What we WANT....

What we Usually GET:
- 39 year-old man
- CVA day 3
- R hemiplegia and neglect
- L arm extends briefly to medial arm pinch

Mass Effect & Tissue Shifts are the Problem!
  - 19 patients deteriorating to Stupor from large ischemic MCA/ICA infarcts
  - ICP > 15 mmHg present in only 5 patients!
  - 48 patients with Malignant MCA infarction
  - ALL patients had signs of herniation PRIOR to an increase in ICP > 20 mmHg
- Routine ICP Monitoring is NOT helpful
Neurologic Deterioration in Noncomatose Patients with ICH
(Mayer et al. Neurology 1994)

- Deterioration occurred in 33%
- Predicted primarily by large hematoma volume on initial CT scan (mean 13 h after onset)
- Worsening was associated with substantial mortality (47% vs. 3%)
- Conclusion: Edema associated with large established hemorrhages is the most important cause of late (>12 hours) clinical deterioration after ICH

Global Cerebral Edema in Acute SAH

- Develops in 20% of SAH patients
- Predicted by LOC at onset
- Delayed edema associated with Triple-H Therapy!
- Associated with increased mortality, disability, and cognitive impairment
Optimization of BP in states of elevated ICP
ICP/CPP Management

Extremes of CPP can aggravate ICP when intracranial compliance is reduced.

Extremes of CPP can aggravate ICP when intracranial compliance is reduced.
Brain Oxygen Tension Monitoring: LICOX

- Adjustment of Cerebral Perfusion Pressure levels based on the needs of each patient
- Early warning of differences between brain tissue oxygen supply and demand
- Independent, sensitive outcome prediction

### Antihypertensives in the Neuro-ICU

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nicardipine</th>
<th>Nitroprusside</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>0.5-15 mg/hr</td>
<td>0.5-15 µg/kg/min</td>
<td>0-2 mg/kg</td>
</tr>
<tr>
<td>Onset/Offset</td>
<td>Rapid 10-20 min</td>
<td>Slow 15-60 min</td>
<td>Slow 1-4 h</td>
</tr>
<tr>
<td>Preload reduction</td>
<td>0-100</td>
<td>0-50</td>
<td>0-50</td>
</tr>
<tr>
<td>Intensity reduction</td>
<td>0-50</td>
<td>0-50</td>
<td>0-50</td>
</tr>
<tr>
<td>Chronology reduction</td>
<td>0-50</td>
<td>0-50</td>
<td>0-50</td>
</tr>
<tr>
<td>Increased CBF</td>
<td>0-50</td>
<td>0-50</td>
<td>0-50</td>
</tr>
<tr>
<td>Common Contraindication</td>
<td>No</td>
<td>Hypovolemia, Low CPP, Infusion &gt;3 days</td>
<td>Hypovolemia, Low CPP, Infusion &gt;3 days</td>
</tr>
</tbody>
</table>

- Bronchospasm
- Cardiogenic shock
- Bacteremia
Treatment Options for Cytotoxic Brain Edema

- Osmotherapy
- Hypothermia
- Hemicraniectomy

Osmotherapy

Fluid Management and Brain Edema: Principles

- Severe acute brain injury results in physiologic changes favoring SIADH and free water retention
- Brain swelling and ICP correlates with serum osmolality, not volume status
  - Free water administration exacerbates brain edema
NICU Fluid Management Principles

- Give only isotonic crystalloids
  - Normal saline
  - Ringer’s Lactate solution

- Avoid all sources of free water
  - NO D5W or half-normal saline
  - NO half-concentrated feeds

- Maintain euvolemia
  - Positive fluid balance
  - CVP >5 mm hg

Hyper-Osmolar Therapy

- Two Solutions
  - 20% Mannitol
  - Hypertonic saline

- Two treatment paradigms
  - Bolus therapy
    - Reduce acutely elevated ICP
    - Reverse brain tissue shifting
  - Standing therapy
    - Establish a hyper-osmolar state
    - “Prune out” water-logged cerebral tissues

ICP: General Care Issues

- Elevate head of bed 30°
- Use only isotonic fluids (0.9% saline)
- Control fevers aggressively
- Seizure prophylaxis
- No routine steroids use

Option: 3% saline or mannitol for target osmolality of 300-320 mOsm/L
STANDING OSMOTHERAPY

1. CODE YELLOW
   - Osm 300-320, Na+ 150

2. CODE ORANGE
   - Osm 320-340, Na+ 155

3. CODE RED
   - Osm 340-360, Na+ 160

Standing Hyper-Osmolar Therapy

- **Two options**
  - **20% Mannitol**
    - 1 g/kg IV every 6 hours
    - NS 1 ml/kg/hr, adjusted to keep CVP 25 and fluid input = output
  - **3% Hypertonic Saline**
    - 1 ml/kg/hr
    - Reduce rate and diurese as needed to keep CVP 18 and output = input

Mannitol

- 0.25 to 1.5 g/kg IV wide open
- Dose up to Q1H on an as-needed basis
- **Mechanisms:**
  - Acute dehydrating effect (osmotic gradient across BBB)
  - Secondary hyperosmolality (diuretic effect)
  - Reflex vasocomstriction (viscosity effect)
- **Mythology**
  - Rebound effect?
  - Loss of efficacy when osms exceed 320 mOsm/L
Hypertonic Saline: Mechanism of Action

- **Osmotic dehydrating effect**
  - Depends on intact BBB
  - Reflection coefficient of NaCl is 1.0, compared to 0.9 for mannitol
  - HS drives water from interstitial and intracellular spaces of the brain into the intravascular compartment
  - Water removed from cerebral tissues is then redistributed throughout the entire intravascular volume

Intracranial 4 Compartment Model

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>150</td>
</tr>
<tr>
<td>Blood</td>
<td>150</td>
</tr>
<tr>
<td>Brain ICF</td>
<td>900</td>
</tr>
<tr>
<td>Brain ECF</td>
<td>450</td>
</tr>
</tbody>
</table>

Na⁺ = 140 mEq/L

Brain swelling
Evidence: 3% Saline Infusion

  - 3% saline reduces ICP and CT midline shift in patients with TBI or neoplasm
  - Effect not seen with ICH or infarction
  - 3% saline infusion reduces ICP in pediatric TBI patients
  - Effect modest: 4 mm Hg over 2 hours
Bolus Hyper-Osmolar Therapy

**Goal:**
- Acutely reduce ICP
- Acutely reduce symptomatic brain tissue shifts

**Two options**
- **20% Mannitol**
  - 0.5-1.5 g/kg IV as needed
- **23.4% Hypertonic Saline**
  - 0.5-2.0 mL/kg

Evidence: 10% Saline Infusion

  - 8 MCA stroke patients
  - 22 episodes of ICP crisis (>20 mm Hg)
    after mannitol
  - 75 mL of 10% HS
  - Effective in all cases
    - 10 mm Hg drop in ICP at 30 minutes
    - CPP increased 15 mm Hg
    - Effect lasted up to 4 hours

Effect of Hypertonic Saline in CBF in SAH patients

  - 10 poor grade SAH patients
  - 2 mL/kg of 23.5% saline
  - ICP fell 74%
  - CPP rose 27%
  - CBF rose 23%
  - Peak effect @ 20-60 minutes
Hypertonic Saline: Other Benefits?

- Can improve CBF, CPP, and brain O2 delivery
  - Presumably results from endothelial dehydration
  - Effect is not seen in all experimental models
- Membrane stabilizing effect
  - Stabilizes membrane resting potentials
- Modulation of inflammatory response
  - Reduced PMN inflammatory response

Hypertonic Saline: Complications

- Congestive heart failure
- Hypokalemia
- Hyperchloremic metabolic acidosis
  - Use 50/50 chloride/acetate solution
- Coagulopathy
- Rebound edema with correction of Na+
- Central pontine myelinolysis
Vasopressin Antagonists in the Neuro-ICU

- Causes a pure “aquaresis”
  - Minimal effect on intravascular volume
- Potential indications
  - Correction of hyponatremia
  - “Fine tuning” of sodium level while weaning hypertonic saline
  - Adjuvant to 20% mannitol or 23.4% hypertonic saline for rapid induction of hyperosmolar state to combat ICP or herniation syndromes

Hypothermia

Hypothermia: Rationale

- **Experimental focal ischemia**
  - Hypothermia reduces infarct volume and postischemic edema
    - Reduces cerebral metabolism
    - Decreases ischemic depolarizations and excitatory neurotransmitter release
    - Stabilizes cell membranes & BBB
    - Reduces heat shock protein expression
    - Reduces proteolytic enzyme activity
    - Attenuates reperfusion injury & inflammatory response
Hypothermia: Rationale

- **Clinical**
  - Lower body temperature is associated with improved outcome after stroke
  - Stroke patients with reduced body temperature (<36.5°C) on admission have reduced mortality & better outcomes (Reith et al)
  - Fever in the first 24 hours is associated with worse outcome (Castillo et al)

Hypothermia Methods: How to Cool the Brain?

- **Systemic cooling**
  - SURFACE BLANKET COOLING
    - SubZero, Aquamatic (conventional water-circulating)
    - Polar Air (forced air convection cooling)
    - Artic Sun (“adhesive” water circulating)
  - ENDOVASCULAR CATHETER COOLING
    - Radiant
    - Alsius
    - Innercool (metallic)
Timing of hypothermia?

- **Hyperacute (begin <6 hours)**
  - GOAL is to reduce infarct volume with a brief, early blast of moderate hypothermia (12-24 hours)
  - Seems feasible only with endovascular catheters
- **Subacute (begin 6-24 hours)**
  - GOAL is to prevent critical swelling and secondary injury with sustained mild hypothermia
  - Feasible with catheter or blankets
- **Late “rescue” hypothermia (>24 hours)**
  - GOAL is to prevent herniation from cytotoxic edema with moderate hypothermia
  - Essentially an alternative to hemicraniectomy

**Moderate Hypothermia Experience**

<table>
<thead>
<tr>
<th>Schwab et al</th>
<th>Krieger et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Patients</td>
<td>50</td>
</tr>
<tr>
<td>Rx Interval</td>
<td>57 yrs; NIHSS 25</td>
</tr>
<tr>
<td>Time to cool</td>
<td>22 hrs (range 4-75)</td>
</tr>
<tr>
<td>Duration</td>
<td>6.5 hrs (range 3.5-11)</td>
</tr>
<tr>
<td>Survival</td>
<td>55 hrs (range 24-72)</td>
</tr>
<tr>
<td>3 mo Rankin</td>
<td>56%</td>
</tr>
<tr>
<td>Complics</td>
<td>2.6 (range 2-4)</td>
</tr>
<tr>
<td>Hypotension (84%)</td>
<td>Hypertension (70%)</td>
</tr>
<tr>
<td>Pneumonia (70%)</td>
<td>Arrhythmia/brady (70%)</td>
</tr>
<tr>
<td>Arterial/brady (62%)</td>
<td>Infection (40%)</td>
</tr>
<tr>
<td>Hypertension (30%)</td>
<td>Hypoproteinemia</td>
</tr>
</tbody>
</table>
ICU Temperature Management Protocol for MCA Infarction?

0-6 HOURS
Begin moderate hypothermia for 12-24 hours followed by controlled rewarming

6 HOURS to 3-7 DAYS
Maintain mild hypothermia until patient is no longer at risk for infarct swelling

THEREAFTER
Maintain normothermia until ICU discharge

THEREAFTER
Maintain normothermia until ICU discharge

Figure 2: Time course of daily maximum ICP values in those patients treated with hypothermia who survived and those who subsequently died. *P<0.05.
Hemicraniectomy

DAY 0

DAY 2
Surgical Decompression

**Rationale**
- Reverse tissue shifts by allowing expansion of edematous brain tissue away from the diencephalon and mesencephalon
- Reduce ICP and increase CPP
- Preserve CBF and minimize secondary ischemic injury
- Similar concept as decompression of large cerebellar hemorrhage or infarction
- Technique used in head trauma

Animal Model

50 Wistar rats - Permanent MCA Occlusion
- Group A: No Hemicraniectomy
- Group B: Hemicraniectomy 1 hour after occlusion
- Group C: Hemicraniectomy 24 hours after occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Mortality</th>
<th>Mean Infarct Size</th>
<th>Neuro Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20</td>
<td>35%</td>
<td>160 mm³</td>
<td>3.1 +/- 0.2</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>0%</td>
<td>26 mm³</td>
<td>1.3 +/- 0.2</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>0%</td>
<td>59 mm³</td>
<td>1.8 +/- 0.2</td>
</tr>
</tbody>
</table>

Forsling M, Stroke 1995 Feb, 26(2): 255-64

Hemicraniectomy Procedure

Clinical Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># of Pts</th>
<th>Dead</th>
<th>Severely Disabled</th>
<th>Not Severely Disabled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reine</td>
<td>1995</td>
<td>32</td>
<td>11</td>
<td>(34%)</td>
<td>10</td>
</tr>
<tr>
<td>Carter</td>
<td>1997</td>
<td>14</td>
<td>5</td>
<td>(21%)</td>
<td>9</td>
</tr>
<tr>
<td>Schwab</td>
<td>1998</td>
<td>31</td>
<td>5</td>
<td>(16%)</td>
<td>9</td>
</tr>
<tr>
<td>Hollkamp</td>
<td>2001</td>
<td>12</td>
<td>4</td>
<td>(33%)</td>
<td>0</td>
</tr>
<tr>
<td>Mori</td>
<td>2001</td>
<td>19</td>
<td>3</td>
<td>(16%)</td>
<td>13</td>
</tr>
<tr>
<td>Georgiad</td>
<td>2002</td>
<td>17</td>
<td>2</td>
<td>(12%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Wiltz</td>
<td>2002</td>
<td>18</td>
<td>6</td>
<td>(33%)</td>
<td>6</td>
</tr>
</tbody>
</table>

Heidelberg Experience

3 month Outcome

- **Overall Mortality 27%**
  - 34% for “late HC”
  - 16% for “early HC”
- All survivors could ambulate (with assistance)
- Of 11 dominant hemisphere
  - No global aphasias
  - 3 returned to work

More Long-term Outcomes

- 18 patients examined 7-26 months after hemispherectomy
- **Mortality 13%**
  - Mean age survivors 40.7 vs non-survivors 54.5 (p<0.006)
  - Mean Barthel Index of Survivors: 61
- Better functional outcomes in younger patients

Hemicraniectomy for MCA Infarction: the HeADDFIRST Trial

Frank J. L. et al

- NIH-funded pilot clinical trial
- 4908 screened
- 66 patients with complete MCA infarction were eligible (1.3%)
- 40 patients enrolled
- 26 patients met the randomization criteria
  - Randomized to surgery or standardized medical therapy for >7.5 septal or >4 mm pineal midline shift

**HEADFIRST: Main Results**

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Hemicraniectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Hemisphere (L/R)</td>
<td>6/5</td>
<td>6/9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.5</td>
<td>52.3</td>
</tr>
<tr>
<td>Dead at 21 days*</td>
<td>5/11 (45.5%)</td>
<td>4/26 (23.1%)</td>
</tr>
</tbody>
</table>

**Hemicraniectomy Metaanalysis**

- 138 patients with MCA infarction
- Minimum F/U of 4 months
- Age was only significant predictor of survival with good recovery
- Side, extra territories, timing, herniation signs did not matter!
Hemicranieotomy

- Likely reduces mortality from malignant MCA infarction
- Appears superior to hypothermia for treatment of space-occupying cerebral infarction
- Early hemicranieotomy (before signs of herniation) more effective than late hemicranieotomy
- Survival with good functional outcome most likely in younger patients