CV/Neuro PY1
The Brain in Cardiac Surgery

# Peri-Operative Brain Monitoring


George M Hoffman MD
Professor, Anesthesiology and Critical Care Medicine
Medical College of Wisconsin
Medical Director, Anesthesiology
Children's Hospital of Wisconsin
Milwaukee, WI

# purpose

- Learning objectives:
  - Brief overview of perioperative brain injury mechanisms
  - Review modalities of brain monitoring
  - Understand targets for intervention

# disclosures

- Funding sources / conflict of interest
  - Medical College of Wisconsin
  - Children's Hospital of Wisconsin
  - George Hoffman
  - Somanetics, Inc
- Off-label use: some data has been derived from patients who have received phenoxybenzamine in an investigational formulation with FDA IND exemption and IRB approval
- Intellectual honesty:
  - all data sources will be identified
  - logic and conclusions will adhere to evidence-based guidelines

# acknowledgements

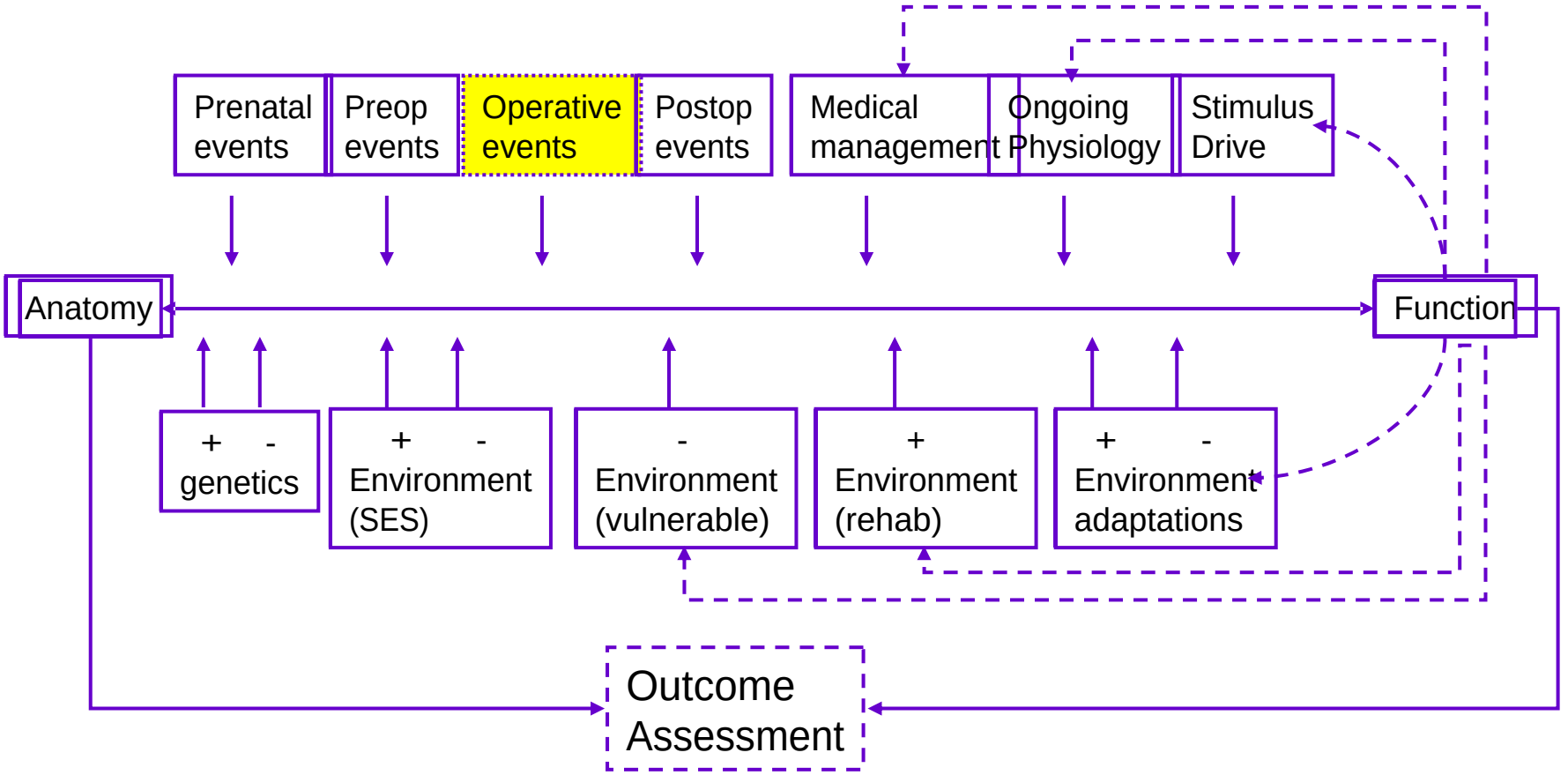

- Kathy Mussatto, Nancy Ghanayem, Jim Tweddell, Ndidi Musa, Eckehard Stuth, Dick Berens, Todd Troshynski, Patrick Vanderwal
- PICU, anesthesia, OR, NICU, cardiology staff, nurses and techs
- MCW anesthesiology and pediatrics
- CHW
- All coworkers
- My family
- Conference organizers and Somanetics, Inc

# What are we trying to accomplish?

- Reduce neurologic disability
  - Maximize functional recovery for patient
  - Minimize complications
- How big is the problem?
  - Overt neurologic signs: 8% (CI 2-25%), with double risk in arch abnormalities
  - decreased developmental potential (based upon parental / sibling models): 33%
  - MRI abnormalities: 33% preop-> 93% postop -? significance of early changes
  - variations in intraoperative management may already be affecting incidence of overt neurologic injury
  - center-specific variation likely
  - Huge economic, social, familial and personal burden

# Complexity of plasticity

- It's a long way from the operating room




- to the developmental psychologist's office

# Postoperative neurologic dysfunction

- prior (intraoperative) injury now manifesting as organ dysfunction

or

- potentially reversible organ dysfunction resulting from ongoing pathophysiology

or

- spectrum of irreversible, reversible, and potential injuries related to modifiable and unmodifiable risk factors

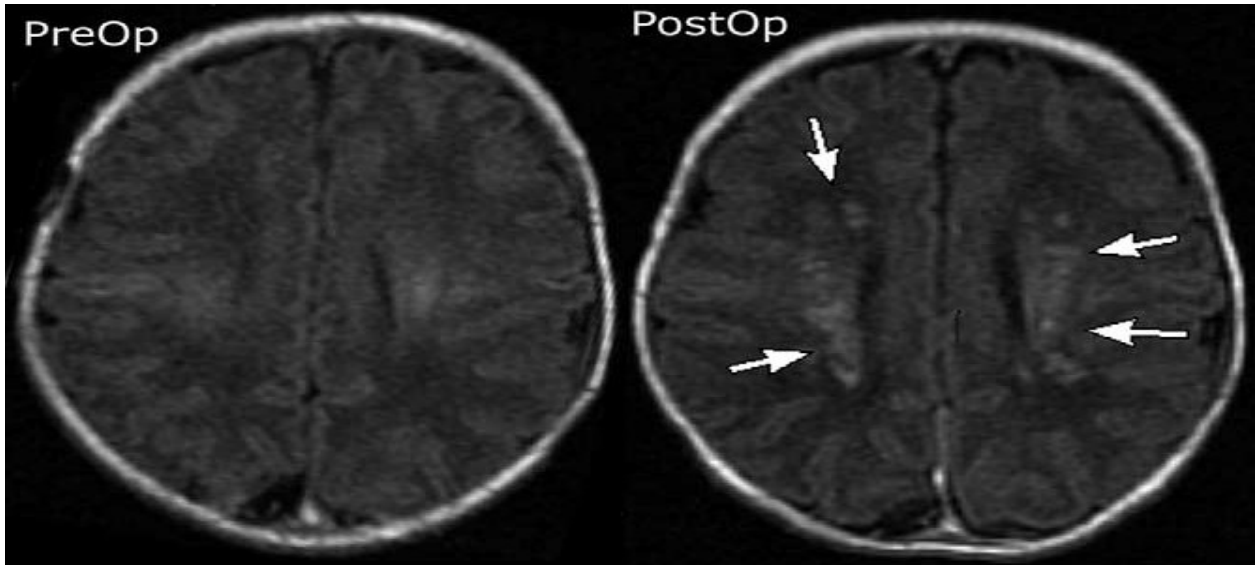
# Causes of brain injury in CHD

- Preoperative/prenatal injury (30-50%)
- global injury
  - DHCA
  - low-flow CPB
  - inadequate perfusion on CPB (collaterals)
  - CPB management issues
    - temperature, pH, glucose, HCT
- emboli
- inflammatory vasculopathy

# Modifiable vs. Unmodifiable Injury

- If you eliminate modifiable injury, then what is left can be attributed to the patient
- Patient-specific risk factors may modify decisionmaking
  - Should a patient with a given apo-E phenotype have a different perioperative strategy?
- what is not modifiable today, may be tomorrow
- What 20% of your brain power will you part with?

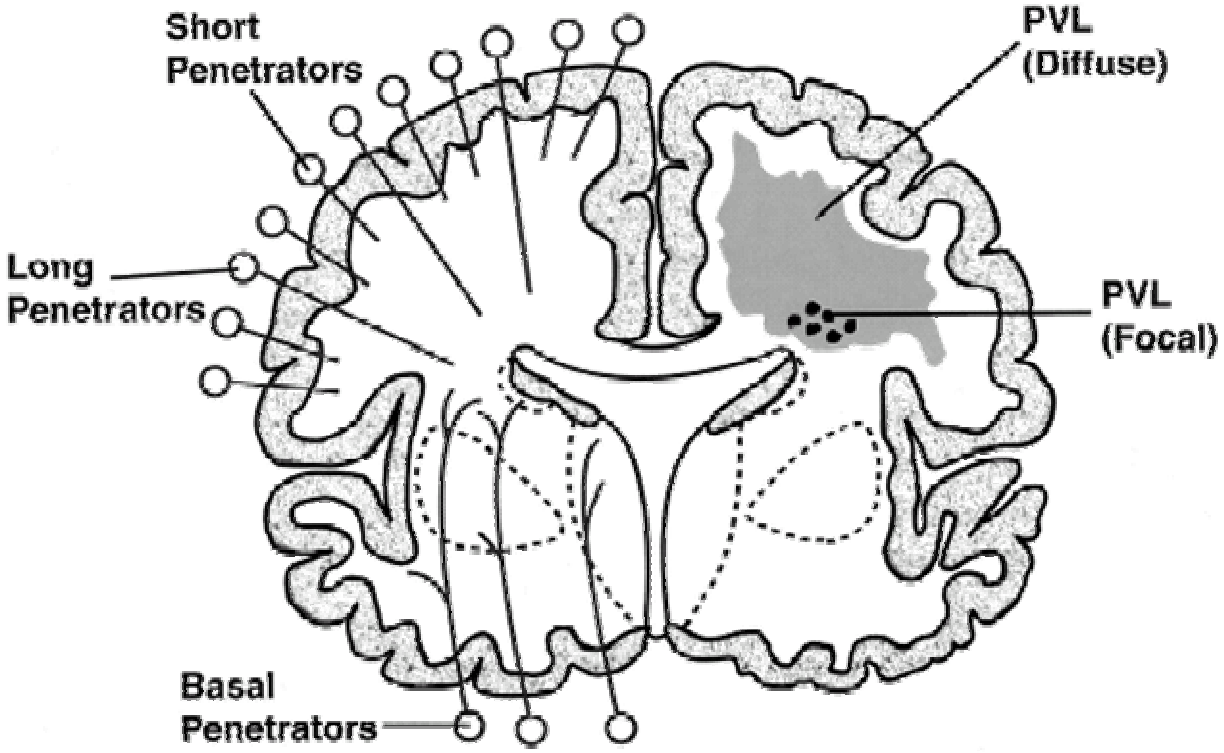
# PVL in medical and cardiac neonates




- Medical neonates (Volpe)
  - immature oliodendrocytes at risk
  - Ischemic cell death (PVL)
  - Embolism (local infarction)
  - free radical injury  (hypoperfusion/reperfusion)
- post-cardiac surgery (Gaynor)
  - PVL in 50% of neonates
  - early postop hypoxemia and hypotension = risk factors

# Hypoxic-ischemic injury

- Localization of injury strengthens pathophysiologic case for hypoxic injury:
  - deep structures more vulnerable
  - perioperative injury may be like premature PVL



# Intraoperative injury

- Period of intense pathophysiologic stress, and intense monitoring
- increasing knowledge about risk factors
- but: inadequate explanation for eventual outcome based on intraoperative events

- provides a model for exploration of opportunities to improve peri-operative care

# intraoperative ischemic injury

- The problem: interruption of adequate brain substrate supply-demand relationship
- Inconsistent blood flow
  - technical limitations
  - technical difficulties
  - deliberate: arch and complex repairs
- inadequate knowledge of brain metabolism
  - technical limitations
  - cost, durability
  - lack of standard

# Historical intraoperative approaches

Strategies to reduce the likelihood of injury in the event of unreliable organ perfusion

- surface cooling (slow)
- hypothermic inflow occlusion
- hypothermic cardiopulmonary bypass
- deliberate deep hypothermic circulatory arrest for arch reconstruction
- DHCA vs. low-flow CPB for complex repairs
- regional perfusion for complex repairs

# Historical intraoperative monitoring

- Arterial blood pressure
- pH, pCO2, pO2
- SpO2
- Temperature
  - Body
  - Brain (tympanic, nasopharyngeal ,esophageal)
- CVP
- SvO2
- CPB flow, perfusate temp

# History: missteps

- rheologic concerns -> low hematocrit strategy
- Low flow CPB
- Prolonged DHCA
- inadequate suppression of brain metabolism
  - rapid cooling
  - alpha-stat pH strategy
  - ? 'pure' narcotic anesthesia
  - limitation of hypothermia

- All these strategies have been associated with later postoperative neurocognitive/neuromotor impairment
- The problem with all these strategies could be detected by brain oxygen monitoring

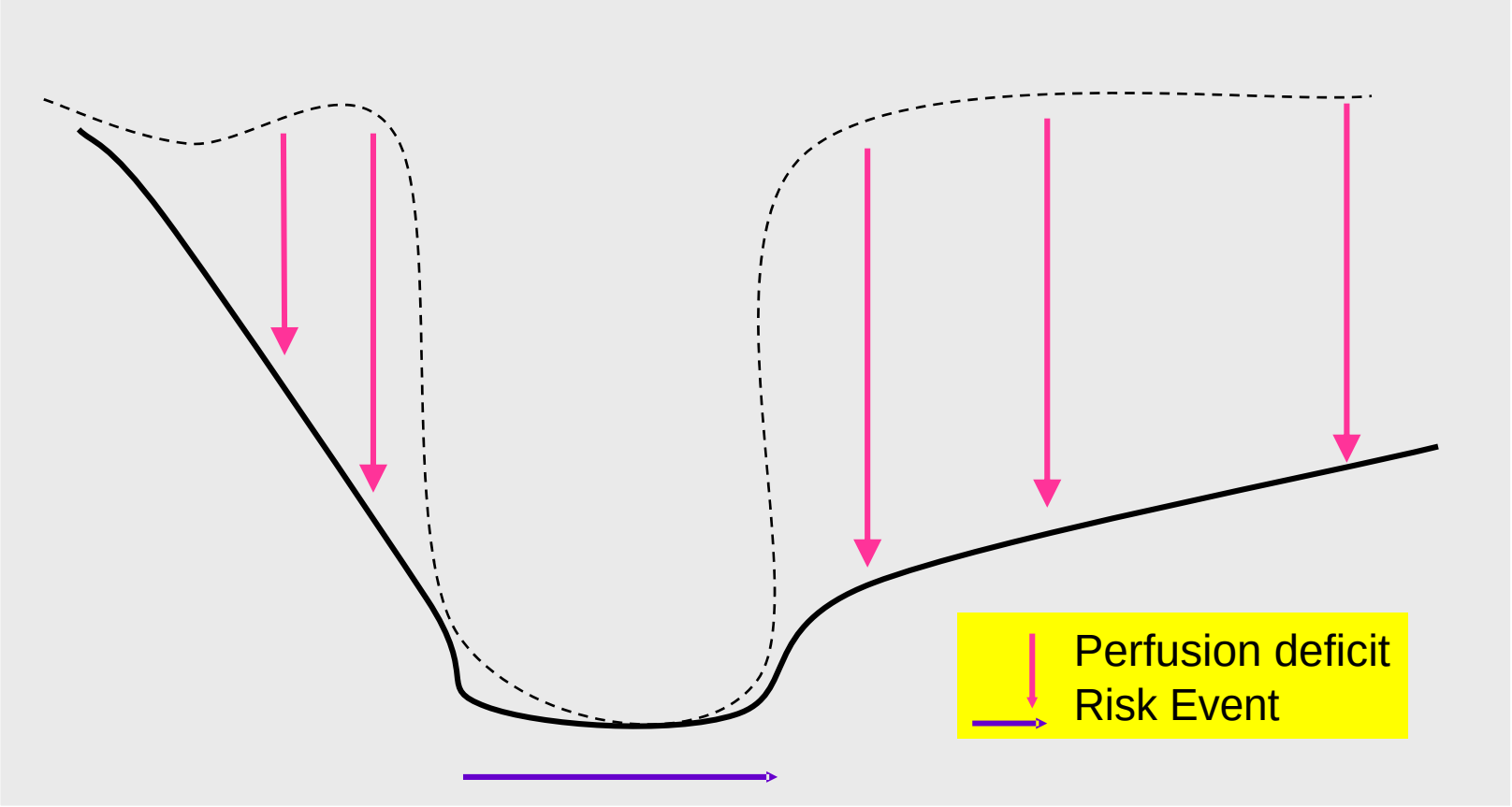
# Why early diagnosis?

- Improve outcome
  - Interrupt risk pathway

  risk ---> reversible dysfunction ---> permanent injury
  - identify patients in need of intensified treatment
  - assess response to interventions
- but: potential for too much intervention for unmodifiable risk
- long-term costs of neurologic impairment impels aggressive strategies to reduce risk
- Holy grail: online monitor of risk conditions to guide intervention before injury occurs

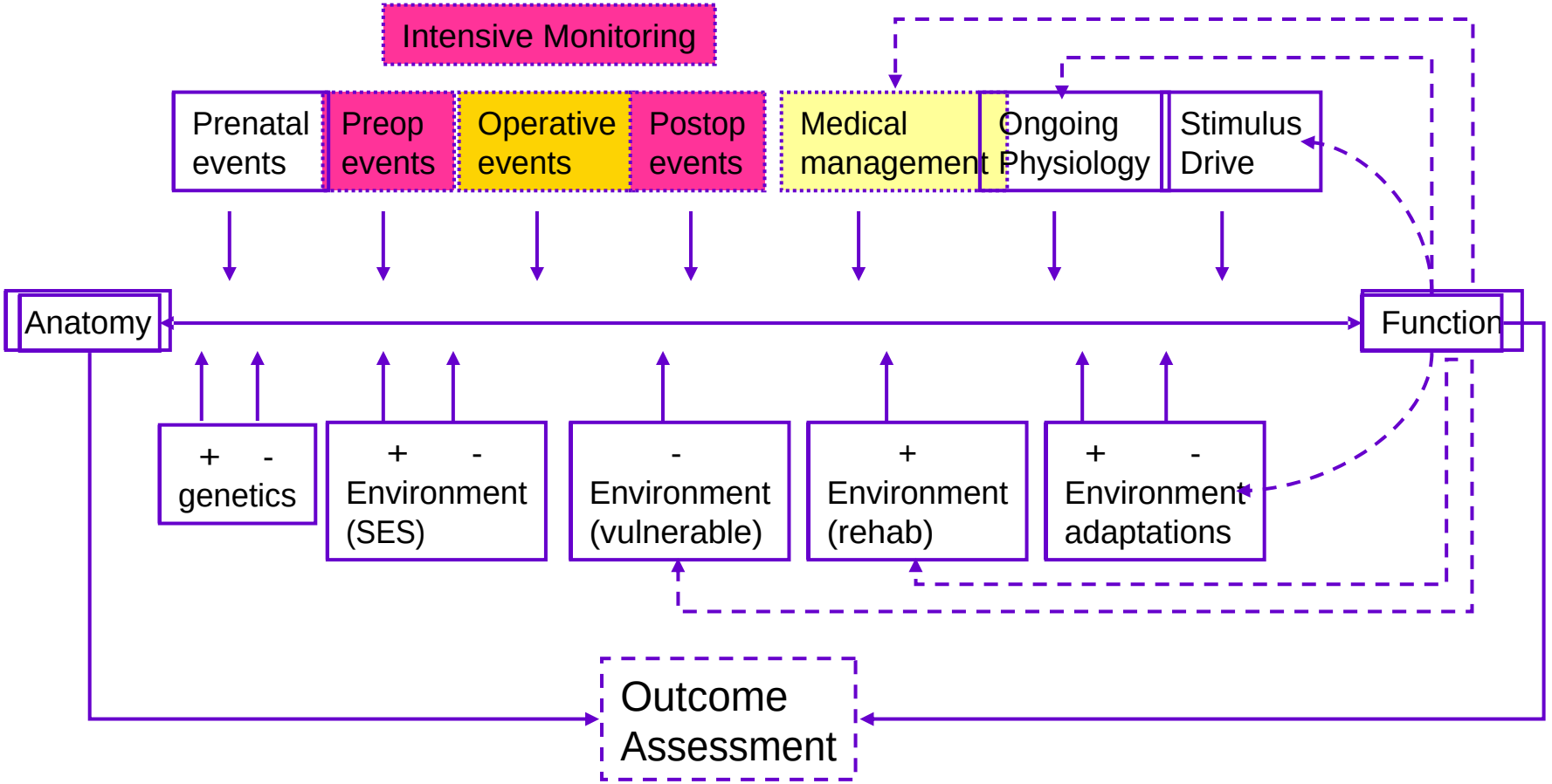
# Is perioperative risk an event or process?

- Inadequate circulation is a continuous function leading to organ injury



# Generalizing intraoperative principles

- Expanded scope of intensive management

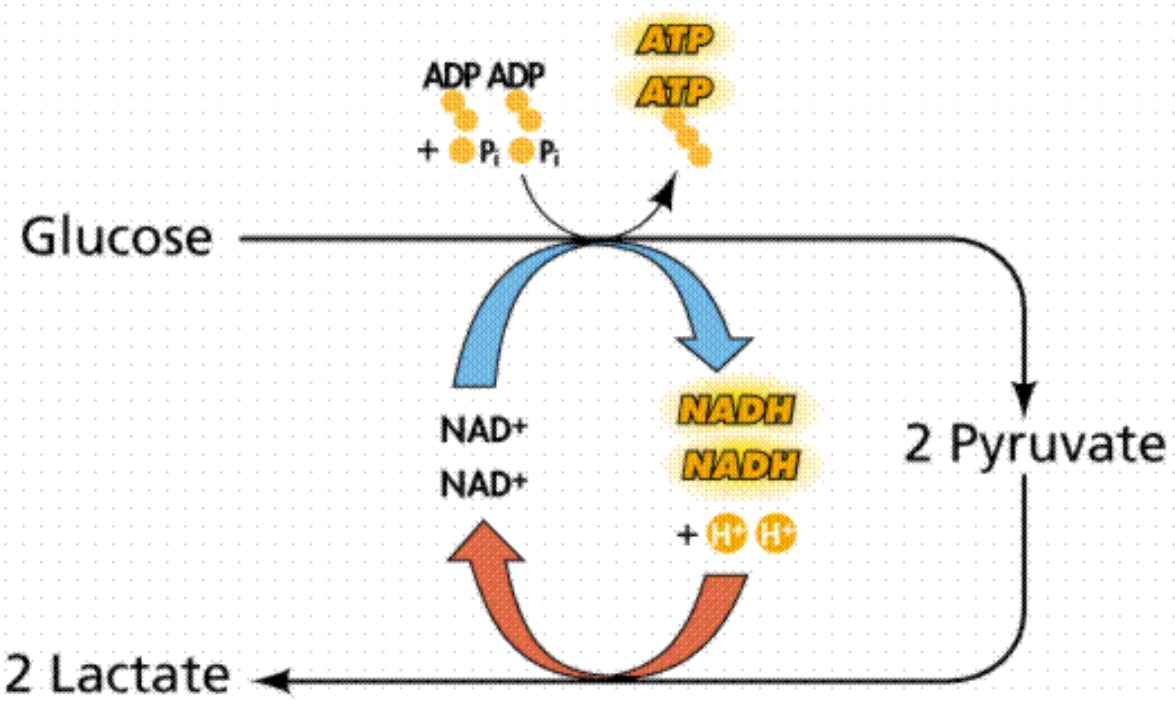


# mechanisms of ischemia-reperfusion injury

- necrotic
  - early cell swelling
  - lysis
  - neutrophil activation
- apoptotic
  - late cell contraction
  - induced by mitochondrial permeability
  - cell death in absence of ongoing metabolic failure
  - important in organ development
  - modifiable
- no ischemia – no reperfusion injury

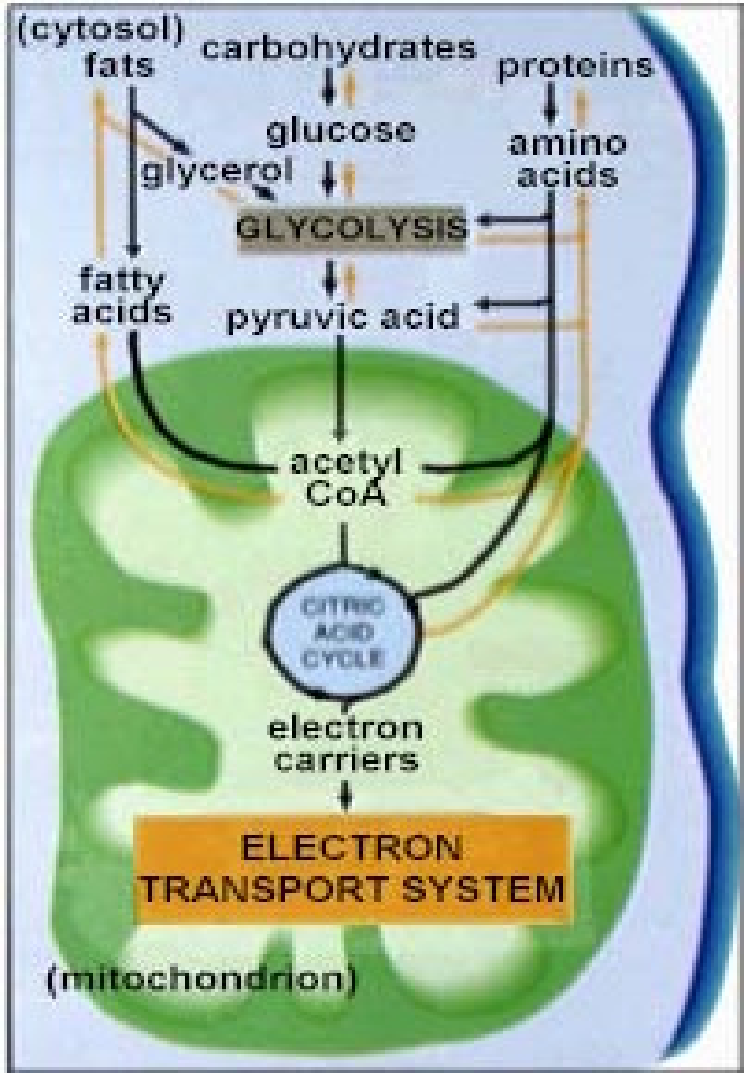
# energy production: glycolysis

- glucose -> pyruvate -> 2 ATP
- pyruvate -> lactate -> NAD+



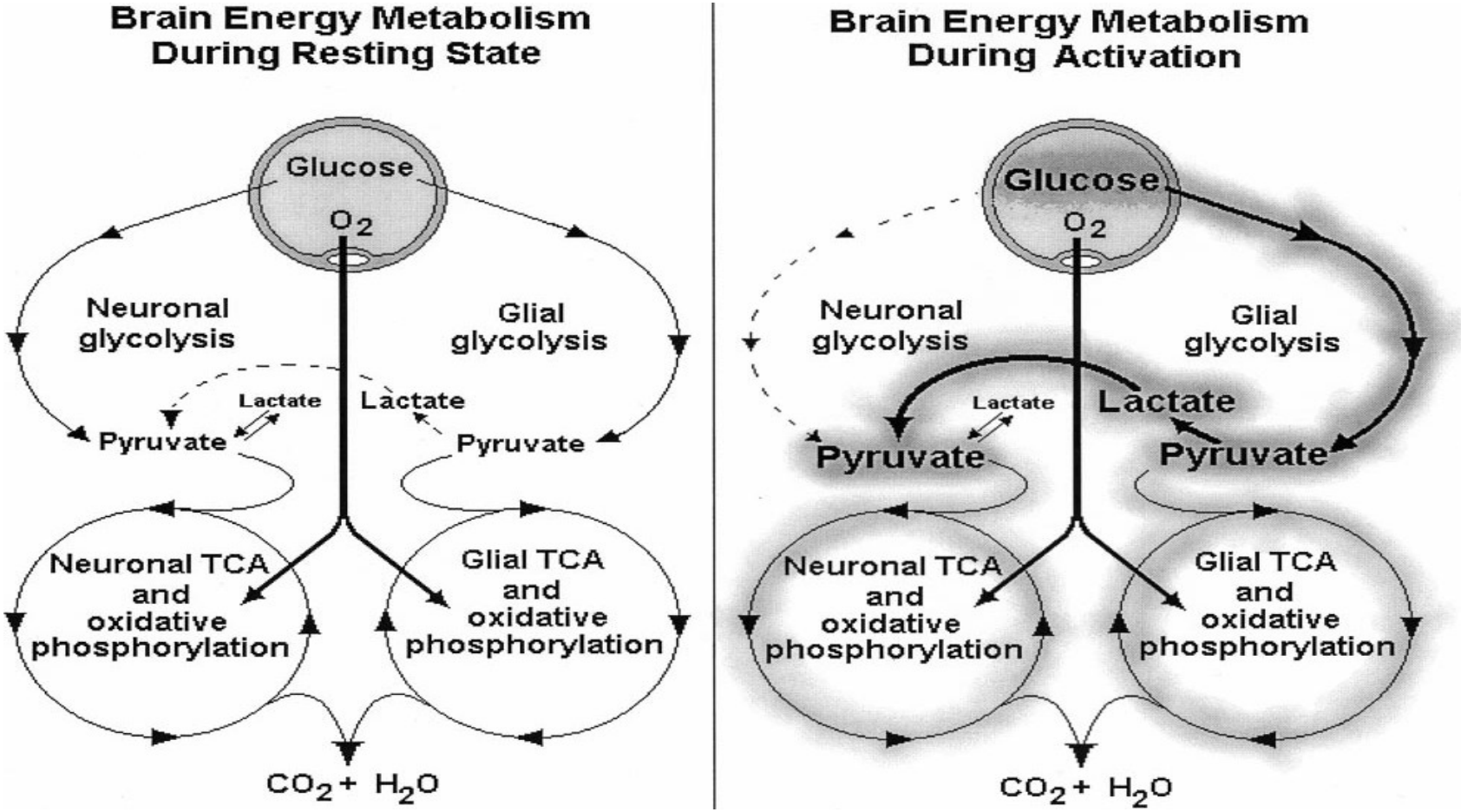
# Measure brain O2: aerobic metabolism

- glucose + O2 -> H2O+ CO2 + 36 ATP
- 20 fold as efficient as glycolytic pathway alone



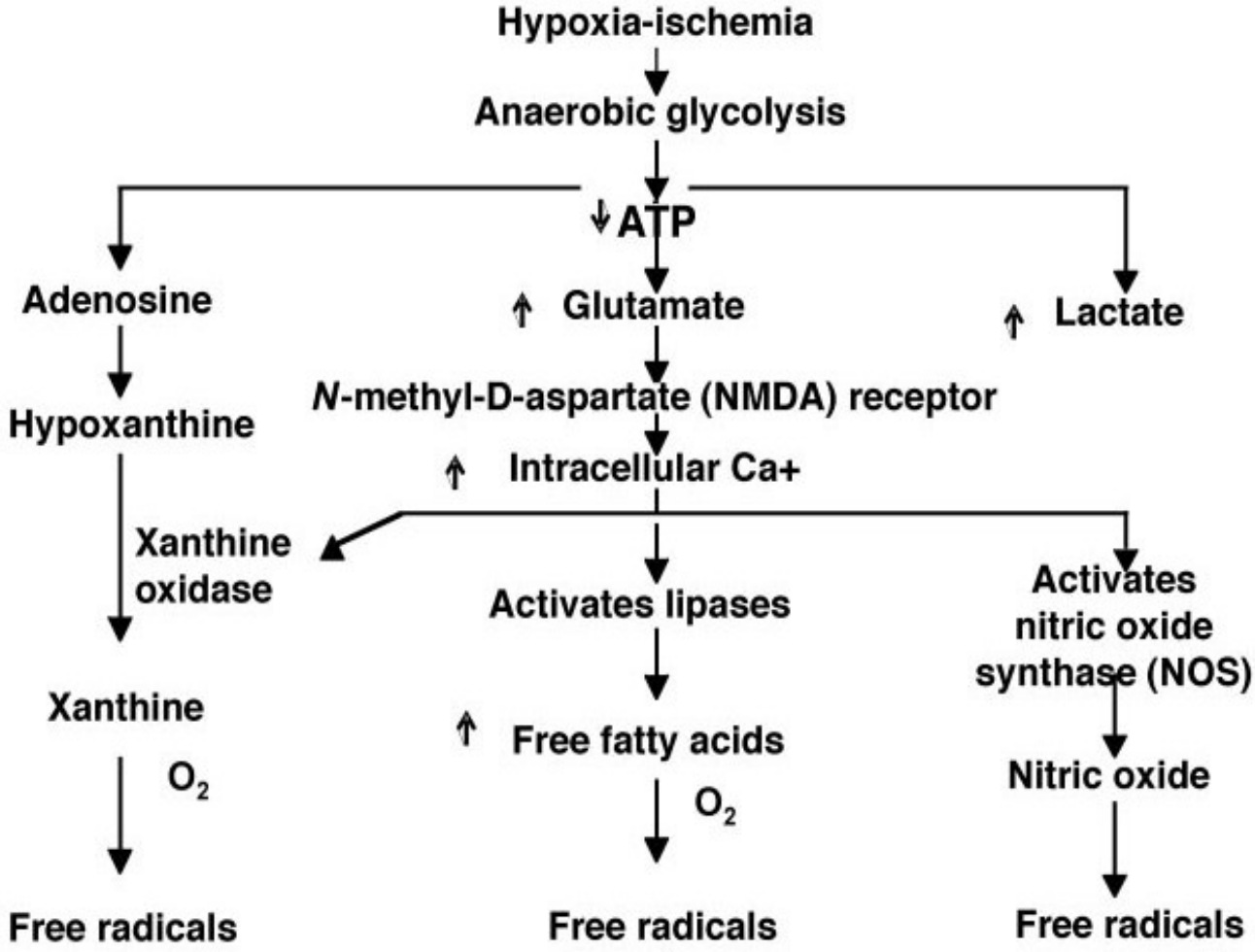
# the neuron uses lactate

- glia generate lactate for neuronal consumption



# Measure glucose

- glucose is limiting substrate in hypoxia

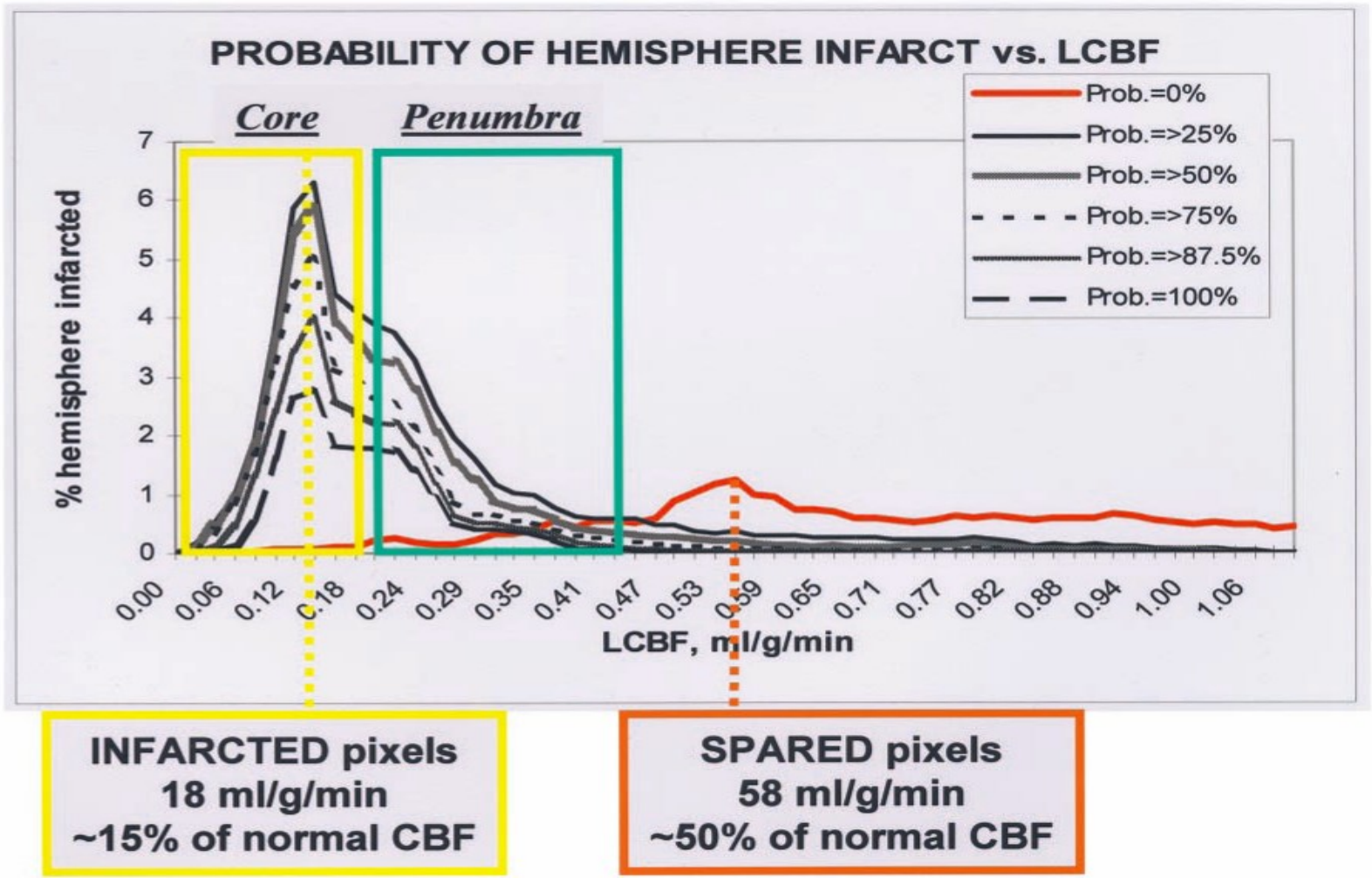


# hypoxic-ischemic cellular injury models

- global ischemia
  - cardiac arrest / resuscitation
  - decapitation
  - DHCA
  - graded flow
- regional ischemia
  - MCA occlusion
- in either model: neuronal injury is related to O2 supply/demand relationship

# cerebral blood flow and ischemic injury

- unsafe range < 50% of normal



# ischemic injury

- fate of ischemic cell is deterministic and highly related to cerebral blood flow

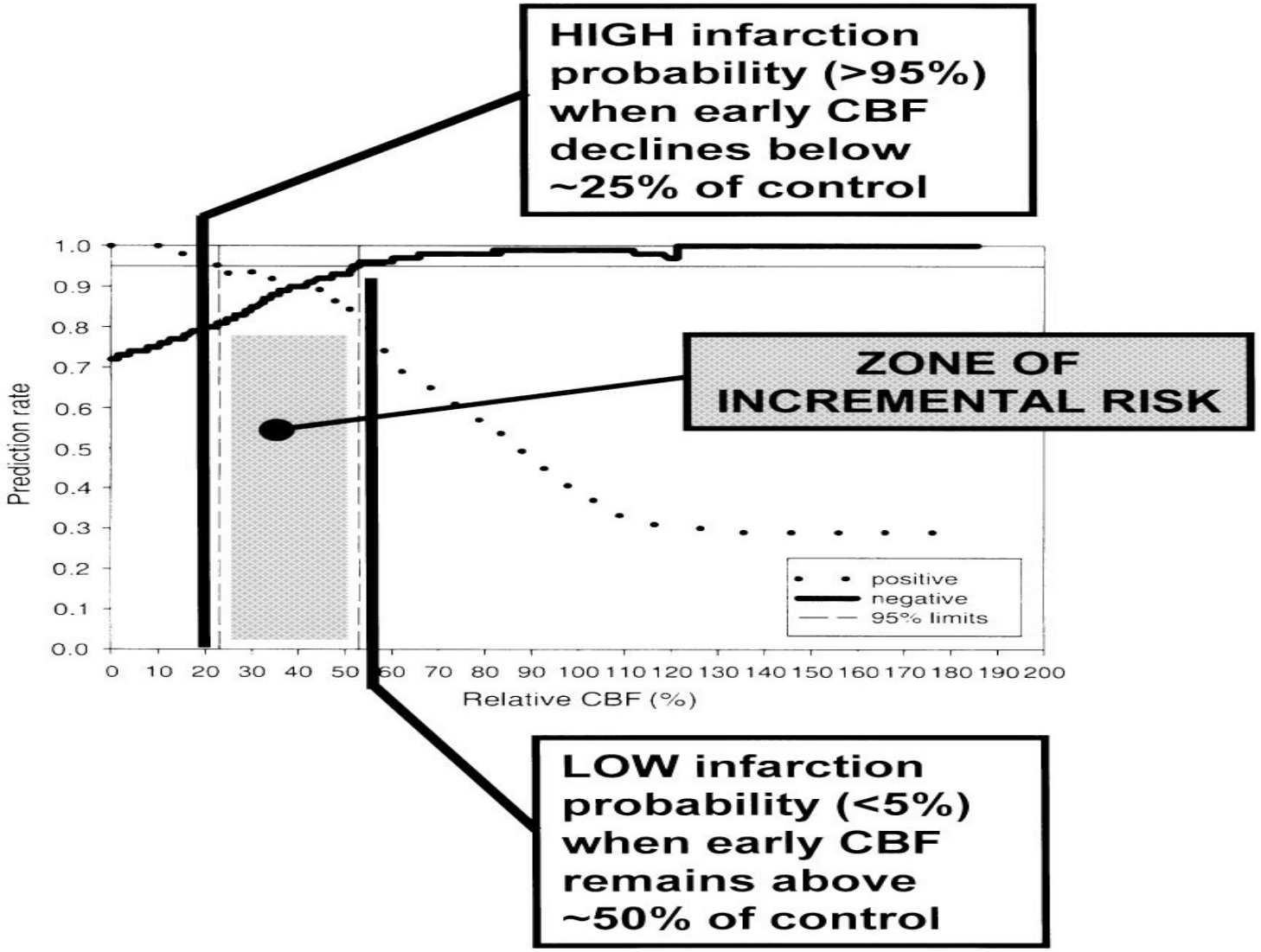
Core ischemic lesion

- CBF < 20% normal
- glucose metabolism limiting
- necrotic cell death
- not reversible by post-ischemic maneuvers

# Sublethal ischemic – tissue at risk

- CBF 20-40% of normal
- glucose metabolism maintained
  - flow/metabolism is reduced in ischemia, but increased on reperfusion
- post-reperfusion
  - episodic depolarization (abnl EEG)
  - ATP decreased
  - Ca++ influx
  - auto-excitation, excitotoxicity
  - ischemic and apoptotic cell death

# ischemic injury is deterministic



# Measure temperature: affects injury

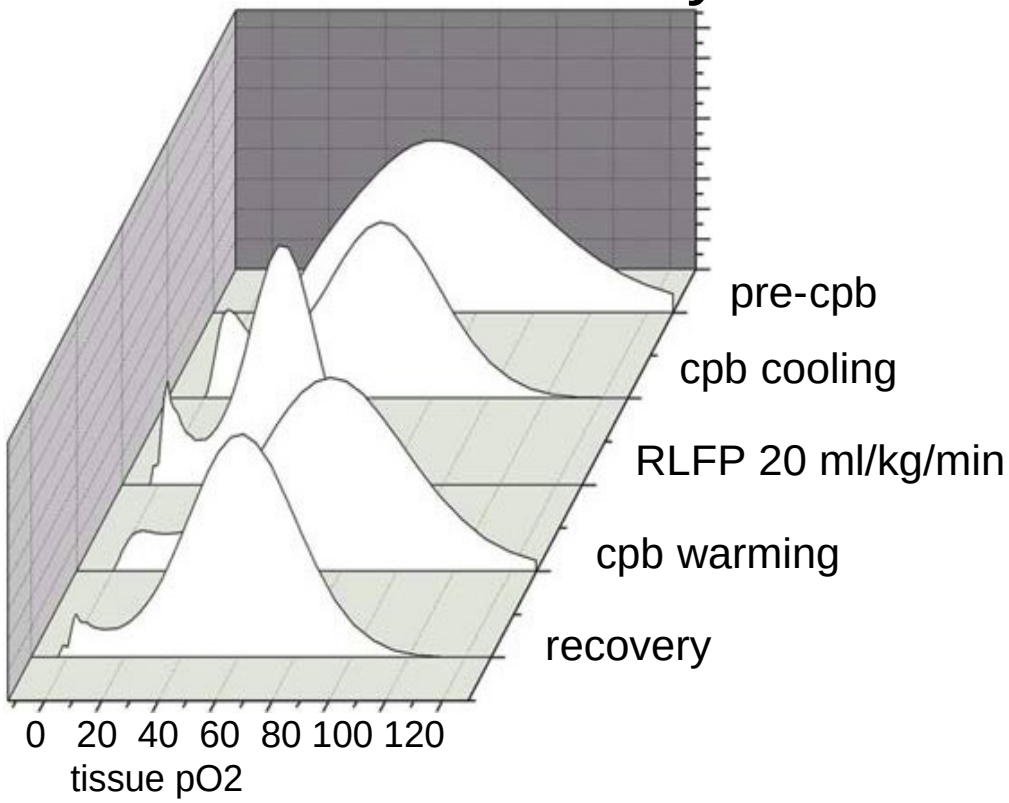
- Q10: metabolic rate changes 3x for each 10C
- probably not that simple

- moderate hypothermia:
  - 2x reduced free radical formation
- mild hyperthemia:
  - 12x increased free radical formation

- temperature affects development of ischemic injury and can modify injury evolution

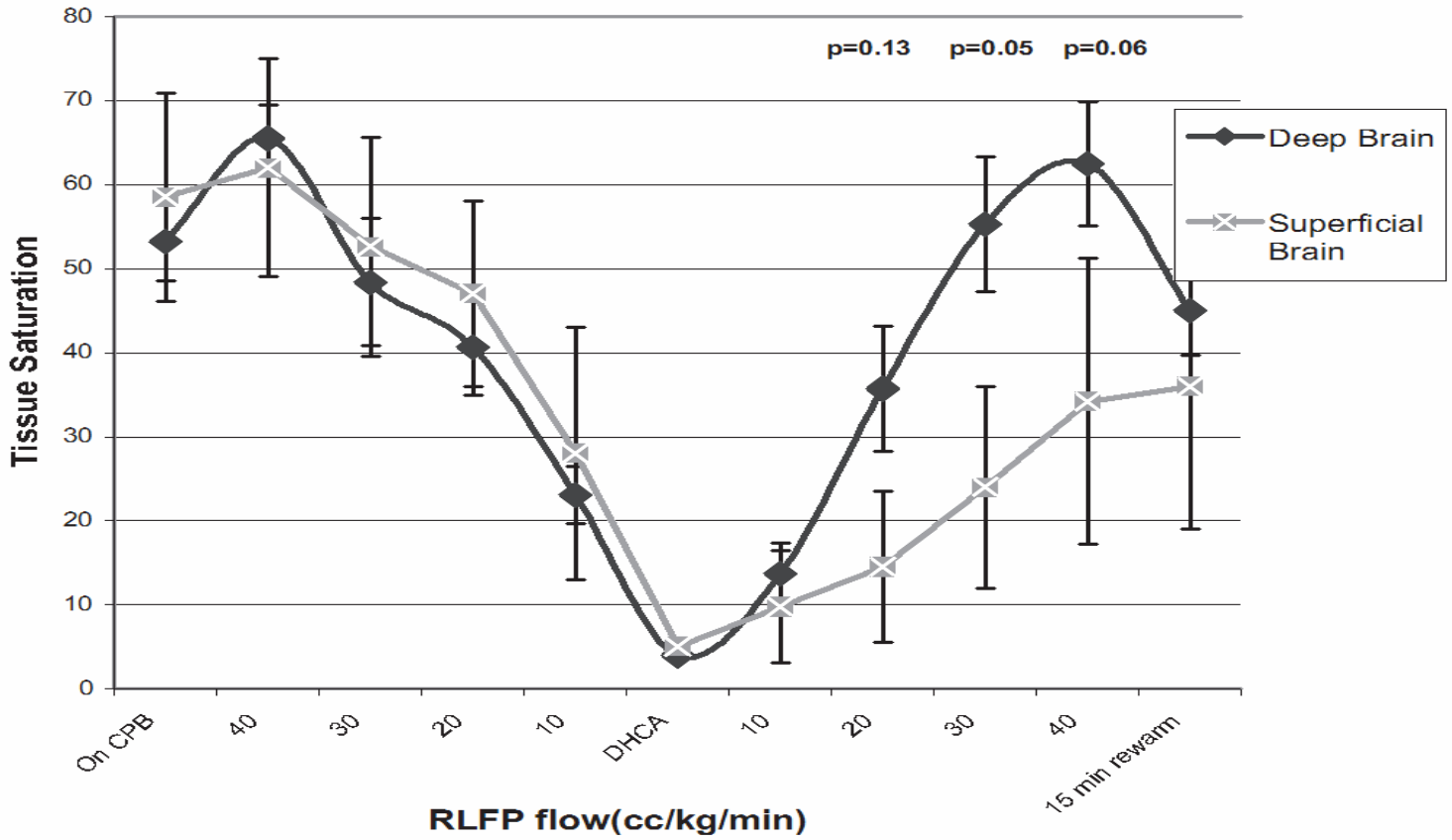
# tissue pO2 distributions during RLFP

- for any flow rate, a range of metabolic conditions can be demonstrated
- some neurons always at risk



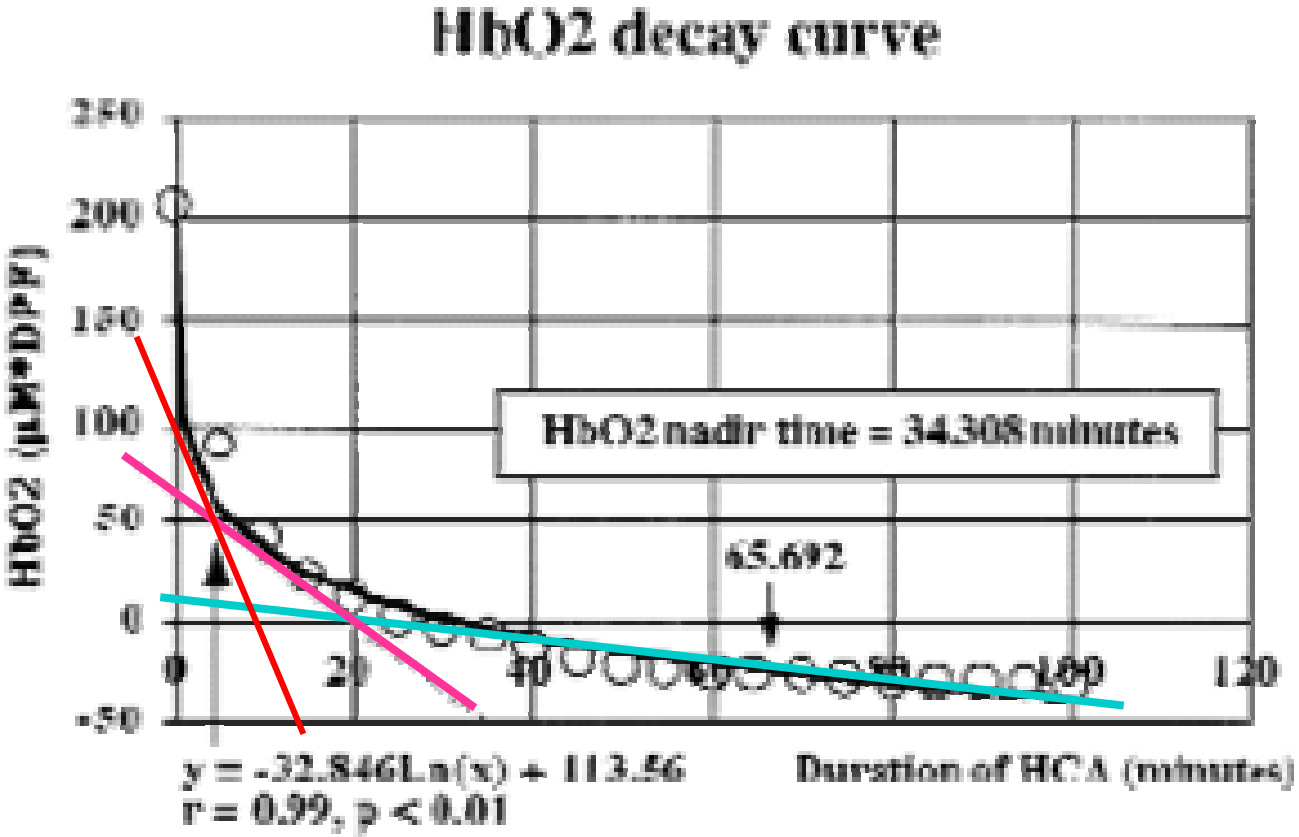
# CPB parameters do matter

- RLFP flow rate affects brain saturation
  - stanford model: amir, ramamoorthy, reddy 2006



# Hypoxia = substrate deficiency

- What is the biochemically safe time for hypoxia?
  - When would the rate of oxygen utilization be limiting?



# NIRS CNS thresholds

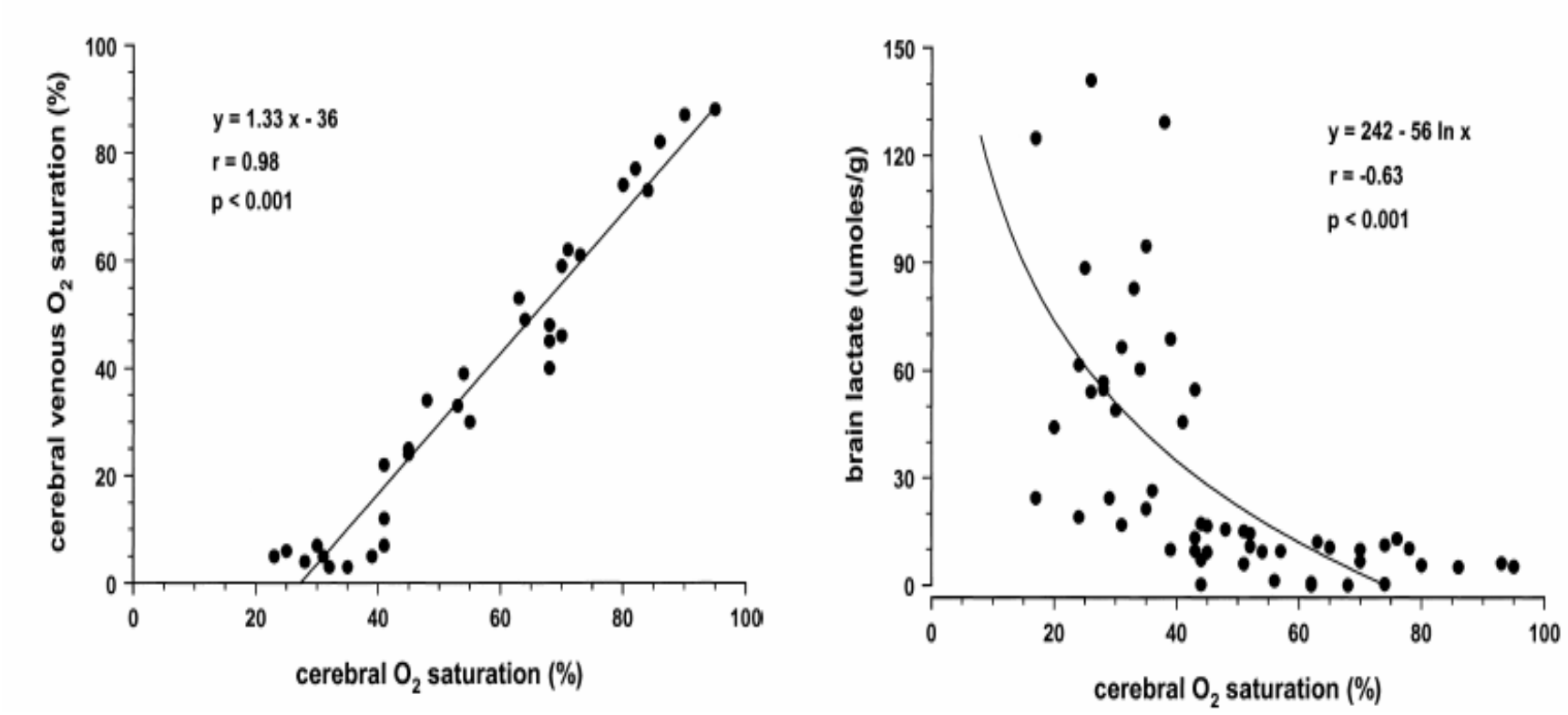
graded hypoxia in piglets

kurth, jcbfm, 2002

## Near-Infrared Spectroscopy Cerebral Oxygen Saturation Thresholds for Hypoxia–Ischemia in Piglets

excellent correlation with SjvO2

lactate threshold ~ ScO2 =42



# What is critical cerebral rSO2?

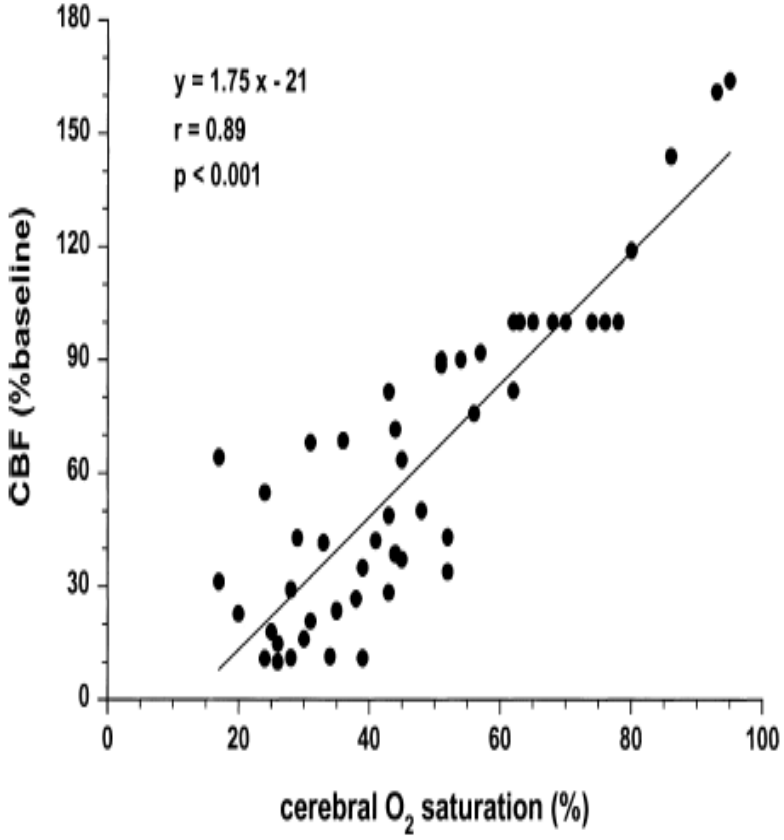
- Adults undergoing AICD testing:
  - EEG silence as indicator of CNS hypoxia
  - Ischemia threshold: rSO2 = 47%
    - Levy, Levin, Chance, 1995
- Neonatal piglets:
  - Lactate at rSO2 = 44%
  - EEG changes at rSO2 42 → 37%
  - ATP depletion at rSO2 = 33%
    - Kurth, Levy, McCann, 2002

# NIRS CNS thresholds

graded ischemia in piglets

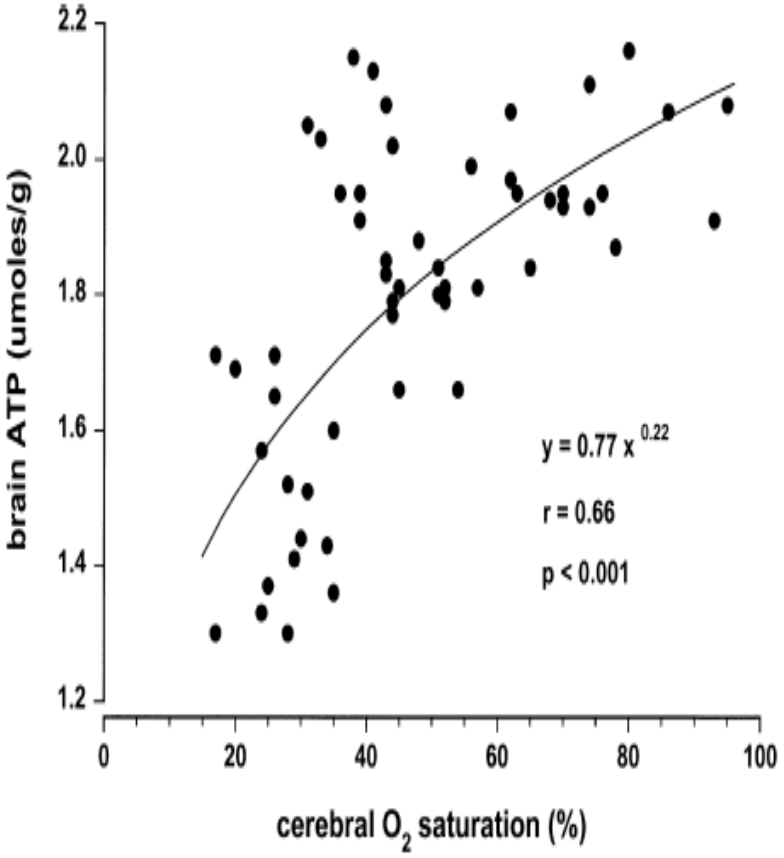
50% reduction in CBF

at ScO2 = 44




kurth, 2002

ATP declines ScO2 < 40



# NIRS CNS thresholds

graded hypoxia in piglets kurth, 2002

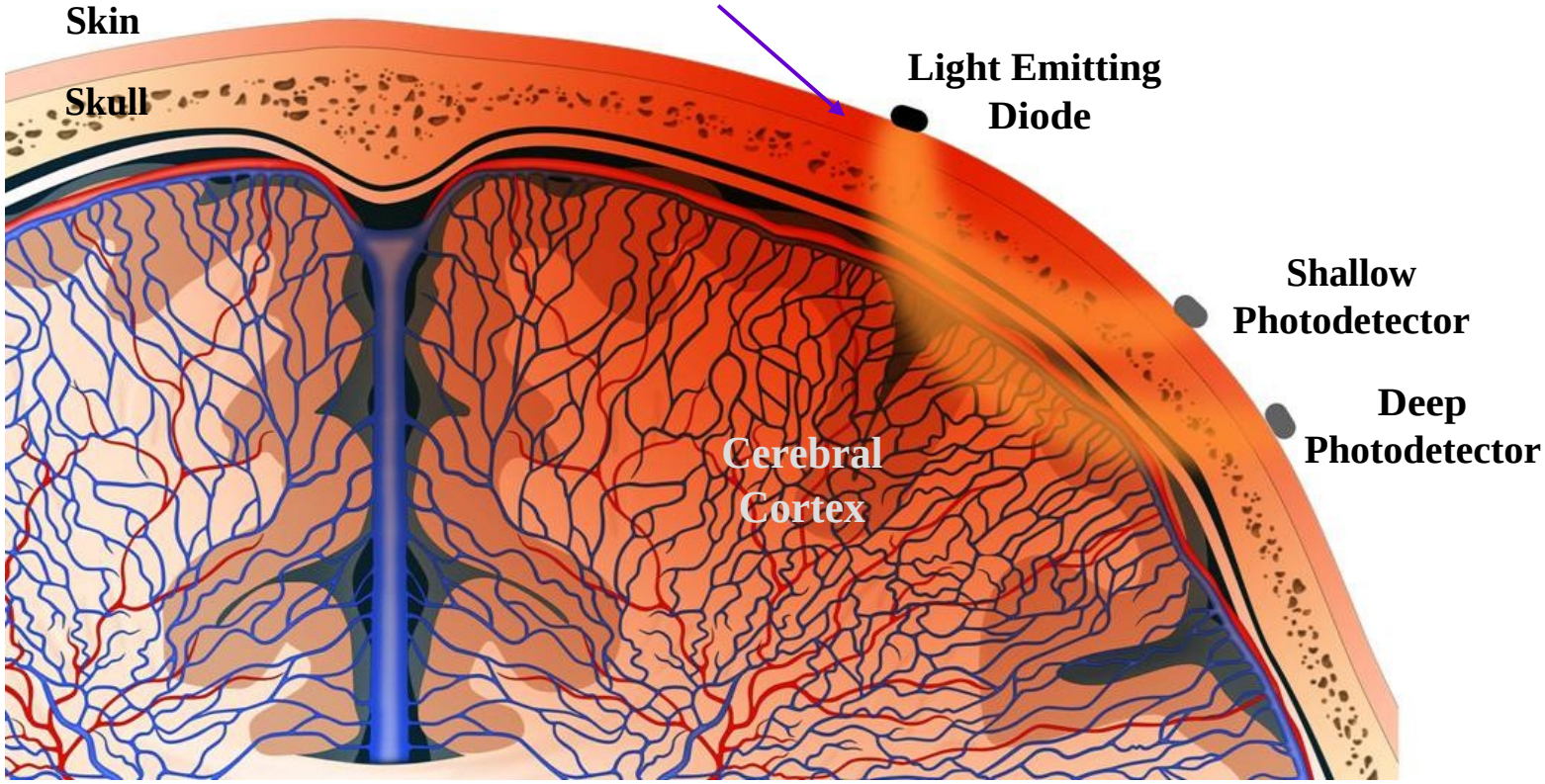
- NIRS provides a continuous signal of regional brain oxygen saturation during progressive hypoxic-ischemic insult

**TABLE 3.** *Cerebral hypoxia–ischemia thresholds*

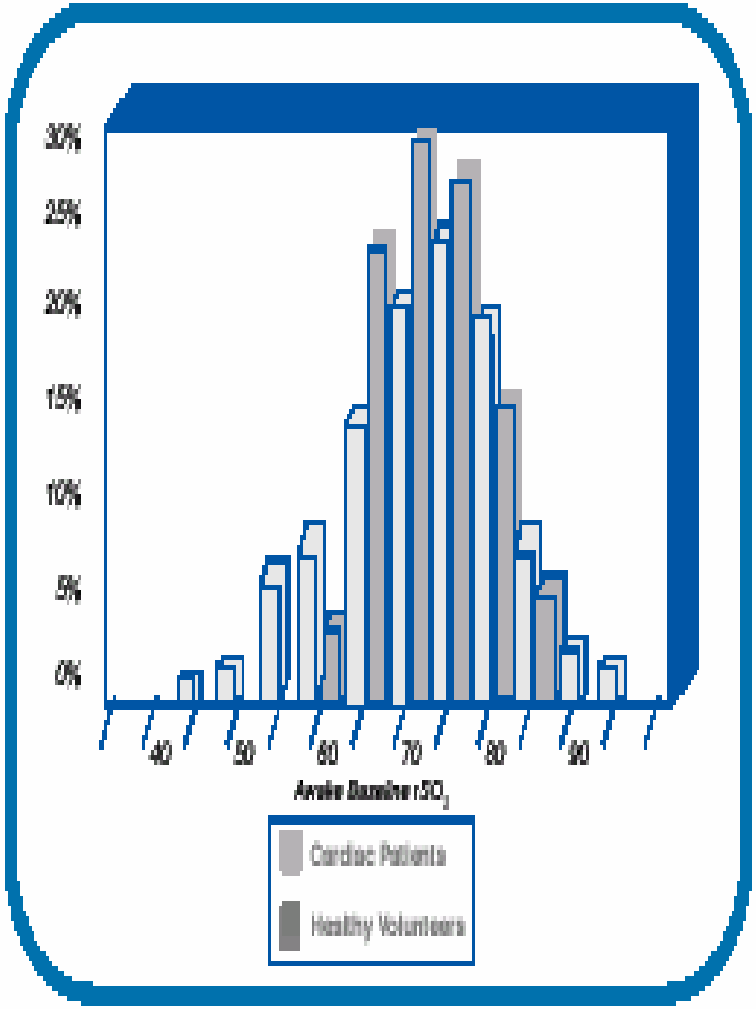
| | $Sco_2$ (%) | CBF (% baseline) | $Svo_2$ (%) |
|---|---|---|---|
| Increased lactate | 44 (33–52) | 56 (37–70) | 23 (8–33) |
| Minor EEG change | 42 (26–70) | 52 (24–100) | 20 (0–57) |
| Major EEG change | 37 (29–46) | 42 (29–59) | 12 (3–25) |
| Decreased ATP | 33 (28–39) | 36 (28–47) | 8 (1–16) |

# cerebral NIRS

- most blood in capillaries and veins
- surface area for scattering mainly in capillaries
- shallow field has different blood supply



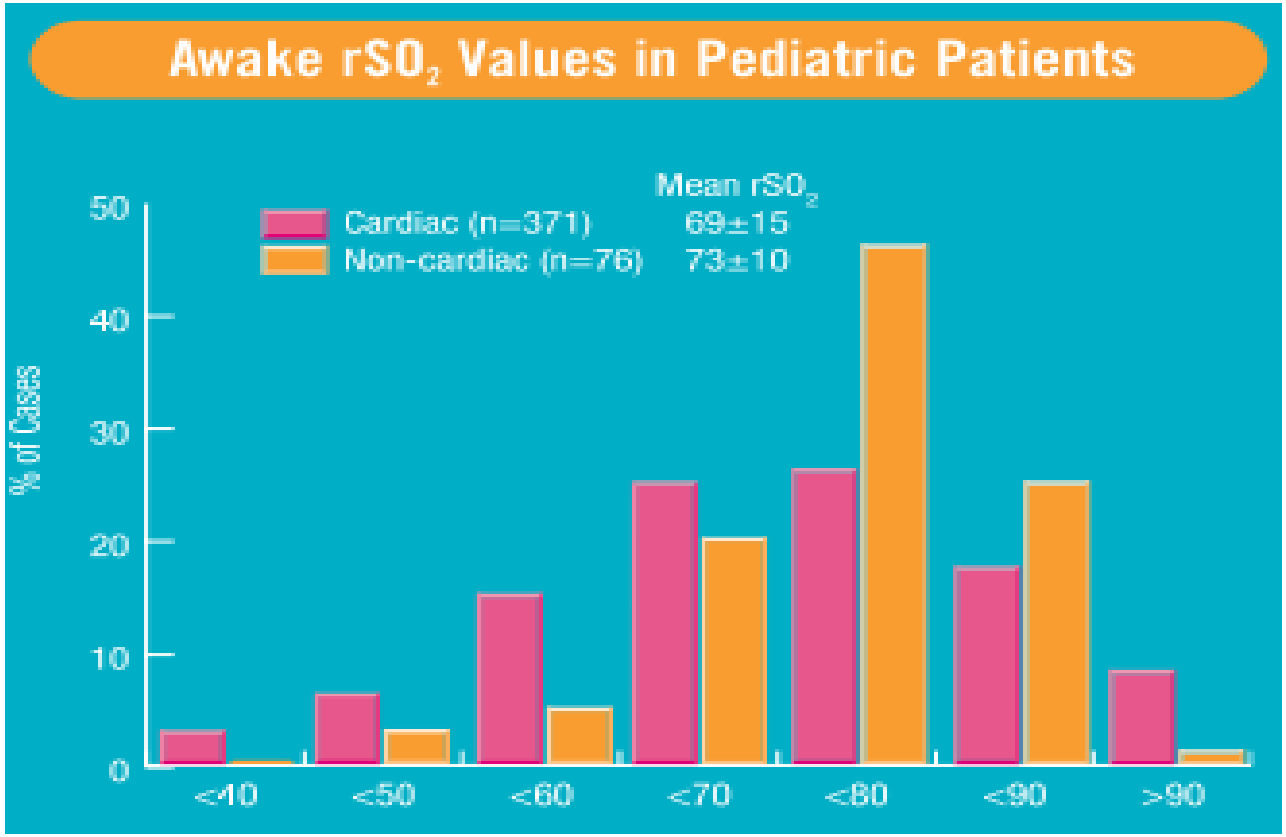
# Cerebral rSO2 – 'normal' values




- Analysis of cardiac surgery patients and young, healthy volunteers show a wide range of normal rSO2 index values.
  - The baseline rSO2 values in the cardiac surgery patients were 65 ± 9 (range 47-83).
  - Volunteer baseline rSO2 values were 70 ± 6 (range 58 to 82).
  - Baseline readings below 50 in cardiac surgery patients are associated with increased cognitive declines and longer length of hospital stay.

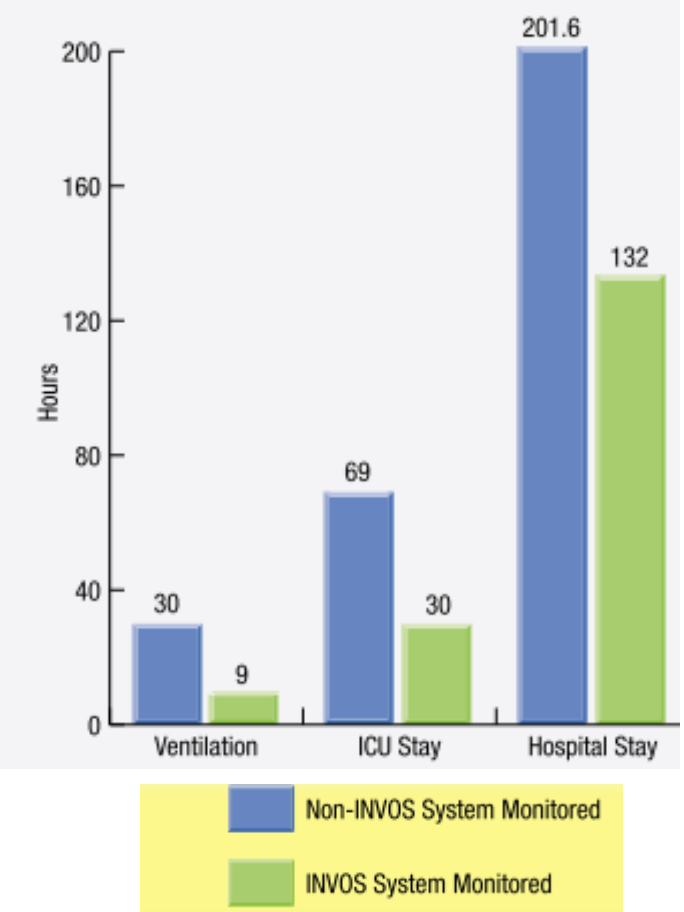
# Pediatric cerebral baseline

- Non-cardiac 73 +/- 10
- Cardiac 69 +/- 15

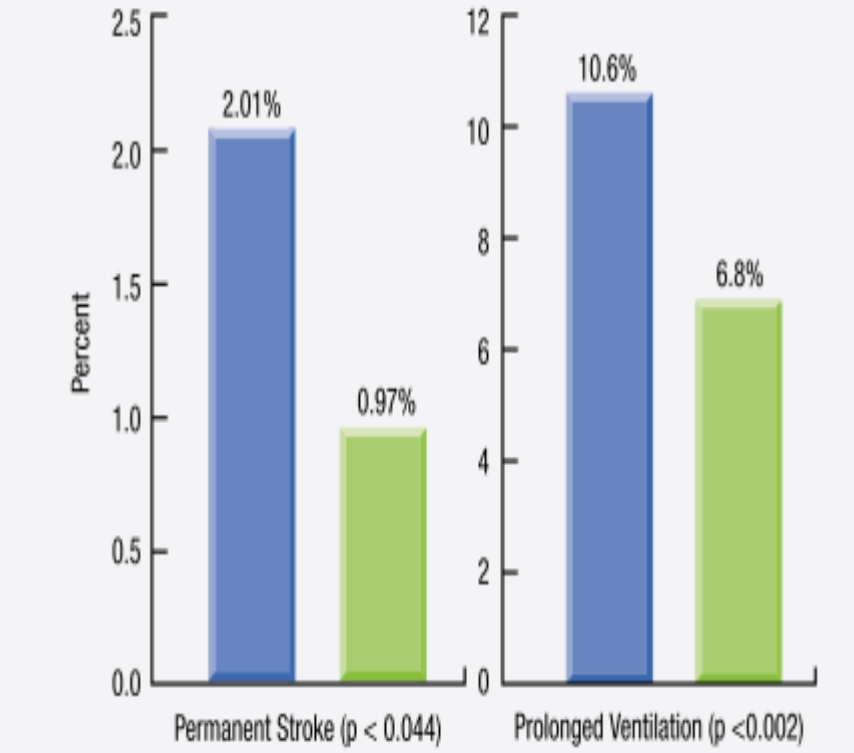


# Adult outcome altered by NIRS

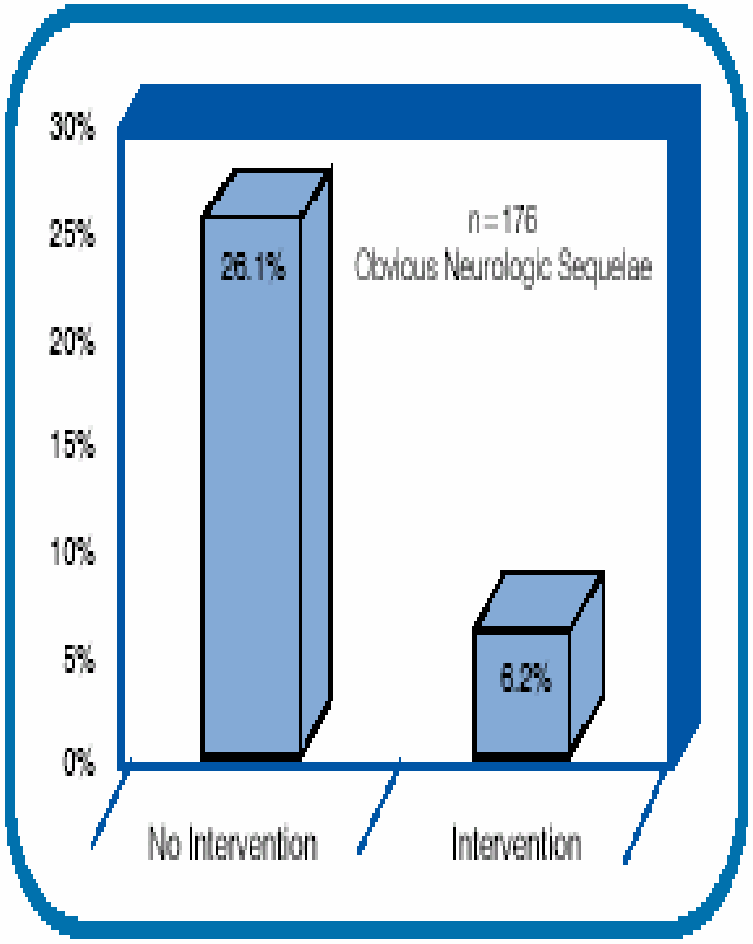
- Murkin, CABG, outcomes




- Goldmann, adult cardiac, n= 2700



# Outcome in Pediatric Cardiac Surgery

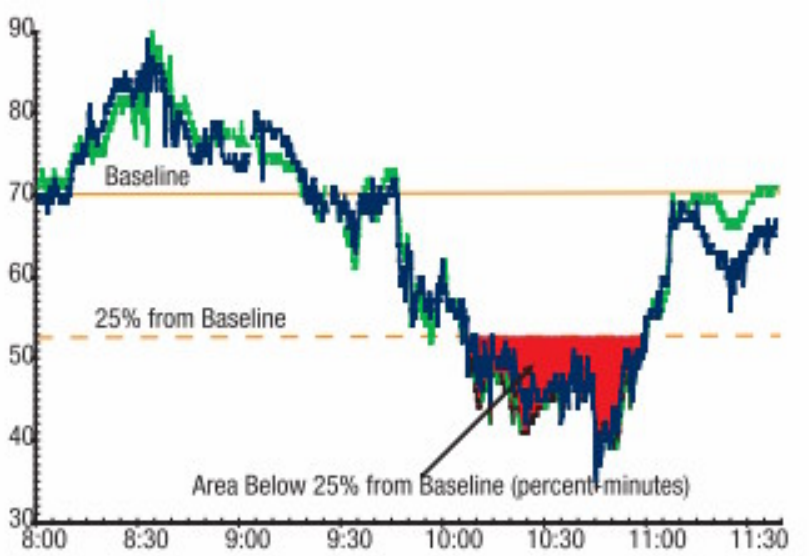



Austin EH, et al., J Thorac Cardiovasc Surg, 1997

- Interventions can improve outcomes in pediatric cardiac surgery.
  - Of 250 patients, 176 (70%) experienced changes in brain perfusion or metabolism.
  - Patient management interventions were deemed appropriate in 130 patients.
  - Obvious neurologic sequelae (i.e., seizure, movement, vision or speech disorder) occurred in 26% of patients without interventions, but only in 6% of patients with appropriate intervention.

# Postoperative NIRS and outcome

- Dent, JTCVS, 2006:
- Pre/postop MRI in HLHS
- Risk factors:
  - preop acidosis
  - postop prolonged rSO2<45




| | Exposed | Unexposed | Total | Exposed |
|---|---|---|---|---|
| Cases | 9 | 2 | 11 | 0.8182 |
| Controls | 1 | 3 | 4 | 0.2500 |
| Total | 10 | 5 | 15 | 0.6667 |
| Odds ratio | 13.5 | | .5536277 | 784.4808 |

chi2(1) = 4.26 Pr>chi2 = 0.0390

# Cerebral NIRS summary

- some variation in baseline, but:
  - biochemical changes with rSO2< 47
  - EEG changes with rSO2< 40
  - ATP depletion at rSO2< 30
- worse outcome:
  - lower baseline rSO2
  - more episodes of decreased rSO2
  - lower average rSO2 or  time< 45
- better outcome: treat the rSO2 number
  - absolute threshold 45-50%
  - relative 20% change

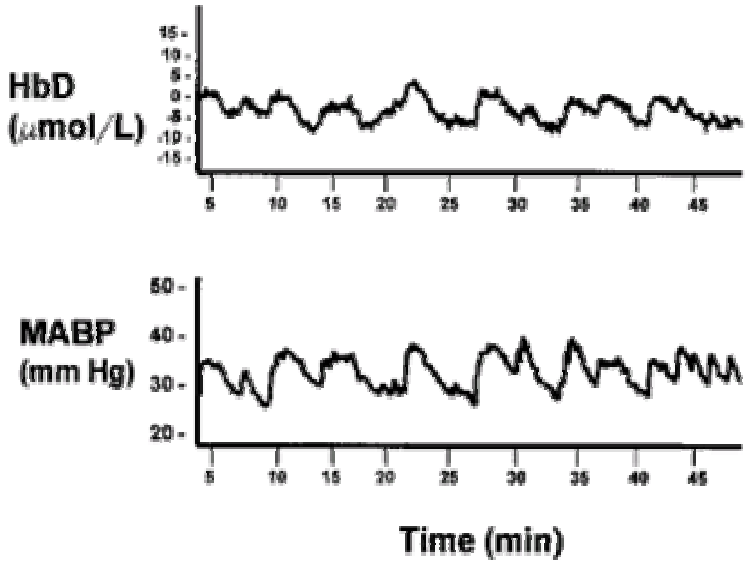
# Regional Saturation during S1P

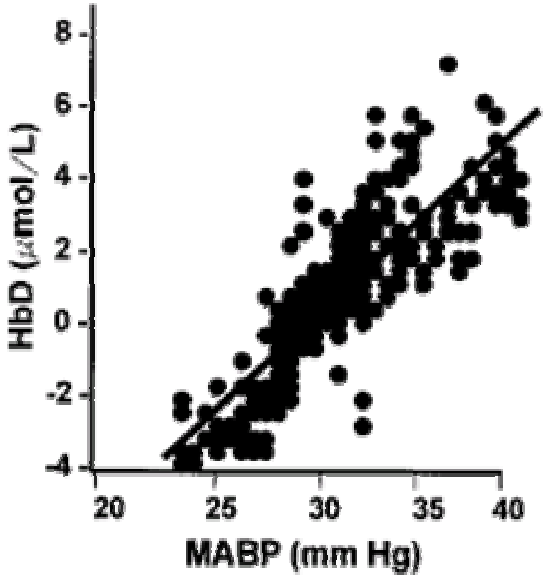
| Time Period | Cerebral $rSO_2$ (%) | Somatic $rSO_2$ (%) |
|---|---|---|
| Pre-CPB | 65.4±8.9 | 58.9±12.4 # |
| | (63.2-67.6) | (57.8-59.9) |
| CPB (cooling) | 87.2±7.8 * | 77.2±12.5 *# |
| | (85.0-89.5) | (75.6-78.8) |
| RLFP | 80.7±8.6 * | 41.4±7.1 *# |
| | (78.6-83.0) | (39.9-42.8) |
| CPB (warming) | 76.8±10.2 * | 83.5±12.9 *# |
| | (74.6-79.0) | (82.2-84.8) |
| Post-CPB | 53.2±14.9 * | 76.4±7.7 *# |
| | (51.0-55.5) | (75.3-77.6) |

data are presented as mean ± SD and (95% CI). Overall N=3176.
# cerebral vs. somatic difference, p<0.001
* difference from baseline, p< 0.001

# Altered cerebral autoregulation

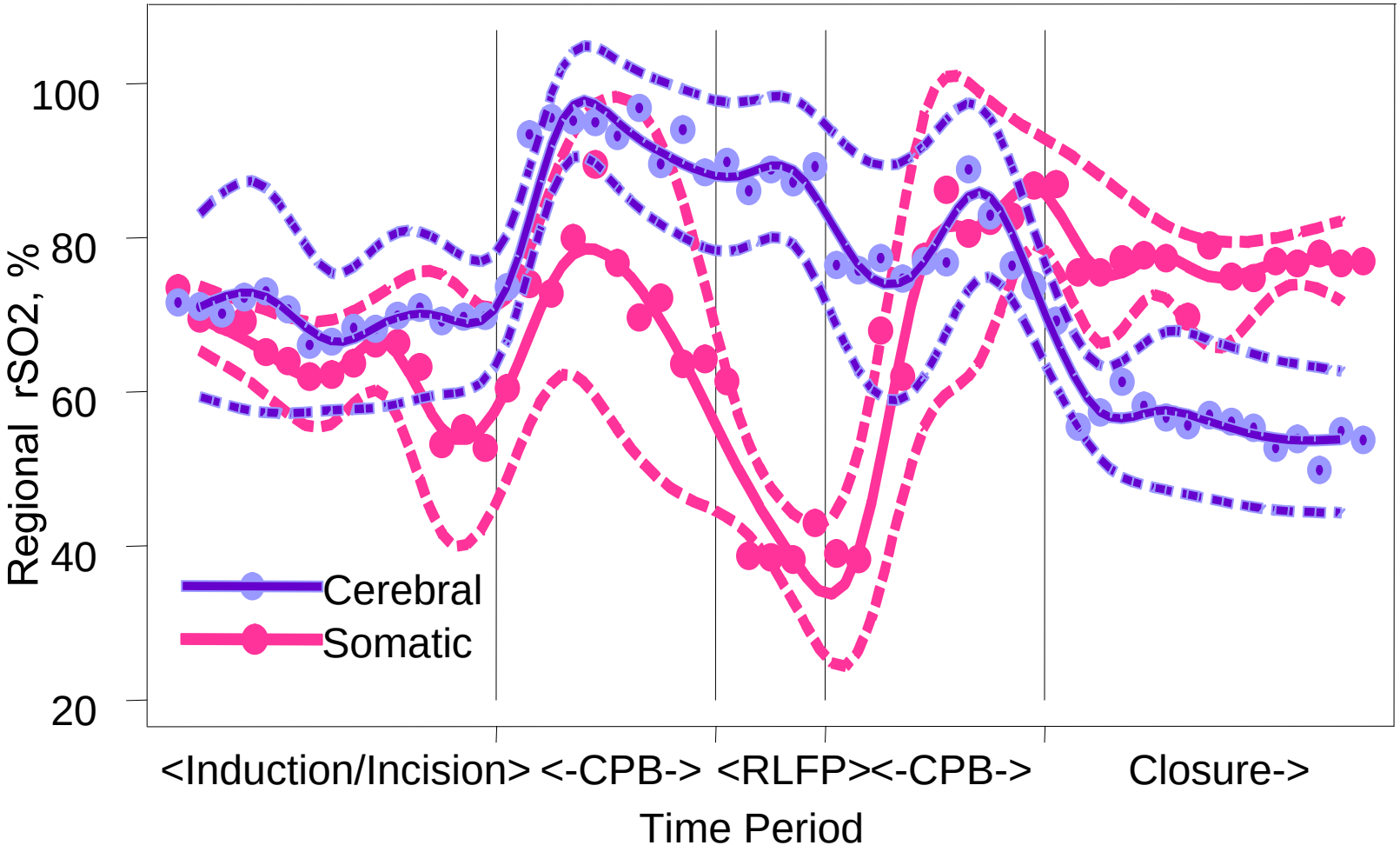
- Pressure-passive cerebral blood flow in premature infants, and post-CPB
  - hypertension -> bleed
  - hypotension -> ischemia



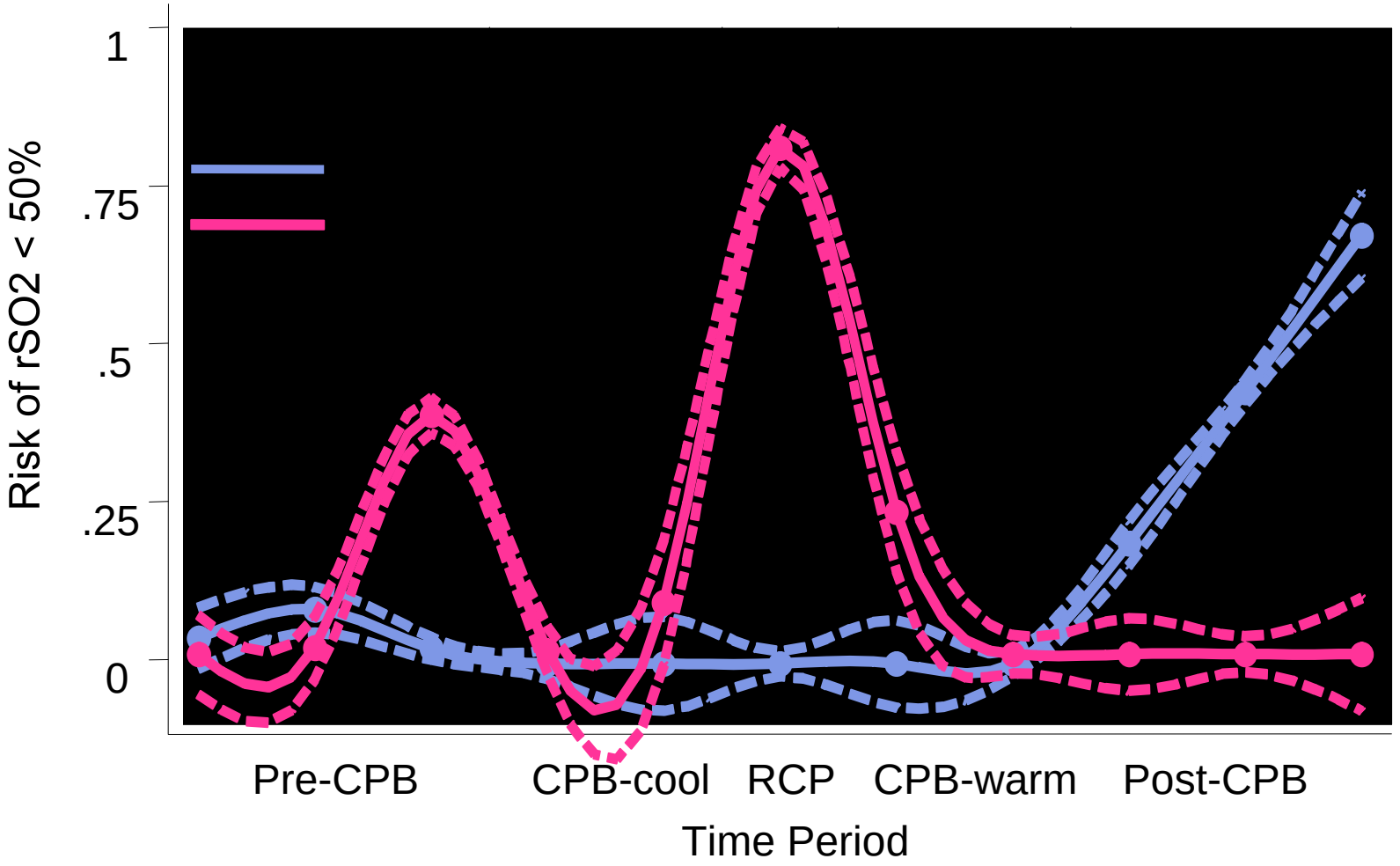
# Regional $rSO_2$ vs. Time

- Cerebral $rSO_2$ approaches threshold post-CPB

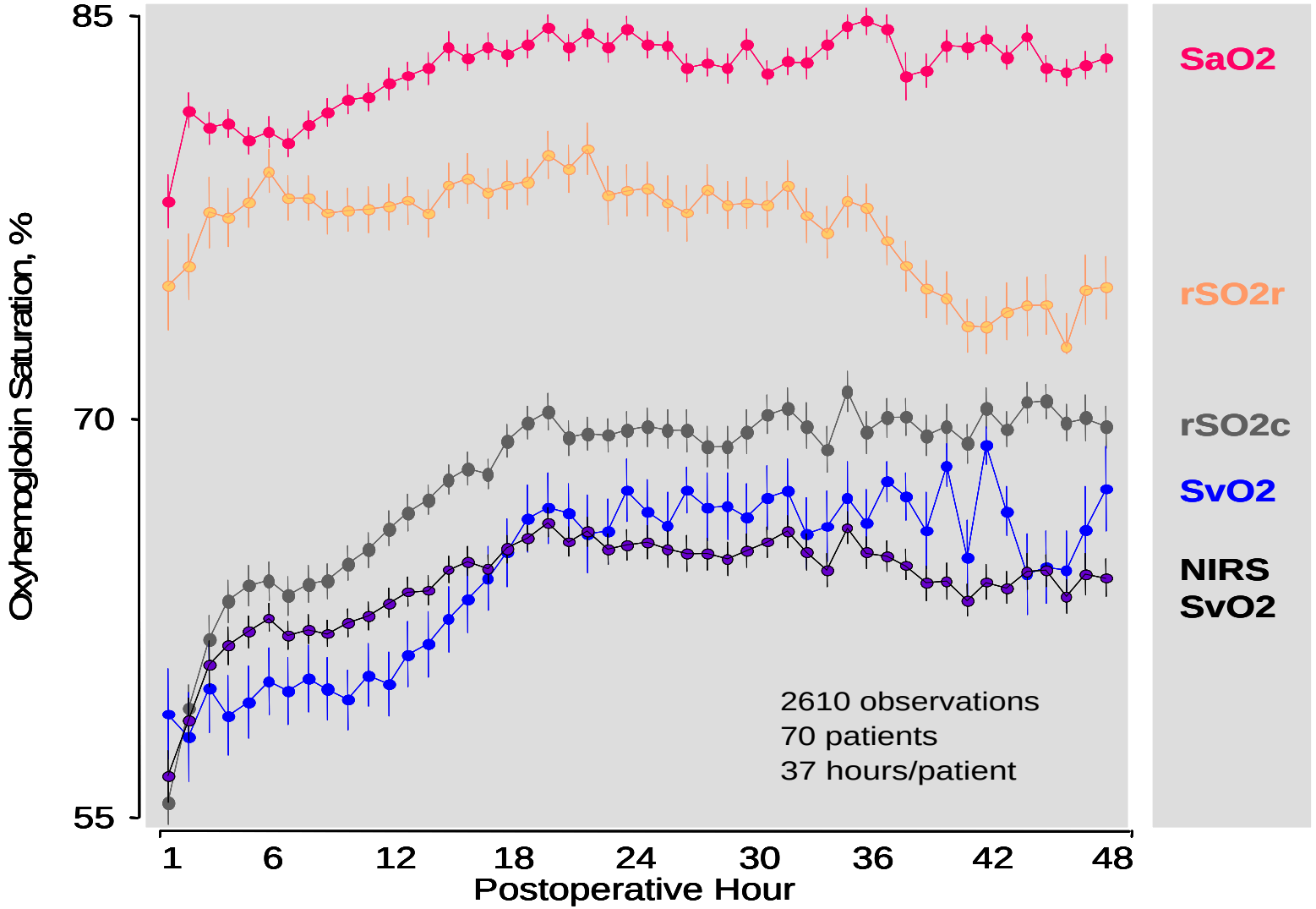


# Risk of critical regional desaturation

- Increasing risk after separation from CPB



# postoperative oxygen dynamics



# periop determinants of cerebral $rSO_2$

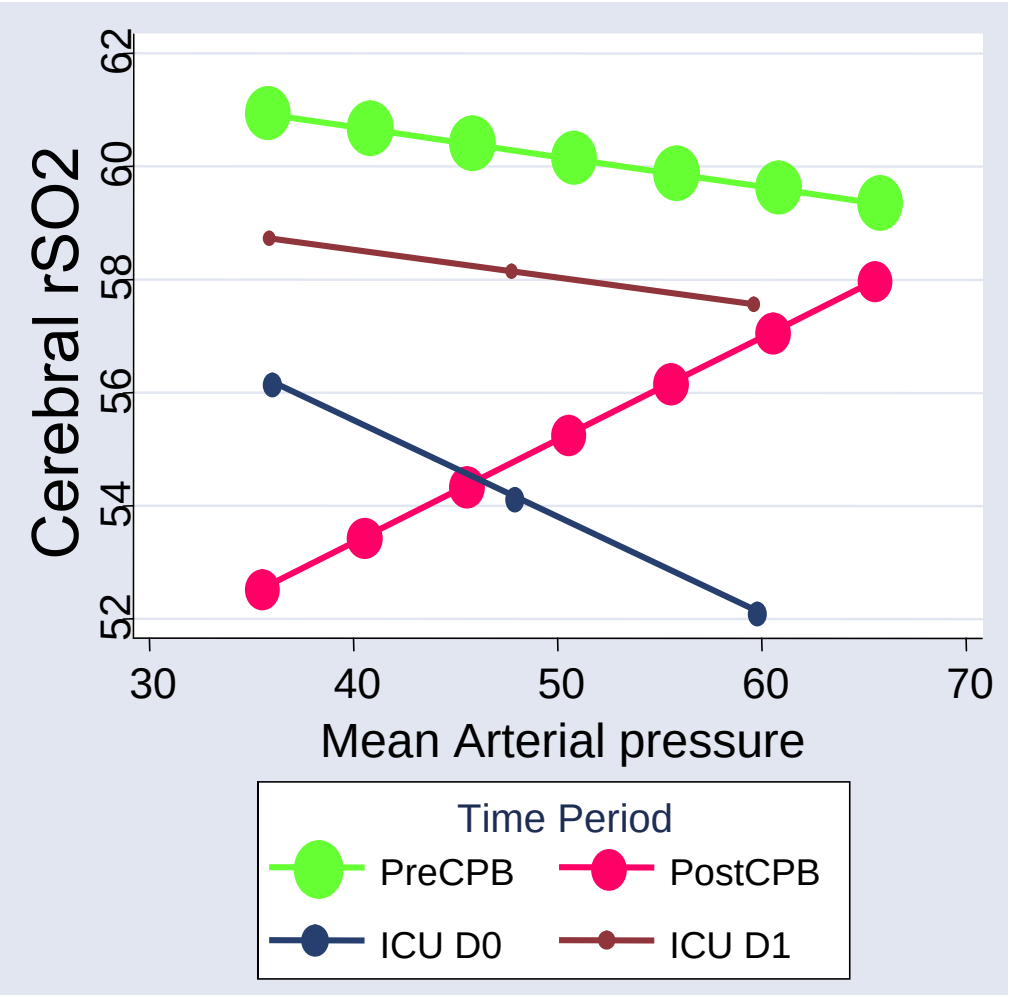
- Evidence for altered autoregulation post-CPB/RCP

| Parameter | Pre-CPB Coefficient | P-value | Post-CPB Coefficient | P-value | pre/post difference |
|---|---|---|---|---|---|
| MABP (mmHg) | 0.14±0.05 | 0.002 | 0.43±0.07 | <0.001 | <0.001 |
| $PaCO_2$ (torr) | 0.38±0.03 | <0.001 | 0.80±0.05 | <0.001 | <0.001 |
| Temp (deg C) | -0.7±0.11 | <0.001 | -4.65±0.32 | <0.001 | <0.001 |
| Isoflurane (%) | -21.5±1.33 | <0.001 | 26.1±1.5 | 0<.001 | <0.001 |
| Hematocrit (%) | -1.39±0.03 | <0.001 | 1.14±0.07 | <0.001 | <0.001 |
| $SaO_2$ (%) | 0.19±0.05 | <0.001 | 0.19±0.05 | <0.001 | -- |
| CVP (mmHg) | -0.14±0.06 | 0.026 | -0.14±0.06 | 0.026 | -- |
| constant | 106.5±8.3 | <0.001 | 106.5±8.3 | <0.001 | -- |

Coefficents ± SD in a multiple linear model for cerebral rSO2

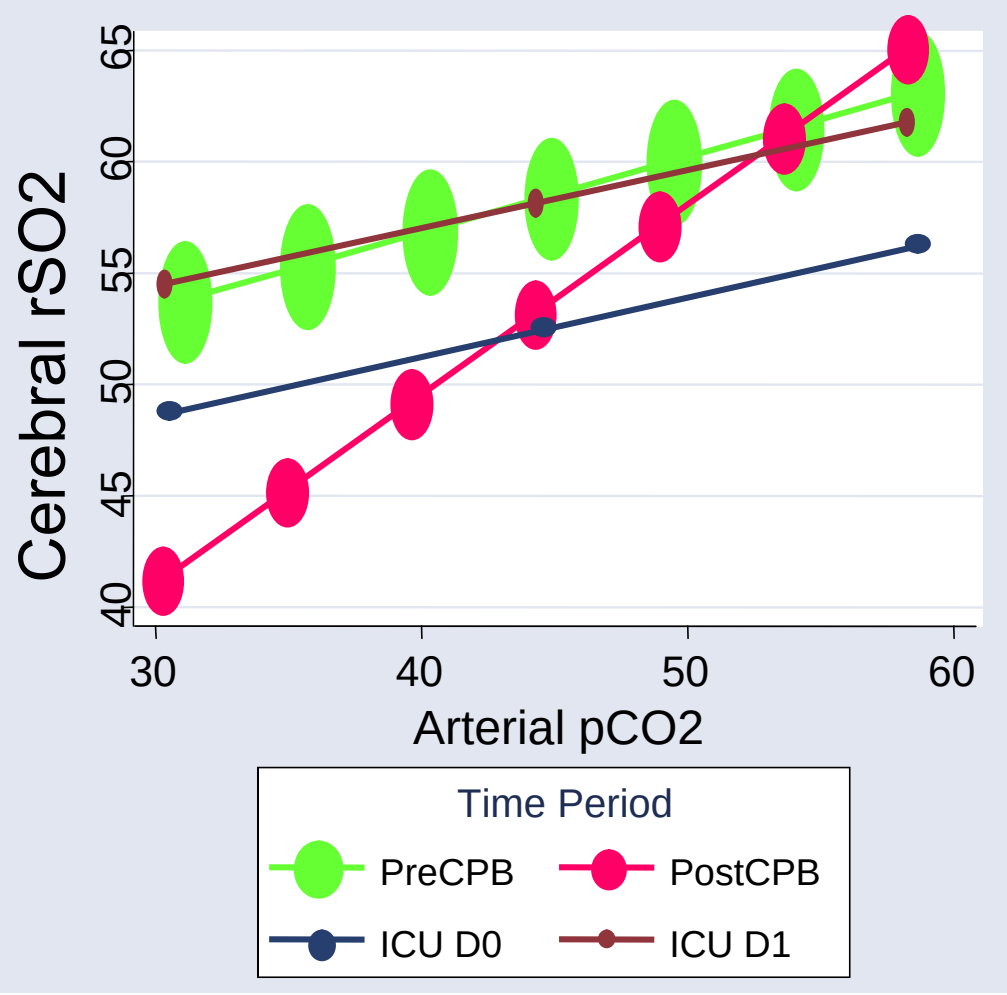
# hypothermic CPB changes autoregulation

- relationship between mean arterial pressure and rSO2c over perioperative period (adjusted for Hgb, SaO2, pCO2)
- BP a difficult way to manipulate cerebral oxygenation
- evidence for cardiac output dependence of rSO2
- approaches normal by POD 1



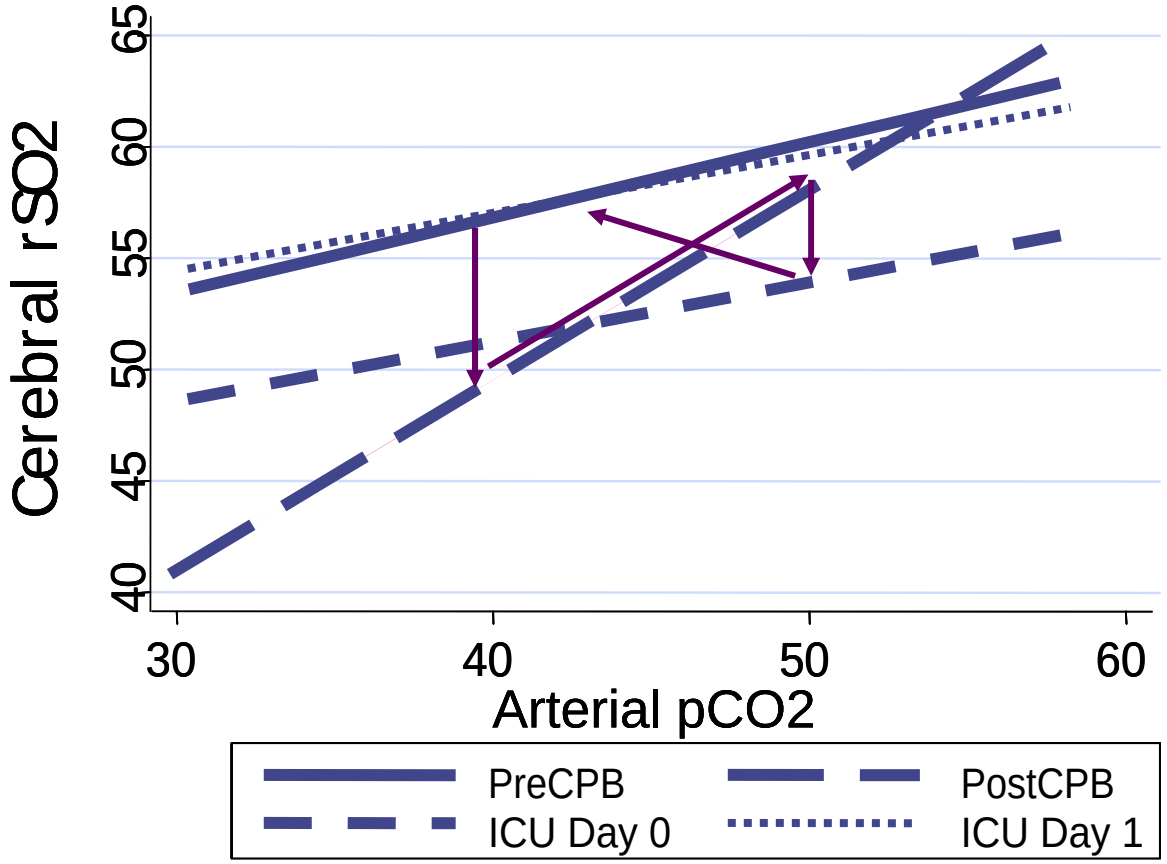
# changes in cerebral autoregulation

- relationship between arterial pCO2 and rSO2c over perioperative period (adjusted for Hgb, SaO2, BP)
- increased CO2 responsiveness in acute post-CPB period
- approaches normal by first postoperative day



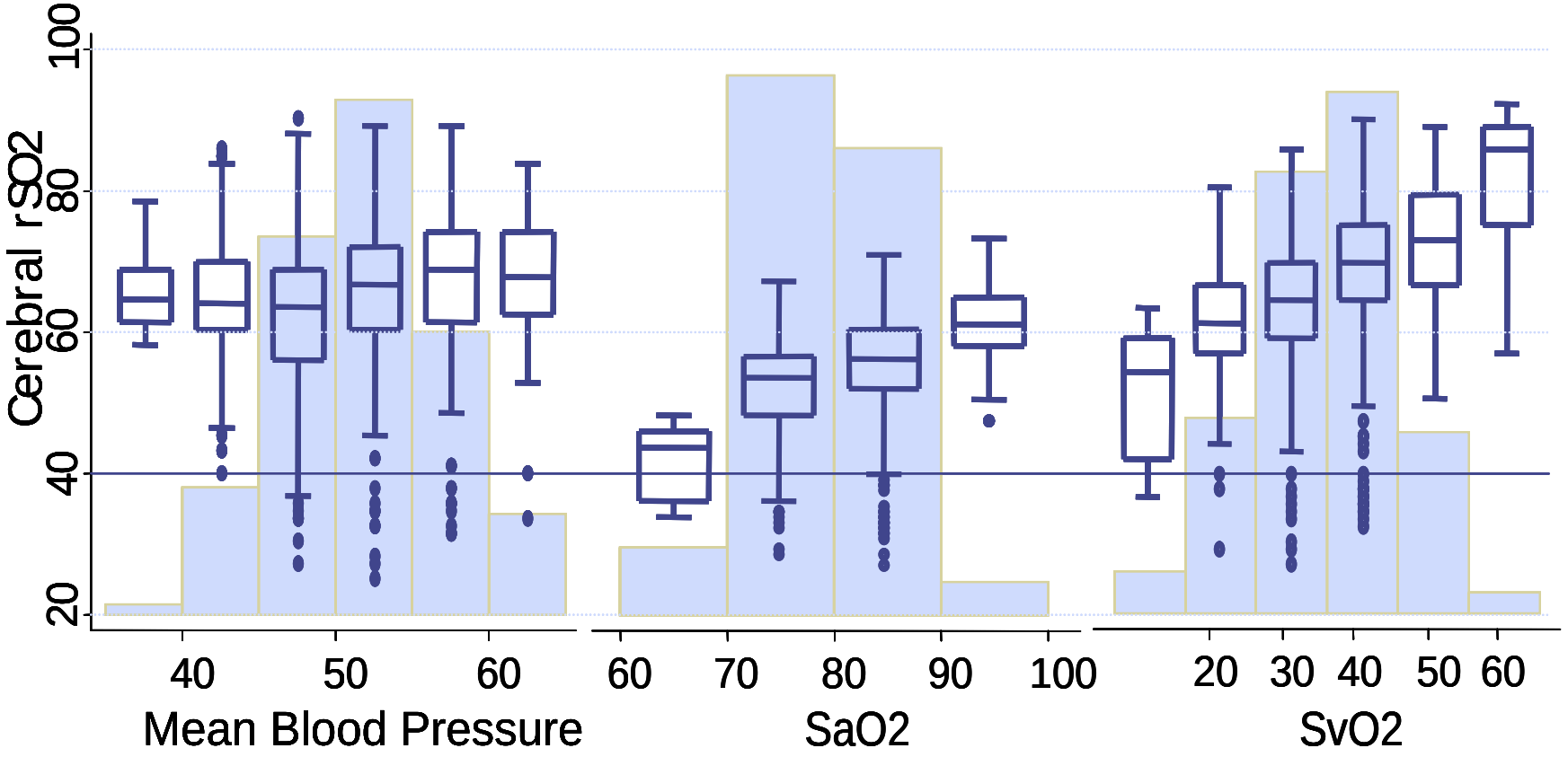
# hypothermic acp alters autoregulation

- changes in CO2 responsiveness over 48 hours



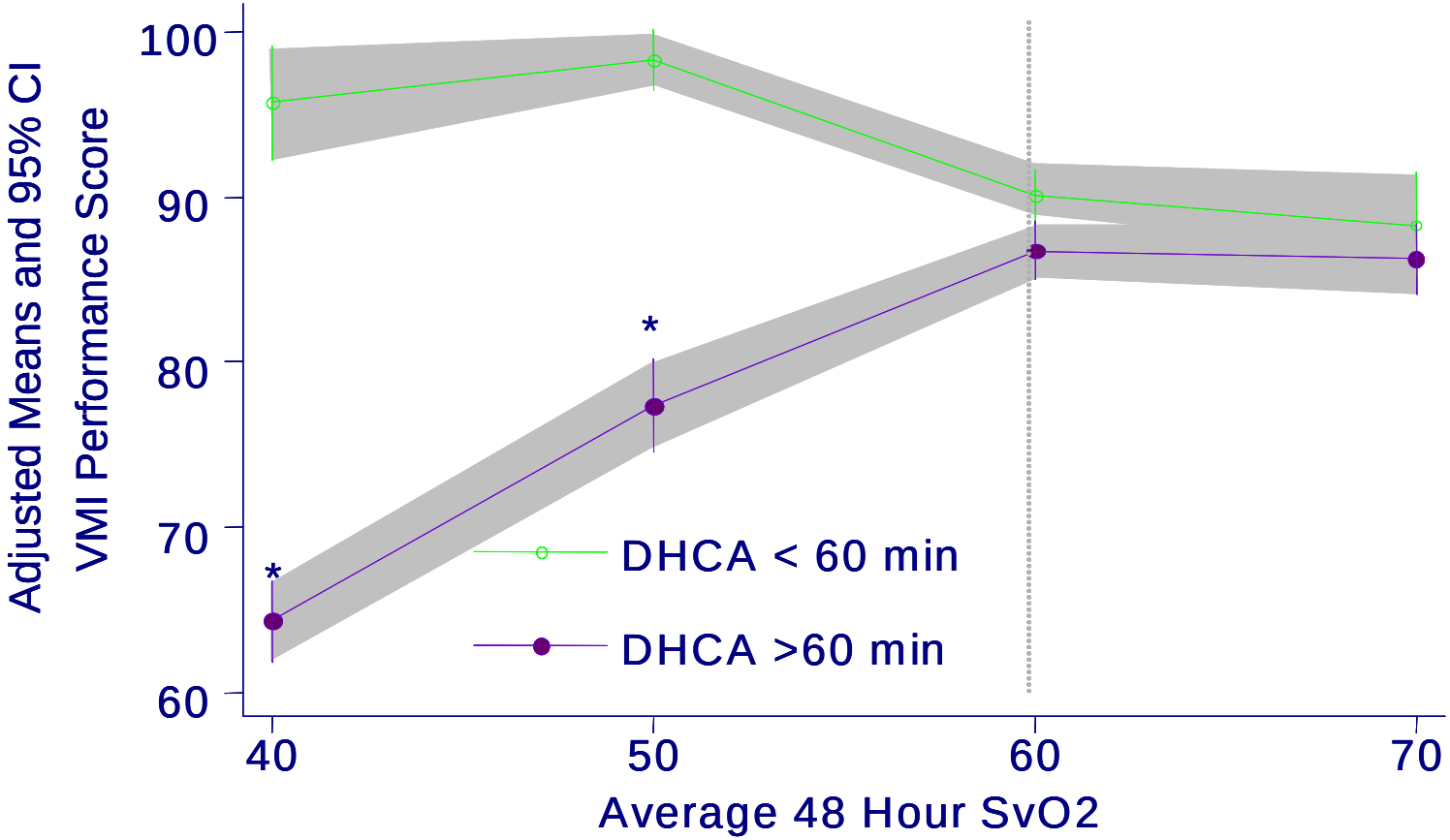
# postoperative cerebral oxygenation

- rSO2c highly related to (deterministic of) SvO2
- low cerebral rSO2 at all levels of BP and SaO2



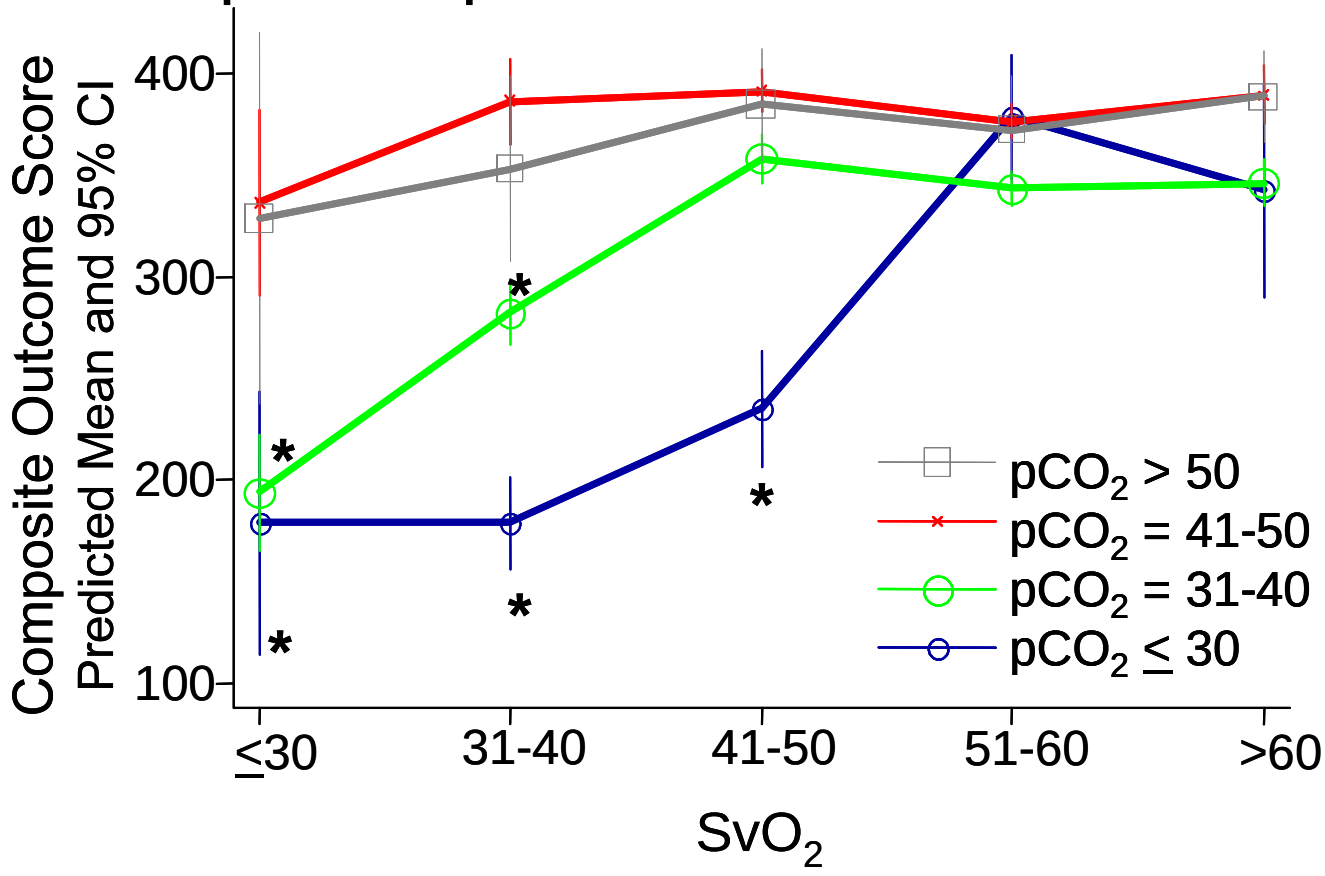
# DHCA-Postop hemodynamics interaction

- postop hemodynamics may be even more important after prolonged DHCA



# postop CO2 also modifies outcome

- CO2 ameliorates DHCA-related low outcome
- CO2 improves post-DHCA 'no-reflow'



# post-CPB temperature strongly determines $rSO_2$

| Parameter | Pre-CPB Coefficient | P-value | Post-CPB Coefficient | P-value | pre/post difference |
|---|---|---|---|---|---|
| MABP (mmHg) | 0.14±0.05 | 0.002 | 0.43±0.07 | <0.001 | <0.001 |
| $PaCO_2$ (torr) | 0.38±0.03 | <0.001 | 0.80±0.05 | <0.001 | <0.001 |
| Temp (deg C) | -0.7±0.11 | <0.001 | -4.65±0.32 | <0.001 | <0.001 |
| Isoflurane (%) | -21.5±1.33 | <0.001 | 26.1±1.5 | <0.001 | <0.001 |
| Hematocrit (%) | -1.39±0.03 | <0.001 | 1.14±0.07 | <0.001 | <0.001 |
| $SaO_2$ (%) | 0.19±0.05 | <0.001 | 0.19±0.05 | <0.001 | -- |
| CVP (mmHg) | -0.14±0.06 | 0.026 | -0.14±0.06 | 0.026 | -- |
| constant | 106.5±8.3 | <0.001 | 106.5±8.3 | <0.001 | -- |

Coefficents ± SD in a multiple linear model for cerebral rSO2

# who should we cool?

- prolonged DHCA
- prolonged hypoperfusion
  - comatose patient
  - low voltage EEG
- embolic stroke
- ischemic stroke
- cerebral oxygenation critically impaired

- patients with many neurons in the 'zone of incremental risk'

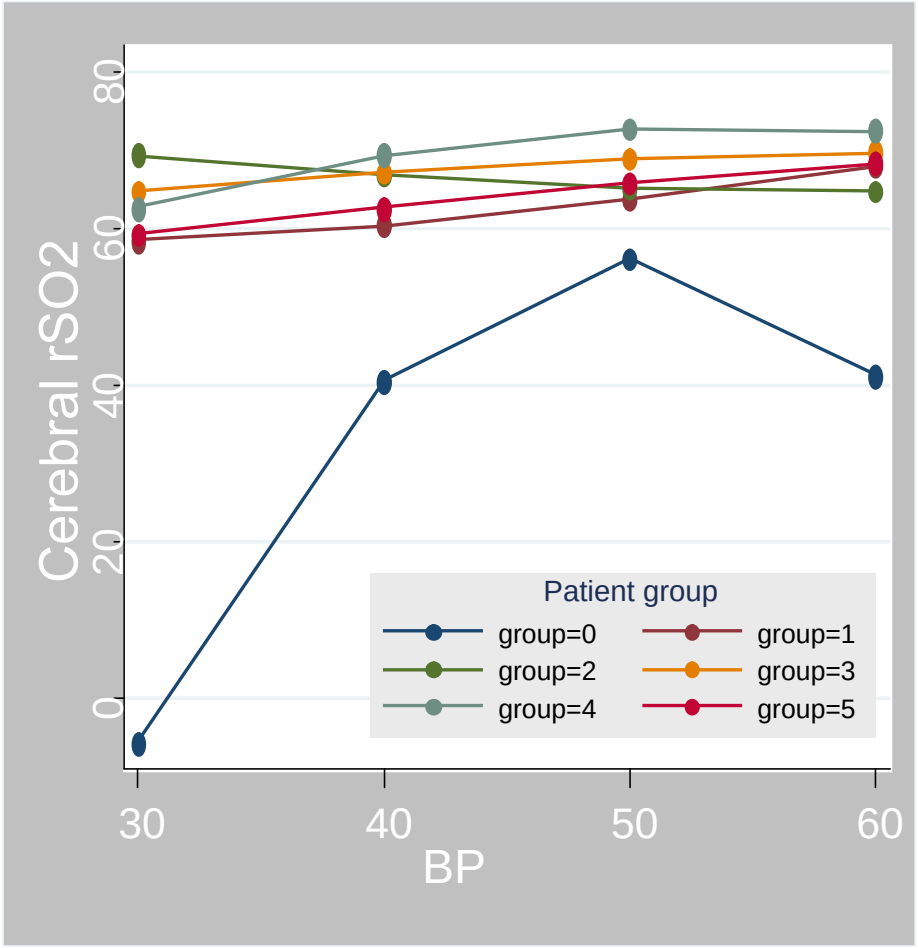
# questions about cooling

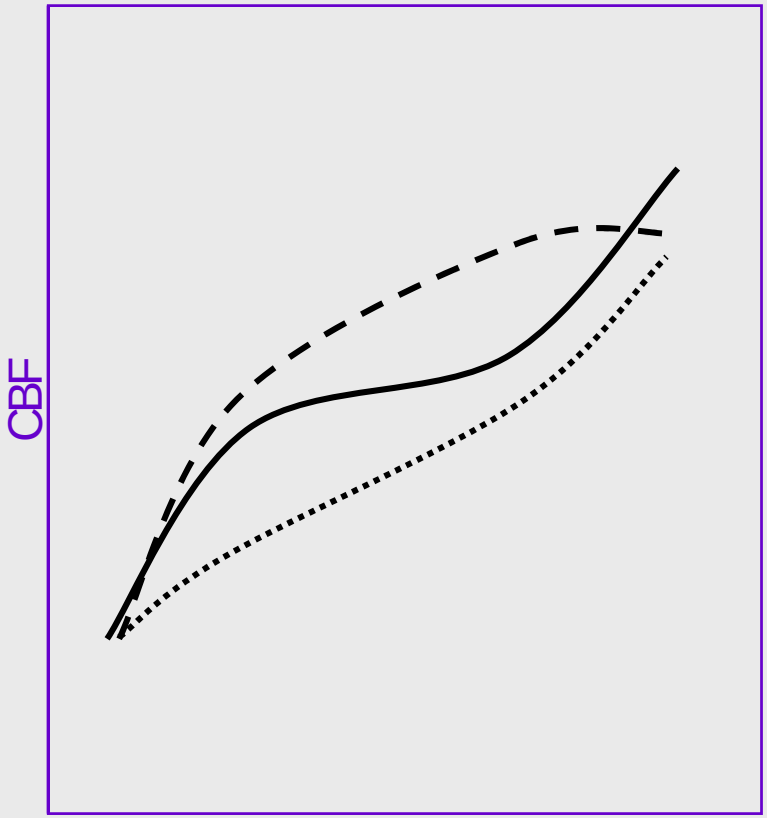
- how low
- how long
- starting when

- use of physiologic endpoints
  - detect effect and adverse effect
  - optimize therapy-patient interaction
  - monitor the organ of interest
  - individualizes treatment

# CBF is not predictably 'autoregulated'

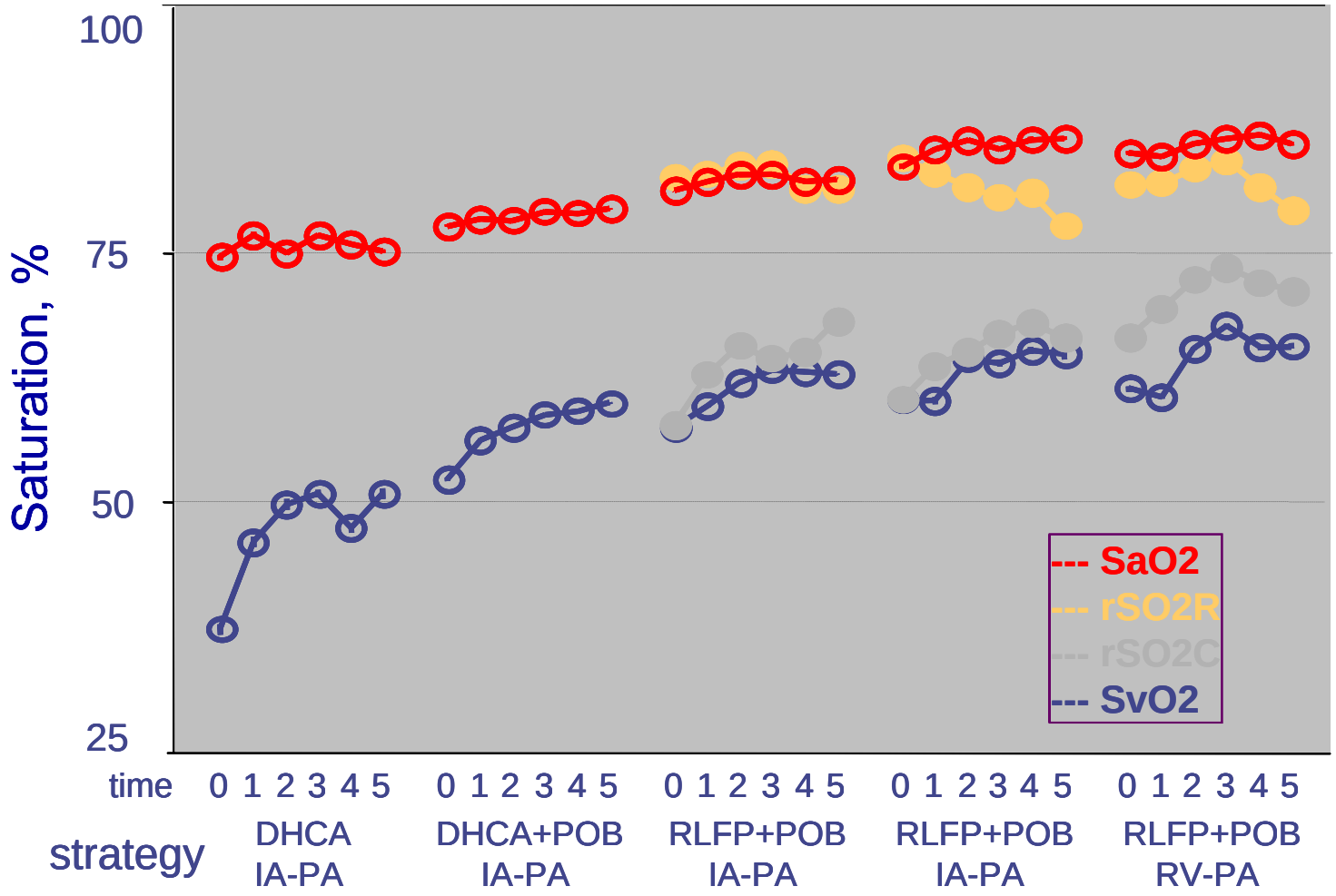
- Autoregulation curves – in reality



# NIRS and programmatic improvement

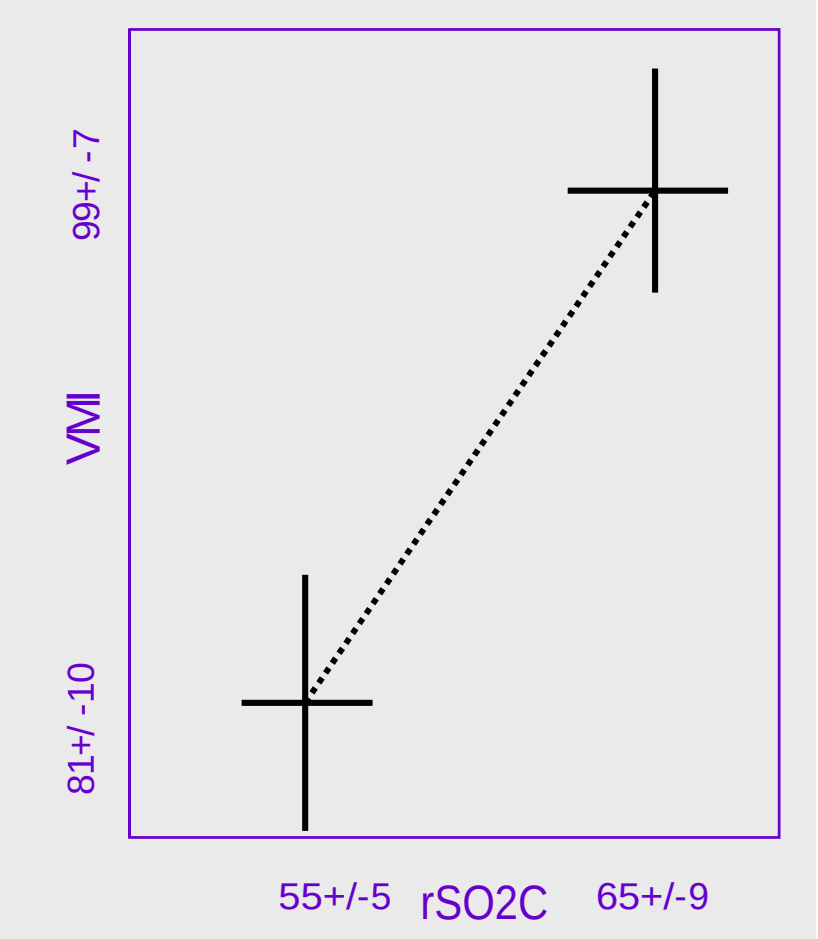
- SaO2, SvO2, rSO2C, rSO2R vs. perioperative strategy



# Program examination - patient outcomes

- Examination of determinants of CBF vs cerebral saturation revealed improvement in postoperative cerebral hemodynamics after patient group 0

- This increase in cerebral rSO2 is associated with an increase in VMI performance 4 years later



# Postoperative cerebral rSO2

- Not completely predicted by usual measured parameters
- Often below critical value of 45-50%
- Improved over time in our program
- Is related to CNS outcomes

# Monitoring summary

- BP – how much is enough?
- Temp – avoid hyperthermia
- Glucose – avoid hypoglycemia
- SpO2 – yes
- EtCO2 / pCO2 – use to modify regional resistance
- TCD – intraoperatively maybe
- EEG – for prolonged neuromuscular blockade of low rSO2
- NIRS allows non-invasive detection and goal-directed treatment of cerebral oxygenation
  - patient-specific treatment
  - Directly related to injury mechanism and outcome