Cerebral oximetry versus no cerebral oximetry
- in extremely preterm infants
- during the first 3 days

Gorm Greisen

and the SafeBoosC-consortium

SafeBoosC III

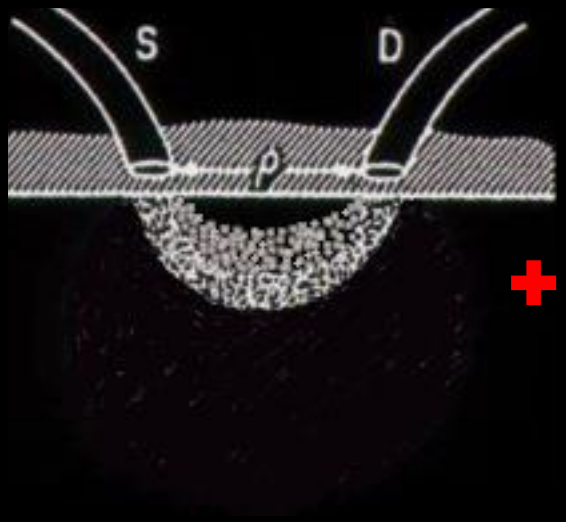
SAFEGUARDING THE BRAIN OF OUR SMALLEST CHILDREN

Faculty Disclosure

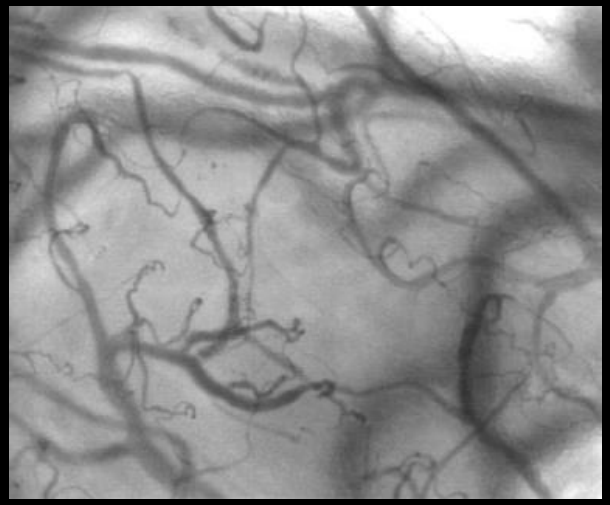
	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria / Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Cerebral oxymeter industry	x		x					

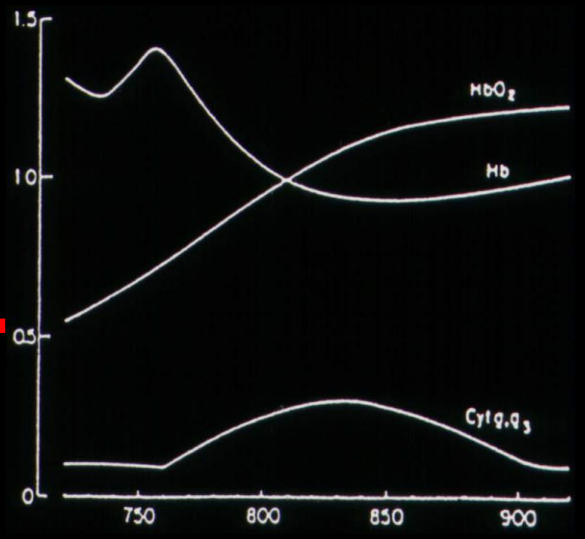
photonics

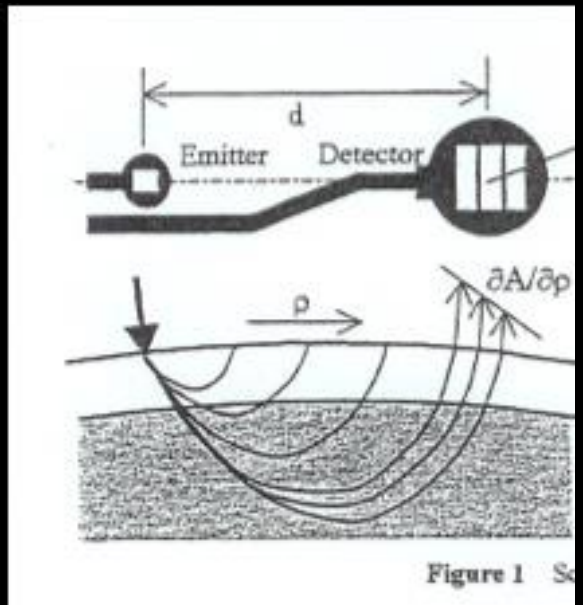


Vascular bed



Haemoglobin spectra

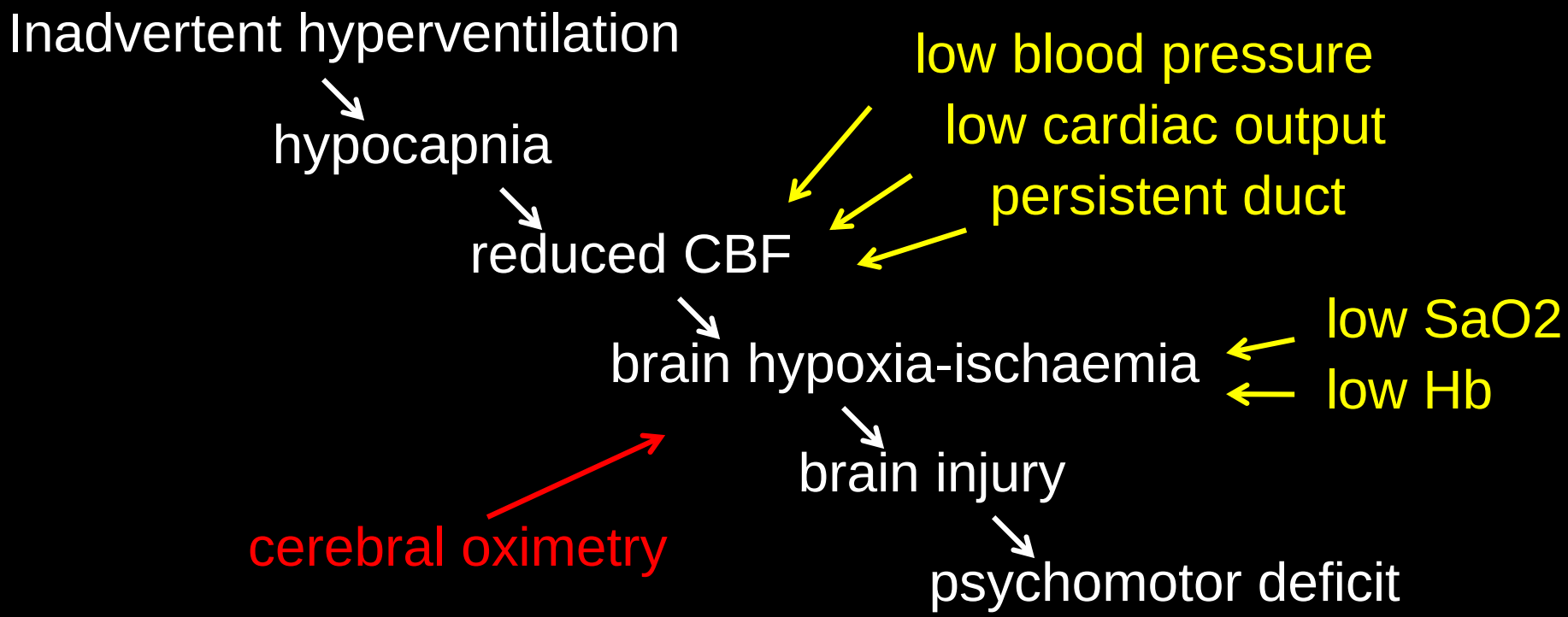




➔ StO2 (0-100%)

venous weighted =
'tissue' oxygenation

➔


Inadvertent hyperventilation
hypocapnia
reduced CBF
low blood pressure
low cardiac output
persistent duct
low SaO2
low Hb
brain hypoxia-ischaemia
brain injury
psychomotor deficit
cerebral oximetry

So should cerebral oximetry used clinically

- in extremely preterm infants?
- during the first days after birth?

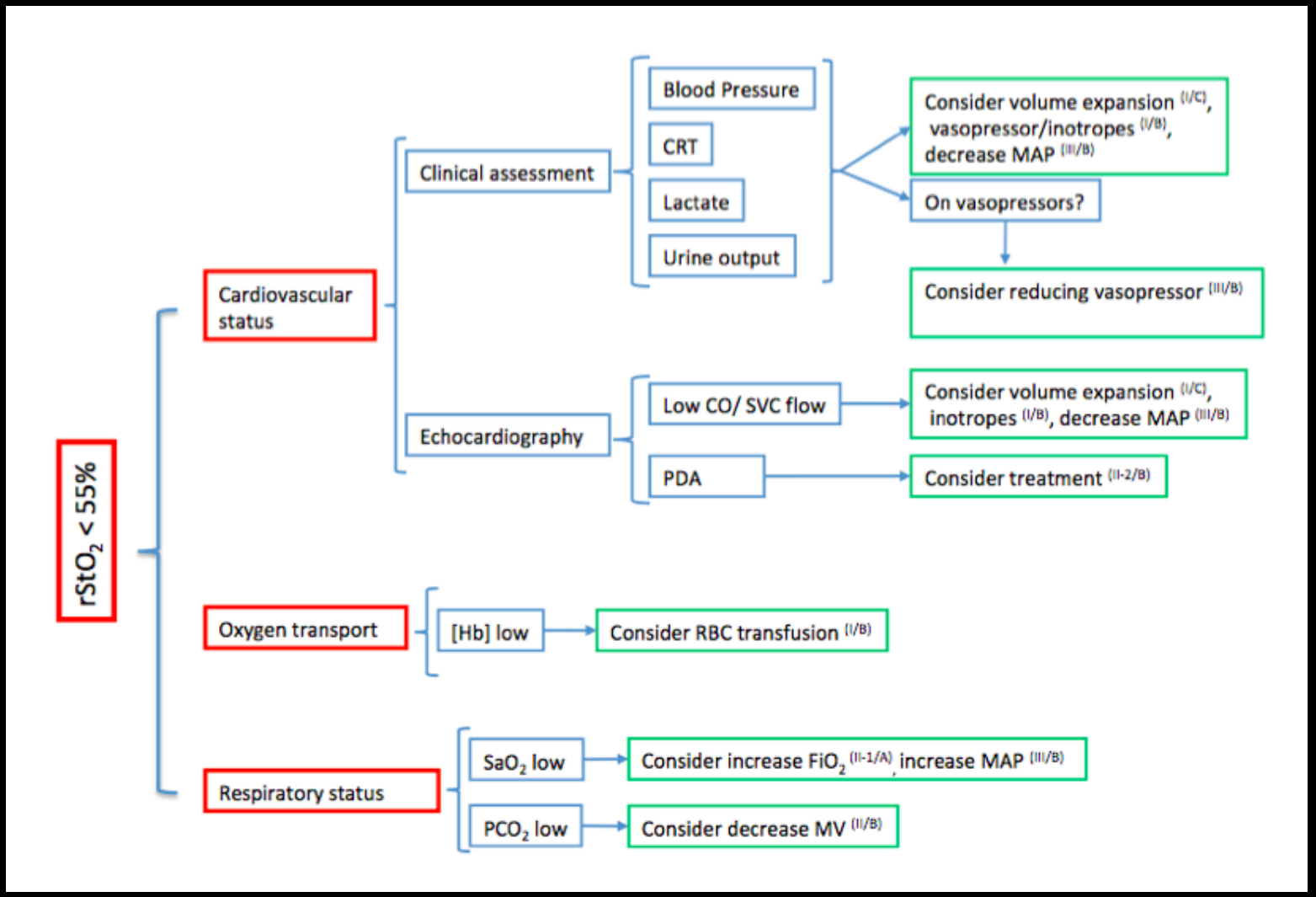
2009: ’we do not want to disturb unless necessary’

Examine the clinical benefits and harms of cerebral oximetry

The SafeBoosC consortium (www.safeboosc.eu)

(Copenhagen, Utrecht, Madrid, Zurich, Leuven, Lyon, Milan, Cork, Cambridge, Tubbingen, Graz, Groningen)

Physiology-based guideline to minimize cerebral hypoxia



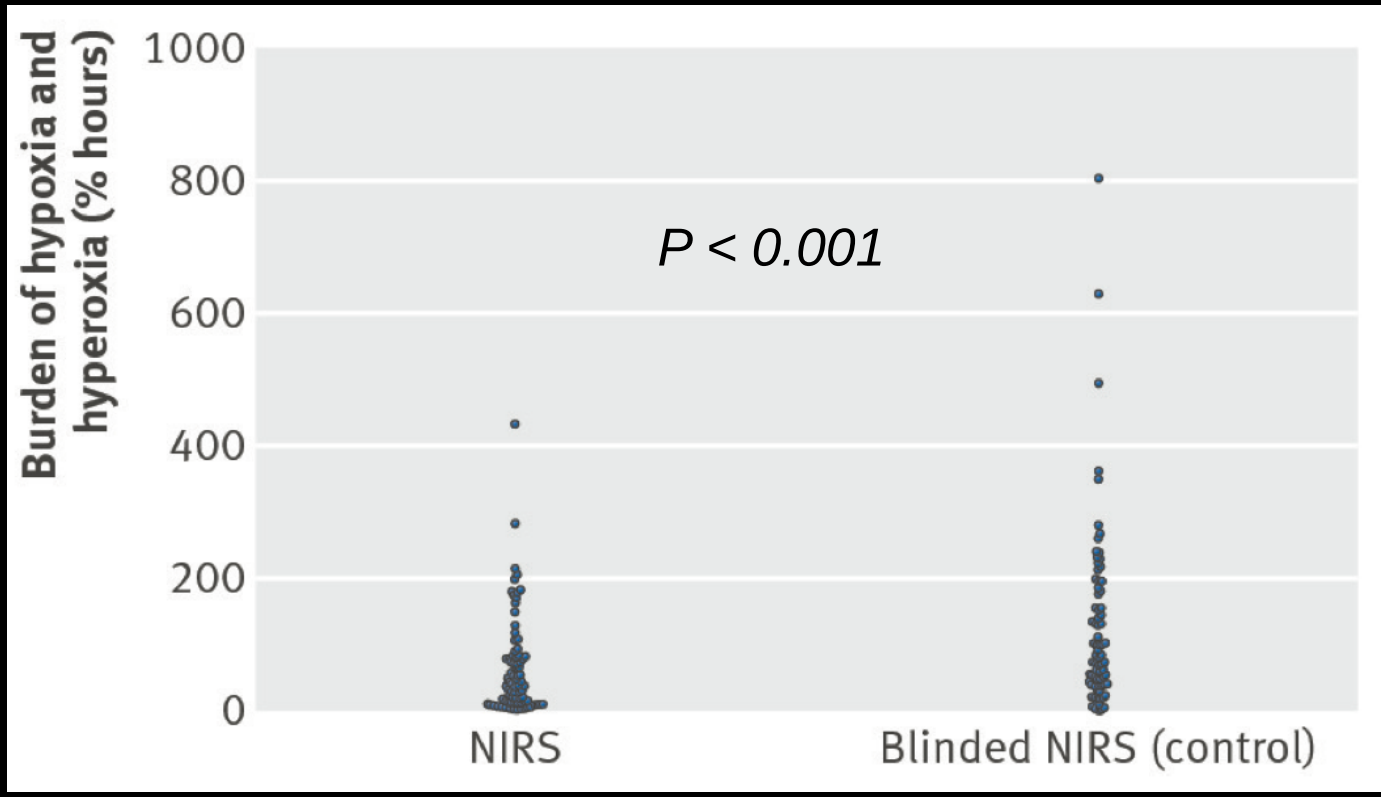
(Pellicer et al Neonatology 2013)

https://www.trialeducation.info/

Burden of cerebral hypoxia can be reduced by 50%

SafeBoosC-II

Infants enrolled in:
Lyon
Madrid
Copenhagen
Cork
Utrecht
Graz
Milan
Cambridge



N = 86
GA = 26.6 wks

N = 80
GA = 26.8 wks

(Sørensen et al. BMJ. 2015)

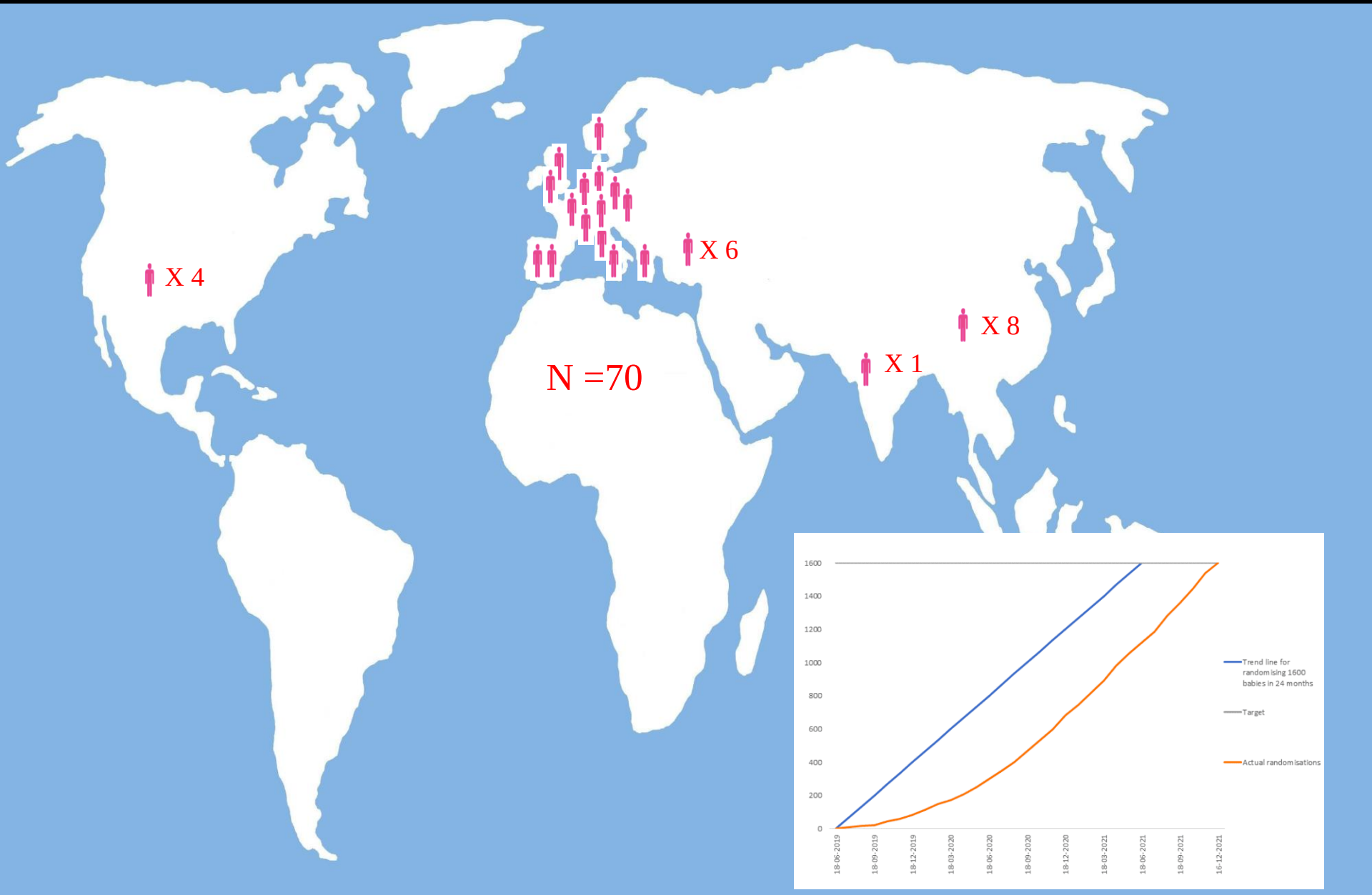
SafeBoosC-III - a pragmatic trial with a clinically relevant outcome

34% death or severe brain injury at 36 wks

Reduction to 26%

N = 800 +800

Using calibrated oximeters approved for clinical use


X 4
X 6
X 8
X 1
N =70
1600
1400
1200
1000
800
600
400
200
0
18-06-2019
18-09-2019
18-12-2019
18-03-2020
18-06-2020
18-09-2020
18-12-2020
18-03-2021
18-06-2021
18-09-2021
16-12-2021
Trend line for randomising 1600 babies in 24 months
Target
Actual randomisations

Primary outcome known for 98.6% of infants (1579 of 1601)

(embargo)	Cerebral oximetry	No Cerebral oximetry
Death and/or severe brain injury	272 (35.2%)	274 (34.0%)
Survived without severe brain injury	500	536

Relative risk = 1.03 [0.9 – 1.18]

European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

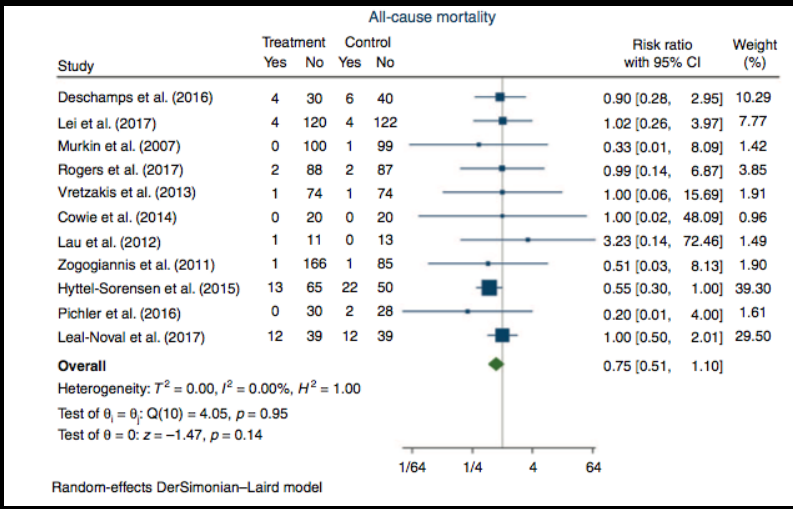
online febr 2022

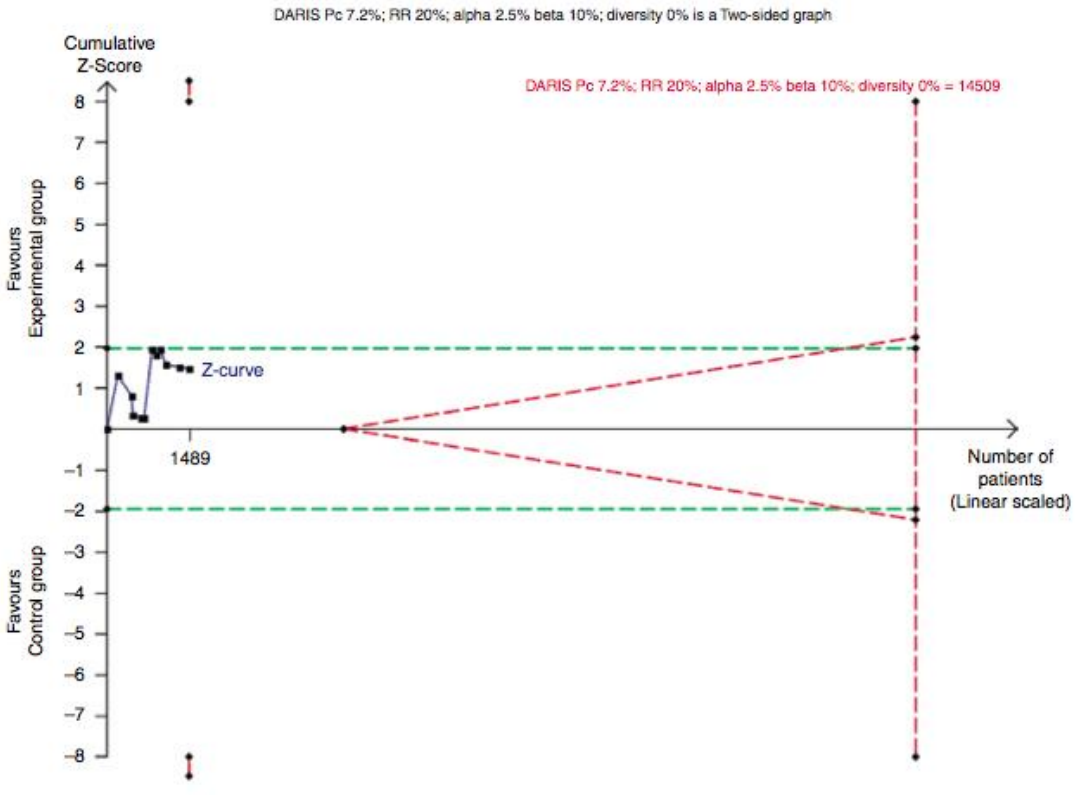
SYSTEMATIC REVIEW OPEN

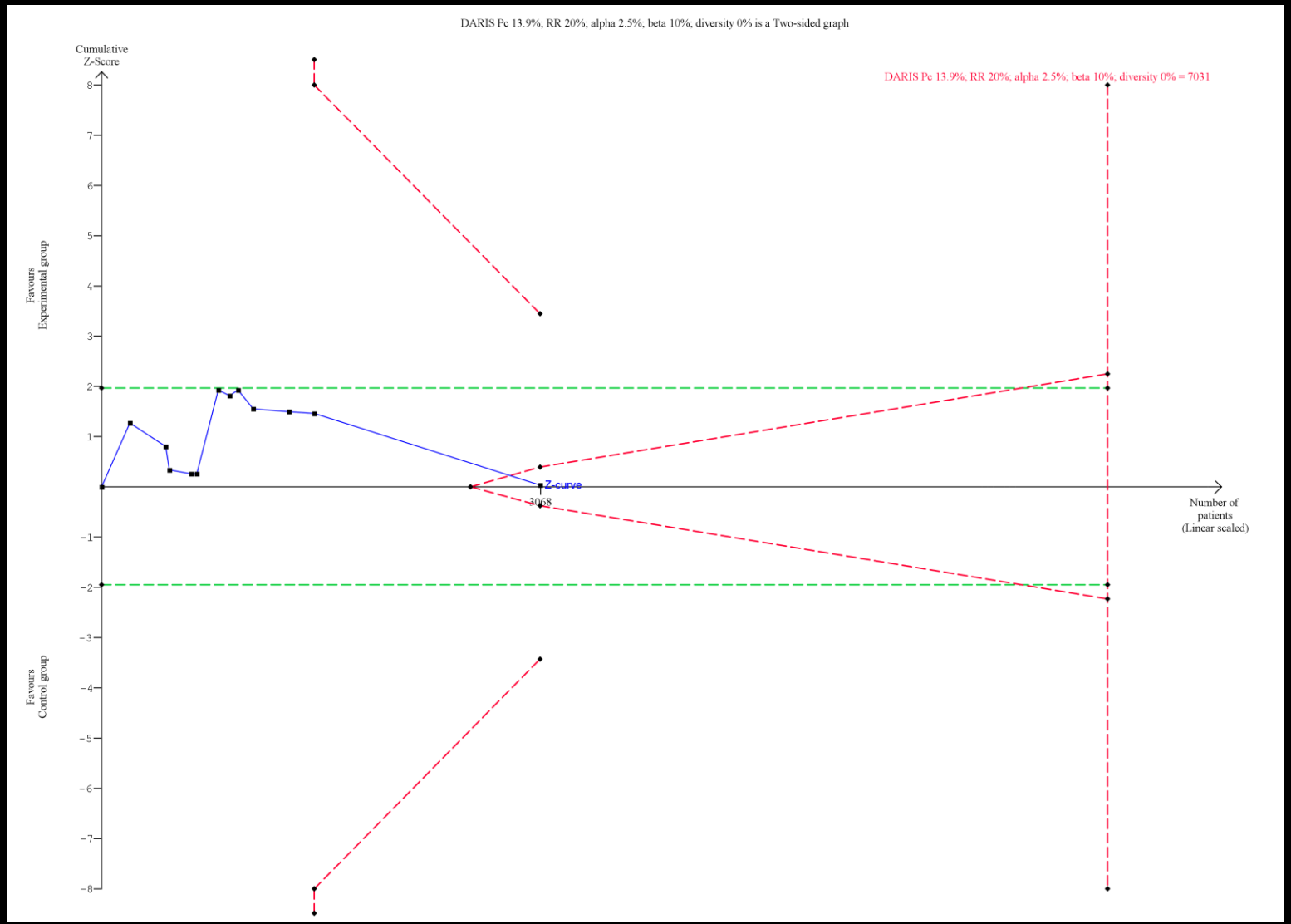
Check for updates

Cerebral near-infrared spectroscopy monitoring (NIRS) in children and adults: a systematic review with meta-analysis

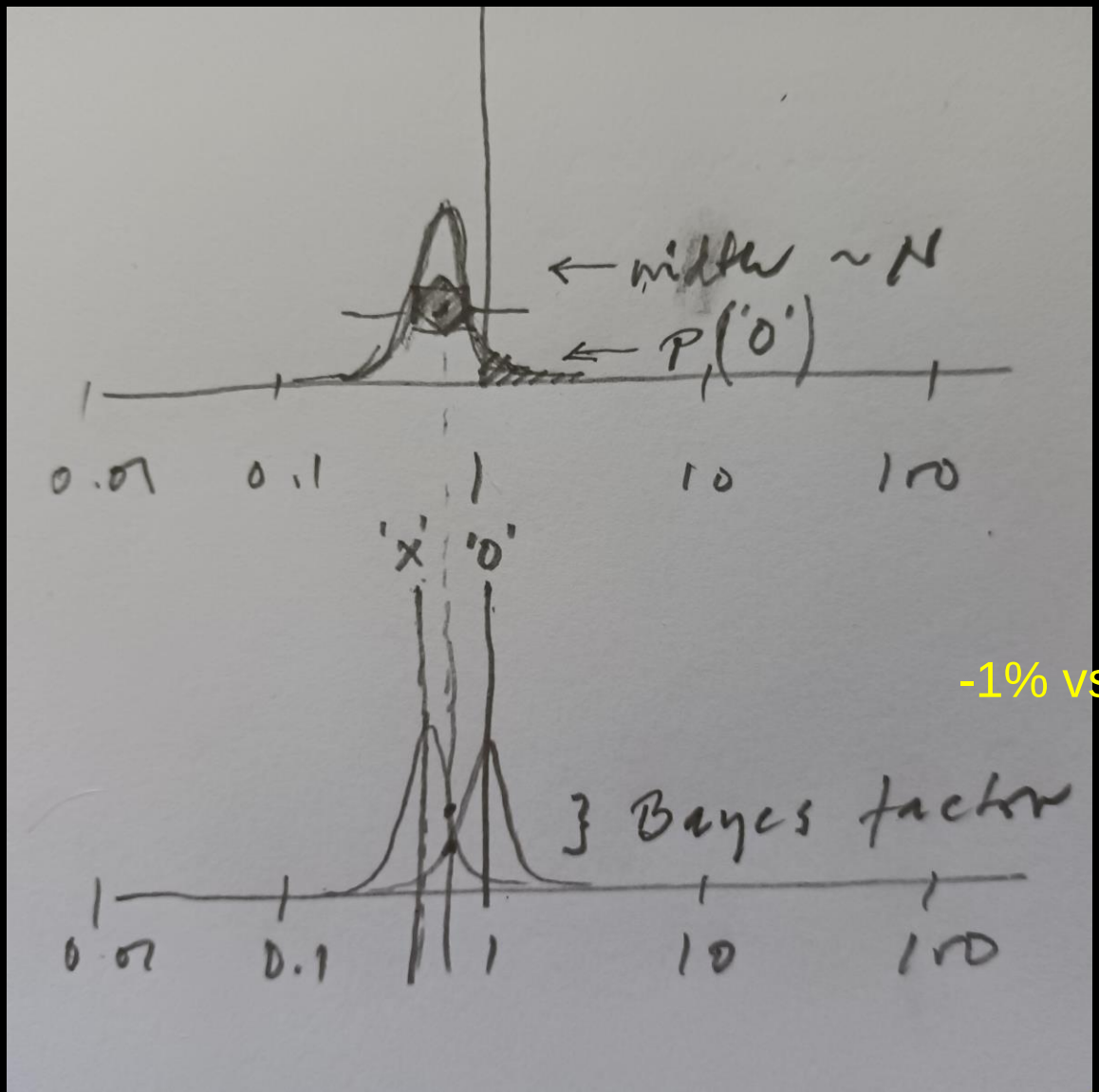
Mathias Lühr Hansen[1]✉, Simon Hyttel-Sørensen[2], Janus Christian Jakobsen[3,4], Christian Gluud[3,4], Elisabeth M. W. Kooi[5], Jonathan Mintzer[6], Willem P. de Boode[7], Monica Fumagalli[8,9], Ana Alarcon[10], Thomas Alderliesten[11], Gorm Greisen[1] and on behalf of the European Society for Paediatric Research Special Interest Group 'NearInfraRed Spectroscopy' (NIRS)*





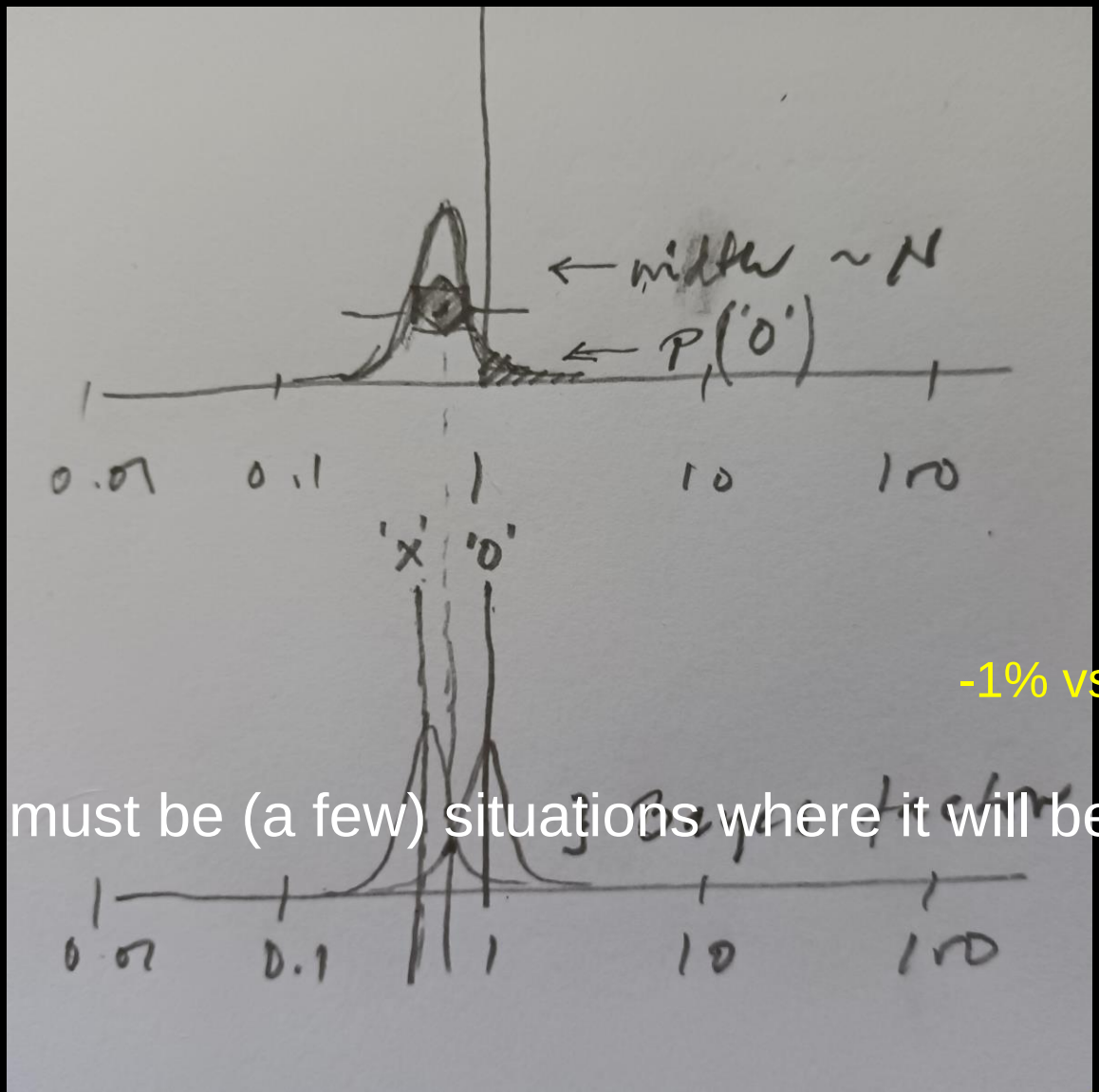

DARIS Pc 13.9%; RR 20%; alpha 2.5%; beta 10%; diversity 0% is a Two-sided graph
Cumulative Z-Score
DARIS Pc 13.9%; RR 20%; alpha 2.5%; beta 10%; diversity 0% = 7031
Favours Experimental group
Favours Control group
Z-curve
3068
Number of patients (Linear scaled)

The play of chance: could the effect be -1% risk?



-1% vs ‘null’ = 0,91

The play of chance: could the effect be -1% risk?



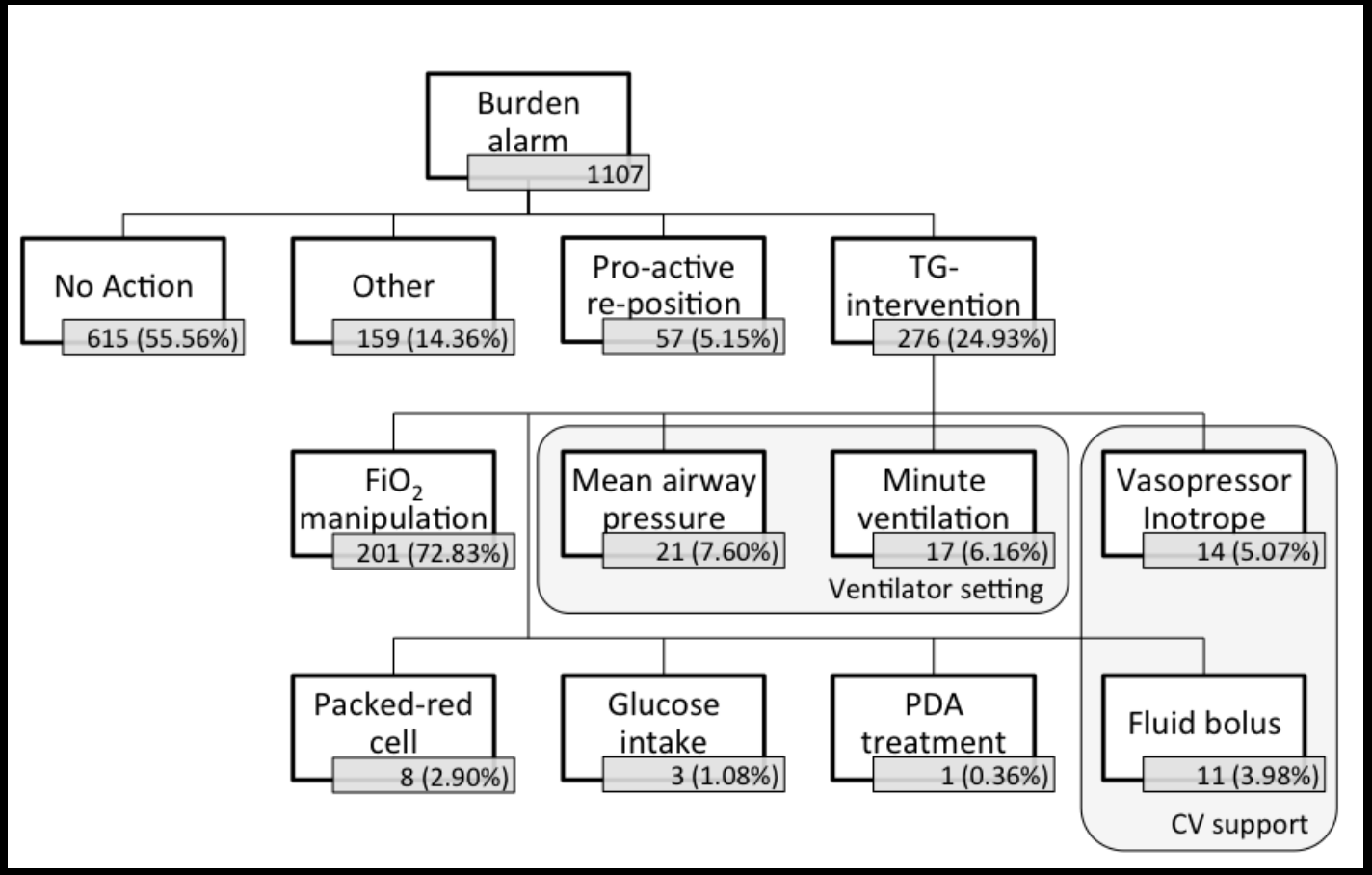
-1% vs ‘null’ = 0,91

& there must be (a few) situations where it will be helpful !?

But why did it not work?
(as well as we thought it would)

- Staff did not react to alarms
- Staff did not know what to do
- Oxymeters are not very precise
- Accuracy is uncertain
- The hypoxic threshold was wrong
- Brain hypoxia is not so important

SafeBoosC-II: Alarms and interventions in the NIRS-open group (N=67)



(Riera et al. Arch Dis Child 2015)

SafeBoosC III Traini ...

Home Dashboard Events My courses This course

> My courses > SafeBoosC III

Moodle-platform

About this page

In the grid below you'll find information from the Trial organising committee, trial protocol and data collection forms. Clicking on the appropriate image will take you to the e-learning to be completed before participating in the trial. You can find a forum where you can ask questions of other trial investigators, nurses and the trial organising committee.

https://www.trialeducation.info/

The modules

Based on your clinical position, we recommend that you complete the following modules:

1) Nurses: introduction, NIRS

2) Neonatologists/residents: introduction, NIRS, treatment guideline, cUS

3) Radiologists: cUS

4) Principal investigators: introduction, NIRS, treatment guideline, cUS, Good Clinical Practice

- **Introduction** ☑
- **NIRS** ☑
- **Treatment Guideline** ☑
- **cUS** ☑
- **Good Clinical Practice** ☑
- **Introduction Chinese 简介模块** ☐

Feasibility of the web-based training and certification of clinical staff for the randomised clinical trial SafeBoosC-III

MI Rasmussen, ML Hansen, G Greisen on behalf of the SafeBoosC consortium

Department of Neonatology, Rigshospitalet, Denmark

SafeBoosC III

SAFEGUARDING THE BRAIN OF OUR SMALLEST CHILDREN

Aim

SafeBoosC-III is a pragmatic, multinational randomised clinical trial evaluating the effects of treatment guided by cerebral oximetry monitoring in extremely preterm infants. In total, 1601 infants were randomised across 70 centres in Asia, Europe, and North America. To heighten the quality of trial data and patient care, we developed a multilingual web-based training program, to train trial staff members and test their competencies, efficiently and consistently.

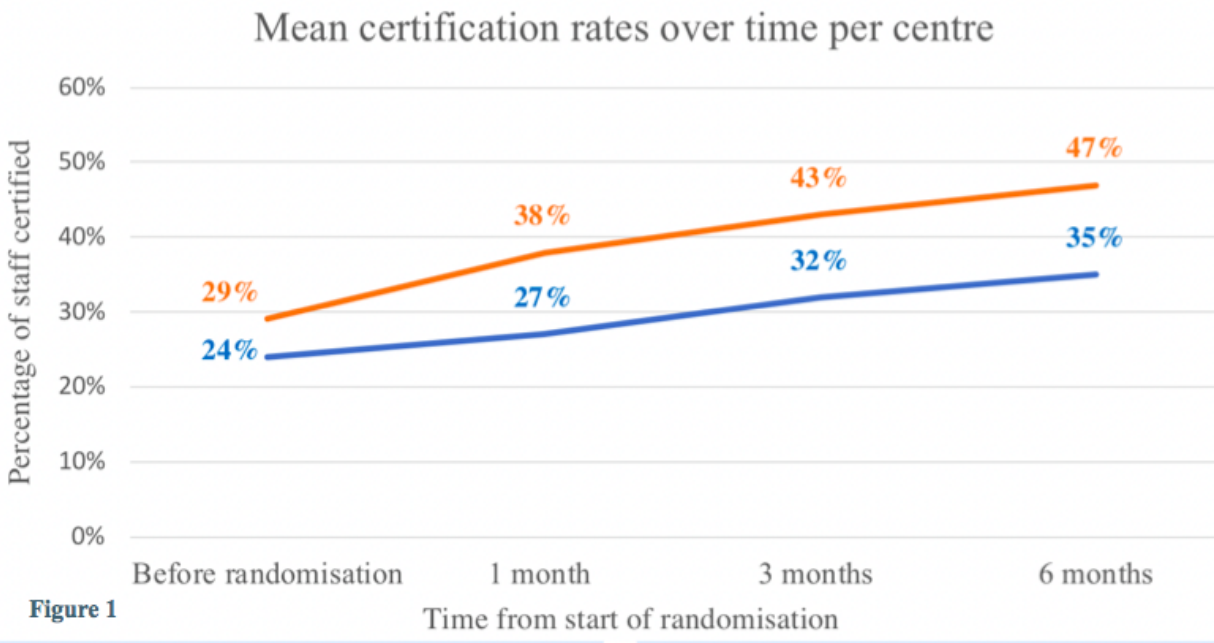
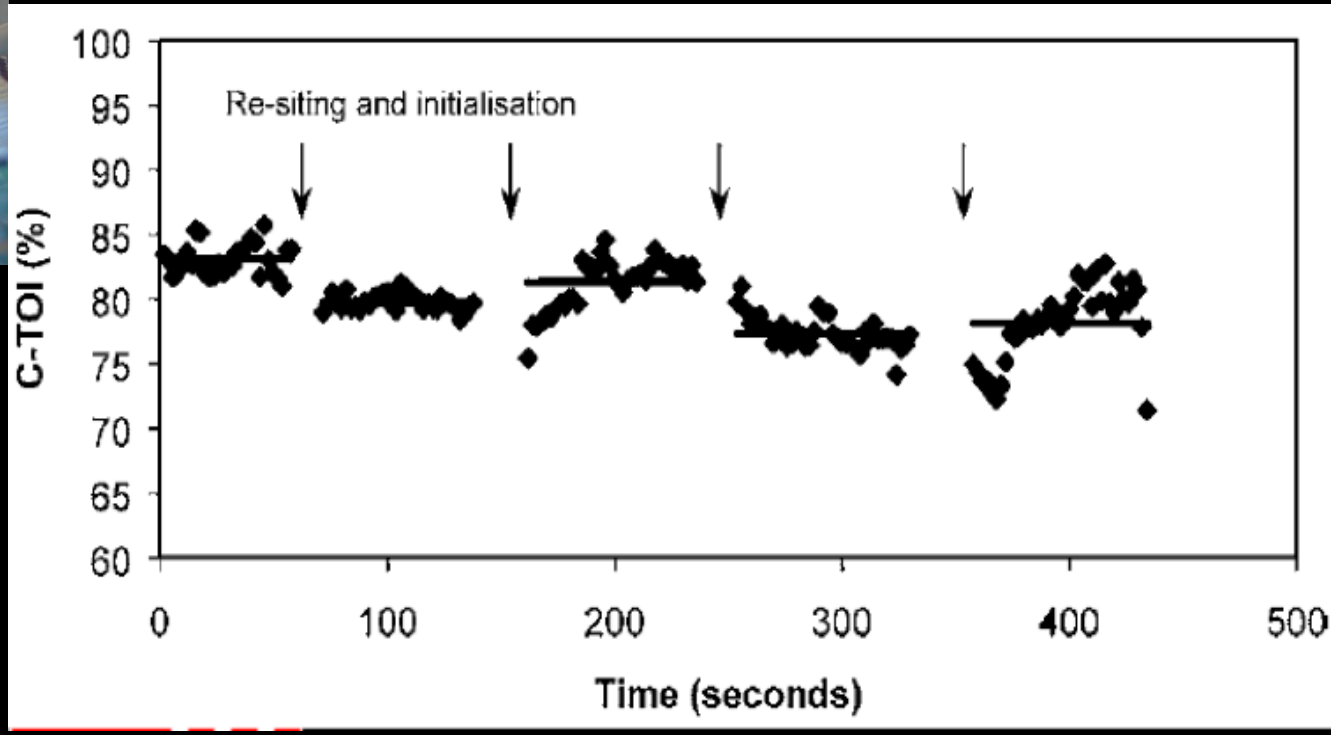


Figure 1

Precision?

Precision is poor

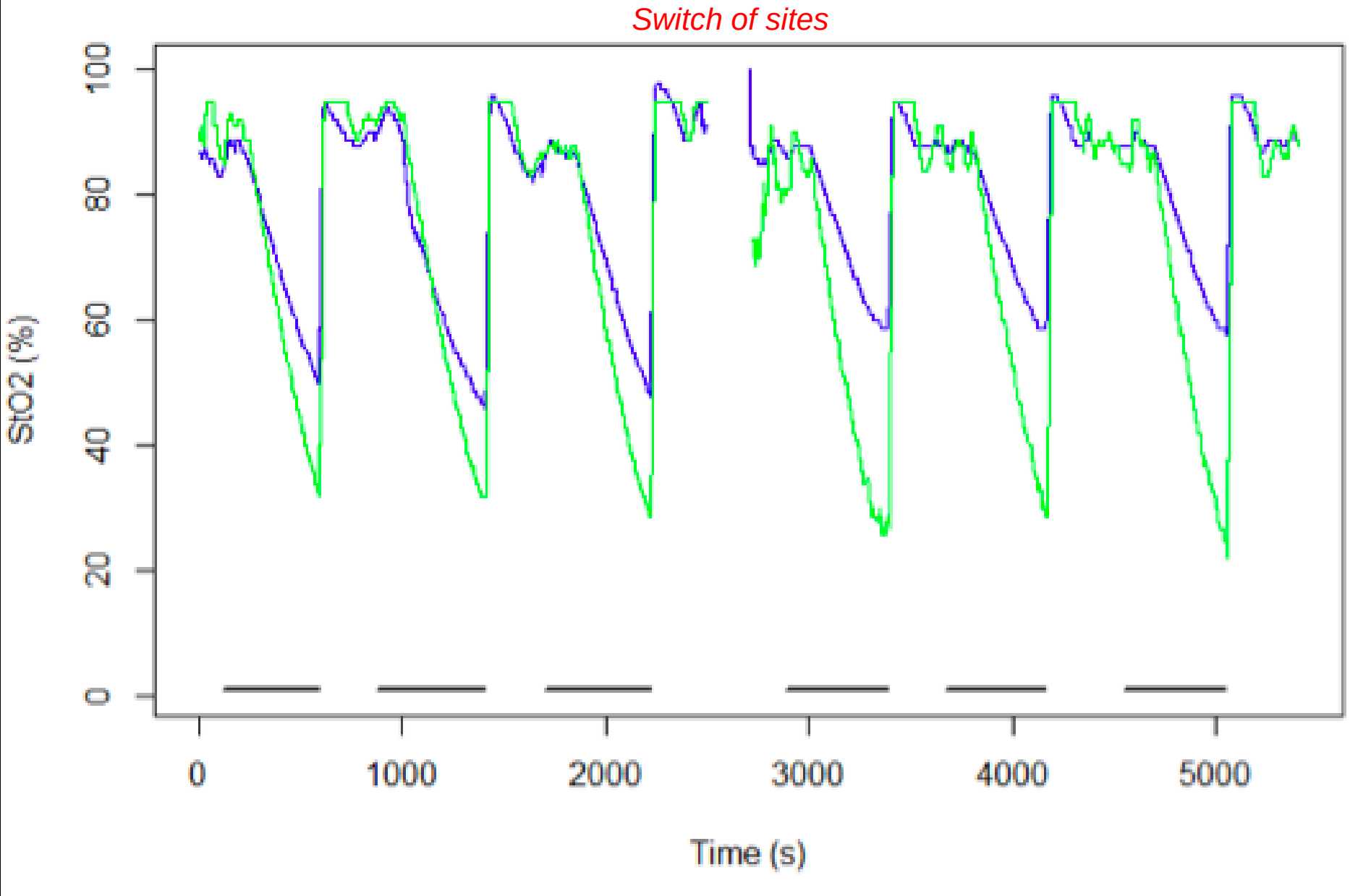


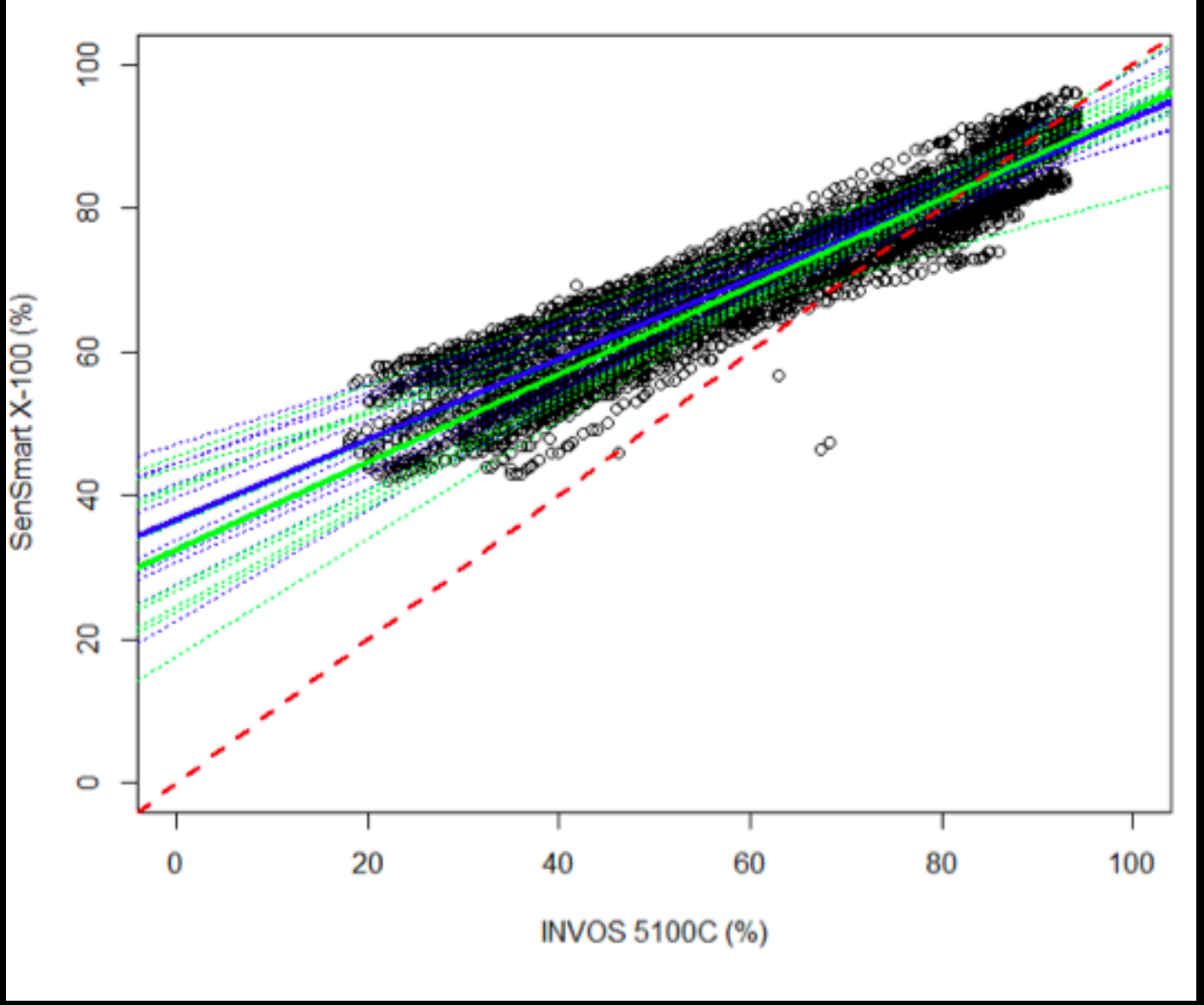
Repeatability (precision) = 5.2%

(Sorensen J Biomed Opt 2006)

Accuracy?

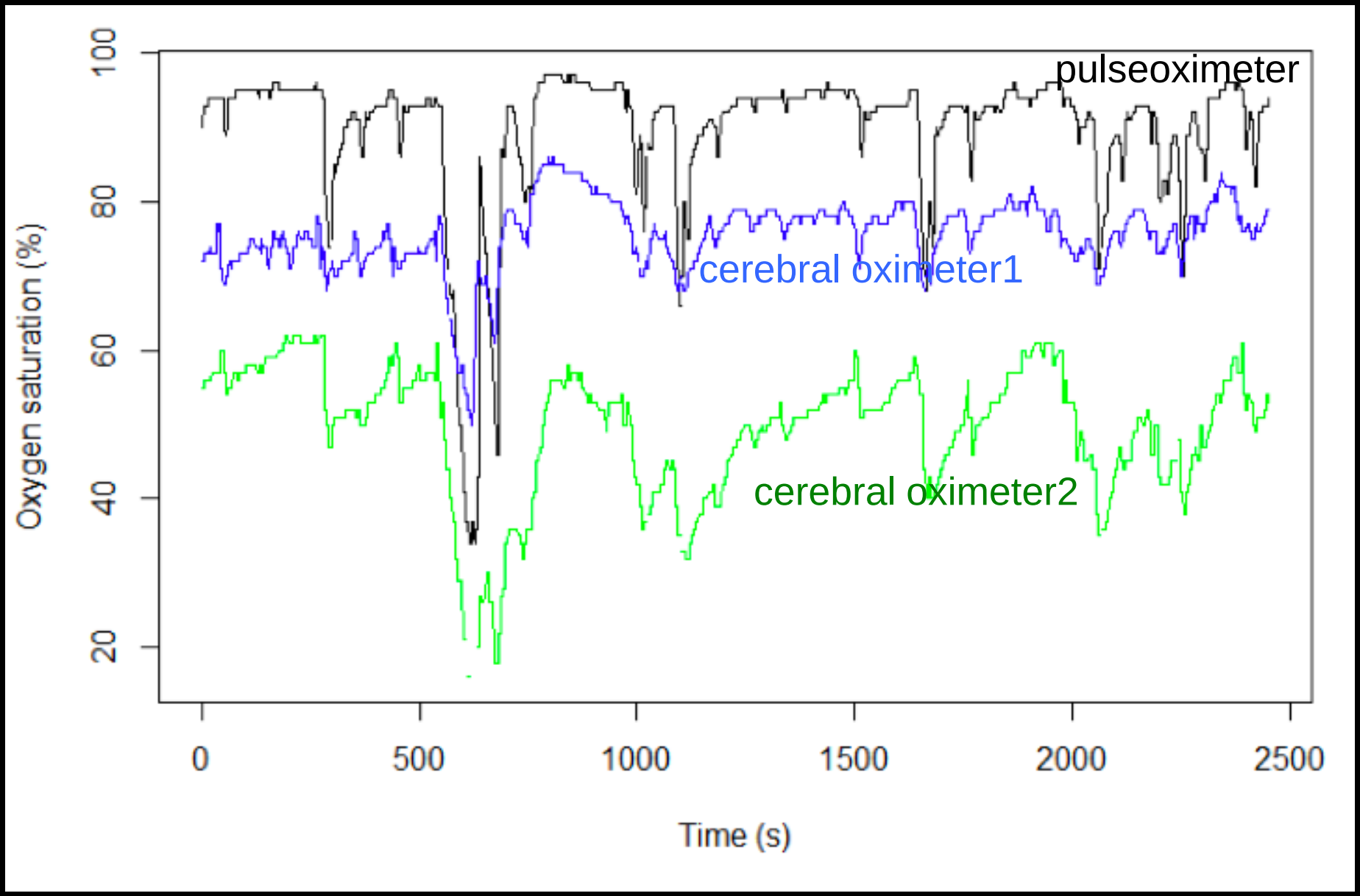
Arterial cuff occlusion and two oximeters on the forearm in healthy adults



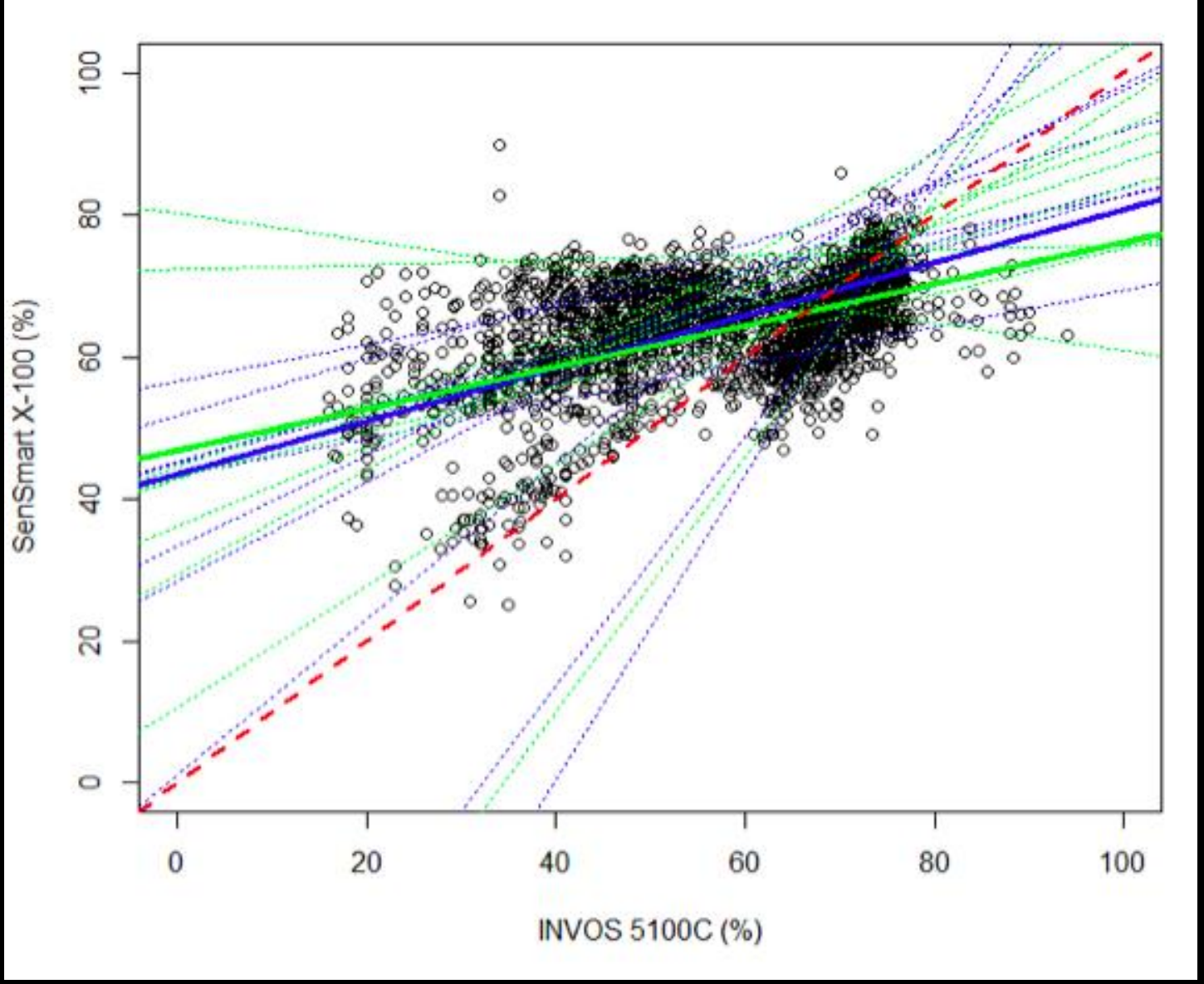


$StO_{2,SenSmart\ X\text{-}100}$ =
0.59 (CI 0.58 to 0.59)* $StO_{2,INVOS\ 5100C}$
+ 34.4% (CI 34.0 to 34.8%) (r^2 of 0.95)

SpO2 and StO2 (two commercial oximeters) in apnea/desaturation

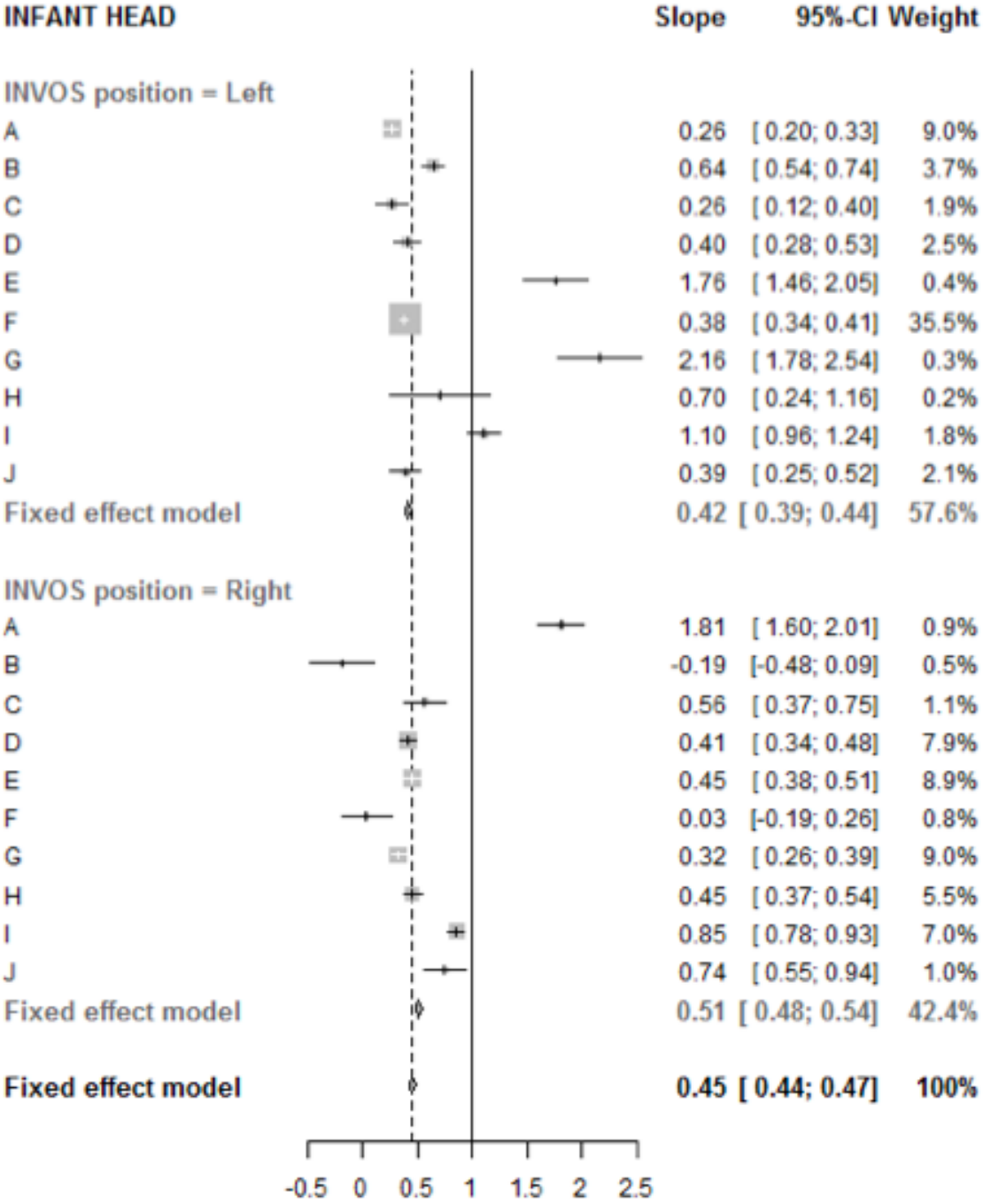


(Andresen et al. Ped Res 2019)



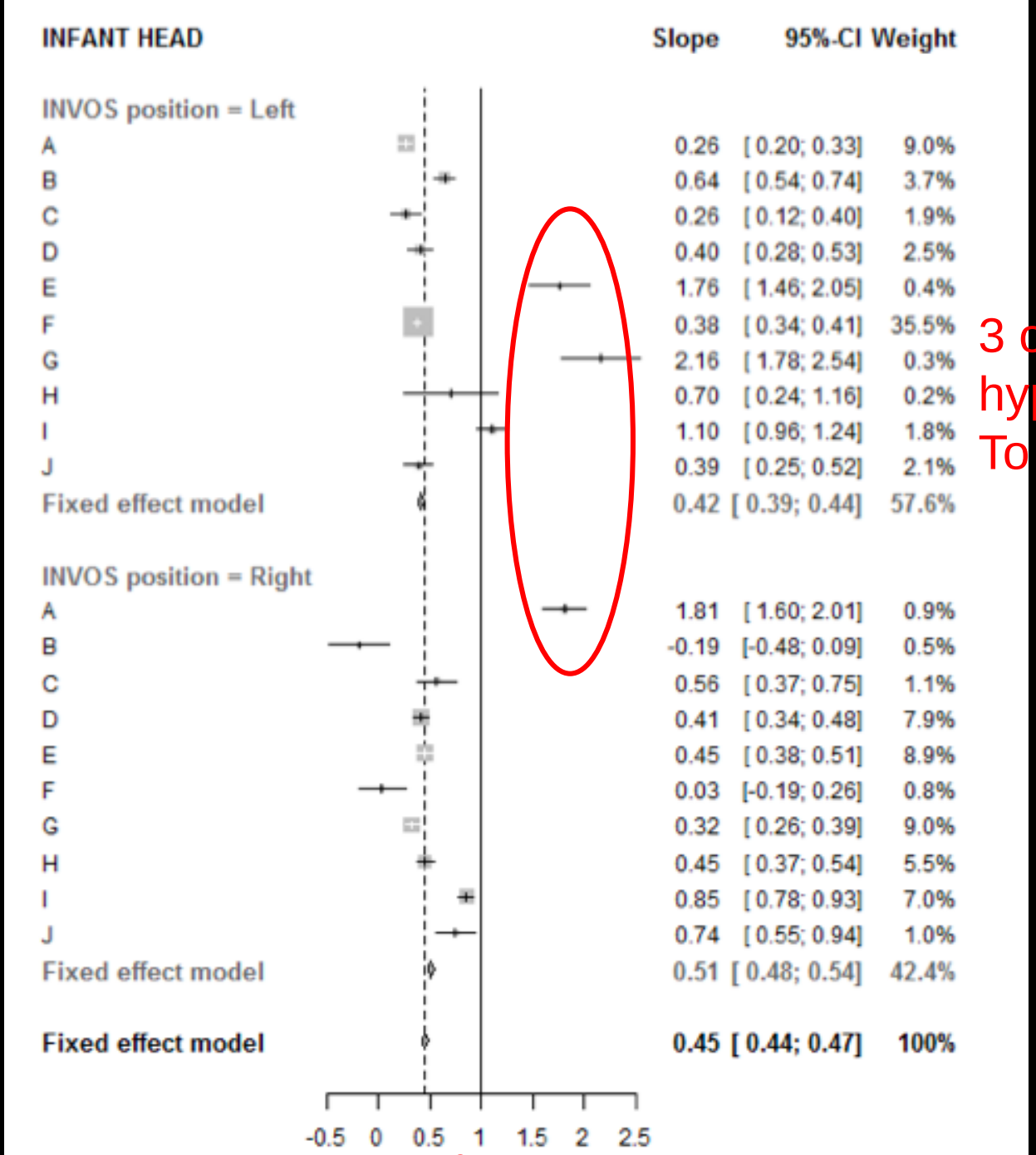
$StO_{2,SenSmart\ X\text{-}100}$ =
0.34 (CI 0.31 to 0.37)* $StO_{2,INVOS\ 5100C}$
+ 44.8% (CI 43.2 to 46.6%) (r^2 = 0.458).

Blood-lipid phantom
0.38
42.7



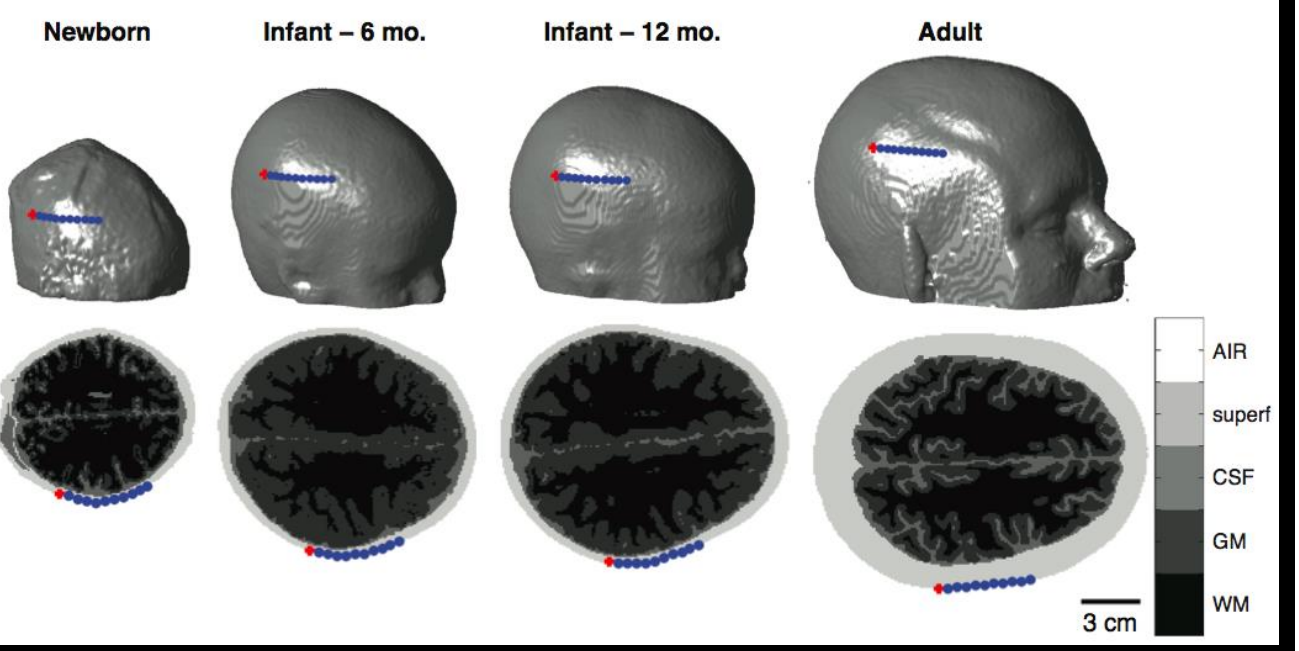
Heterogeneity: $I^2 = 97.0\%$ ($P < 0.0001$).

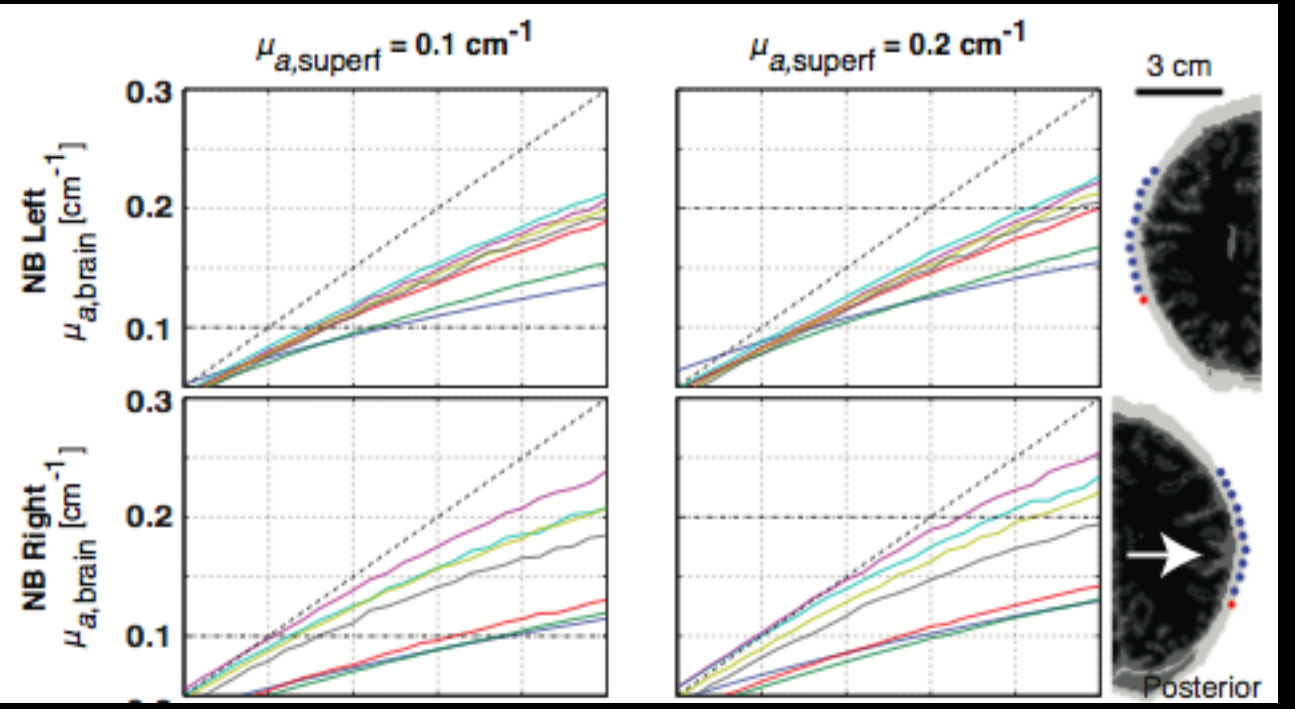
The third problem

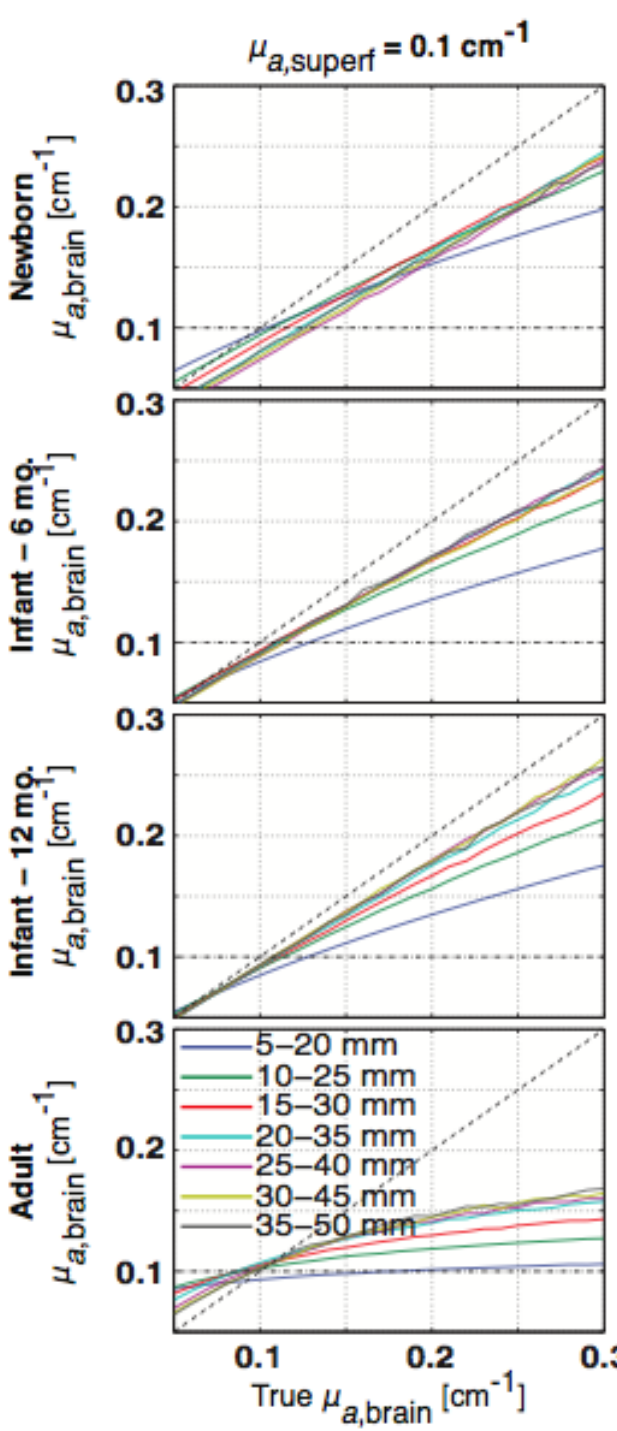


3 of 20 were hyporeactive To hypoxia

Heterogeneity: $I^2 = 97.0\%$ ($P < 0.0001$).



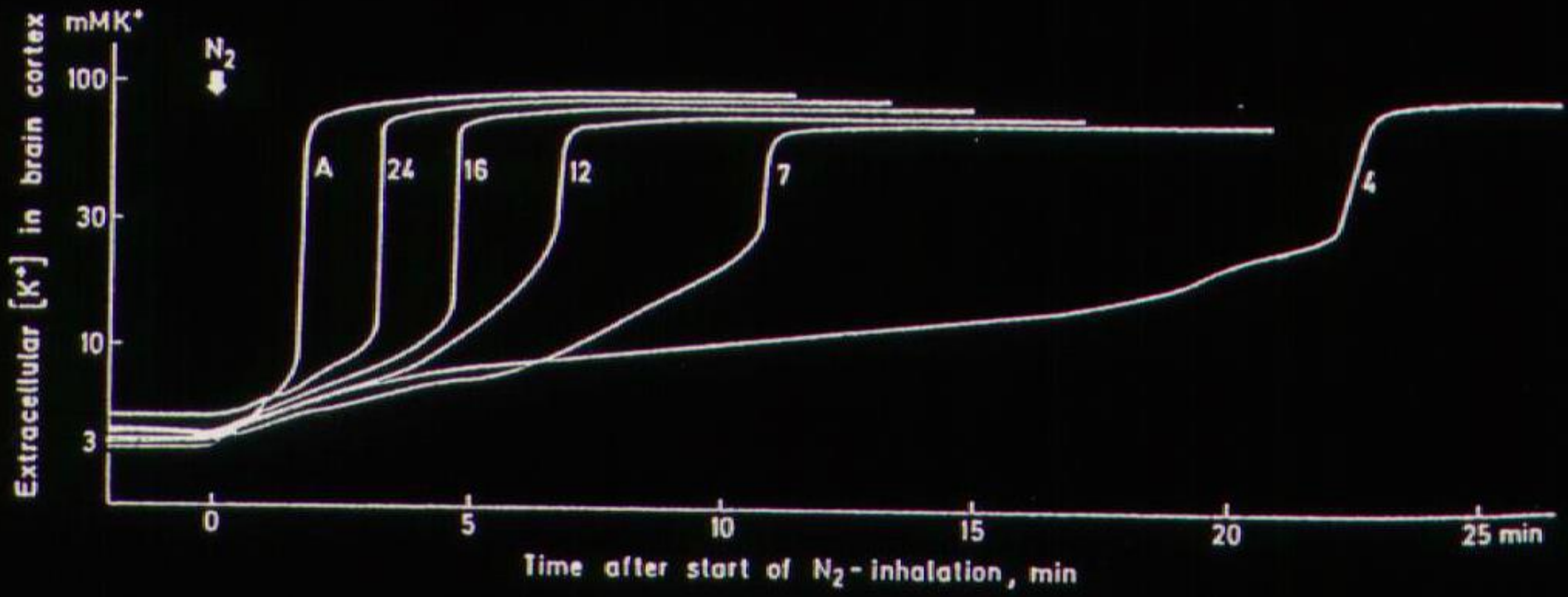




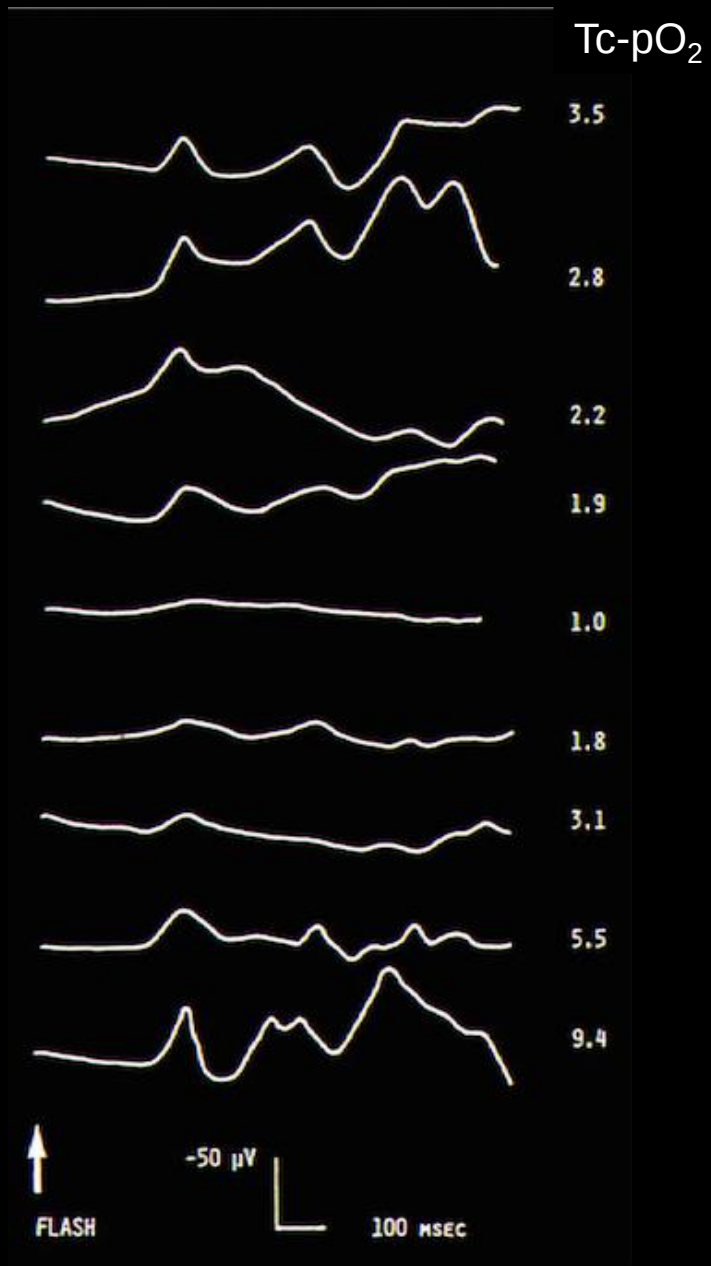
(Dehaes et al. J Biomed Opt 2011

The hypoxic threshold?

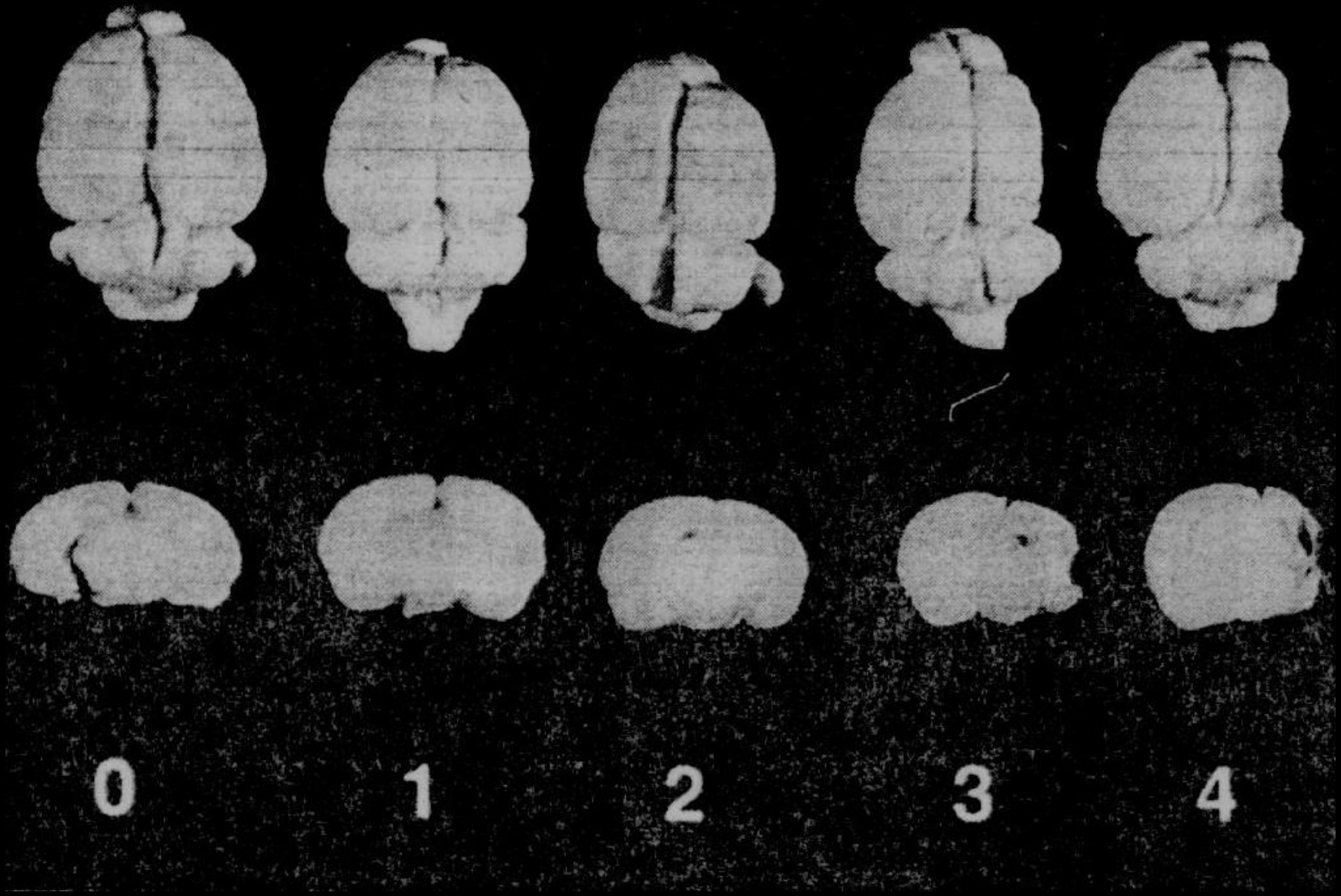
Rats in N_2 – with a K-electrode in the brain stem



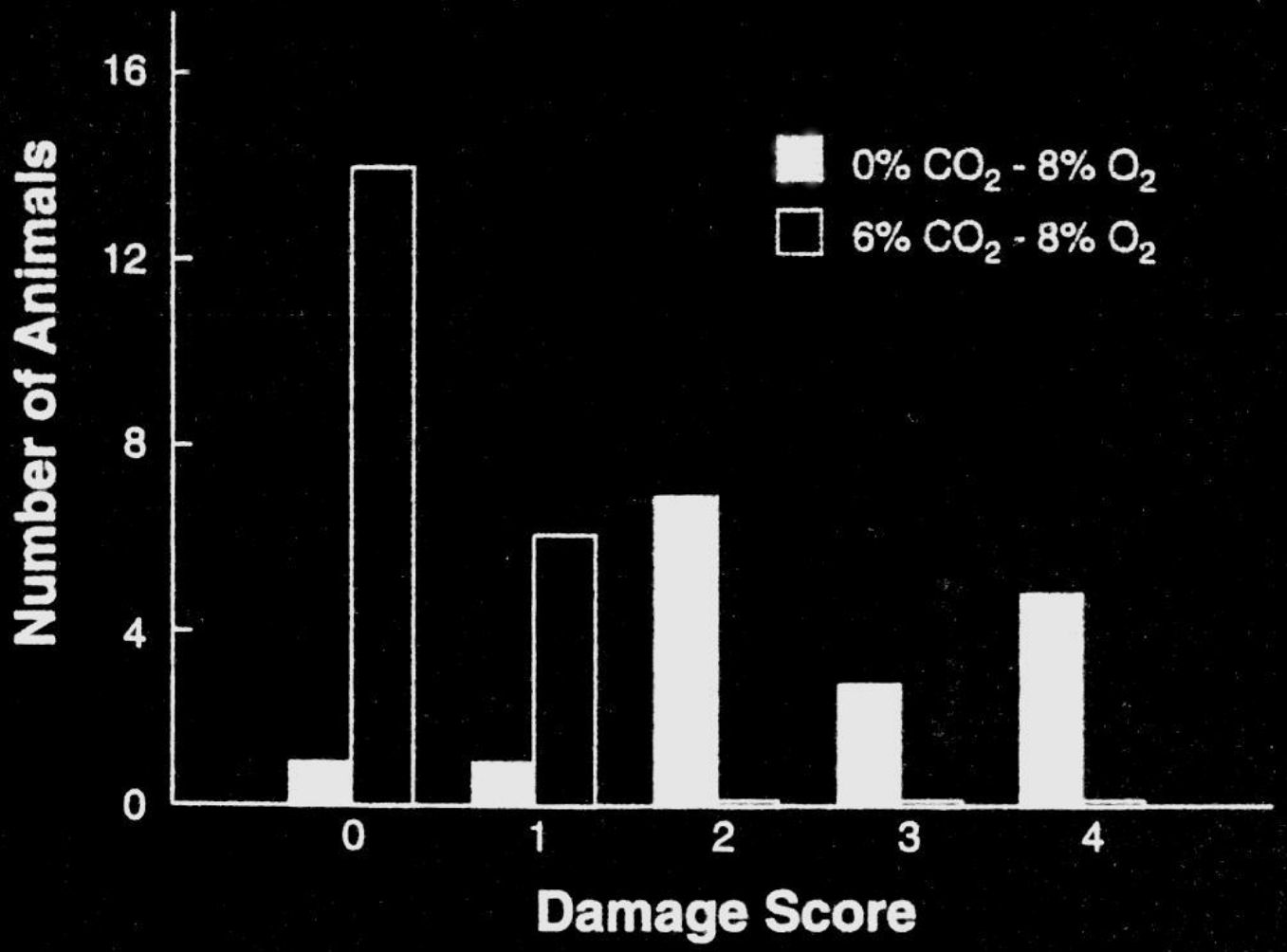
Single flash-VEP



Levene's model for hypoxic-ischaemic brain injury

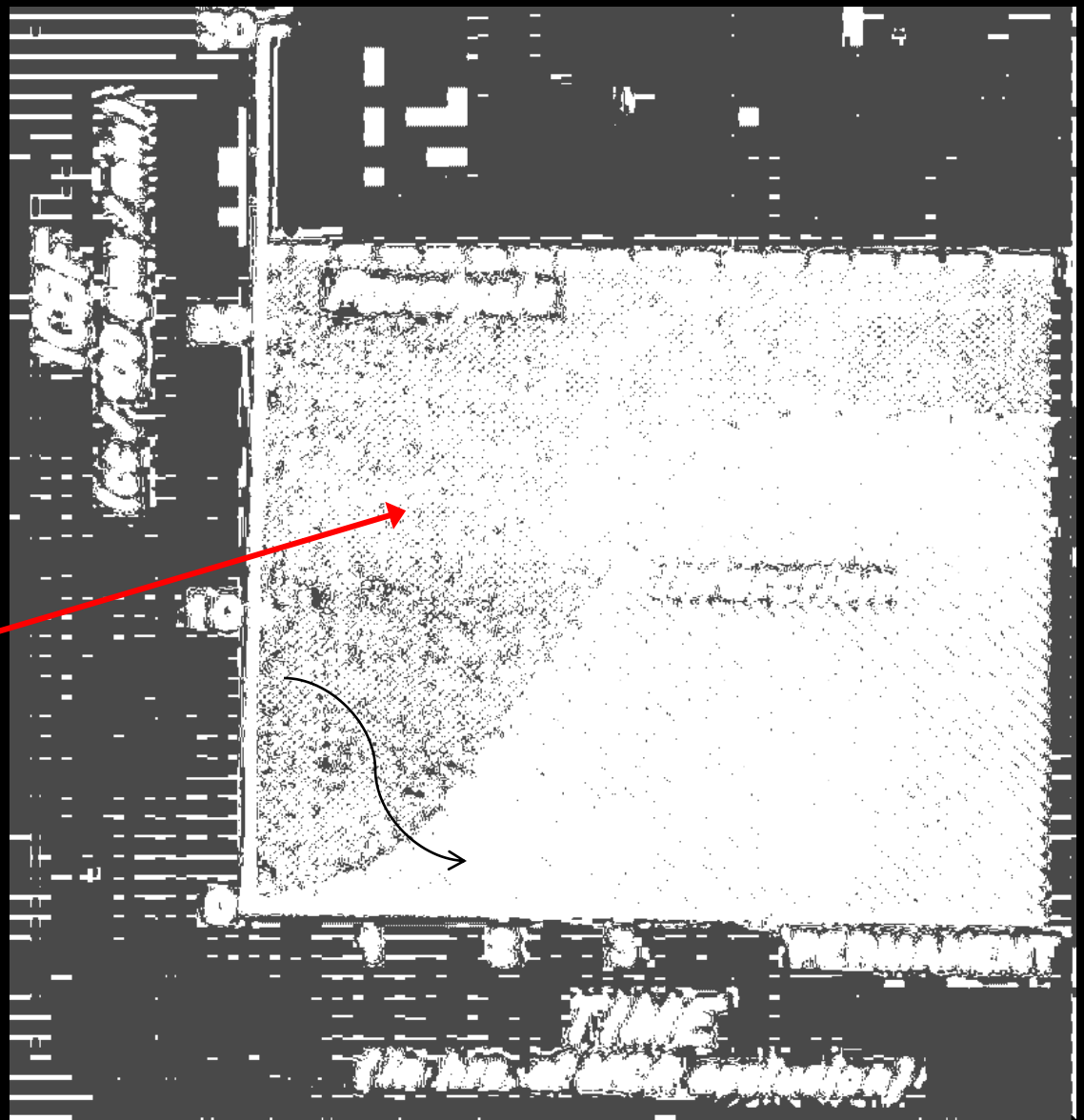


Adding CO2-gas to the hypoxic gas improves outcome



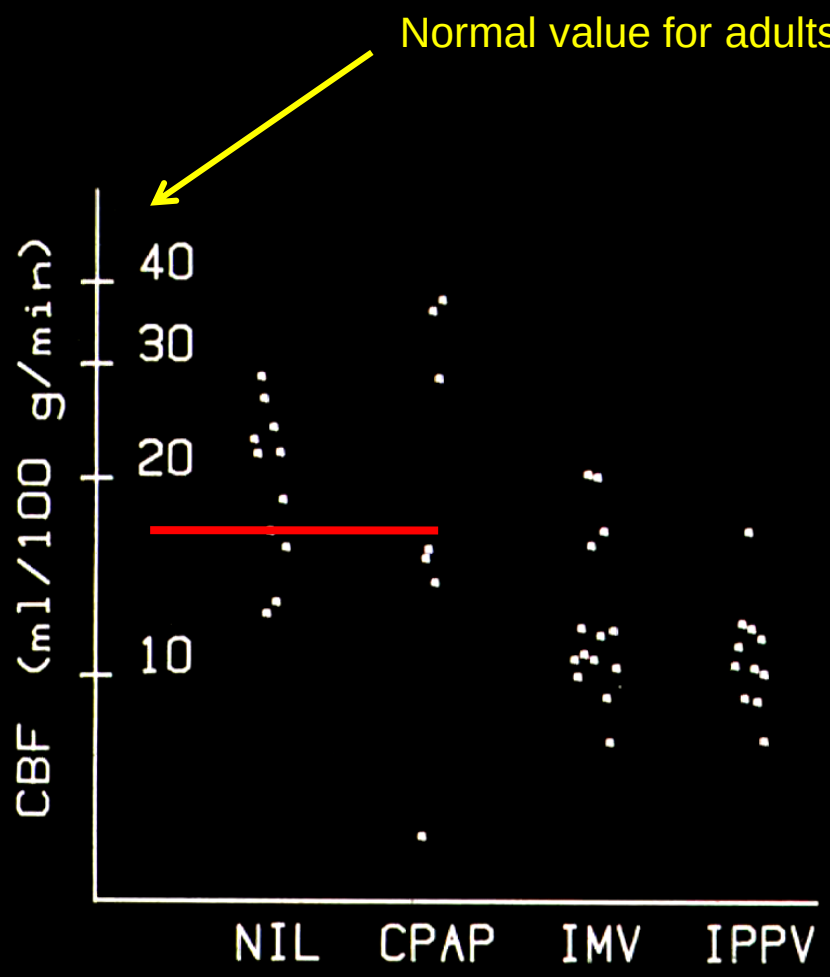
(Vannucci et al. Pediatr Res 1997)

Too low blood flow = ischeamia

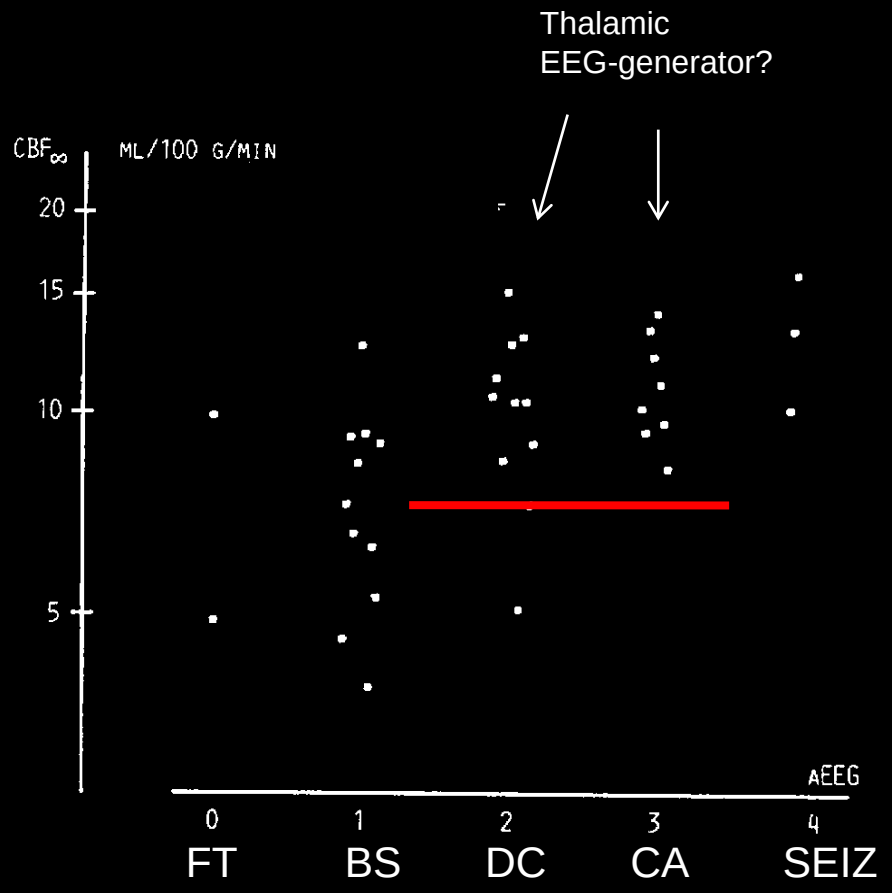


50% of normal

Warning zone



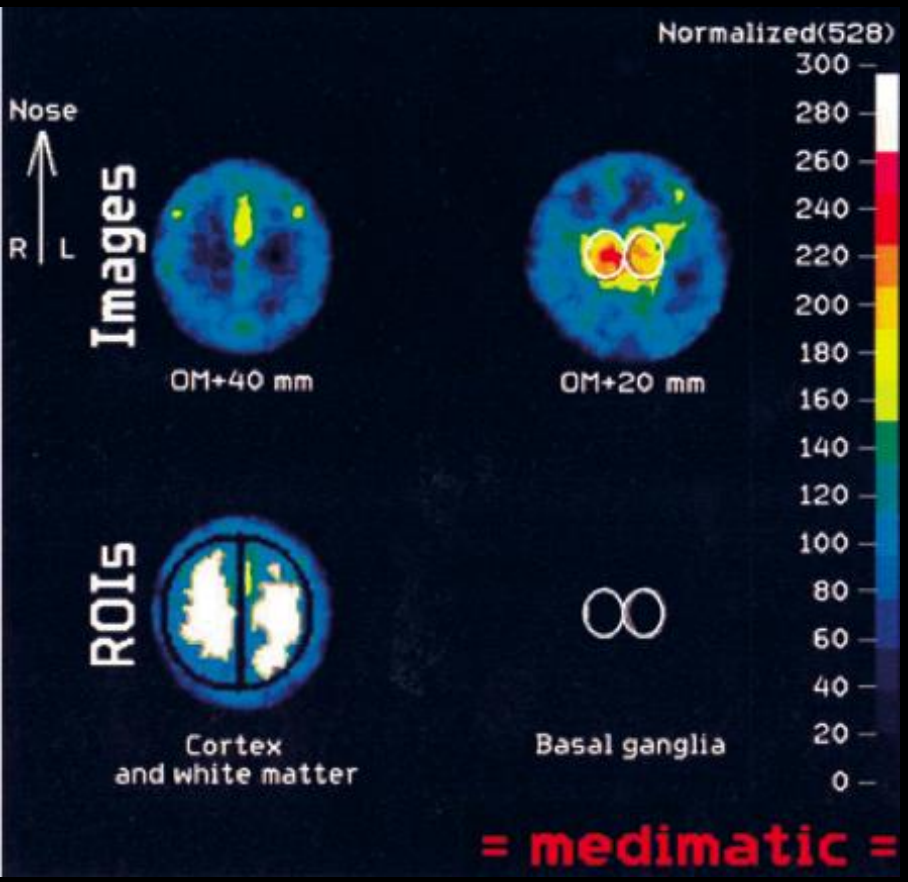
(Greisen. Acta Pædiatr Scand 1986)

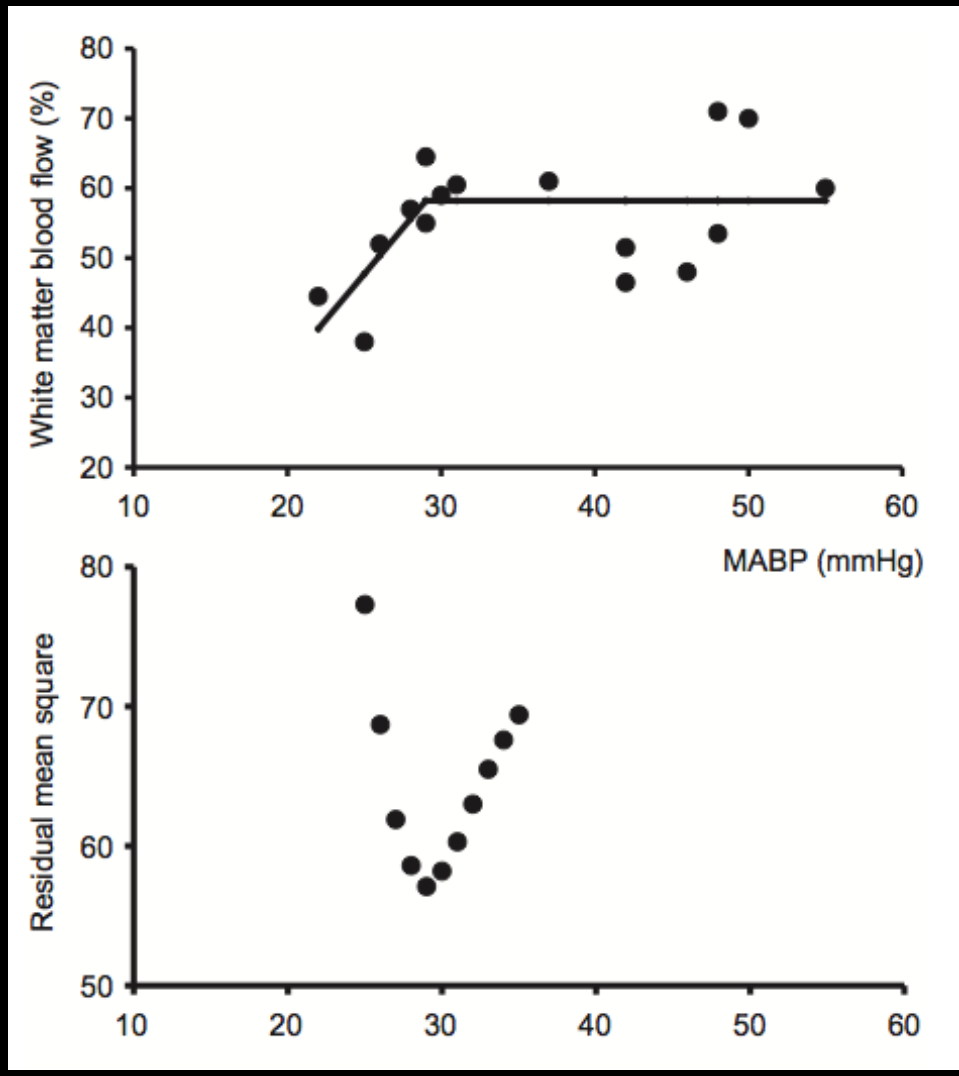


(Greisen et al. Brain Dev 1990)

White matter flow in 16 preterm babies, 26-32 weeks gestation

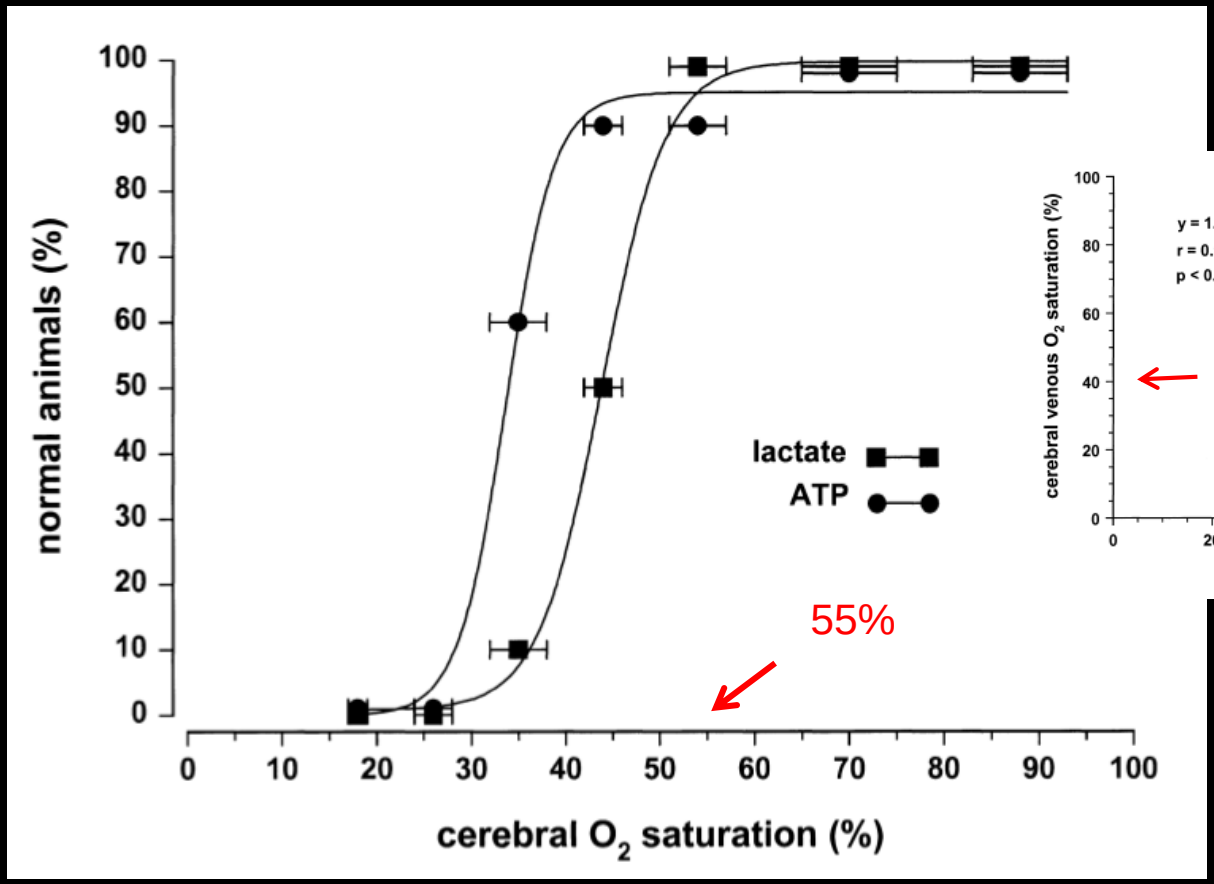
(Børch et al. Acta Paediatr 2010)





Mean arterial blood pressure (mm Hg)

The safe level of cerebral oxygenation in the newborn? (piglet)



Device calibration

(Kurth JCBFM 2002)

Causation of brain injury is likely to be (very) complex.

Prenatal

genetic

teratogenic/toxic

nutritonal

hormonal

Antenatal

hypoxic

infection/inflammation

Peripartal

asphyxic

traumatic

Neonatal

Maladaptation

haemorrhagic

hypoxaemic

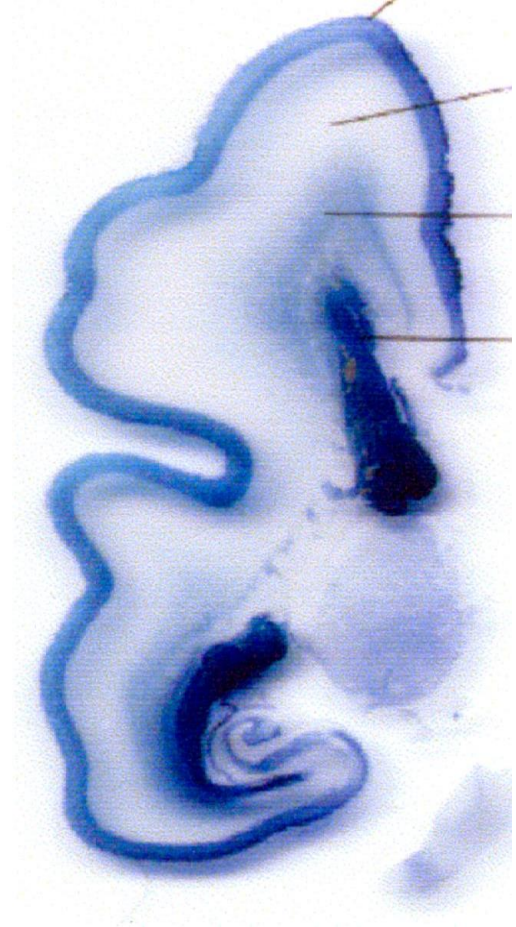
ischaemic

} Monitoring of cerebral oxygenation

infection/inflammation

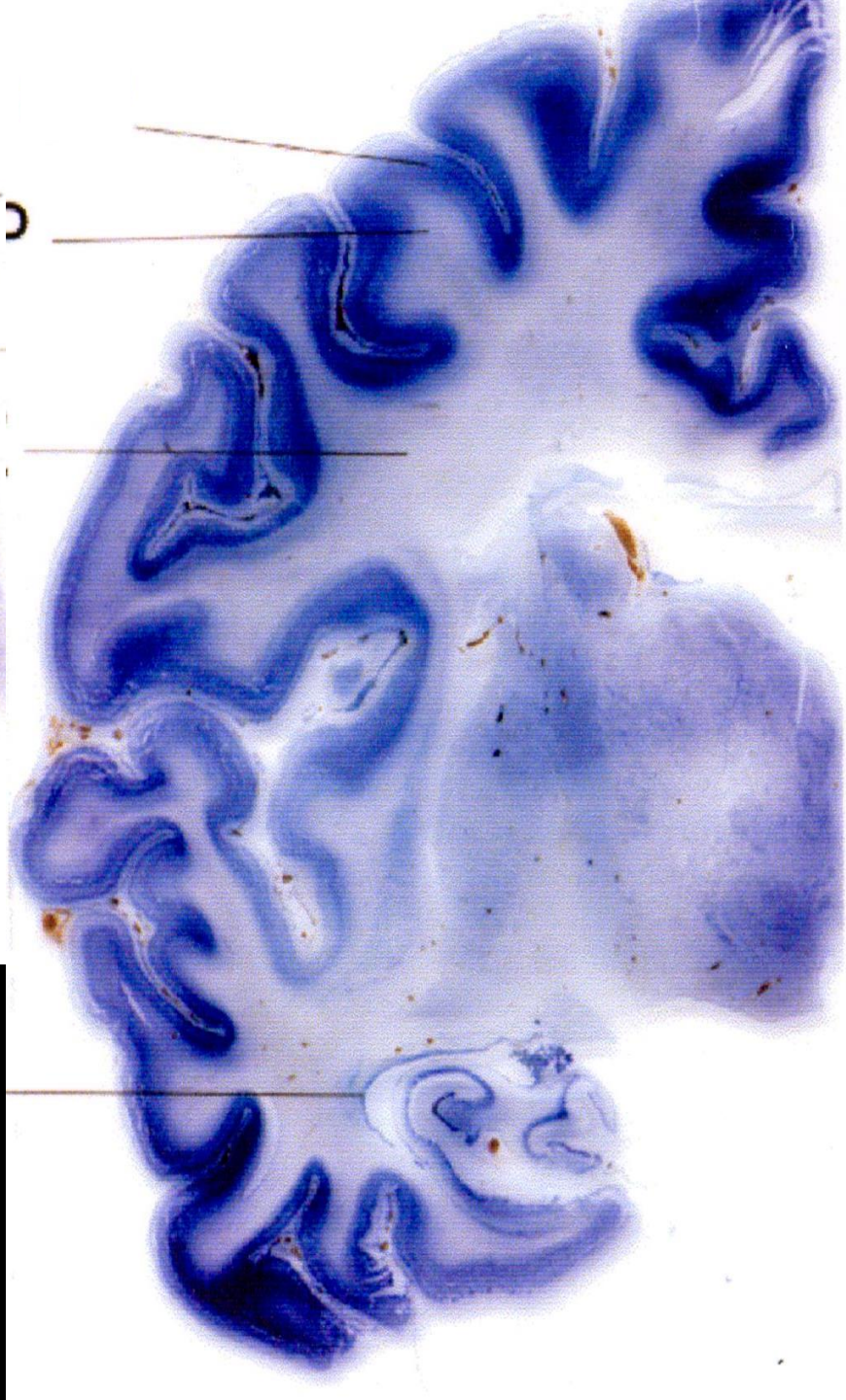
hormonal

Nutritional



24 wks

25 wks



40 wks

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Nov-3 2022

Early Amino Acids in Extremely Preterm Infants and Neurodisability at 2 Years

Bloomfield FH et al. DOI: 10.1056/NEJMoa2204886

CLINICAL PROBLEM

The appropriate protein intake to support the growth and development of infants with extremely low birth weight is unknown. Findings from observational studies that suggested improved outcomes with higher protein intake led to recommendations for early higher intake of amino acids, but data from randomized, controlled trials are lacking.

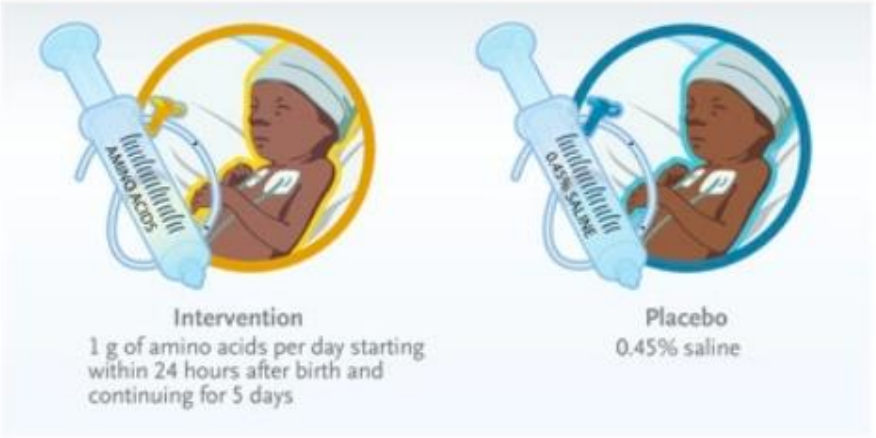
CLINICAL TRIAL

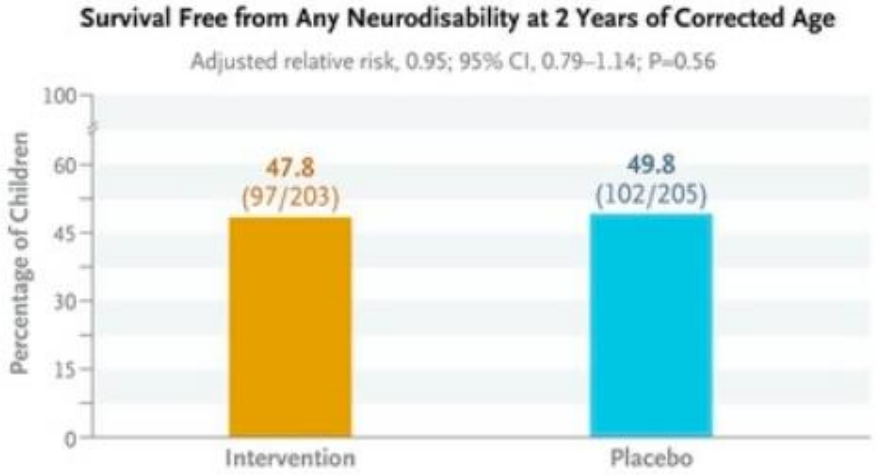
Design: A multicenter, double-blind, randomized, controlled trial examined whether early higher intake of amino acids would improve outcomes in infants with extremely low birth weight.

Intervention: 434 infants with a birth weight of less than 1000 g (217 infants per group) were assigned to receive, in addition to usual parenteral nutrition, an extra 1 g of amino acids per day or placebo through an umbilical artery catheter for a period of 5 days starting within 24 hours after birth. The primary outcome was survival free from any neurodisability at 2 years of age, corrected for gestational age at birth.

RESULTS

The proportion of participants alive and free from neurodisability at a corrected age of 2 years did not differ sig-





?

+ more than brain injury

What now?

Clinical use?

Research?

… the end