

Biosensors of Neonatal Physiology

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Objectives

- Define the neonatal population
- Consider the motivations for developing neonatal biosensors
- As an example of obstacles to monitoring sick newborns, review the current approaches of monitoring for neonatal shock
- Explore the advantages offered by neonatal biosensors
- Expand the possibilities for developing other biosensors of neonatal physiology

Define the Neonatal Population We Are Talking About

Most of us know about low-risk newborns

- 83% of all newborns
- Essentially 100% survival following delivery
- Discharged home in 1-3 days
- Mean hospital cost \$2,800
- Problems limited to slow feeding, spitting up, and jaundice



Define the Neonatal Population We Are Talking About

Who are the high-risk newborns?

- 17% of all newborns
- 25-95% survival following delivery
- Discharged home in days to years
- Mean hospital cost \$44,300
- Slow feeding, spitting up, and jaundice are the least of their problems

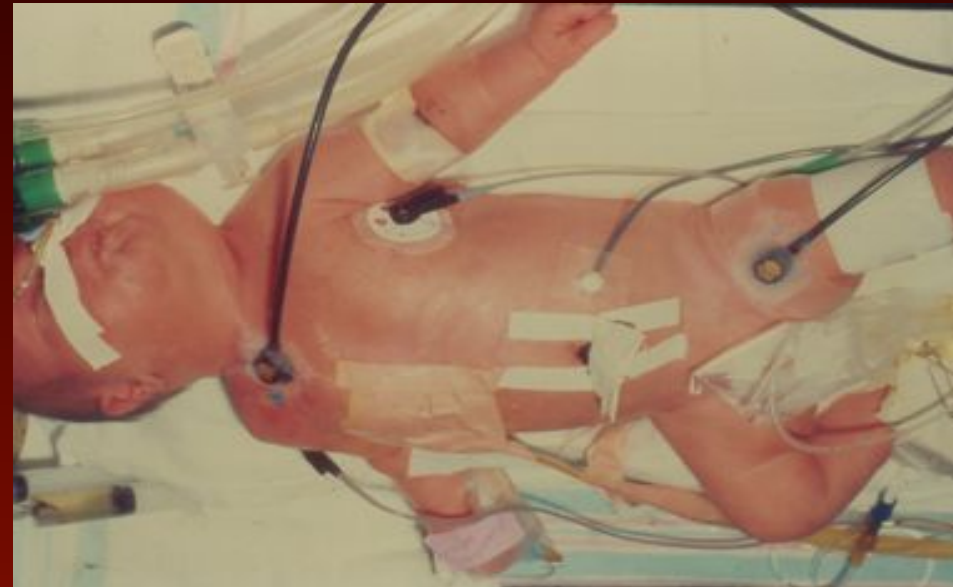
Yes, that's a BIC pen



Not All High-Risk Newborns Are Small BUT Are Slow to Adapt

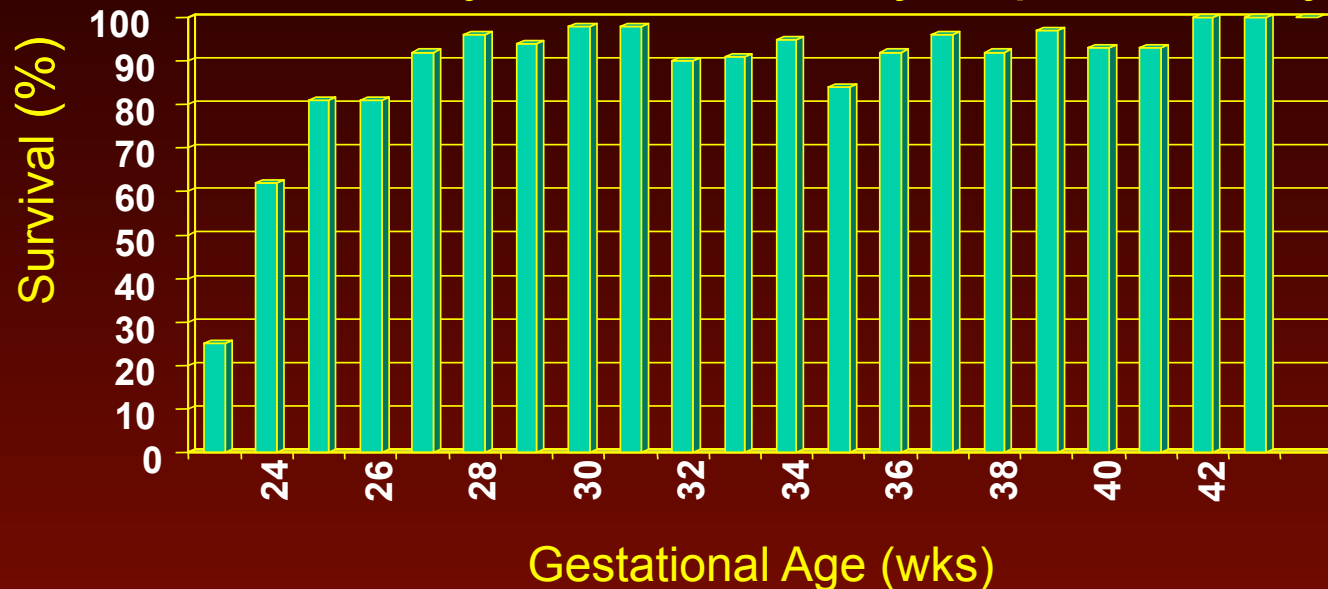
All they have to do to go
home is:

- Pee
- Poop
- Breathe
- Feed by nipple
- Grow
- And keep their temperatures and heart rates normal
- Usually occurring within 1-3 weeks



Why Are These Newborns Called High-Risk?

- Because they are at risk of dying
 - Survival is inversely tied to severity of prematurity



- Because they are at risk of permanent disabilities
 - ~2/3 of ELBW survivors have impaired QOL as adolescents
 - 25-40% of ELBW survivors have CP or MR

Consider the Motivations for Developing Neonatal Biosensors

As scientists and engineers interested in the development of sensors for human health monitoring, we are motivated by the:

- Potential for saving lives and promoting the health of high-risk newborns
- Cross-application to other patient populations
- Economic incentives

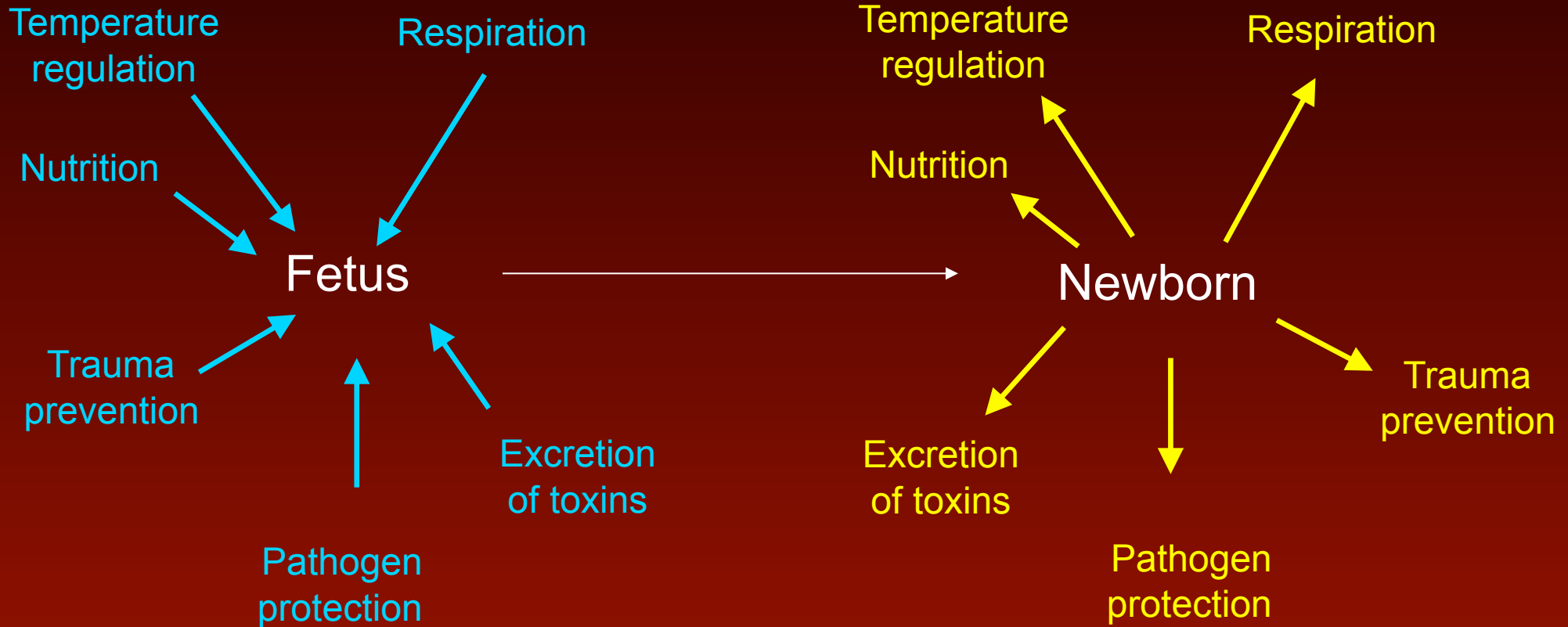
Motivation: Potential for Saving Neonatal Lives

- Most are born without disease and are **structurally and functionally normal** for gestational age
 - But are immature and unprepared for life outside the womb
- Disease develops
 - As their bodies adapt to extrauterine life
 - As their bodies respond to life-saving therapies
 - As their bodies are invaded by microorganisms

Adaptation from Placental Dependency to Extrauterine Survival

Placenta, fetal membranes and umbilical cord

Extrauterine environment



Responses to Life-Saving Therapies Have Their Benefits and Their **Costs**



Invasion by Microorganisms

- After the first week of life, infection is a contributing factor to at least 50% of all neonatal deaths

Motivation: Cross-Application to Other Patient Populations

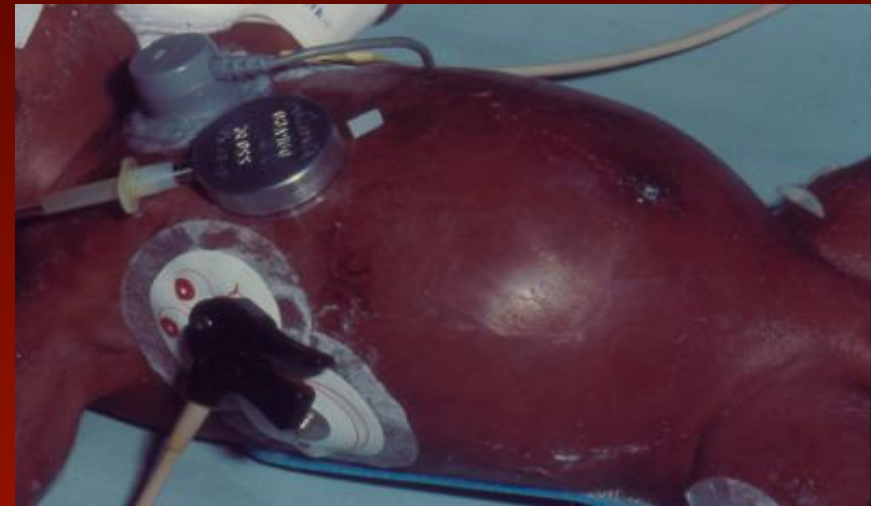
- In the world of critical care medicine - the causes of failing organ systems may differ among patients, but the presentations of organ failure are the same:
 - Hemodynamic failure → Shock
 - Renal failure → Anuria
 - Respiratory failure → Hypoxia, high pCO₂
 - CNS failure → Coma

Motivation: Economic Incentives

- At least 35% of all US infant health care costs relates to the care of high-risk newborns
- Direct costs of high risk neonatal care ($\$10 \times 10^9$) are comparable to those of other major US healthcare problems
 - HIV/AIDS - $\$10 \times 10^9$
 - Alzheimer's - $\$18 \times 10^9$
 - Cancer - $\$25 \times 10^9$
- Cost of newborn care is more cost-effective than most adult therapies because of the extended lifespan of survivors
 - In cost per year of life saved, a 1% improvement in mortality provided by a sensor device that costs \$10,000 per infant translates to the cost of \$1,430 per year of life saved ($\$1,000/[0.01 \times 70 \text{ years}]$)
 - Versus costs of \$16,400 for thiazides in hypertension, \$54,000 for heart transplantation in heart failure, and \$178,000-314,000 for lithotripsy or cholecystectomy in gallstone treatment

Obstacles to Monitoring Sick Newborns with Shock As An Example

- How do I determine whether this infant is entering shock when:
 - Withdrawal of 4-6 cc blood for blood testing will contribute further to shock
 - Total blood volume is as little as 1.3 ounces in a 500 g newborn
 - Violation of skin integrity increases infectious risk
 - Vascular access is limited
 - Serum markers of shock are nonspecific and insensitive – there is no bedside-available gold standard for defining shock in newborns
 - Serum data are non-continuous
 - Turnaround time is minutes to hours
 - Newborn can't tell me anything
 - Newborn is too sick to move elsewhere for sophisticated imaging procedures



What Might Be the Best Approach to Monitoring for Shock?

- Shock occurs when the cardiovascular system fails to meet the metabolic needs of organs
- Because organs are composed of cells dependent on aerobic metabolism, organs begin to fail when insufficient oxygen delivery drives cells from aerobic to anaerobic metabolism
- In clinical medicine, direct markers of this switch from aerobic to anaerobic metabolism are not available

What Is the Best Clinically-Available Approach to Monitoring for Shock?

- Insufficient oxygen delivery occurs when the balance between O_2 delivery (DO_2) and consumption (VO_2) is not maintained
- This balance is measured as the fractional oxygen extraction (FOE)
 - $FOE = VO_2/DO_2 = (S_aO_2 - S_vO_2)/S_aO_2$
 - $DO_2 = \text{cardiac output } (Q_s) \times \text{arterial oxygen content}$
 $= \frac{\text{arterial BP} - \text{central venous P}}{\text{systemic vascular resistance}} \times (\text{Hgb} \times 1.39 \times S_aO_2)$
 - $VO_2 = \text{cardiac output } (Q_s) \times \text{extracted oxygen content}$
 $= Q_s \times (\text{Hgb} \times 1.39 \times [S_aO_2 - S_vO_2])$

For these equations, the only measurable parameters directly available to clinicians are S_aO_2 and Hgb

And even if we did know S_vO_2 at the systemic level, early shock of a particular organ system could be masked by preserved perfusion at the systemic level

Currently Available or Investigatory Noninvasive Methods for Detecting Shock in Newborns

- Heart rate
 - Heart rate is a determinant of cardiac output (Q_s) that tends to increase with established shock ($R^2 = 0.07$)
- Systolic/diastolic/mean blood pressures
 - Blood pressure variables are the most widely used clinical indicators of shock
 - Correlation with Q_s varies with changes in systemic vascular resistance ($R^2 < 0.2$)
- Capillary refill time
 - Highly subjective and influenced by environment and ductal patency ($R^2 < 0.5$)
- Extremity temperature / core-peripheral temperature gradient
 - Strongly influenced by autonomic maturity, environment, capillary refill time – very unreliable

Available Noninvasive Methods for Detecting Shock

- Tissue pH
 - Has potential but currently invasive technique
- Indirect Calorimetry
 - Measures VO_2 and VCO_2
 - Sequential monitoring provides the opportunity to detect onset of anaerobic metabolism
 - Not clinically available in nursery
- CO_2 rebreathing techniques
 - Permits calculation of cardiac output
 - But assumptions limit the validity and small tidal volumes eliminate the utility in patients weighing < 15 kg

Available Noninvasive Methods for Detecting Shock

- Bio-impedance technique
 - Measures changes in electrical impedance across chest as function of thoracic gas and blood volume
 - Influenced by changes in lead placement, posture, temperature, respiratory effort and blood volume
 - Lacks validation in infants
- Perfusion Index (PI)
 - Calculated from pulse oximetry as ratio of absorbed arterial inflow light divided by nonpulsatile absorbed light
 - $R^2 = 0.10$ for blood flow and DO_2 as determined by NIRS
 - Does not correlate with VO_2 or FOE

Available Noninvasive Methods for Detecting Shock

- Near-Infrared Spectroscopy (NIRS) methods
 - Clinically available in one device from Somanetics[®]
 - (~\$30,000 for device + ~\$150/sensor pair)
 - Provides continuous measurement of regional oxygenation (rSO₂)
 - rSO₂ purportedly evaluates the regional balance between O₂ delivery and consumption for comparison of regional differences
 - e.g. cerebral rSO₂ vs intestinal, renal, or somatic rSO₂
 - This is the most promising, clinically-available, noninvasive method for detecting early neonatal shock
 - But R² values vary from <0.50 to 0.80 in early neonatal studies

Potential Advantages Offered by Neonatal Biosensors

- Noninvasive biosensors
 - Provide valid, reproducible, sensitive and specific, easily interpreted data that predict need for intervention
 - Are safe, nontoxic, noninfectious, non-inflammatory and without significant adverse side effects
 - Are small and portable
 - Do not interfere with transmission of other electromagnetic radiation
 - Are cost-effective
 - Take advantage of possible marker molecules (natural vs synthetic)



Possibilities for Developing Other Biosensors of Neonatal Physiology

- Refer back to the concepts that
 - Most high-risk newborns are born without disease and that disease develops
 - As their bodies adapt to extrauterine life
 - As their bodies respond to life-saving therapies
 - As their bodies are colonized by microorganisms
- We need noninvasive monitoring techniques that monitor
 - Organ system adaptation to extrauterine life
 - Organ system responses (+/-) to therapy
 - Organ system colonization/infection by microorganisms

Thank you!

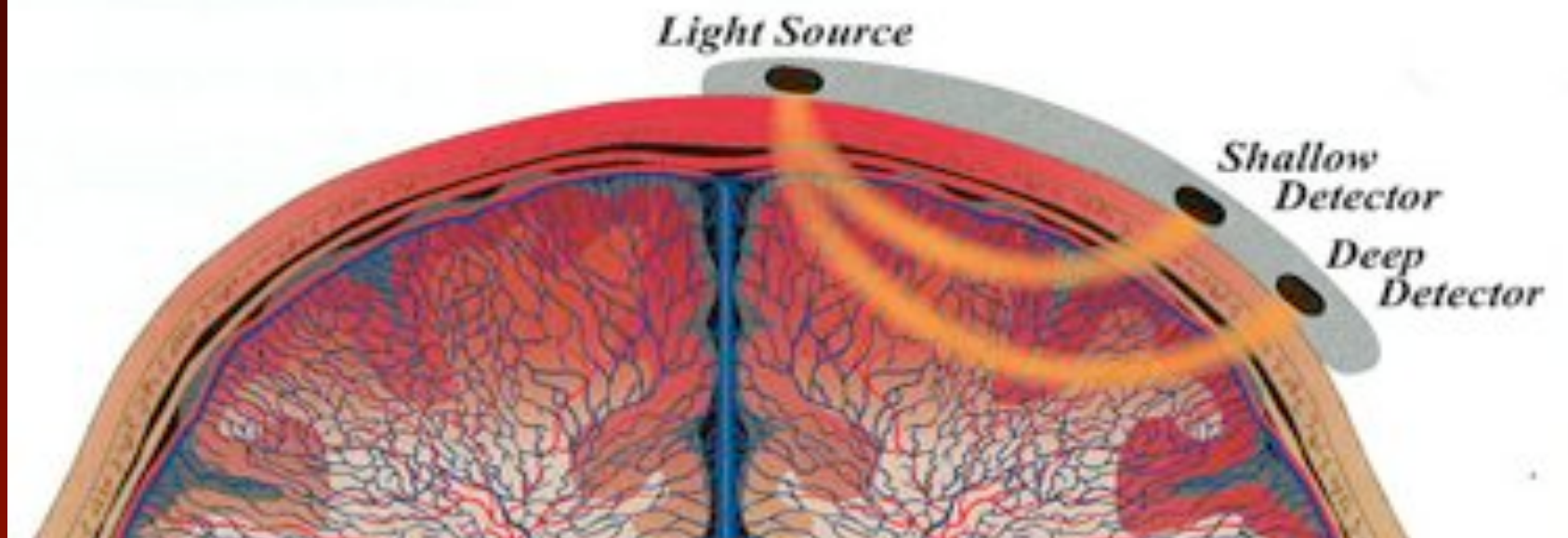
- Any questions?
- Email:
DOelberg@chkd.org





Somanetics' Device for Monitoring rSO₂

The INVOS System uses two depths of light penetration to subtract out surface data, resulting in a regional oxygenation value for deeper tissues.



Neonatal Organ Systems Assuming Placental Functions

- Temperature regulation
 - Endocrine/Metabolic
 - Skin
 - Central nervous system
- Trauma prevention
 - Skin
- Pathogen protection
 - Hematopoietic/Immune
 - Skin
- Nutrition
 - Gastrointestinal tract
 - Endocrine/Metabolic
- Respiration
 - Pulmonary
 - Cardiovascular
- Toxin excretion
 - Renal
 - GI

What's the Noninvasive Approach to Monitoring for Shock

- $FOE = VO_2/DO_2 = (S_aO_2 - S_vO_2)/S_aO_2$
- $DO_2 = \text{cardiac output } (Q_s) \times \text{arterial oxygen content}$
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