Impaired Right Ventricular-Pulmonary Vascular Interactions in Adults Born Premature

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Disclosures: None

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When I grow up, I want to be a…?

http://www.nicuhelpinghands.org/

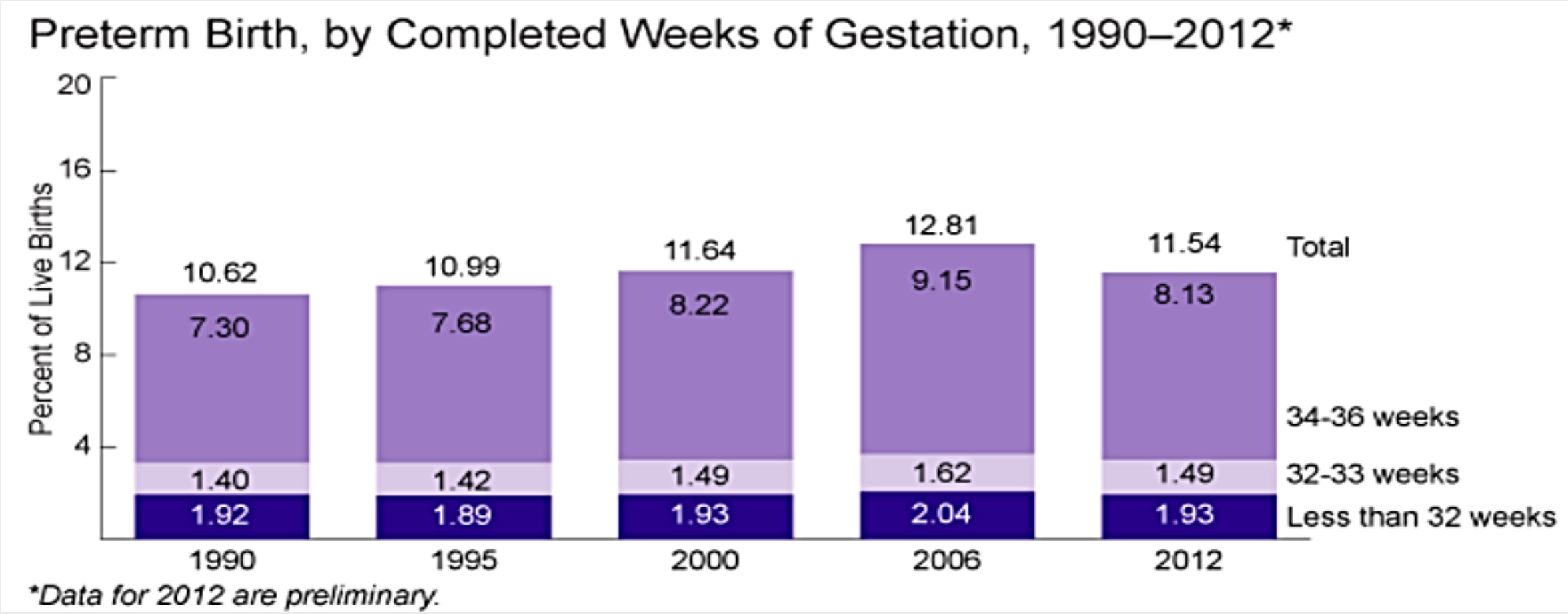
Outline

- Prematurity in the US
  - Definitions and epidemiology
- Long-term right ventricular and pulmonary vascular outcomes after preterm birth
  - Newborn Lung Project Cohort
  - Insights from animal models

Objectives

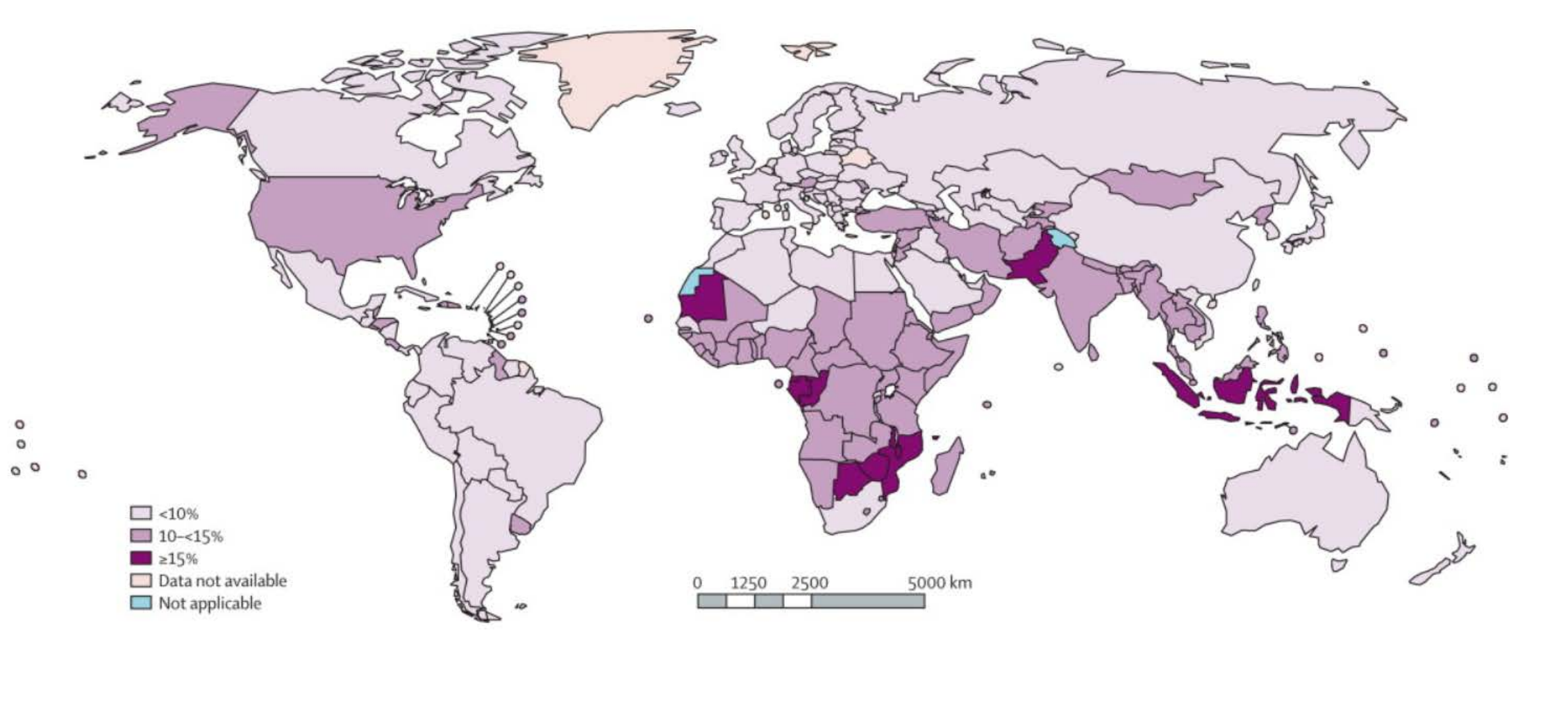
- Identify a history of premature birth as a risk factor for adult pulmonary hypertension and right ventricular dysfunction
- Incorporate screening for key components of birth history in the standard evaluation of pulmonary hypertension patients

Incidence of Premature Birth Is Rising



http://mchb.hrsa.gov/chusa13/perinatal-health-status-indicators/p/preterm-birth.html

Incidence of Premature Birth Is Rising



Blencowe, Lancet 2012

Terminology

- GESTATIONAL AGE:
  - Term: ≥37 wks
  - Moderate to late preterm: 32 to <37 wks
  - Very preterm: 28 to <32 wks
  - Extremely preterm: <28 wks

Terminology

- BIRTH WEIGHT:
  - Low birth weight (LBW):
    - <2500 g (5lbs 8oz)
  - Very low birth weight (VLBW):
    - <1500 g (3lb 5oz)
  - Extremely low birth weight (ELBW):
    - <1000 g (2lbs 3oz)

The First US Neonatal Care Unit

- 1904: Dr. Martin Couney and the Coney Island “Child Incubator Exhibit”

Luna Park, Coney Island, New York, 1890

“Growing Pains” in Neonatal Care

- 1930s: Routine use of oxygen for cyanotic infants
- 1960s: First NICUs opened, ventilators in infants with Respiratory Distress Syndrome

The Detroit Free Press

NEW KENNEDY SON IS HIT BY BREATHING AILMENT

Baby Rushed To Specialists

Born 5½ Weeks Early; Named Patrick Bouvier

Officer Clear In Scott Case —Edwards

But Patrolman Is Taken Off Duty in Scout Cars

19 Nations Sign A-Ban Pact Today

Auto Plunges Into River; 2 Women Die

Invasion Crushed, Haiti Says

Modern Neonatal Care

- 1980s: Initial trials of surfactant
- 1990s: Routine use of surfactant, antenatal steroids, antenatal antibiotics

Vincent, born at 31 wks

Felix, born at 24 wks

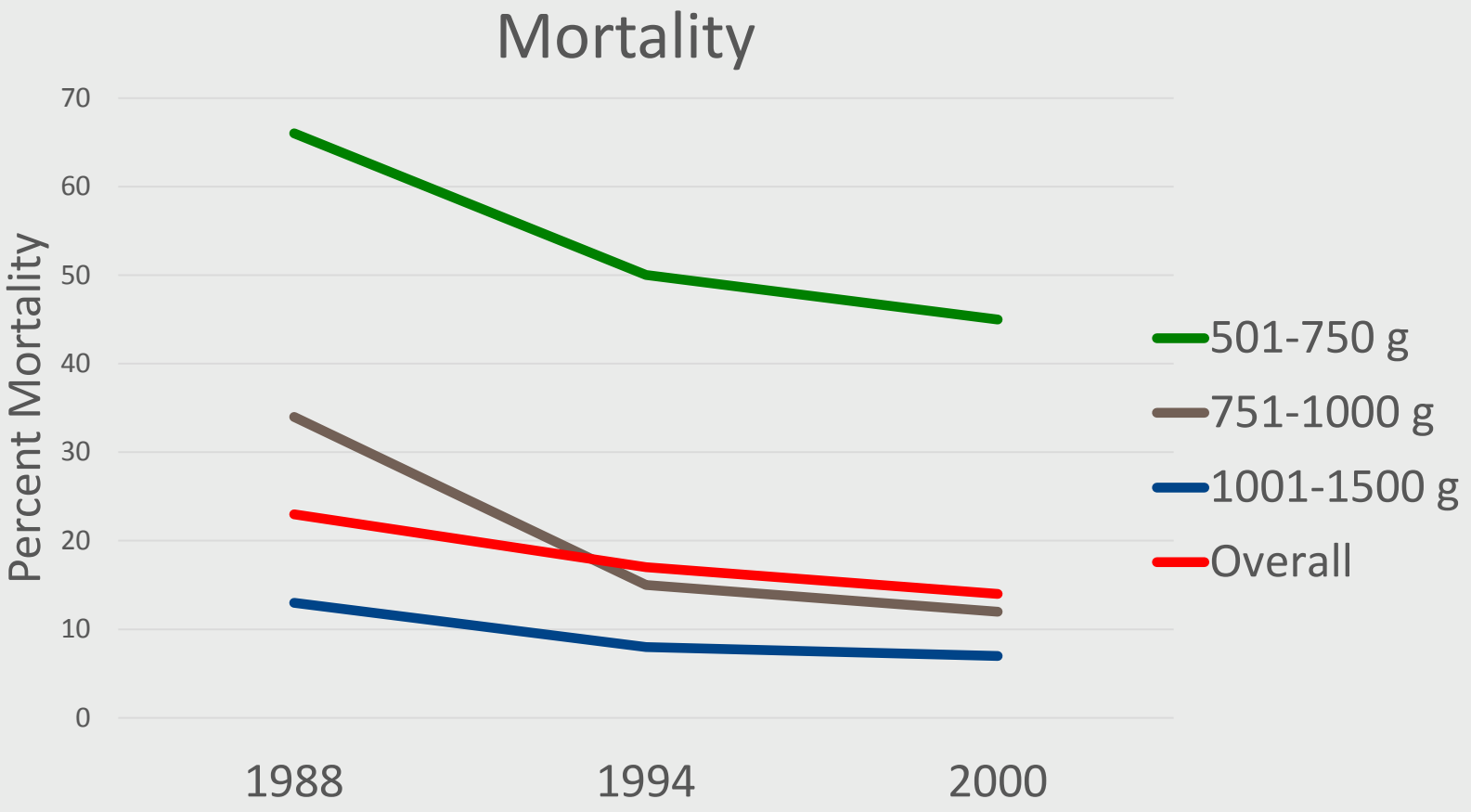
Karine, born at 28 wks

Lexiani, born at 25 wks

"Les Premes"
RedM Photography by Red Méthot
https://www.facebook.com/pg/RedMPhoto/photos/?tab=album&album_id=679320625546362

Advances in Neonatal Care Improve Mortality

NICHD Neonatal Research Network - 1986

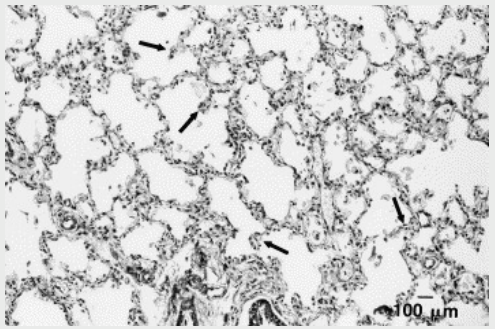


Adapted from: Fanaroff, Seminars in Perinatology 2003

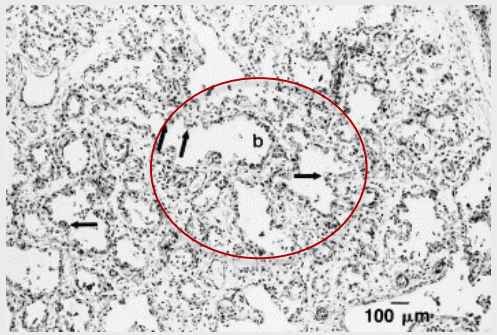
Major Neonatal Comorbidities: Bronchopulmonary Dysplasia

Thomas, born at 23 wks
“Les Premes” Collection

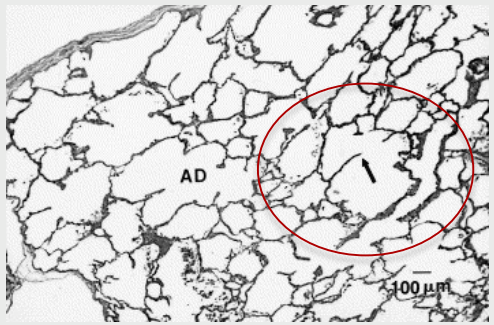
- BPD:
  - Persistent oxygen requirement inappropriate for the GA
  - Arrest in alveolar and vascular development



38 wk infant,
non-respiratory death



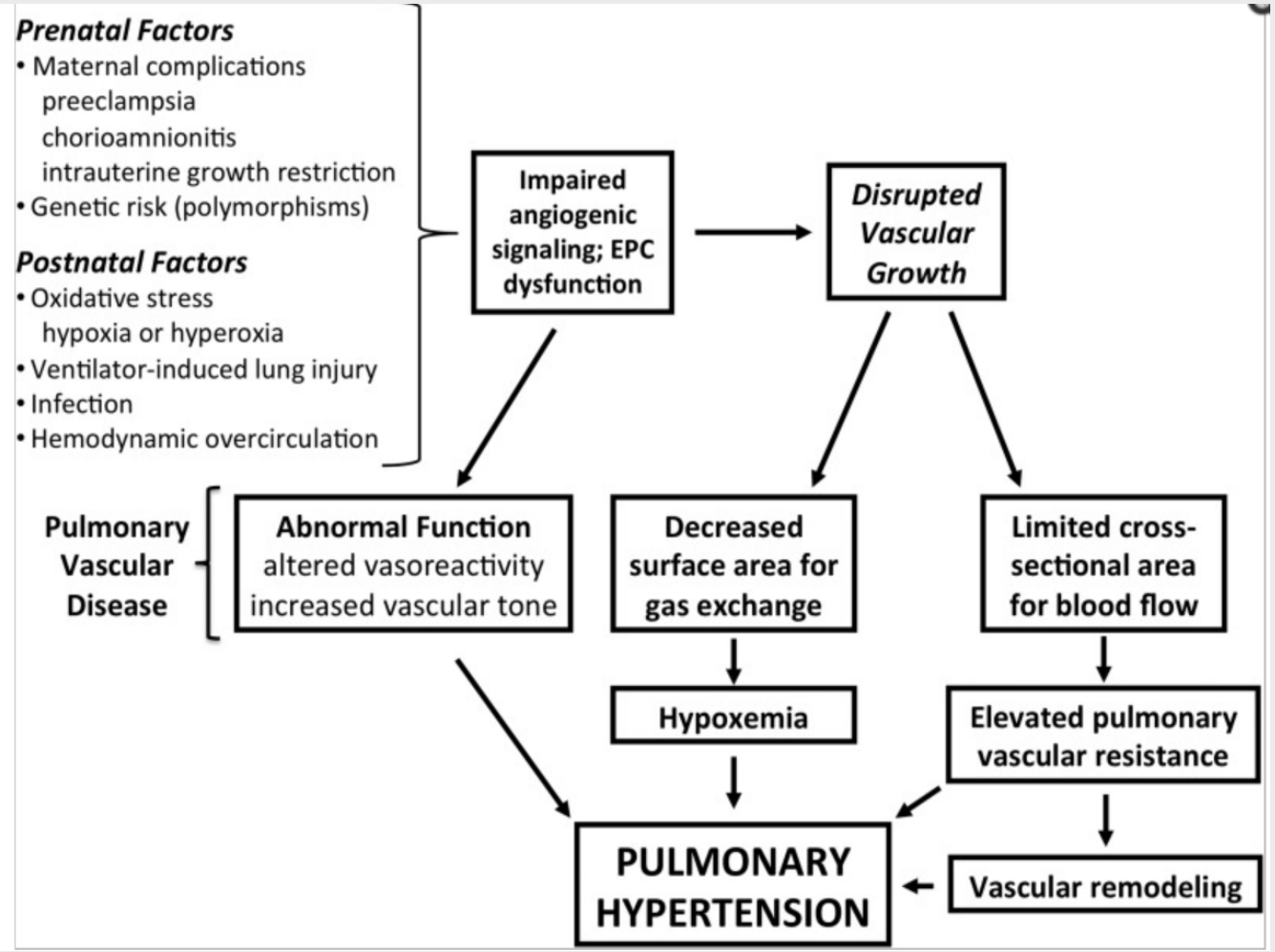
24 wk stillborn infant

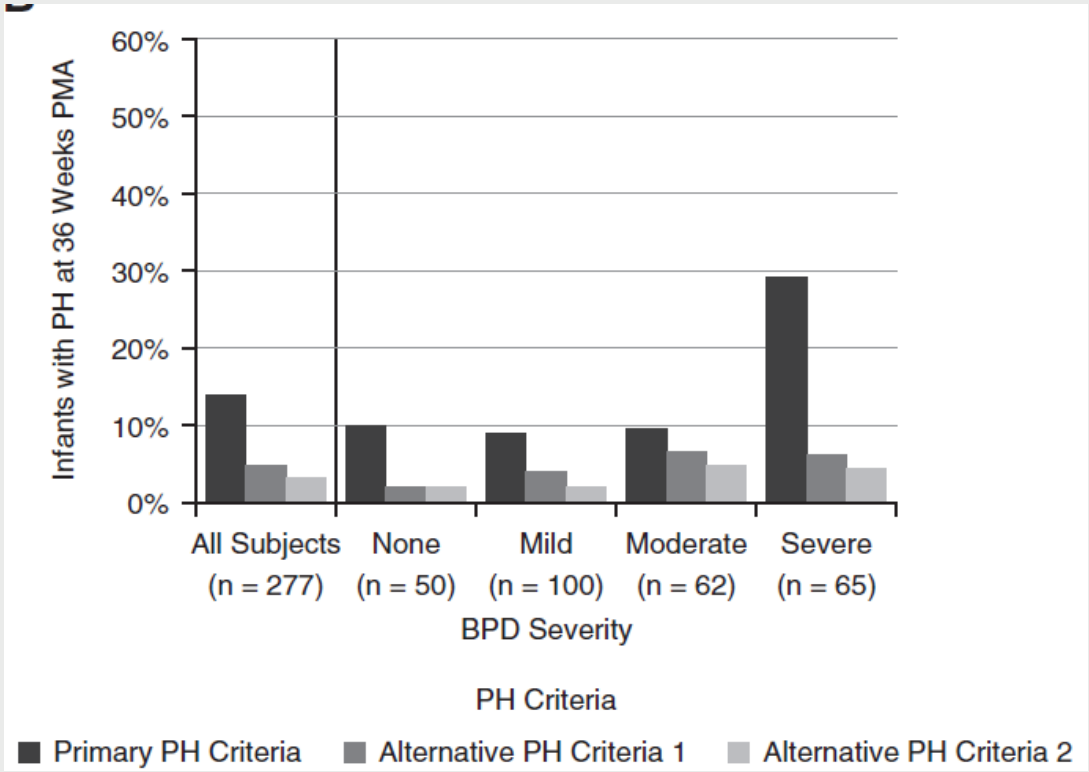


8 mo with BPD,
born at 28 wks

Coalson, Seminars in Neonatology 2003

Premature Birth Is a Risk Factor of Neonatal Pulmonary Vascular Morbidity





Baker, Pediatr Allergy Immunol Pulmonol 2014.
Mourani, AJRCCM 2015.

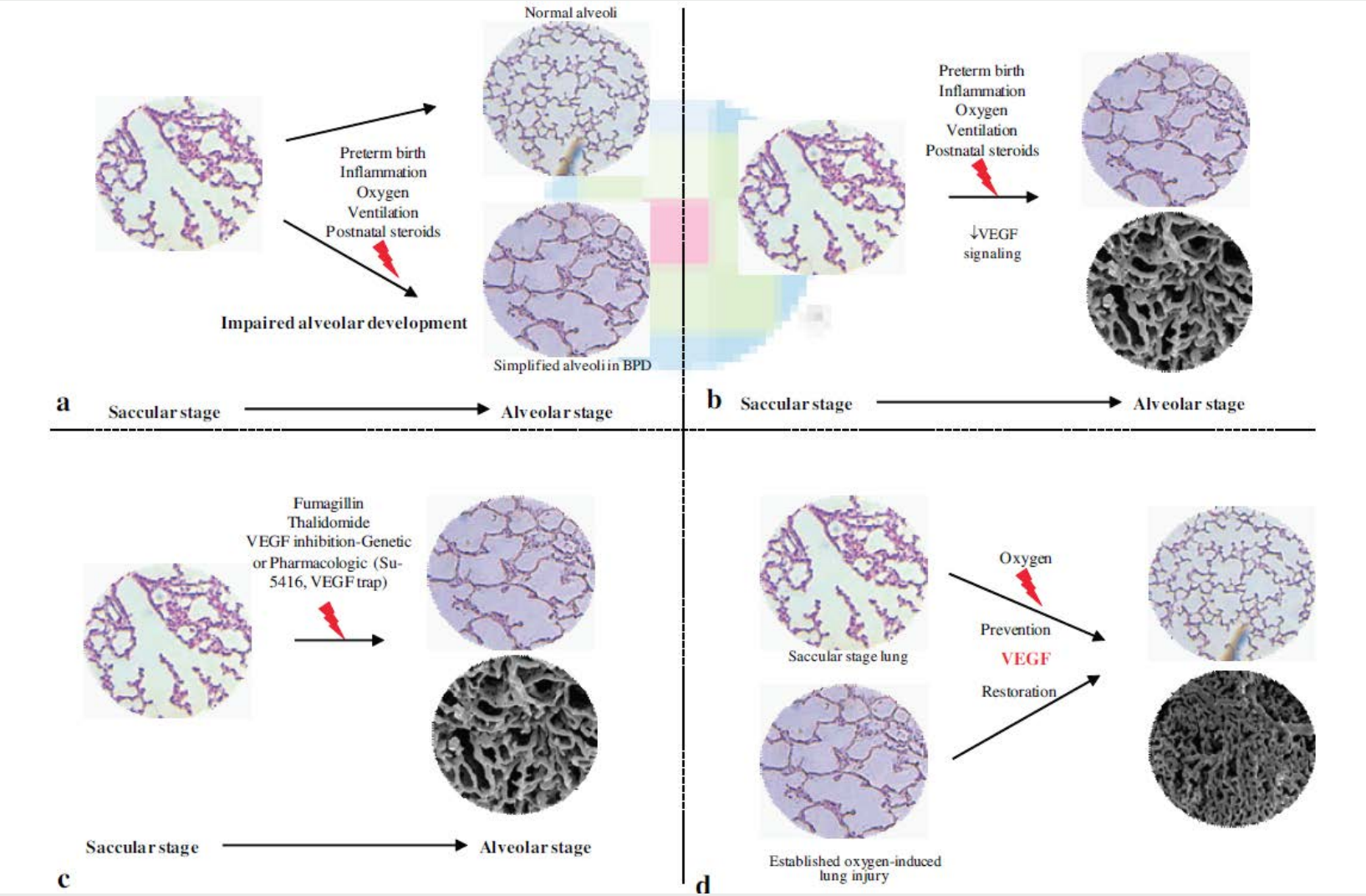
Adults Born Premature Demonstrate Poorer Respiratory Outcomes

- Lower FEV_1 and $FEV_{25\text{-}75\%}$
- Increased respiratory symptoms
- Increased airway obstruction/bronchial reactivity
- Reduced diffusing capacity
- Reduced exercise tolerance

- LACKING data on <u>long term</u> pulmonary vascular health

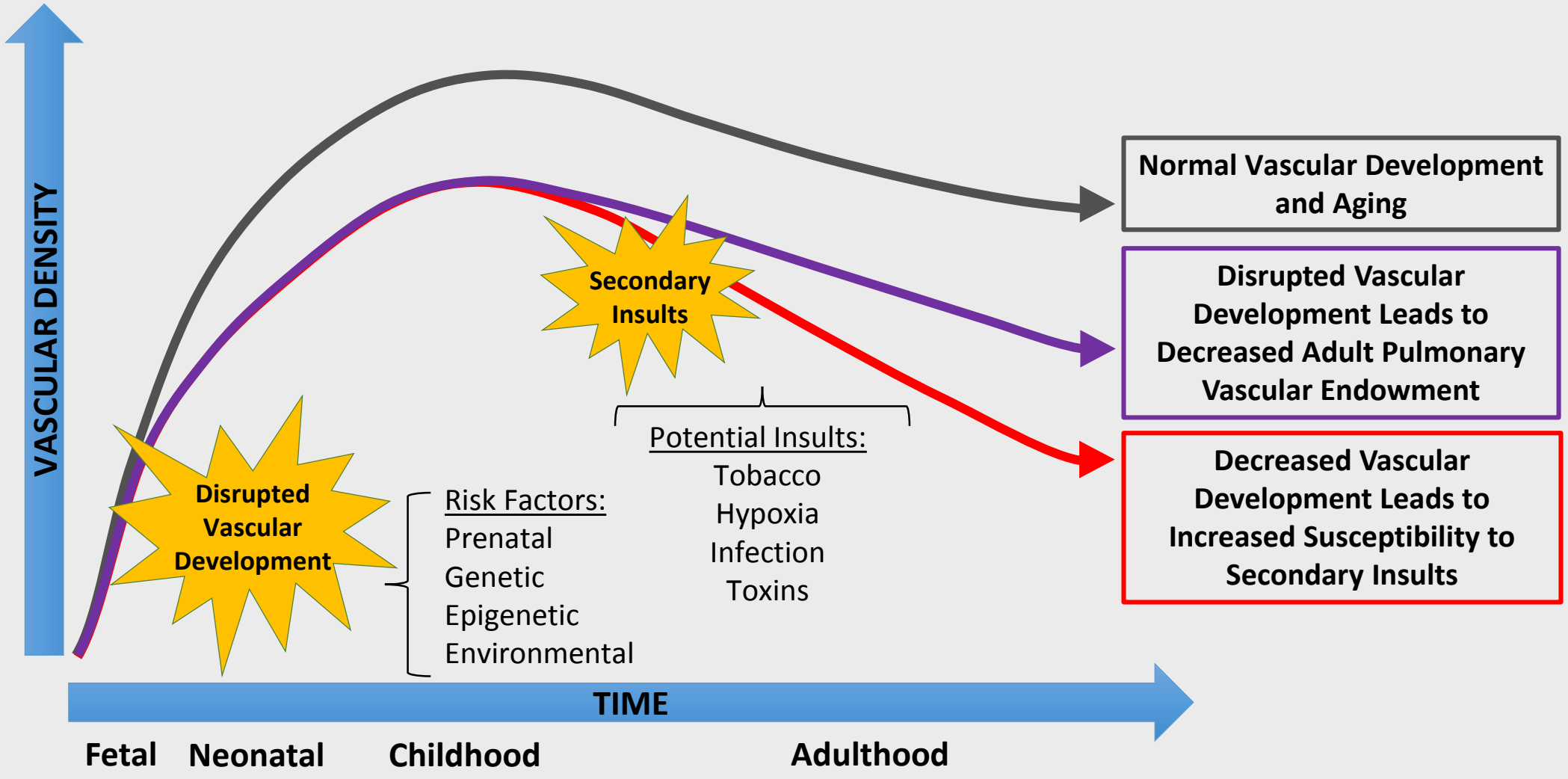
Vrijlandt, AJRCCM 2006.
Gough, CHEST 2012.
Farrell, Ann Am Thorac Soc 2015.
Islam, AJRCCM 2015.
Crump, Pediatrics 2011.

Alveolar and Vascular Development are Integrally Linked



Thebaud, PVRI Review 2010.

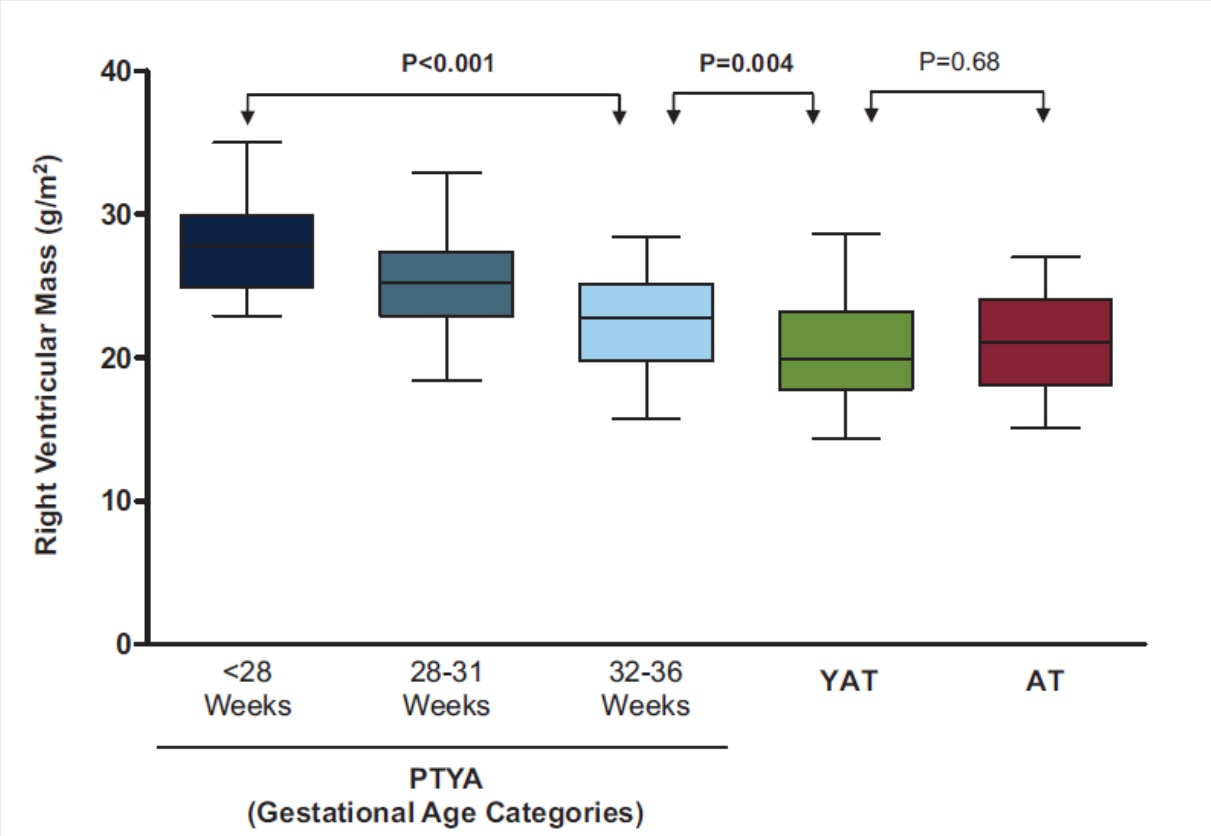
Preterm Birth May Limit Adult Pulmonary Vascular Endowment

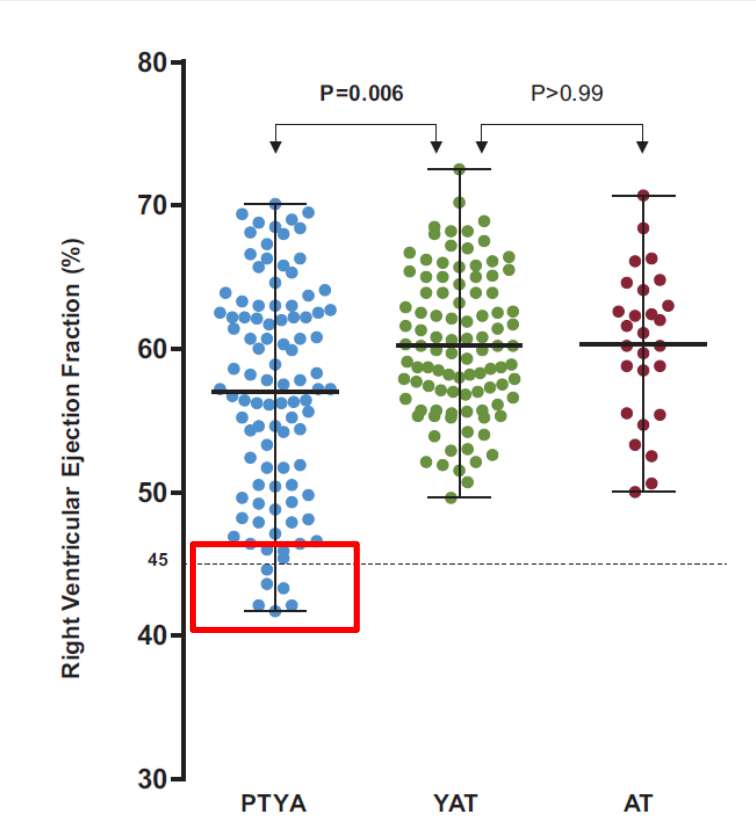


Goss, Pulmonary Circ 2017.

Right Ventricular Systolic Dysfunction In Young Adults Born Preterm

Cardiac MRI in 102 adults born preterm
Avg GA 30.3 wks; Assessed at 25.1 yr (23-28)





Lewandowski, Circulation 2013

Premature Birth Increases Risk for Pulmonary Hypertension

Case control study of adults in the
Swedish Pulmonary Arterial Hypertension Registry

Risk factor	OR	p-Value	95% Confidence interval	
			Lower	Upper
Congenital heart defect	26.01	<0.0001	7.26	93.21
Female gender	3.45	0.0002	1.78	6.69
Gestational age ≤ 36 weeks	4.85	0.0047	1.59	14.84

Naumburg, Acta Paediatr 2015

Long-term Effects of Premature Birth on the Pulmonary Vasculature?

- Newborn Lung Project Cohort
  - Neonates enrolled at birth from 6 NICUs in Wisconsin and Iowa
  - Years 1988-1990
  - Weight ≤ 1500 g
  - Average gestational age 28 wks
- Healthy controls
- All subjects free from adult cardiopulmonary disease

Palta M, J Peddiatr 1991; Palta M, Arch Pediatr Adolesc Med 1994;
Palta M, J Pediatr 1998; Palta M, Arch Pediatr Adolesc Med 2000;
Palta M, Am J Epidemiol 2001; Palta M, Pediatr Pulmonol 2007; Farrell ET, Ann Am Thorac Soc 2015

Long-term Effects of Premature Birth on the Pulmonary Vasculature?

- Visit 1:
  - Screening: PFT, VO2 Max (normoxia/hypoxia)
- Visit 2:
  - Exercise at 70% P_{Max} during cardiac MRI
- Visit 3:
  - Exercise at 70% P_{Max} during right heart cath

Rest - Exercise
Normoxia - Hypoxia

Baseline Characteristics

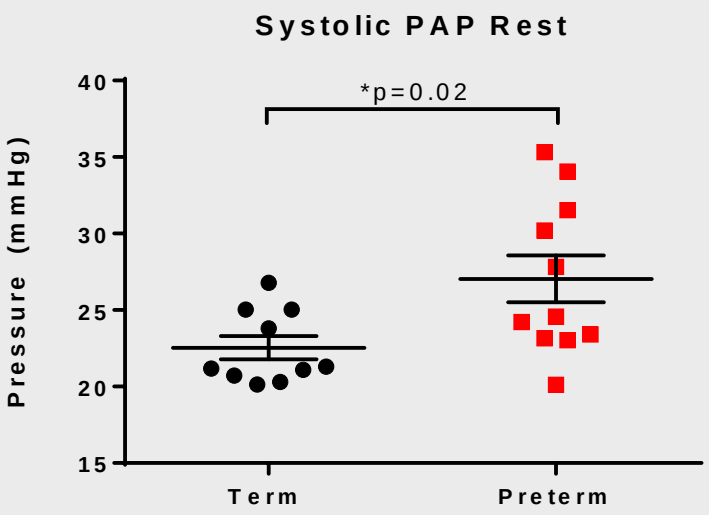
	Term	Preterm
Number of subjects (male)	10 (7)	11 (5)
Age (years)	25.8 ± 0.8	26.9± 1.1*
Weight (kg)	72.9 ± 9.8	69.4 ± 13.3
Height (m)	1.8 ± 0.1	1.7 ± 0.1
BMI (m^2)	23.3 ± 1.6	23.4 ± 3.2
Pulmonary function		
FEV1 (L)	4.4 ± 1.0	3.7+/-0.7
FEV1 % pred	101 ± 17	99 ± 21
FVC (L)	5.4 ± 1.1	4.6 ± 0.8
FVC % pred	108 ± 11	107 ± 19
FEV1/FVC (%)	0.9 ± 0.3	0.8 ± 0.1
DL_{CO} (ml/min/Torr)	31.0 ± 7.0	23.9 ± 4.2*
DL_{CO} % pred	106 ± 16	90 ± 1*
DL_{CO}/ VA (ml/min/Torr/L)	5.2 ± 0.6	4.5 ± 0.5*
DL_{CO}/ VA %pred	113 ± 13	96 ± 11*
Exercise test		
VO_{2peak}(ml/min/kg)	54.4 ± 17.1	34.4 ± 6.6*
P_{max} (watt)	246 ± 45	184 ± 41*
70% P_{max} (watt)	179 ± 27	134 ± 23*

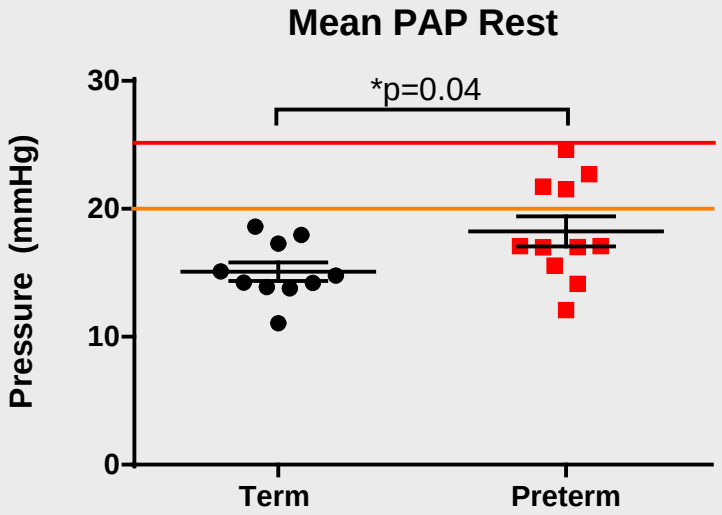
Neonatal Characteristics

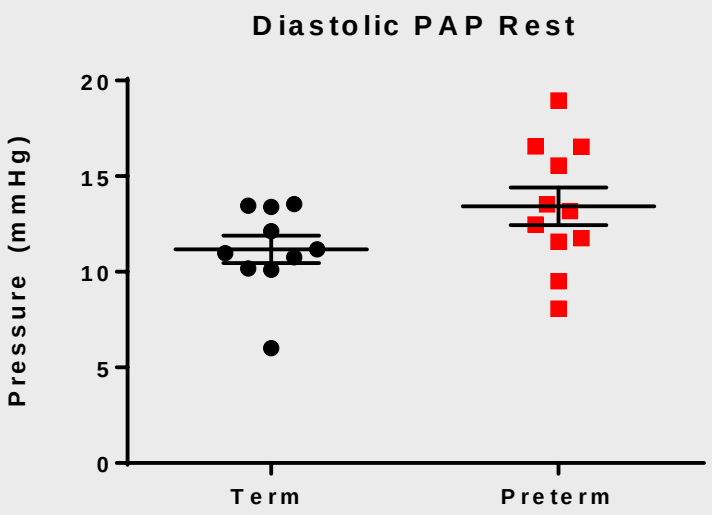
Neonatal Characteristics (n=11)	
Gestational age (weeks)	28.2 ± 2.8
Birth weight (g)	1071 ± 310.4
Delivered by C-section (n)	9
Singleton/multiple	5/6
Received antenatal steroids	0
Intubation at 24 hrs. (n)	9
Received surfactant (n)	4
Days on mechanical ventilation	16.6 ± 25.1
Days on oxygen	96.3 ± 159.7
Days in the NICU	63.8 ± 32.0
BPD diagnosis (n)	5
Persistent PDA (n)	8
Acute pulmonary complications (n)	3
Diagnosis of PH by echo in the NICU	0
Discharge home on supplemental oxygen (n)	5

Adults Born Premature Have Elevated Resting Pulmonary Pressures

Arij Beshish, MBBCh



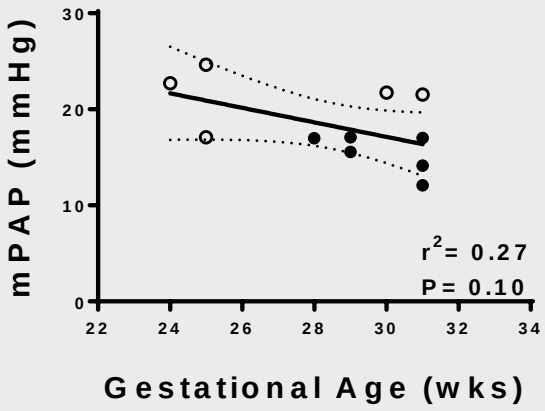


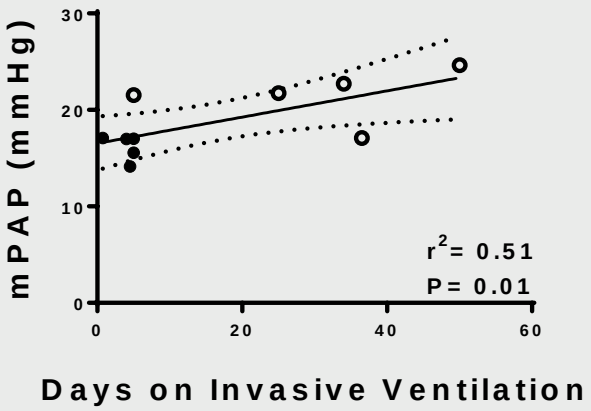


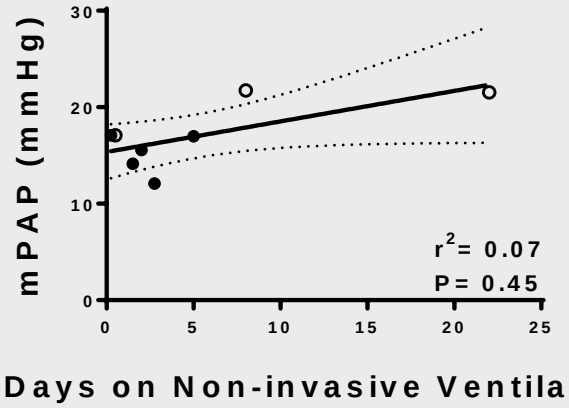
Beshish, AJRCCM, *in revision*

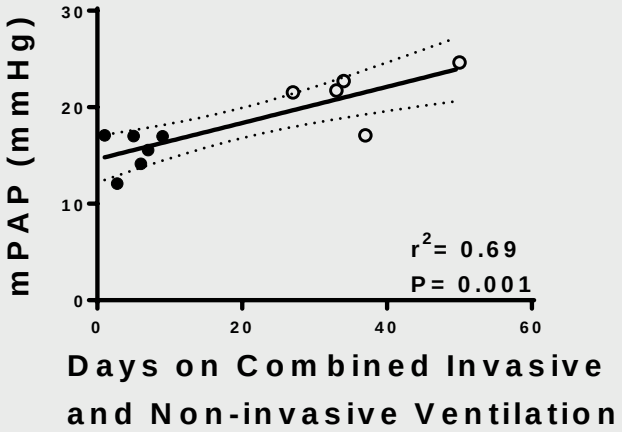
Neonatal Days on Ventilatory Support is Strongest Predictor of Adult PAP

Arij Beshish, MBBCh





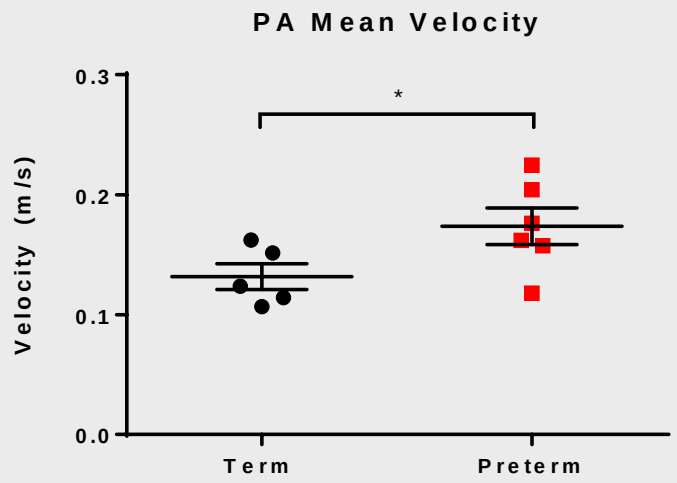


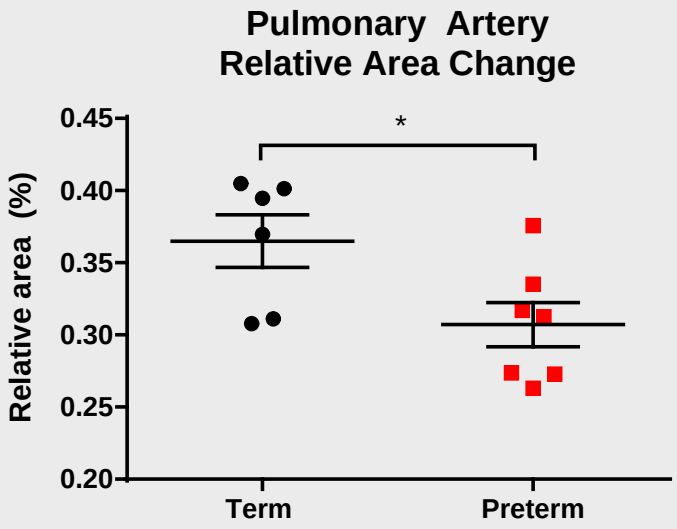


Beshish, AJRCCM, *in revision*

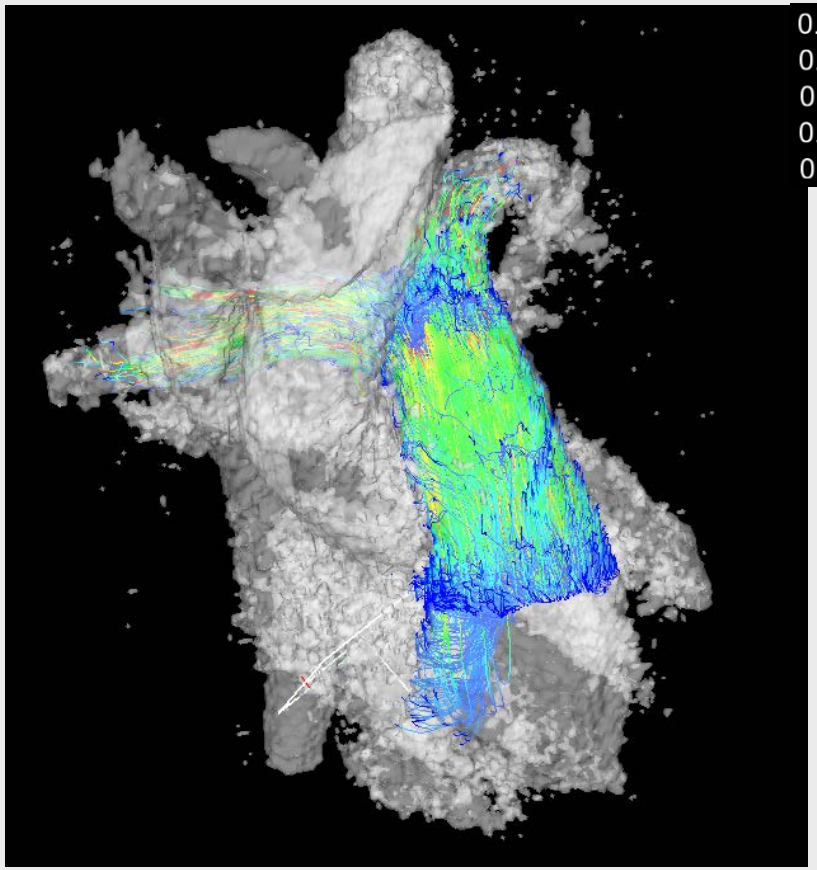
Adults Born Premature Have a Stiffer Pulmonary Vascular Bed

Jacob Macdonald

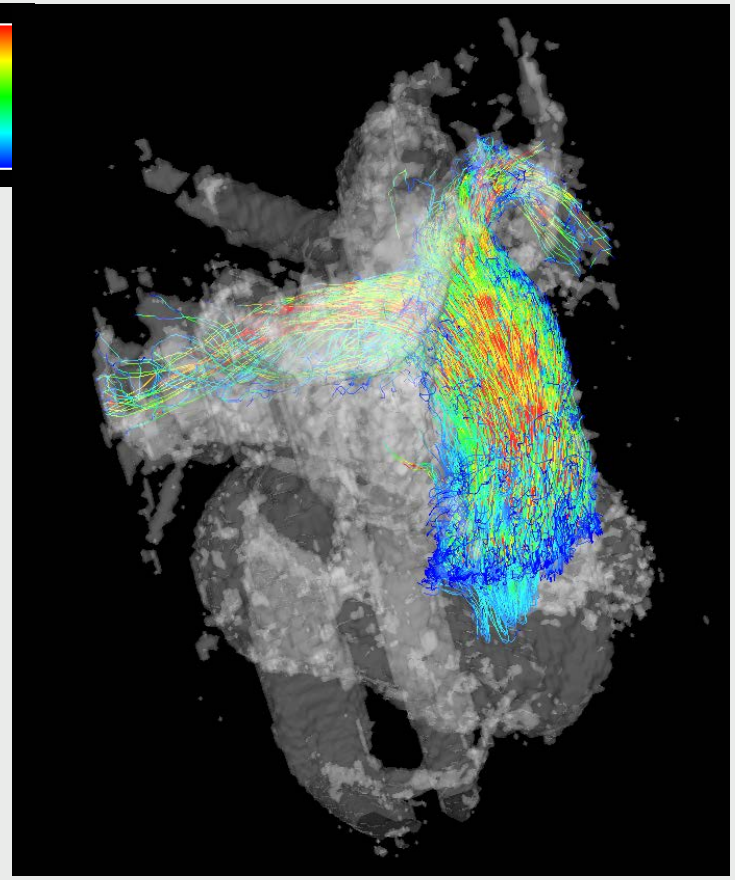




Control

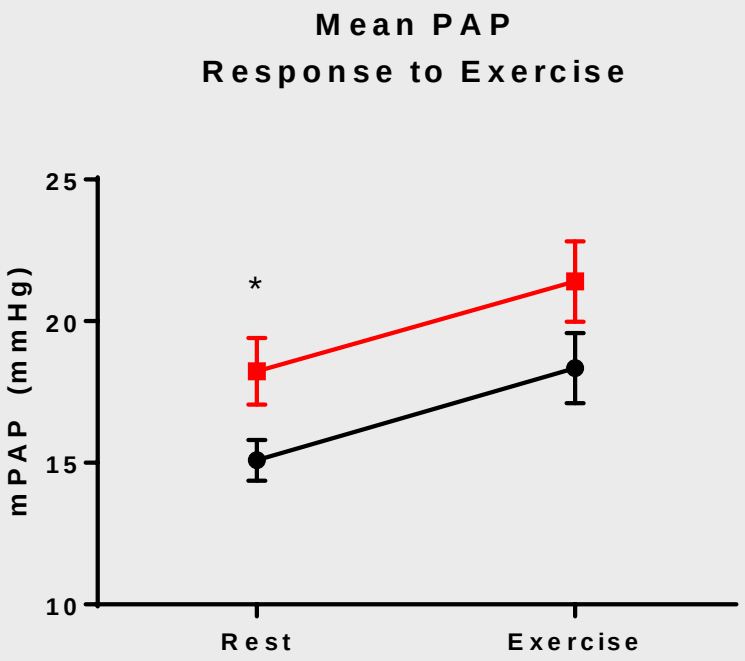


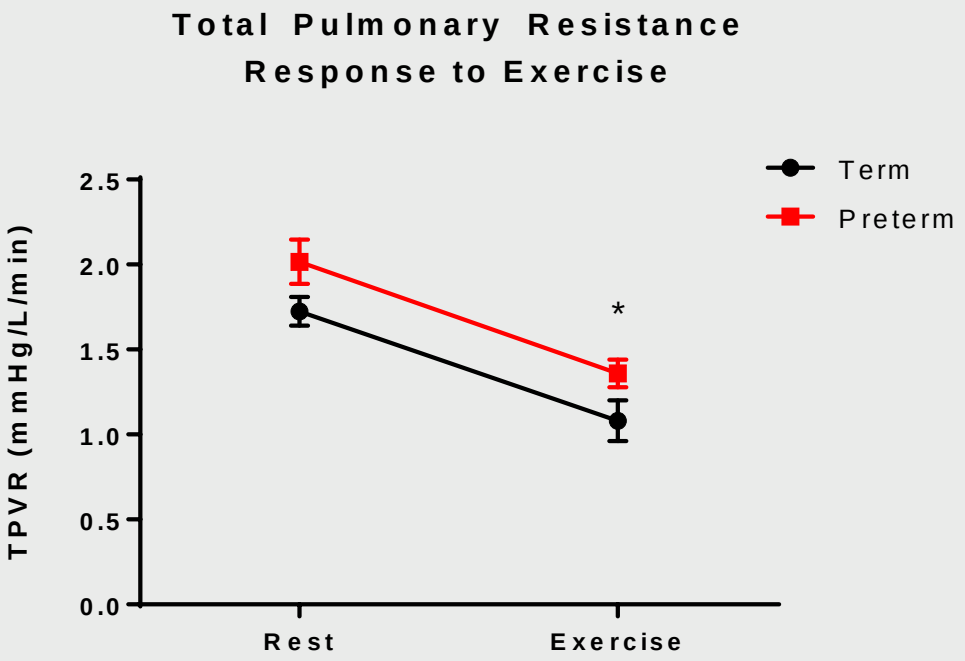
Preterm



Exercise Reveals Decreased Pulmonary Vascular Recruitability

Arij Beshish, MBBCh





Beshish, AJRCCM, *in revision*

Adults Born Premature Unable to Augment Stroke Volume During Exercise

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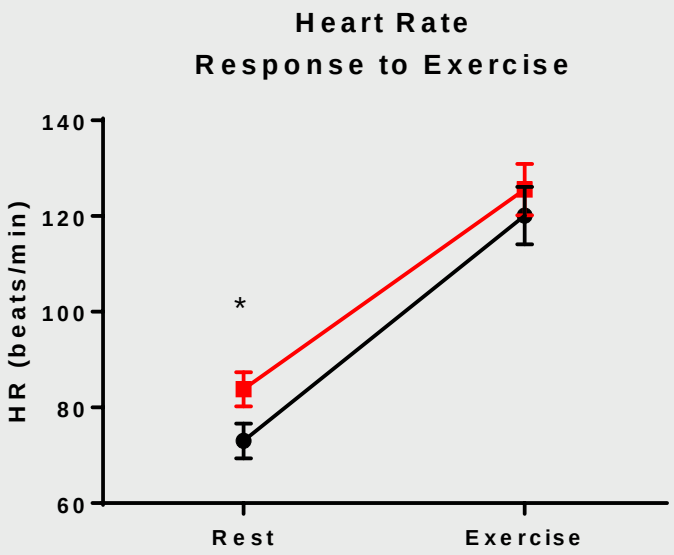
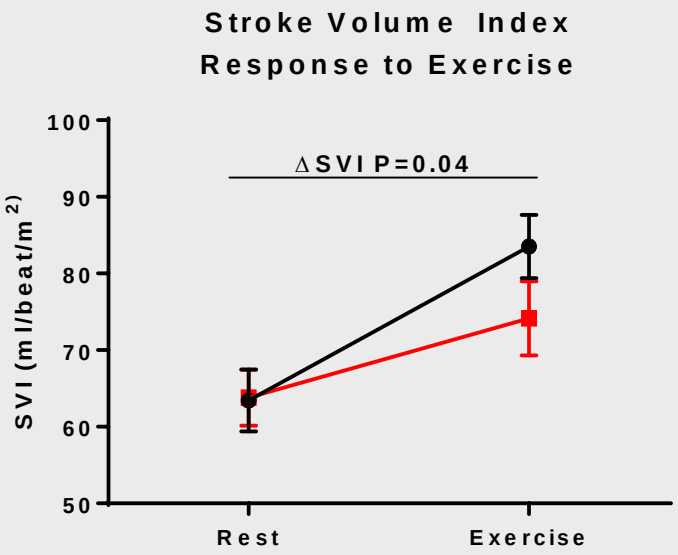
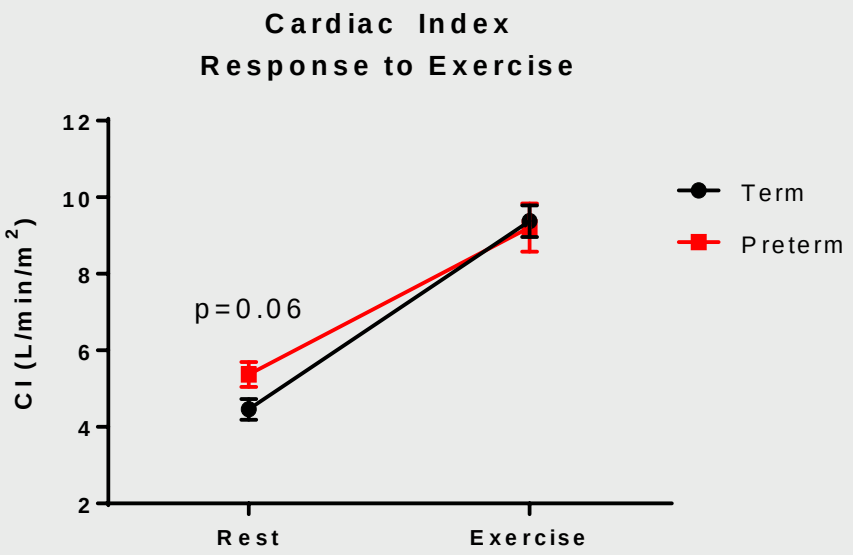


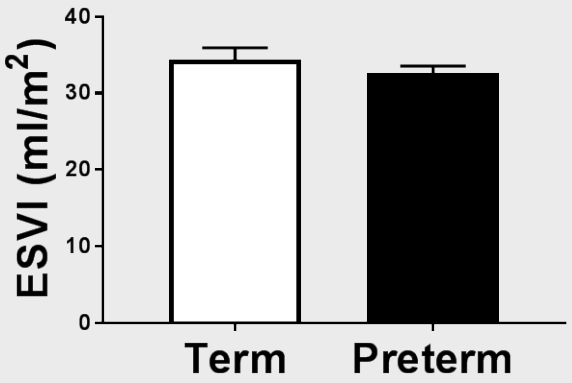


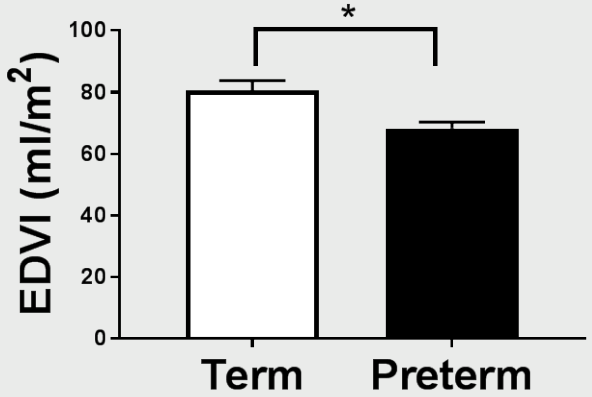


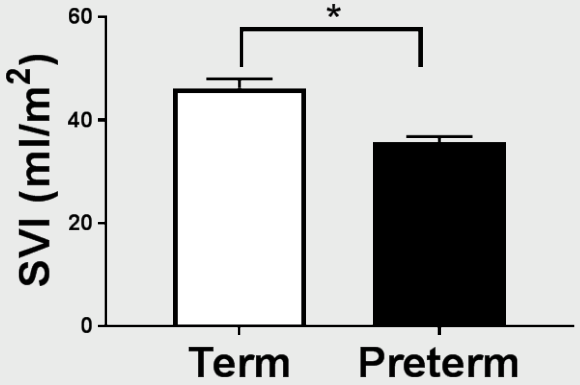
Beshish, AJRCCM, *in revision*

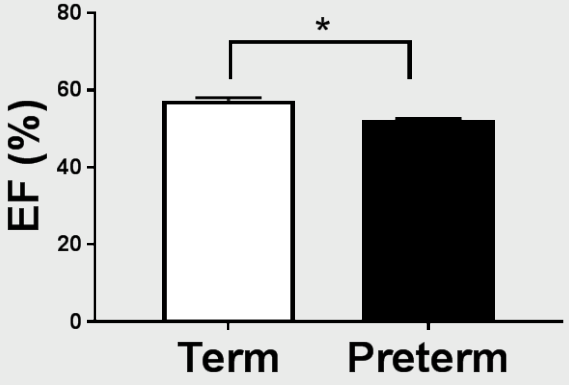
Smaller, Less Efficient RV in Adults Born Premature

Arij Beshish, MBBCh







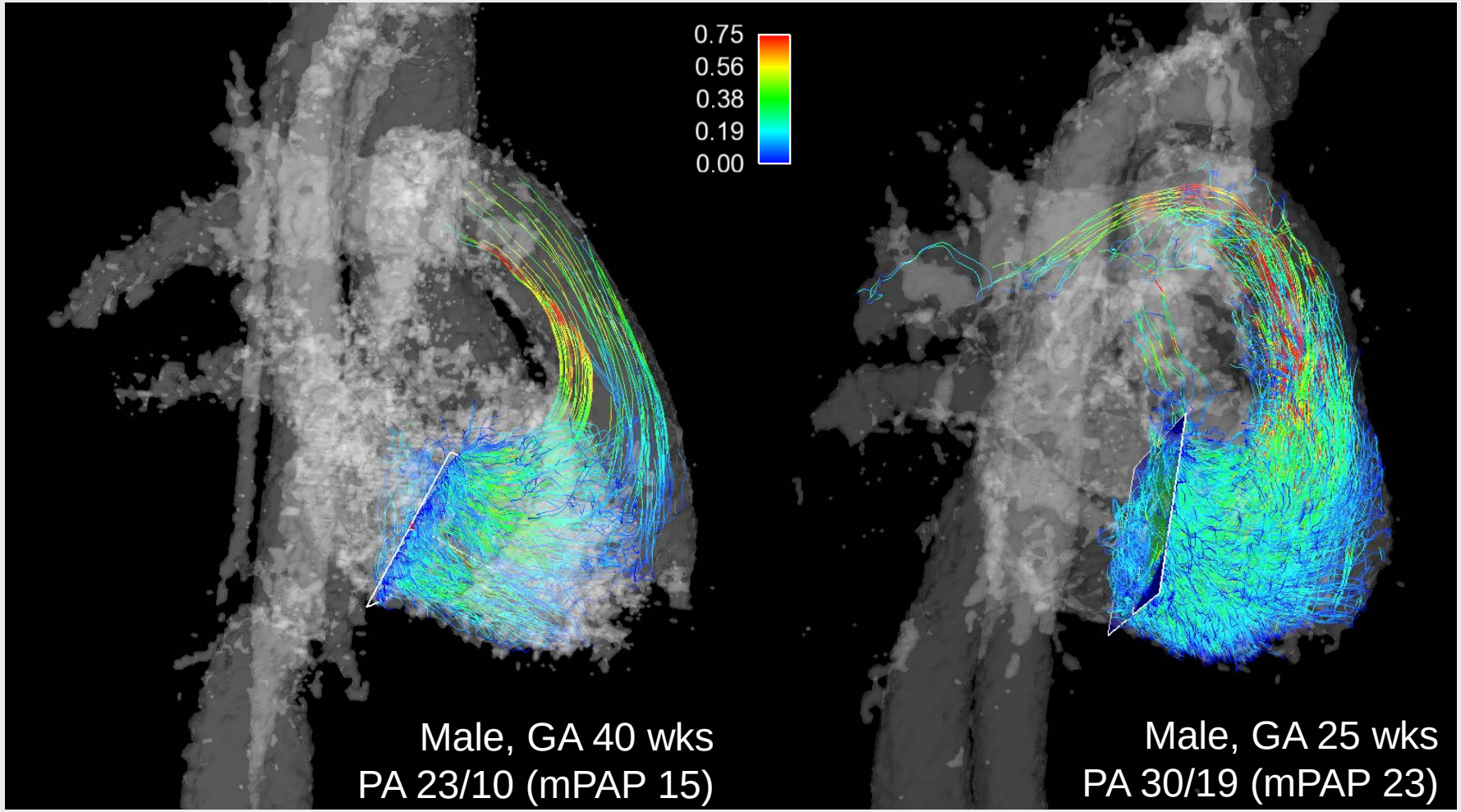


Cardiac Flow Is Less Laminar in Adults Born Preterm

Jacob Macdonald

Term

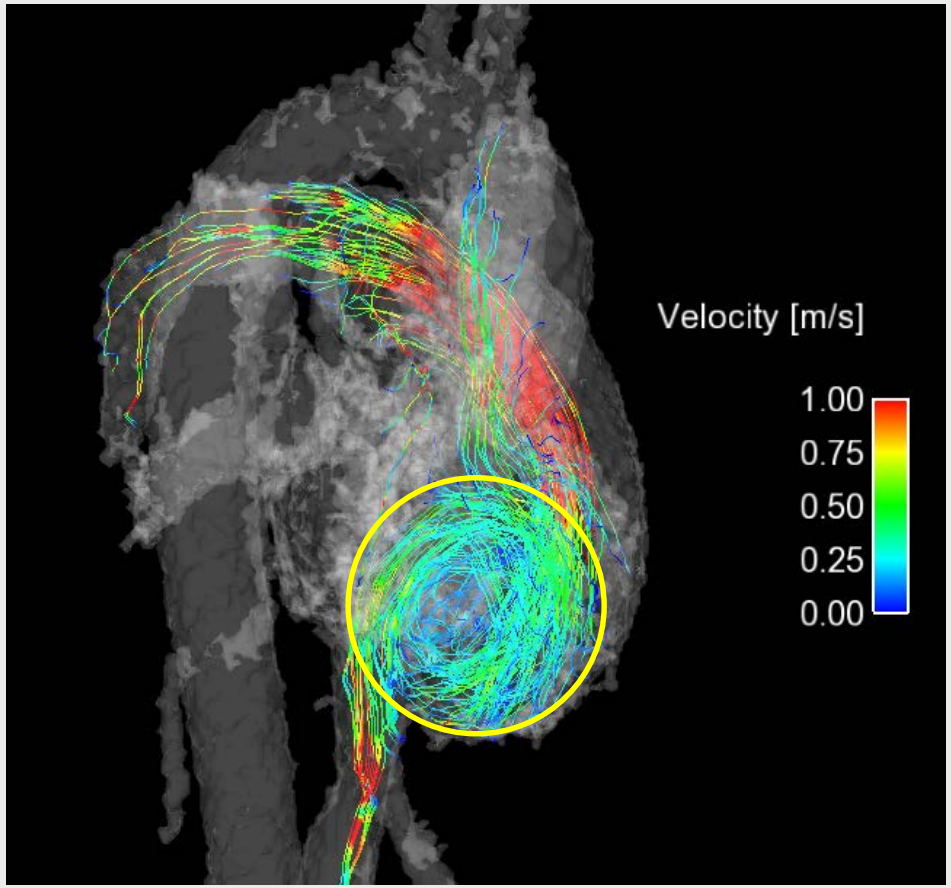
Preterm



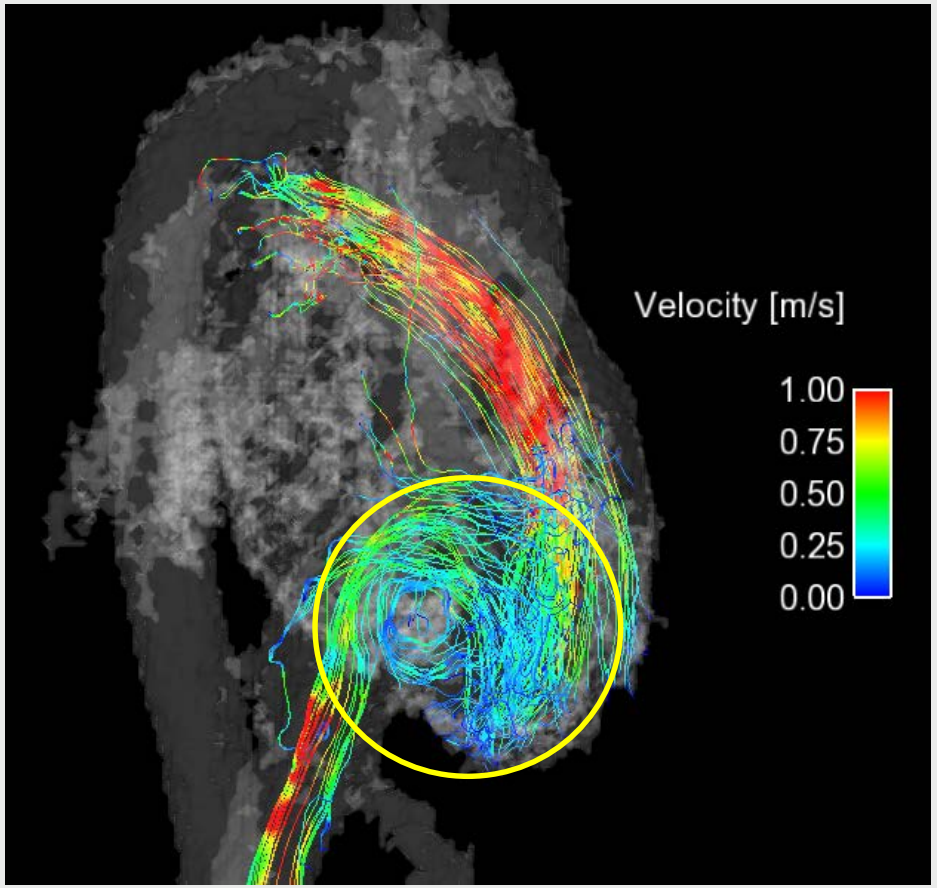
RV Filling Vortex Is Less Structured in Adults Born Preterm

Jacob Macdonald

Term



Preterm



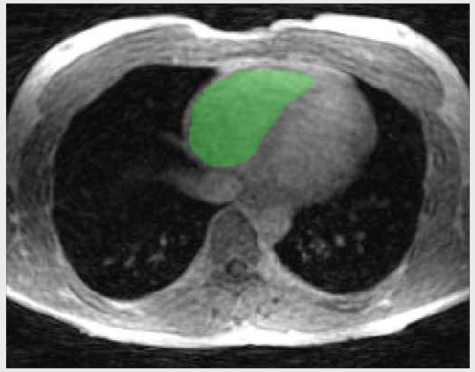
RV Energetically Less Efficient in Adults Born Preterm

Jacob Macdonald

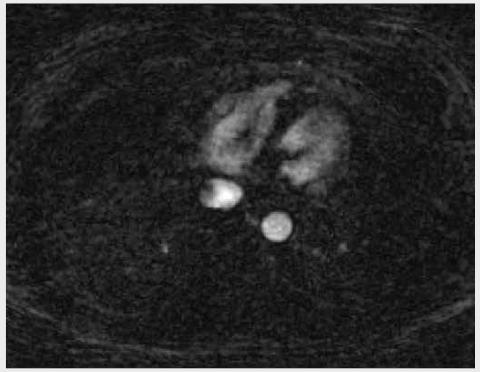
Total kinetic energy in the RV was normalized by each subject's stroke volume to evaluate energetic efficiency

Time-averaged magnitude data

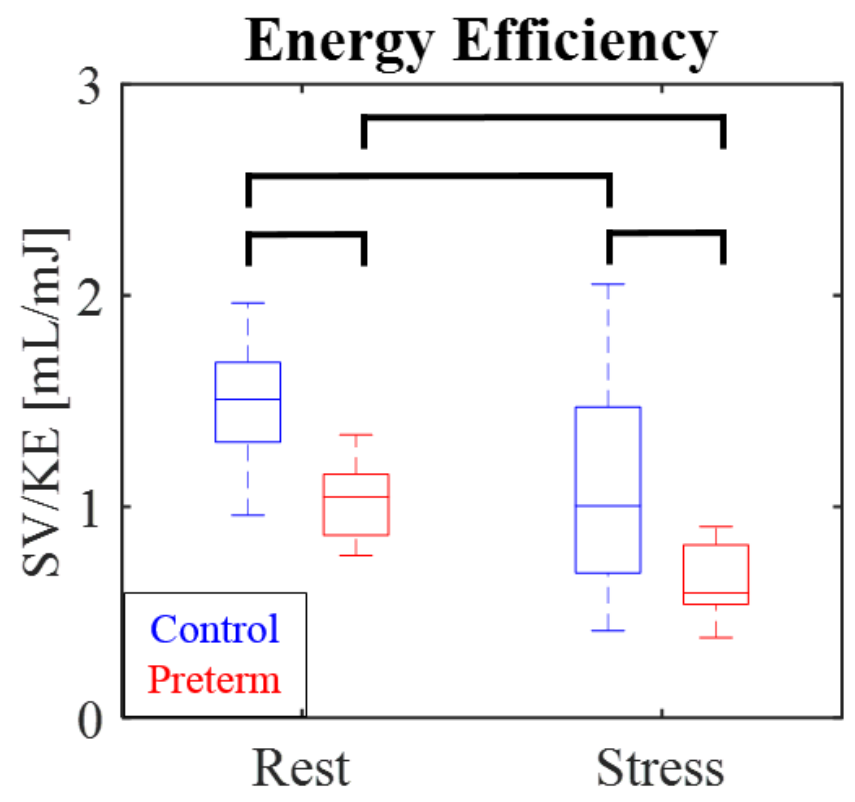
RV mask segmented



Mask applied to velocity data for each time frame

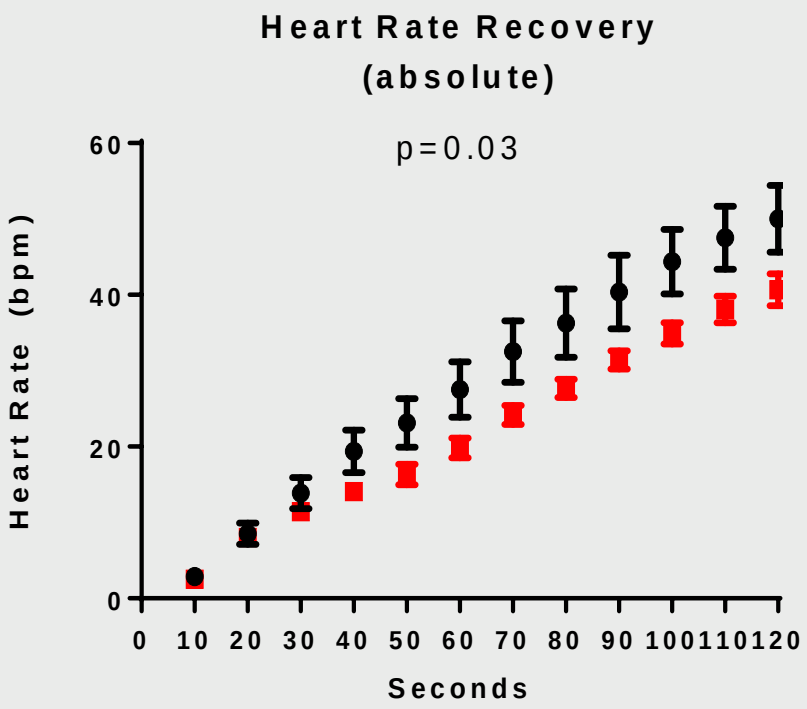


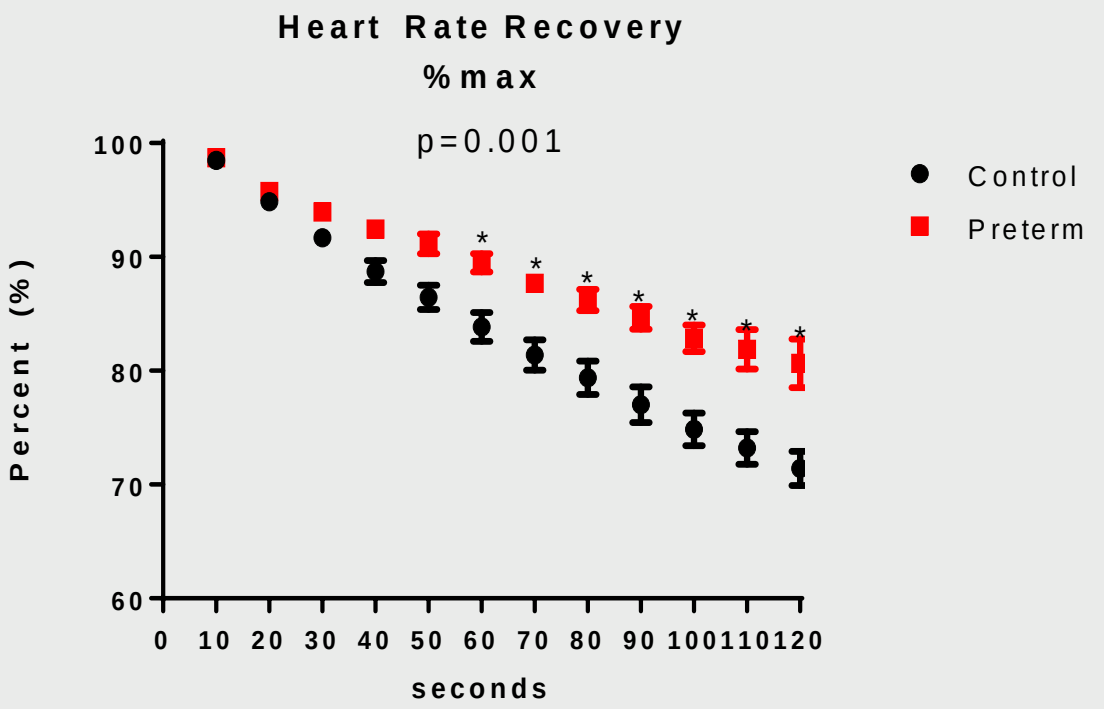
$$KE = \sum_{1}^{frame} \sum_{1}^{voxel} \frac{1}{2} m v^2$$



Adults Born Premature Demonstrate Impaired Heart Rate Recovery

Kristin Haraldsdottir, MS

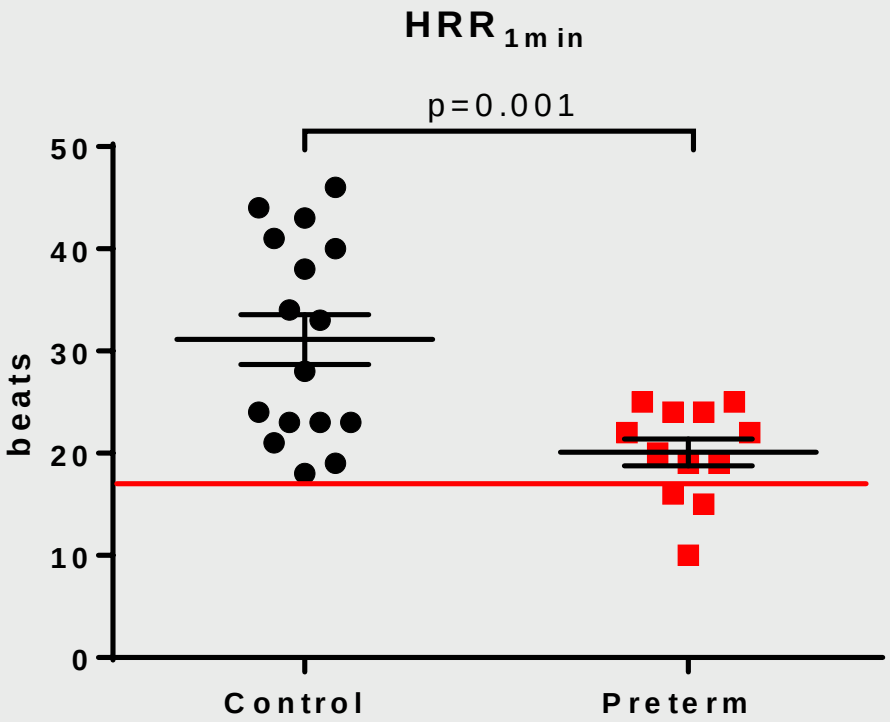




Haraldsdottir, JAP, *in revision*

Adults Born Premature Demonstrate Impaired Heart Rate Recovery

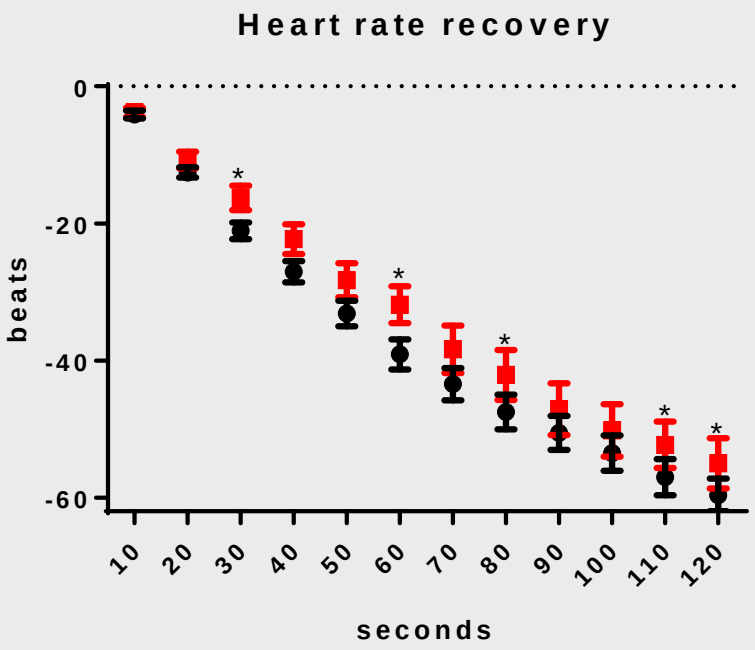
Kristin Haraldsdottir, MS

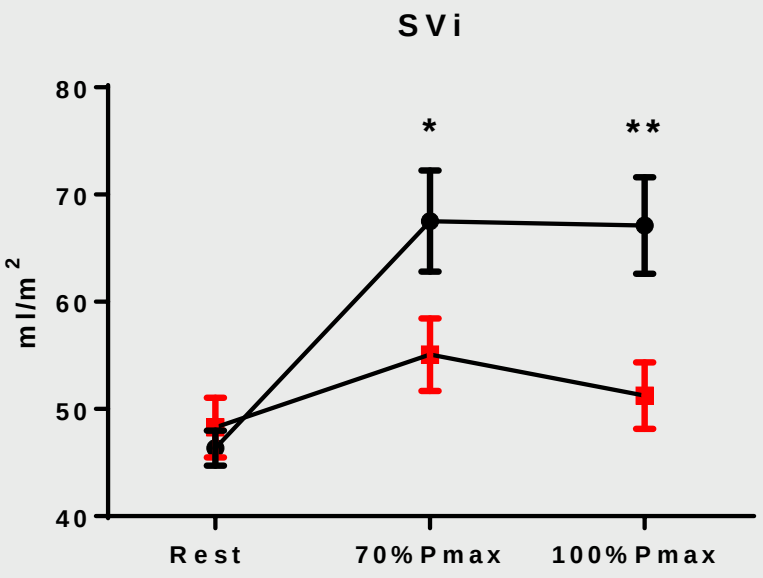


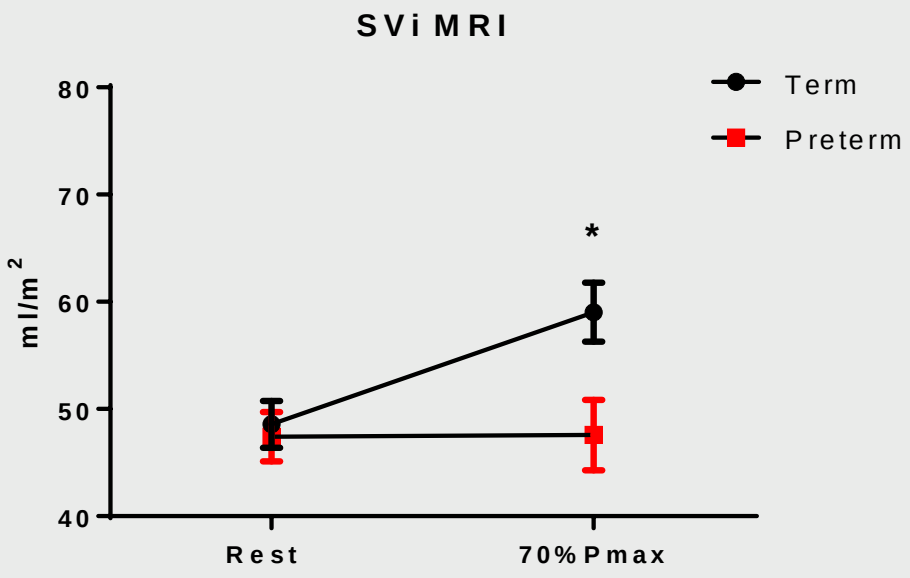
Haraldsdottir, JAP, *in revision*

Adolescents Born Preterm Appear to Have Similar Cardiac Dysfunction

Kristin Haraldsdottir, MS





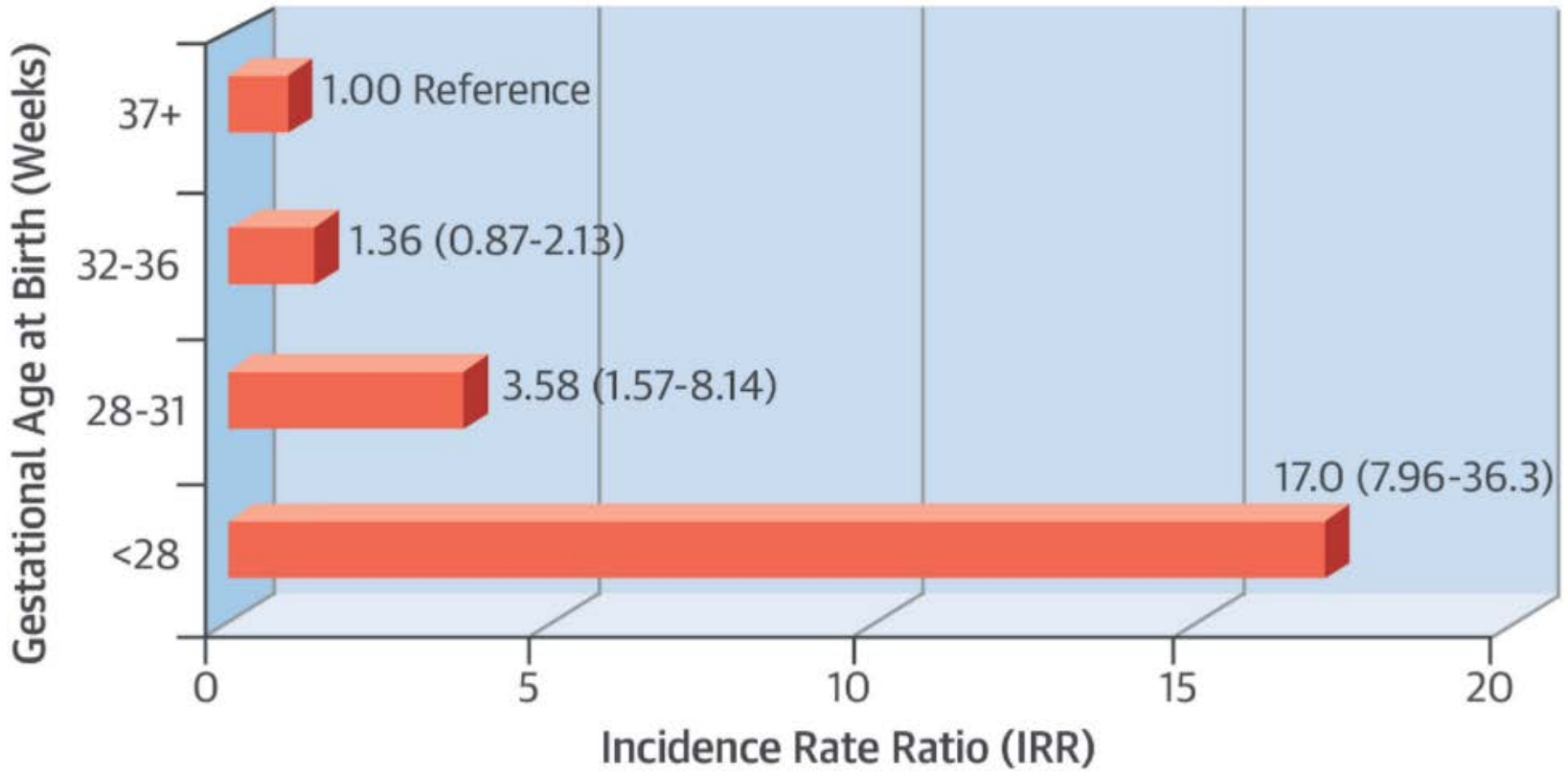


Summary: Cardiopulmonary Impairment in Adults Born Premature

- Adults born premature have:
  - Mild elevations in pulmonary arterial pressure
  - Stiffer pulmonary vasculature
  - Impaired cardiac response to exercise (SV limitation)
    - Also seen in adolescent population
  - Impaired heart rate recovery after maximal exercise

Premature Birth Associated with a Markedly Increased Risk for Heart Failure

CENTRAL ILLUSTRATION: Risk of HF in Childhood and Young Adult Age in Relation to Gestational Age at Birth

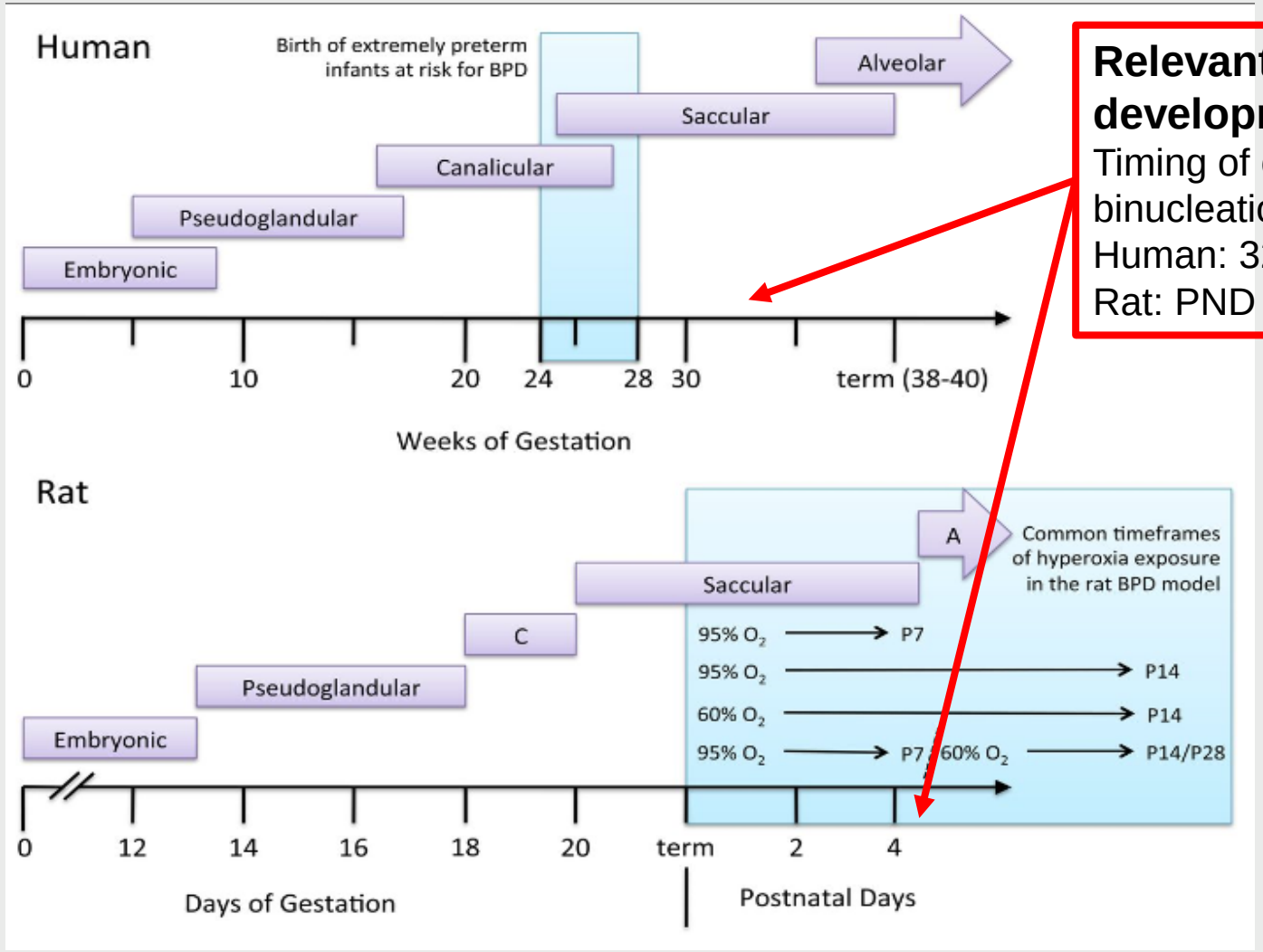


Carr, H. et al. J Am Coll Cardiol. 2017;69(21):2634–42.

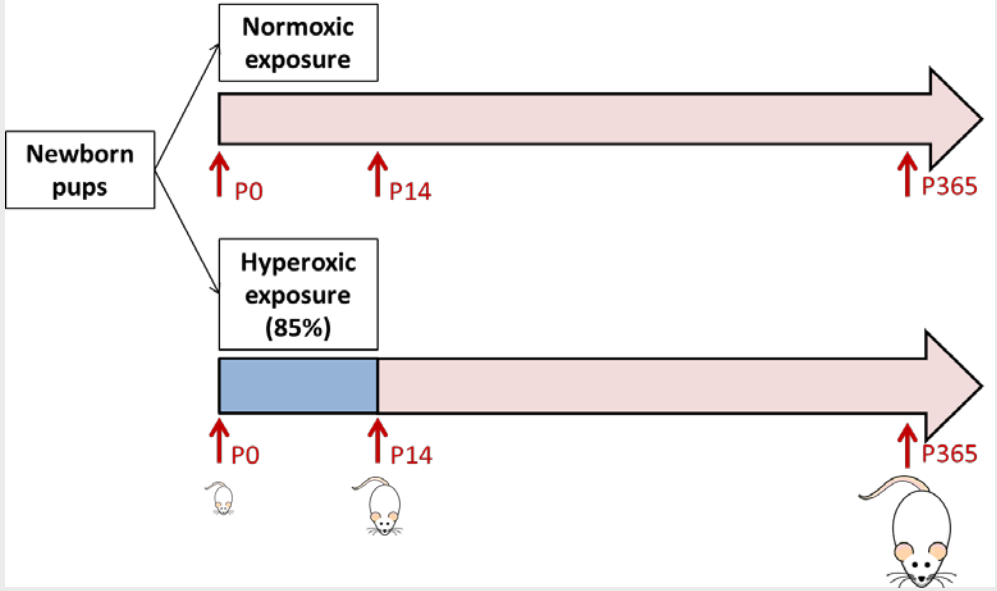
Why such a marked increase risk for heart failure?

Right ventricular dysfunction out of proportion to degree of pulmonary vascular disease?

Animal Models of Chronic Lung Disease of Prematurity

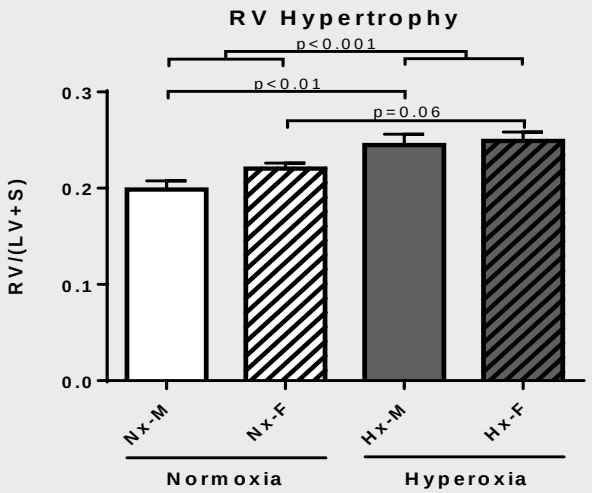


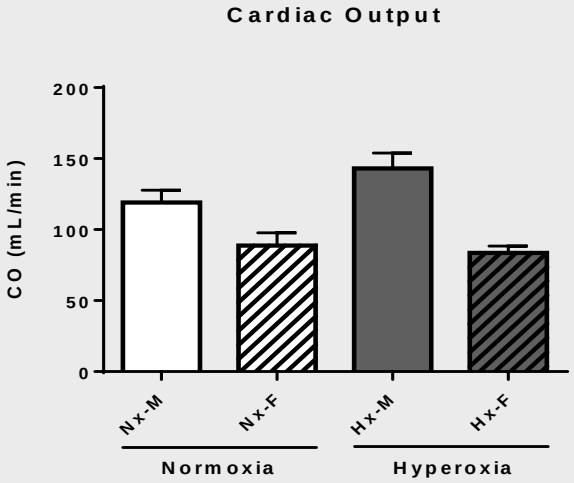
Relevant for cardiac development as well?
Timing of cardiac binucleation
Human: 32 weeks gestation
Rat: PND 4

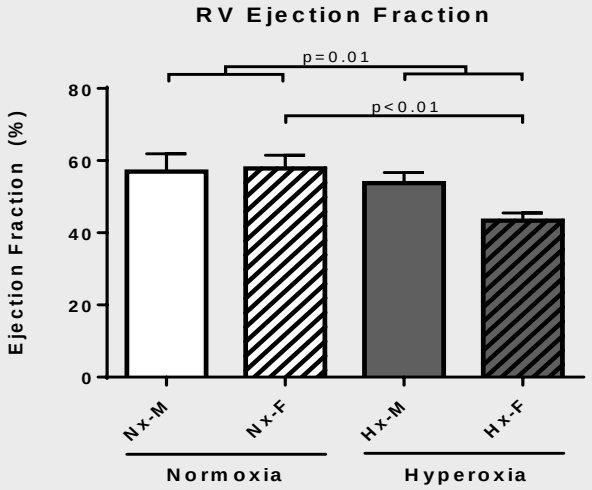


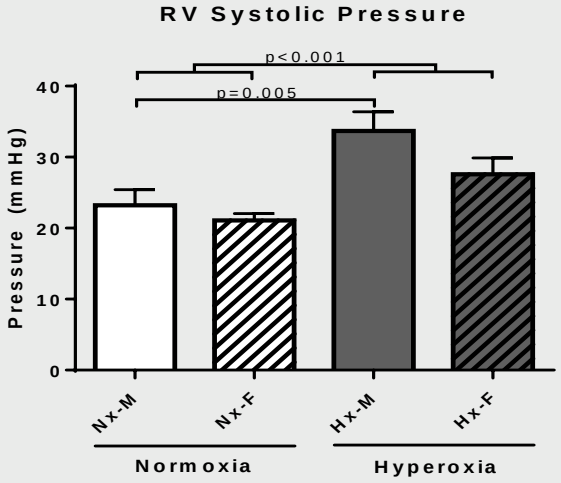
O'Reilly, AJP Lung 2014.
Botting, Clin Exp Pharmacol Physiol 2012

Postnatal Hyperoxia Exposure in Rats Recapitulates the known RV-PV Phenotype in Humans



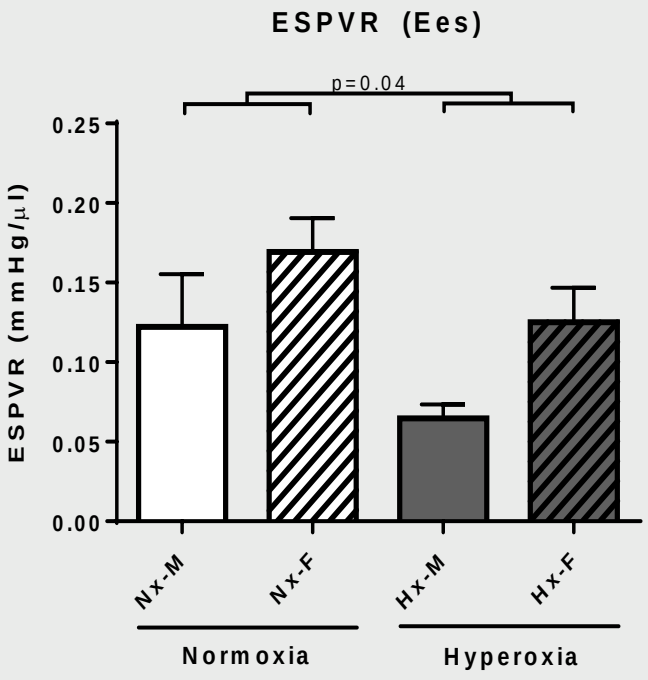


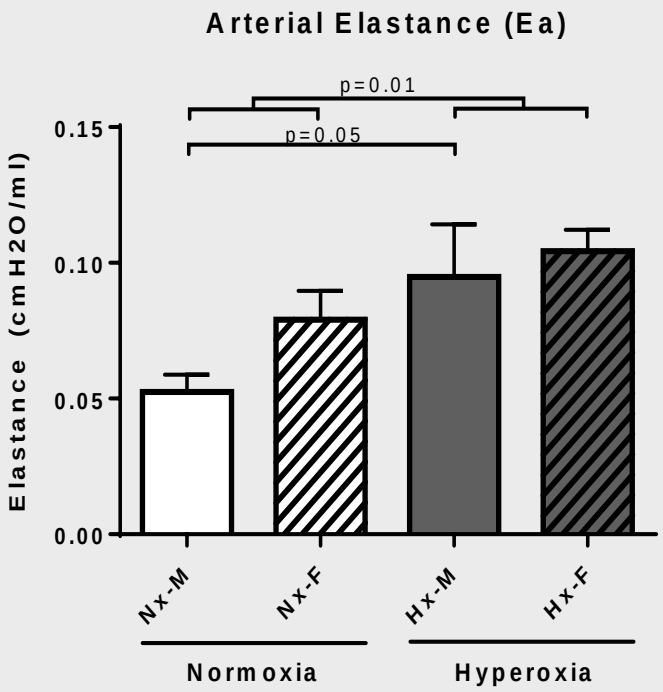


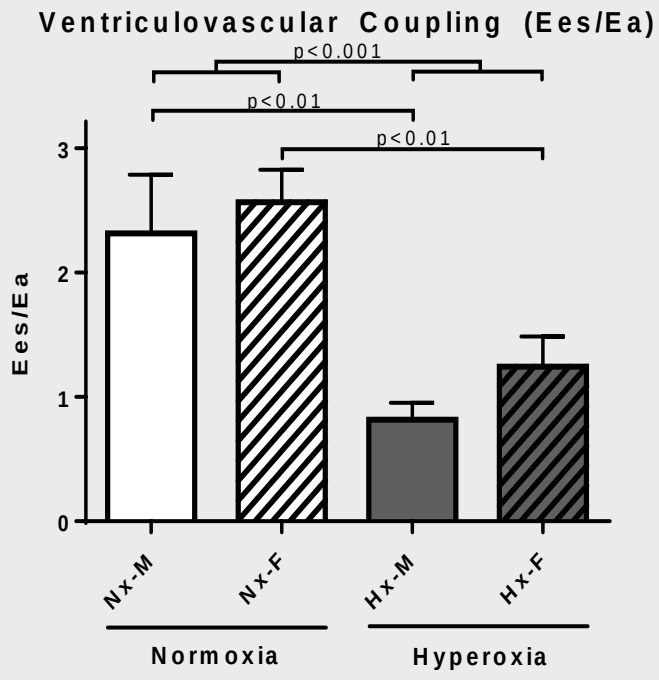


Goss, AJRCMB 2017.

Postnatal Hyperoxia Exposure in Rats Results in RV Dysfunction and RV-PV Uncoupling







Goss, AJRCMB 2017.

RV Dysfunction is “Out of Proportion” to a Mild Chronic Pressure Overload State

- Adaptive RV hypertrophy gene expression persists
  - ↑ VEGF and Apelin, ↓ Hexokinase 1
- Absence of fibrosis or impaired autophagy

- BUT appear to have increased mitochondrial dysregulation
  - Increase in RV mitochondrial number
  - Decreased mitochondrial biogenesis
  - Evidence of mitochondrial DNA damage
  - Mitochondrial dysfunction not typical of rat PAB models

Goss, AJRCMB 2017.

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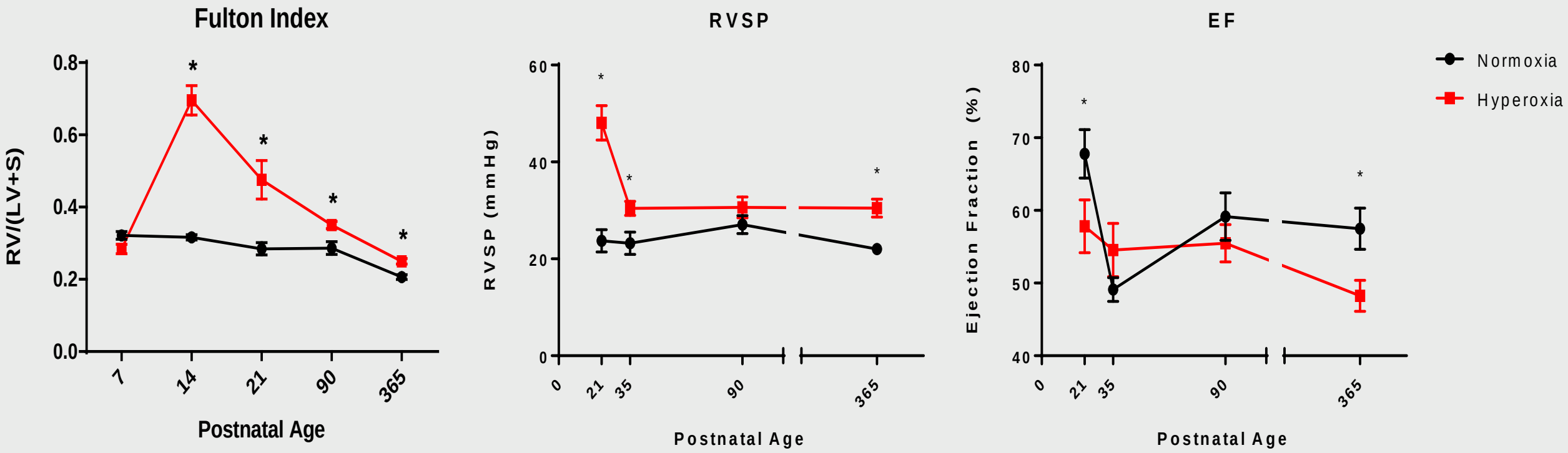
Neonatal Hyperoxic Lung Injury Favorably Alters Adult Right Ventricular Remodeling Response to Chronic Hypoxia Exposure

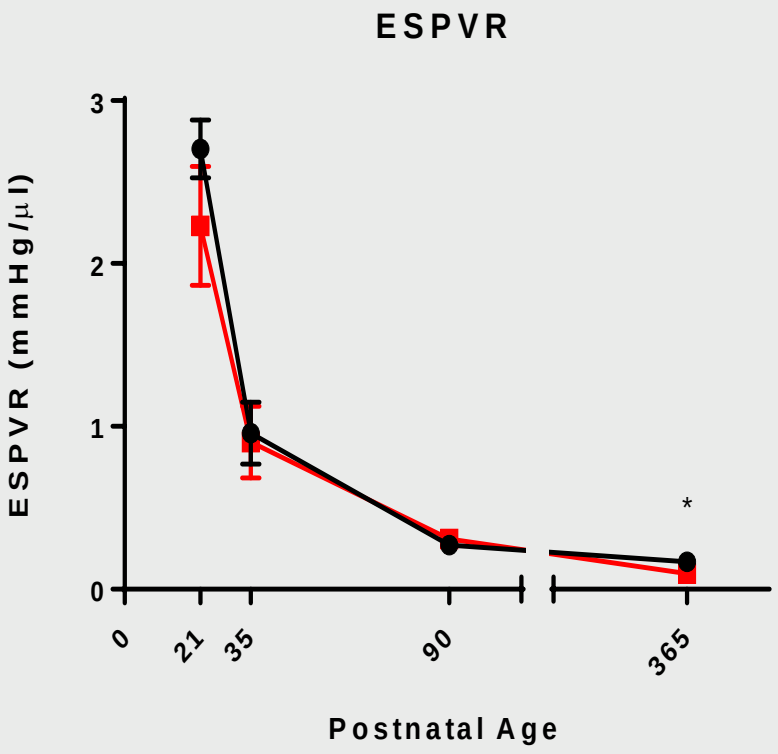
Kara N. Goss, Anthony R Cucci, Amanda Jo Fisher, Marjorie Albrecht, Andrea L Frump, Roziya Tursunova, Yong Gao, Mary Beth Brown, Irina Petrache, Robert S. Tepper, Shawn Kristopher Ahlfeld, Tim Lahm

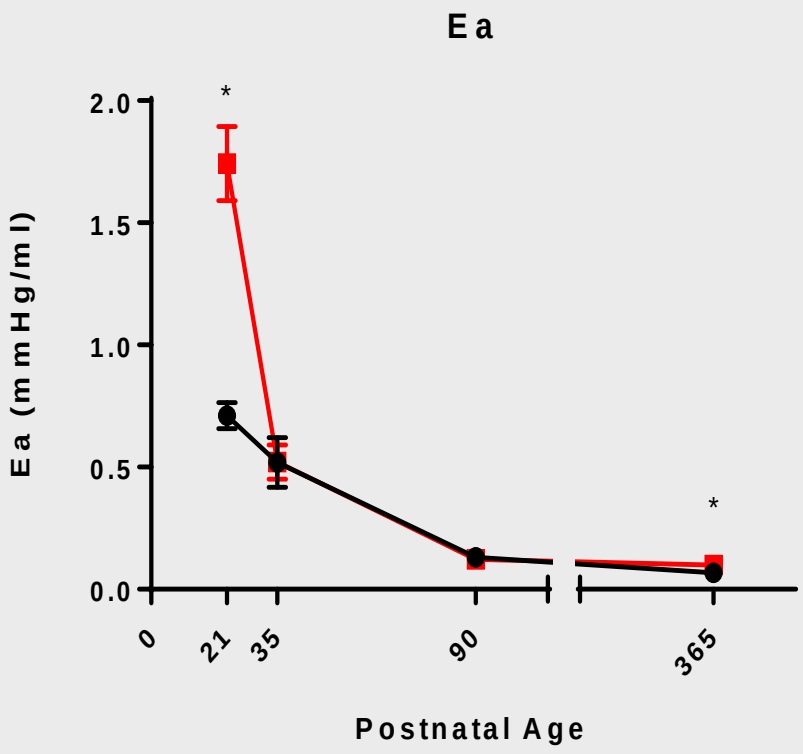
American Journal of Physiology - Lung Cellular and Molecular Physiology Published 6 February 2015 **Vol. no.** , **DOI:** 10.1152/ajplung.00276.2014

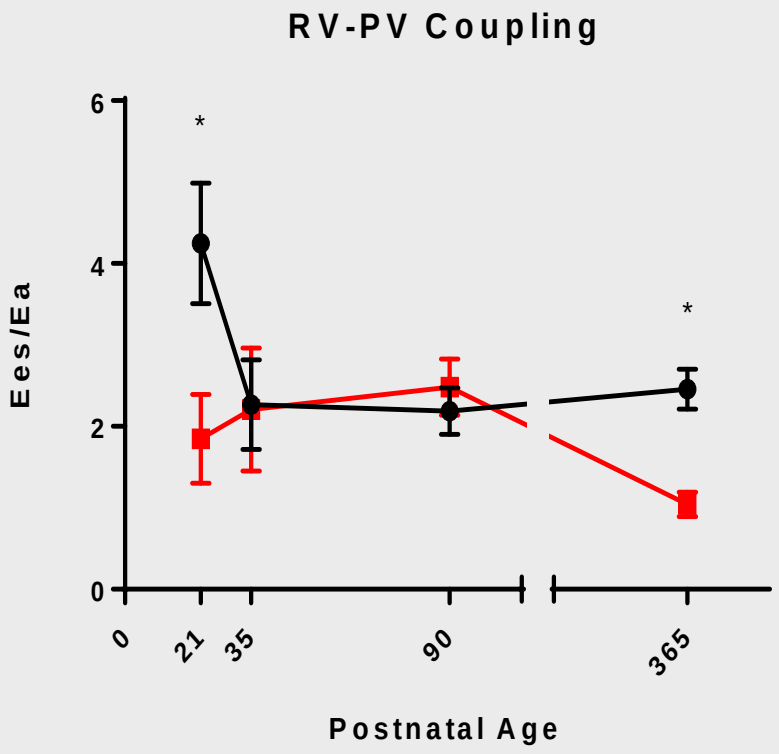
Pulmonary Vascular Disease Stabilizes, Bimodal RV Dysfunction



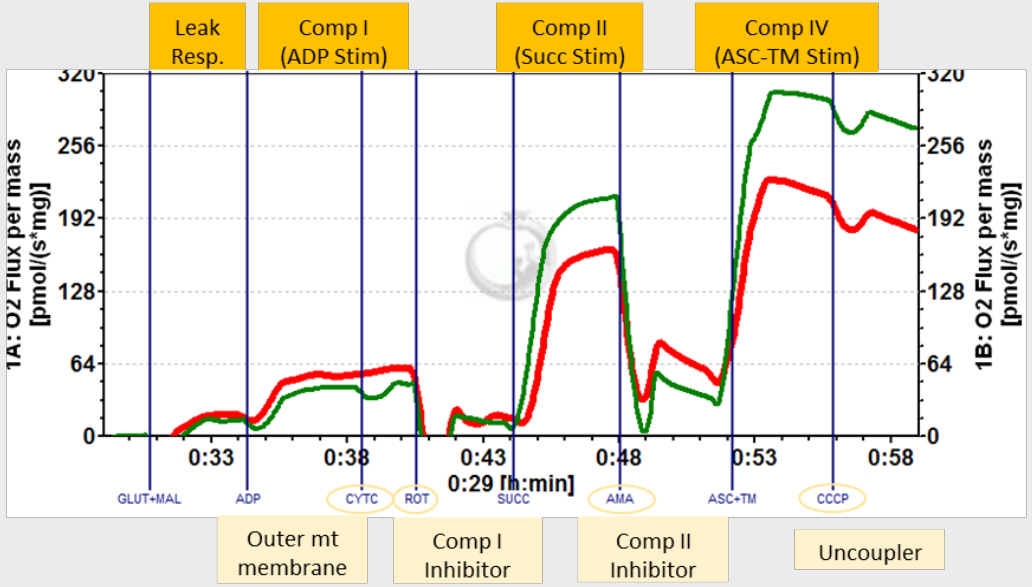
Pulmonary Vascular Disease Stabilizes, Bimodal RV Dysfunction

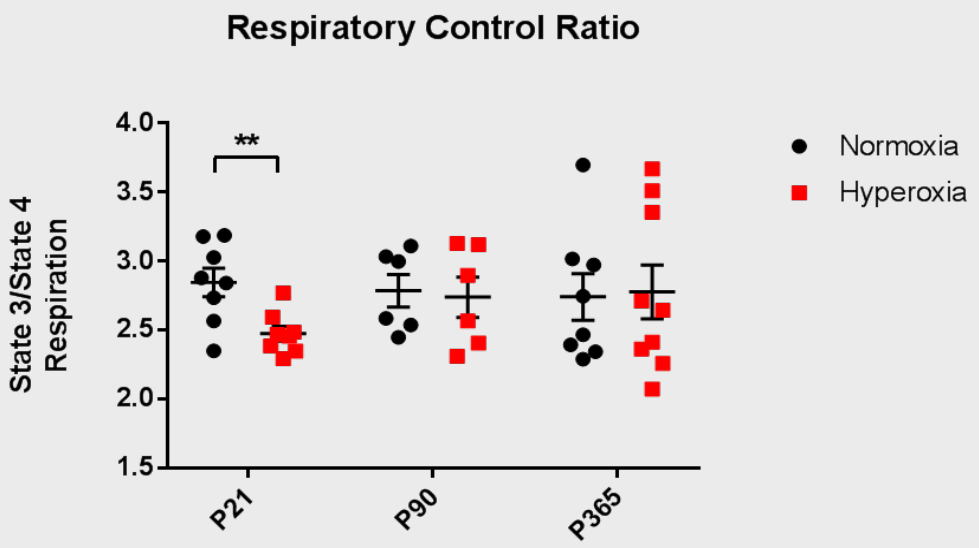


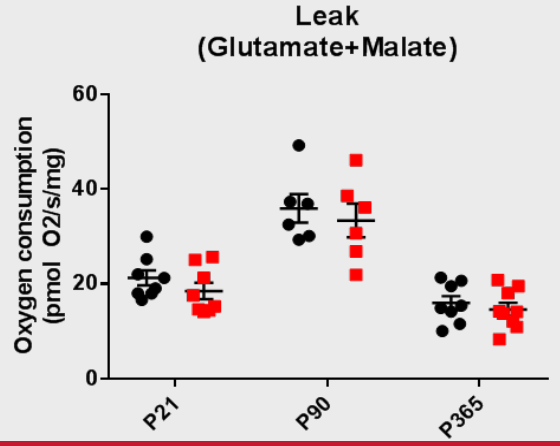


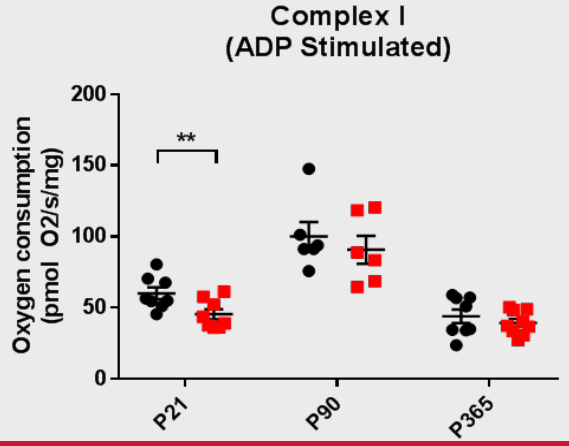


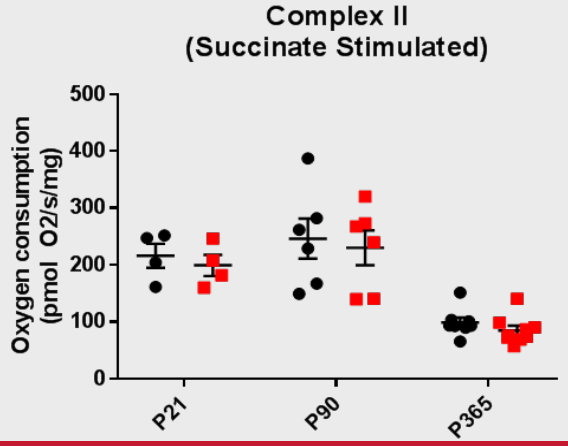
RV Dysfunction Due to Mitochondrial Dysfunction

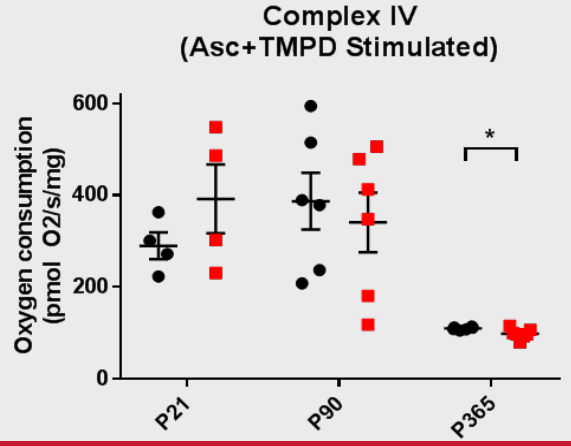




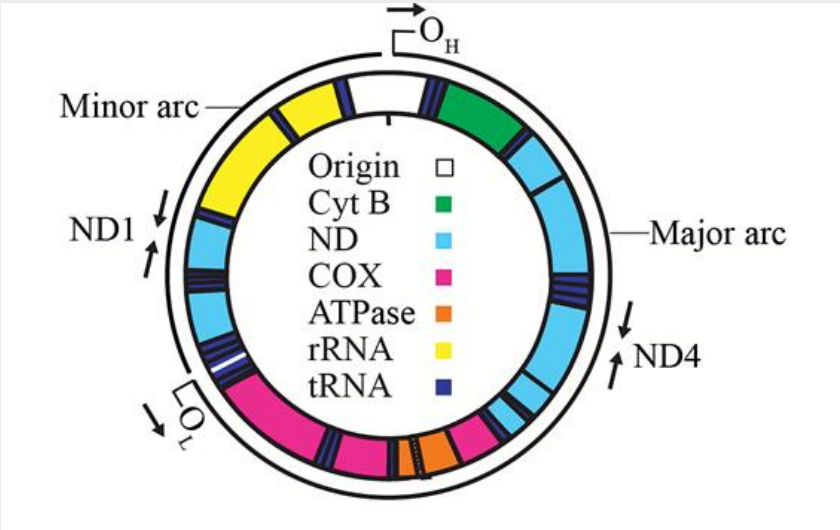


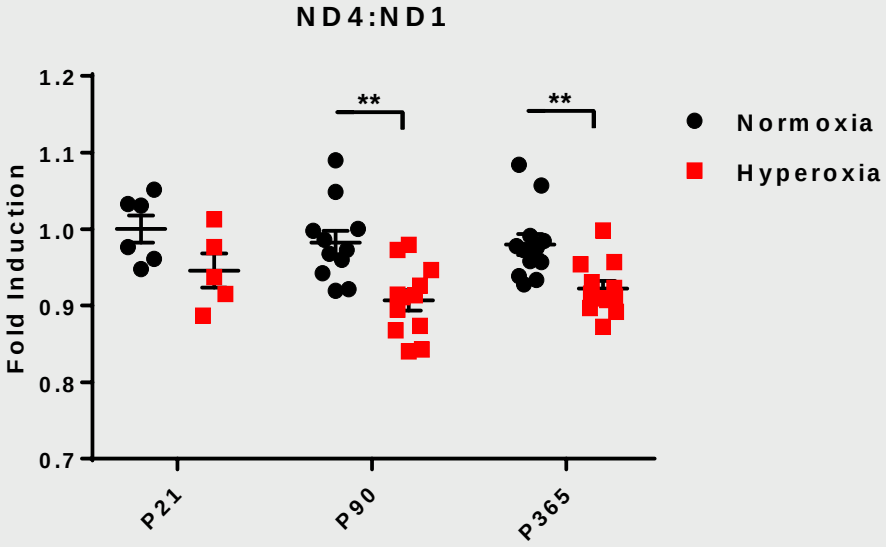


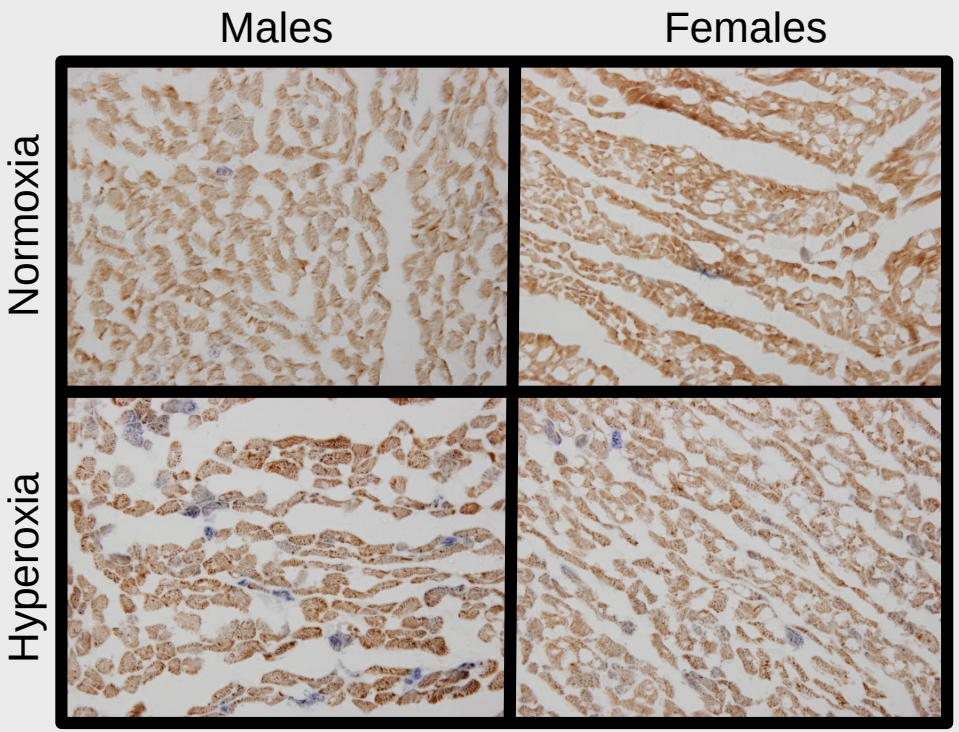




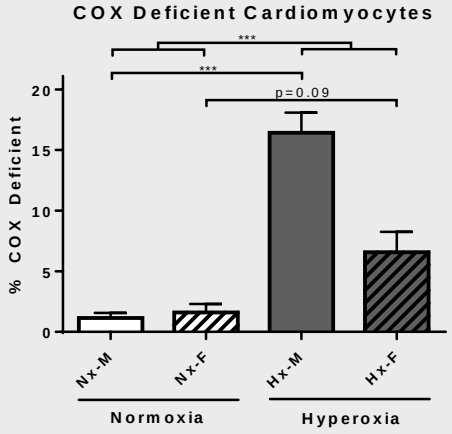
Late RV Mitochondrial Dysfunction Caused by Accumulation of mtDNA Mutations

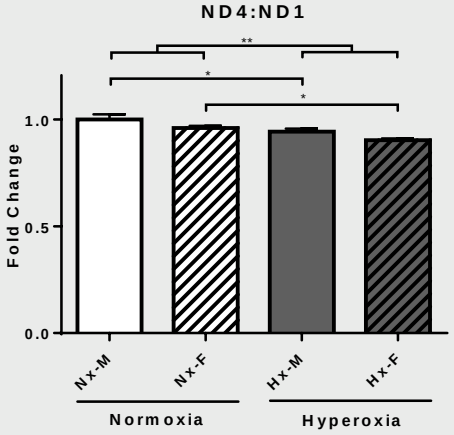




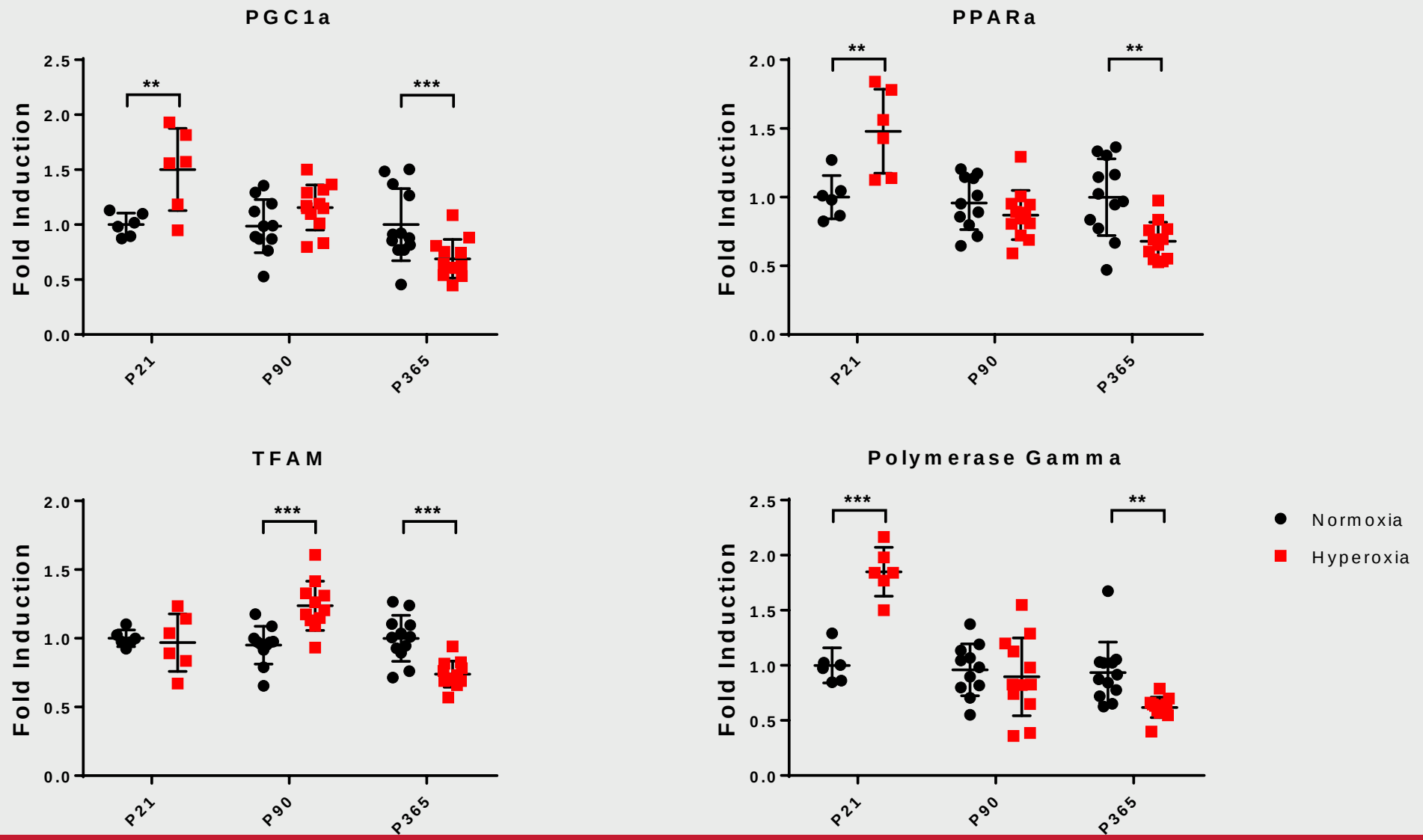


Goss, AJRCMB 2017.





Accumulation of mtDNA Mutations Follows Increased Mitochondrial Biogenesis



The Barker Hypothesis: Developmental Origins of Heath and Disease

- Key concepts:
  - Predictive adaptive responses of the fetus to environmental cues
    - Mismatch between prenatal and postnatal environments

"To survive in a stressful or nutrient-poor environment, a fetus must make "choices" about how to use scarce resources in a way that maximizes the likelihood of survival in early life, even at the expense of greater susceptibility to chronic illnesses and increased mortality in adulthood."

Wadhwa, Semin Reprod Med 2009

Summary: Right Ventricular-Pulmonary Vascular Interactions in Adults Born Preterm

- Adults born preterm have elevated resting PAP
  - Increased pulmonary vascular stiffness
  - Decreased pulmonary vascular recruitability
- RV dysfunction out of proportion to pulmonary vascular disease
  - Inability to augment stroke volume
  - RV energetically less efficient, increased work
  - Animal studies suggest impaired mitochondrial function in RV
- Bimodal RV response likely to have implications for screening

Acknowledgements

- **Marlowe Eldridge, MD**
- **Collaborators:**
  - Mari Palta, PhD (Newborn Lung Project)
  - Luke Lamers, MD (Peds Cardiology)
  - Chris François, MD (Radiology)
  - Oliver Wieban, PhD (Med Physics)
  - Alan McMillan, PhD (Radiology)
  - Naomi Chesler, PhD (Biomedical Engineering)
  - Tim Hacker, PhD (CV Physiology Core)
- **Lab Members:**
  - Santosh Kumari, PhD
  - Arij Beshish, MBBCh
  - Greg Barton, PhD
  - Ruedi Braun, PhD
  - Kristin Haraldsdottir, MS
  - Laura Tetri, MD/PhD candidate
  - Jacob McDonald
  - Ashley Mulchrone
  - David Pegelow
  - The undergraduate army

Funding: NHLBI R01 HL115061 (Eldridge), NHLBI R01 HL115061-03, Suppl (Eldridge/Goss), CTSA grant UL1TR000427 (Goss KL2), PHA Barst Award (Goss)

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