PULSE OXIMETRY TO NIRS: ADVANCED OXYGENATION MONITORING IN THE NICU AND ITS IMPACT ON NEONATAL BRAIN PROTECTION

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Learning objectives

1. Review the role of regional and systemic hypoxia in neonatal disease.
2. Discuss fundamentals of SpO2 function and clinical applications.
3. Discuss fundamentals of NIRS function and clinical applications.
4. Examine hypoxia monitoring in action through case-based examples.

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Hypoxia in neonates

- Hypoxia is defined by *inadequate delivery* of oxygen to tissues
- Neonates have <u>many</u> risk factors for hypoxia
  - Lung disease of prematurity (respiratory distress syndrome, hyaline membrane disease)
  - Hemoglobin F binds oxygen with high affinity but less effective at delivery
  - Impaired oxygen carrying capacity from anemia
  - Smaller functional residual capacity
  - Higher heart rates with decreased ability to modify stroke volume
  - Higher metabolic needs due to growth
- Oxygenation monitoring (with pulse oximetry and near-infrared spectroscopy) provides an opportunity for **early recognition** and **intervention**

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Oximeters are critical monitors for brain injury

- Hypoxia is a powerful risk factor for neonatal brain injury
  - 30x increase in SpO_2 hypoxia burden for preterms with severe IVH (**Vesoulis et al.,** *J Perinatol*, 2018)
  - Preterm infants with IVH spent ~15% more time with cerebral hypoxia (**Ng et al.,** *Arch Dis Child,* 2019)
  - Delivery room cerebral hypoxia associated with increased risk of abnormal GMA (**Pansy et al.**, *Early Hum Dev*, 2017)
  - Cerebral saturations < 50% associated with increased risk of NDI or death (**Chock et al.**, *JAMA Netw Open*, 2023)
- Pulse oximeters and near-infrared spectroscopy (NIRS) monitors are the cornerstone of oxygen saturation monitoring

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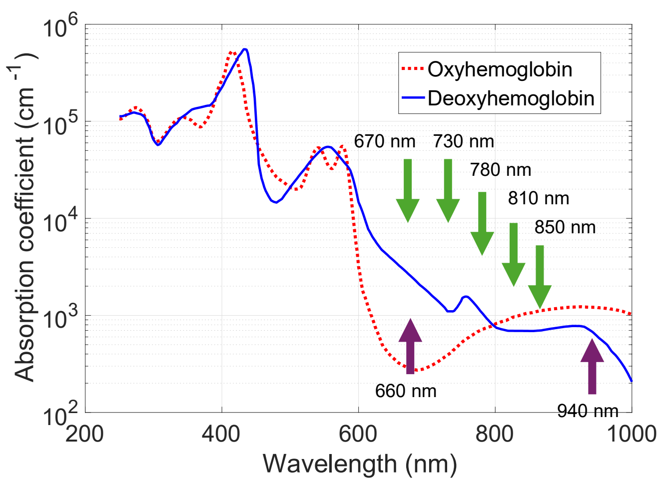
Hemoglobin absorption spectra

- Red and near-infrared light (700-900 nm) passes easily through skin, bone, connective tissue
- HbO absorbs more IR light, less red light; HbD absorbs less IR light and more red light
- Applying these principles, three values can be measured
  - HbD (deoxyhemoglobin)
  - HbO (oxyhemoglobin)
  - HbT (total hemoglobin, HbD + HbO)
- Saturation is HbO/HbT



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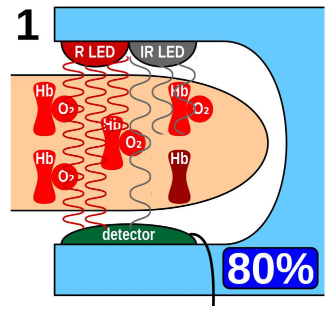
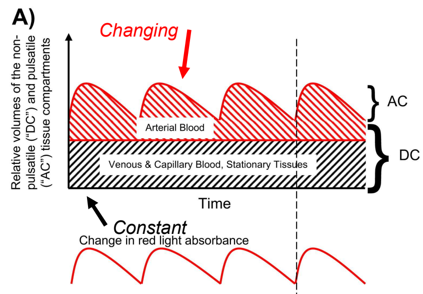
How do pulse oximeters work?

- Pulse oximeters transmit red and infrared (IR) light through tissue – emitter to detector
- Absorption = emitted light – returned light
- Two components of absorption
  - Non-pulsatile: Skin, bone, fat, muscle, and non-pulsatile blood
  - Pulsatile: arterial blood (mix of oxyhemoglobin (HbO) and deoxyhemoglobin (HbD)
  - Ratio of absorbencies compared against calibration table from healthy volunteers to generate SpO_2



CMG Lee, *Wikimedia*



Chan et al., *Resp Med*, 2013

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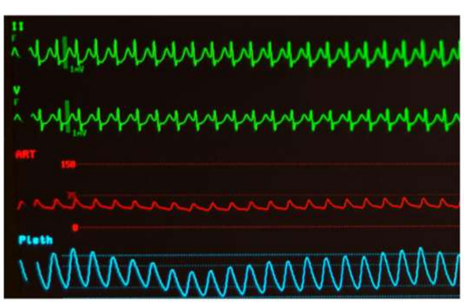
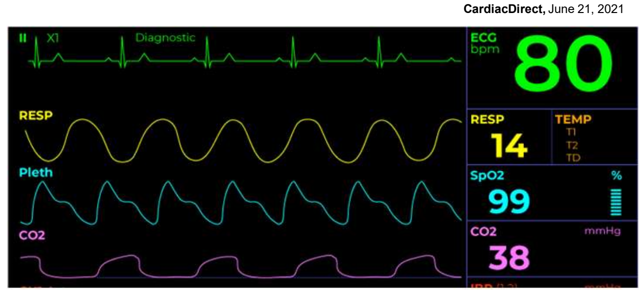
How is pulse ox displayed?

- Absorption of IR light is displayed on patient monitors as the **Pleth waveform**
- Depending on perfusion, may resemble arterial waveform with dicrotic notch or may look more like sine wave
- Posted SpO_2 number represents an average (8-10 seconds) -- large swings will take time to be reflected

CardiacDirect, June 21, 2021





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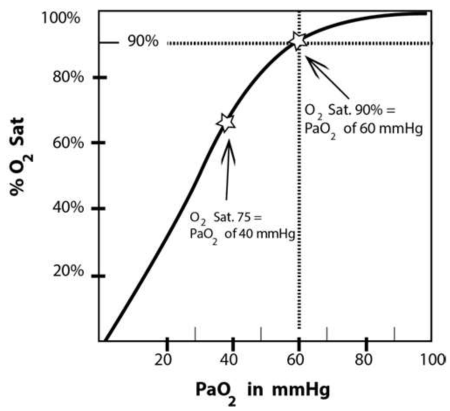
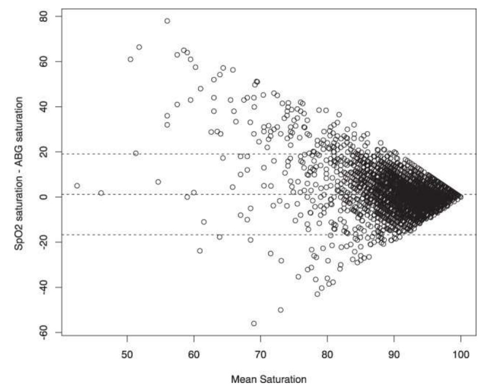
Pulse ox error

Caution– the relationship between SpO_2 and PaO_2 is non-linear!



Courtesy of Christine Whitten MD

Pulse oximeters have proportional bias, **error increases as saturation decreases**



Vesoulis et al., *J Perinatol*, 2021

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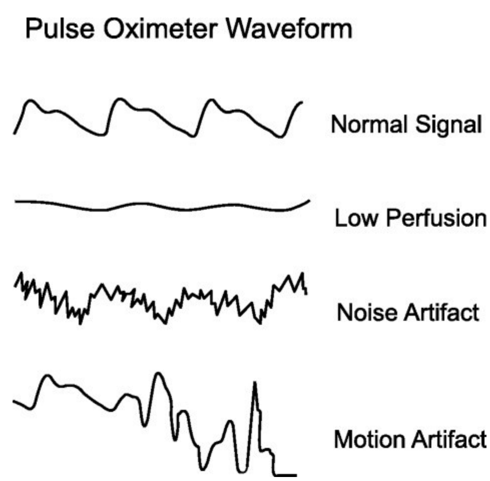
Pleth waveforms – identifying problems

- The pleth waveform is valuable tool for identifying SpO_2 problems
- The appearance of the waveform provides insight about perfusion, motion, noise
  - If SpO_2 number is not posted, pleth waveform can help to diagnose reason
  - If SpO_2 number is posted, pleth waveform can provide information on level of confidence
- Compare ECG and SpO_2 HR – significant discordance suggests unreliable signal



Jubran, *Crit Care*, 2015

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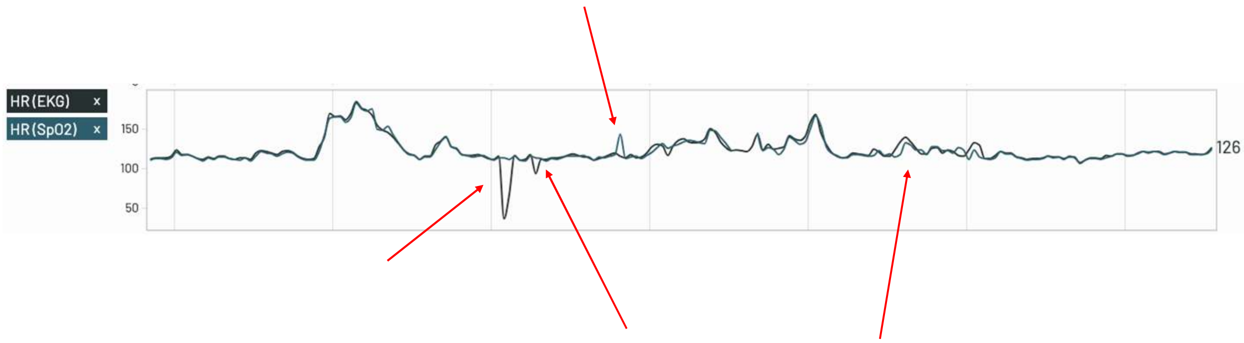
Heart rate – Pulse rate concordance



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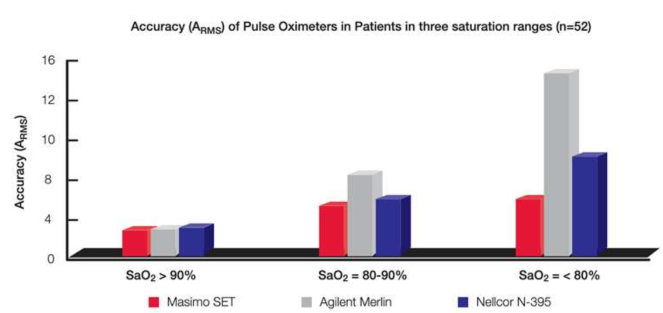
Pulse ox reliability danger zones

- Poor perfusion (e.g., 22-week infant) – pleth wave amplitude too small
  - Brighter light? ↑heat = burns
- Motion
  - Value “hold” during motion
- Lower saturations
  - Exponential increase in error as saturations decrease



Olivier et al., *Anesthesia and Analgesia*, 2003

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Role of a pulse oximeter in the NICU

- Non-invasive measure of arterial oxygen saturation (avoids frequent arterial blood gas)
- Can be obtained continuously throughout NICU stay
- Superior to observation alone, cyanosis visually apparent only when SaO_2 < 80%
- Alternative source of heart rate measurement
- Soft and flexible sensor can be positioned on hands, feet, fingers, toes

Beichl et al., *Case Rep Pediatr*, 2013

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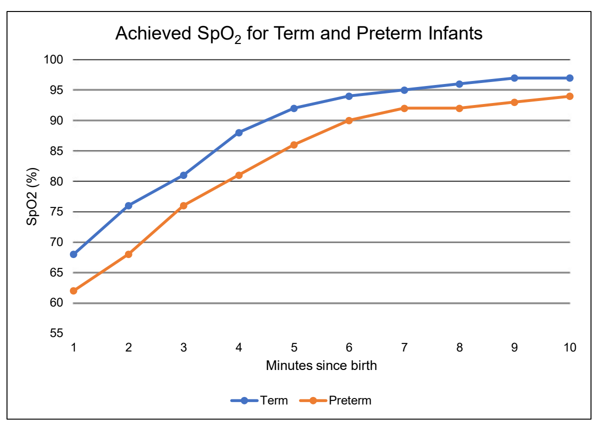
SpO_2 Use Case – Delivery Room Oxygen Titration

- Oxygen saturations naturally rise following birth as PVR drops and cardiac output increases
- Dawson et al. studied 468 infants and 61,650 SpO_2 points to define reference SpO_2 values by time
  - **Helpful in guiding resuscitation!**
- Failure to achieve 80% by 5 minutes associated with increased risk of IVH in VLBW (**Oei et al.**, *Arch Dis Child*, 2016)
- Term infants with severe birth asphyxia (Apgar <4 at 1 minute) have lower SpO_2 than infants with mild asphyxia (**Saugstad et al.**, *Acta Paediatr*, 2005)



Adapted from Dawson et al., *Pediatrics*, 2010

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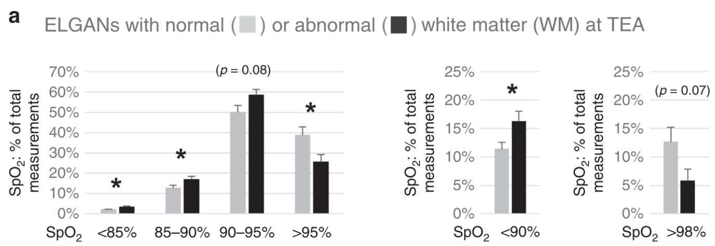
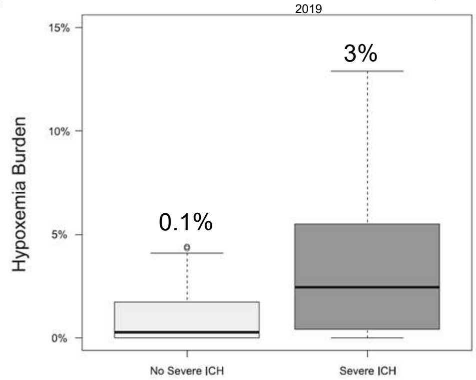
Hypoxia outcomes – Brain Injury

- Preterm infants are at risk for intraventricular hemorrhage (IVH), cerebellar hemorrhage (CH), and white matter injury (WMI)
- Acute and chronic hypoxia are driving factors behind preterm brain injury
- 30x increase in SpO_2 hypoxia for infants with severe IVH in one study
- Significantly greater SpO_2 hypoxia for infants with white matter injur



Rantakari et al. *Ped Res*, 2021

Vesoulis et al. *J Perinatol*, 2019



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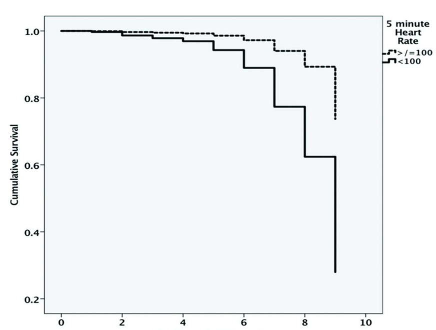
Hypoxia outcomes – NICU Mortality

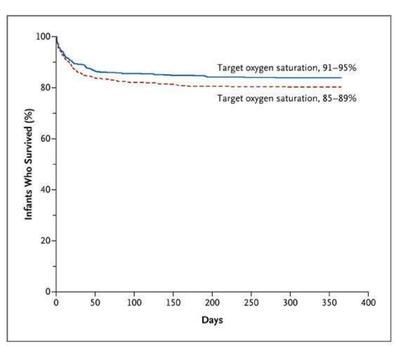
- Excessive supplemental oxygen causes ROP, but too little increases risk of death
- Target limits have been intensely debated; SUPPORT trial had surprising finding of increased mortality in "low normal" target group (19.9% vs 16.2%)

Increased mortality in the delivery room....

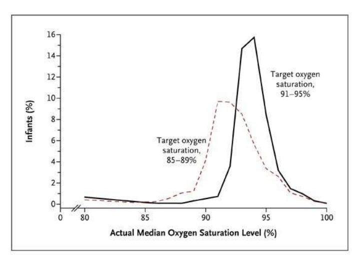


Oei et al. *Arch Dis Child*, 2016

and the NICU



SUPPORT Study Group, *NEJM* , 2010



Despite study design, "low-normal" group achieved saturations 89-94% and still had ↑mortality!

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How are pulse oximeters validated?

- Regulatory clearance provided by through FDA 510(k) clearance pathway, based on ISO 80601-2-61 standard (last updated in 2017)
  - Invasive laboratory testing on healthy adult volunteers
  - Controlled hypoxia between 70-100% SpO_2 using a controlled air-nitrogen-carbon dioxide rebreather circuit with nose pinched shut
  - 10 individuals, at least 2 of which are "darkly pigmented"
  - At least 200 paired SaO_2-SpO_2 samples
- Must achieve $A_{rms} \leq 3$ % for approval
  - $A_{rms} = \sqrt{\frac{\sum_{i=1}^{n}(SpO2 - SaO\ )^2}{n}}$
  - Combines measures of bias and precision (consistently close to real value)
- Big gaps
  - Most test subjects are repeat volunteers at UCSF, are they even "normal"?
  - Skin tone not assessed in objective way
  - Sick patients are never tested
  - Children (much less neonates) generally not tested
    - **"Adult subjects are acceptable in this case due to the uncertainty of determining the accuracy of sensors intended for use in neonates"**
    - We found A_{rms} = 8.9% for White neonates, 9.5% for Black neonates
  - Validation data rarely available to the public

Volunteer undergoing testing at UCSF Hypoxia lab

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The current state of neuromonitoring in the NICU, 2025

- Neonates are at risk for stroke, hemorrhage, hypoxic-ischemia, elevated intracranial pressure, and seizures
- Neonates have the highest risk of seizures across the lifespan
- Standard ICU monitoring is comprehensive, *EXCEPT FOR THE BRAIN*

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What is the ideal monitor?

- Continuous, real-time
- Non-invasive
- Organ (brain) specific
- Includes elements of oxygen delivery and consumption
- Regulatory approval for neonates

Cerebral NIRS!

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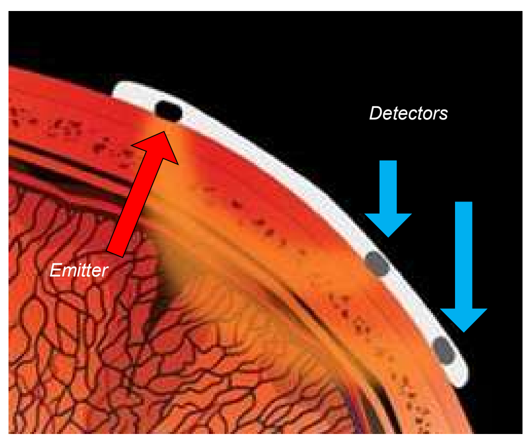
What is NIRS and how does it work?

- Near-infrared light can penetrate through skin, bone, connective tissue
  - Depth depends on spacing between emitter/detector
- NIR light is scattered, reflected, absorbed – but some returns to the sensor
  - Scatter and reflection remain constant
  - HbD absorbs more red, less NIR light
  - HbO absorbs more NIR, less red light
- NIRS measures oxygen saturation in all tissue spaces
  - Most blood is in venous space (70% venous, 25% arterial, 5% capillary) so NIRS is a **venous weighted measure**
- Second shallow detector removes superficial blood flow signal



Sami Barrit, Harvard Medical School

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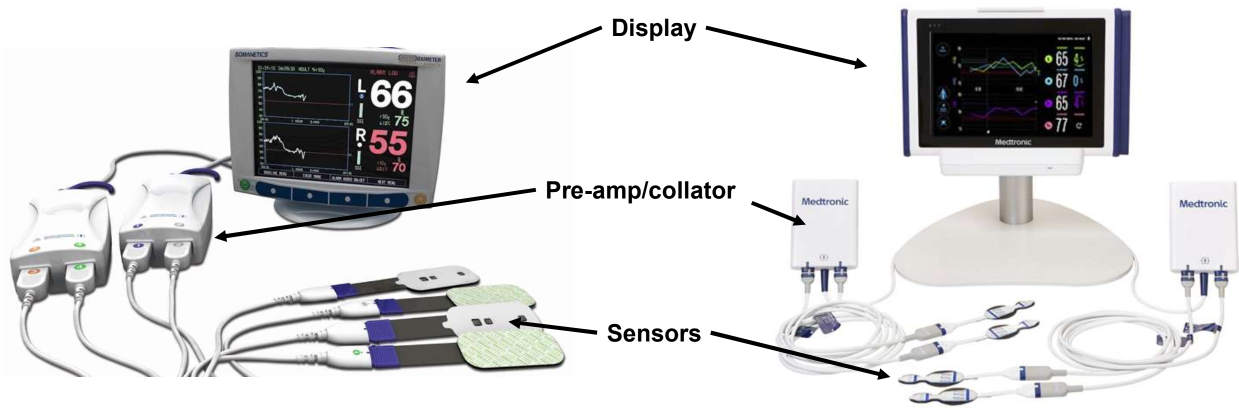
NIRS hardware anatomy



INVOS 5100c **INVOS 7100**

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NIRS sensor placement

- **Cerebral** (temporal placement to right or left of midline)
- **Splanchnic** (right or left lower quadrant)
- **Renal** (right or left flank)
- Most monitors support up to 4 simultaneous channels

Image courtesy Halana Whitehead MD, Washington University

Bailey et al., *J Biomed Opt,* 2016

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NIRS is not just a pulse oximeter

Pulse oximeter	NIRS
Uses red and NIR light to measure oxygenation	Uses red and NIR light to measure oxygenation
Non-invasive continuous monitor	Non-invasive continuous monitor
Measures of hypoxia are associate with bad outcomes	Measures of hypoxia are associate with bad outcomes
Transmission-based measure, limited to thin body parts	Reflectance-based measure, can be applied to any tissue
Arterial saturation: measure of oxygen supply	Mixed-venous saturation: measure of oxygen **delivery** and **consumption**
Detects oxygenation problems in whole body	Detects oxygenation problems in specific tissue

↑ SpO_2 = too much supplemental oxygen
↓ SpO_2 = not enough supplemental oxygen

↑ rSO_2 = too much supplemental oxygen *or* decreased extraction by tissue
↓ rSO_2 = not enough supplemental oxygen *or* increased extraction by tissue

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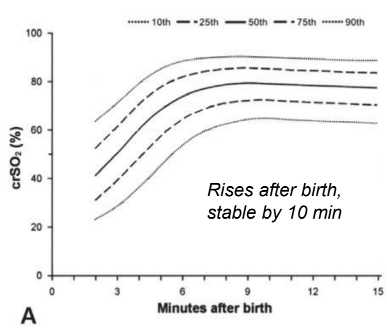
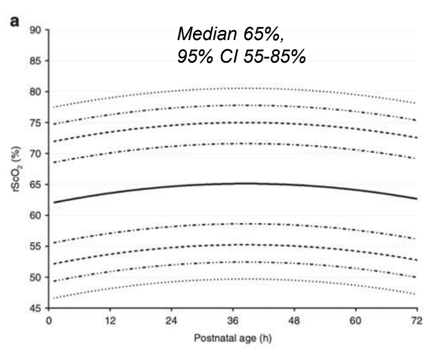
What is a "normal" cerebral NIRS value?

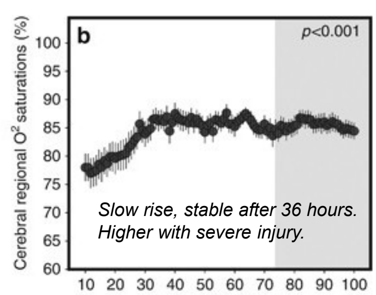
- Large reference studies have been done in delivery room, VLBW, HIE populations
- rSO_2 55-85% (median 65%) widely used in preterm population as "normal" bounds
- These values were established using INVOS 5100c and small adult sensor. **INVOS neonatal sensor equivalent is 63-93%** *(other device-sensor combinations will vary)*



Pichler et al., *J Pediatrics*, 2013



Alderliesten et al., *Pediatr Res*, 2015



Forman et al., *Pediatr Res*, 2017

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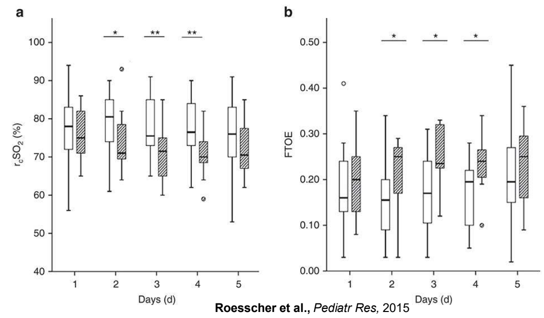
Fractional tissue oxygen extraction (FTOE)

- The fractional tissue oxygen extraction (FTOE) is the percentage of delivered oxygen that is consumed
- It can be calculated from the NIRS signal (rSO2) and the pulse oximeter (SpO2)
- Should be about 20% in healthy humans
- Influenced by functional metabolism, inflammation, injury

$$FTOE = \frac{SpO_2 - rSO_2}{SpO_2}$$

FTOE = 0.305

Infants with chorioamnionitis (shaded bars) have lower rSO2 and higher FTOE.



Roesscher et al., *Pediatr Res*, 2015

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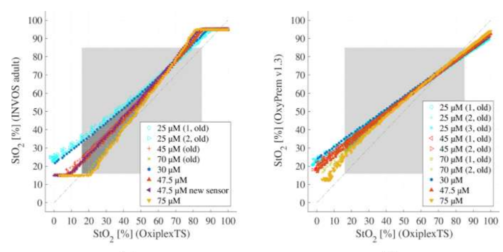
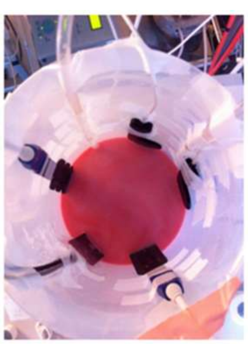
Between-device differences in NIRS

- Conceptually NIRS monitors all work the same way
- BUT each device has subtle differences in hardware and software which result in **different** measurements on the **same** patient
- Kleiser et al. have evaluated a broad range of devices using a blood lipid phantom and have published transforms to convert measures





Blood-lipid phantom

NIRS Device	Hypoxic threshold %
FORESIGHT small	66
FORESIGHT non-adhesive small	67
NIRO small	61
NIRO small re-usable	63
NIRO large	62
NIRO large re-usable	62
INVOS neo	63
SenSmart neo 8004CB-NA	66

1. **Kleiser et al.,** *Biomed Opt Express*, 2017
2. **Kleiser et al.,** *Adv Exp Med Biol*, 2016
3. **Hansen et al.,** *NEJM*, 2023

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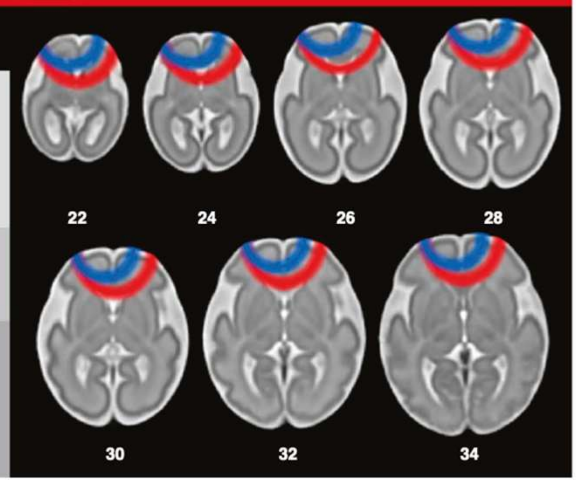
Head size may make a difference

a

GA (weeks)	HC (cm)	Diameter (cm)	Radius (cm)	cNIRS probe location (2.5 cm measures- red arch)
22	19.5	6.2	3.1	Ventricle
24	21.4	6.8	3.4	Ventricle
26	24.5	7.8	3.9	Ventricle
28	25.3	8.1	4.0	Ventricle
30	27.0	8.6	4.3	Ventricle
31	28.4	9.0	4.5	Corpus callosum/ventricle
32	29.5	9.4	4.7	Corpus callosum/ventricle
33	29.8	9.5	4.7	Corpus callosum/ventricle
34	30.4	9.7	4.8	Anterior limb/white matter tract
35	31.7	10.1	5.0	Anterior limb/white matter tract
36	32.0	10.2	5.1	White matter tract
37	32.0	10.2	5.1	White matter tract
38	32.3	10.3	5.1	White matter tract

b



Kolnik et al., *Pediatr Res*, 2023

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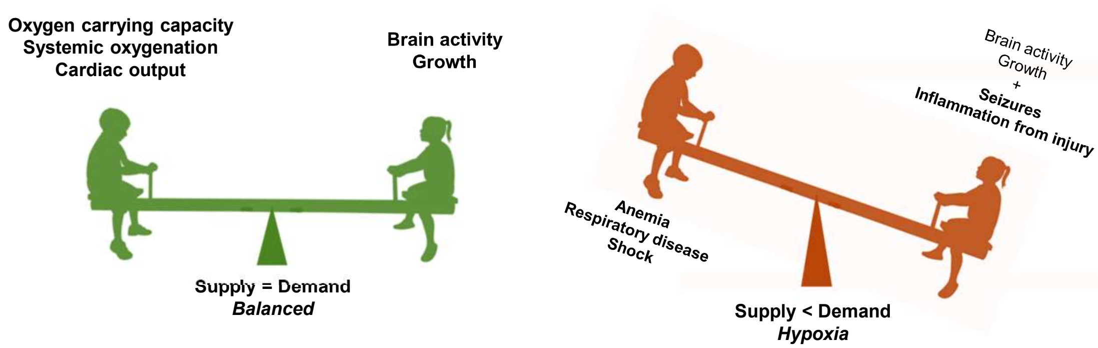
What causes cerebral hypoxia?



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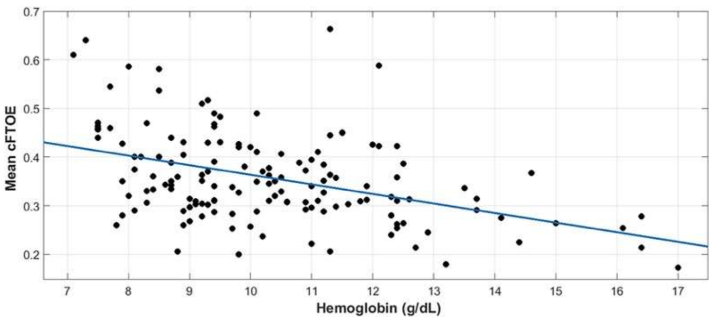
NIRS and anemia

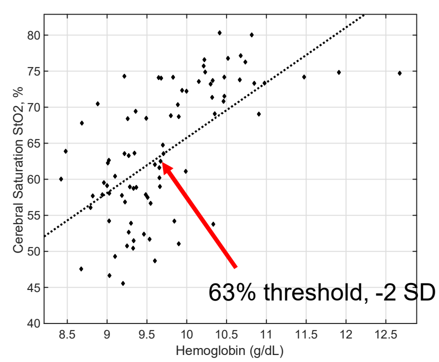
Halana Whitehead

WashU Medicine

- We studied 39 healthy VLBW infants (no IVH, no congenital anomalies) with paired cerebral NIRS recording and hemoglobin measurement
- Cerebral saturation drops, FTOE increases as hemoglobin decreases
- Potential implications for pRBC transfusion threshold- what FTOE threshold risks injury?



Whitehead et al., *J Perinatol*, 2018



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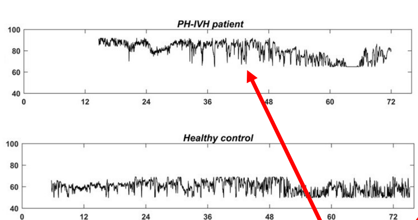
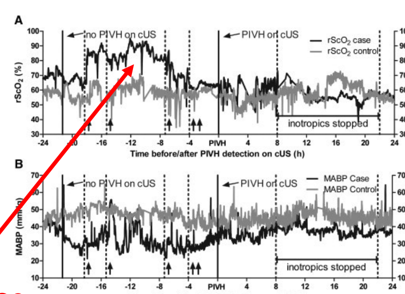
NIRS and IVH

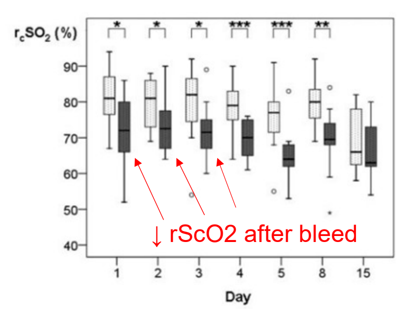
- Cerebral oxygenation patterns in IVH have two phases
  - Hyperoxia (impaired autoregulation, temporary decrease in O_2 demand by injured tissue)
  - Hypoxia (increased O_2 demand from inflammation, seizures, ↑metabolism)



Beausoleil et al., *Sci Rep*, 2018



Alderliesten et al., *J Pediatr*, 2012



Verhagen et al., *Stroke*, 2010

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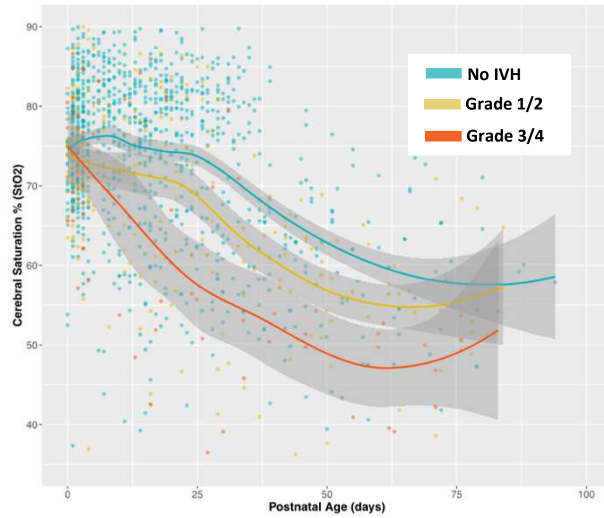
Cerebral hypoxia over time and injury

- We made 1287 NIRS recordings from 187 VLBW infants, each 6-8 hours long
- Cerebral saturations drop over time (with anemia)
- Infants with IVH have lower saturations, remain lower for at least 60 days
- High grade IVH has more cerebral desaturation than mild IVH or no IVH



Vesoulis et al., *Pediatr Res*, 2021

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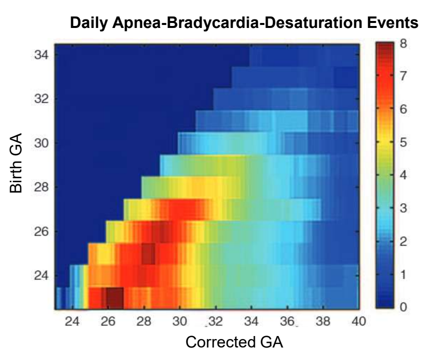
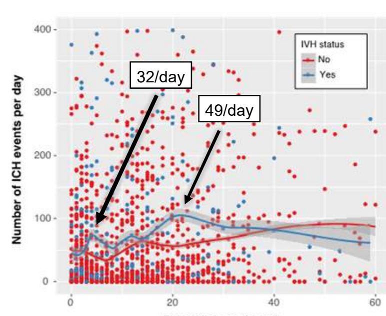
Silent cerebral hypoxia

- Apnea-bradycardia-desaturation (ABD) events occur in 100% of infants < 32 weeks and may cause impaired cerebral autoregulation
- Recent evidence suggests presence of **significant silent cerebral hypoxia** (low $rScO_2$ with normal SpO_2)
- We made 1616 recordings from 209 infants with mean length 5.1 hours
  - Daily intermittent cerebral hypoxia (ICH) events increased from 32/day at birth to 49/day at 21 days of life
  - Most events (48%) were silent, increased proportion in infants with IVH (67%)

Fairchild et al., *Pediatr Res*, 2016





Unpublished data

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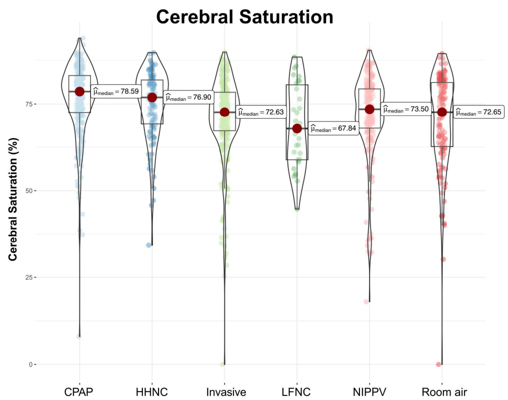
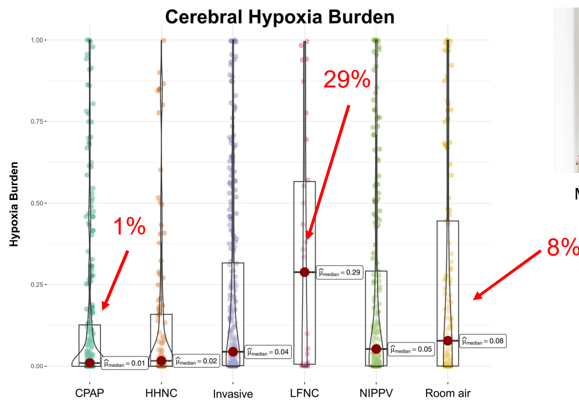
Silent cerebral hypoxia and respiratory support

- Many NICUs are focusing on less invasive respiratory support, more rapid weaning guided by pulse oximetry and blood gases
- We made 1013 recording from 174 infants over the entire NICU course, mean $rScO_2$ and hypoxia burden were evaluated
- Infants on lowest respiratory support (room air, low flow nasal cannula) had highest cerebral hypoxia burden, no difference in SpO_2 values





Mona Noroozi-Clever

WashU Medicine

Noroozi-Clever et al., *J Peds*, 2023

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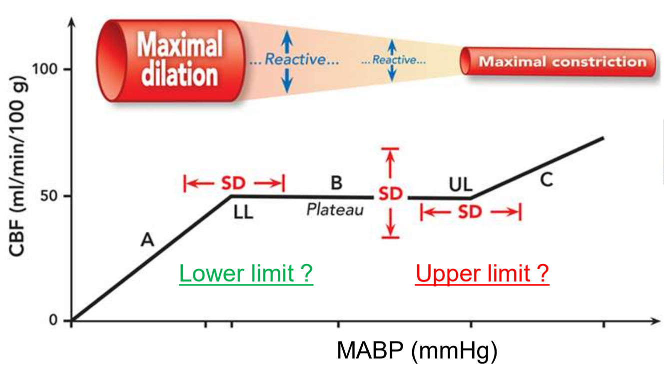
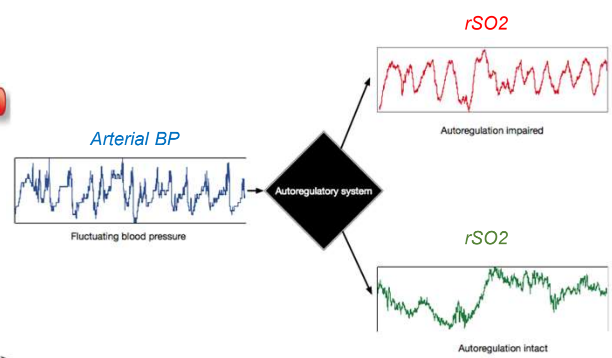
Cerebral autoregulation





Cerebral autoregulation maintains blood flow regardless of cardiac output

When autoregulation fails, the brain is exposed to systemic fluctuations in blood pressure

Adapted from **Meng et al.** *Anesthesiology*, 2015

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Balancing factors in cerebral autoregulation

- The goal of cerebral blood flow is **sufficient oxygen delivery for maintenance of cerebral metabolism**
- Optimally, changes in CBF are driven ONLY by changing metabolic needs
- In reality, CBF can be influenced by many factors
  - pCO_2
  - Medications (especially sedation)
  - Systemic blood pressure/cardiac output
  - Position
- Theoretical control mechanisms
  - Myogenic (stretch)
  - Neurogenic (autonomic)
  - Metabolic

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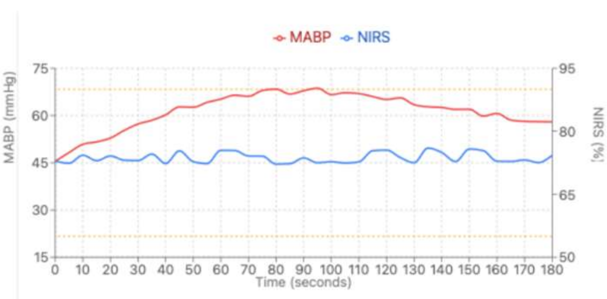
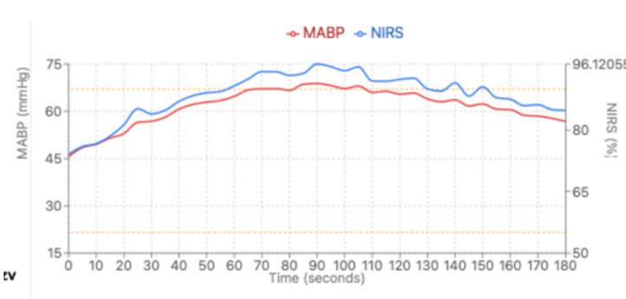
What is "time domain" ?

- Examines the correlation **over time** between two variables **without** mathematical transformation
- Cerebral blood flow and cardiac output should be independent (zero correlation)
- Relationship can be examined in blocks, over time



Low correlation = intact autoregulation



High correlation = dysfunctional autoregulation

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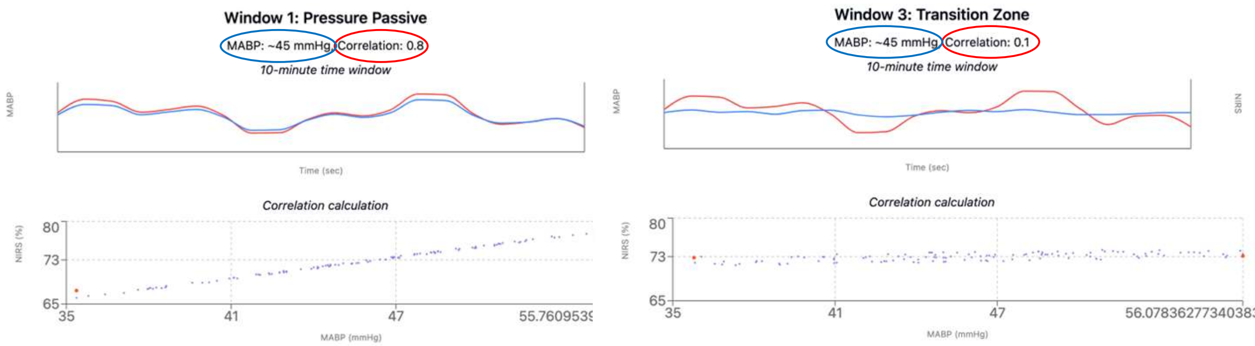
Time domain autoregulation measure

- Technique pioneered at University College London, variations using transcranial Doppler and NIRS
- Three steps
  - Divide recording into 10-min windows, calculate correlation coefficient between BP and CBF measure
  - Store correlation coefficient in "bins" organized by MABP
  - Average the correlation coefficient in each "bin"



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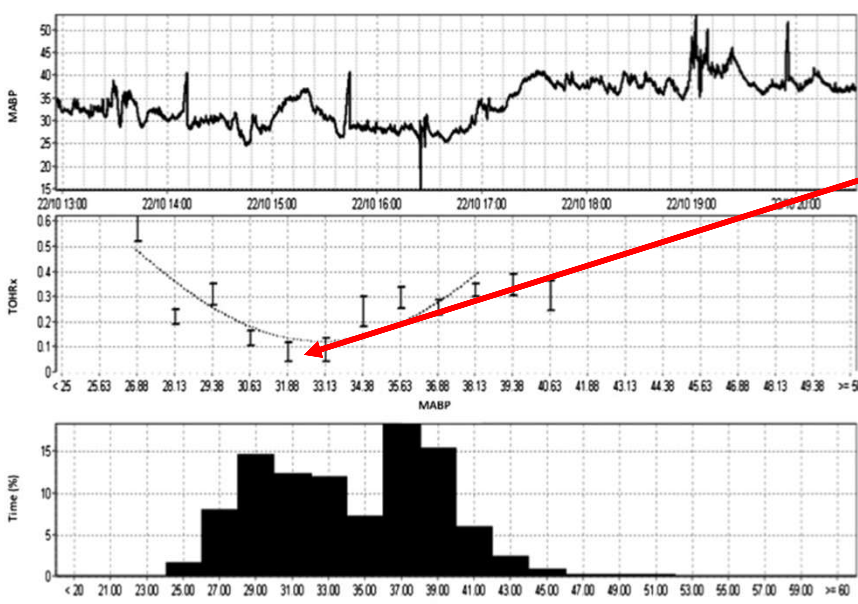

"Optimal MAP" defined as BP bin with most negative mean correlation coefficient

da Costa et al., *J Peds*, 2015

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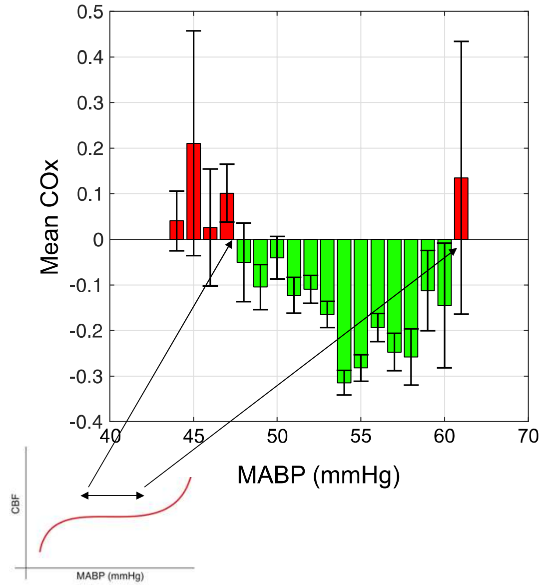
Autoregulation failure in HIE

- Study of 16 term infants with HIE; 7 with MRI injury
- Continuous rSO_2 and MABP measurements for 72 hours
- Using sliding 10-minute windows, calculate the average correlation coefficient (COx) for each BP bin
- Determine the autoregulatory window and percentage of time spent above (hyperperfusion) or below (hypoperfusion)
- Mean lower limit = 46.7 mmHg
- Mean upper limit = 55.6 mmHg



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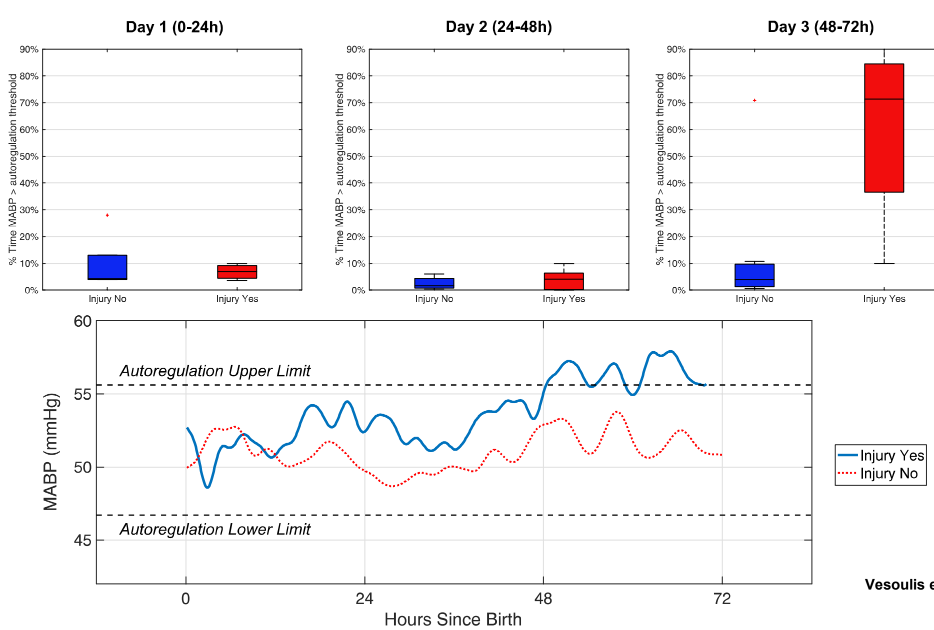

Vesoulis et al., *Physiol Meas*, 2018

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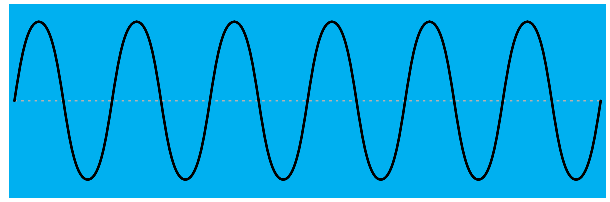
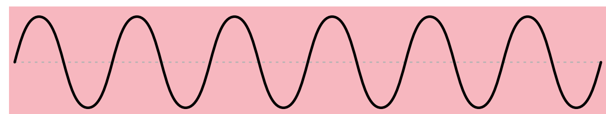
What is the "frequency domain" ?

Systemic blood flow



Blood flow is a sine wave, alternating between systolic and diastolic pressures

Cerebral blood flow – weak dampening



Autoregulation may dampen these oscillations a little….

Cerebral blood flow – strong dampening

…Or dampen them a lot

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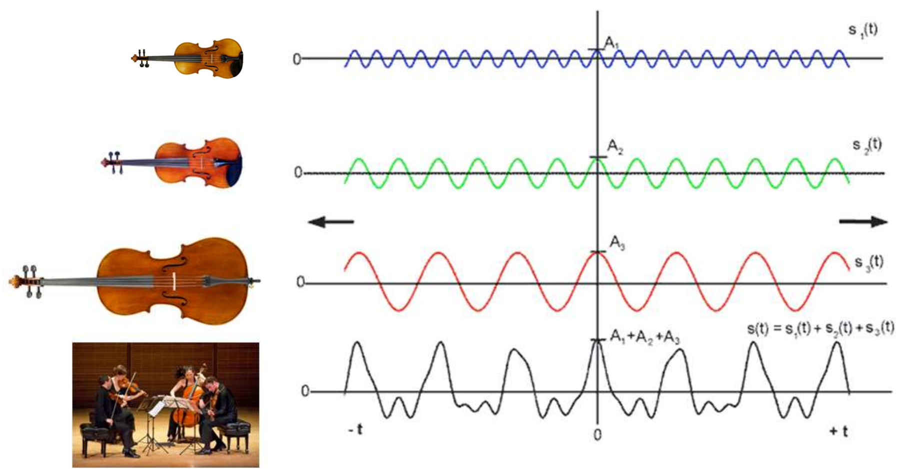

- Much as music is the composite of different sounds at different frequencies, BP is not a single sine wave, but interposed sine waves at varying frequencies
- We can **separate** out the contribution of BP oscillations at different frequencies
- We can evaluate how autoregulation **dampens** BP oscillations at different frequencies

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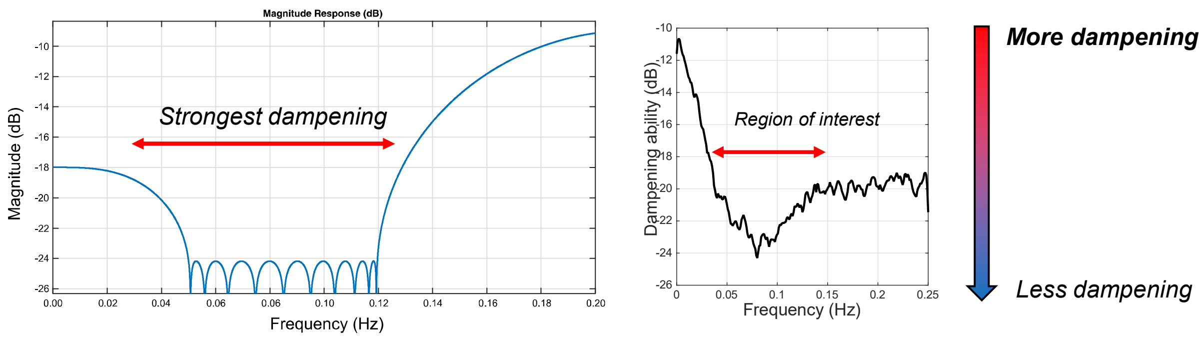
Autoregulation as a band-stop filter

- Most of the fluctuation in blood pressure occurs at **low frequencies**
- Autoregulation…
  - Strongly attenuates oscillations in a narrow frequency band (0.02-0.15 Hz)
  - Weaker attenuation at
    - Very low (<0.02 Hz)
    - High frequencies (>0.15 Hz)
- Autoregulation essentially functions as a band-stop filter



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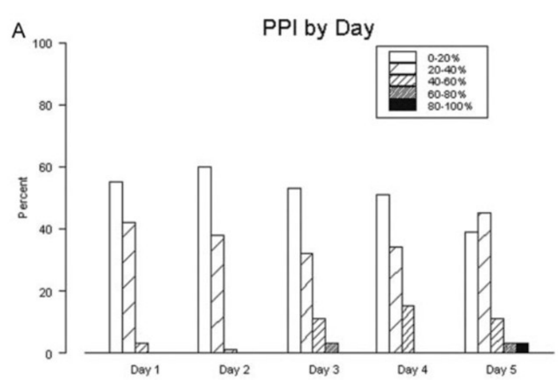
Coherence approach - Preterm

- Low-frequency coherence (statistical correlation between MABP and NIRS at 0-0.04 Hz) calculated over serial 10-minute epochs
- Defined as "pressure passive" (impaired autoregulation) if coherence was **greater than 0.5**
- In this study, 90 preterm infants were examined
- The average infant spent 20% of the first 5 days in a pressure-passive state
- Greater passivity amongst lower GA, sicker infants



Soul et al., *Pediatr Res*, 2007

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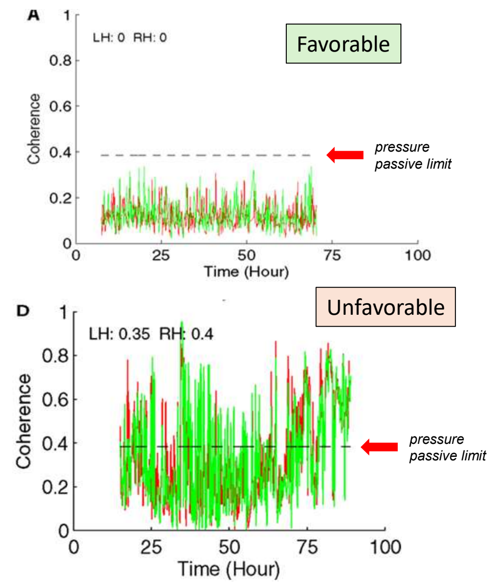
Coherence approach – Term HIE

- 4 infants with HIE, 2 with favorable (survived, no injury on MRI) and 2 unfavorable (1 died, 1 with injury)
- Low-frequency coherence calculated over serial 10-minute epochs (0.05-0.25 Hz)
- Defined as "pressure passive" (impaired autoregulation) if **coherence was greater than 0.384**
- Significantly more coupling between NIRS and MABP signal in unfavorable outcome infants



Govindan et al., *Front Hum Neurosci.* 2014

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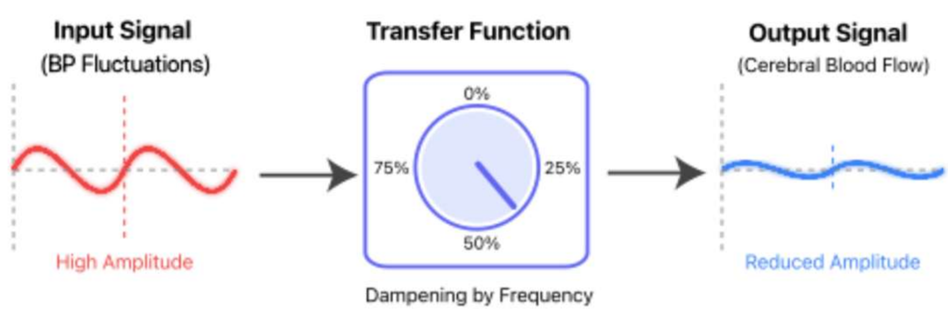
Transfer function as the "volume control" of physiology

- Transfer function is a mathematical model of an input-output system, modeling the output as a function of the frequency of the input
- Essentially, over a series of discrete frequencies how much does the system dampen or "turn down the volume" before passing to output?



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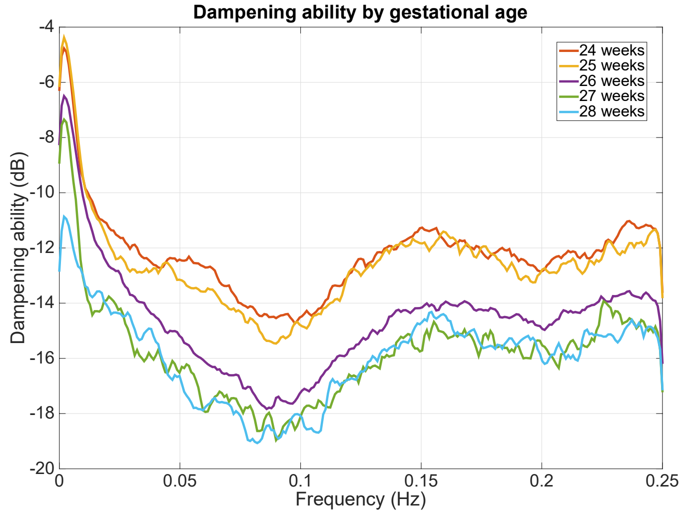
Autoregulation in preterm infants using TF

- 62 infants < 28 weeks
- All infants had 72 hours of continuous MABP/NIRS
- Data was error-corrected and transfer function gain coefficient was calculated between 0 and 0.25 Hz



Vesoulis et al., *Pediatr Res*, 2016

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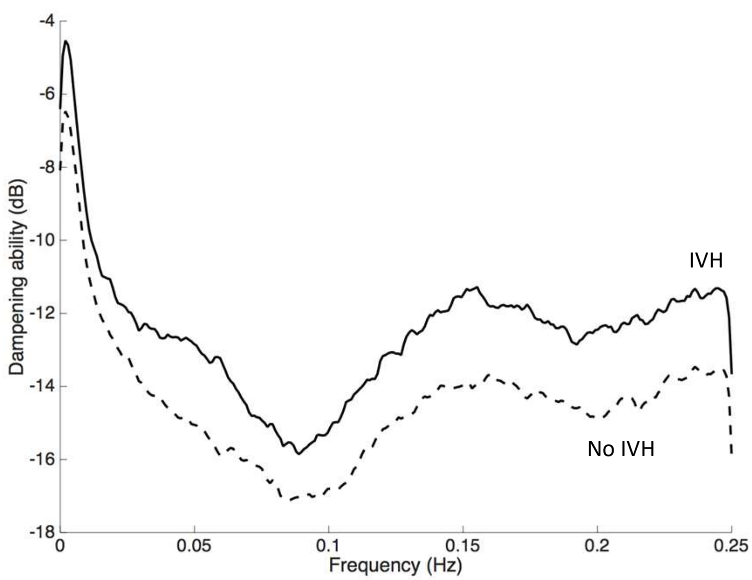
TF and IVH



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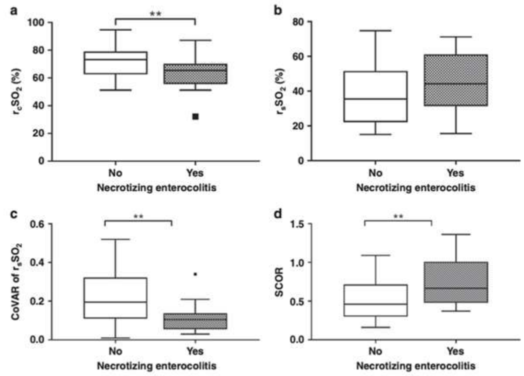
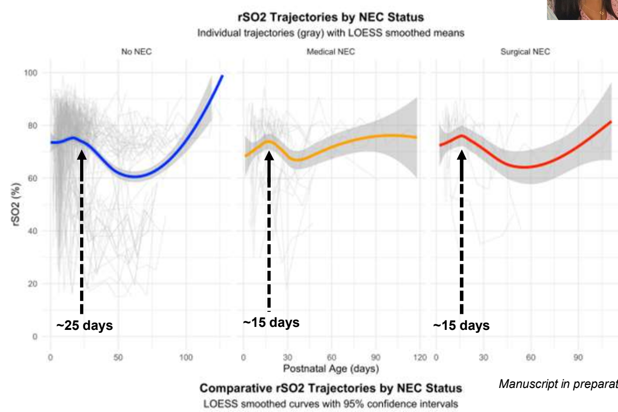
NIRS and NEC

Bella Anadkat



van der Heide et al., *Pediatr Res*, 2021



Manuscript in preparation

- NIRS applied at first suspicion of NEC in 75 babies
- Infants with NEC had **lower saturations** and **less variability**
- NEC ruled out (100% specificity) if rSO2 > 87.8%
- NEC ruled in (100% specificity) if rSO2 < 51.3%

- **No normative values in preterm infants!**
- N=194 infants <32 weeks, weekly monitoring 1976 recordings
- Overall pattern resembles Hb in anemia of prematurity
- Infants who later develop NEC have early drop in intestinal oxygenation

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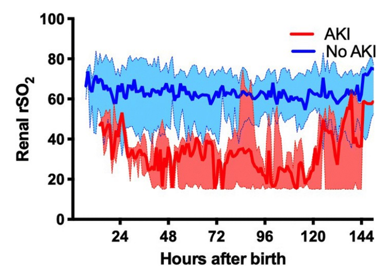
Renal NIRS and AKI

- NIRS is also useful for identifying "silent" kidney injury
- Laboratory markers lag AKI, NIRS provides early recognition
- As with brain injury, renal injury induces persistent tissue hypoxia
- Recent study shows strong correlation between decreasing renal rSO2 and increasing risk of AKI

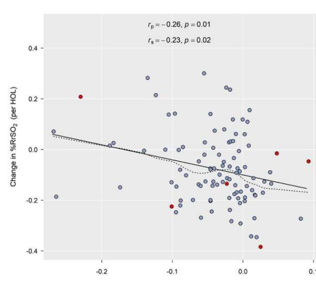
WISCONSIN MEDICINE

Matt Harer

Persistent ↓ rSO2 after birth related AKI



Harer et al., *Pediatr Nephrol*, 2021



Condit et al., *Preprint*

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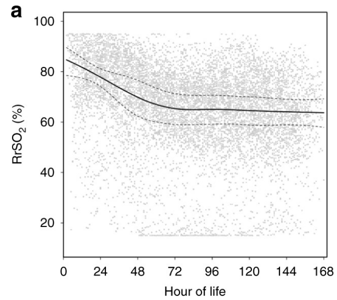
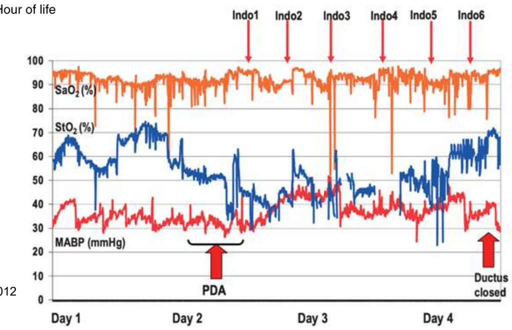
Renal NIRS and PDA

- Useful for detection of hemodynamically significant PDA
- Two studies
  - Renal rSO2 < 43% is 85% sensitive, 83% specific (**Underwood et al.,** *Neonatology*, 2007)
  - Renal rSO2 < 66% is 81% sensitive, 77% specific (**Chock et al.**, *Pediatr Res*, 2016)
- rSO2 values are restored to normal values after treatment



Reference values for renal rSO_2 in preterm infants

Harer et al., *Pediatr Res*, 2022



Wolf et al., *JNIRS*, 2012

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If NIRS monitoring is so great, why isn't it more widely used?

-RCT evidence not compelling
-Implementation challenges

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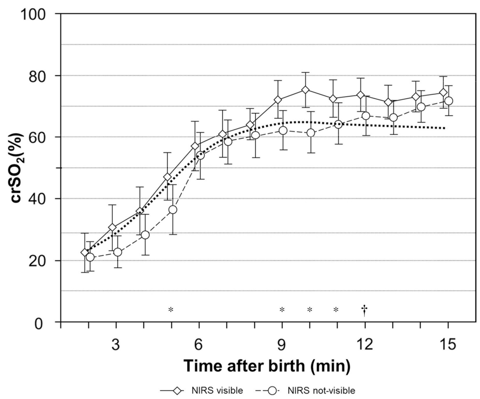
COSGOD-II

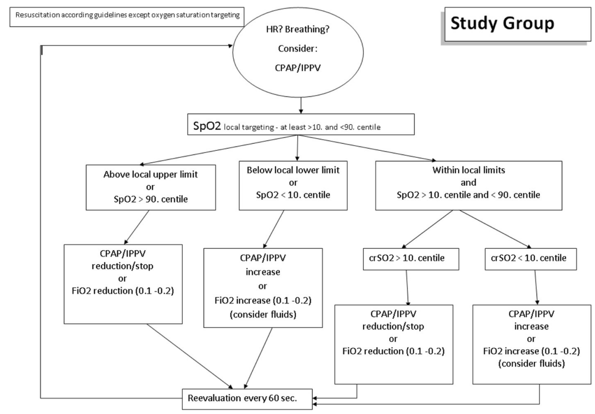
- 2-center RCT of 60 infants < 32 weeks GA
- Randomized to NIRS visible/not visible in delivery room
- Cerebral hypoxia burden reduced by 55% in NIRS visible group



Pichler et al., *J Peds*, 2016

COSGOD-III

- 11-center RCT of 607 infants < 32 weeks GA
- Randomized to NIRS visible vs. standard of care for first 15 minutes after birth
- Improved survival without brain injury for NIRS group (82.9 vs 78.5%) but not statistically significant



Pichler et al., *BMJ*, 2023

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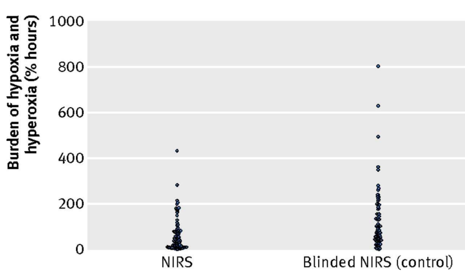
SafeBoosC-II

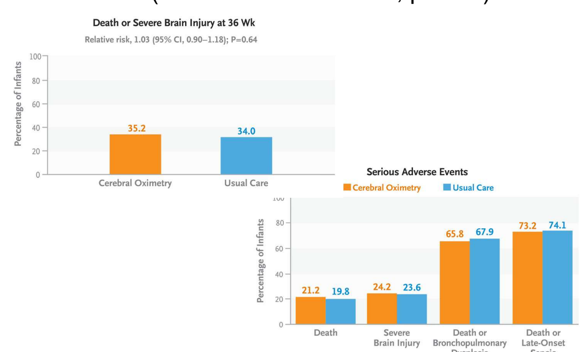
- 8-center RCT of 166 infants < 28 weeks GA
- Randomized to NIRS visible/not visible for 72h after birth
- Standardized interventions for abnormal $rScO_2$
- Combined hyperoxia/hypoxia burden reduced by 58% in NIRS group
- Reduction in mortality or severe brain injury (25% vs 14%, not statistically significant)



Hyttel-Sorenson et al., *BMJ*, 2015

SafeBoosC-III

- 70-center RCT of 1601 infants < 28 weeks GA
- Randomized to NIRS visible vs. standard of care for 72h after birth
- No difference in mortality or severe brain injury on ultrasound (35.2 vs 34%)
- Small non-significant improvement in MRI score (Kidokoro score 2 vs. 3, p=0.11)



Hansen et al., *NEJM*, 2023

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Three challenges ahead

- **Devices are not validated against outcomes**
  - FDA requires monitoring devices to accurately measure current physiology against gold standards (heart rate, SaO_2, SvO_2, etc.)
- **RCTs study protocols, not devices**
  - Represent decisions about population, timing, threshold, and choice of interventions
- **Provider trust is essential, an ignored "box in the corner" does not help the patient!**

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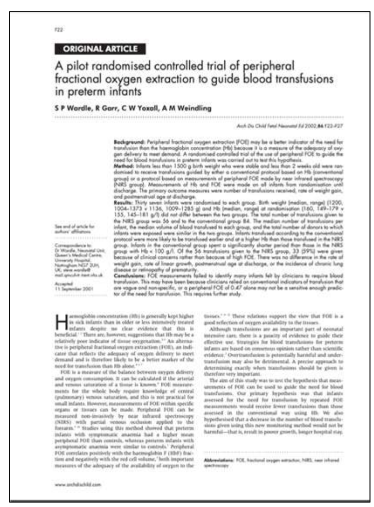
Didn't trust it – an example from the literature

- 74 infants randomized
- Hgb-based threshold
  - 14 g/dL for $FiO_2 > 0.35$
  - 12 g/dL for $FiO_2 < 0.35$
  - Any time for VS instability
- NIRS-based threshold
  - Fractional tissue oxygen extraction (FTOE) > 47%
- FTOE improved significantly after transfusion, regardless of arm
- No difference in number of transfusions, death, LOS, ROP
- Failure of randomization, **nearly 70% of transfusions in NIRS arm were given on "clinical basis" before hitting NIRS threshold**


ORIGINAL ARTICLE
A pilot randomised controlled trial of peripheral fractional oxygen extraction to guide blood transfusions in preterm infants
S P Wardle, R Garr, C W Yoxall, A M Weindling

Wardle et al., *Arch Dis Child, 2002*

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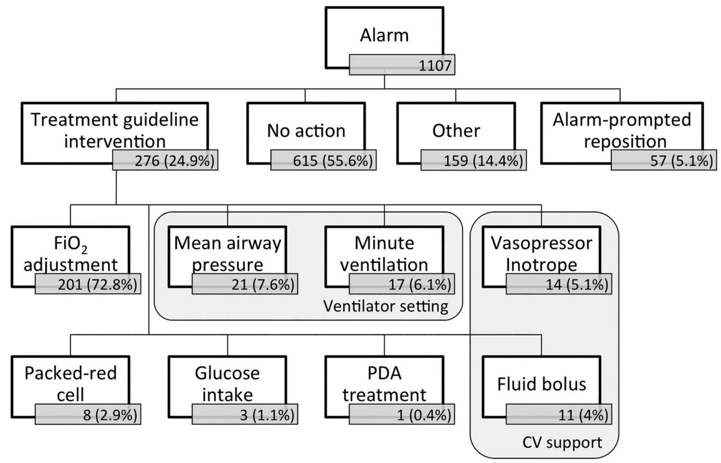
Didn't use it or used it wrong – an example from the literature

- SafeBoosC-II, 8-center phase II RCT of NIRS visible vs. not visible
- Treatment algorithm with 10 different options
- Number and type of interventions per site were tracked
- More than half of alarms were ignored
- 73% of interventions were ↑FiO_2



Riera et al., *Arch Dis Child*, 2016

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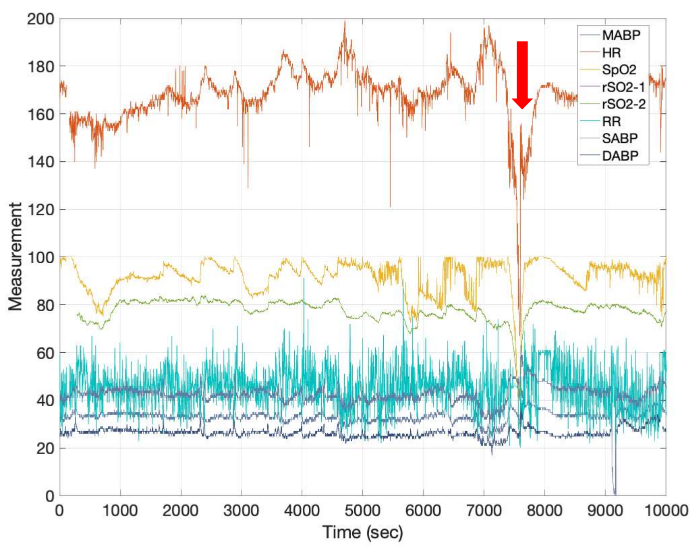
Case example 1



Bradycardia event (arrow) has broad impact on BP, SpO_2, rSO_2. NIRS doesn't provide much additional information here.

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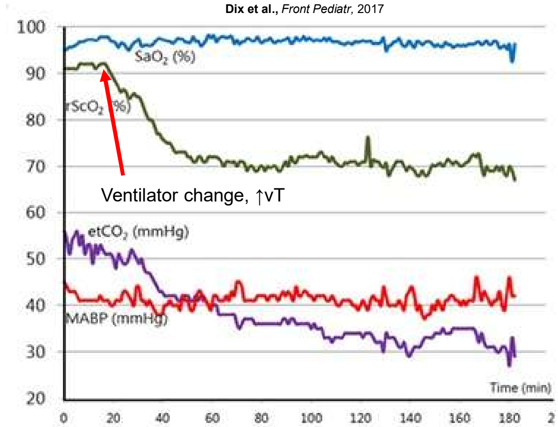
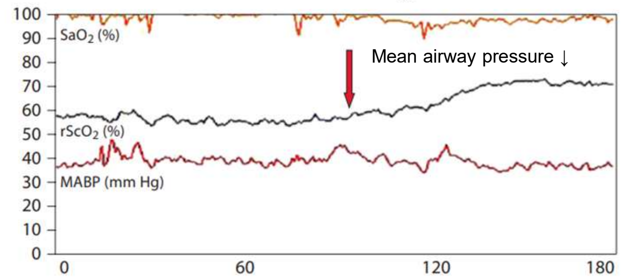
Case example 2: Ventilator management

Dix et al., *Front Pediatr*, 2017



The tidal volume was increased on this child's ventilator and resulted in overventilation. Rapid cerebral desaturation follows ↓pCO_2, which would otherwise be undetectable without NIRS (normal HR, normal BP, normal SpO_2).

Van Bel et al., *Neonatology*, 2008



This preterm infant is on high-frequency oscillatory ventilation. rSO_2 monitoring demonstrates saturations at threshold with normal SpO_2 and MABP. Mean airway pressure was decreased (red arrow) and rSO_2 improved into normal range.

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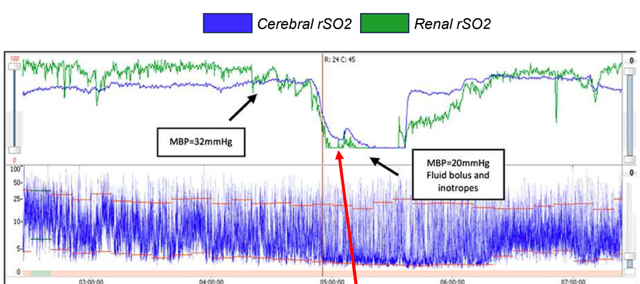
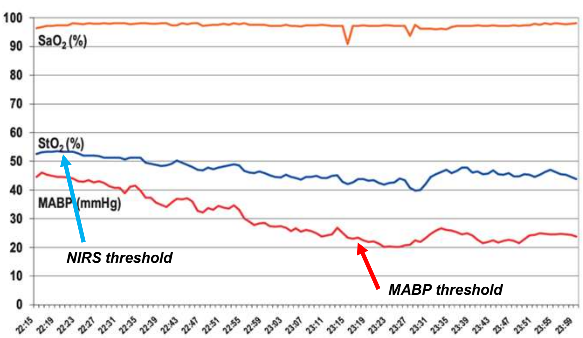
Case example 3: Hypotension



Varianne et al., *Front Pediatrics*, 2020

In this infant with **septic shock**, an early decrease in renal rSO_2 is noted, despite normotension. A rapid drop in MABP is accompanied by falling cerebral and renal rSO_2. After fluid bolus and inotropes, a recovery of renal and cerebral rSO_2 is noted.



Wolf et al., *JNIRS*, 2012

This 24-week infant gradually becomes hypotensive. Standard treatment would indicate intervention for MABP < 24 mmHg (red arrow). NIRS-guided management would indicate intervention nearly 1 hour earlier (blue arrow). Note SpO_2 remains normal the entire time.

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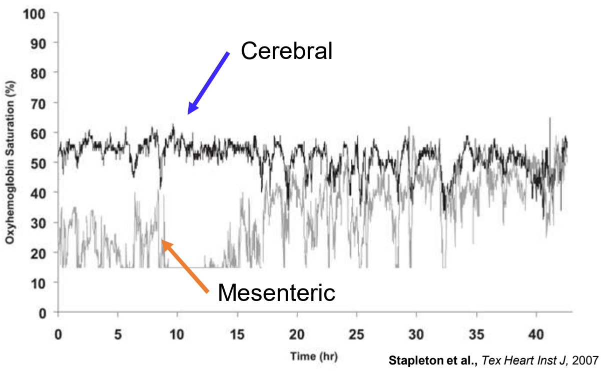
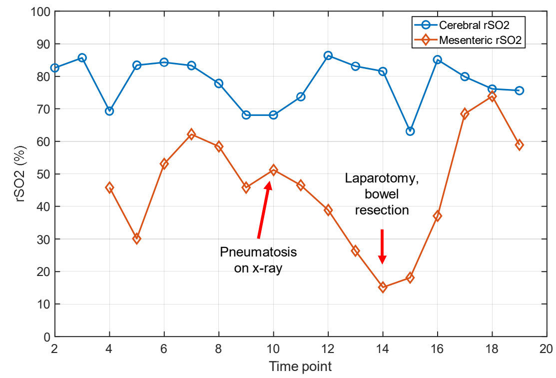
Case examples 4: Necrotizing enterocolitis





2400g term infant with pulmonary valve/artery atresia with MAPCAs awaiting surgical treatment when larger size. Diagnosed with NEC (pneumatosis, hematochezia). NIRS monitoring started 48 hours later, showed low-normal cerebral rSO2 and mesenteric rSO2 at lower limits of detection. Gradually improved and feeding restarted once normal.

26-week preterm infant, donor twin of twin-twin transfusion syndrome. Abdominal distention and pneumatosis at 2 weeks. Mesenteric rSO2 drops with onset of pneumatosis, continuing for multiple days, improving only after resection of necrotic bowel and washout .

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Case examples 5: ECMO complications

Noh et al., *J Extra Corpor Technol*, 2022

- Term neonate with meconium aspiration syndrome placed on VA ECMO for hypoxic respiratory failure.
- Cerebral and renal NIRS (green and blue, bottom panel) gradually decline over a 24-hour period.
- Ultrasound revealed large pericardial effusion which was drained with rapid improvement in cerebral and renal rSO_2.
- Note that MABP, SpO_2 remained normal throughout, subtle tachycardia.

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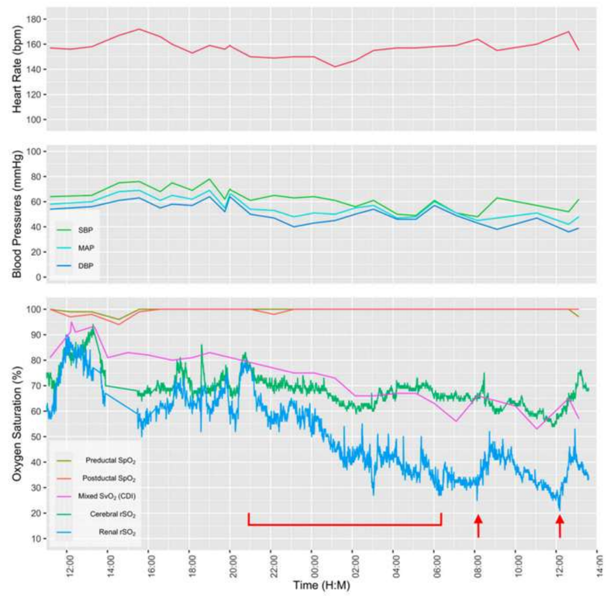
Case examples 6: More ECMO complications

- Term neonate placed on VA ECMO for congenital diaphragmatic hernia and hypoxic respiratory failure.
- Marked decrease in renal rSO2 (blue bottom panel) with preserved cerebral rSO2 (green)
- pRBC transfusion given (first red arrow) with transient improvement, second pRBC transfusion given (second red arrow) also with transient improvement.
- Abdomen became rigid and discolored, exploratory laparotomy demonstrated 400 mL abdominal hematoma



Noh et al., *J Extra Corpor Technol,* 2022

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NIRS monitoring indications

- Preterm infants
  - First 72 hours for early recognition of acute cerebral hypoxia related brain injury (IVH)
  - Identifying chronic hypoxia over NICU course, especially silent cerebral hypoxia
  - Evaluating response to treatments (hypotension, ventilator, transfusion, PDA)
- Term infants
  - HIE
  - Early detection of acute kidney injury
  - Adequate cerebral/renal perfusion, safety monitor during ECMO
  - Hemodynamic management during anesthesia

Van Bel and Mintzer, *Pediatr Res,* 2018

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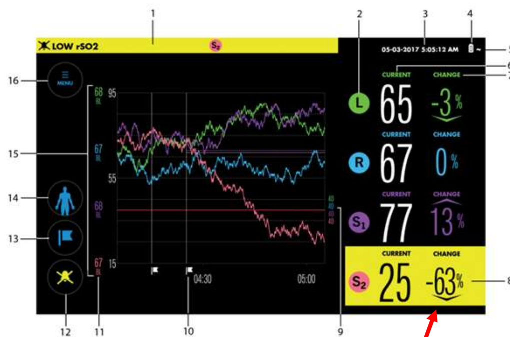
NIRS-directed hemodynamic management

- NIRS provides regional circulation monitoring and the opportunity to provide tissue-specific, directed interventions
- For many neonates, reference ranges (63-93%) can provide helpful target values
- For all patients, a lower threshold of 45% should be strictly avoided
- Baseline-Bottomline approach for critical care
  - Establish rSO_2 **baseline** in awake, stable patients
  - Monitor deviation from baseline, use corroborating evidence to provide directed interventions to maintain baseline values or higher
  - Decrease from baseline of more than 20% (**bottom line**) associated with adverse outcomes

Figure 2-8. Sample Monitoring Screen Elements



Change from baseline automatically calculated by monitor

Olbrecht et al., Anesthesiology, 2018; **Gomez-Pesquera et al.**, J Pediatr, 2019; **Weber and Scoones et al.**, Pediatr Anes, 2019

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Conclusions

- Hypoxia is an important driver of neonatal disease
- Pulse oximeters have a high degree of utility in clinical practice, but we must be cognizant of pitfalls
- NIRS is a distinct tool with a distinct use; it isn't just a fancy pulse oximeter
- There is compelling observational data that cerebral hypoxia is associated with true pathology -- this has not translated to successful NIRS RCTs

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SafeBoosC-III Intervention Algorithm

Rationale: Low cerebral oxygenation is the result of impaired cerebral oxygen delivery.
Approach: If cerebral oxygenation drops below the critical threshold (e.g. < 67% for ForeSight Elite monitors) and probe is properly positioned, intervention from one of these prongs should be considered. Responsiveness to assessment and any interventions should be evaluated **every 30-60 minutes.**

Cardiovascular Status	Oxygen transport	Respiratory status	IVH
Sign: Blood pressure below normal range[a]	Sign: Blood hemoglobin concentration below locally defined normal range (<8 or <10 g/dL)	Sign: SaO2 below normal range	Sign: Persistence of low NIRS (<67%) without evidence of other clinical problems
Interventions *(one or more interventions may be implemented)* • Fluid resuscitation with normal saline • Initiate vasopressor-inotropes • Decrease mean airway pressure (impaired venous return)	Intervention • Red blood cell transfusion	Intervention • Increase FiO_2 while maintain compliance with SpO_2 saturation alarm guidelines **(DO NOT EXCEED SPO2 of 95%)** • Increase mean airway pressure (*consider obtaining chest x-ray to evaluate lung expansion prior to increasing airway pressure*)	Intervention • Obtain head ultrasound at earliest convenience
Sign: Poor perfusion, defined as low cardiac output on ECHO or at least two of a) elevated lactate, b) prolonged capillary refill, or c) decreased urine output		Sign: pCO2 below normal range	
Intervention • Fluid resuscitation with normal saline • Decrease mean airway pressure • Initiate inotropes • Reduce vasopressor (decrease afterload)		Intervention: • Decrease minute ventilation	
Sign: Hemodynamically significant patent ductus arteriosus			
Intervention • Medical treatment (indomethacin, acetaminophen per local practices)			

Footnotes: [a]There are not well-established guidelines for normative blood pressure in preterm infants. The most common convention is the Zubrow definition(18) which targets a mean arterial blood pressure ≥ gestational in weeks (e.g. 24 mmHg for infant born at 24 weeks EGA). However, treatment decisions should not be based solely on a number, but rather the combination of cerebral desaturation, hypotension, and evidence of impaired perfusion.

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