |
| Cerebral perfusion pressure‡                    | HYPOTHERMIA (mm Hg)                           | 79.9  | NORMOTHERMIA (mm Hg)                          | 74.8  | HYPOTHERMIA (mm Hg)                           | 78.0  | NORMOTHERMIA (mm Hg)                          | 78.0  | HYPOTHERMIA (mm Hg)                           | 76.3  | NORMOTHERMIA (mm Hg)                          | 79.7  | 0.003                                          |
| Patients in whom pressure was ever <50 mm Hg (%)| 22                                             |        | 18                                            |        | 13                                            |        | 11                                            |        | 9                                             |        | 0.73                                           |        | 0.07                                           |

* Induction and maintenance of hypothermia occurred on days 1 and 2, rewarming occurred on day 3, and post-rewarming treatment occurred on day 4.
† The Therapy Intensity Level was designed to quantify the effects of therapy on the analysis of levels of intracranial pressure — for example, to distinguish between levels of intracranial pressure maintained with sedation alone and the same levels achieved with barbiturate coma. It is a 16-point scale with values ranging from 0 to 15, with higher values indicating more treatment. This score was calculated every 24 hours according to the therapies used during that period.
‡ Cerebral perfusion pressure equals the mean arterial pressure minus the intracranial pressure.
Physiologic Effects on CNS:

- Hypothermia may act as an anticonvulsant. (1)
- Hypothermia decreases excitatory AA and lactate during ischemia and reperfusion. (2,3)
- In a rat model, Hypothermia reduced the microvessel expression of ICAM-1 protein and the number of neutrophils migrating into ischemic tissue. (4)
- In head injury patients, IH decreased IL-10 concentrations in CSF. (5)

Physiologic Effects on CVS:

- Accidental Hypothermia $\rightarrow$ 34°C < intense shivering < 36°C.
- Shivering increased metabolic rate and oxygen demand.
- Increase incidence of MI in patients with Ischemic heart Disease.

Frank et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A Randomized Clinical Trial. JAMA 1997.
Physiologic Effects on CVS:

- During IH→the patient is sedated/paralyzed to avoid shivering.

Physiologic Effects on CVS:

- Cardiac arrhythmias are rarely seen at 33C, even in patients with myocardial ischemia.

- In accidental hypothermia, there is a risk of V-fib if core temperature decreases below 28C.

Physiologic Effects of Therapeutic Hypothermia on CVS:

- Sinus bradycardia ensues as temperature drops below 35.5°C, with a progressive decrease in heart rate as temperature decreases further.

- At core temperatures of 32°C the heart rate typically decreases to around 40–45 beats/min or even lower (wide inter and intraindividual variability)

- Electrocardiographic changes include:
  - prolonged PR interval
  - widening of the QRS complex
  - increased QT interval
  - Osborne waves.
Physiologic Effects of Therapeutic Hypothermia on Respiratory system:

- At 33°C, metabolic rate decreases by 25-33%, Minute volume is decreased to maintain normal pH/pCO2.
- Pneumonia is a risk of IH → uncommon during brief periods of hypothermia (12-24H). (1,2)
- In a series of patients who underwent 7 days of IH (for severe head injury) → Nosocomial pneumonia in 45%. (3)

Physiologic Effects of Therapeutic Hypothermia on Renal System:

- Diuresis $\rightarrow$ decreased reabsorption of solute in the ascending limb of the loop of henle.\(^{(1)}\).
- Induction of hypothermia shifts K into the cells. (Hyperkalemia during rewarming).\(^{(2,3)}\).
- Hypothermia decreased phosphate concentrations.\(^{(4)}\).

- Volume status, Potassium and phosphate concentrations require careful monitoring.

Physiologic Effects of hypothermia on ABG:

• As temperature decreases, the solubility of gases in blood increases.
• When ABG of hypothermic patients are corrected for temperature, patients appear to have a respiratory alkalosis.
Physiologic Effects of hypothermia on ABG:

• If it is not possible to obtain blood gas results measured at the patient’s true core temperature, values can be estimated using the following rule of thumb:

  - For PO2, subtract 5 mm Hg for every 1°C below 37°C.

  - For PCO2, subtract 2 mm Hg for every 1°C below 37°C.

• For pH, add 0.012 points for every 1°C below 37°C.
Physiologic effects of Therapeutic Hypothermia on GI system:

- Decreased gut motility $\rightarrow$ delay enteral feeding. (1)

- Increases blood glucose concentration (? Decrease insulin release) (2) $\rightarrow$ keep tight glucose control by administering Insulin.

Physiologic effects of Therapeutic Hypothermia on hematologic system:

- The numbers and function of WBCs decrease $\rightarrow$ increase incidence of sepsis (pneumonia during $>24$H IH). (1)
- Prolonged hypothermia decreases the number and function of platelets (<35 degrees) (1)
- Hypothermia prolongs clotting times (<33 degrees) $\rightarrow$ increase in risk of bleeding in the setting of major trauma (2)

Effects of Therapeutic Hypothermia on the skin:

- Increases the risk of wound infections:
  - diminished leukocyte function
  - hypothermia-induced vasoconstriction in the skin.

- Thus extra care should be taken in cooled patients to prevent bedsores.
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??

Suppression of Epileptic activity And seizures ?
Coagulation activation, Formation of microthrombi
Increased blood-Brain barrier Permeability, Edema formation
Increased vascular Permeability, Edema formation

Mitochondrial Injury and Dysfunction.
Apoptosis, Calpain-mediated Proteolysis, DNA injury
Local brain Hyperthermia, “cerebral Thermo-pooling”

...and inhibited by HYPOTHERMIA
Research on Hypothermia

• 2 studies published in New England Journal of Medicine in February, 2002
  – HACA
  – Bernard
HACA Study: Hypothermia After Cardiac Arrest Group

- 9 centers, 5 countries in Europe
- CPR within 5 to 15 minutes of arrest
- Presumed ventricular tachycardia or fibrillation
- ROSC within 60 minutes from collapse
- 275 patients randomized to hypothermia or normothermia
- Cooled to 32º - 34ºC for 24 hours
HACA Study: 6 to 8 hours to reach target

Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups. The error bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.
Outcomes

• Primary end point was favorable neurologic outcome (live independently and work at least part-time) within 6 months after cardiac arrest

• Secondary end points were mortality within 6 months and rate of complications within 7 days
Results

• 75/136 patients (55%) in the hypothermia group had a favorable neurologic outcome within six months after arrest as compared with 54/137 patients (39%) in the normothermia group

• Six month mortality was 41% in the hypothermia group (56/137) as compared with 55% (76/138) in the normothermia group

• No significant difference in complications between the groups
Australian Study, Bernard et al

- 4 hospitals in Melbourne
- Initial cardiac rhythm of ventricular fibrillation
- Successful ROSC with persistent coma
- 77 patients randomized to hypothermia or normothermia
- Cooling initiated in ambulance
- Cooled to 33ºC for 12 hours
Outcomes

• Survival to hospital discharge either to home or to a rehabilitation facility
Results

• 21/43 patients (49%) in hypothermia group discharged to home or rehab as compared with 9/34 (26%) in normothermia group

• No difference in frequency of adverse events

• Mortality rates were not statistically significant
Metaanalysis:

• Therapeutic Hypothermia is associated with a risk ratio of 1.68 (95% CI, 1.29-2.07) favoring a good neurologic outcome when compared with Normothermia.

• NNT to generate one favorable neurological recovery = 6.

• Improve neurological recovery in > 10,000 patients/Year.
Updated 2005 AHA Guidelines for CPR

Editorial

Major Changes in the 2005 AHA Guidelines for CPR and ECC

Reaching the Tipping Point for Change

Mary Fran Hazinski, RN, MSN; Vinay M. Nadkarni, MD; Robert W. Hickey, MD; Robert O’Connor, MD; Lance B. Becker, MD; Arno Zaritsky, MD

Circulation 2005; 112:IV-206 – IV-211
Thus, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa. Weight of evidence/opinion is in favor of usefulness/efficacy
IIb. Usefulness/efficacy is less well established by evidence/opinion.
Cooling Techniques: Early Cooling
Does it matter?

  – 49 pt $\rightarrow$ good (28) vs poor (21) outcome
    • Predictors of good outcome:
      – Time to Coldest Temperature
      – Time to Target Temperature
Cooling Techniques: Early Cooling
Can it be done?

• Bernard et al reported the results of a clinical trial of the rapid infusion of large-volume (30 mL/kg), ice-cold (4°C) lactated Ringer’s solution in comatose survivors of out-of-hospital cardiac arrest. (1)
  – Decreased core temperature by 1.6°C over 25 mins
  – Associated with improvements in MAP, renal f(x), and acid-base.
  – No pulmonary edema.
  – Inexpensive, convenient, and applicable to the prehospital setting.
  – Higher BP may be of additional benefit after cardiac arrest.

• Minneapolis Heart Institute (2)
  – Each 1hr delay in time to target temperature results in 25% higher risk of death or poor neurologic outcome

The Miracle on Ice: Therapeutic Hypothermia for Cardiac Arrest Patients. December 2009. Unpublished data
PreHospital Cooling: Randomized trials

- **Kim et al. Circulation. 2007;115:3064-3070**
  - EMS infused up to 2L of 4°C normal saline
  - 125pt randomized to receive standard care with or without intravenous cooling
  - 49/63 randomized to cooling received an infusion of 500 to 2000 mL of 4°C normal saline before hospital arrival.
  
  - *Cooling group had mean T decrease of 1.241°C to 34.7°C*

  - Control group had mean T increase of 0.1°C (*P* < 0.0001) with a hospital arrival temperature of 35.7°C.

  - *Secondary end points of awakening and discharged alive from hospital trended toward improvement in ventricular fibrillation patients randomized to in-field cooling.*
PreHospital Cooling: Randomized trials


  - 44 patients screened,
    - 19 were cooled w/ LVICF
    - 18 received conventional IVF
  - Mean volume/patient in the treatment group was 2370 (± 500) ml.
  - Mean decrease in nasopharyngeal temperature of 1.5 (± 0.8)°C.
  - At the time of hospital admission, the mean (± SD) nasopharyngeal temperature was markedly lower in the hypothermia group compared to the control group; 34.1 ± 0.9°C vs. 35.2 ± 0.8°C, respectively (p < 0.001).
PreHospital Cooling: During CPR?


  – 17 patients, paramedics initiated cooling using infusion of cold fluid during CPR and after ROSC.
  – Infusion rate = 57 ± 21 ml/min with a target temperature of 33°C.
  – The mean infused volume of cold fluid per patient was 1571 ml.
  – *Mean admission temperature = 33.83 ± 0.77°C (n = 11, -1.34°C decrease compared to initial nasopharyngeal temperature)*
  – *No apparent increase in the rate of re-arrest or hemodynamic instability.*
  – *The treatment was easily carried out by paramedics.*
PreHospital Cooling: Improve Outcome?


- 33 patients, 20 w/ ROSC
- A *mean esophageal temperature decrease of 2.1°C*
- Mean rate of infusion: 67 ml/min
- Volume of cold saline per patient was 2L
- Cooling was continued in hospital
- 4 *patients out of 11 surviving to ICU admission were alive after 6 months.*
- 3 *with a CPC score <= 2*
PreHospital Cooling

“Prehospital TH appears to be safe and remains a promising approach that not only decreases the time to therapeutic temperature, but if applied by emergency management service protocols, may increase the overall utilization of TH, resulting in important epidemiological gains.”

Temperature Control and Brain Injury

Hypothermia
Current Strategies to Manage Fever

Carhuapoma et al (2003) found pharmacological therapy (acetaminophen and nonsteroidal anti-inflammatory drugs) to be ineffective, with only 36% success rate.

Mayer et al (2004) have found water-circulating cooling blankets ineffective to moderate temperature, with success rates <40% (Mayer, 2004).
Endovascular Cooling Devices:

- Outflow Lumen
- Inflow Lumen
- Radio-opaque Tip
- Heat Exchange Balloon
- Tip Infusion Lumen
- Suture Tabs on Manifold
- Radio-opaque Band

Hypothermia
Non-invasive temperature control

- Water immersion is the most effective way to modify patient temperature non-invasively

Olga Platner, et al Anesthesiology V87 No 5 Nov 97
Arctic Sun Energy Transfer Pads

Simulates water immersion

Biocompatible hydrogel material: 50% water based matrix with temperature controlled water flowing beneath the thin film.
Contraindication...?

- Hypotension? NO
- Active Bleeding? Maybe
- Arrhythmias? NO (provided Temp stays > 30)
- Older Age? NO

If the patient is worth admitting to the ICU, He/she should receive therapeutic Hypothermia
Clinical experiences*

- Neurogenic fever control
- Heat stroke
- Malignant Hyperthermia
- Sudden cardiac arrest
- Refractory ICP.
- SAH/ICH
- Ischemic stroke (COOL AID)
- Traumatic Brain Injury (EUROTERM)
- Spinal Cord Injury.
- Hepatic Encephalopathy – bridge to transplant
- Myocardial Infarction (COOL MI, ICE-T..)
- Contrast-Induced Nephropathy (COOL-RCN...)
- Refractory Status Epilepticus (case reports/series).
Sepsis: A Disease of the Microcirculation.

David Tannehill, DO
Farid Sadaka, MD
“Five to fifteen minutes after its [endotoxin] intravenous administration, there were strong waves of contraction along the small arteries, arterioles and metarterioles. These could arrest flow and last for several minutes. There would afterwards be a phase of dilatation, followed again by a strong contraction. As time went on, the phases of relaxation became more prominent until preagonally there was a general and permanent vasodilation. The circulation would slow progressively until death.”

From Delauney and coworkers (1955),
Number of publications regarding microcirculation in humans
SBP < 90 mmHg or MAP < 65 mmHg after 20-30 cc/kg crystalloid IVF

- OR -

Lactate > 4 mmol/L regardless of blood pressure

Supplemental oxygen ± endotracheal intubation and mechanical ventilation (if necessary)

Perform central venous catheterization while continuing crystalloid IVF resuscitation (250-1000 ml boluses)

Critical care consultation

CVP

< 8 mmHg

Crystalloid IVF

8-12 mmHg

MAP

< 65 mmHg

Vasopressor(s) (Norepinephrine or dopamine preferred)

≥ 65 mmHg

ScvO2

< 70%

Transfusion of red cells to hematocrit ≥ 30%

≥ 70%

Inotropic agents. (If PA cath inserted, keep cardiac index ≥ 3.0 L/min/m²)

No

Yes

Goals achieved

Resuscitation complete.

Establish new goal.
EGDT

- Individuals with severe sepsis who initially presented with a MAP >100 mmHg and a serum lactate level > 4 mM (n = 23) had a significantly increased mortality rate (60.9%) compared with patients who had originally presented with hypotension (MAP < 70 mmHg) (n = 68, 42% mortality).
The microcirculation consists of the smallest blood vessels (<100 μm diameter)-Arterioles, capillaries, and venules.

The main cell types comprising the microcirculation are the endothelial cells lining the inside of the microvessels, smooth muscle cells (mostly in arterioles), RBCs, leukocytes, and plasma.

The microcirculation, with its huge endothelial surface, is in fact the largest ‘organ’ in the human body.

The Microcirculation is the primary site of oxygen and nutrient exchange.

The Microcirculation delivers therapeutic drugs to target cells.
What exactly comprises the Microcirculation?

- It is where oxygen exchange takes place.

- Every parameter in the microcirculation is different than in the systemic circulation.

- It plays a central role in the immune system.

- During sepsis and shock it the first to go and last to recover.

- Rescue of the microcirculation = resuscitation end-point.
Disturbed microcirculation in sepsis

- Redistribution of organ blood flow
- DIC
- Cardiopulmonary pathology
- Disturbance of red and white cell rheology
- Viscosity alterations
- Vasoplegia
- Altered microvascular blood flow and vascular resistance
- Opening of AV shunts
- Increased microvascular permeability
- Decreased red cell deformability
- Congestion and hemorrhage
- Intravascular pooling
- Edema formation
- Endothelial activation

Shunting model of sepsis
How perfused vessel density plays a critical role in oxygen transport.
MIROCIRCULATION:

- Inflammatory activation
- Coagulatory/RBC dysfunction
- Endothelial barrier dysfunction
  - Capillary fall out
- Weak microcirculatory units are shunted
- Hypoxia, apoptosis, organ dysfunction

*Not detected by systemic variables*
Mitochondrial Dysfunction in Sepsis.

<table>
<thead>
<tr>
<th></th>
<th>Septic survivors (A)</th>
<th>Septic non-survivors (B)</th>
<th>Controls (C)</th>
<th>p (A vs B vs C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex I activity*</td>
<td>0.18 (0.14-0.23), n=16</td>
<td>0.15 (0.11-0.18), n=10</td>
<td>0.21 (0.18-0.24), n=8</td>
<td>0.03</td>
</tr>
<tr>
<td>Complex II and III activity*</td>
<td>0.13 (0.10-0.16), n=16</td>
<td>0.13 (0.12-0.15), n=12</td>
<td>0.12 (0.11-0.14), n=9</td>
<td>0.35</td>
</tr>
<tr>
<td>Complex IV activity*</td>
<td>0.014 (0.01-0.02), n=16</td>
<td>0.020 (0.013-0.02), n=12</td>
<td>0.011 (0.01-0.017), n=8</td>
<td>0.05</td>
</tr>
<tr>
<td>Reduced glutathione (nmol/mg total protein)</td>
<td>5.0 (3.5-5.8), n=13</td>
<td>3.9 (2.2-4.8), n=11</td>
<td>9.8 (8.4-11.0), n=8</td>
<td>0.0004</td>
</tr>
<tr>
<td>Nitrite/nitrate (µmol/mg total protein)</td>
<td>118 (99-159), n=8</td>
<td>176 (173-197), n=7</td>
<td>86 (45-103), n=6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Expressed as a ratio of nitrate synthase activity. Data are median (IQR), number of patients as shown, p value as unadjusted. 

Lancet 2002;360:219-23
Microcirculatory Mitochondrial Distress Syndrome


Initial Hit

Co-morbidity
Genes

Circulatory Shock + Inflammation

Resuscitation based on correction of systemic hemodynamics + inflammation

Microcirculatory Dysfunction

Endothelial Dysfunction
- Barrier, Communication
- Coagulation, Regulation

RBC
- Deformability, Aggregation
- O₂ transport

Coagulation
- ↓Natural Anticoagulants
- Microvascular Thrombosis

Leukocytes
- Adhesion, Cytokines, ROS

Dysfunction Autoregulation
- Microcirculatory shunting
- supply-demand mismatch
- Hypoxia

Cellular Distress
- Mitochondria
- Hibernation
- Apoptosis

Organ Failure
SDF: Sidestream Dark Field
- **Vessel density** = the number of vessels crossing the lines divided by the total length of the lines. 

- **Perfusion**: categorized by eye as present (continuous flow for at least 20 s), absent (no flow for at least 20 s), or intermittent (at least 50% of the time with no flow).

- **The proportion of perfused vessels (PPV [%])** = \(100 \times \frac{\text{total number of vessels} - \left[\text{no flow} + \text{intermittent flow}\right]}{\text{total number of vessels}}\).

- **Perfused vessel density (PVD)**: calculated by multiplying vessel density by the proportion of perfused vessels.
The image is divided into four quadrants and the predominant type of flow (absent = 0, intermittent = 1, sluggish = 2, and normal = 3) is assessed in each quadrant.

**-The MFI:** represents the averaged values of the four.

A 20 μm cut-off is used to separate small vessels (mostly capillaries) from large vessels (mostly venules).

**-Heterogeneity index:**
Evaluate three to five sites and measure the MFI in the quadrants. Take the difference between highest MFI minus the lowest site MFI divided by the mean flow velocity of all sublingual sites at a single time point.
SEVERE SEPSIS
De Backer, Creteur, Preiser, Dubois, Vincent

There was no difference in systemic hemodynamic and oxygenation variables or the amount or type of drugs used between survivors and non-survivors.

Microcirculatory dysfunction was the single most sensitive and specific predictor of outcome.
Nitroglycerin promotes microvascular recruitment in septic and cardiogenic shock patients.

Sublingual OPS imaging in a patient with septic shock after pressure guided volume resuscitation.

the same patient after subsequent nitroglycerin 0.5 mg ivbolus

Capillary flow but to a much lesser degree venular flow, is impaired during pressure guided resuscitation from septic shock.

NO donor can recruit the microcirculation by promoting flow.
The effects of Dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects.

Hydrocortisone in septic shock resulted in a consistent improvement in capillary perfusion, independent of the response to the ACTH test. DeBacker et al. Crit Care Med 2009 Vol. 37, No. 4
-Activated protein C (DAA) **rapidly improves** sepsis-induced microvascular alterations.
-Its cessation is associated with a transient deterioration.
There was no relation between the changes in cardiac index or in arterial pressure and changes in capillary perfusion.
Activated protein C (DAA):

- This study demonstrates that DAA ameliorates microcirculatory alterations in patients with severe sepsis.

Nitroglycerin dose-dependently increases microcirculatory perfusion in patients with severe heart failure as observed by an increase in sublingual perfused capillary density.

Near InfraRed Spectroscopy:
Near InfraRed Spectroscopy:
Near-Infrared Spectroscopy:

- A non-invasive technique that uses the differential absorption properties of oxygenated and deoxygenated hemoglobin to evaluate skeletal muscle oxygenation.
- Near-infrared light (680–800 nm) easily crosses biological tissues, which have a low absorption power and is absorbed only by hemoglobin, myoglobin, and oxidized cytochrome (the contribution of the latter two to the light attenuation signal is very small.)
- Hence, the NIRS signal is derived predominantly from hemoglobin present within the volume of tissue crossed by the near-infrared light.
- **NIRS monitors only vessels with a diameter < 1 mm (arterioles, capillaries, and venules)**
Near InfraRed Spectroscopy:

- Thenar site minimally affected by:
  - age
  - gender
  - edema
  - adipose

- StO2 not confounded by hypothermia
Near-Infrared Spectroscopy:

\[
\text{StO}_2 \approx \frac{\text{O}_2 \text{ Hb}}{\text{O}_2 \text{ Hb} + \text{HHb}}
\]

Total Hemoglobin Index (THI):
a indicator of blood volume in the region of microvasculature sensed by the probe expressed in arbitrary units (AU)
Both the current value and trend of StO2 are important.

- StO2 low; assess patient; resuscitate if indicated
- StO2 rising toward normal; assess continued resuscitation
- StO2 adequate; assess need for further resuscitation; stop if indicated
- StO2 falling; assess patient; resume resuscitation if indicated
- StO2 high; consider late sepsis/spinal cord damage
- StO2 adequate; assess need for further resuscitation; stop if indicated
Early Goal-Directed therapy:

- Patients who failed to normalize StO2 during early treatment in the ICU had more severe organ dysfunction and disease severity.
- Low StO2 levels does not reflect global hemodynamic effects (HR, CVP, MAP, ScvO2) or vasoconstriction from pharmacologic intervention.
- Patients who consistently showed low StO2 values within the first 8 hours of ICU treatment had a significantly higher rate of unfavorable outcome.
- The absence of low StO2 levels identified patients with a more favorable outcome.
Reactive Hyperemia:

• Reactive hyperemia may be considered as a test of microcirculatory reactivity

• It evaluates the tissue’s ability to adjust oxygen extraction capabilities to oxygen delivery after a hypoxic stimulus induced by a transient interruption of blood flow.

• This process is complex, involving capillaries, arterioles, and small arteries, increasing flow in previously patent capillaries and recruiting additional capillaries.

• Altered reactive hyperemia has been reported in septic patients using various techniques.
Arterial occlusion is obtained by inflating a cuff on an upper extremity to 50 mmHg greater than the current SBP for 3-5 minutes.

- **NIRS-derived thenar oxygen consumption** \( \text{nirVO}_2 \):  
  - can be calculated from the slope of \( \text{StO}_2 \) during arterial occlusion
Reactive Hyperemia:

- On release of the arterial cuff, $\text{StO}_2$ rises rapidly and eventually peaks at a level of tissue oxygen saturation greater than before occlusion.
- This peak is part of the hyperemic response after arterial occlusion.
- The area under the hyperemic response curve but above the baseline $\text{StO}_2$ value is the hyperemic area.
- The time required to reach 63% of the hyperemic peak from the release of the cuff is the $\text{StO}_2$ recovery time.
Correlation between SOFA score and the thenar muscle StO2 decrease rate during stagnant ischemia.

\[ r = 0.739, \ p < 0.001 \]
StO2 decrease rate:

- NIRS-derived Thenar oxygen consumption (nirVO$_2$I):
  - is reduced significantly in severe sepsis subjects.

[Graph showing comparison between control and severe sepsis in terms of tissue VO$_2$ in arbitrary units.]
The rate of increase of StO2 in the hyperemic phase (slope) was lower in the septic patients than in the ICU controls and the healthy volunteers.
The hyperemic phase (slope):

- Altered recovery in StO2 after an ischemic challenge is frequent in septic patients and more pronounced in the presence of shock.

- The presence and persistence of these alterations in the first 24 h of sepsis are associated with worse outcome.
Reoxygenation Rate (RR) = The hyperemic phase (slope)

- Reoxygenation rate (RR) is related to organ injury in sepsis.

- *RR was impaired significantly in sepsis subjects with severe organ failure (SOFA 10, dark gray bar) compared with septic subjects with modest organ dysfunction (light gray bar) and control subjects (white bar).*

- *RR tended to be slower in those that did not survive hospitalization than in those who survived.*
• a linear relationship between \text{nimVO}_2I and RR in severe sepsis subjects.
Activated Protein C:

- rh-aPC treatment significantly lowered the SOFA score, increased the mean arterial pressure, and reduced the blood lactate concentration.

Donati et al. Critical Care 2009, 13(Suppl 5):S12
- rh-aPC had positive effect on StO2 downslope indicating raised oxygen consumption/metabolism.
- rh-aPC had positive effect on StO2 upslope indicating improved microvascular reperfusion following ischemia.

Microvascular function is therefore improved by rh-aPC treatment.
Signs of regional dysoxia in the presence of apparent adequate oxygen delivery.

- **Cytopathic hypoxia:** mitochondrial dysfunction in the presence of adequate tissue oxygenation.  

- **Shunting theory of sepsis:** microcirculatory shut down of weak microcirculatory units creating hypoxic pockets.  
Conclusion:

- The microcirculation consists of the smallest blood vessels (<100 μm diameter) - arterioles, capillaries, and venules.
- The microcirculation, with its huge endothelial surface, is the largest ‘organ’ in the human body.
- During sepsis and shock it is the first to go and last to recover.
- Microcirculatory dysfunction is the single most sensitive and specific predictor of outcome (irrespective of systemic hemodynamic and oxygenation variables).
- Noninvasive means to evaluate Microcirculation (SDF, NIRS) (Therapeutic Interventions...).
- MMDS.
- Resuscitation end-point: Microcirculation = Mitochondria
Endotoxin adsorption

- Lipopolysaccharide (LPS) endotoxin
  - Important in sepsis
    - Especially gram negative

- Polymixins
  - Bind LPS
  - Hemadsorption of endotoxin
    - Japan, Europe
    - EUPHUS → EUPHRATES
Endotoxin adsorption

• 1970’s – benchwork
• 1980’s – animal studies
  – Plasmapheresis in rat model cleared LPS
• 1990’s – Human studies in Japan
  – UF or hematodesorption through a special cartridge w/ polymixin coated fibers.
  – Clinical use since 1994
  – Subsequent small, poor quality studies
• 2005 European study suggested benefit
Endotoxin adsorption

• Mechanism of action
  – Removes endotoxin
  – Decreases cytokines
    • By way of decreasing LPS
  – Decreased PAI-1 activity
  – Decreased neutrophil respiratory burst
  – Removal of monocytes
  – Removal of endogenous cannabinoids
    • (effects microcirculation...)

Multicenter, RCT in Italy

64 pt w/ severe sepsis/shock
  – Intraabdominal sepsis

Primary endpoint
  – Change in MAP/pressors

Secondary endpoint
  – p/F
  – Change in SOFA
  – 28 day mortality
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

Figure 3. Estimation of Survival Rate According to Treatment Group

Table 3. Physiological End Points

<table>
<thead>
<tr>
<th>Physiological End Point</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>Therapy</td>
</tr>
<tr>
<td>Inotropic score</td>
<td>Therapy</td>
</tr>
<tr>
<td>Vasopressor dependency</td>
<td>Therapy</td>
</tr>
<tr>
<td>PaO₂/FIO₂</td>
<td>Therapy</td>
</tr>
<tr>
<td>Renal replacement therapy No. (%)</td>
<td>Therapy</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; *See “Methods” section for details.

Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.
CURRENT CONCEPTS

Point-of-Care Ultrasonography

Christopher L. Moore, M.D., and Joshua A. Copel, M.D.

Ultrasound Images of the Pleural Line in a Healthy Patient and in a Patient with Alveolar Interstitial Syndrome.

Telemedicine