Neonatal Anesthesia

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Objectives

- Provide brief overview of Pertinent Neonatal Physiology and Pharmacology
- Discuss basic management strategies to reduce the risk of neonatal anesthesia

Neonatal Anesthesia

- Neonate- First 28 days of life (GA)
- ↑ risk of perioperative cardiac arrest
  - 13% in POCA studies, 1994-2004[1]
  - ↑ Risk in Mayo Study, 1988-2005[2]
  - Critical events 4X greater in infants < 1 year[3]
  - Highest incidence of adverse events <1 month[4]
  - Higher with co-morbidities and emergency procedures

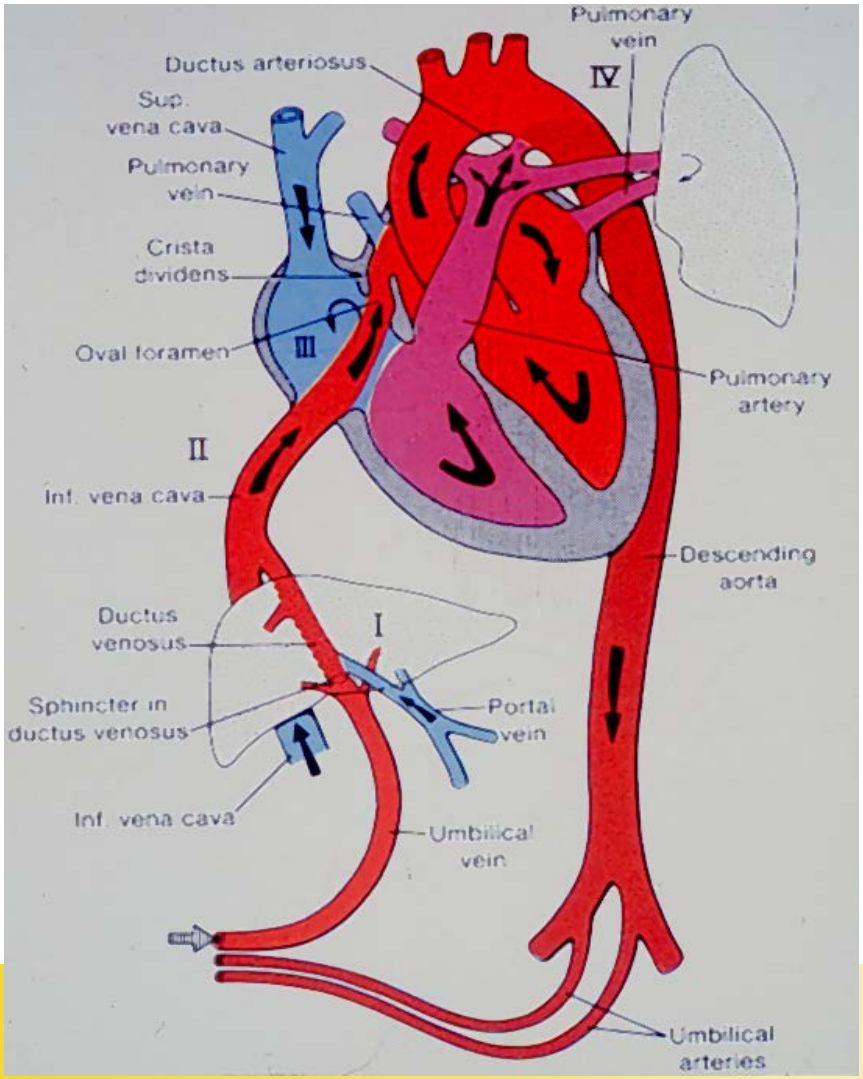
1.Bhanaker S. Anesth Analg 2007, 105:344

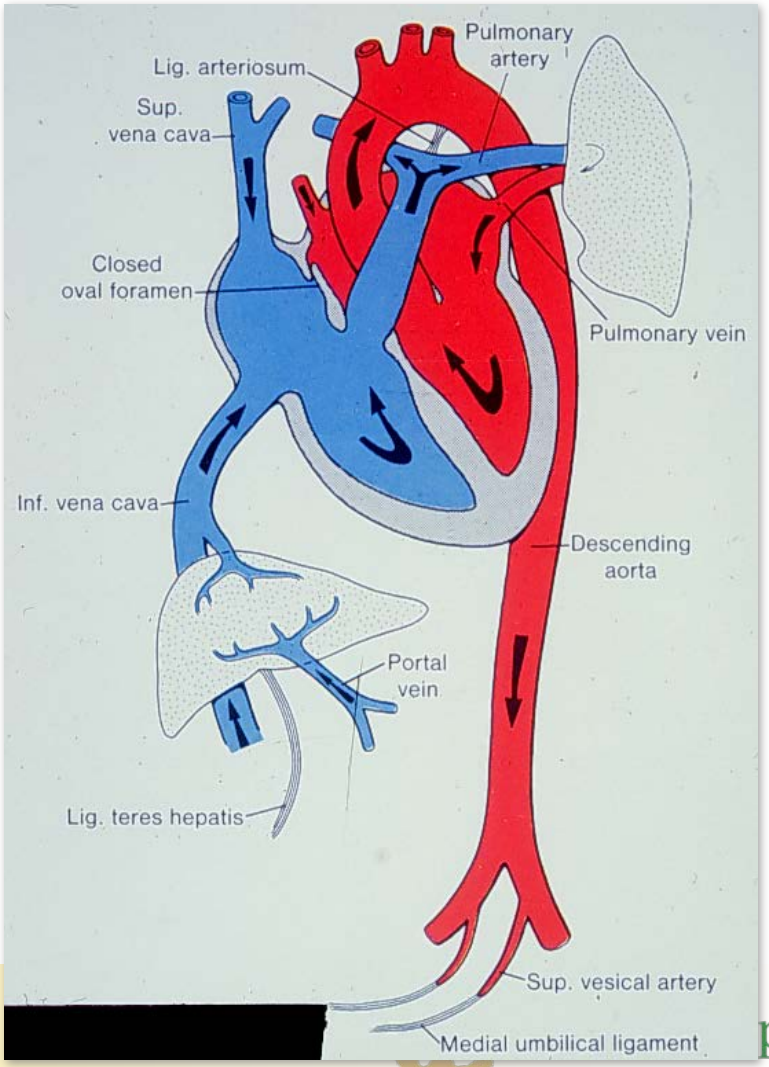
2. Flick R. Anesthesiology 2007, 106:226

3. Tay C. Pediatr Anesth 2001,11:711

4. Cohen M. Anesth Analg 1990, 70:160

TRANSITION

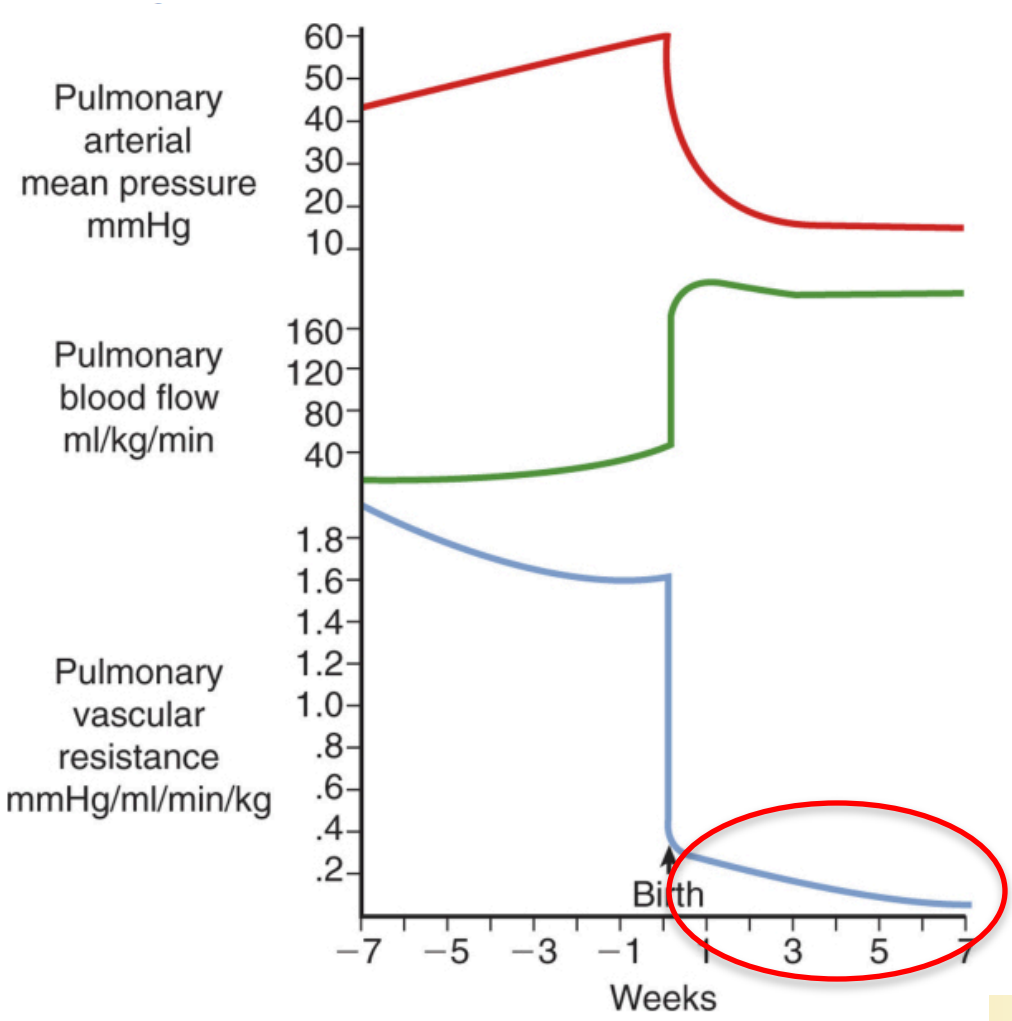




Transitional circulation

- Functional closure of DA: 10-15 hours
  - Increased PaO2 and decreased circulating prostaglandins
  - Full term 58% by DOL 2 and 98% by DOL 4
- Ductal fibrosis: 2-3 weeks → ligamentum arteriosus
- Functional closure of the foramen ovale
  - LAP > RAP
  - Anatomical closure delayed and variable
    - 50% of children < 5y/o
    - 25% of adults
- Serial circuit: two different systems (LV and RV) with two different resistances to flow (PVR and SVR)

The Normal *Transition*



- Very high PVR in utero
- Largest decrease in PVR occurs at birth
- Second drop: 4 to 6 weeks
- Level at about 6 months of age
- Initially the pulmonary vasculature is very reactive
- PFC and RV dysfunction

Rudolph, A.M., *Congenital diseases of the heart: Clinical-physiological considerations*. 2009, Wiley-Blackwell: West Sussex, UK. p. 89.

Conditions Prolonging Transitional Circulation

- **H**ypoxemia
- **H**ypercarbia
- **H**ypothermia
- **H+** Acidosis
- Congenital Heart Disease (CHD)
- Prematurity
- Sepsis
- Pulmonary Disease
- Hypo/Hyperglycemia
- Hypocalcemia
- High Altitude
- Prolonged Stress

How is the neonatal heart different?

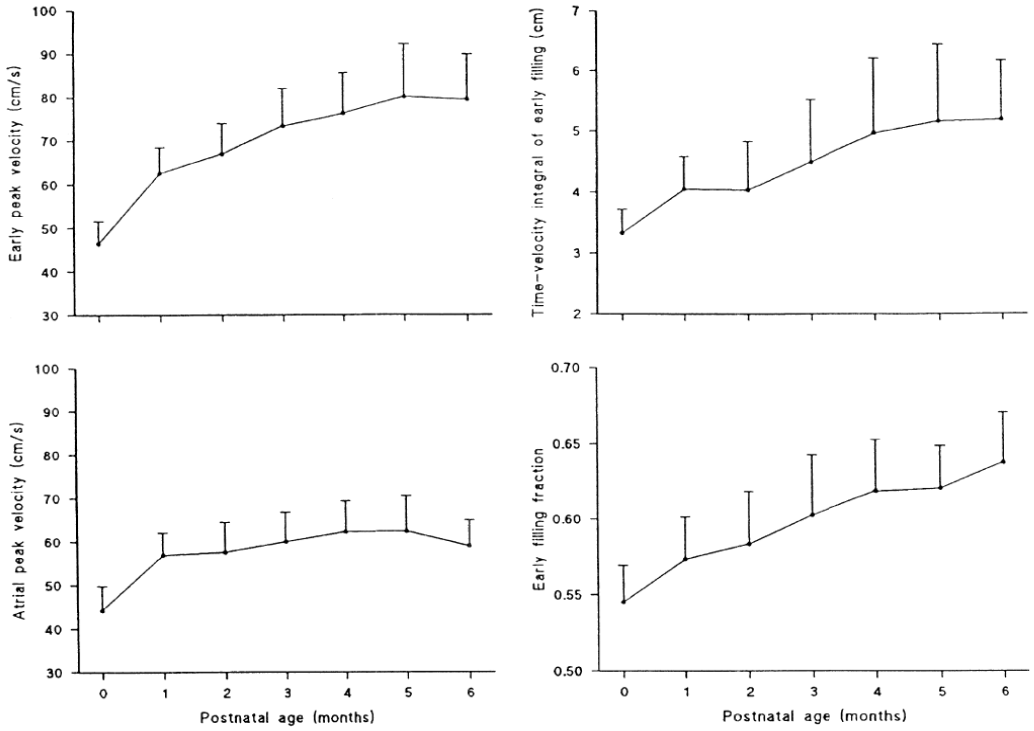
- Myocardial cells are disorganized
  - Less compacted
  - Increased non contractile tissue and water
  - High amount of collagen in relation to myocytes
  - Type I (rigidity) >>>type III collagen (elasticity)
  - Ventricular compliance is reduced-Delayed diastolic relaxation
  - Inefficient as a filling and contracting unit

Marijianowski M. JACC 1994,23:1204

How is the neonatal heart different?

- ↓capacity to ↑stroke volume in response to ↑preload FLAT Starling curve CO is HR dependent
- Vulnerability to overfilling
- Wall tension rises rapidly
- Coronary perfusion falls
- Over distention
- Heart failure.
- **Good news-**diastolic relaxation improves within the first month

Efficiency of left ventricular diastolic function increases in healthy full-term infants during the first months of life



ig. 1. Doppler echocardiographic mitral filling indices (mean±S.D.) with response to age in full-term ıfants ($N = 20$).

E velocity - LV relaxation
A velocity - LV compliance

Early Human Development 57 (2000) 49–59

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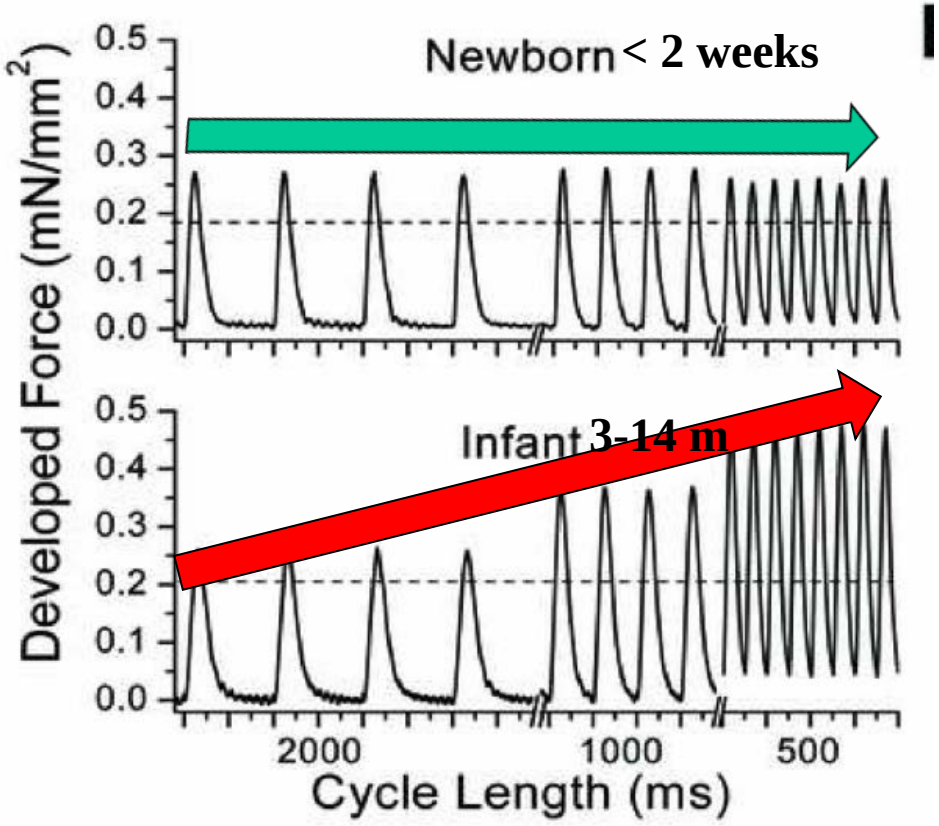
Force Frequency Relationship of the Human Ventricle Increases During Early Postnatal Development

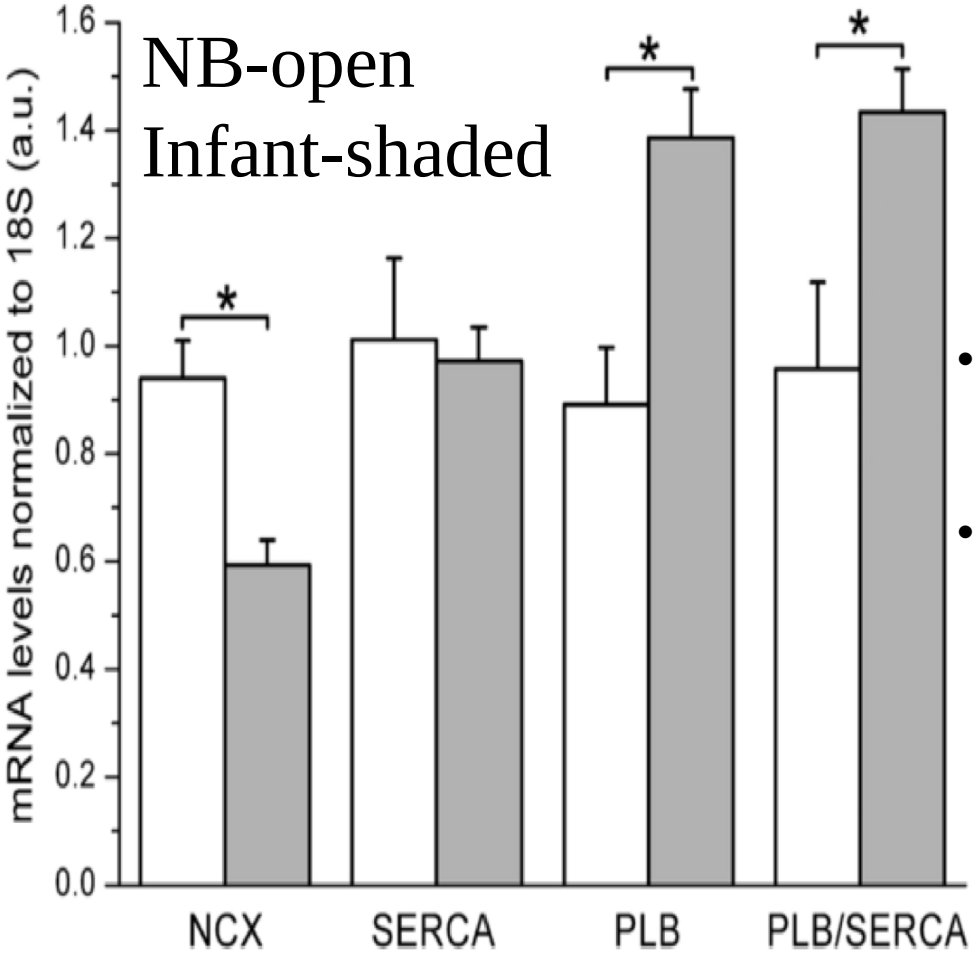
Wiegerinck R, Pediatr Res 2009,65: 414



Flat or negative FFR is a characteristic feature of heart failure

Force Frequency Relationship of the Human Ventricle Increases During Early Postnatal Development

Wiegerinck R, Pediatr Res 2009,65: 414



- Decreased levels of PLB or PLB/SERCA -associated with the blunted FFR seen in heart failure
- May be caused by developmental changes in calcium handling

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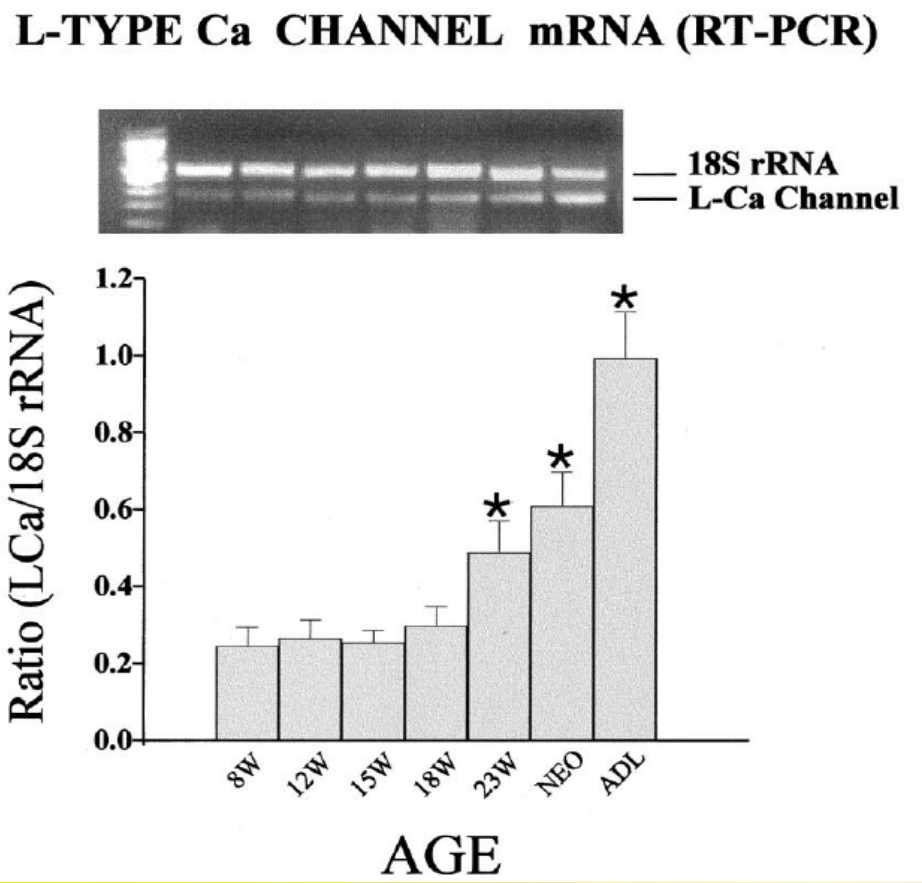
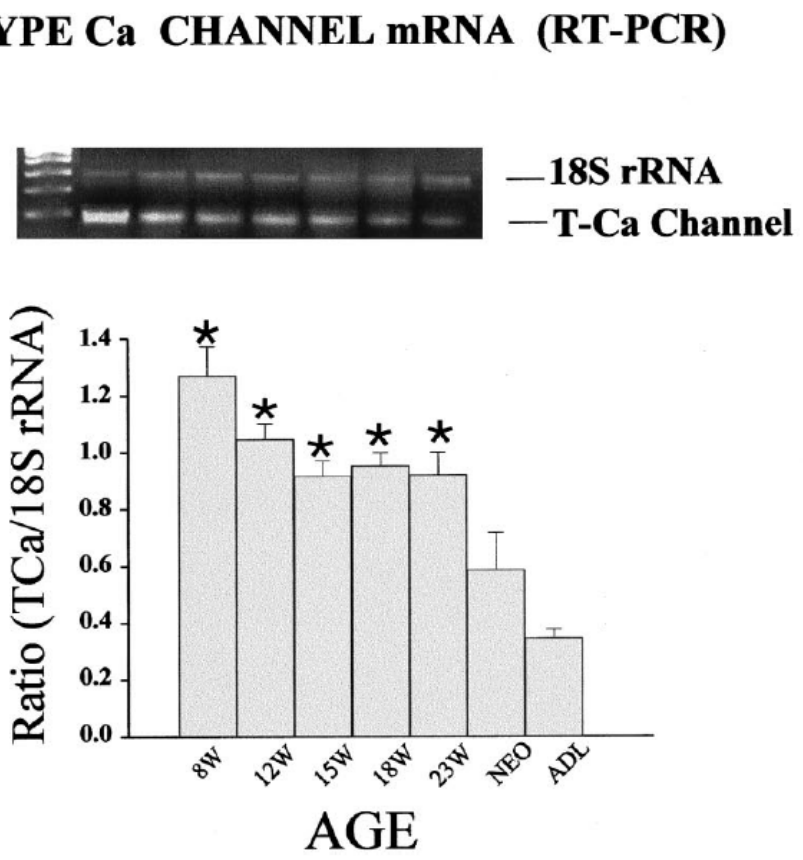
Gene Expression of SERCA2a and L- and T-type Ca Channels during Human Heart Development

QU Y, Pediatr Res 2001, 50:569





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How is the neonatal heart different?

- Poor calcium flux into the cell due to the immaturity of the t-tubular and SR system
- Decreased ryanodine receptors- limits release of calcium to activate contraction
- Reuptake of Ca^{+} into SR is limited preventing diastolic relaxation
- Neonate VERY dependent on extracellular calcium for cardiac contraction
- **Good News-**Rapid development of SR, t-tubular system and calcium handling proteins

How is the Neonatal Heart different?

- Parasympathetic innervation more developed than sympathetic
  - Increased cholinergic receptors
- High levels of catecholamines at birth
  - Maximal adrenergic stimulation of myocardium
  - Reduced functional reserve

How is the neonatal heart different?

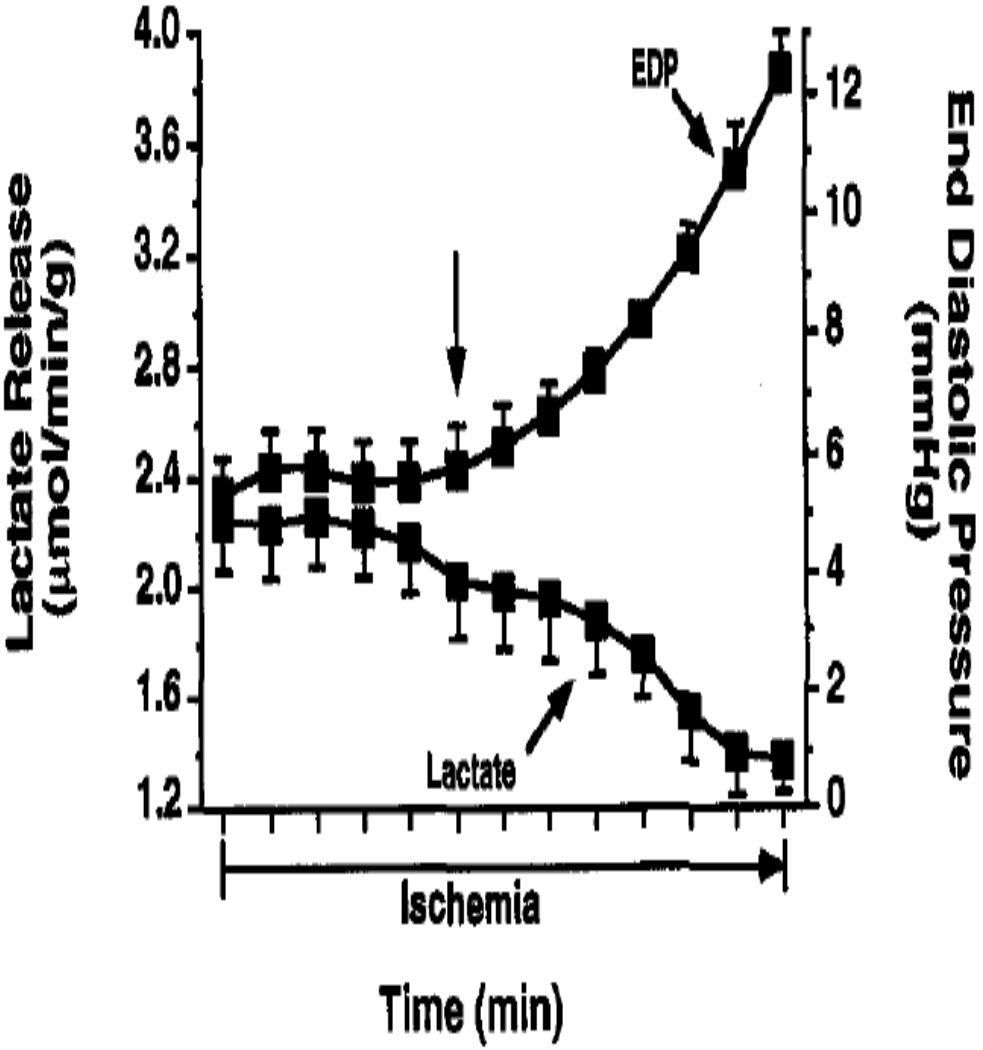
Cellular energy derivation

- Fetus-glucose and glycolysis
- Neonate- carbohydrate and short chain fatty acids
- Adult-long-chain fatty acids

Substrate Metabolism in the Developing Heart

Ischemia

Ascuitto R. Seminars in Perinatology1996, 20:542



⬇ =Depletion of ATP & myocardial contracture

- Lactate is an end product of Glycolysis
- Decreased Myocardial Lactate with onset of contracture
- Contracture may indicate cessation of glycolysis

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Substrate Metabolism in the Developing Heart

Ascuitto R. Seminars in Perinatology1996, 20:542

Hypoxia

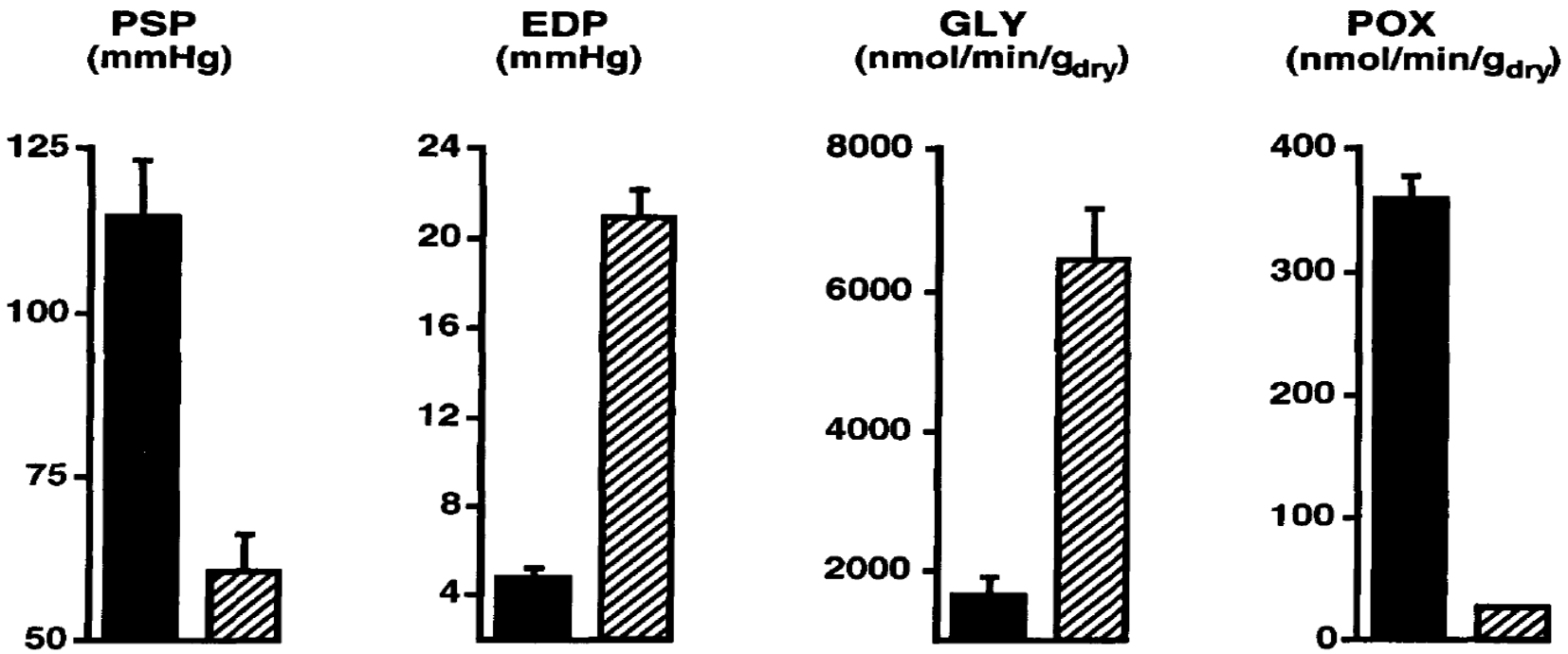

Figure 3. Average values of left ventricular peak systolic pressure (PSP) and end diastolic pressure (EDP), glycolysis (GLY) and palmitate oxidation (POX) in a group of hearts perfused with glucose (5.5 mmol/L) and palmitate (0.5 mmol/L) as the substrates. Hearts were perfused during a 30-minute baseline (pO_2 ~ 550 mm Hg, ■), followed by 30 minutes of hypoxia (pO_2 ~ 55 mm Hg, ▨). Values are expressed as means ± SEM.

Substrate Metabolism in the Developing Heart

Ascuitto R. Seminars in Perinatology1996, 20:542

Tachycardia

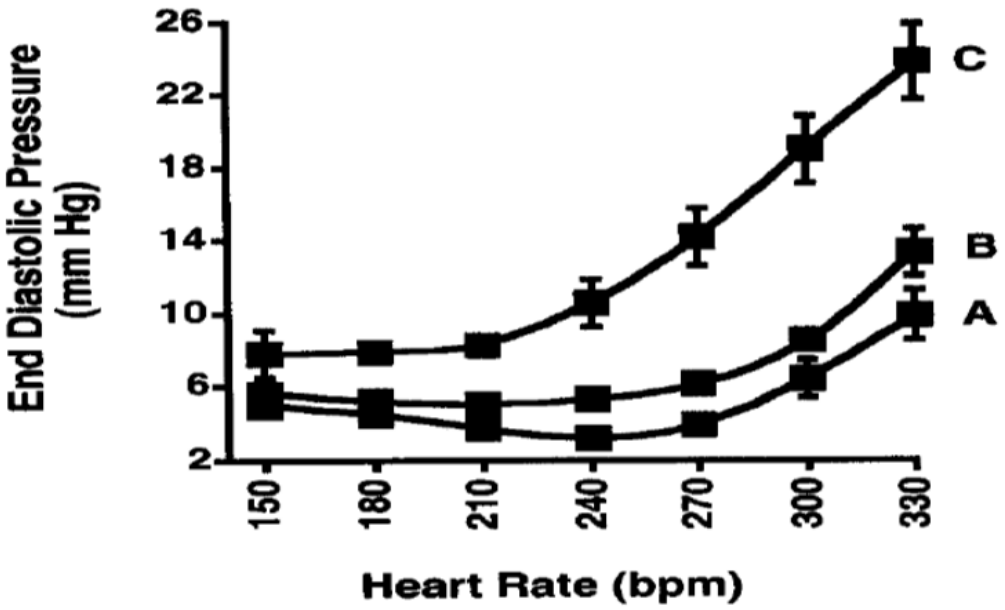

Figure 4. Left ventricular end diastolic pressure (EDP) versus HR (diastolic HR-response curve), for neonatal pig hearts subjected to pacing-induced tachycardia. (A) Hearts perfused with glucose (5.5 mmol/L) alone. (B) Hearts perfused with glucose (5.5 mmol/L) and palmitate (0.5 mmol/L). (C) Hearts perfused with glucose (5.5 mmol/L), iodoacetate (50 μmol/L) to inhibit glycolysis and pyruvate (5.5 mmol/L) to sustain oxidative metabolism. (Reprinted with permission.[87])

Treatment of Low Cardiac Output Syndrome (LCOS)

- Goal: Increase oxygen delivery to tissues
  - Optimize volume and hemoglobin
  - ***Glucose and Calcium are essential for neonatal myocardial function***
  - Drugs that increase afterload are usually NOT helpful
  - CO is HR dependent
  - Are catecholamines most useful?

0031-3998/94/3601-0049$03.00/0
PEDIATRIC RESEARCH

Vol. 36, No. 1, 1994
Printed in U.S.A.

Heart Rate Independence of Catecholamine-Induced Myocardial Damage in the Newborn Pig

JOSEPH CASPI, JOHN G. COLES, LEE N. BENSON, STANLEY L. HERMAN, JANET AUGUSTINE ACT, AND GREGORY J. WILSON

Table 1. *Comparison of mean hemodynamic variables and contractile indices between pacing and high-dose E groups**

	Epinephrine			Pacing		
	Before	30 min	After	Before	30 min	After
ESP (mm Hg)	60 ± 8.6	110 ± 19†	56 ± 9.6	68 ± 9.6	72 ± 12	67 ± 12
SV (mL)	5 ± 2.4	4.5 ± 2.8	4 ± 1.2	5.4 ± 1.2	4.8 ± 1.4	5 ± 2.4
SW (erg · 10^3)‡	200 ± 25	310 ± 35†	160 ± 18†	210 ± 18	240 ± 20	185 ± 20
CO (mL/min)	800 ± 130	1150 ± 240†	640 ± 140†	700 ± 120	1000 ± 320†	680 ± 160
Ees (mm Hg/mL)	9.8 ± 3.5	16 ± 6†§	5 ± 2.4†	8.2 ± 2	9.6 ± 3.3	7.4 ± 2.4
V_{100} (mL)	4 ± 3	3 ± 2.2	8 ± 2.4†§	4.3 ± 2.4	4 ± 1.4	5 ± 1.9

* All data are expressed as mean ± SD. ESP, end-systolic pressure; SV, stroke volume; SW, stroke work; CO, cardiac output.

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Table 2. *Comparison of diastolic data between pacing and E groups**

	Epinephrine			Pacing		
	Before	30 min	After	Before	30 min	After
EDP (mm Hg)	4 ± 2.8	5 ± 3	7 ± 2.4†	3 ± 1.2	2.5 ± 2	4 ± 2.4
EDV (mL)	9.4 ± 2.4	8 ± 2.2	13 ± 2.2†	10 ± 1	9 ± 1.2	10 ± 2.4
k (mL^{-1})	0.36 ± 0.2	0.6 ± 0.3†‡	0.58 ± 0.2†‡	0.4 ± 0.2	0.36 ± 0.1	0.4 ± 0.2

* All data are expressed as mean ± SD. EDP, end-diastolic pressure; EDV, end-diastolic volume; k, chamber stiffness index.

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- Pathological changes- age related
- Neonatal heart most vulnerable

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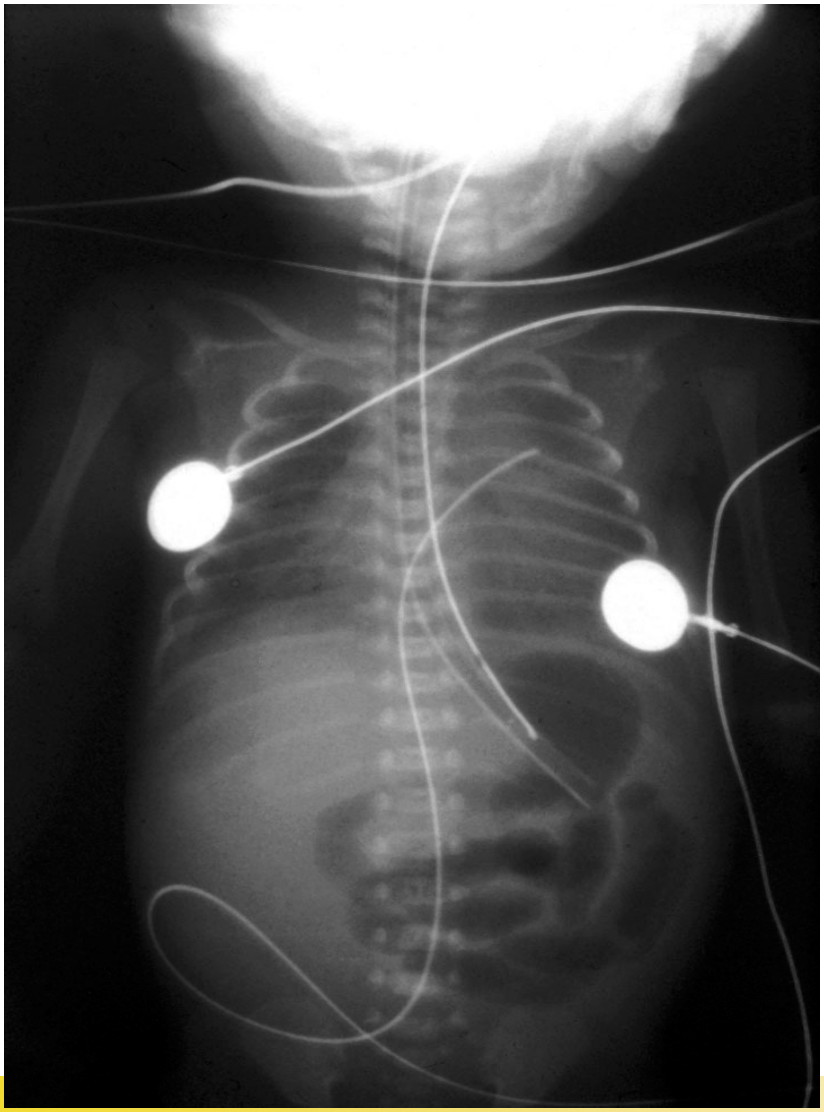
Pharmacology Mechanism of Action and Uses of Selective Phosphodiesterase Inhibitors

Skoyles JR, Br J Anaesth1992, 68: 293

- Milrinone inhibits hydrolysis of cAMP within the myocardium via blockade of phosphodiesterase enzyme (PDE)
- Increases the availability of calcium within the sarcolemma during systole
- Beneficial for neonatal heart due to poor diastolic relaxation and limitations of calcium flux into myocyte

Neonatal Respiratory Mechanics



- Neonatal chest wall VERY Compliant → difficulty sustaining FRC against lung elastic recoil
- Diaphragm is relatively flat
- Diaphragm and ICS contain less type 1 fibers (slow twitch, fatigue-resistant)
  - <37 wk < 10%
  - Term infant 25%
  - Adult 50%
- Glycogen and fat storage is less in respiratory muscles

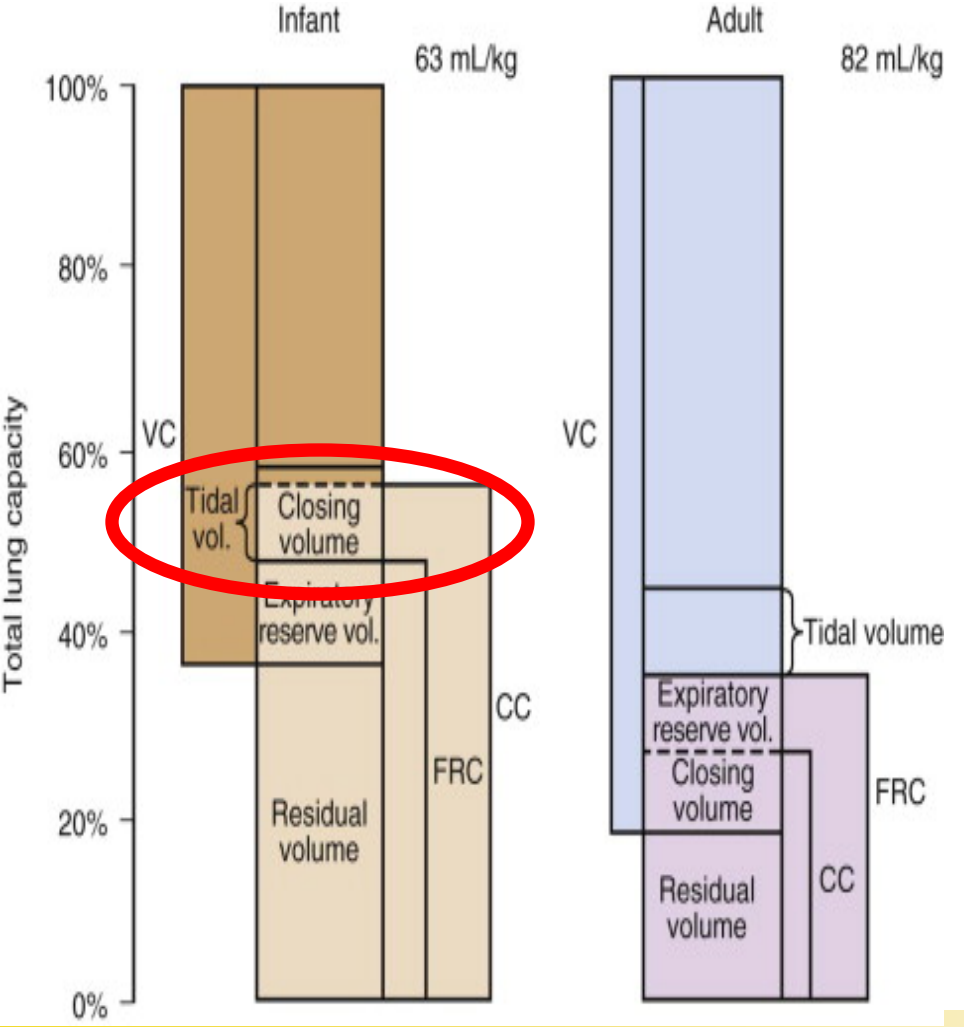
Ventilation - Neonates

- Periodic breathing → apnea < 10 sec
  - Without cyanosis or brady
  - During quiet sleep
  - 80% of term neonates
  - 100% of preterm
  - 30% of infants up to 1 yo

Ventilation Central Apnea

- Apnea > 15 seconds
- Apnea associated with HR< 100, cyanosis or pallor
- Rare in full term
- Majority of premature

Lung Volumes in Infants and Adults



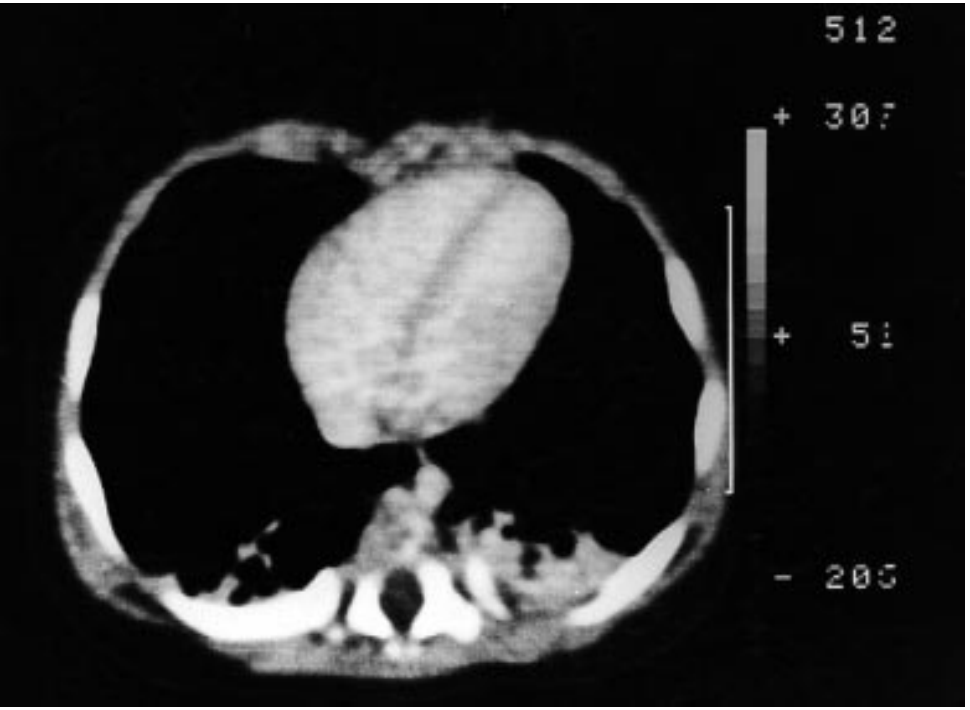
Great risk for atelectasis, VQ mismatch, desaturation. Airway closure may occur during TV ventilation PEEP Helps!

Neonatal Respiratory Mechanics
Elastic Properties

- Awake infants maintain FRC actively
  - "premature" stop of expiration
  - Fast breathing
  - Glottic closure during expiratory phase (*laryngeal braking*)
  - Diaphragmatic "braking"
  - Tonic contractions of diaphragm/intercostals (*higher tone*) → stiffens chest wall → maintain higher end expiratory Volume
- ***All*** lost by GA

Pulmonary atelectasis during paediatric anaesthesia: CT scan evaluation and effect of positive end expiratory pressure (PEEP)

Serafini G. Paediatric Anaesthesia 1999 9: 225–228



- ASA 1-2
- CRANIAL OR ABD CT
- OETT;3 sighs;TV 10ml/kg
- MV set for ETCO2 35mmHg
- Resting lung level after 5 minutes with ZEEP

Pulmonary atelectasis during paediatric anaesthesia: CT scan evaluation and effect of positive end expiratory pressure (PEEP)

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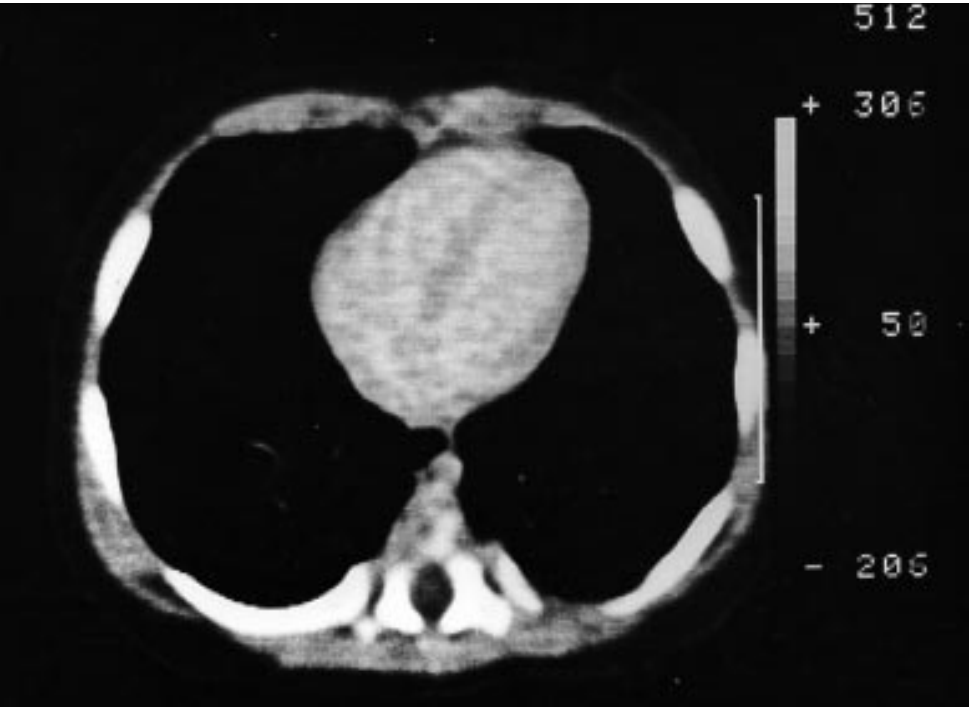

- Second CT after ventilation for 5 minutes with

  5 cm H_2O PEEP
- Observed densities disappeared

Static Lung Volumes

	Newborn	6 months	1 year	3 years	5 years	12 years	adult
TV	6-8 ml/kg						6-7 ml/kg
VE	1050 ml 200-260 ml/kg/min	1350	1780	2460	5500	6200	6400 90 ml/kg/min
FRC	30 ml/kg						30ml/kg
TLC	160 ml 63 ml/kg			1100	1500	4000	6000 82 ml/kg
VD/VT	0.3						0.3
Vo2	6-8 ml/kg/min						3-4 ml/kg/min

Respiratory Control

- ↓CO_2 Response: Slope function of gestational age, postnatal age & pO_2
- ↓ O_2: ↑ Ventilation → ↓ Ventilation
- Anemia, Hypoglycemia, Hypocalcemia & Hypothermia → ↓ Ventilatory Drive
- Hering Breuer Reflex: Lung Inflation → Apnea
- Vagus-mediated airway reflexes → Apnea

Neonatal Respiratory Physiology

GOMER BLOG
Earth's Finest Medical Satire News Site

Rectal Tone of Anesthesiologists Varies with Patients' Oxygen Saturation

Anesthesiology | Editor's Picks | Full Articles | Respiratory Therapist | Surgery by Gomerblog Team - Dec 21, 2014

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BERLIN – A new and controversial study out of the esteemed Higginstein Community Surgery Center describes a curious phenomenon regarding rectal tone of anesthesiologists in response to the oxygen saturations of their patients.

Noted researcher and board game enthusiast Dr. Doggles Heister designed an unconventional study to examine the conflicting experiences of anesthesiologists during acute intraoperative events. Heister explains: "Some physicians say their sphincters get tight enough to crack walnuts when patients desaturate. Others report crapping their scrubs. I've done both, and I wanted to understand what's going on down there."

The study was performed after the IRB had left for the day. Soviet Army surplus manometers roughly the size of soda cans were inserted into resident anesthesiologists who were volunteered by their classmates. Senior partner Kris Kanlaz

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Oxygen- The Good Gas?

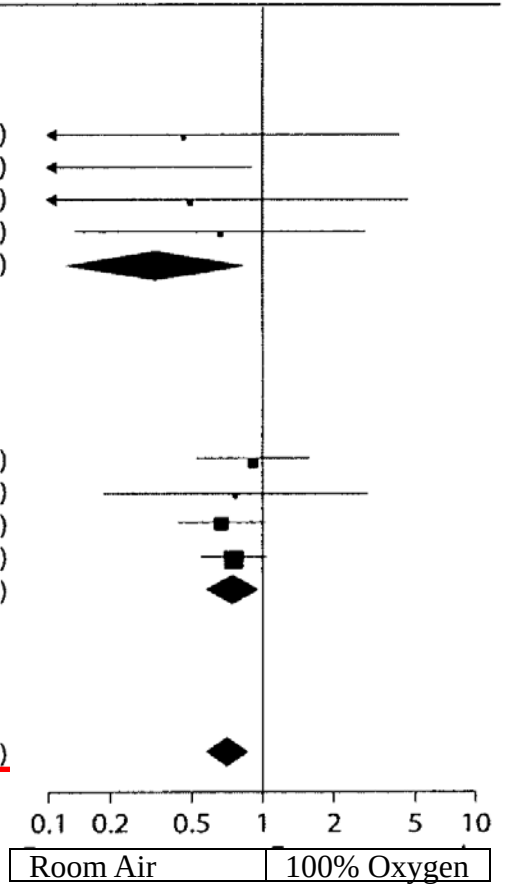
- Oxidative stress, free radical production [1]
- Organ damage, including Chronic Lung Disease
- ↓ Short & long term morbidity/mortality with neonatal resuscitation using RA rather than 100% O_2 [2]

1. Van Der Walt J, Pediatric Anesthesia 2006, 16:1107
2. Tan A, Cochrane Analysis 2009

Resuscitation of Newborn Infants with 21% or 100% Oxygen: An Updated Systematic Review and Meta-Analysis

Saugstad Neonatology 2008;94:176

Study or subgroup	Room Air events	Room Air total	100% Oxygen events	100% Oxygen total	Weight	Risk ratio M-H, fixed, 95% CI
Randomized trials						
Toma, 2006 [15]	0	27	0	27		Not estimable
Toma, 2006 [16]	0	20	0	24		Not estimable
Toma, 2007 [17]	1	30	2	26	1.6%	0.43 (0.04, 4.51)
Vento, 2001 [9]	1	300	7	237	5.9%	0.11 (0.01, 0.91)
Vento, 2003 [10]	1	55	2	51	1.6%	0.46 (0.04, 4.96)
Vento, 2005 [13]	2	17	4	22	2.6%	0.65 (0.13, 3.13)
Subtotal (95% CI)		449		387	11.7%	0.32 (0.12, 0.84)
Total events	5		15			
Heterogeneity: χ^2 = 1.87, d.f. = 3 (p = 0.60), I^2 = 0%						
Test for overall effect: Z = 2.30 (p = 0.02)						
Quasi-randomized trials						
Bajaj, 2005 [14]	17	107	17	97	13.5%	0.91 (0.49, 1.67)
Ramji, 1993 [7]	3	42	4	42	3.0%	0.75 (0.18, 3.15)
Ramji, 2003 [11]	24	204	39	214	28.8%	0.65 (0.40, 1.03)
Saugstad, 1998 [8]	40	280	60	311	43.0%	0.74 (0.51, 1.07)
Subtotal (95% CI)		633		664	88.3%	0.74 (0.57, 0.95)
Total events	84		120			
Heterogeneity: χ^2 = 0.74, d.f. = 3 (p = 0.86), I^2 = 0%						
Test for overall effect: Z = 2.35 (p = 0.02)						
Total (95% CI)		1,082		1,051	100.0%	0.69 (0.54, 0.88)
Total events	89		135			
Heterogeneity: χ^2 = 4.16, d.f. = 7 (p = 0.76), I^2 = 0%						
Test for overall effect: Z = 2.98 (p = 0.003)						



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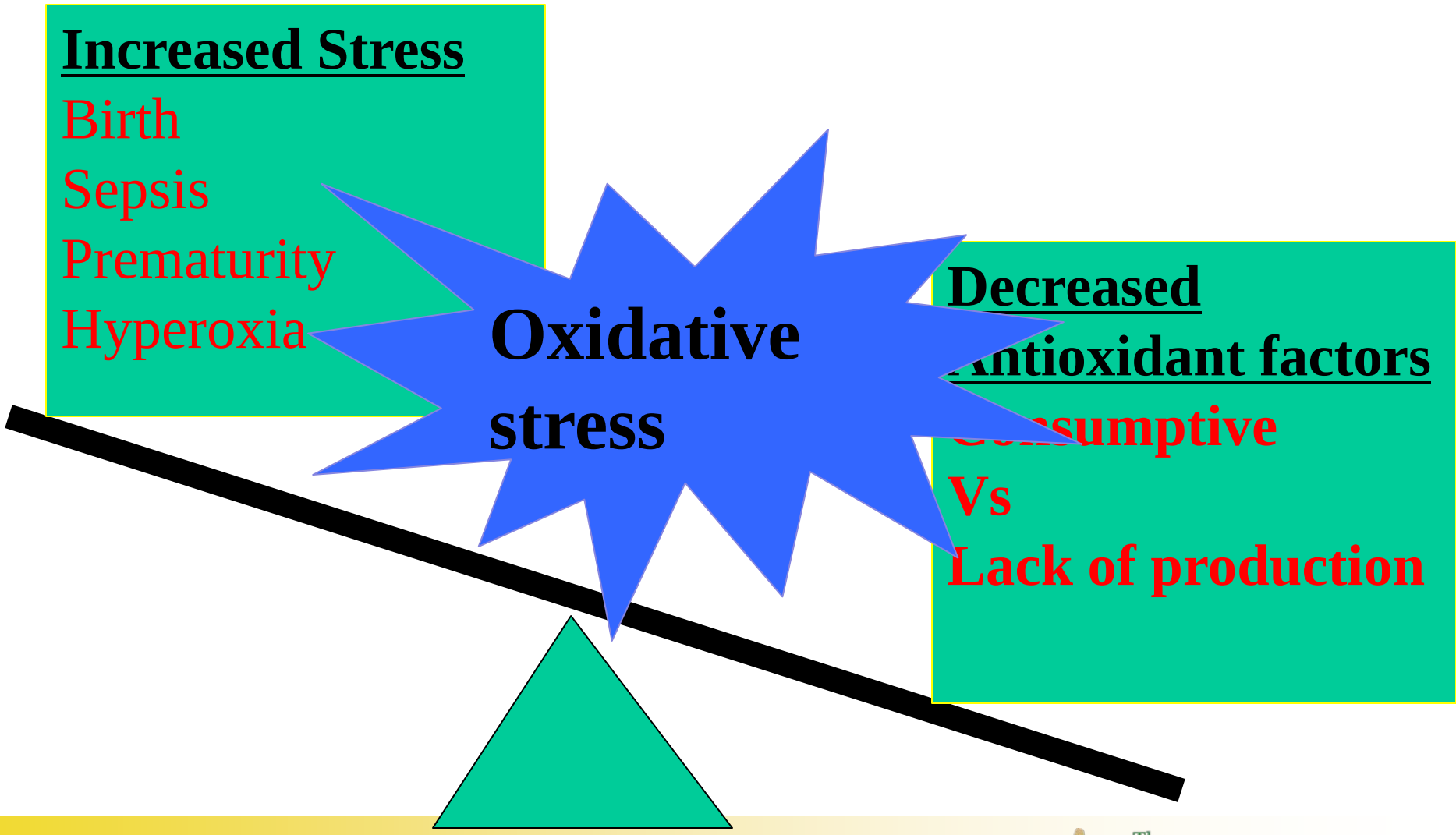
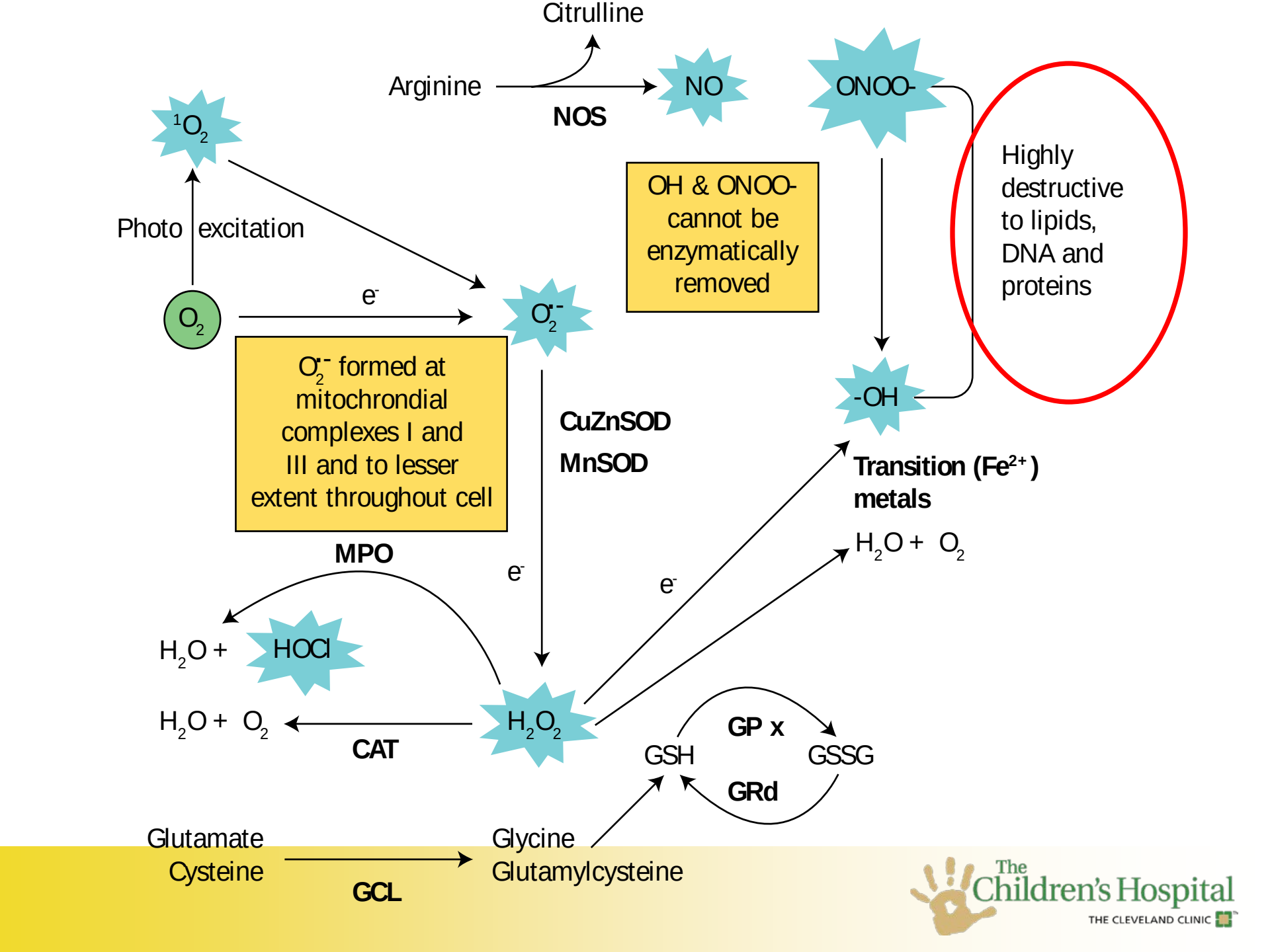
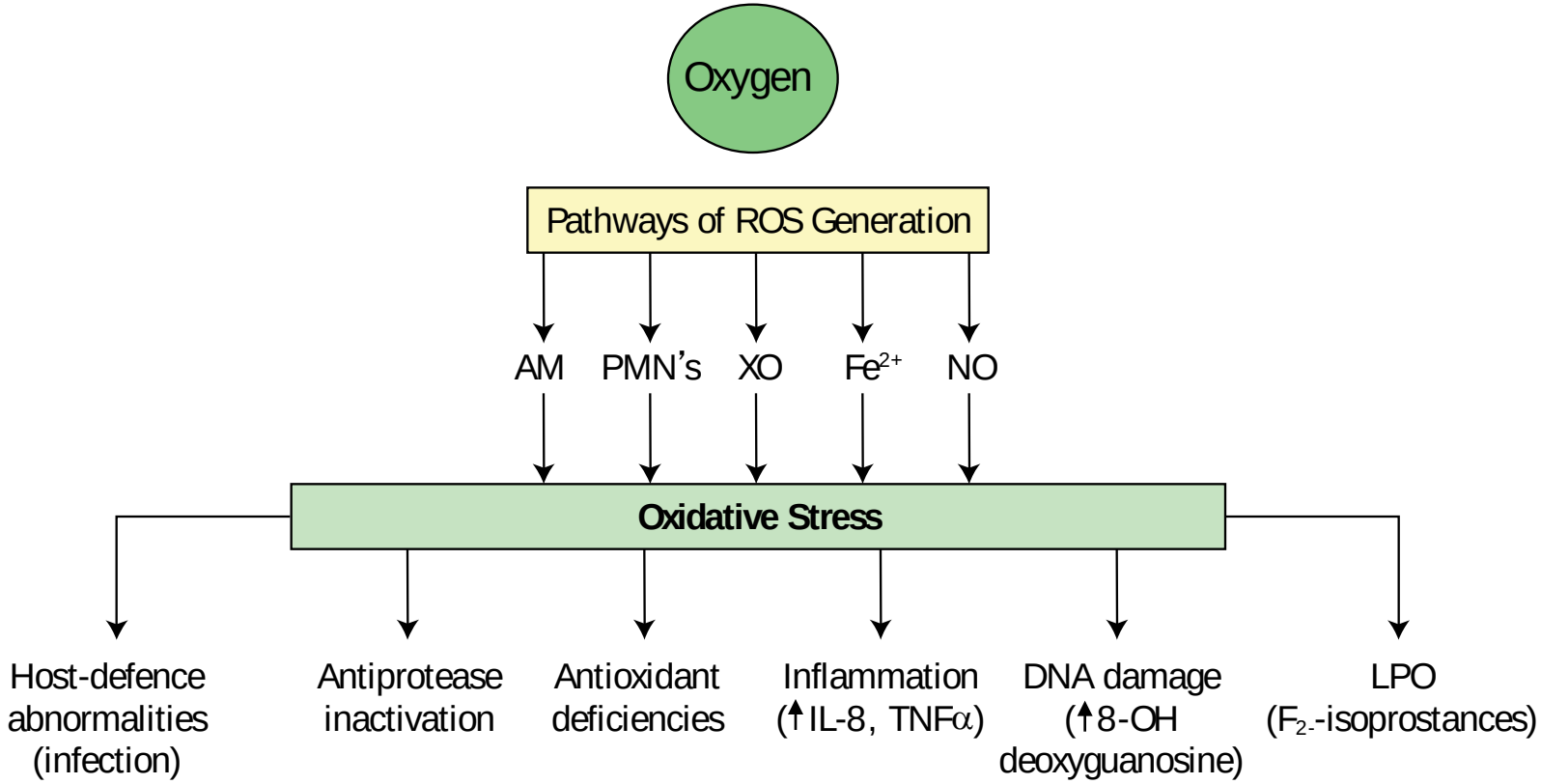
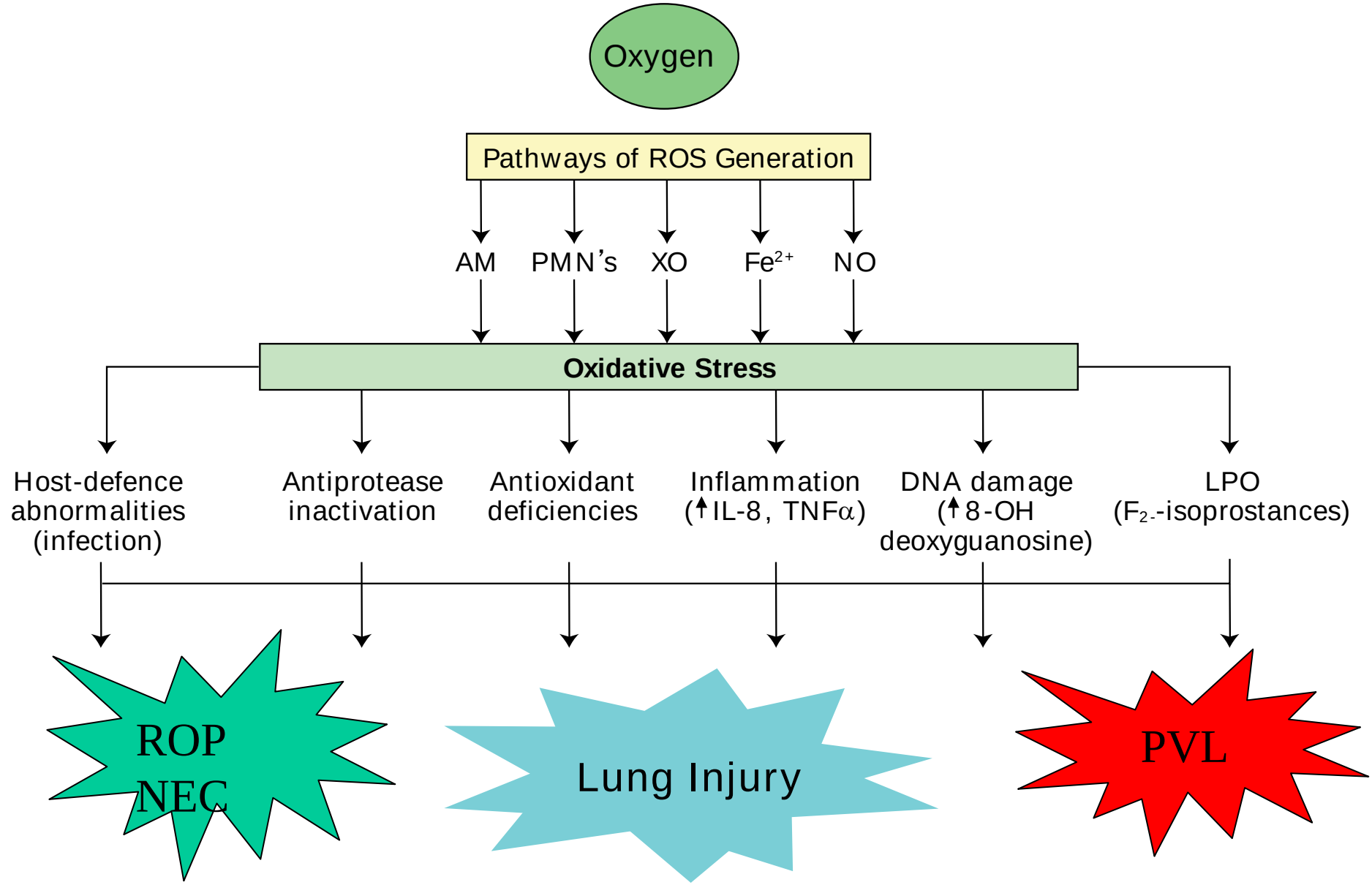
Oxygen Toxicity and Oxidative Stress






Oxygen
Pathways of ROS Generation
AM
PMN's
XO
Fe^{2+}
NO
Oxidative Stress
Host-defence abnormalities (infection)
Antiprotease inactivation
Antioxidant deficiencies
Inflammation (↑IL-8, TNFα)
DNA damage (↑8-OH deoxyguanosine)
LPO (F_2-isoprostances)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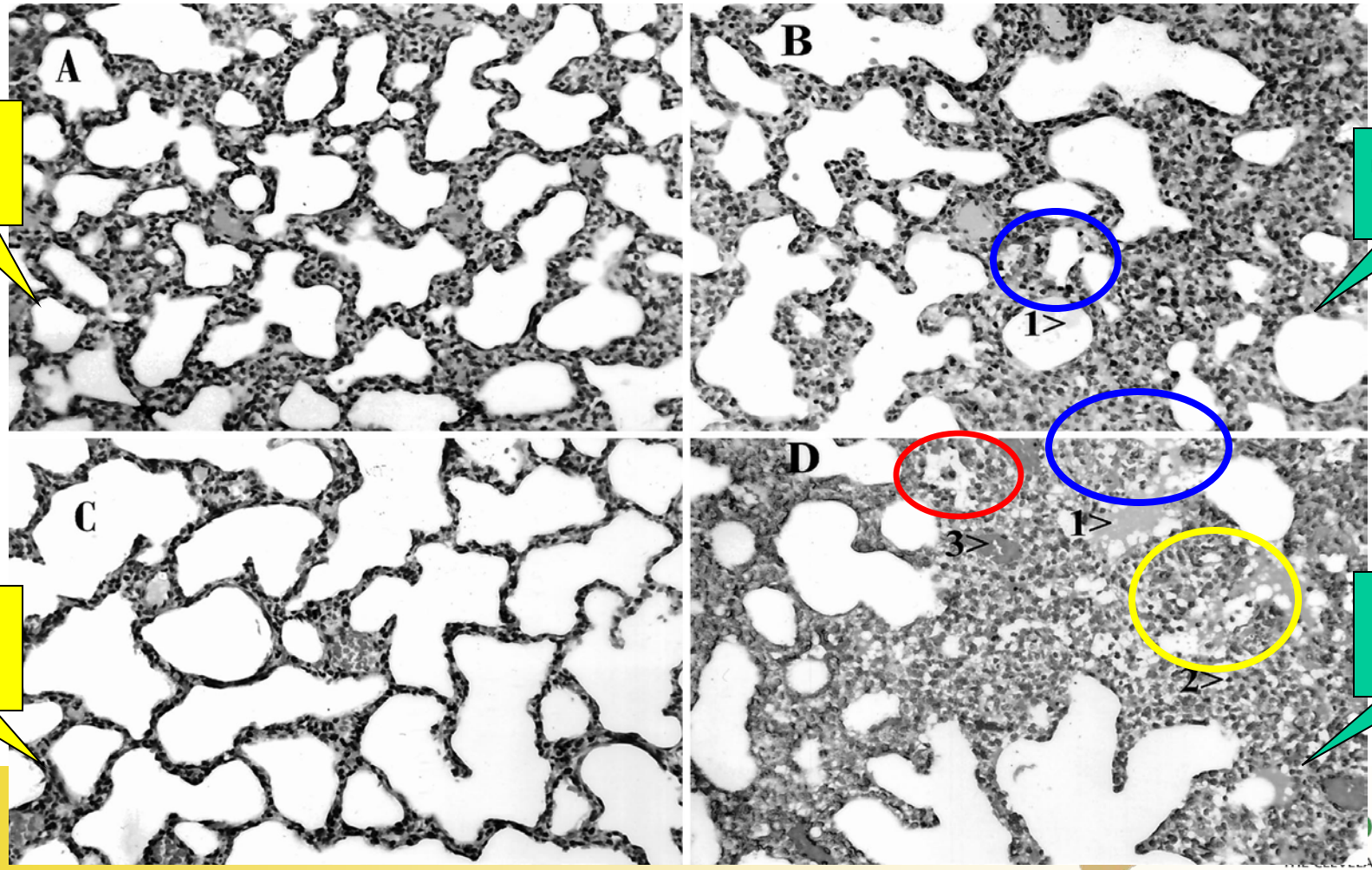
Inflammation (↑IL-8, TNFα)
DNA damage (↑8-OH deoxyguanosine)
LPO (F_2-isoprostances)
ROP
NEC
Lung Injury
PVL

Oxidative Stress- Saugstad 1988

- Saugstad coined the phrase : “Oxygen free radical disease of the newborn”
- He included BPD,PVL, NEC, ROP, PDA
- Theory: neonatal conditions were *not* different disease entities but different organ manifestations of the complex processes of oxidative stress and metabolism

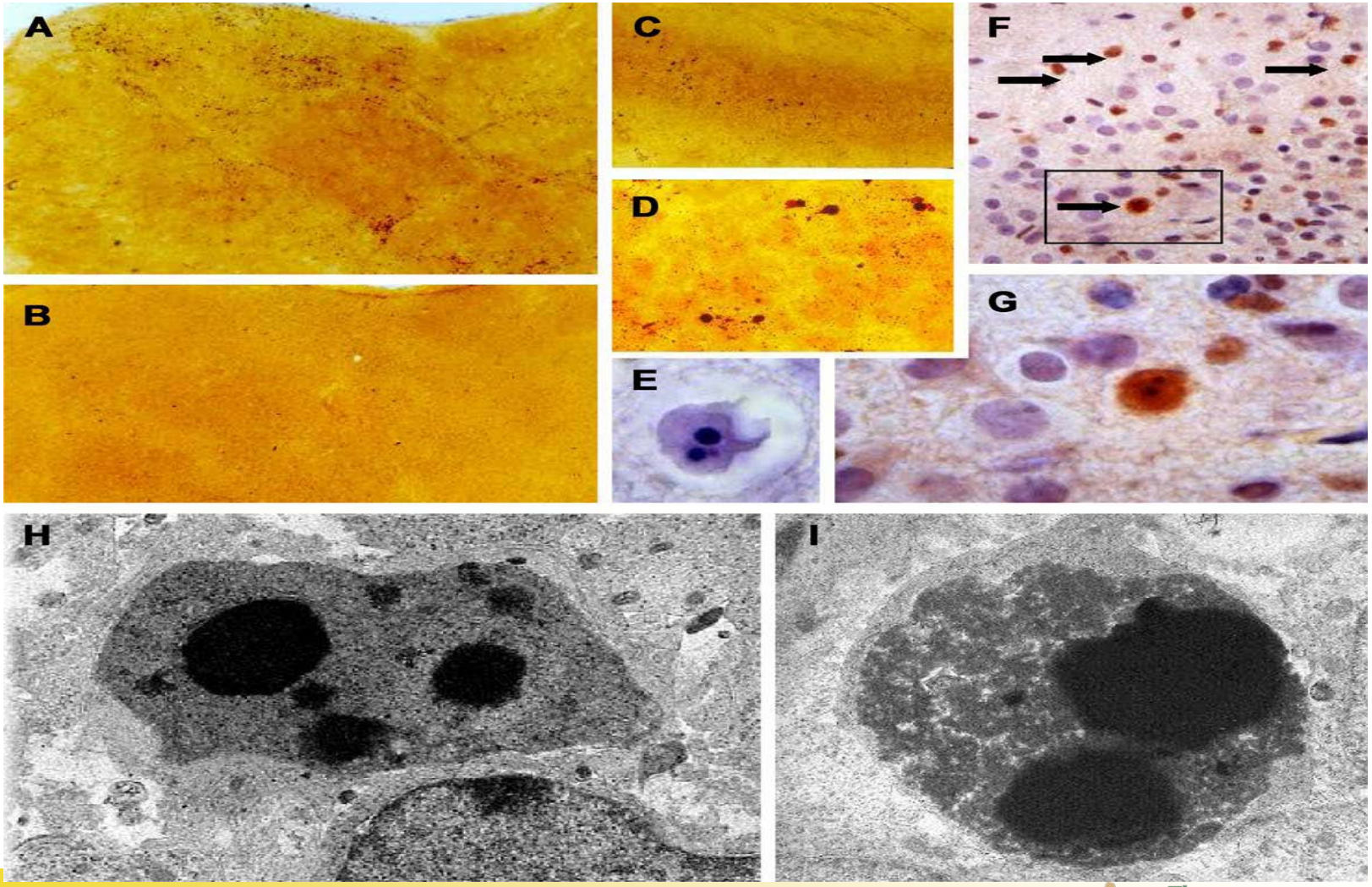
Magnetic Resonance Imaging of Pulmonary Damage in the Term and Premature Rat Neonate Exposed to Hyperoxia

Appleby;Pediatr Res 2001



Oxygen causes cell death in the developing brain

Neurobiology of Disease 2004;17:273-282



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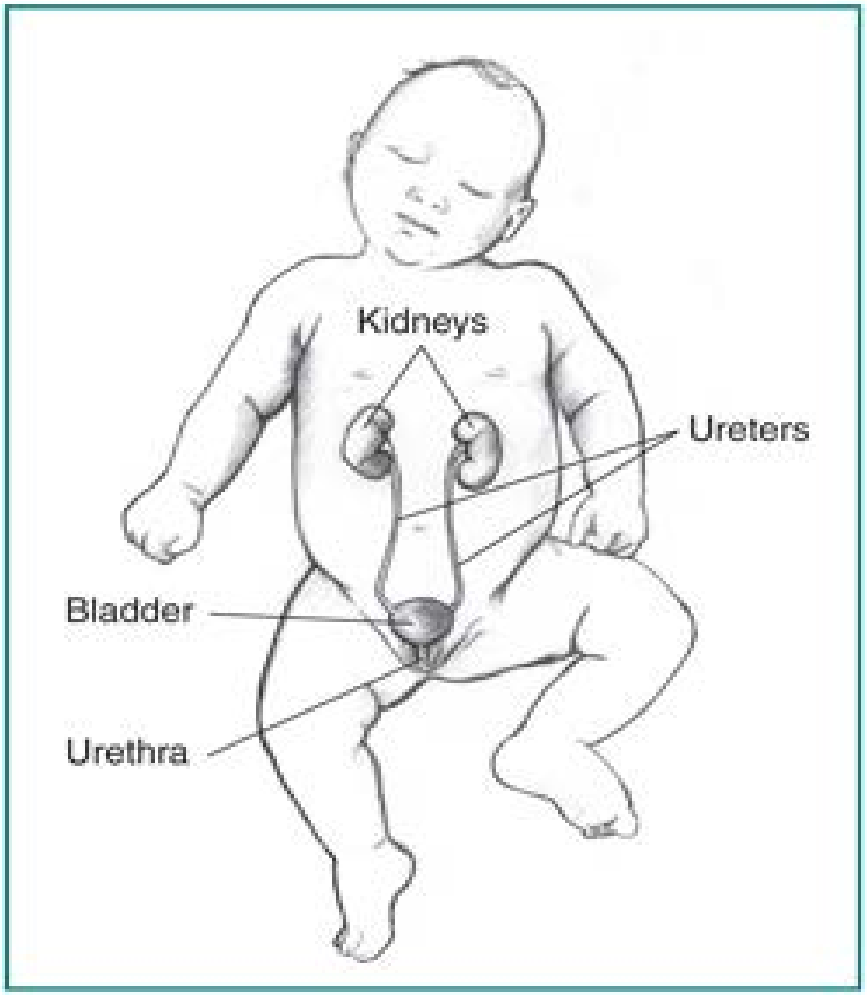
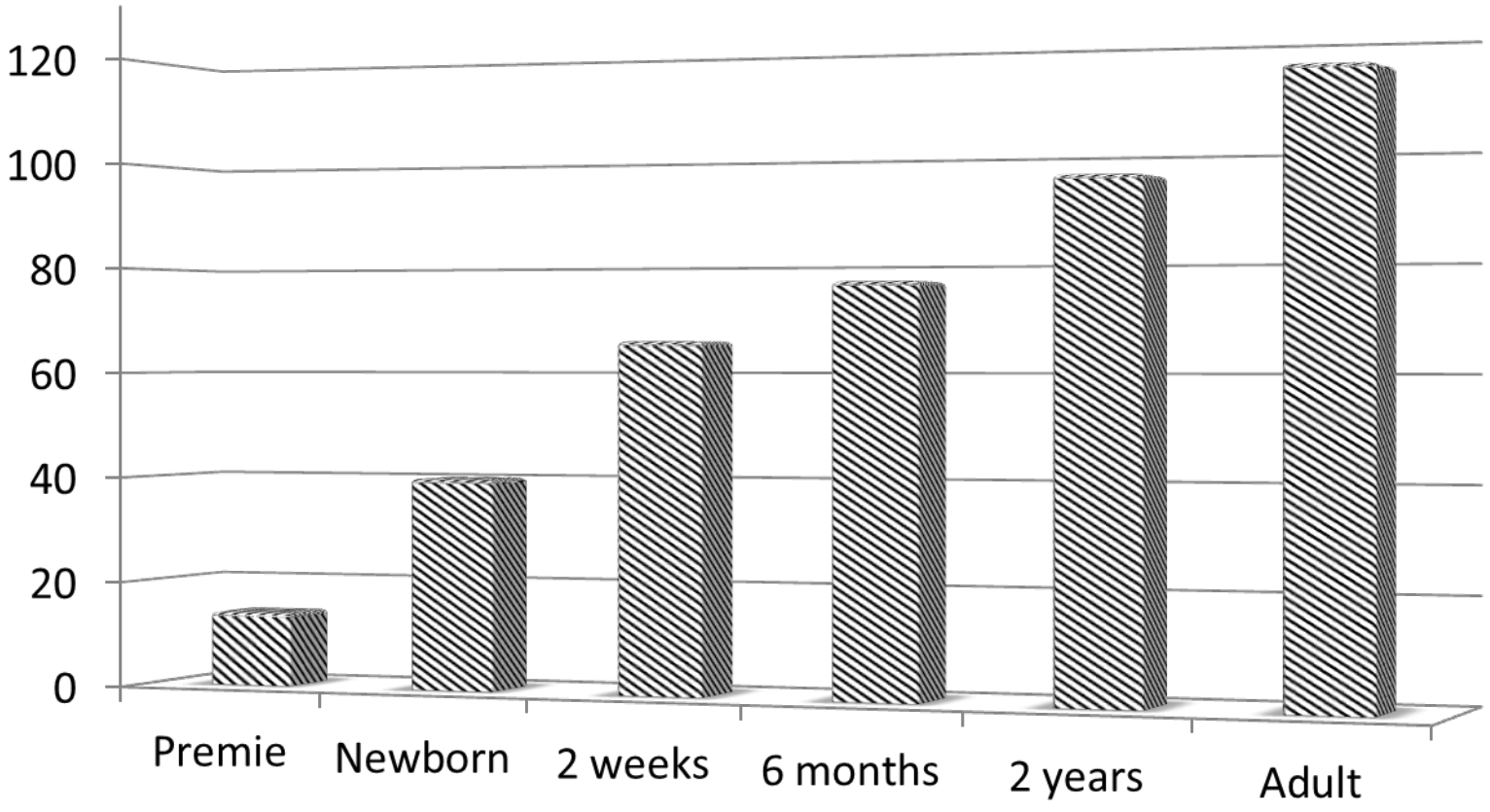
Neonatal Renal Physiology

- Lots of blood flow
  - 25% of Cardiac Index
  - (650 mL/min/1.73m^2)
- Low GFR
- Low Systolic blood pressure
- Mean BP=gestational age in weeks
- High renal artery resistance



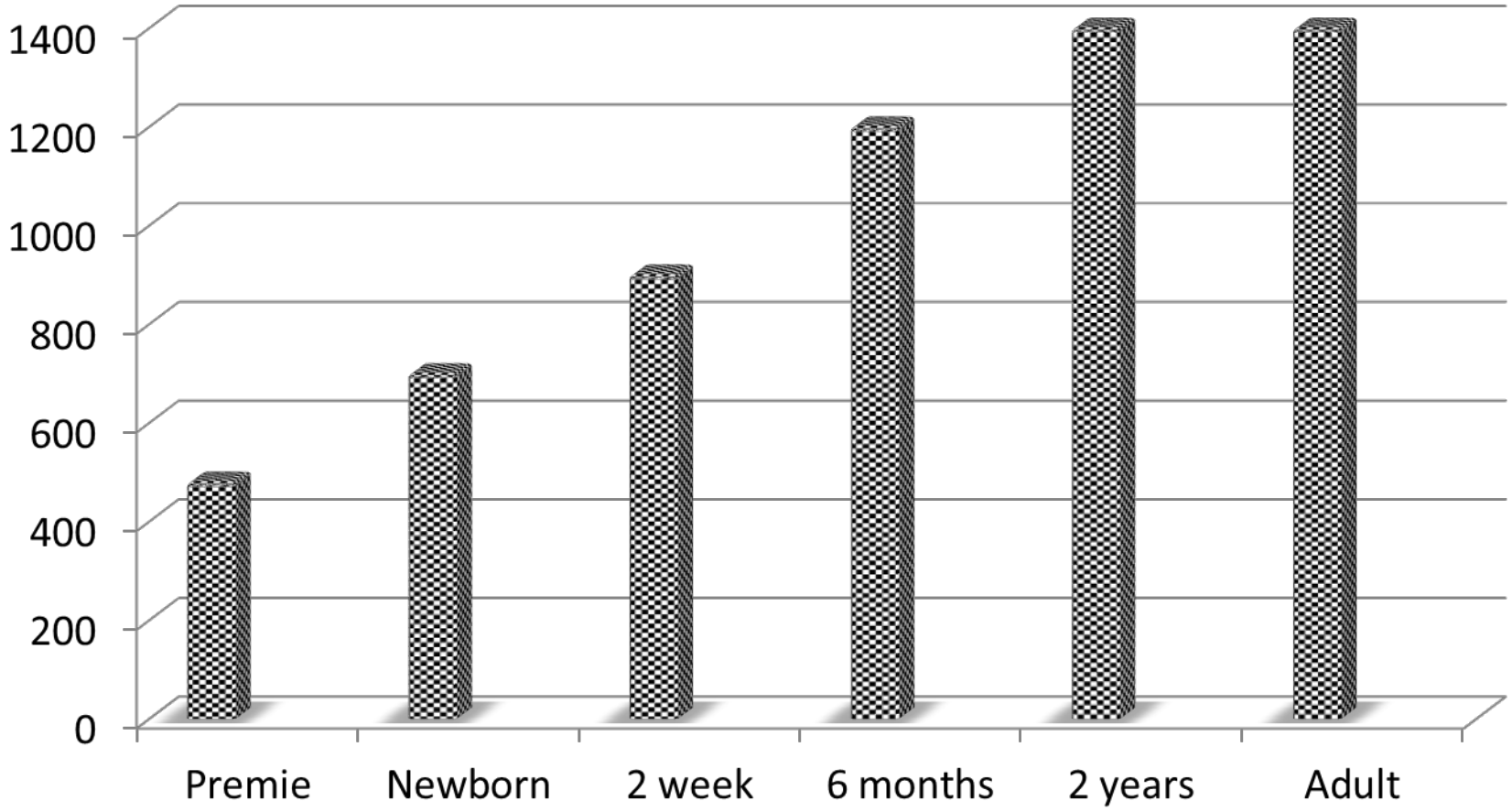
Glomerular Filtration Rate

mL/min/1.73m^2



Maximal Urine Concentration

mOsm/kg



Neonatal Renal Physiology

- ↓ Creatinine Clearance
- ↓ Tubular Function
- Limited ability to conserve & excrete water
- **Net Effect:** ↓ clearance of medications

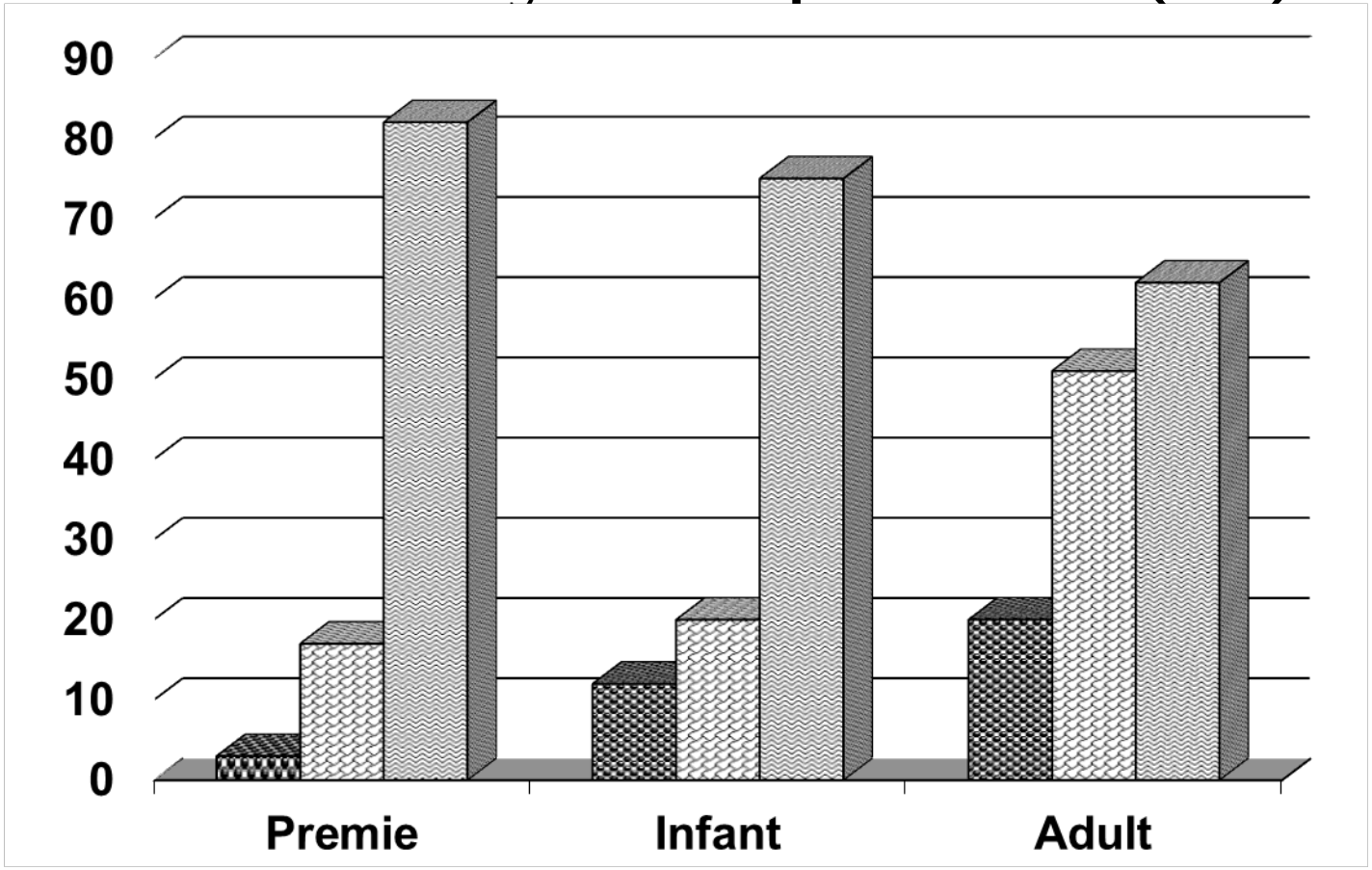
  ↓ ability to handle Na+ loads

  ↓serum Na+

  ↑ serum K+

  ↑ urine glucose

Body Composition (%)



75%of BW is Water

60%of BW is Water

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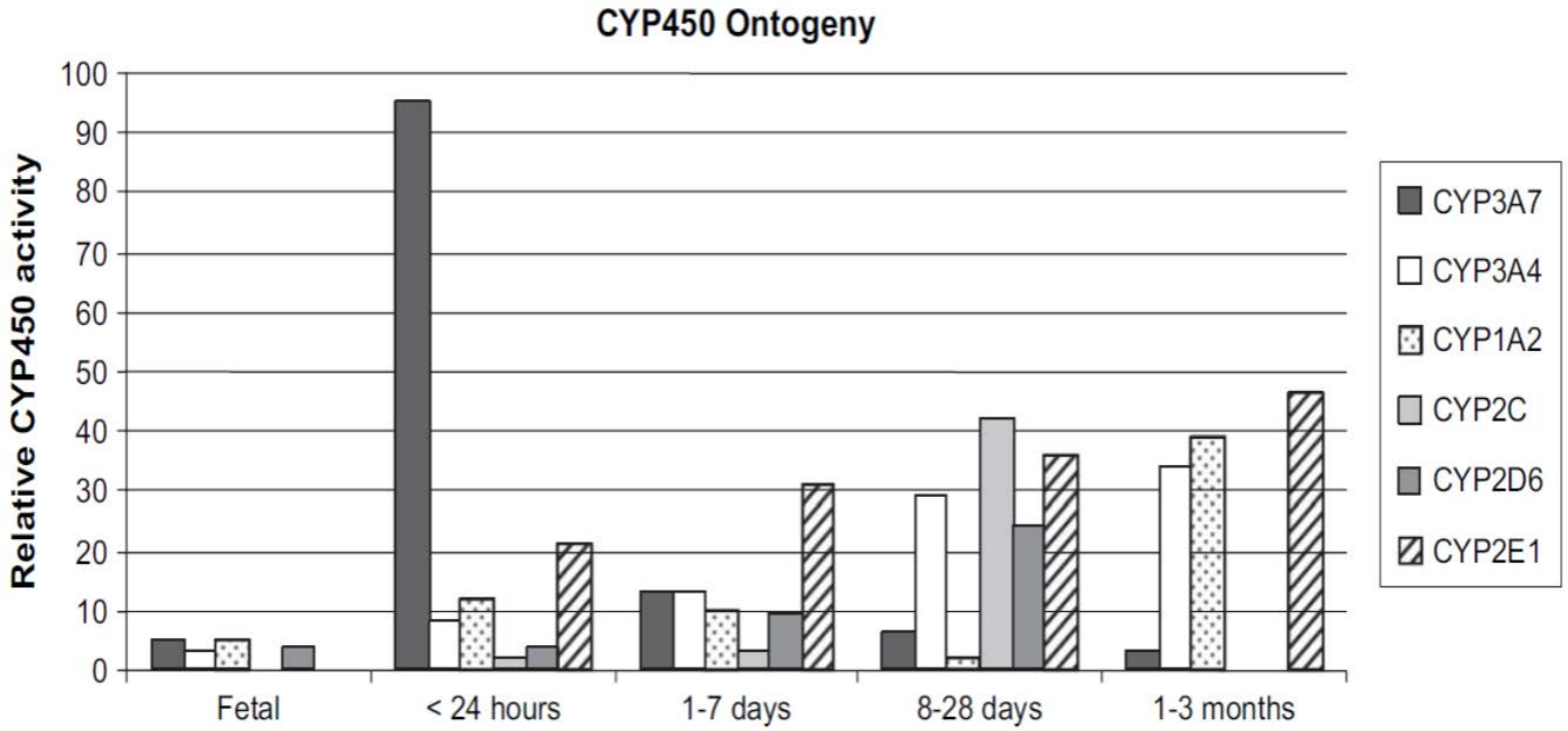
Hepatic Physiology

- ↓ Drug Metabolism
- Phase I = oxidation, reduction, hydrolysis (Cytochrome P-450 system): e.g. caffeine
- Phase II = conjugation (e.g. glucuronidation, sulfation, acetylation): morphine, acetaminophen

Ontogeny of drug metabolizing enzymes in the neonate

Michael J. Blake, Lisa Castro, J. Steven Leeder, Gregory L. Kearns*

Seminars in Fetal & Neonatal Medicine 2005 10, 123e138



Ontogeny of drug metabolizing enzymes in the neonate

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Seminars in Fetal & Neonatal Medicine 2005 10, 123e138

Table 1 Ontogeny of human hepatic Phase II enzymes (adapted from ref.[127])

Enzyme	Prenatal trimester			Neonate	1 month to 1 year
	1	2	3		
GSTA1/A2	+	+	+	+	+
GSTM	+	+	+	+	+
GSTP1	+	+	+	+	0
NAT2	+	+	+	+	+
UGT1A1	0	0	0	+	+
UGT1A3	?	+	+	+	+
UGT1A6	0	0	0	+	+
UGTB7	?	+	+	+	+
UGTB17	?	+	+	+	+
EPHX1	+	+	+	+	+
EPHX2	?	+	+	+	+
SULT1A1	?	+	+	+	+
SULT1A3	?	+	+	+	+
SULT2A1	0	0	+	+	+

+, activity or protein detectable; 0, activity or protein not detectable; ?, undetermined.

Hepatic Physiology

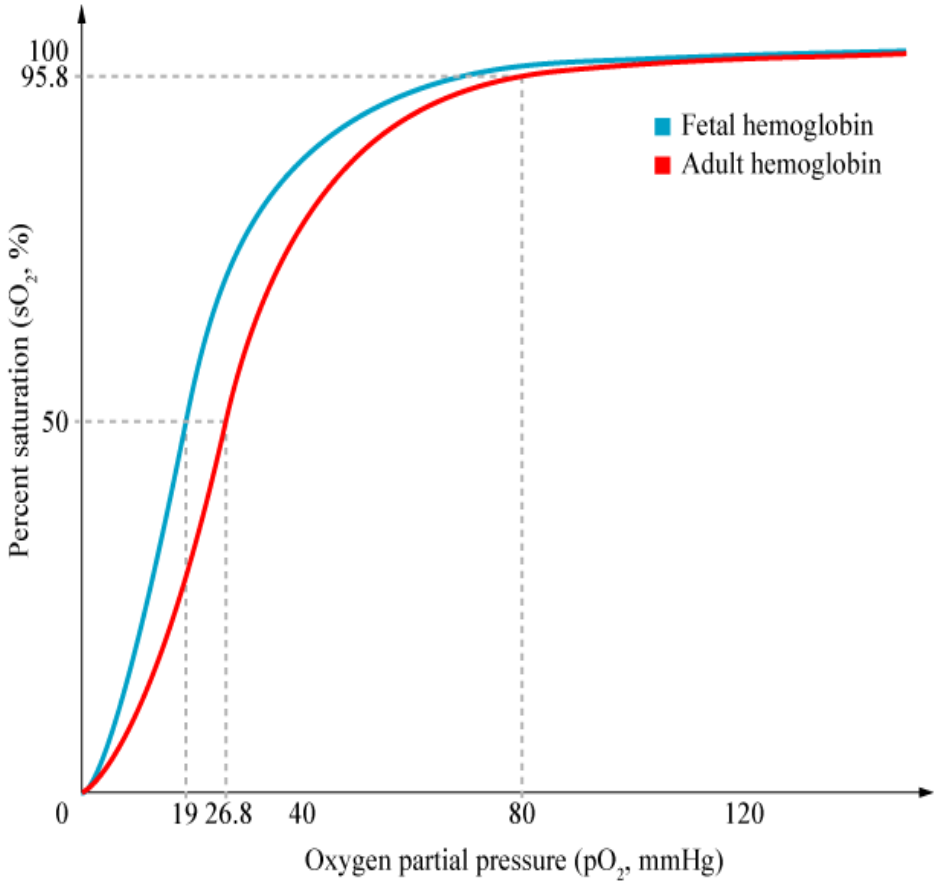
- ↓ Hepatic blood flow
- ↓ Glycogen stores- esp in premature
- ↓ Insulin responsiveness
- ↓ total protein and albumin
- ↓ alpha 1 glycoprotein
- ↓ clotting factors

Estimated Blood Volume

Age Group	EBV (mL/kg)
Premie	100
Neonate	90
Infant	80
Child	75
Adult	70

Hemoglobin F

- ↑ Hemoglobin F : 70% at term
- Hb-18-20 g dl^{-1}
- Hb O_2 affinity changes during first months
- Low P_{50} -19 mmHg
- P_{50} increases and peaks in later infancy



The conundrum of neonatal coagulopathy

Shoshana Revel-Vilk[1]

Hematology Am Soc Hematol Educ Program 2012,12: 450

Table 1. Neonatal hemostasis versus older children/adult hemostasis

	Preterm neonates vs term neonates	Neonates vs older children/adults	Approximate age of adult values*
Primary hemostasis			
Platelet count	Decreased (< 32 w)	Same	
Platelet function	Decreased	Decreased†	2-4 wk
% of reticulated platelets	Higher	Higher	NA
VWF level	NA	Higher	3 mo
VWF large multimers	NA	Higher	3 mo
Coagulation factors			
FII, FVII, FIX, FX	Lower	Lower	16 y
FV	Lower	Same or lower	16 y
FVIII	Higher	Same or higher	1 mo‡
FXI	Lower	Lower	1 y
FXII	Lower	Lower	16 y
Fibrinogen level	Same	Same	
Fibrinogen function	NA	Decreased	5 y
Regulation of coagulation			
Antithrombin	Lower	Lower	3 mo
Protein C	Lower	Lower	16 y
Total protein S	Lower	Lower	1 mo
Free protein S	NA	Higher	NA
APCR generation	NA	Reduced	NA
Free TFPI	NA	Lower	Adult
Fibrinolysis			
Plasminogen level	Lower	Lower	6 mo
Plasminogen function	NA	Decreased	NA
tPA	Same§	Higher	5 d
α2 antiplasmin	Lower	Lower	5 d
α2M	Same	Higher	Adult
PAI	Same§	Same or higher	5 d

The conundrum of neonatal coagulopathy

Shoshana Revel-Vilk[1]

Hematology Am Soc Hematol Educ Program 2012,12: 450

Table 2. Screening laboratory tests for hemostasis: neonates versus adults

	Preterm neonates vs term neonates	Neonates vs older children/ adults	Approximate age of adult value*
aPTT	Longer	Longer	16 y
Prothrombin time	Longer	Same or longer	16 y
INR	Higher	Same or higher	16 y
Thrombin time	Longer	Same or longer	5 y
Bleeding time	Longer†	Shorter	1 mo
PFA-100	Longer†	Shorter	1 mo
ROTEM/TEG			
Clotting time	Same	Shorter	3 mo
Clot formation time	Same	Shorter	3 mo
Maximal clot firmness	Stronger	Stronger	3 mo

The conundrum of neonatal coagulopathy

Shoshana Revel-Vilk[1]

Hematology Am Soc Hematol Educ Program 2012,12: 450

Clinical implications of developmental hemostasis

- Despite the quantitative and qualitative deficiencies of multiple hemostatic factors ***healthy*** neonates have normal hemostasis.
- "Immature" neonatal hemostatic system is functionally balanced with no tendency toward coagulopathy or thrombosis.

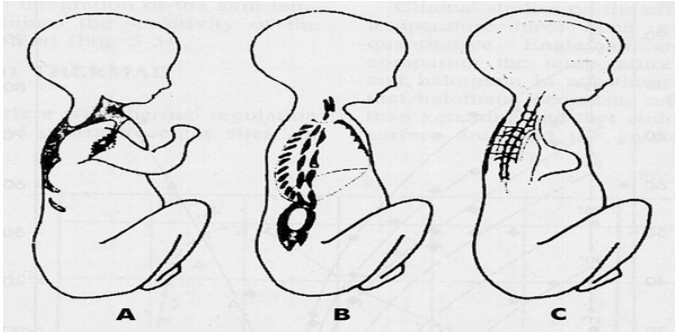
Temperature Regulation in Infants

- Neonates are homeotherms
- Etiology of heat loss in neonates
  - large surface area to volume ratio
  - thin skin
  - minimal subcutaneous fat
- Infant's thermoregulatory range is easily overwhelmed.

Non-Shivering Thermogenesis

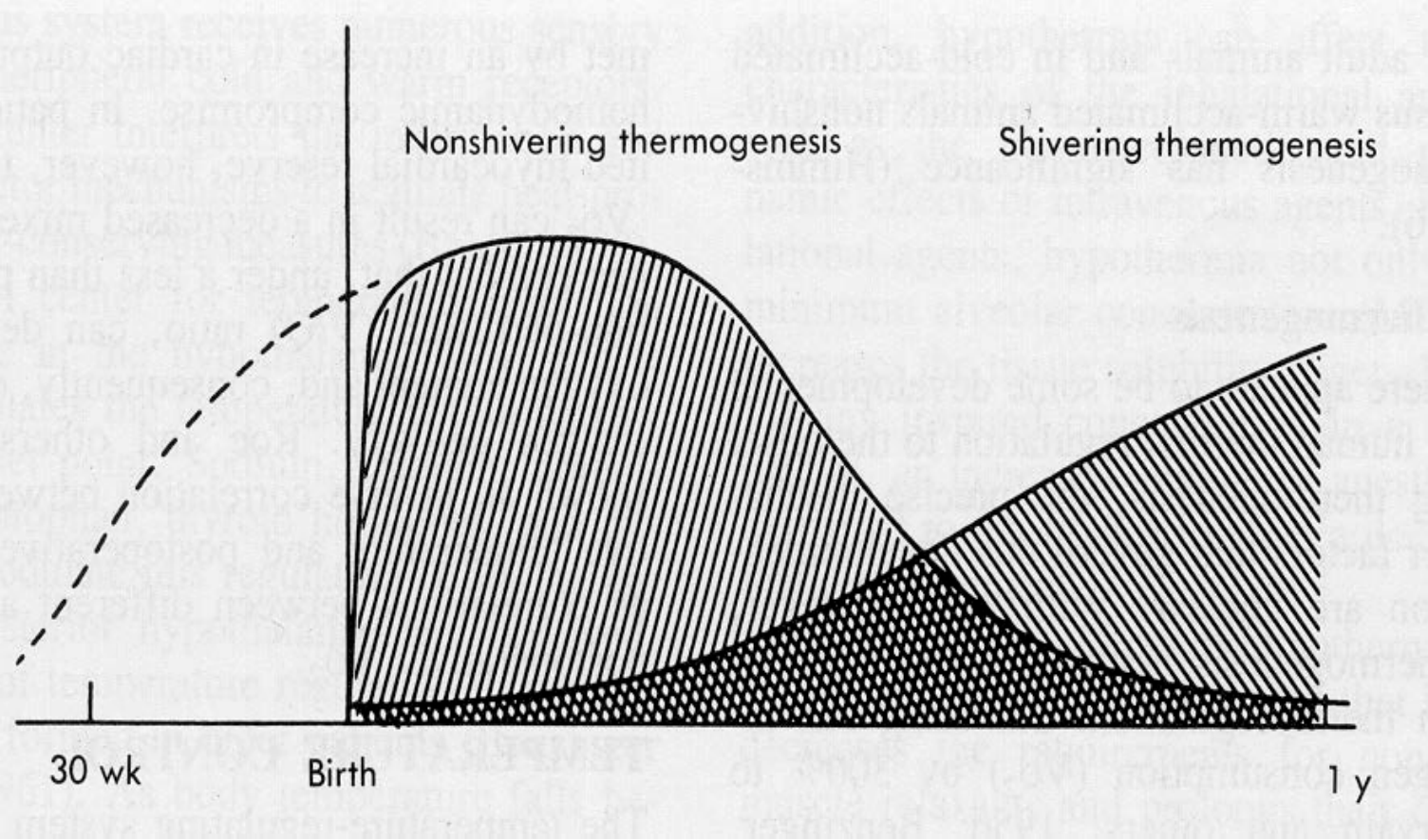
Brown Fat

- 26-30 weeks of gestation
- 2-6% of body weight
- Scapulae (b/t) , axillae, mediastinum, adrenal glands, and kidneys



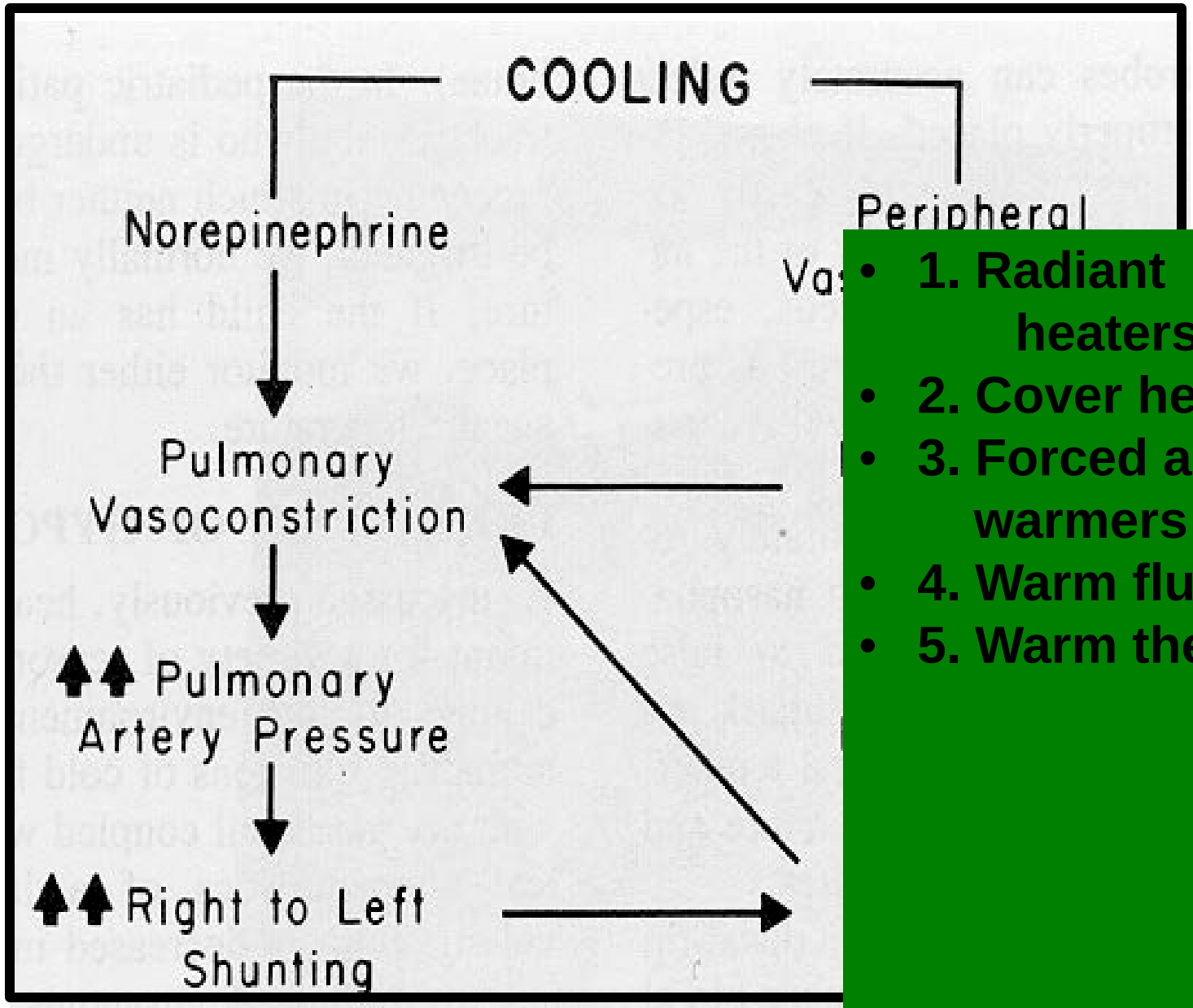
- Mitochondria
  - uncoupled oxidative phosphorylation
    - produce heat instead of ATP
  - Mediated by UCP (Uncoupling Protein 1), *thermogenin*
- C.O. (up to 25%) diverted to brown fat deposits
  - More efficient warming of blood
  - With cold stress, neonates may double metabolic heat production via non-shivering thermogenesis
- Attenuated by GA (volatile and intravenous)

Temperature Regulation in Infants



Heat Transfer by Radiation

- ***Most significant route of heat loss for babies***
  Single largest factor for heat loss in most cases (up to 70% of losses)
- Transfer of heat from object (patient) to an object *not* in direct contact.
  - Method of transfer of heat by light (e.g. sun -> earth)
  - Infrared spectrum
- Increased with
  - Temperature gradient between two objects
- Not affected by
  - distance between two objects
- Patient factors
  - Increased surface area: volume increases radiated losses
  - Babies have large surface area



- 1. Radiant heaters
- 2. Cover head
- 3. Forced air warmers
- 4. Warm fluids
- 5. Warm the OR

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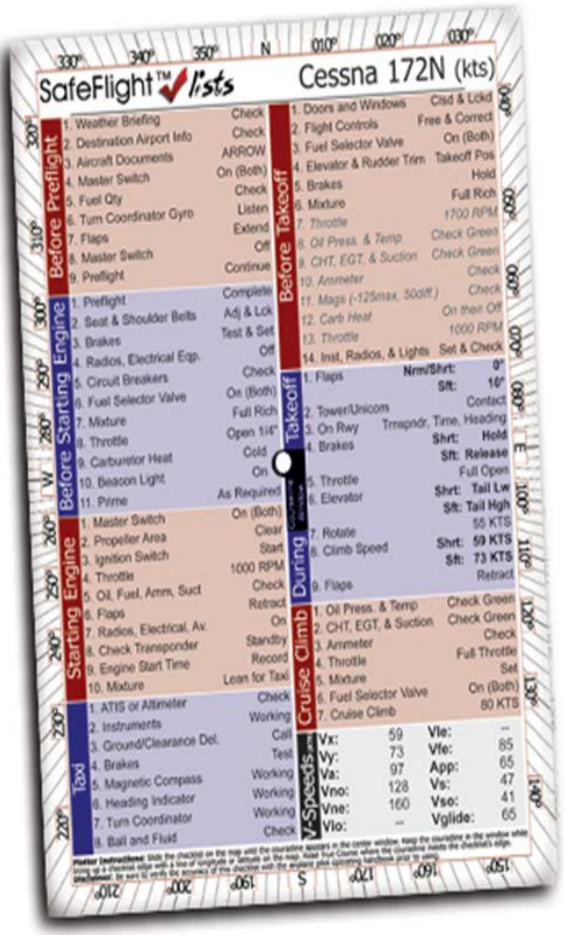
How can we reduce the Risk of Neonatal Anesthesia?

Neonatal Anesthesia Check List



- ✓ Preoperative evaluation
  - ❑ Maternal and Birth Hx
  - ❑ Congenital anomalies/syndromes
  - ❑ Laboratory data & Imaging studies based on preop assesment
- ✓ Surgical Issues
  - ❑ Urgent vs Emergent (Can the case be delayed ?)
  - ❑ Special equipment or Techniques impacting anesthetic management – Thorascopic or Laparoscopic
  - ❑ Blood products- Date of Collection, Irradiated
- ✓ OR set up "Ms. Maids"
  - ❑ **M**achine-appropriate ventilator -Min FiO2 & PIP, Applied Peep
  - ❑ **S**uction
  - ❑ **M**onitors (arterial, CVP, Umbilical, pre and post ductal pulse oximeter
  - ❑ **I**V -Dextrose maintenance fluid, Smallest Size ,IV pump for drips and fluids
  - ❑ **A**irway- Appropriate circuit, bag, airway equipment, SGA
  - ❑ **D**rugs- Unit dose ,TB or small syringes, Labeled and double checked dilutions Vasopressors -Milrinone& Epi ,Calcium, Drips prepared by Pharmacy
  - ❑ **S**pecial Equipment – Ultrasound, Weight specific code sheet, Bair hugger, fluid warmer, radiant warmers

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Premature Infant

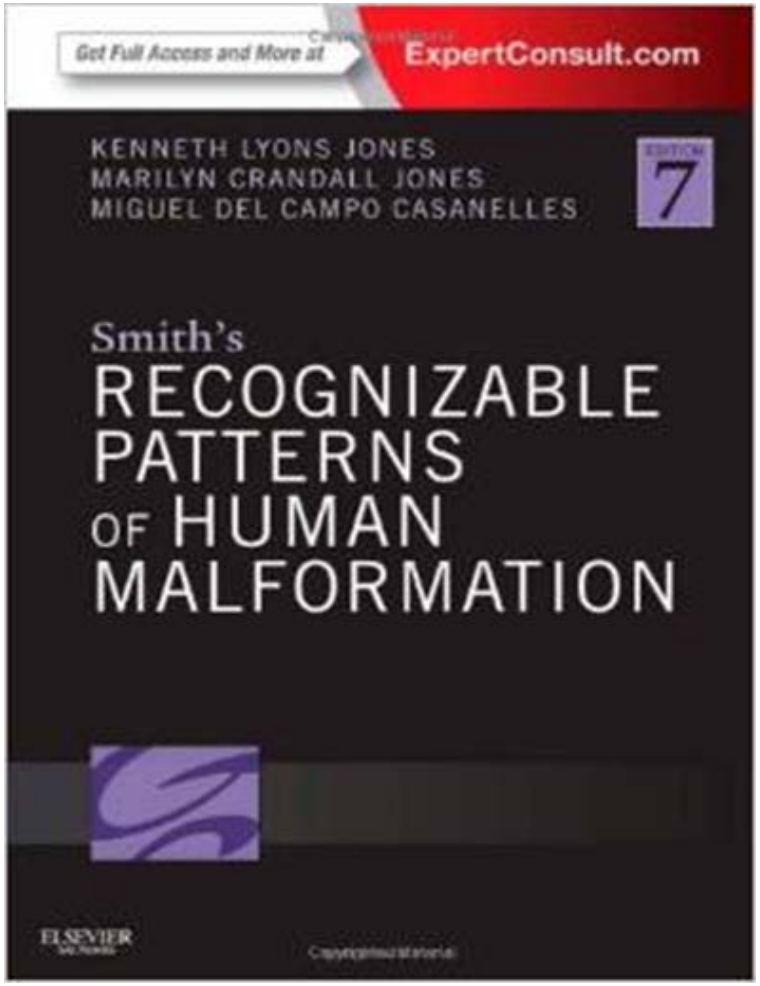
- Extreme Prematurity
- IVH-Seizures
- Hemodynamic instability
- Respiratory failure
- 4 H's
- PDA & PFO = PFC
- Renal Insufficiency
- NEC

Congenital anomalies:

- Congenital Diaphragmatic Hernia= 1:2500
- Tracheoesophageal Fistual= 1:3000
- Omphalocele = 1:5000
- Gastroschisis= 1:2200

I. Laughon M,J Perinatology, 2003, 23:291

SYNDROMES



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Specific Genetic Diseases at Risk for Sedation/Anesthesia Complications

Butler ANESTH ANALG 2000,91:837-55

- Alphabetically listed
- Overview of Specific Genetic Disorders

Specific Genetic Diseases at Risk for Sedation/Anesthesia Complications

ANESTH ANALG 2000;91:837-55

Disease/Etiology (see References 3 and 4)	Brief Description	Potential Sedation and Anesthesia Complications	Recommendations for Presedation Evaluation (see References 5–10)
Aarskog Syndrome: X-linked recessive; FGDY1 gene mapped to Xp11.21	Growth and mental deficiencies, dental anomalies, mild pectus, hypertelorism, shawl scrotum, brachydactyly	Structural: Cleft lip/palate, cervical vertebral anomalies (including hypoplasia and synostosis of cervical vertebrae), cardiac and renal defects	Radiologic evaluation for vertebral anomalies; renal and cardiac evaluation

Specific Genetic Diseases at Risk for Sedation/Anesthesia Complications

ANESTH ANALG 2000;91:837-55

- Checklist Items
  - Difficult Airway
  - Altered Respiratory Mechanics
  - Gastric Reflux
  - Cardiovascular Disorder
  - Neuromuscular Problems
  - Liver disease
  - Renal Disease

Table 1. Sedation and Anesthesia Considerations/Complications for P ients with Selected C

Disease/Etiology (see References 3 and 4)	Brief Description	Potential Sedation and Anesthesia Complications	Recommendations fo Presedation Evaluati (see References 5–1	Difficult airway	Altered spiratory echanics	Gastric reflux
Aarskog Syndrome: X-linked recessive; FGDY1 gene mapped to Xp11.21	Growth and mental deficiencies, dental anomalies, mild pectus, hypertelorism, shawl scrotum, brachydactyly	Structural: Cleft lip/palate, cervical vertebral anomalies (including hypoplasia and synostosis of cervical vertebrae), cardiac and renal defects	Radiologic evaluatio or vertebral anomali renal and cardiac evaluation	X	X	
Achondrogenesis, Type I: autosomal recessive; mutations in sulfate transporter gene allelic to diastrophic dysplasia	Severe micromelia, incomplete ossification of lower spine, early lethal condition	Structural: Micrognathia, poorly ossified vertebral bodies, multiple rib anomalies	Radiologic evaluat for rib and vertebra anomalies	X		
Achondrogenesis II-Hypochondrogenesis Type II (Langer-Saldino Achondrogenesis, Hypochondrogenesis): sporadic; mutations of COL2A1 gene which codes for type II collagen	Extremely short stature, short limbs, large calvarium, short ribs, variable degrees of failure of ossification of lumbar spine, cervical spine, sacrum, ischial and pubic bones; early lethal condition	Structural: Cleft soft palate, micrognathia, failed ossification of lumbar and cervical spine Pulmonary: Severe hypoplasia	Radiologic evalu on for rib and verteb anomalies; pul onary evaluation	X		
Acrodysostosis: autosomal dominant	Growth and mental deficiencies, short hands with peripheral dysostosis, small nose	Structural: Vertebral defects (may collapse), spinal canal stenosis, nasal hypoplasia, pronathism, renal anomalies Neuro: Hydrocephalus	Radiologic eval ion for vertebral ano lies; neurologic a renal evaluations	X		
Aicardi Syndrome: X-linked dominant; lethal in males	Structural brain anomalies including agenesis of corpus callosum, microcephaly, mental deficiency, optic nerve colobomata, rib anomalies	Structural: Hemivertebrae, butterfly and block vertebrae, cleft lip/palate Neuro: Infantile spasms, hypotonia Misc: Growth hormone and cortisol deficiencies	Radiologic eval tion for vertebral an NS anomalies; c k cortisol level	X	X	
Achondroplasis: autosomal dominant; 90% from new mutation of FGFR3 gene at 4p16.3	Short-limbed dwarfism, retardation of endochondrial bone formation, low nasal bridge, spinal canal stenosis, hyperextensibility (3)	Structural: Diminished air entry in lungs, fine basal crepitations, anteriorly placed epiglottis, difficulty in intubation, lumbar lordosis, narrowing of spinal cord, small chest (11) Behavioral: Very high anxiety (11)	Radiologic eva tion of foramen c dle; preoxygenati before anesth ia, administrati of oxygen after extubation; u of Sellick's man ver to guard agains regurgitation; void use of subara noid blockade in e erly patients (11)	X	X	X
Alpha-Thalassemia/ Mental Retardation Syndrome: X-linked recessive	Severe mental retardation, characteristic face and genital abnormalities (3)	Structural: Large tongue, hemivertebra, renal agenesis Neuro: Lack of coordination, cerebral atrophy, seizures (12)	Radiologic eval ion for vertebral, CN and renal anomali evaluate for u er airway obstru on or defects; check r anemia	X	X	X
Angelman Syndrome (Happy Puppet Syndrome): maternal 15q11-q13 deletion	"puppet-like" gait, mental retardation, seizures, brachycephaly, inappropriate laughter	Neuro: Hypotonia, seizures, electroencephalogram (EEG) abnormalities, ataxia	Maintain patient n anticonvulsant medication du g perioperative p iod			
Antley-Bixler Syndrome: autosomal recessive	Craniosynostosis, choanal stenosis/atresia, radiohumeral synostosis (3)	Structural: Choanal atresia, multiple joint contractures, narrow chest, cardiac, renal and gastrointestinal defects, femoral fractures (13,14)	Evaluation for up r airway obstruc n, apnea spells, ca ac, gastrointestinal d renal defects (14	X		X
Apert Syndrome: autosomal dominant; FGFR2 gene mutation at 10q25	Irregular craniosynostosis, mid face hypoplasia, syndactyly with "mitten" hand (3)	Structural: narrow palate and airway, hypertelorism and proptosis, cleft palate, heart and kidney defects, abnormal tracheocartilage (48% of patients require tracheostomy) Neuro: agenesis of corpus callosum, ventriculomegaly, increased intracranial pressure (9,10)	Careful maintenan of airway, sleep stu es in preoperative evaluation to rule ut sleep apnea, keep patient in prone position, monitor patient's fluid level (9,10)	X	X	X
Arteriohepatic Dysplasia (Alagille Syndrome): autosomal dominant;	Growth retardation, typical facies, chronic cholestasis,	Structural: Butterfly and other vertebral anomalies, cardiac defects, cleft	Radiologic evaluation fo vertebral anomalies; evaluate cardiac, liver	X		

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NEWSLETTER
The Official Journal of the Anesthesia Patient Safety Foundation
Volume 29, No. 1, 1-24 Circulation 107,515 June 2014

Preventing Pediatric Transfusion-Associated Incidents of Hyperkalemic Cardiac Arrest

A Wake Up Safe Quality Improvement Initiative

by Angela C. Lee, MD, and Eugenie S. Heitmiller, MD

- 1970s- there have been 11 case reports of transfusion-associated hyperkalemia in children
- 7 of those 11 cases in the last 4 years-WUS
- K+ -8 mmol/L during transfusion of red cells that were 28 days and 23 days old; irradiated blood
- Infants seem to be at greatest risk- 6/11 cases were less than 6 months old

NEWSLETTER
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Preventing Pediatric Transfusion-Associated Incidents of Hyperkalemic Cardiac Arrest

A Wake Up Safe Quality Improvement Initiative

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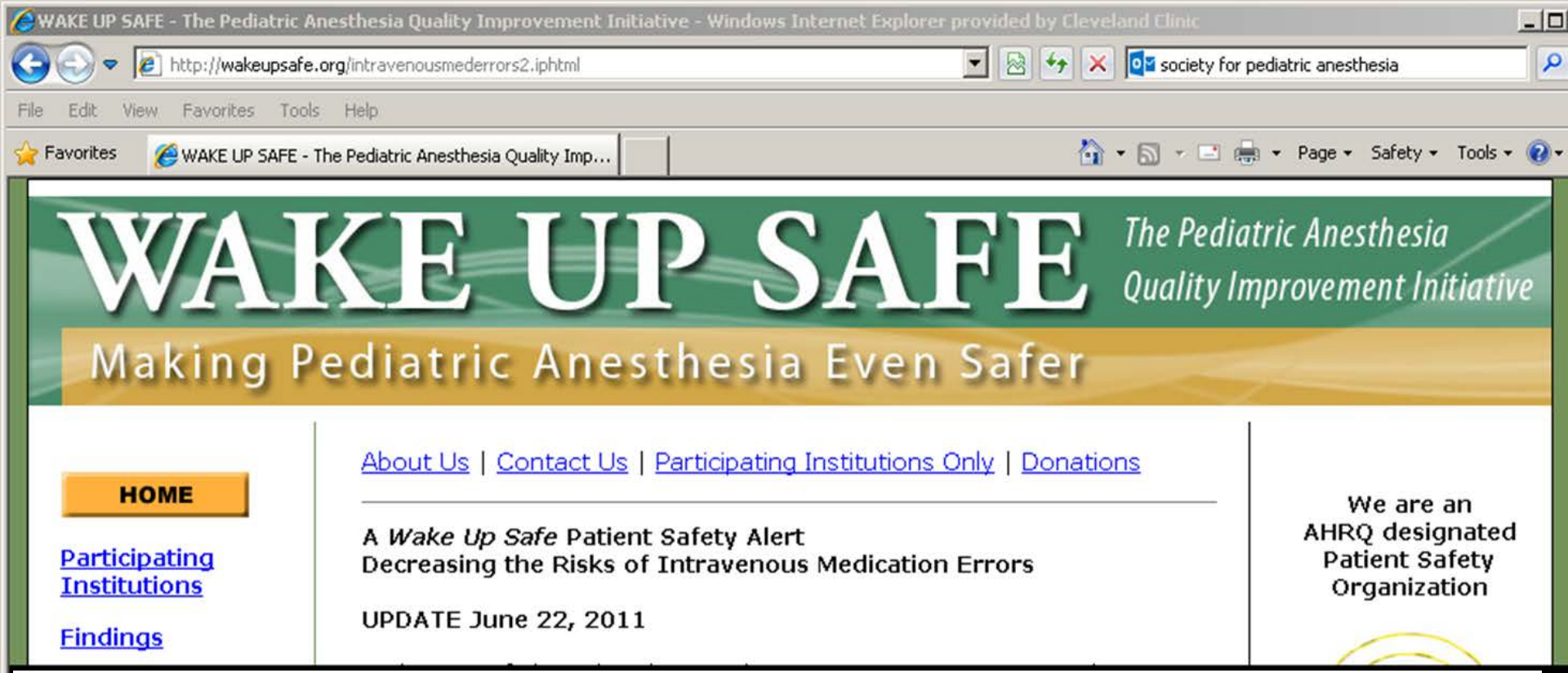
- Transfuse "fresh" (< 7 day) red cell products
- Transfuse irradiated blood as soon as possible
- If red cell products with relatively high potassium levels are the only readily available option
  - Wash the red blood cell products
  - Transfuse slowly!
  - Avoid a hypovolemia-associated low cardiac output state



Serious medication errors of about 1 per 12,500 anesthetics

23 reports:

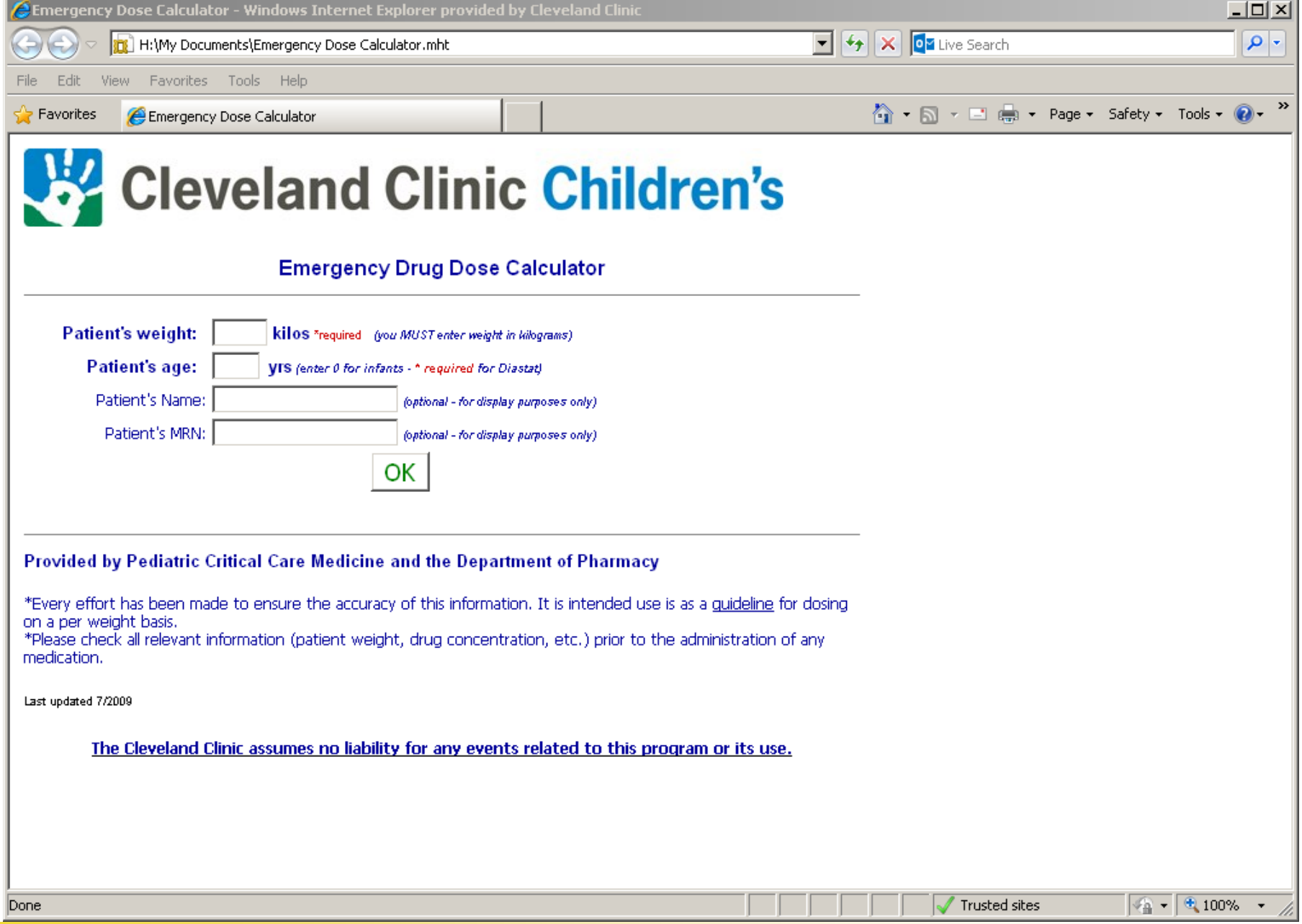
5 were wrong drug

12 were wrong dose

1 wrong route

2 omissions of needed drugs

3 were possible adverse reactions



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Weight **1.8 kg** (4 lbs.)
Maintenance fluids **7.5 ml / hr**

John Neonate
Age: 0 yrs

CODE DRUGS

Drug	Concentration	Dose	Amt (mg)	Amt (ml)
*Adenosine (1st dose)	3 mg / ml	0.1 mg / kg	0.18 mg	0.06 ml
*Adenosine (subsequent doses)	3 mg / ml	0.2 mg / kg	0.36 mg	0.12 ml
Amiodarone	50 mg / ml	5 mg / kg	9 mg	0.2 ml
Atropine (*patient less than 13 yrs)	0.1 mg / ml	0.02 mg / kg	0.1 mg	1 ml
Bicarbonate ($NaHCO_3$)	1 mEq / ml	1 mEq / kg	1.8 mEq	1.8 ml
Calcium Chloride ($CaCl_2$)	100 mg / ml	20 mg / kg	36 mg	0.36 ml
Dextrose 10 % (D_{10}) *for less than 5 kg	0.1 gm / ml	1 gm / kg	1.8 gm	18 ml
Epinephrine 1:10,000	0.1 mg / ml	0.01 mg / kg	0.02 mg	0.18 ml
*Flumazenil (Romazicon)	0.1 mg / ml	0.01 mg / kg	0.02 mg	0.18 ml
Naloxone (Narcan)	0.4 mg / ml	0.01 mg / kg	0.02 mg	0.05 ml

INTUBATION DRUGS

Drug	Concentration	Dose	Amt (mg)	Amt (ml)
Fentanyl	50 mcg / ml	2 mcg / kg	4 mcg	0.1 ml
Ketamine	10 mg / ml	1 mg / kg	1.8 mg	0.18 ml
Lorazepam * for wt of 5 kg or less	4 mg / ml	0.1 mg / kg	0.18 mg	0.05 ml
Propofol	10 mg /ml	1 mg / kg	2 mg	0.2 ml
Rocuronium	10 mg / ml	1 mg / kg	1.8 mg	0.18 ml

IV INFUSIONS

Drug	Stock Solution	Dilution	Initial Dose	Initial Rate
Amiodarone	50 mg / ml	100 mg (2 ml) / 50 ml	5 mcg / kg / min	0.27 ml / hr
Dopamine	800 mg /250 ml (premix)	80 mg (12.5 mL of premix) / 50 mL	5 mcg / kg / min	0.34 ml / hr
Dobutamine	12.5 mg / ml	100 mg (8 ml) / 50 ml	5 mcg / kg / min	0.27 ml / hr
Epinephrine (1:1000)	1 mg / ml	0.8 mg (0.8 ml) / 50 ml	0.1 mcg / kg / min	0.68 ml / hr

Cleveland Clinic

Department of PHARMACY

Peds CTS Anesthesia pre-op infusions

Doctor Name Beeper#

Please Enter the Patient's Weight: 1.7 kg *required Enter

(weight must be entered in kg!)

** Default base solutions: weight > 5 kg = D5W, weight < 5 kg AND age < 1 month = D10W*

Dopamine 800 mcg/mL in 50 mL syringe
Rate: 0.64 mL/hr = 5 mcg/kg/min

Milrinone 50 mcg/mL in 50 mL syringe
Rate: 1 mL/hr = 0.5 mcg/kg/min

Nitroglycerin 200 mcg/mL in 50 mL syringe
Rate: 1.5 mL/hr = 3 mcg/kg/min

Nitroprusside 200 mcg/mL in 50 mL syringe
Rate: 0.51 mL/hr = 1.0 mcg/kg/min

Norepinephrine (Levophed) 16 mcg/mL in 50 mL syringe
Rate: 0.64 mL/hr = 0.1 mcg/kg/min

Morphine 50 mcg/mL in 50 mL syringe
Rate: 1.4 mL/hr = 40 mcg/kg/hr

Epinephrine 16 mcg/mL in 50 mL syringe
Rate: 0.64 mL/hr = 0.1 mcg/kg/min

Dobutamine 500 mcg/mL in 50 mL syringe

Errors by pediatric residents in calculating drug doses

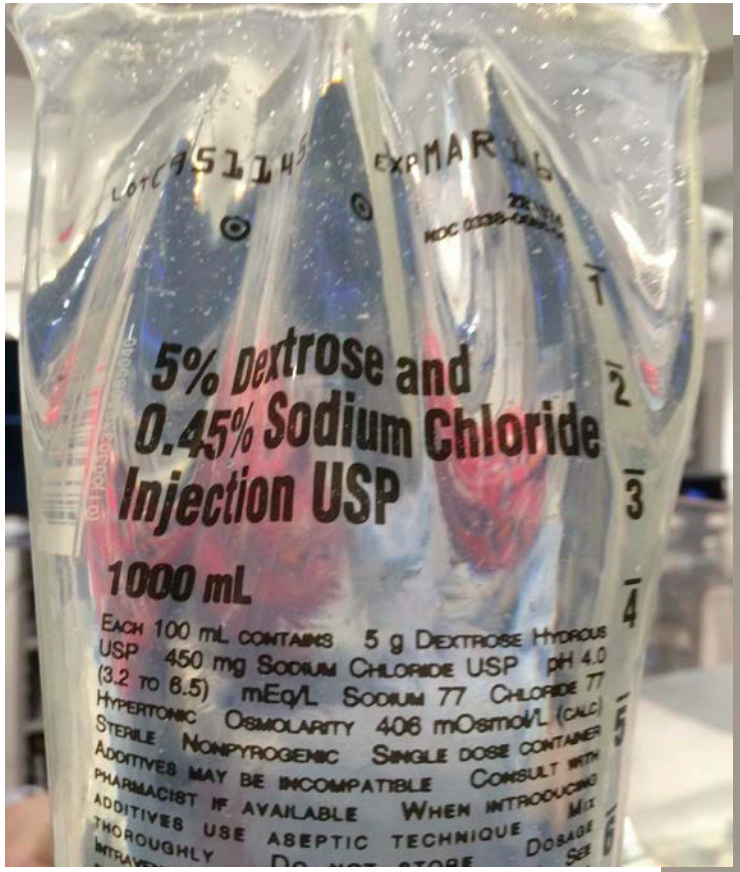
Rowe C. Arch Dis Child. 1998, 79(1): 56–58

- Loyal S, Kussman BD, Kovatsis PG. Formula to Prevent Overdoses of Muscle Relaxants. SPA 2001.
- Formula to Prevent Muscle Relaxant Overdose
- Weight Kg/10=ML of Muscle Relaxant
- Calculate precise dose provides a reasonable tool to double check the dose

Table 1: Intubating doses (ID) in ml of muscle relaxants as calculated by formula

Weight (kg)	Rocuronium (10mg/ml): 1D-1 mg/kg	Cisatracurium (2mg/ml): 1D-0.2 mg/kg	Pancuronium (1mg/ml): 1D-0.1 mg/kg	Rapacuronium (20mg/ml): 1D-2mg/kg	Mivacurium (2mg/ml): 1D-0.2 mg/kg	Vecuronium (10mg/kg): 1D-0.1 mg/kg	Succinylcholine (20mg/ml): ID-2mg/kg
1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	1	1	1	1	1	1	1
20	2	2	2	2	2	2	2
30	3	3	3	3	3	3	3
40	4	4	4	4	4	4	4

IV Fluids



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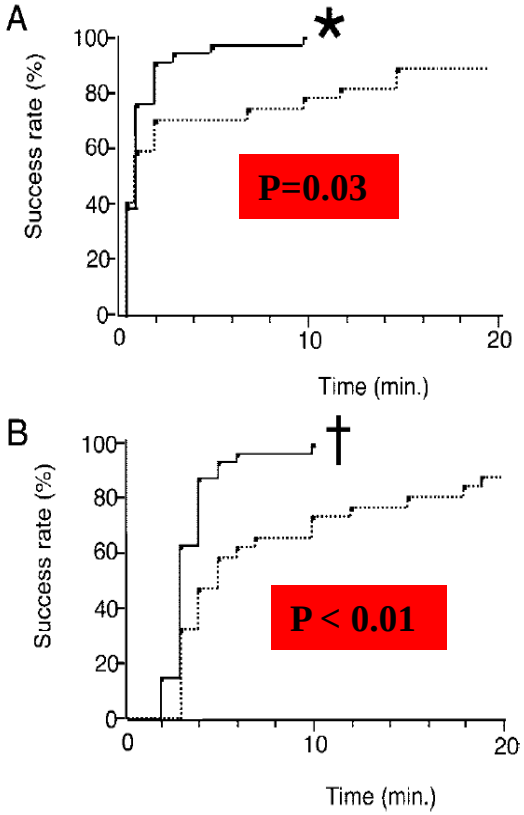
- Post Transfusions
- Di George Syndrome
- LCOS
  - Milrinone &Epinephrine

Anesthesiology 2007; 107:720–4

A Randomized Trial of Ultrasound Image–based Skin Surface Marking versus *Real-time Ultrasound-guided Internal Jugular Vein Catheterization in Infants*

Koji Hosokawa, M.D., Nobuaki Shime, M.D., Ph.D.,† Yuko Kato, M.D.,‡ Satoru Hashimoto, M.D., Ph.D.§*



A. The time to successful puncture

B. The time to successful catheterization

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Neonatal Clinical Pharmacology

Historical observations

- Gray baby syndrome-chloramphenicol toxicity impaired glucuronidation
- Neonatal gasping syndrome-benzyl alcohol toxicity
- Hexachlorophene bathing encephalopathy- increased transcutaneous absorption and limited clearance capacity
- **Illustrate clinical need to know more about neonatal pharmacology**

Neonatal Clinical Pharmacology

- ***Rapid changes*** -organ size and function

  body composition –cellular function and metabolic activity which affects population-specific pharmacokinetics & pharmacodynamics
- Neonatal population-specific vulnerability:
  - Apoptosis following sedative and anesthetic exposure
  - Cerebral palsy after dexamethasone exposure
  - Reduced # of glomeruli after exposure to nephrotoxic compounds

Anesthetic Neurotoxicity — Clinical Implications of Animal Models

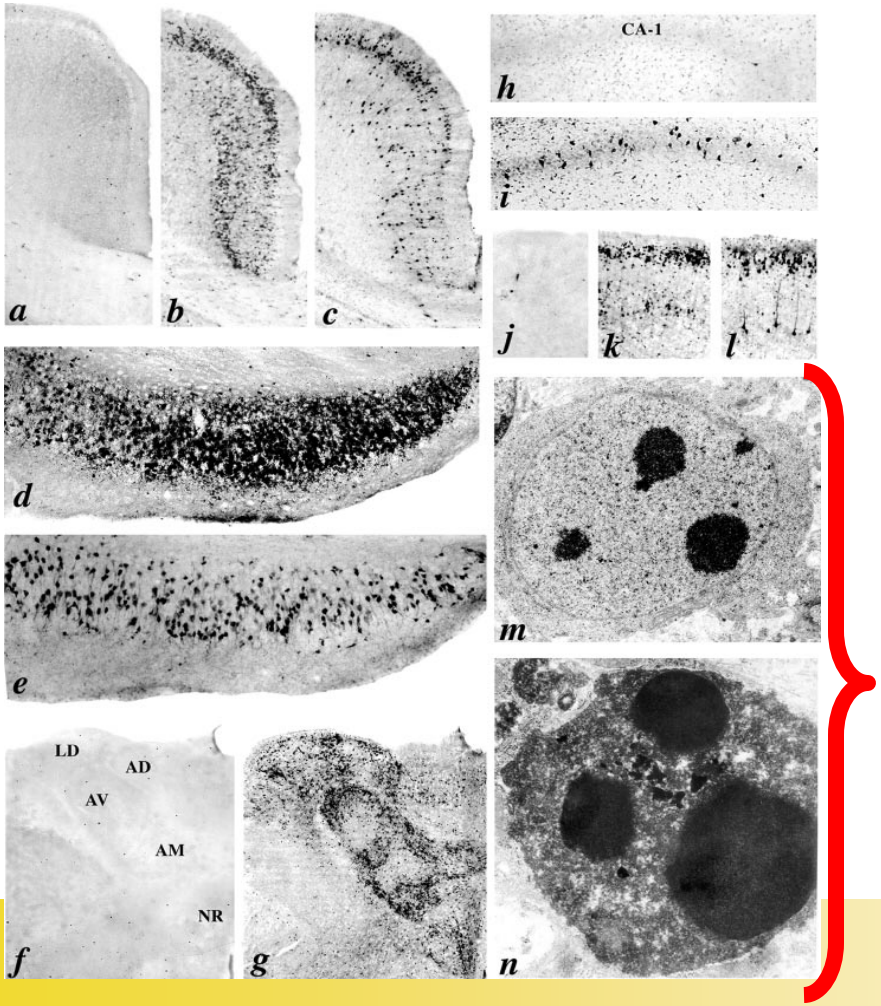
Rappaport B. NEJM 2015, 372;9: 796-97

To address the growing concern about the potential adverse consequences of general anesthesia in young patients, in 2009 the FDA established a public–private partnership with the International Anesthesia Research Society (IARS) called **Strategies for Mitigating Anesthesia Related Neurotoxicity in Tots, or SmartTots.**

New statement recommending

“surgical procedures performed under anesthesia be avoided in children under 3 years of age unless the situation is urgent or potentially harmful if not attended to.”

Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits.



J.Neurosci 2003 Feb 1;23(3):876-82

EM of Neurons undergoing Apoptosis

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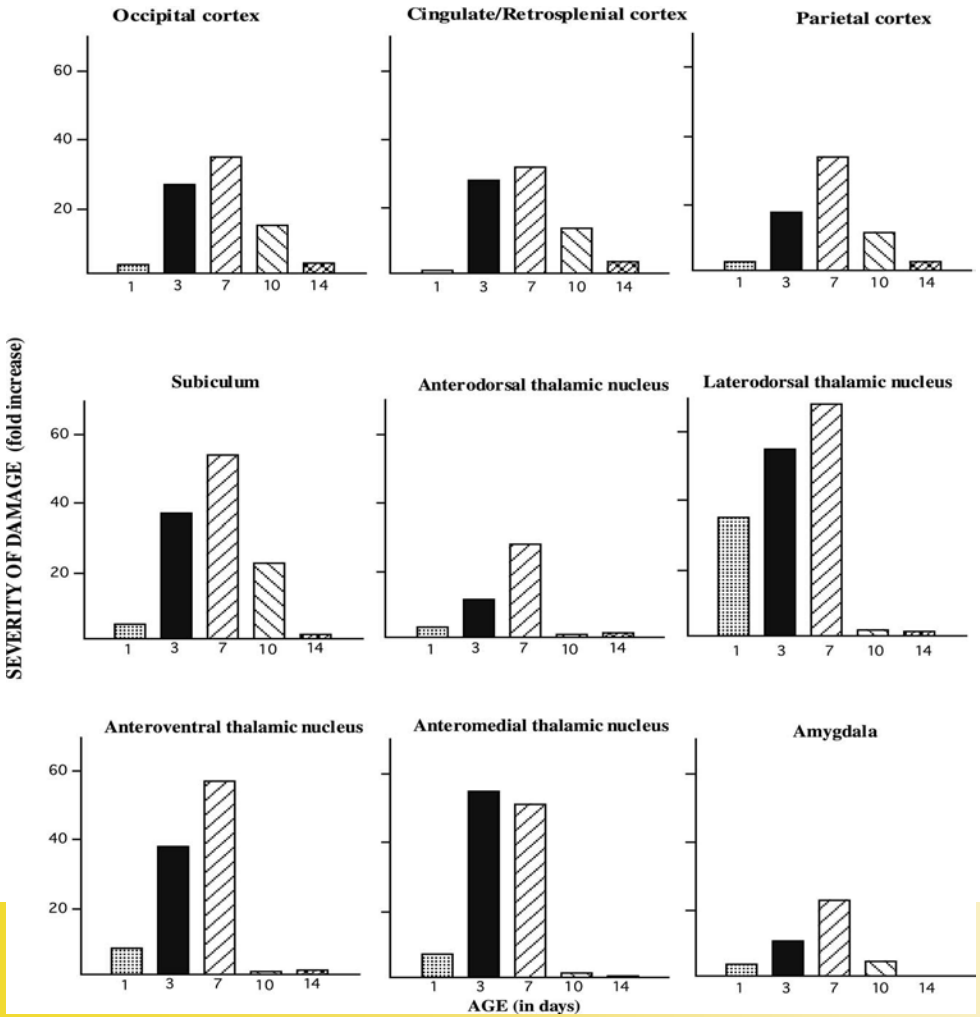
ANESTHESIA INDUCES NEURONAL CELL DEATH IN THE DEVELOPING RAT BRAIN VIA THE INTRINSIC AND EXTRINSIAPOPTOTIC PATHWAYS

Neuroscience 135 (2005) 815–82



Anesthesia-induced Neurodegeneration:

- Age-dependent
- Brain region-specific

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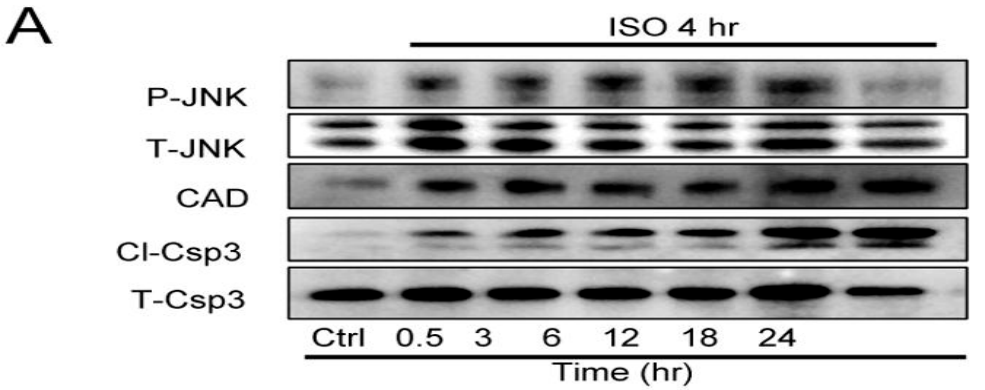
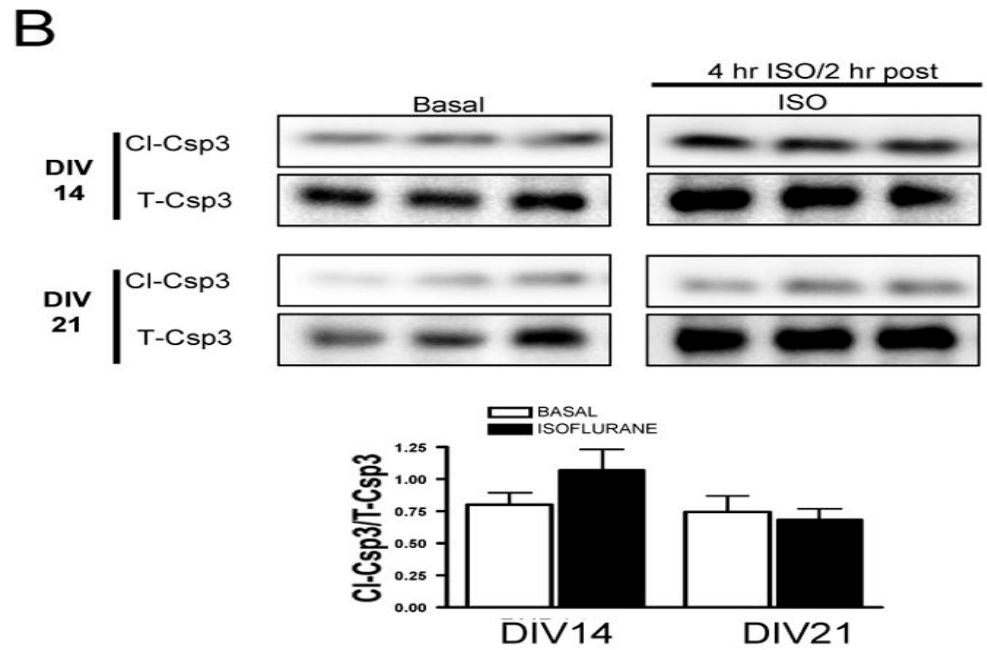
Inhibition of p75 Neurotrophin Receptor Attenuates Isoflurane-mediated Neuronal Apoptosis in the Neonatal Central Nervous System

Anesthesiology 2009; 110:813–25





Pro-apoptotic proteins

Post isoflurane exposure

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Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits.

J.Neurosci 2003 Feb 1;23(3):876-82

- Exposed rats were slow learners
- Cognitive abilities lagged behind controls
- Gap of learning disabilities widened into adulthood
- Other studies confirmed single exposure to clinically relevant GA caused permanent impairment to cognitive impairment
- Anesthetic combinations were most detrimental

Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys.

Neurotoxicol Teratol 2011, 33: 220-30.

- Low dose continuous infusion of Ketamine
- During critical period of their brain development (postnatal days 5 or 6).
- Ketamine-exposed monkeys showed a significant and long-lasting cognitive impairment
- Ketamine-treated monkeys demonstrate lower training scores in all aspects of the Operant Test Battery
- Assesses motivation, short-term memory, color discrimination and learning
- Starting about 10 months of postnatal age and lasting beyond 3 years of age

British Journal of Anaesthesia **111** (2): 143–51 (2013)
Advance Access publication 30 May 2013 · doi:10.1093/bja/aet177

BJA

SPECIAL ARTICLE

Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar

V. Jevtovic-Todorovic[1*], A. R. Absalom[2], K. Blomgren[3], A. Brambrink[4], G. Crosby[5], D. J. Culley[5], G. Fiskum[6], R. G. Giffard[7], K. F. Herold[8], A. W. Loepke[9], D. Ma[10], B. A. Orser[11], E. Planel[12], W. Slikker Jr[13], S. G. Soriano[14], G. Stratmann[15,16], L. Vutskits[17], Z. Xie[18] and H. C. Hemmings Jr[19*]

Choice of Anesthetic Medications?

- Anesthetics and sedatives that produce neurotoxic effects in laboratory animals
  - Increase (GABA) receptor activity (propofol, etomidate, sevoflurane, desflurane, isoflurane)
  - Blockade of excitatory glutamate receptors (ketamine)
- Dexmedetomidine and Xenon not been shown to be neurotoxic in animal studies

Choice of Anesthetic medications?

Dexmedetomidine

- Sole & adjunctive agent [1]
- ? Kinetics: Highly protein bound, hepatic metabolism & renal excretion
- ↑ Risk of bradycardia

1. Yuen M, Pediatric Anesthesia 2010, 20:256

Choice of Anesthetic medications?

- REMIFENTANIL

  Metabolism is unaffected by renal or hepatic maturity

  - = or ↑ clearance by tissue and plasma esterases [1]
  - Safety & efficacy in surgery [2,3]
  - Safety & efficacy in NICU [4,5]

1. Sammartino M, Pediatric Anesthesia 2010, 20:246
2. Davis P, Pediatric Anesthesia 2001, 93:1380
3. Galinkin J, Pediatric Anesthesia 2001. 93:1387
4. Sammartino M, Pediatric Anesthesia 2003, 13:596
5. Silva Y, Pediatric Anesthesia 2008, 18:176

Neonatal Clinical Pharmacology

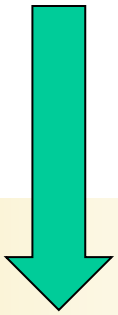
- Maturational **pharmacokinetics** consider maturational changes in either drug ***A***bsorption, ***D***istribution, ***M***etabolism and ***E***limination (**ADME**)
- Maturational **pharmacodynamics** consider maturational changes in the concentration-effect profile –differences in receptor expression, function, or specific tissue/organ

Neonatal Clinical Pharmacology

Highly Water Soluble Medication

- Displays a higher distribution volume
- Necessitating higher loading dose (mg/kg)
- Lower clearance capacity(↓GFR)= lower maintenance doses or prolonged dosing interval to avoid accumulation
- Succinylcholine or antibiotics
- Gentamicin $T_{1/2}$ –

Age	Hours
Preterm	8.5
NB 1wk	6
NB 2 wk	4
Adult	2



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Neonatal Clinical Pharmacology

Neuromuscular Blocking Agents

Pharmacokinetics & dynamic affected by:

- ↑ Volume of distribution
- ↓ Clearance
- ↓ Myoneural junction
- ↓ Muscle Mass

Neonatal Clinical Pharmacology

- Decreased weight as muscle- lower dose or plasma level needed for most muscle relaxants for clinical effect
- Decreased total body fat- prolonged sedation for drugs that redistribute into fat

Aims of Anesthesia for the Neonate

- Essentially the same as those for adult of child [1]
- Ablation of consciousness & recall
- Minimization of physiological, humoral and behavioral signs of distress
- Minimize short ***and*** long term effects
- Maximization of perioperative outcomes [2]

1.Davidson A, Pediatric Anesthesia 2007, 17:102

2. Anand K, Lancet, 1987, 1:62

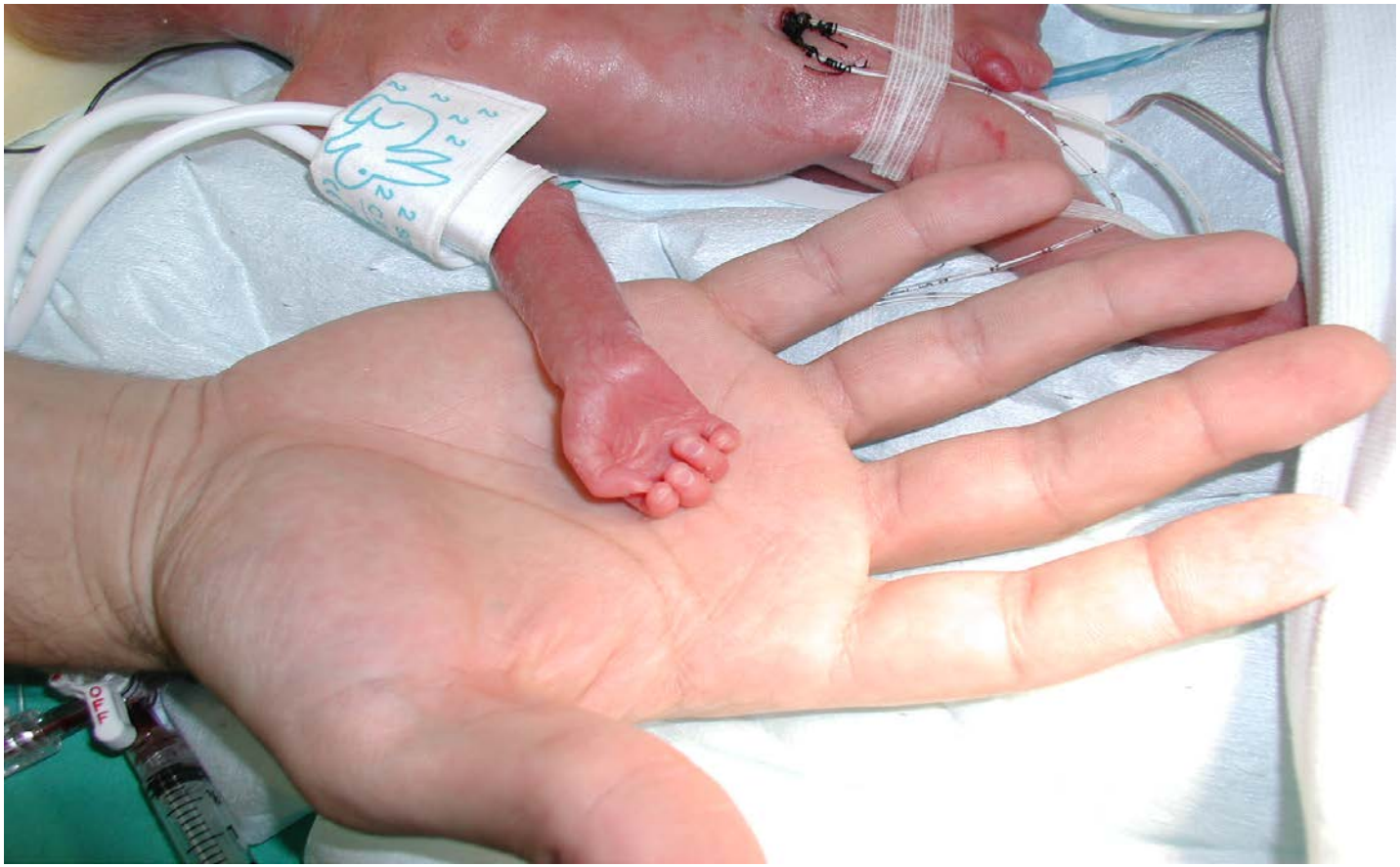
An Ounce of Prevention Is Worth a Pound of Cure ... as Well as a Pound of Cash

Julie Niezgoda, MD

Anesth Analg 2012 ,115:743

There needs to be a paradigm shift from **"morbidity and mortality conferences"** where health care workers implement changes after mistakes have happened to **"prevent and protect conferences"** in which strategies and studies are designed to recognize, prevent, and mitigate harm.

These vulnerable neonates are placed in our capable hands. Future research, EBM protocols and adequate training of practitioners promises a brighter future…..



Pediatric Anesthesia

Special Issue: Neonatal Anesthesia: Frontier Concepts in Theory and Practice

January 2014 Volume 24, Issue 1

Pages 1–136

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