

Lecture Objectives

- Objectives: After the lecture the listener will be able to:
- List the major causes of raised intracranial pressure (ICP) [Head trauma as a model]
 - Describe the physiological and neurological consequences of raised ICP
 - Describe the strategies for managing raised ICP
 - ICP directed therapy
 - CPP directed therapy
 - CBF directed therapy
 - Volume directed therapy (Lund)
 - Brain Trauma Foundation Recommendations

Box 1. Causes of intracranial hypertension

Intracranial (primary)

- Brain tumor
- Trauma (epidural and subdural hematoma, cerebral contusions)
- Nontraumatic intracerebral hemorrhage
- Ischemic stroke
- Hydrocephalus
- Idiopathic or benign intracranial hypertension
- Other (eg, pseudotumor cerebri, pneumoencephalus, abscesses, cysts)

Extracranial (secondary)

- Airway obstruction
- Hypoxia or hypercarbia (hypoventilation)
- Hypertension (pain/cough) or hypotension (hypovolemia/sedation)
- Posture (head rotation)
- Hyperpyrexia
- Seizures
- Drug and metabolic (eg, tetracycline, rofecoxib, divalproex sodium, lead intoxication)
- Others (eg, high-altitude cerebral edema, hepatic failure)

Postoperative

- Mass lesion (hematoma)
- Edema
- Increased cerebral blood volume (vasodilation)
- Disturbances of CSF

Rangel-Castillo Crit Care Clin 22:713, 2007

Head Injury

- Most common cause of death and disability in young people and children
- 1.6 million head injuries per year (US) [150,000 pediatric HI]
- 250,000 admitted to hospital
- 70,000-90,000 left with permanent neurologic disabilities [29,000 children]
- 52,000-80,000 deaths per year [7,000 children]
- Approximate mortality 25%

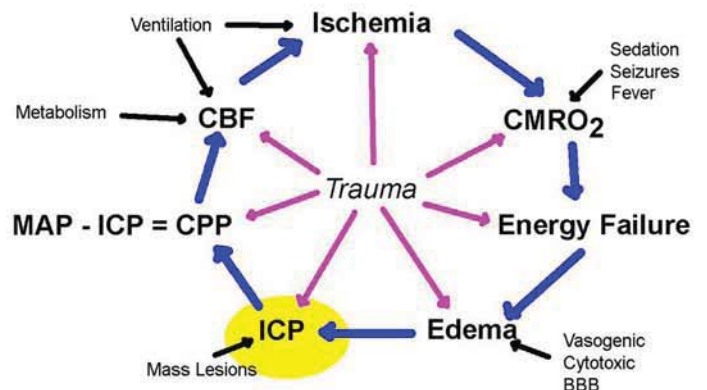
Marik Chest 122:699, 2002

Traffic accidents, assaults (firearms), falls, (esp. ETOH, drugs)

Head Trauma – ICP

- 54% had raised ICP
- 42% pneumonia
- 36% hypoxia and vent dysfunction
- 30% with critically low CBF w/in 12 hours
- 15-20% Seizures (50% subclinical)
- 3.5% Papilledema
- ? Pupil dilation, decerebrate posturing occurs without elevated ICP

Pathophysiology of Edema-ICP



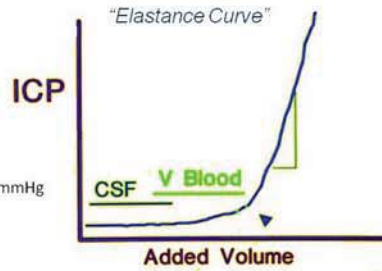
Management of the Swollen Brain

- **Reduce the volume of the compartments**

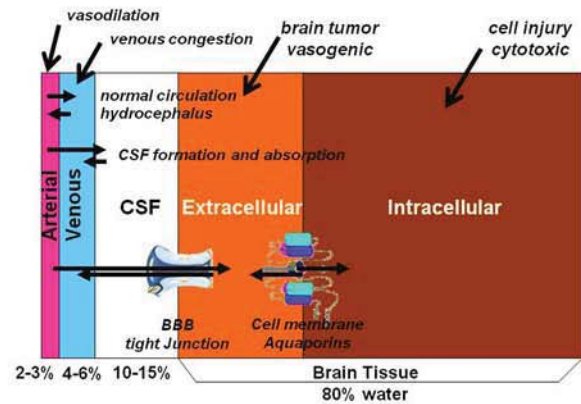
- Extra volumes (e.g. hematoma, tumor)
- Brain water
- CSF
- Venous Blood
- Arterial Blood

- **Normal**

- Adult, Older children: 10 – 15 mmHg
- Young Children: 3 - 7 mmHg
- Term Infant: 1.5 – 6 mmHg



Intracranial Volumes



Management of the Swollen Brain

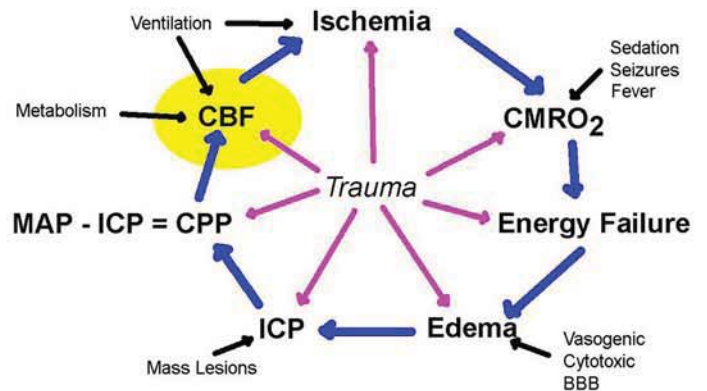
- Reduce the volume of the compartments
 - Remove volumes (e.g. hematoma, tumor)
 - Change the physiology of the volume



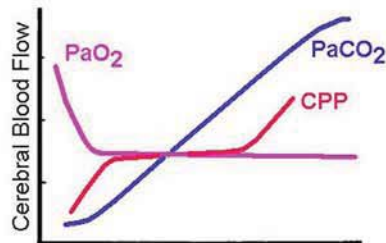
Clearly the most desirable way to reduce intracranial bulk is to remove the pathologic matter that is present.

Pathophysiology of Edema-CBF

Reducing arterial blood volume



Control of CBF



Coupled to:

- Metabolism
- O₂ content
- Vasodilation blunted or abolished with TBI
- pH (ventilation - carbon dioxide)
- Blunted with TBI for a few days
- Blood viscosity
- **Blood pressure (autoregulation)**

Initial Resuscitation – ABC's

	Outcome (%)		
	Favorable	Poor	Dead
Total cases (n=699)	43	20	37
Neither (n=456)	51	22	27
Hypoxia (n=78)	45	22	33
Hypotension (n=114)	26	14	60
Both (n=52)	6	19	75

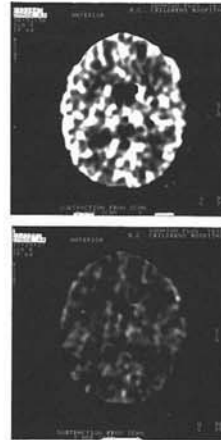
Systolic BP < 90 mmHG
SaO₂ < 90%, PaO₂ < 60 mmHg

How does Hyperventilation Work?

- Basically thought to be a property of endothelial function [chemoregulation]
- Requires nitric oxide for basal vascular tone and for increases and decreases.
- NO donors reduces basal vascular tone and blunts CO₂ related vasoconstriction and augments CO₂ related vasodilation (left shift of curve)
- Postulate altered pH modulates NO synthetase.
- Also pharmacologic manipulation of opioid receptors, prostaglandin production and ATP-dependant K⁺ channel activation modulates CO₂-NO reactivity.
- Perhaps vasodilation to hypoxemia is endothelial cell failure

Lavi Circulation 107:1901, 2003

Hyperventilation: Double Edged Sword



Xenon-enhanced computed tomography perfusion images

Top: - PaCO₂ of 45 mmHg
 - ICP 44 mm Hg
 - CPP 54 mm Hg
 - CBF 59 mL/min/100 g

Bottom: -15 min after hyperventilation
 - PaCO₂ of 30 mmHg
 - ICP 15 mmHg
 - CPP 82 mmHg
 - CBF 14 mL/min/100 g

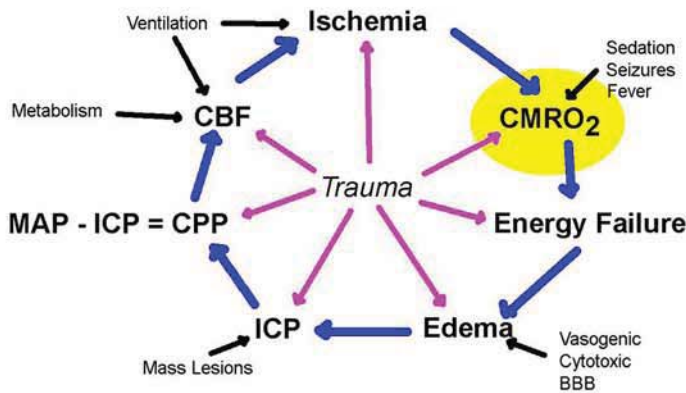
(Several local areas of this scan had regional cerebral blood flow rates lower than 10 mL/min/100 g.)

Is it better to keep the perfusion or the ICP level?

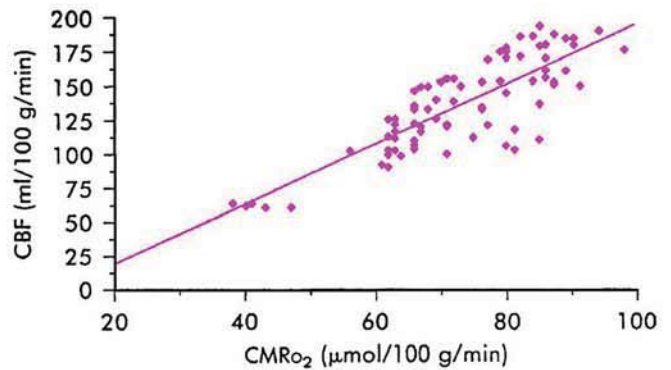
FANZCA, CCM, 1997

Pathophysiology of Edema-CMRO₂

Reducing arterial volume by lowering metabolism

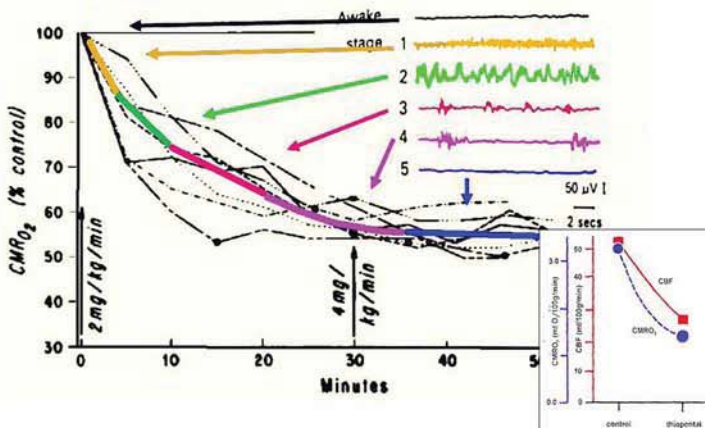


Metabolic Coupling: Matching CBF to Metabolism



Sloan / Anesthesiology Clin N Am 20 (2002) 265

Barbiturate CMRO₂ EEG

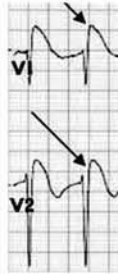


Metabolic Suppression

- Synaptic suppression (max 50%)
 - Barbiturates: prolonged sedation, other benefits
 - Propofol: quicker reversal, hypotension, hypertriglycerides, risk PRIS – refractory metabolic acidosis, with rhabdomyolysis. Hypothermia precipitates hyperlipidemia.
- Global suppression (max > 50%)
 - Hypothermia

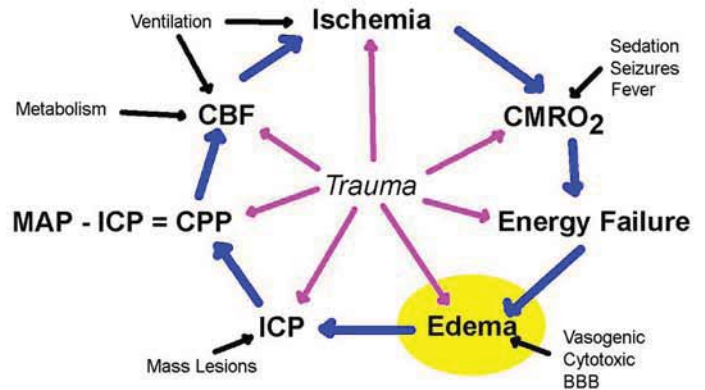
Propofol Infusion Syndrome

- Associated with prolonged infusions in adults and children (≥ 5 mg/kg/Hr, 83 ug/kg/min)
- Early signs: acidosis, lipemic serum, Brugada-like ECG changes
- Late signs: CV collapse, rhabdomyolysis, hyperkalemia, heart block, renal failure
- Pathophysiology: uncoupled oxidative phosphorylation in mitochondria: blocks free fatty acid utilization.
- Treatment: Hemodialysis, hemoperfusion, ECMO
- Avoid in sepsis, inborn errors in carnitine or mitochondrial metabolism



Pathophysiology of Edema

Reducing Tissue Vasogenic Edema



Edema

- Cytotoxic edema – intracellular water from neuronal injury
- **Vasogenic edema** – Extracellular water regulated by balance hydrostatic & oncotic/osmotic forces: Starling equation:

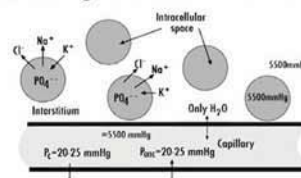
$$- \text{Water movement} = L_p (P_c - P_i) + \sum \sigma (\pi_i - \pi_c)$$

- L_p = capillary wall hydraulic conductivity
- P_c = hydrostatic pressure capillary/interstitium
- σ = solute reflection coefficient
- π = oncotic pressure capillary/interstitium

Tissue edema is promoted by CBF/hydrostatic forces

Water Regulation at BBB

Volume regulation of the normal brain



Normal: BBB impermeable to small and large molecules:

Osmolar [Na] = 5500 mmHg
Osmolar [Protein] = 20-25 mmHg

Conclusion – primary determinant [Na]

Tissue edema is promoted by osmotic forces

Grande Int Care Med 32:1475, 2006

ICP Directed Therapy

- **Focus is lowering ICP:**
- Based on poor prognosis ICP > 20-25 mmHg
- Goal: < 20 mmHg
- Mannitol/hypertonic saline, hyperventilation, barbiturates
- Better outcome when autoregulation is lost (pressure passive)
- Optimal method to lower ICP unclear

Osmotic Dehydration Across the Blood Brain Barrier

- The BBB is formed by the brain endothelial cells with tight junctions (zona occludens) with an effective pore size of 0.7-0.9 nm (periphery 4-5 nm freely permeable to electrolytes)
- Easily permeable to water and small or lipophilic molecules
- Impermeable to electrolytes
- Brain functions as an osmometer
- No lymphatics to remove excess interstitial fluid
- Oncotic changes exert little influence

Serum Osmolarity

- Target 300-320 mOsm (higher associated with hypovolemia, renal failure, hyperosmolarity)
- Mannitol (0.5-1.4 gm/Kg)
 - Onset 1-5 min, peak 20-60 min, lasts 1.5-6 hrs
 - Rheologic benefits
 - Contraindicated in hypovolemia
- Hypertonic saline (3-23.4%)
 - Better in dehydrated patients
- Alcohol!

Reflection Coefficient:

Maximal effect, minimal rebound

Table 1

Substance	Reflection coefficient
Urea	0.44-0.59
Glycerol	0.48
Mannitol	0.90
Sucrose	0.91-1.00
NaCl	1.00
Albumin	1.00

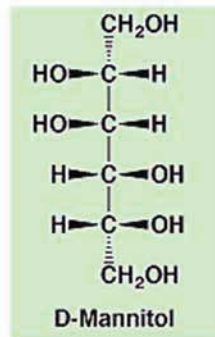
The reflection coefficients of various substances for the blood-brain barrier (BBB).

$$\text{Water movement} = L_p (P_c - P_i) + \sum \sigma (\pi_i - \pi_c)$$

Nordstrom Neurocrit Care 2:83, 2005

Mannitol: the standard

- Non-metabolized sugar
- Creates osmotic gradient across tissues
 - Expands circulating blood volume
 - Vasodilates cerebral vasculature
 - early increase brain edema/ICP
 - Diuresis
 - later decrease edema/ICP
 - only works across normal BBB
- Dose 0.35-1 mg/kg



Mannitol: the down side

- Side effects
 - Hypovolemia
 - Hyperkalemia
 - Hypomagnesemia
 - Hypophosphatemia
 - Renal failure
 - Rebound inc. ICP



Strawberry preserves anyone?

Latorre The Neurologist 15:193, 2009

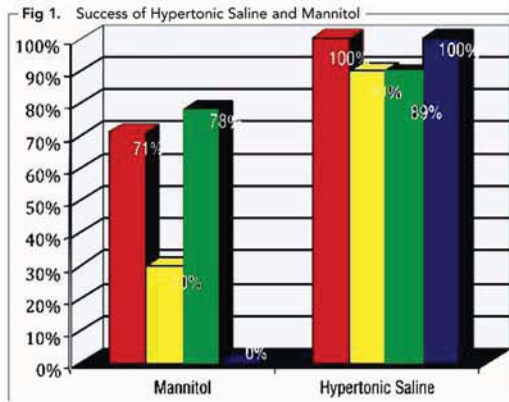
Hypertonic Saline

- First studied in 1919 in cats (Weed & McKibben)
- Used in combination with colloid for resuscitation in Europe
- Blood volume expansion
- Osmotic cerebral dehydration
- Reduce ICP
- Useful when mannitol has failed
- Growing interest with colloid for TBI

Hypertonic Saline

- Available: 2 – 29.2%
- Target [Na] 145-155 mmol/L, 300-320 mOsm/kg
- Side effects:
 - Electrolyte disturbances
 - Volume overload
 - Renal failure
 - Acute pulmonary edema
 - Dilutional coagulopathy
 - Hyperchloremic metabolic acidosis
 - ? Central pontine myelinosis (theoretical), esp. with alcoholism & malnutrition

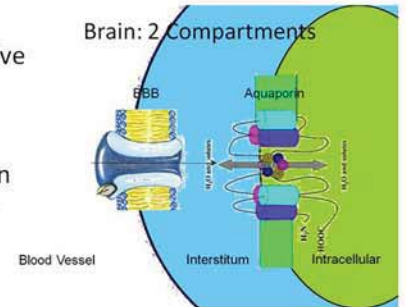
Mannitol vs. Saline



Infanti J Neurosci Nursing 6:362, 2008

Intracellular Dehydration Across the Cell Membrane using Aquaporins

- Furosemide:
 - Likely the site of furosemide on the brain water regulation
 - Particularly effective in Glial cells
- Dexamethasone:
 - Likely site of action of glucocorticoids on brain water regulation

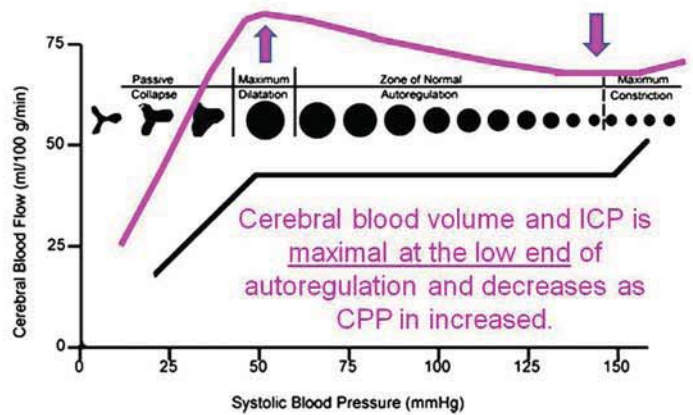


Reducing Hydrostatic Forces of Edema

Vasoconstrictors

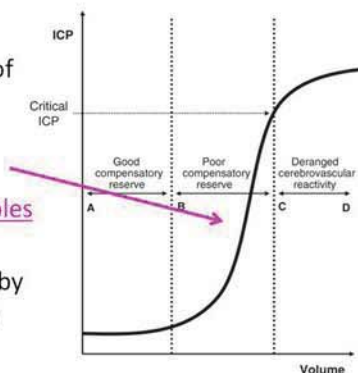
- Alkalosis
 - Hyperventilation
- Vasoconstrictors
 - Indomethacin
 - Dihydroergotamine (venous)
- Metabolic reduction (arterial)
 - Barbiturates, propofol, hypothermia
- Increased MAP (arterial)
 - Intact autoregulation

Autoregulation: paradoxical volume



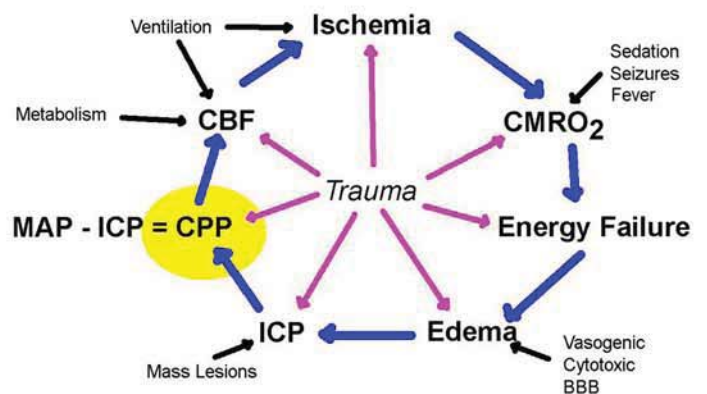
Monroe – Kellie Doctrine

- Volume constant
- Very High ICP – collapse of arterioles
 - Midrange ICP – loss of compensation, pressure rises with volume, arterioles dilate with dec CPP
 - Low ICP – compensation by reducing CSF and venous volume



Smith Anesth Analg 1:240, 2008

Pathophysiology of Edema-CPP



How does Autoregulation Work

- Basically unknown, but **thought to be “myogenic” [mechanoregulation]**
- Minimal effect autonomic effects despite adrenoceptors being present
- Ganglionic blockade with minimal effects
- Sodium nitroprusside lowers resting cerebral vascular resistance but CBF remains unaffected
- Nitric oxide does not appear to be involved
- Postulate altered autoregulation with TBI is alterations in vascular smooth muscle.

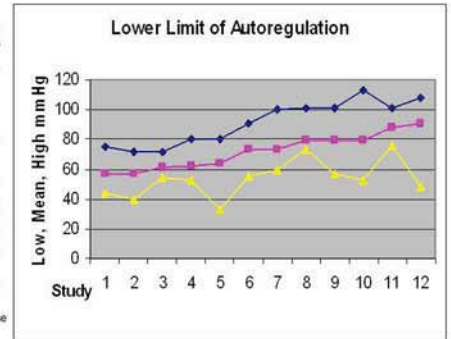
Lavi Circulation 107:1901, 2003

Autoregulation – Human Data

Table 1. Data Regarding the Lower Limit of Autoregulation in Nonanesthetized, Nonconscious Adults

Author	Hypotensive Technique	CBF Method	LLA Mean (Range)
McCull ¹¹	Hydralazine	K-SNDO	<64 (53–80)
	Veratrum viride	K-SNDO	<57 (46–72)
Moyer, et al. ⁴	Hexamethonium	K-SNDO	>62 (53–103)
	Trimethaphan	K-SNDO	>57 (44–73)
	Pyridostigmine	K-SNDO	<61 (54–72)
Strandgaard ⁸	Trimethaphan/VE	1/A-VDO2	72 ± 9
Waldemar, et al. ¹⁶	Trimethaphan/lower body negative pressure ± captopril	1/A-VDO2	79 (57–101)
Larsen, et al. ¹⁷	Lower body negative pressure/abetolol	1/A-VDO2	79 (53–113)
Olsen, et al. ¹²	Labetalol/lower body negative pressure	CBF/mus	81 (61–108)
Olsen, et al. ¹⁸	Lower body negative pressure/abetolol	1/A-VDO2	88 (76–101)
Olsen, et al. ¹⁹	Lower body negative pressure/abetolol	1/A-VDO2	73 (60–102)
	A-NIRS diff		79 (73–101)

Data are presented as mean values with ranges (when available) or standard deviations.
 * The subjects were 42 pregnant women near term, 24 of whom had histories of pregnancy.
 The Lower Limit of Autoregulation: Time to Revise Our Thinking?
 John C. Drummond, M.D., F.A.C.P.C.
 Anesthesiology, Y. 86, No. 5, June 1997



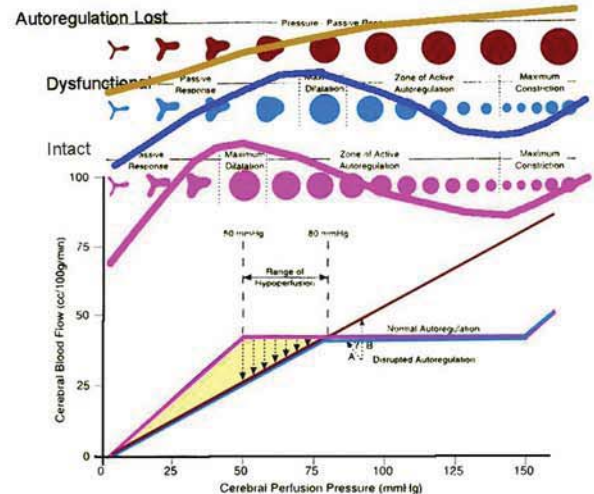
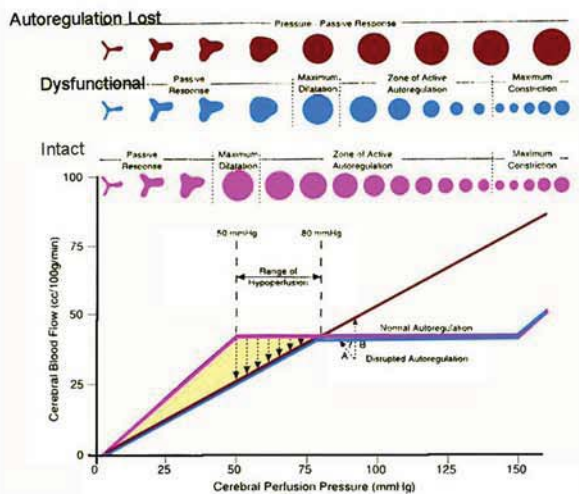
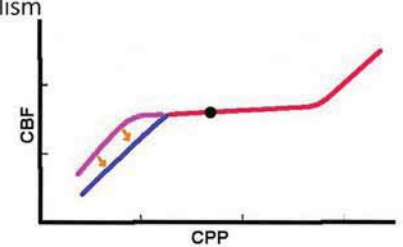
We really don't know the lower limit of autoregulation?

CPP Directed Therapy (Rosner)

- **Assumption: autoregulation is intact but shifted to right** (need higher CPP)
- Increase MAP (diastolic BP < 120 mmHg)
- Inc CPP reduces ICP by vasoconstriction and reduced edema
- Mannitol, vasopressors, CSF drainage
- Goal CPP 60 – 70 mmHg (critical < 60)
- Excessive CPP:
 - ARDS
 - Promote vasogenic edema
- Better outcome when autoregulation is intact

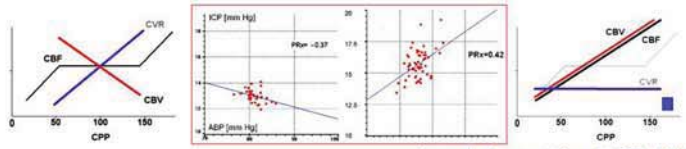
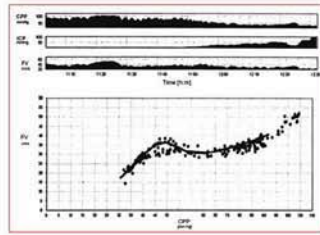
Mild SC Injury Raises the Lower Limit of Autoregulation

- Disrupted autoregulation
 - Loss - Allows pathologic vasodilation
 - Raise lower limit of autoregulation
 - Decreased metabolism
 - Loss of metabolic vascular coupling
- A higher blood pressure may be required



Assessing Autoregulation

- Lassen's Curve: Plot TCD velocity vs. CPP
- Pressure Reactivity Index < 0 normal > 0 non-reactive



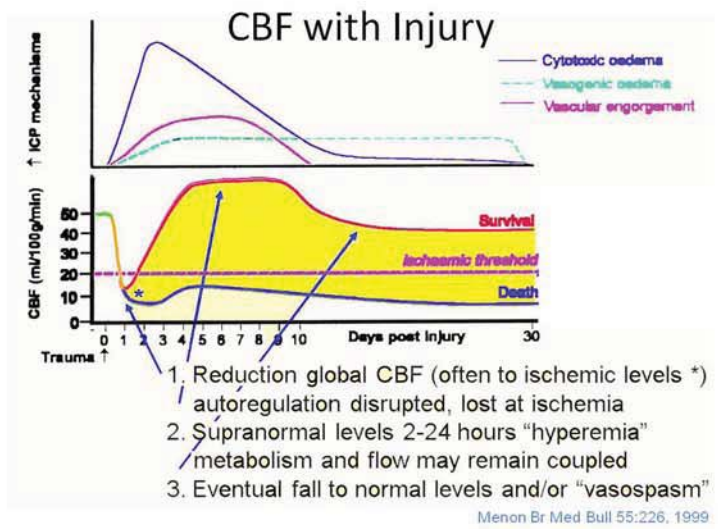
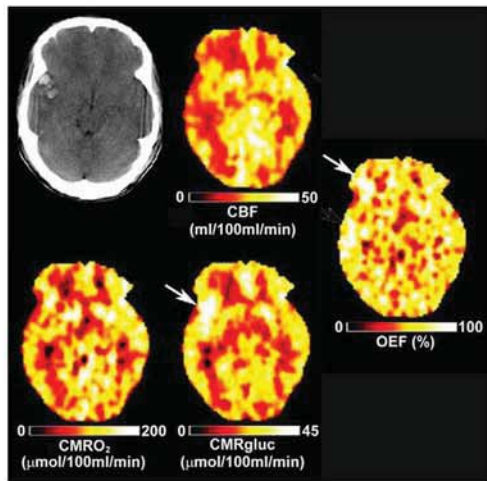
Czosnyka Neurocrit Care 10:373, 2009
Bhatia Int Care Med 33:1263, 2007

CBF Targeted Approach (Cruz)

- Assumption is that CBF is abnormal – low requires inc CPP, or high – use optimized ventilation
- Maintain CBF in normal range (50 cc/min/100 gm) and above critical threshold for injury (15 cc/min/100 gm)
- Balance Flow and oxygen extraction (metabolic coupling) – measure by SjVO₂
- Treatment to maintain CPP in adequate region (60-70 mmHg) by focusing on adequate MAP (mean > 90 mmHg)
- Increase MAP reduces ICP by reducing arterial volume by autoregulation
- Avoid treatments than may lower MAP

Abnormal CBF with TBI

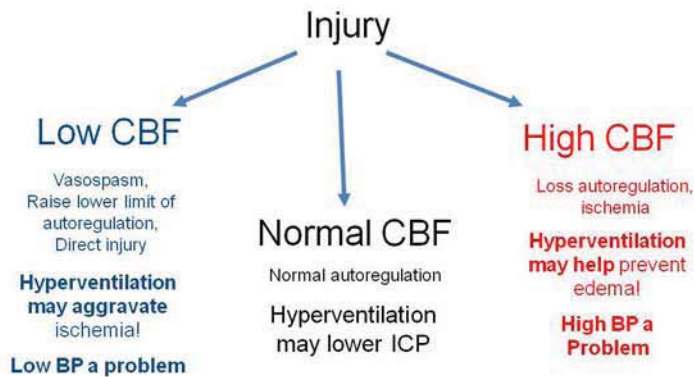
CBF regionally variable and reduced. Metabolism regionally variable. Regional mismatch of oxygen extraction / flow-metabolism coupling



1. Reduction global CBF (often to ischemic levels *) autoregulation disrupted, lost at ischemia
2. Supranormal levels 2-24 hours "hyperemia" metabolism and flow may remain coupled
3. Eventual fall to normal levels and/or "vasospasm"

Menon Br Med Bull 55:226, 1999

Injury and Autoregulation



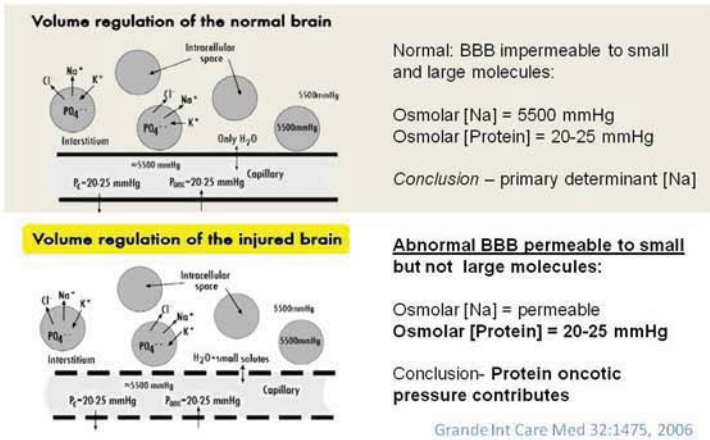
SjVO₂ used to assess relative balance high and low CBF (balance supply demand) to vary use of hyperventilation

Volume Targeted Approach (Lund)

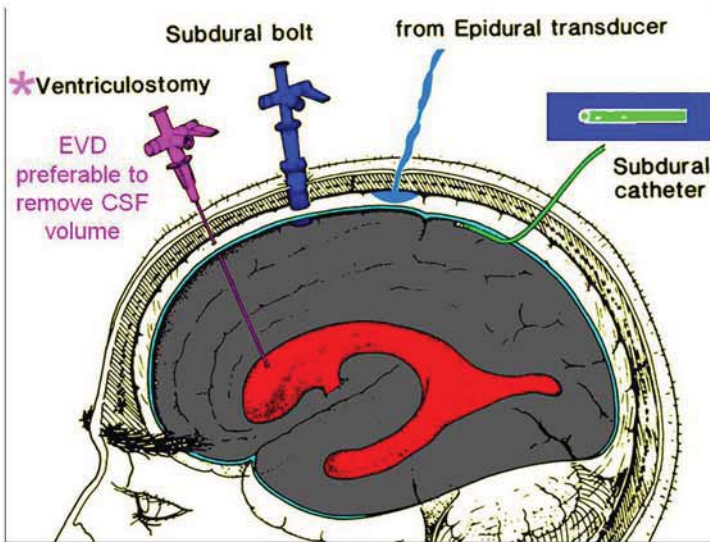
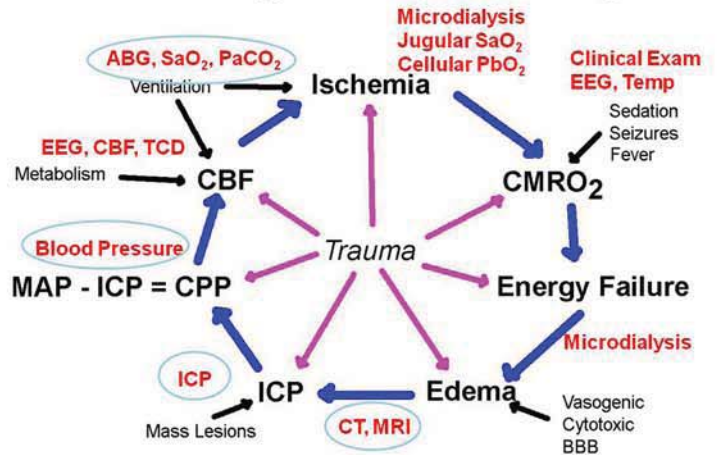
- Assumption BBB leakage small molecules
- Focus is minimizing edema formation by trans-capillary water transfer and improve microcirculatory flow
- Normalize blood volume: CVP 5-12, PCWP 10-15 mmHg (albumin, blood)
- Normal blood pressure (metoprolol, clonidine to treat HTN)
- CPP individualized (50-80 mmHg)
- Protein oncotic pressure (albumin), avoid crystalloids
- One bolus steroids for edema
- Hemoglobin (12.5-14 gm/dL)
- Treat transient ICP increase with dihydroergotamine (venous vasoconstriction)
- Avoid mannitol, CSF drainage, hyperventilation (OK for acute ICP inc.)
- Monitor with microdialysis

Grande Acta Anaesthesiol Scand 46:929, 2002

Water Regulation at BBB

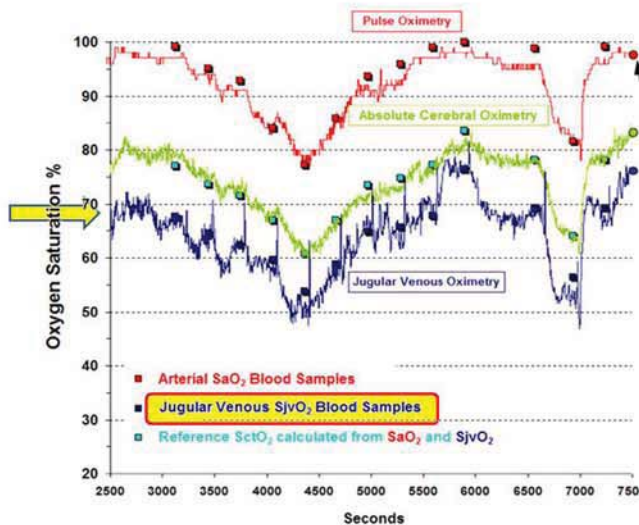


Monitoring: How are we doing?

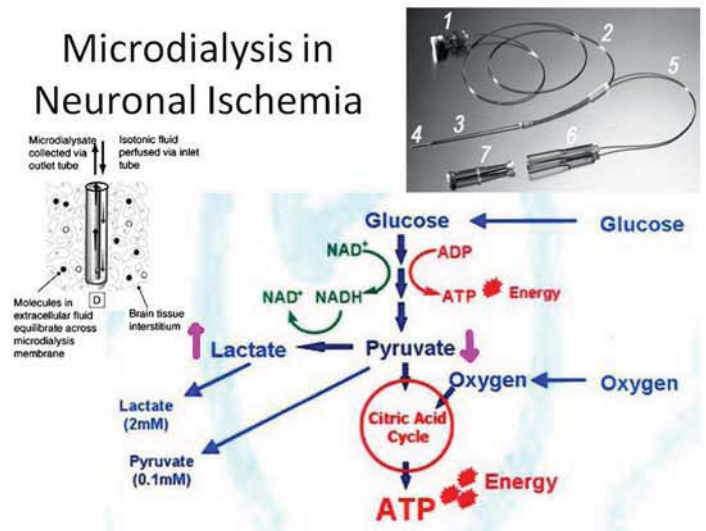


Endpoint Monitoring

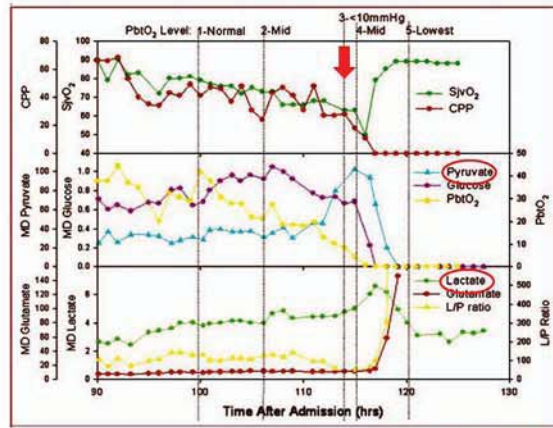
- Cerebral Blood Flow
- Transcranial Doppler
 - Surrogate for CBF
- Jugular venous Oxygenation Saturation (SjvO₂)
- PET scan
 - Estimate CBF, CBV, CMRO₂, O₂ extraction
- Tissue Oxygenation Measurement (PbO₂)
 - Target > 20 mmHg (normal 20-40 mmHg)
- Microdialysis
 - Measure glucose, lactate, pyruvate, glycerol, glutamate



Microdialysis in Neuronal Ischemia



Microdialysis with Ischemia



Valadka Neurosurgery 61:5H:208, 2007

Tissue Oxygen Measurement

- PbO₂ correlates with:
 - FiO₂, PaO₂, Hb
 - MAP, CPP
 - Fever, Hypothermia

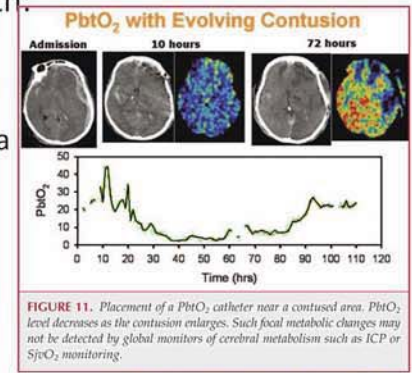


FIGURE 11. Placement of a PbtO₂ catheter near a contused area. PbtO₂ level decreases as the contusion enlarges. Such focal metabolic changes may not be detected by global monitors of cerebral metabolism such as ICP or SjvO₂ monitoring.

Rose. Curr Opin Crit Care 12:97, 2006

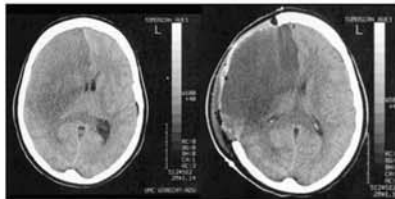
When all else fails!

Decompressive Craniotomy

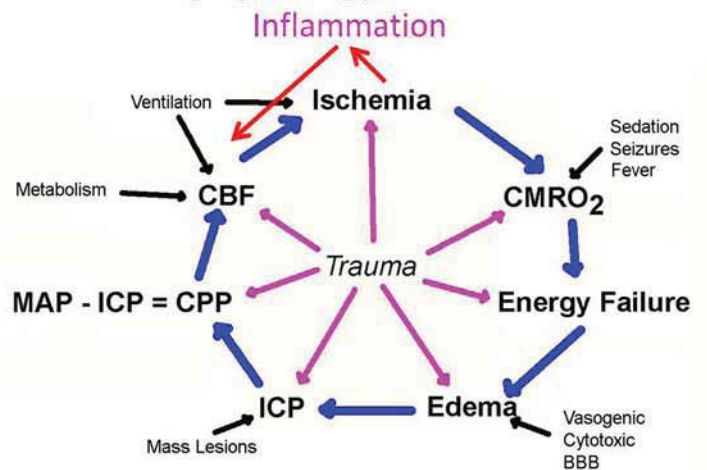
- Known to Hippocrates (460-370 BC)
- Reduces ICP in 85% patients refractory to medical treatment
- Useful with massive hemispheric stroke
- Useful with very focal injury



19th century French trephination.



Pathophysiology of Ischemia -



Inflammation: Pro/Con

- Infiltration of macrophages and granulocytes: Obstruction and reduction of capillary flow (extends infarct into penumbra)
- Tumor Necrosis Factor: released rapidly, blockage improves outcome
- Interleukins: Positive and negative effects
- Cytokines: released in minutes, may contribute to BBB dysfunction
- **Conclusion**: inflammation clearly involved, unclear net role: Hence role of steroids is unclear in this regard

Raised ICP – General Measures

- Avoid hypercarbia, hypoxemia
- Avoid prolonged hypocarbia
- Normoglycemia (?80-140 mg/dL)
- Normothermia (36-37 deg C)
- Avoid hypotension, hypovolemia
- Sedation and analgesia
- Head elevated 30 deg. Neutral position if BP OK
- Seizure prophylaxis (first 7 days)
- Low PEEP and low tidal volume ventilation
- Nutrition

Brain Trauma Foundation Recommendations

Initial Management

- **O:** ABC's Physiologic Resuscitation
- **O:** Sedation and neuromuscular blockade
- **G:** Avoid BP <90 mmHg
- **G:** Avoid O₂ saturation <90%

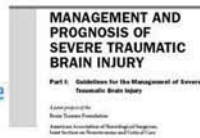
ICP Monitoring

- **G:** appropriate with severe HI and CT abnormalities
- **G:** Treat ICP >20-25 mmHg
- **O:** CPP maintained >70 mmHg

Hyperventilation

- **S:** Avoid prolonged PaCO₂ <25 mmHg
- **R:** Avoid prophylactic PaCO₂ <25 mmHg
- **O:** Brief PaCO₂ <25 mmHg to control ICP

Standards, Guidelines, Options



Brain Trauma Foundation Recommendations

Mannitol

- **G:** Effective for control ICP 0.25-1 gm/Kg if volume resuscitated
- **O:** Boluses better than infusion, Keep serum Osm <320 mosm

Barbiturates

- **G:** High dose may be considered in salvageable severe HI with refractory inc ICP

Steroids

- **S:** Not Recommended

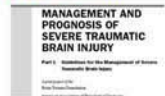
Nutrition

- **G:** replace metabolism with enteral or parenteral feedings with 15% protein.

Antiseizure Prophylaxis

- **S:** Prophylaxis of late seizures not recommended
- **O:** Recommended prevention early seizures with phenytoin and carbamazepine

Standards, Guidelines, Options



Conclusion

- Raised Intracranial Pressure represents a mix of pathology (regional and global edema) with varying disturbances in CBF, autoregulation.
- Various approaches have been used (goal directed therapy for ICP, CPP, CBF, trans capillary water transfer (Lund) all with success and failure.
- As such many management recommendations do not have good medical evidence.
- Advances in care will likely require individualized care based on better cellular monitoring.

