CDH 2020

The International Congenital Diaphragmatic Hernia Symposium

February 10-12

InterContinental Houston Medical Center, Houston, TX, USA

Program Planner

CDH | The Comprehensive Center for CDH Care

Congenital Diaphragmatic Hernia – 25 years of Collaboration

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Dick Tibboel, MD, PhD
Rodrigo Ruano, MD, PhD
Theresa Grover, MD
Richard Keijzer, MD, PhD
Kevin Lally, MD, MS

SPEAKERS:

WHAT BASIC/TRANSLATIONAL BREAKTHROUGHS ARE GOING TO CHANGE THE WAY WE UNDERSTAND CDH AND CARE FOR THESE PATIENTS IN THE FUTURE
Speaker I: Dick Tibboel……PG. 55 - 123

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Welcome to CDH 2020!

While some of you traveled just down the street, others have come from halfway around the world… though usually separated by distance, we come together (sometimes via phone, text, or email – but these three days in person) because we are bound by a common goal:

To preserve and improve the lives of children and families touched by congenital diaphragmatic hernia.

On behalf of the program committee, we welcome you to Houston, Texas, USA! We hope to capture all aspects of CDH research and to celebrate 25 years of the CDH Study Group. Perhaps the best part of the CDHSG is that it has focused on the collaborative aspect of research – the fact that so many people and centers could put aside "previous biases and large egos to collectively address CDH patient management and outcome" - actual words from the charter meeting of the CDH study group in 1991!

CDH is a complex disease extending from the prenatal period through adolescence and into adulthood. So many different specialists and providers unite to manage this challenging disease. Each of us plays a unique role on the team that it takes to provide the best care possible to the patients. For that effort, we are offered the most incredible reward, the opportunity to see a child grow up and a family that truly understands the depths of the challenge that life can throw at them, right from the start. This meeting is an opportunity to learn, an opportunity to teach, an opportunity to collaborate, and an opportunity to build and foster the relationships that make the difference in our collective effort to advance our understanding and therapeutic approach to this disease. Each of you has a unique journey and a unique perspective - you have all come a long way to be a part of this CDH discussion.

No matter where you are from, we extend a warm Texas-sized welcome. We hope you enjoy the meeting, we encourage your feedback, and your engagement. Here, over the next 3 days and beyond until we meet again, physicians, nurses, investigators, and families come together to bring hope to those touched by CDH.

On behalf of the Program Committee,

Matthew T. Harting and Kevin P. Lally

The CDH 2020 Program Committee:

Alexandra Benachi	**Matthew Harting**	**Richard Keijzer**	**Kevin Lally**	**Matias Luco**
FRANCE	USA	CANADA	USA	CHILE
Francesco Morini	**Kouji Nagata**	**Neal Patel**	**Jay Wilson**	**Brad Yoder**
ITALY	JAPAN	SCOTLAND	USA	USA

Welcome to the CDH2020 Conference in Houston, Texas

Please load these two apps on your cell phone **BEFORE** the conference begins.

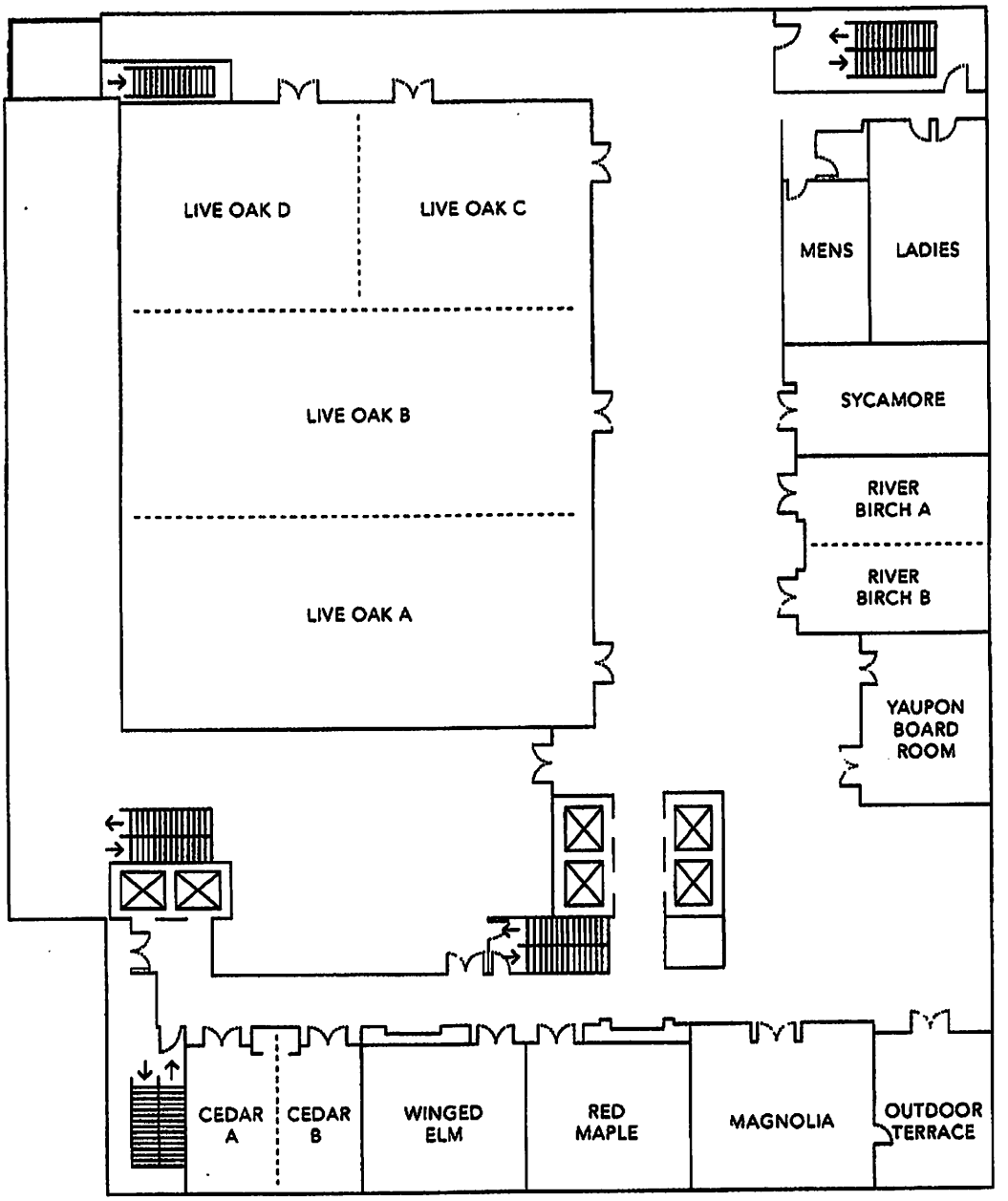
We will be using ***Poll Everywhere*** during the conference. Please load the free app ***Poll Everywhere*** on your cell phone.

Using app
User name – PollEv.com/**matthewthart564**

Using text
Text **MATTHEWTHART564** to **22333**

We will also use QR code to complete a daily conference survey. Please load a free **QR code reader** app on your cell phone.

The **WIFI password** during the conference is **8332**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MENS
LADIES
SYCAMORE
RIVER BIRCH A
RIVER BIRCH B
YAUPON BOARD ROOM
CEDAR A
CEDAR B
WINGED ELM
RED MAPLE
MAGNOLIA
OUTDOOR TERRACE

Congenital Diaphragmatic Hernia – 25 years of collaboration

Sunday, February 9

4.00pm - 7.00pm – **Check-in / Registration / Load Presentations ~ located in front of *Live Oak A/B***

Monday, February 10 – Introduction, Overview and Long-Term Follow-Up

6.00am – **Check-in / Registration / Load Presentations**

6.00am – **Breakfast ~ *Live Oak C/D***

7.00am – **Welcome and Introduction** Matthew Harting and Kevin Lally **~ *Live Oak A/B***

7.15am - 9.00am – **Case Presentation/Discussion** with panel & audience response **~ *Live Oak A/B***

Lead: Matthew Harting
Panel: Kevin Lally, Dick Tibboel, Theresa Grover, Richard Keijzer and Rodrigo Ruano

9.10am - 10.00am – **Family perspective/discussion** with family & *audience response* **~ *Live Oak A/B***

Leads: Terry Buchmiller and Ashley Ebanks
Family Panel: Isabel Duque and Brent Wunderlich; Jana and Kris Schneider; Marlen and Kevin Spivey; Josh Hensley

10.00am - 10.15am – **Brief break** (remain in auditorium)

10.15am - 10.45am – **Speaker I ~ *Live Oak A/B***

Dick Tibboel – What basic/translational breakthroughs are going to change the way we understand CDH and care for these patients in the future?

10.45am - 11.30am – **Research presentations – Podium Day 1 ~ *Live Oak A/B***

Moderators: Jay Wilson and Roberta Keller

Improving exercise capacity following neonatal respiratory failure; a randomized controlled trial
Presenter: Monique H.M. Van der Cammen (AB41)

Amniotic fluid stem cell exosomes rescue impaired surfactant expression in hypoplastic fetal lungs through an RNA-mediated mechanism
Presenter: Lina Antounians (AB19)

Transplacental delivery of nanoparticles for the prenatal treatment of CDH with miR-200b
Presenter: Wai Hei “Andrew” Tse (AB14)

Likely pathogenic de novo variants in congenital diaphragmatic hernia patients are associated with worse clinical outcomes
Presenter: Julia Wynn (AB33)

11.30am - 12.00pm – **Speaker II ~ *Live Oak A/B***

Kevin Lally – The CDH Registry Study Group – Past, Present and Future

12.00pm - 1.00pm – **Lunch ~ *Live Oak C/D***

1.00pm - 1.45pm – **Debate**: **Timing of repair with ECLS ~ *Live Oak A/B***

Moderator: Pietro Bagolan
Debaters: Adam Vogel (On ECLS) vs. Erin Perrone (Off ECLS)
Format: 10 min Powerpoint presentation, 5 min rebuttal each, 15 min group discussion

1.45pm - 2.15pm – **Speaker III ~ *Live Oak A/B***

Francesco Morini – Long-term follow-up

2.15pm - 3.15pm – **Research Presentations** – **Long Term Follow Up ~ *Live Oak A/B***

Moderators: Terry Buchmiller and Priscilla Chiu

The Morbidity of CDH Uncovered by Multidisciplinary Clinic Follow-up
Presenter: Kiloran Metcalfe (AB59)

Longitudinal Analysis of Ventilation Perfusion Mismatch in Congenital Diaphragmatic Hernia Survivors
Presenter: Duy Dao (AB86)

Longitudinal Analysis of Pulmonary Function in Survivors of Congenital Diaphragmatic Hernia
Presenter: Duy Dao (AB83)

Pulmonary complications in Children survivors of Congenital Diaphragmatic Hernia
Presenter: Hina Emanuel (AB69)

"Virtual" long-term outcomes of children with congenital diaphragmatic hernia
Presenter: Gabrielle Derraugh (AB25)

Weight gain velocity and adequate amount of nutrition for infants of congenital diaphragmatic hernia
Presenter: Keita Terui (AB23)

Nutritional outcome at the age of 16 years of infants included in the Northern France CDH Cohort
Presenter: Dyuti Sharma (AB47)

Emergency presentation and hospital re-admission for CDH patients within one year of discharge
Presenter: Vikas Gupta (AB80)

3.30pm - 4.45pm – **Breakout Structured/Focused Meetings**

LTFU data collection ~ Priscilla Chiu ~ ***Cedar A/B***
Development of CDHSG v5 ~ Matthew Harting and Pam Lally ~ ***Red Maple***
Cardiac dysfunction – the role of the heart in CDH ~ Neil Patel ~ **River Birch**

Standardization in CDH – should/can we achieve it*?* ~ Tim Jancelewicz ~ ***Winged Elm***
Note: These are the exact same discussions each day so choose 2 of the 4 to attend

5.00pm - 7.00pm – **Cocktail reception ~ *Magnolia and Outdoor Terrace***

7.00pm – **Dinner** – *on your own*

Tuesday, February 11 – Neonatology, ECLS & Surgery

6.00am - 7.00am – **Breakfast ~ *Live Oak C/D***

6.30am - 7.00am – **Check-in / Registration / Load Presentations**

7.00am - 8.00am – **Quick-Shot Breakout Presentations**

Neo+ECLS – Moderator: Bob DiGeronimo ~ ***Cedar A/B***

Prognosis of Neonates with Congenital Diaphragmatic Hernia who are Small for Gestational Age: A Multicenter Study
Presenter: Julia Wynn (AB32)

High Frequency Jet Ventilation for Rescue from High Frequency Oscillatory Ventilation in Congenital Diaphragmatic Hernia
Presenter: Michelle Yang (AB26)

Morphometric Mri To Evaluate Cortical Thickness In Neonates With Congenital Diaphragmatic Hernia
Presenter: Francesco Morini (AB81)

Routine intubation in all newborns with congenital diaphragmatic hernia at delivery in the era of advanced prenatal screening: too much too soon?
Presenter: Suzan Cochius – den Otter (AB13)

Congenital diaphragmatic hernia in southern South America: stratified outcomes in two high volume, ECMO centers
Presenter: Matias Luco (AB87)

Comparison of two early predictors of mortality for congenital diaphragmatic hernia.
Presenter: Matias Luco (AB79)

Infant's First Blood Gas Predicts Required Therapies at 30 Days of Life in Infants with Congenital Diaphragmatic Hernia
Presenter: Etze Chotzoglou (AB76)

Persistent Pulmonary Hypertension in Congenital Diaphragmatic Hernia: Impact on Postnatal Outcome and Antenatal Prediction
Presenter: David Basurto (AB29)

Completing the physiological approach to Congenital Diaphragmatic Hernia
Presenter: Stephen Keeley (AB94)

Impact of time point of ECMO initiation on mortality and morbidity in CDH
Presenter: Neysan Rafat (AB3)

Basic science – Moderator: Augusto Zani ~ ***Red Maple***

Cytokeratin Fragment 21-1 is Associated with Mortality and Long-Term Oxygen Therapy in Neonates with Congenital Diaphragmatic Hernia
Presenter: Florian Kipfmueller (AB27)

Activation of aryl hydrocarbon receptor determined by molecular docking suggests a role in CDH pathogenesis
Presenter: Wai Hei "Andrew" Tse (AB44)

Abnormal Lung Development In Congenital Diaphragmatic Hernia Might Be Due To An External Viral Stimulus To The Innate Immune System
Presenter: Wai Hei "Andrew" Tse (AB39)

Maternal vitamin A status and susceptibility to teratogen-induced congenital diaphragmatic hernia
Presenter: Robin Clugston (AB7)

Adult stem cells in newborns with congenital diaphragmatic hernia undergoing ECMO
Presenter: Neysan Rafat (AB2)

Using Bosentan to Treat Pulmonary Hypertension in miR-200b Knockout Mice as a Model of Congenital Diaphragmatic Hernia
Presenter: Chelsea Day (AB45)

Long Term Follow-up – Moderator: Priscilla Chiu ~ ***Magnolia***

Longitudinal follow-up with radiologic imaging is essential to reliably detect recurrence in patients with congenital diaphragmatic hernia
Presenter: Neysan Rafat (AB15)

Long-term neurologic follow-up of CDH-patients with and without ECMO
Presenter: Neysan Rafat (AB24)

Exercise capacity in adolescents born with congenital diaphragmatic hernia
Presenter: Monique H.M. van der Cammen (AB40)

Long-term feeding issues impact on the daily life of congenital diaphragmatic hernia survivors: first patient-led survey of CDH UK
Presenter: Beverley Power (AB64)

Multiple breath washout measurement in patients with CDH at school age compared to Chest CT score and spirometry
Presenter: Anne Debeer (AB97)

Presence of a hernia sac does not impact lung perfusion in CDH
Presenter: Akila Ramaraj (AB54)

25 Year Demographics from CDH International
Presenter: Dawn Ireland (AB18)

Evaluation of Neurologic Morbidity in Neonates with Congenital Diaphragmatic Hernia Using Plasma Biomarkers of Brain Injury
Presenter: Jenifer Cuestas (AB12)

8.15am - 8.45am – **Speaker IV ~ *Live Oak A/B***

Richard Keijzer – miRs in CDH

8.45am - 9.45am – **Research Presentations – Podium Day 2 ~ *Live Oak A/B***

Moderators: Brian Gray and Erik Skarsgard

Early Left Ventricular Dysfunction and Severe Pulmonary Hypertension Predict Adverse Outcomes in "Low-Risk" Congenital Diaphragmatic Hernia
Presenter: Duy Dao (AB88)

Perinatal hypoxia in congenital diaphragmatic hernia pulmonary parenchyma
Presenter: Vikas Gupta (AB85)

Extracorporeal life support is associated with improved survival for newborns with severe congenital diaphragmatic hernia
Presenter: Tim Jancelewicz (AB70)

Neurocardiovascular coupling during surgical repair of congenital diaphragmatic hernia.
Presenter: Sophie Costerus (AB57)

Levosimendan is associated with improvement of cardiac dysfunction and pulmonary hypertension in infants with congenital diaphragmatic hernia
Presenter: Lukas Schroeder (AB51)

The effect of mechanical compression in Ex vivo model of congenital diaphragmatic hernia
Presenter: Soichi Shibuya (AB65)

In vitro cell compression model of congenital diaphragmatic hernia inhibits pulmonary angiogenesis and cell proliferation
Presenter: Kathleen Marulanda (AB74)

Perioperative cerebral autoregulation in congenital diaphragmatic hernia neonates
Presenter: Sophie Costerus (AB56)

9.45am - 10.15pm – **Speaker V ~ *Live Oak A/B***

Neil Patel – The Role of the Heart in CDH

10.15am - 10.45am – **Break**

10.45am-11.45am – **Brief Research Presentations ~ *Live Oak A/B***

Moderators: Tim Jancelewicz and Kouji Nagata

Elevated proBNP levels are associated with disease severity, cardiac dysfunction, and mortality in CDH
Presenter: Vikas Gupta (AB84)

The aryl hydrocarbon receptor (AHR) is involved in the pathogenesis of CDH
Presenter: Landon Falk (AB37)

Prostaglandin E1 in infants with Congenital Diaphragmatic Hernia (CDH) and life-threatening pulmonary hypertension
Presenter: Kevin Le Duc (AB8)

Administration of amniotic fluid stem cell exosomes promotes mesenchymal maturation of hypoplastic lungs in fetuses with Congenital Diaphragmatic Hernia
Presenter: Lina Antounians (AB20)

GMP-grade exosomes derived from clinically compliant human amniotic fluid stem cells regenerate the lung epithelium in a model of pulmonary hypoplasia
Presenter: Lina Antounians (AB21)

Risk factors for cardiac dysfunction at discharge in congenital diaphragmatic hernia (CDH)
Presenter: Neil Patel (AB43)

Does Left Ventricular Dysfunction Contribute to elevated pulmonary vascular resistance in CDH?
Presenter: Neil Patel (AB48)

Abnormal cardiac function at discharge in infants with congenital diaphragmatic hernia
Presenter: Neil Patel (AB42)

Cytokine Profiles In Fetal Tracheal Fluids Can Distinguish Feto CDH Survivors From Non-Survivors
Presenter: Wai Hei "Andrew" Tse (AB38)

Prenatal miR-200b Treatment in the Nitrofen Rat Model of Congenital Diaphragmatic Hernia normalizes vascular development
Presenter: Chelsea Day (AB36)

Early, Postnatal Pulmonary Hypertension Severity is Predictive of Early Outcomes in Congenital Diaphragmatic Hernia
Presenter: Dalya Ferguson (AB1)

11.45am - 12.45pm – **Lunch – *Live Oak C/D***

1.00pm - 1.30pm – **Speaker VI ~ *Live Oak A/B***

David Kays – ECLS & Surgery: Achieving Optimal Outcomes

1.30pm - 2.30pm – **Brief Research Presentations ~ *Live Oak A/B***

Moderators: Yigit Guner and Natalie Rintoul

Centrifugal Pumps Are the Strongest Predictor of Hemolysis During ECLS for CDH
Presenter: Yigit Guner (AB90)

Increased soluble ST2 concentration in neonates with congenital diaphragmatic hernia and pulmonary hypertension hernia with and without ECMO support
Presenter: Florian Kipfmueller (AB52)

The Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative Smartphone App: A Guideline Uptake and Care Standardization Strategy
Presenter: Kathryn LaRusso (AB53)

Contemporary Cost Trends in the Treatment of Congenital Diaphragmatic Hernia (CDH)
Presenter: Ruth Lewit (AB34)

Congenital Diaphragmatic Hernia: Prevalence and risk factors across the world
Presenter: Lina Antounians (AB22)

Clinical exome sequencing data reveals high diagnostic rates and new susceptibility genes for congenital diaphragmatic hernia plus (CDH+)
Presenter: Tiana Scott (AB6)

2.30pm - 3.00pm – **Speaker VII ~ *Live Oak A/B***

Pramod Pulingandla – Standardization of Care

3.15pm - 4.15pm – **Breakout Structured/Focused Meetings**

LTFU data collection ~ Priscilla Chiu ~ ***Cedar A/B***
Development of CDHSG v5 ~ Matthew Harting and Pam Lally ~ ***Red Maple***
Cardiac dysfunction – the role of the heart in CDH ~ Neil Patel ~ **River Birch**
Standardization in CDH – should/can we achieve it*?* ~ Tim Jancelewicz ~ ***Winged Elm***
Note: These are the exact same discussions each day so choose 2 of the 4 to attend

4.30pm - 5.30pm – **Update on Current Postnatal Clinical Trials in CDH ~ Live Oak A/B**

Resuscitation in CDH ~ Jason Gien
RCT of IV sildenafil vs iNO for PH in CDH - CoDiNos ~ Suzan Cochius and Dick Tibboel
Delayed cord clamping ~ Natalie Rintoul
Intact cord resuscitation in CDH ~ Laurent Storme
Milrinone in CDH ~ Brad Yoder for Satyan Lakshminrusimha
UCB mononuclear cells for hypoxic neurologic injury in infants with congenital diaphragmatic hernia ~ Vikas Gupta/Matthew Harting

6.00pm – **Cocktails ~ *Live Oak C/D***

7.00pm – Dinner ~ *Live Oak C/D*

Wednesday, February 12 – Fetal diagnosis & Intervention

6.00am - 7.00am - **Breakfast ~ *Live Oak C/D***

6.30am - 7.00am – **Check-in / Registration / Load Presentations**

7.00am - 8.00am – **Quick-Shot Breakout Presentations**

Fetal – Moderator: Anthony Johnson ~ ***Cedar A/B***

Physiological-Based Cord Clamping for Infants with Congenital Diaphragmatic Hernia: pinC Trial Study Protocol
Presenter: Philip DeKoninck (AB98)

Prediction of survival in right sided congenital diaphragmatic hernia in the FETO era
Presenter: Francesca Russo (AB58)

Antenatal sildenafil for congenital diaphragmatic hernia: development of a pharmacokinetic model to predict human fetal exposure
Presenter: Francesca Russo (AB63)

Variability in antenatal prognostication of diaphragmatic hernia across the North American Fetal Therapy Network
Presenter: Anthony Johnson (AB101)

Foetoscopic endotracheal occlusion (FETO) for severe congenital diaphragmatic hernia vs expectant management
Presenter: Vivien Dutemeyer (AB49)

Incidence and impact of prematurity on the clinical course of newborns with CDH
Presenter: Neysan Rafat (AB4)

General – Moderator: Matias Luco ~ ***Red Maple***

Congenital Diaphragmatic Hernia and associated Omphalocele: A study from the CDHSG Registry
Presenter: Carmen Mesas Burgos (AB5)

Left ventricular parameters from initial ECHO predict survival without ECMO in left-sided congenital diaphragmatic hernia (CDH)
Presenter: Bradley Yoder (AB28)

Benchmarking against the CDH Study Group (CDHSG) Database – the first 10 years
Presenter: Mark Davis (AB60)

Does the sac correlate to the better prognosis of congenital diaphragmatic hernia with hernia sac?
Presenter: Takuya Kondo (AB61)

Right Sided Congenital Diaphragmatic Hernia: The Role of Prenatal Predictors And Perinatal Characteristics On Early Outcomes - A Fourteen-Year Prospective Study
Presenter: Laura Valfre (AB77)

Therapy at 30 days of life predicts lung function at 6-12 months in infants with Congenital Diaphragmatic Hernia (CDH)
Presenter: Etze Chotzoglou (AB75)

The risk factors of pneumothorax associated with isolated congenital diaphragmatic hernia: results of a Japanese multicenter study
Presenter: Kazunori Masahata (AB46)

Novel Decision Aids and Technology in Neonatal Resuscitation
Presenter: Natalie Rintoul (AB95)

Surgery – Moderator: Tim Jancelewicz ~ ***Magnolia***

Impact of Objective Echocardiographic Criteria for Timing of Congenital Diaphragmatic Hernia (CDH) Repair.
Presenter: Timothy Crombleholme (AB31)

Hepatopulmonary Fusion: A Rare Variant of Congenital Diaphragmatic Hernia.
Presenter: Dalya Ferguson (AB50)

Optimal timing of surgery in infants with neonates with left-sided congenital diaphragmatic hernia diagnosed prenatally
Presenter: Masaya Yamoto (AB10)

Mesh matters: patch material in congenital diaphragmatic hernia affects recurrence rate
Presenter: Kristin Aigner (AB35)

Surgical Complications In Congenital Diaphragmatic Hernia Survivors: Long-Term Follow-Up
Presenter: Laura Valfre (AB78)

How to improve long-term outcome after minimal-invasive repair of congenital diaphragmatic hernia – a critical review of all cases in 10 years
Presenter: Neysan Rafat (AB16)

Does inimal-invasive surgery in neonatal age cause cerebral damage and neurologic deficits?
Presenter: Neysan Rafat (AB17)

Perioperative Prognostic Factors and Short-Term Outcome in CDH: Application in a Single Centre Population
Presenter: Camilla Pagliara (AB9)

8.15am - 8.45am – **Speaker VIII ~ Live Oak A/B**

Alexandra Benachi – Update on fetal diagnosis

8.45am - 10.00am – **Research Presentations - Fetal ~ Live Oak A/B**

Moderators: Paul Losty and Anthony Johnson

Prenatal brain development is altered in Congenital Diaphragmatic Hernia on ultrasound
Presenter: Francesca Russo (AB30)

Pharmacokinetics and pharmacodynamics of sildenafil in fetal lambs on extracorporeal support
Presenter: Felix De Bie (AB67)

Reproducibility of fetal lung-to-head ratio in left diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)
Presenter: Anthony Johnson (AB99)

Inter-rater agreement for sonographic stomach position classification in fetal diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)

Presenter: Anthony Johnson (AB100)

Optimal gestational age at delivery for congenital diaphragmatic hernia
Presenter: Hanane Bouchghoul (AB11)

The effect of tracheal occlusion on lung development pathways and vascular morphology in a rabbit model of congenital diaphragmatic hernia
Presenter: Nathalie Carey (AB82)

Evaluation of a new balloon for fetal endoscopic tracheal occlusion in the non-human primate model
Presenter: Nicolas Sananes (AB66)

Safety and efficacy of the "Smart" Tracheal Occlusion™ balloon for congenital diaphragmatic hernia: in-vitro and in- vivo study
Presenter: David Basurto (AB62)

10.00am - 11.00 am – **Speaker IX ~ *Live Oak A/B***

Jan Deprest – Update on Fetal Therapies and the TOTAL Trial

11.00am - 11.15am – **Closing remarks ~ *Live Oak A/B***

Meeting Concludes

Future Meetings

2022 – Glasgow, Scotland ~ Hosted by Neil Patel, Carl Davis and Gregor Walker

2024 – Lille or Paris, France ~ Alexandra Benachi and Laurent Storme and the Center for Rare Disease for CDH

Congenital Diaphragmatic Hernia

Panel discussion & audience feedback

Dick Tibboel, MD, PhD
Rodrigo Ruano, MD, PhD
Theresa Grover, MD
Richard Keijzer, MD, PhD
Kevin Lally, MD, MS

Matthew Harting, MD, MS

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

CDH The Comprehensive Center for CDH Care

Children's Memorial Hermann Hospital

Disclosures

I have no conflicts of interest to disclose.

CDH case presentation

Using the app:

- Download Poll Everywhere
- Join a presentation
  - PollEv.com/matthewthart564

By text:

- Text “MATTHEWTHART564” to 22333

Introductory questions

What is your current role?

Faculty physician

Training physician

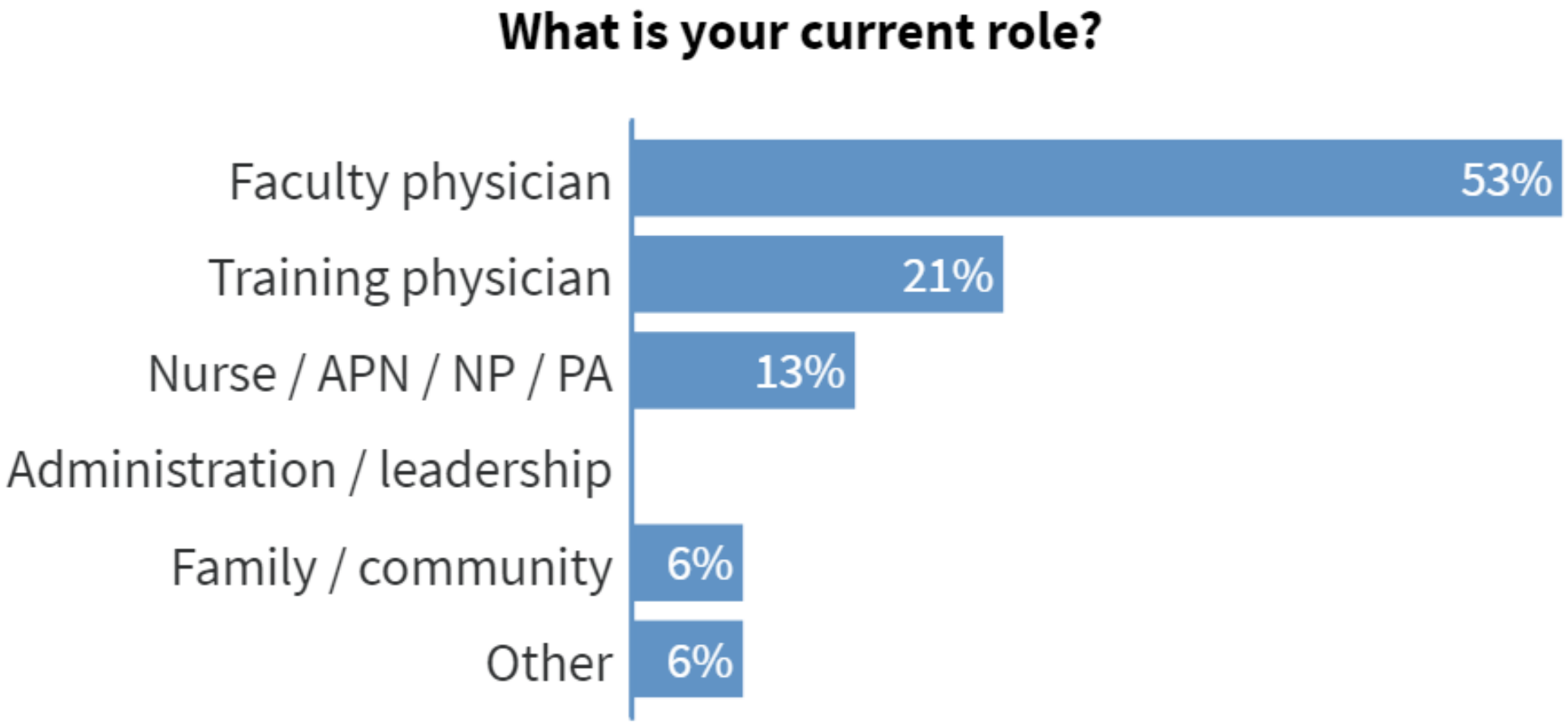
Nurse / APN / NP / PA

Administration / leadership

Family / community

Other

Introductory questions



Introductory questions

What is your current / desired area of specialty?

Pediatric surgery

Neonatology

Pediatric critical care

Maternal fetal medicine / obstetrics

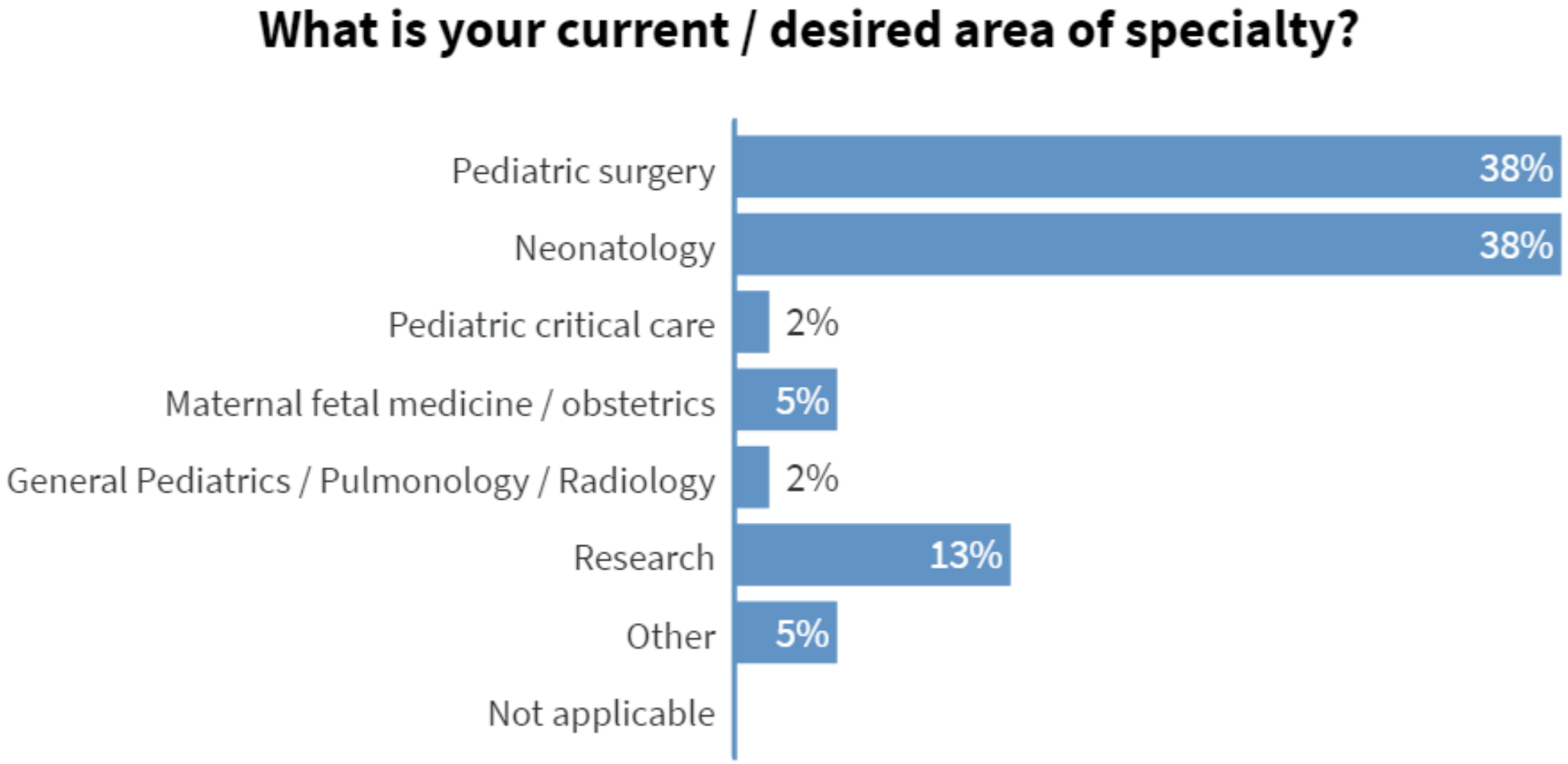
General Pediatrics / Pulmonology / Radiology

Research

Other

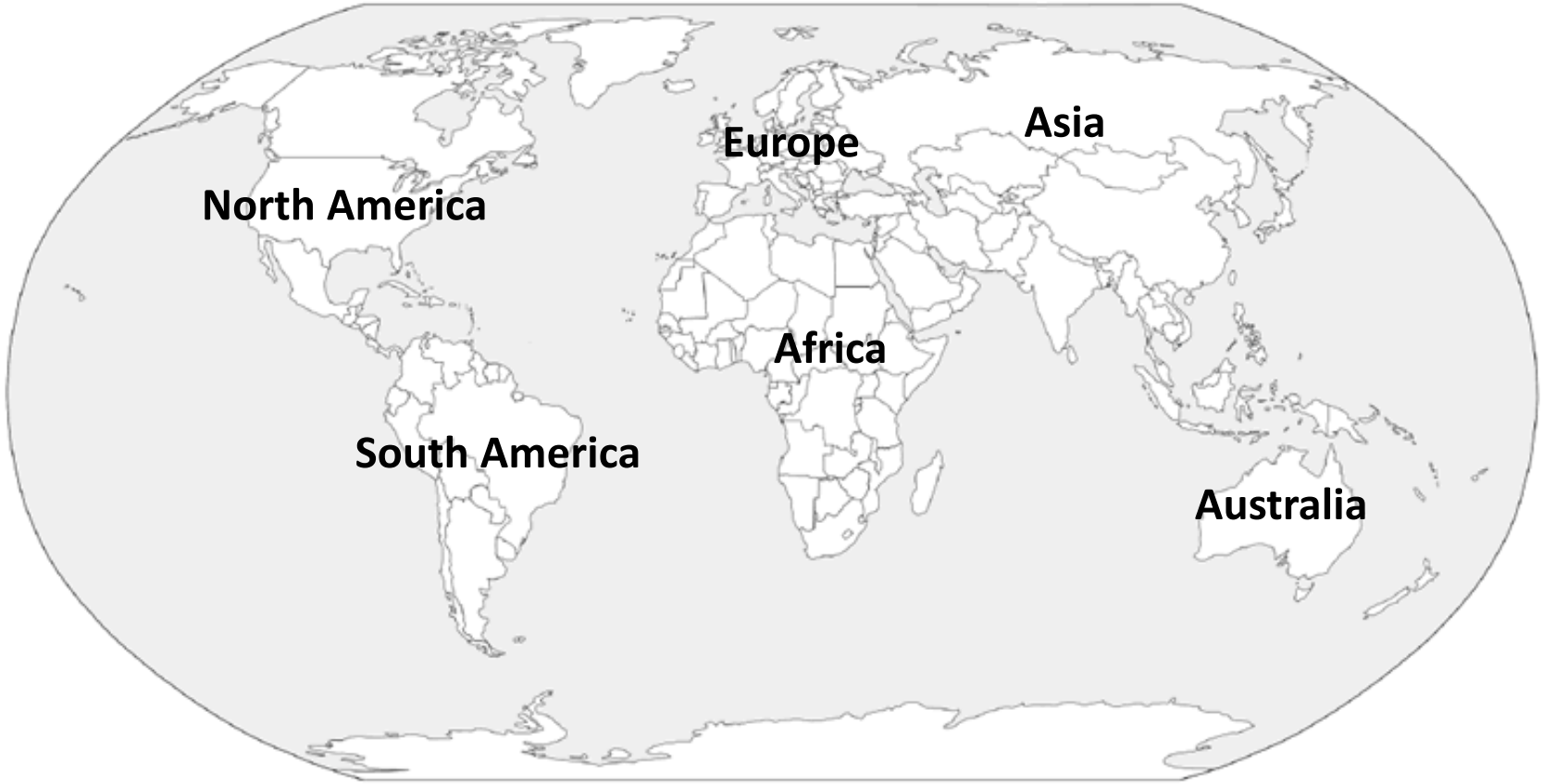
Not applicable

Introductory questions



Introductory questions

Where are you from?



Where are you from?

Total Results: 79

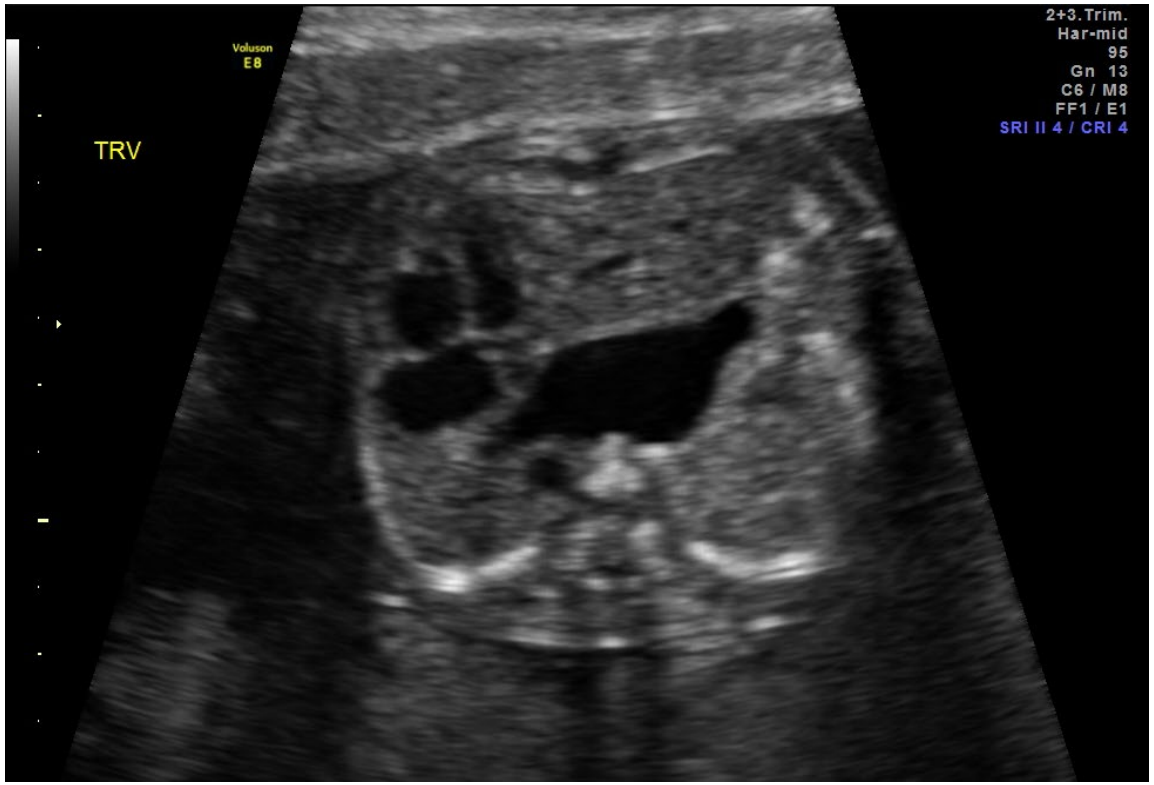
Reminders…

Feel free to come to the microphone anytime – audience participation makes this way more fun and educational…

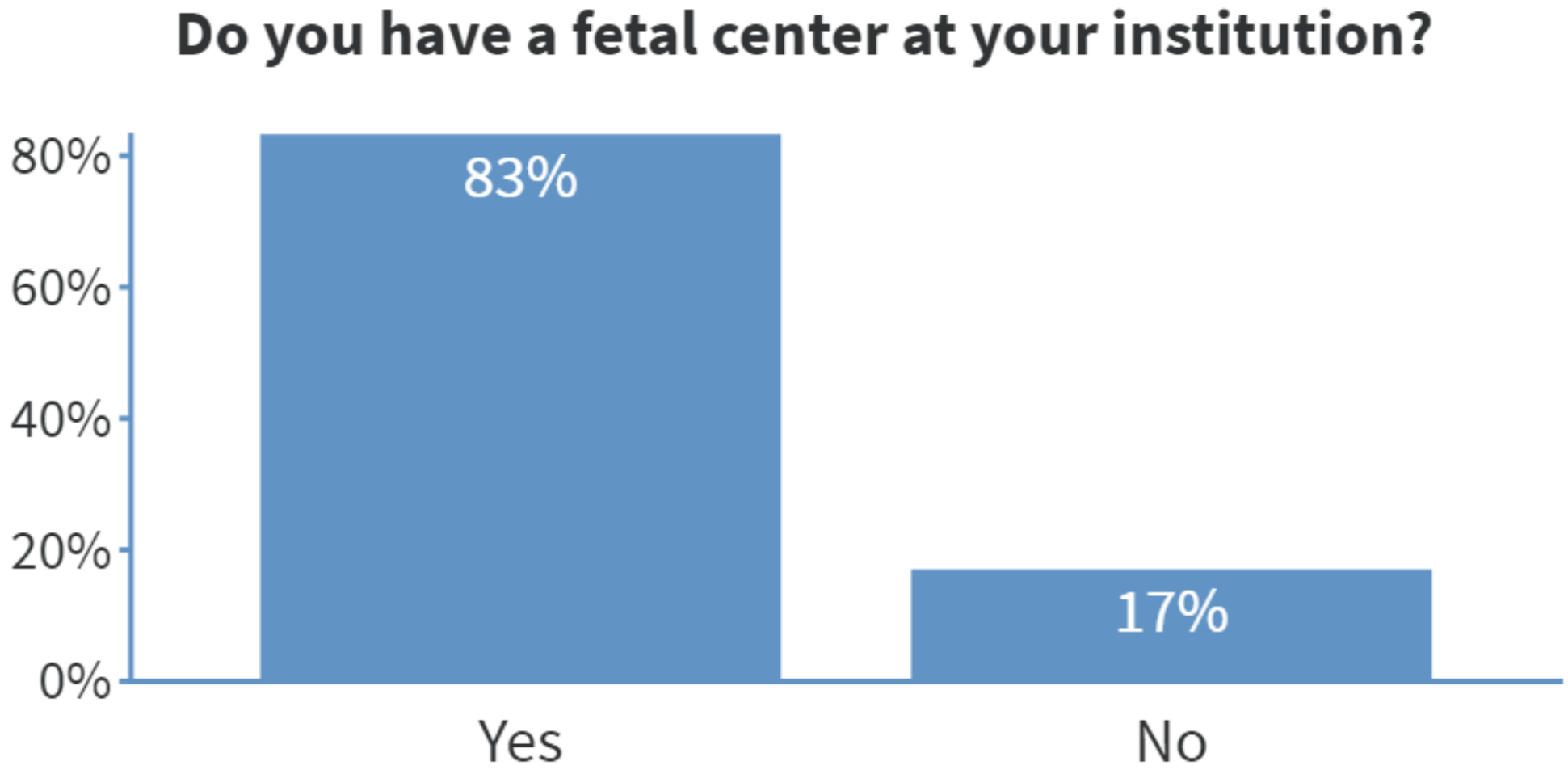
If I cut you off, only trying to stay on time – lot of ground to cover.

CDH case presentation

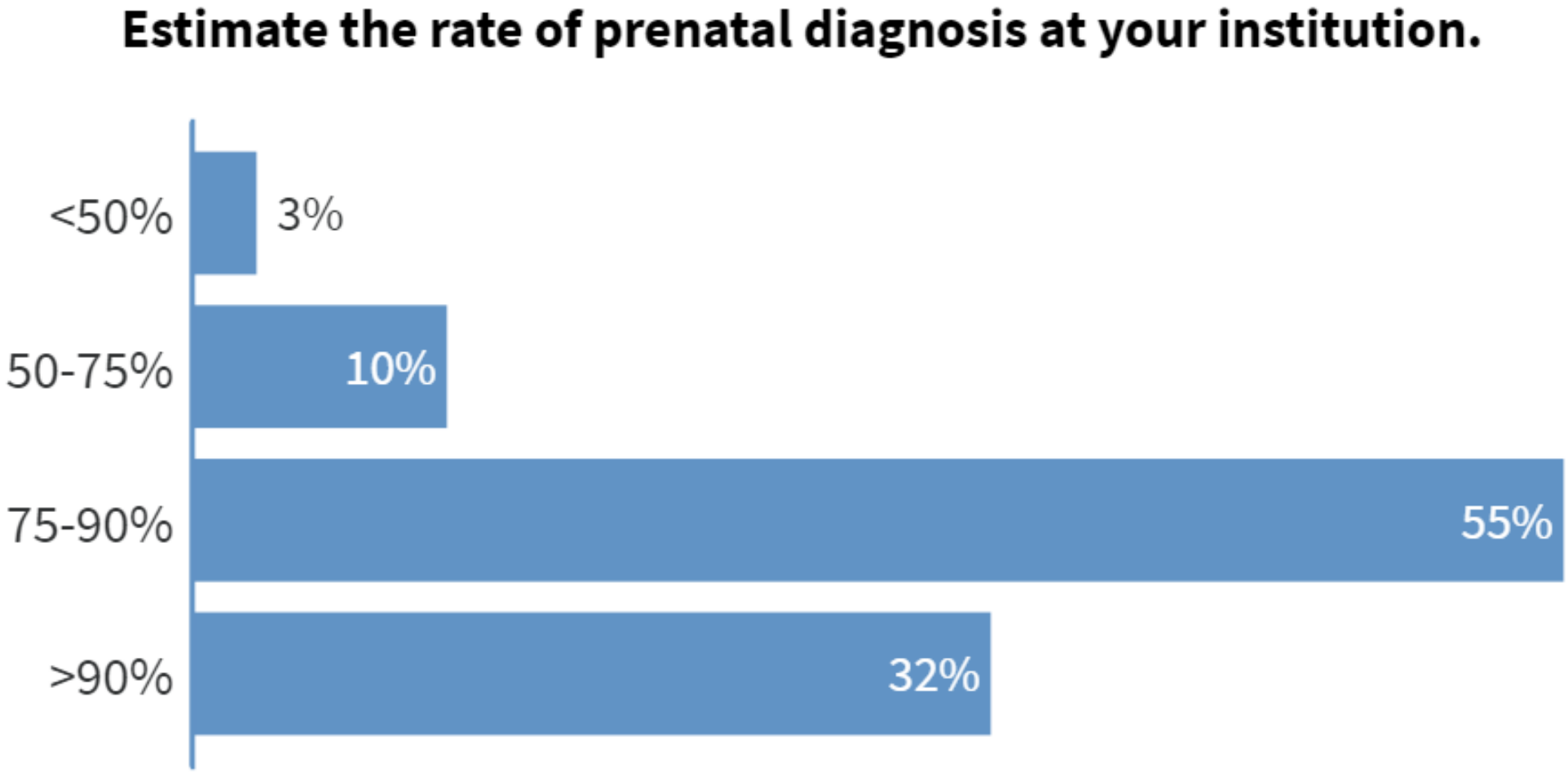
- You are asked to see a 29 yo mother (first pregnancy) with a 20 week EGA fetus who has a suspected left CDH on an initial screening US



Fetal

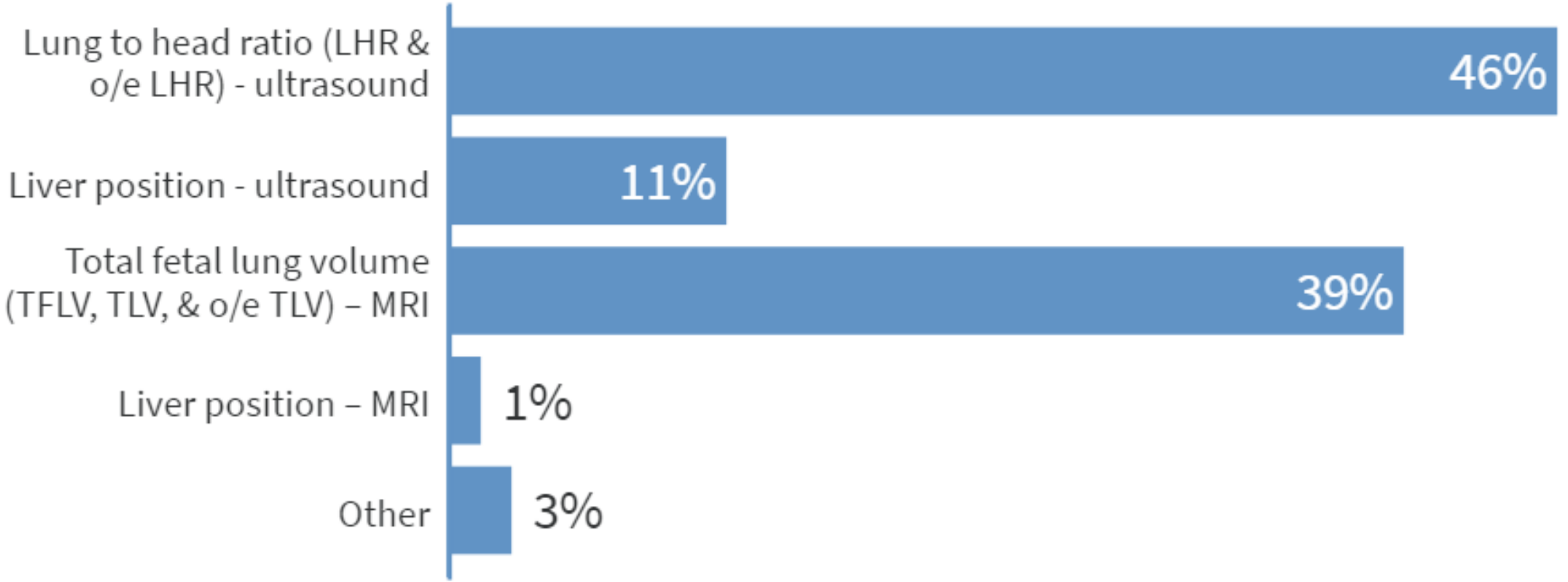

Do you have a fetal center at your institution?
80%
60%
40%
20%
0%
83%
17%
Yes
No

Fetal

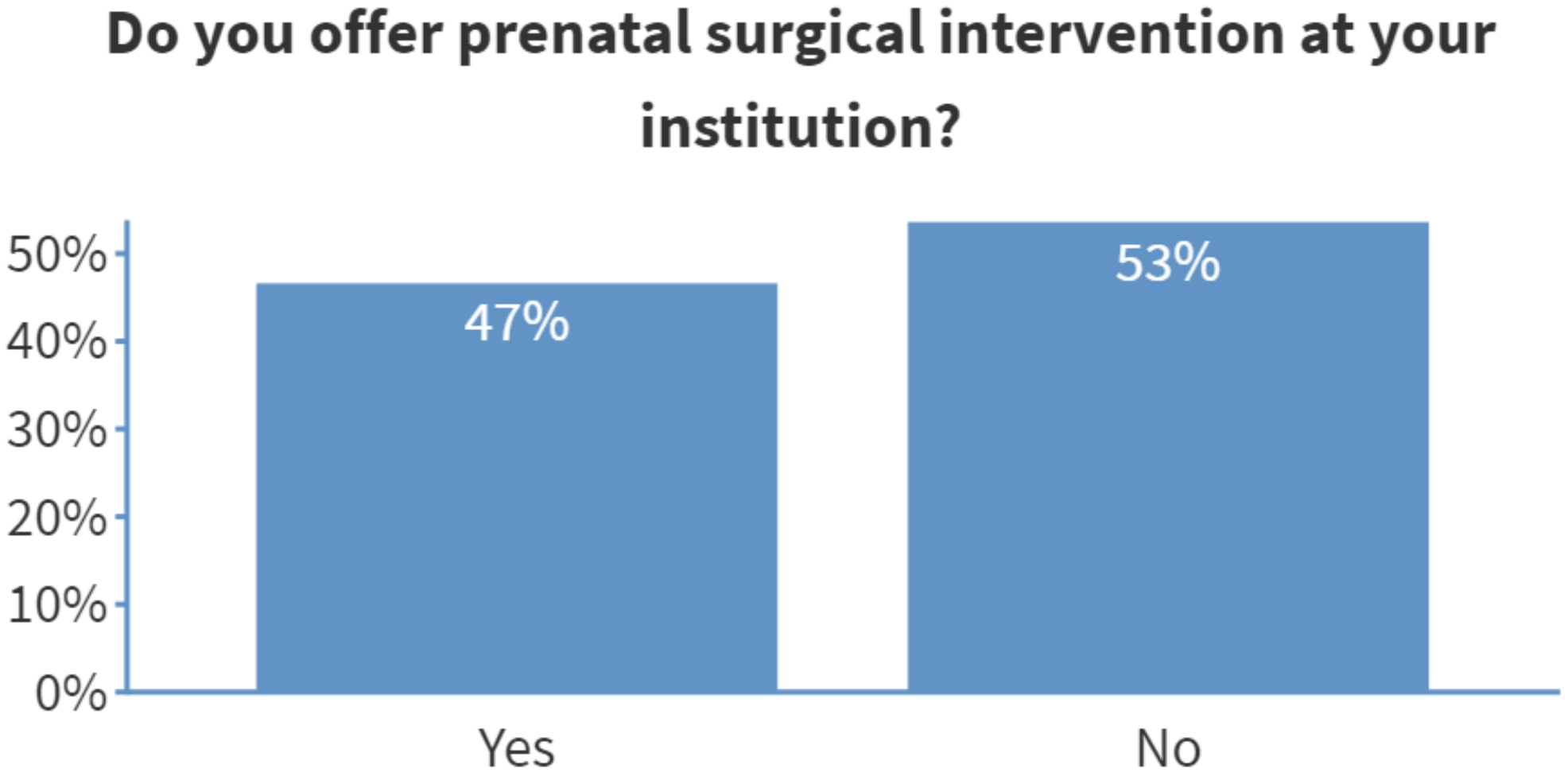

Estimate the rate of prenatal diagnosis at your institution.
<50%
3%
50-75%
10%
75-90%
55%
>90%
32%

Fetal

What CDH-specific prenatal prognostic evaluation is most important to you when discussing severity of disease with the family?



Fetal

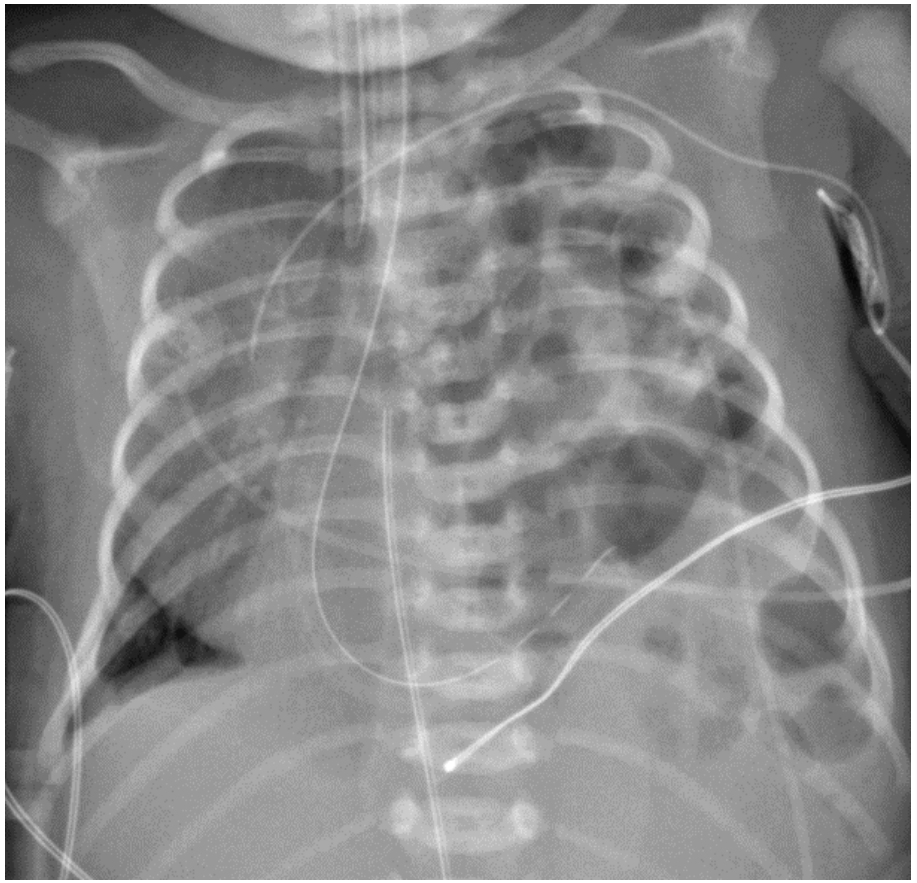

Do you offer prenatal surgical intervention at your institution?
50%
40%
30%
20%
10%
0%
47%
53%
Yes
No

Fetal

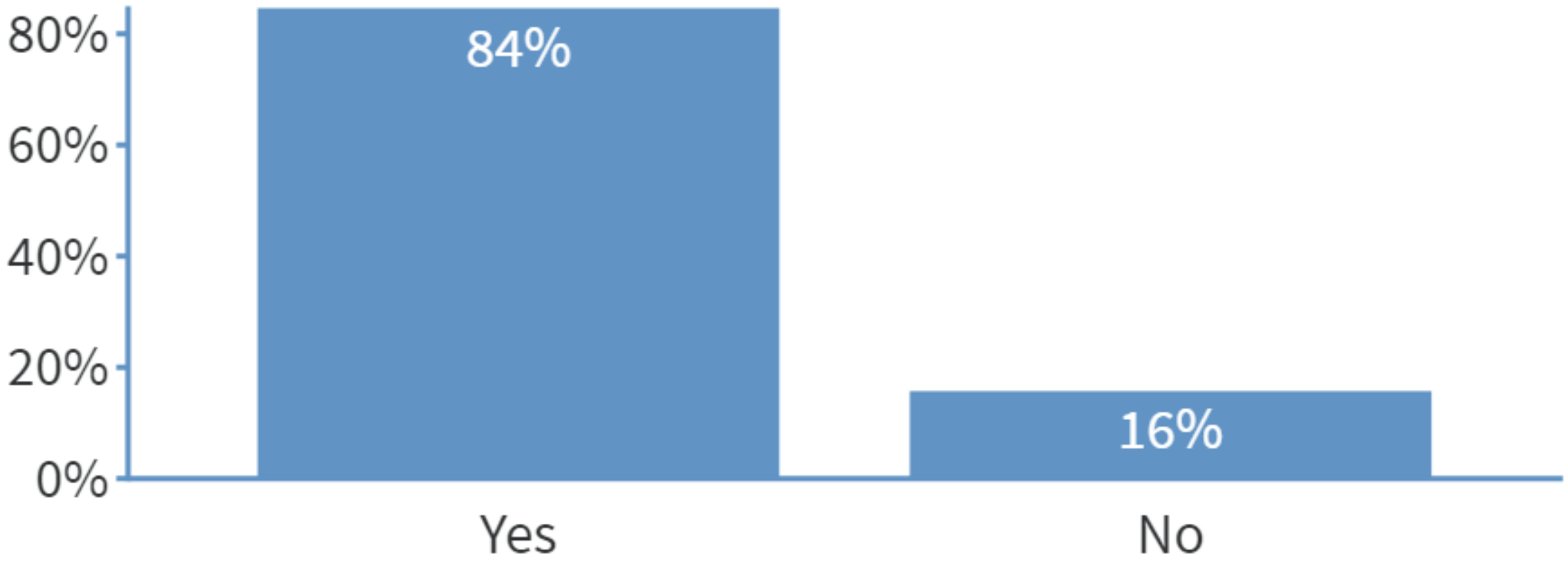
Final thoughts…

CDH case presentation

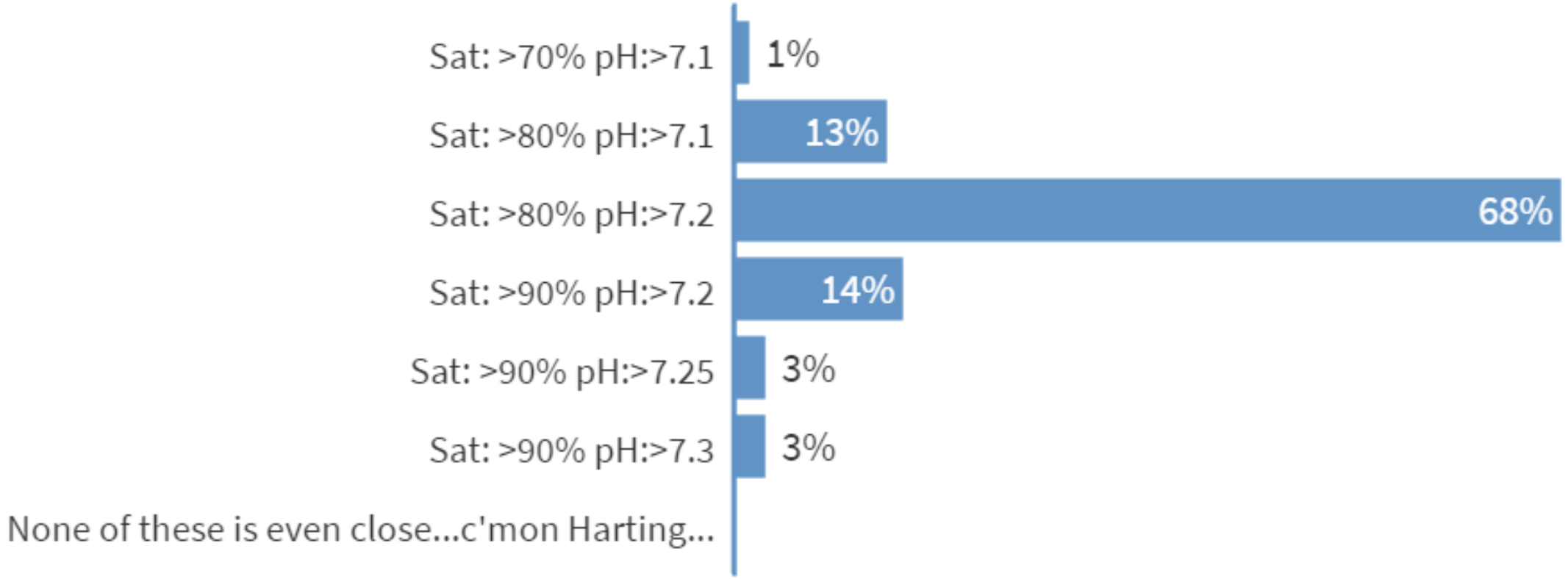
- You are asked to see a newborn with the following chest radiograph



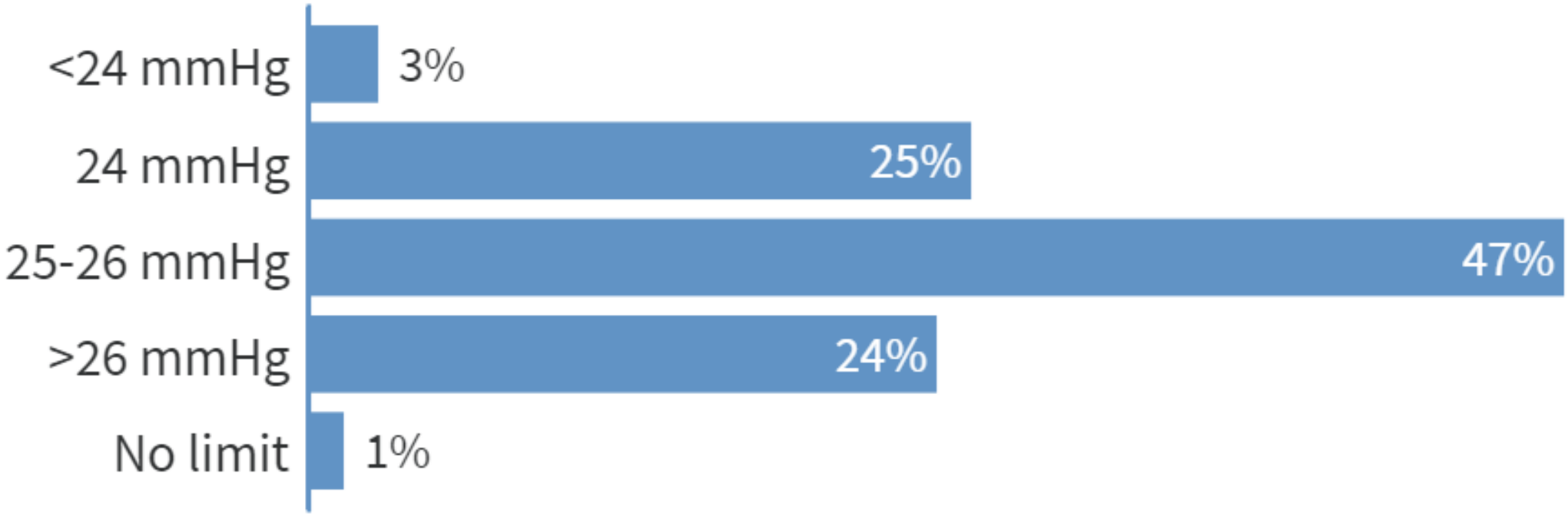
Are CDH patients delivered and managed in the same building at your hospital?



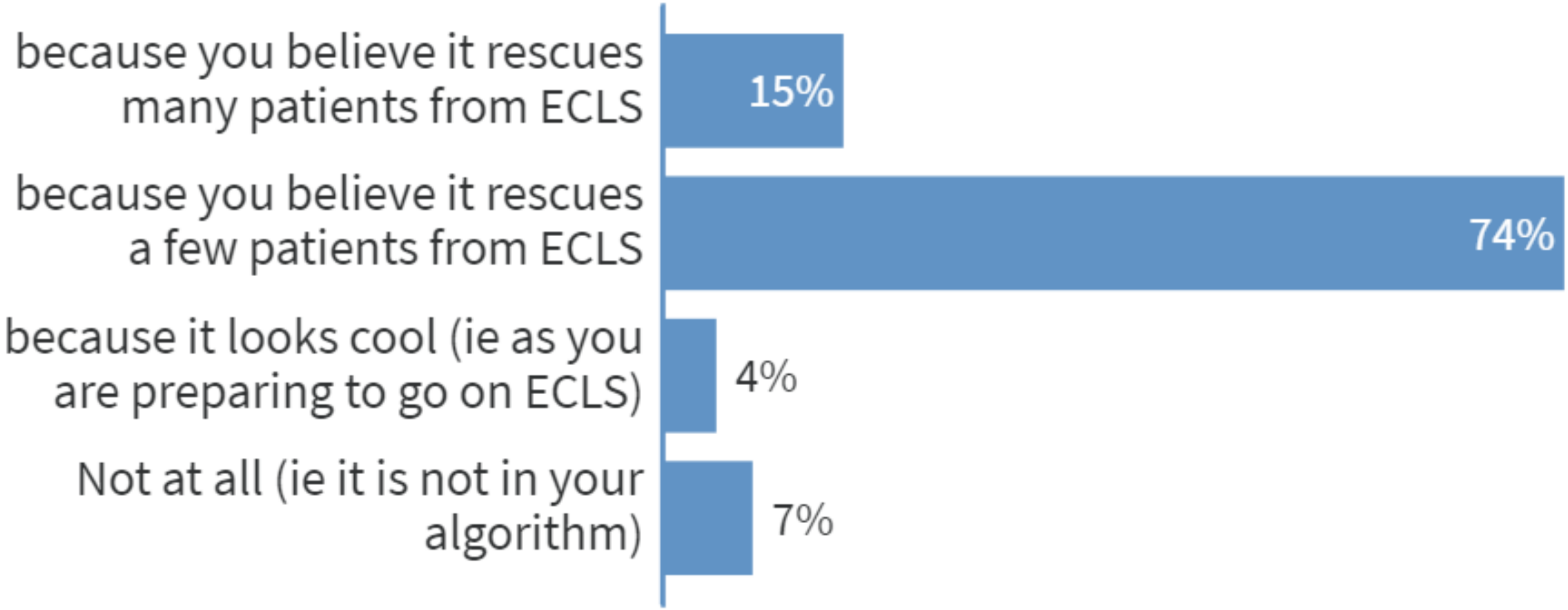
By 3-4 hours of life, what are your target goals for oxygen saturation and pH?



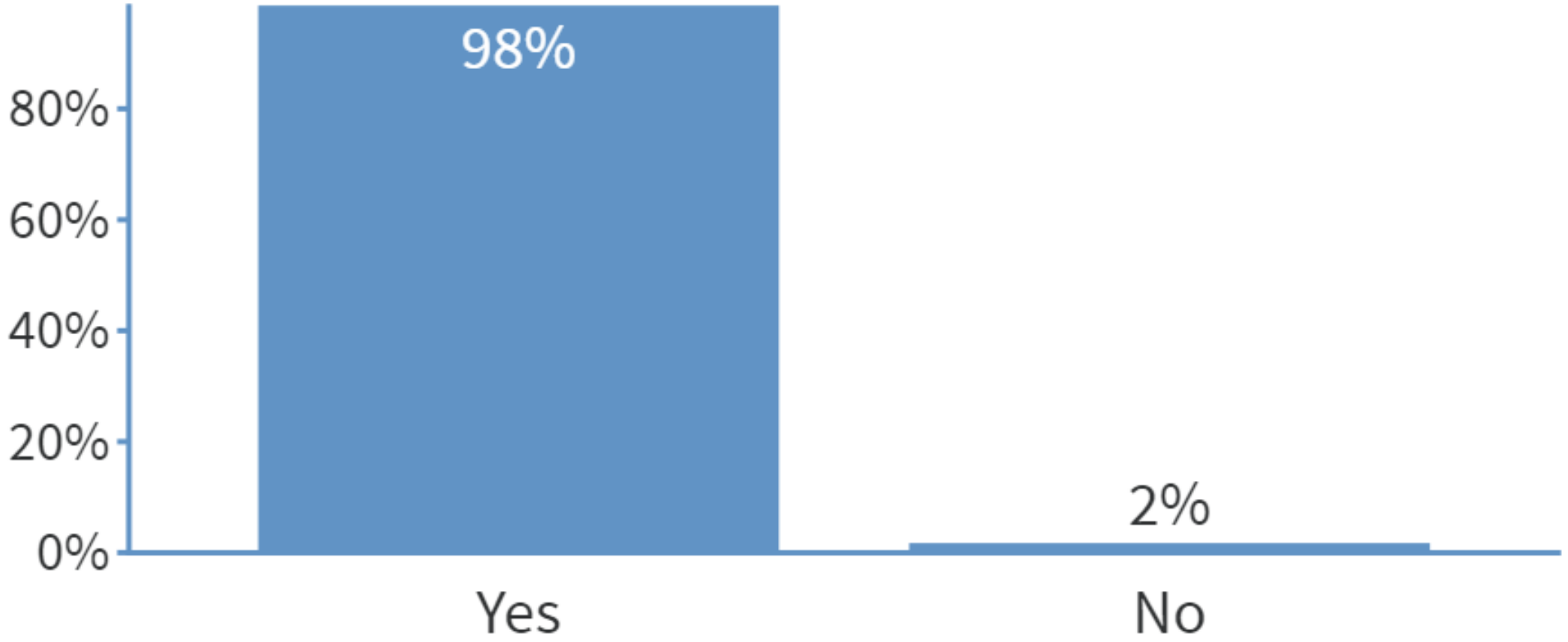
What are your maximum ventilator peak inspiratory pressures (PIP) that you would use prior to changing to HFOV, ECLS, or some other method?



At your institution, HFOV is used for CDH patients:

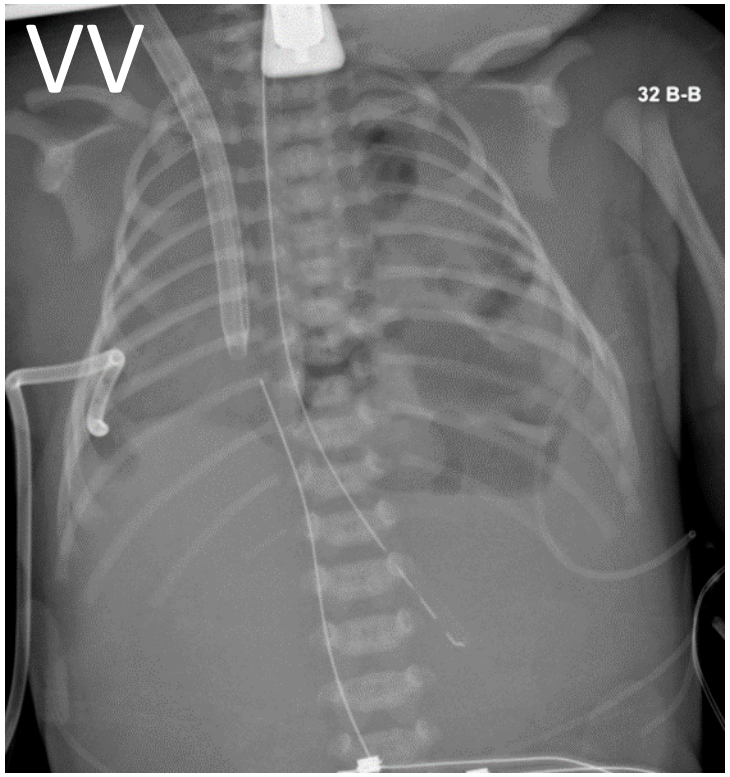


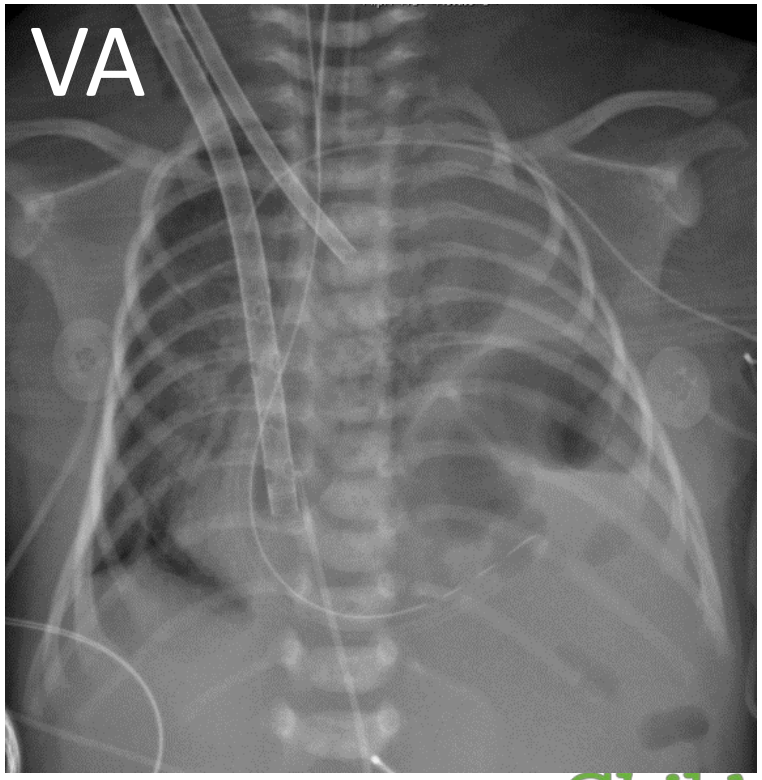
Is ECLS used to support CDH patients at your institution?



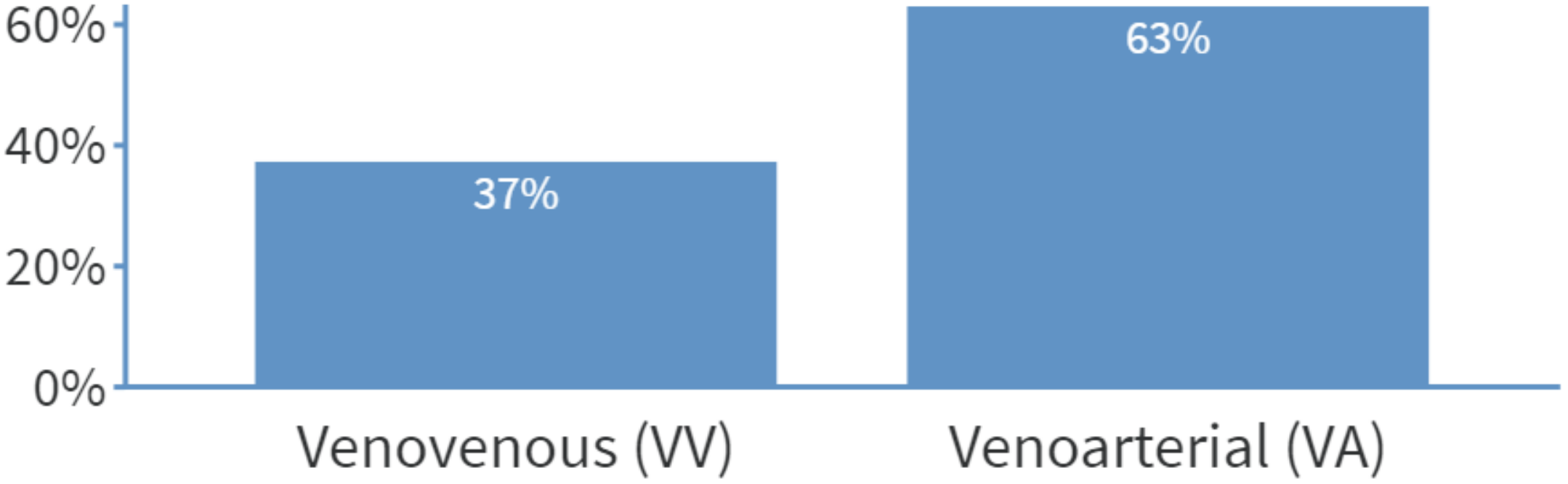
Postnatal

If you are to cannulate to ECLS secondary to not meeting goals but your hemodynamics are stable – what mode would you try first?



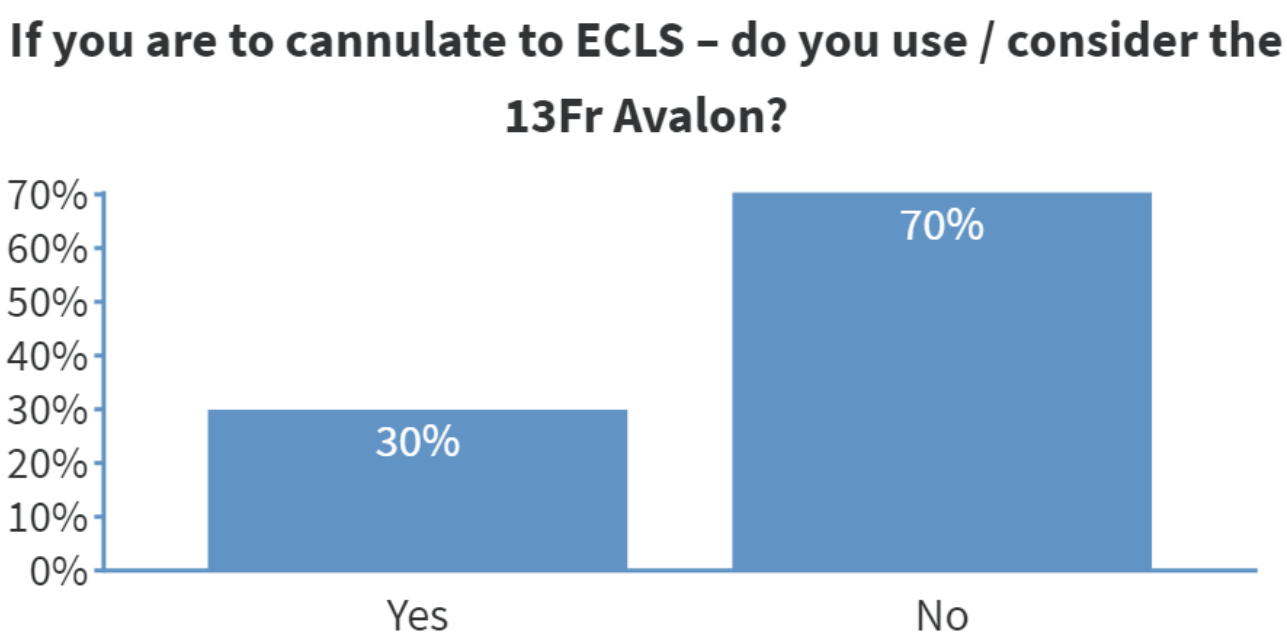


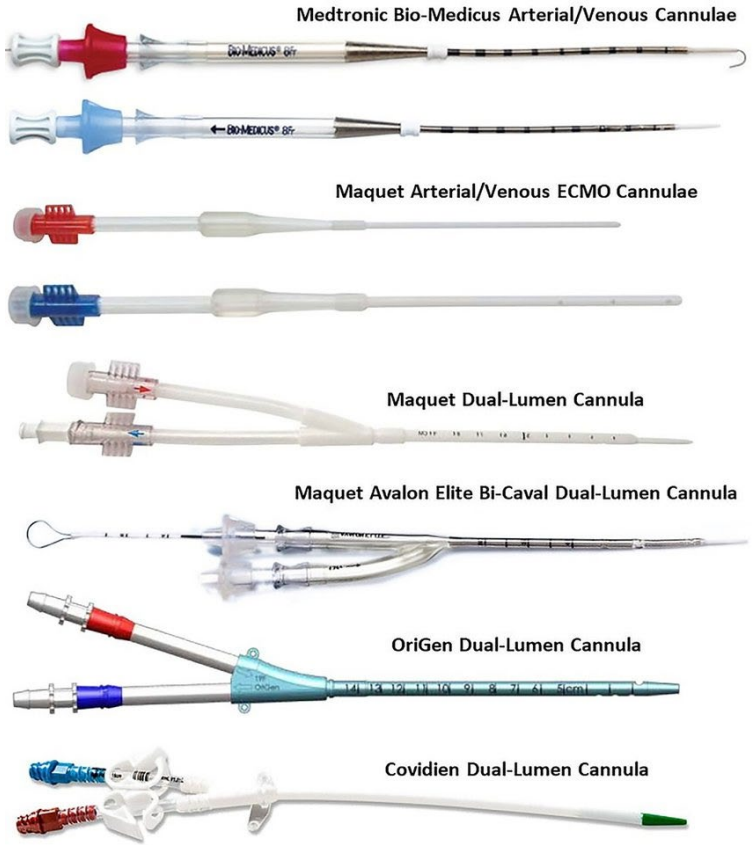
If you are to cannulate to ECLS secondary to not meeting goals but your hemodynamics are stable – what mode would you try first?



Postnatal

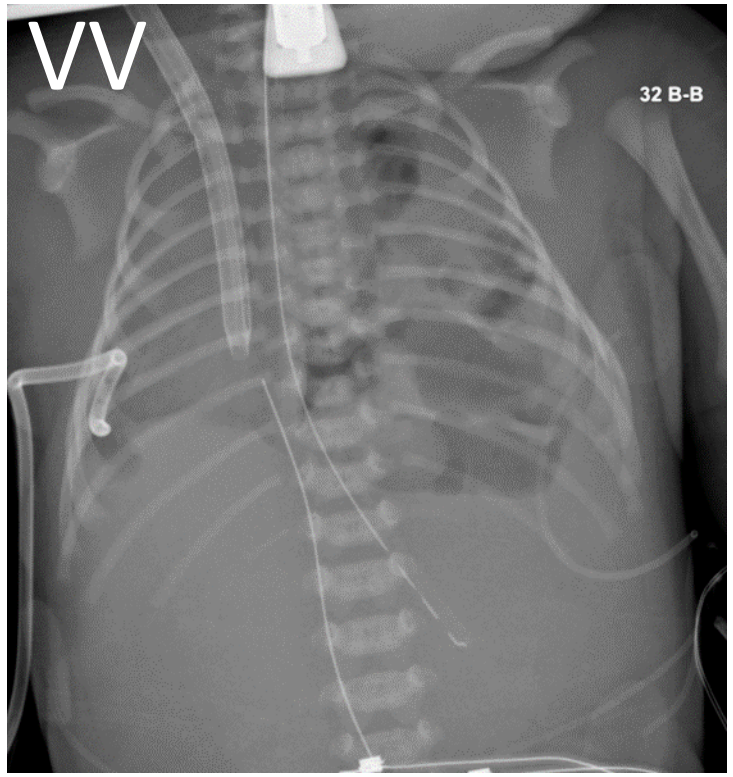
If you are to cannulate to ECLS – do you use the 13Fr Avalon?

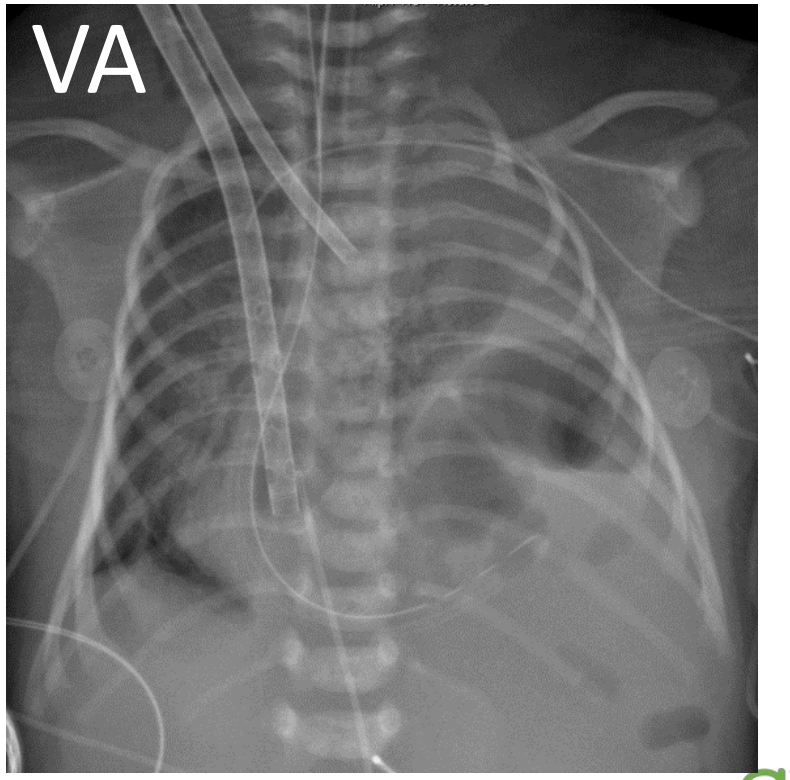




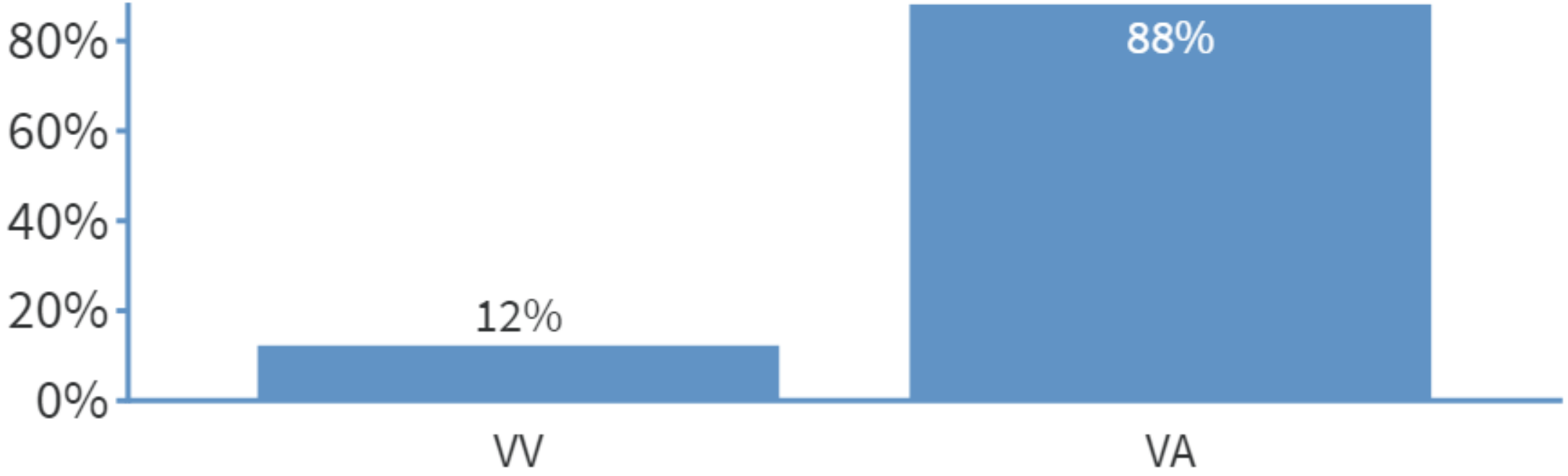
Postnatal

If you are to cannulate to ECLS secondary to not meeting goals and your hemodynamics are ***unstable*** – what mode would you try first?

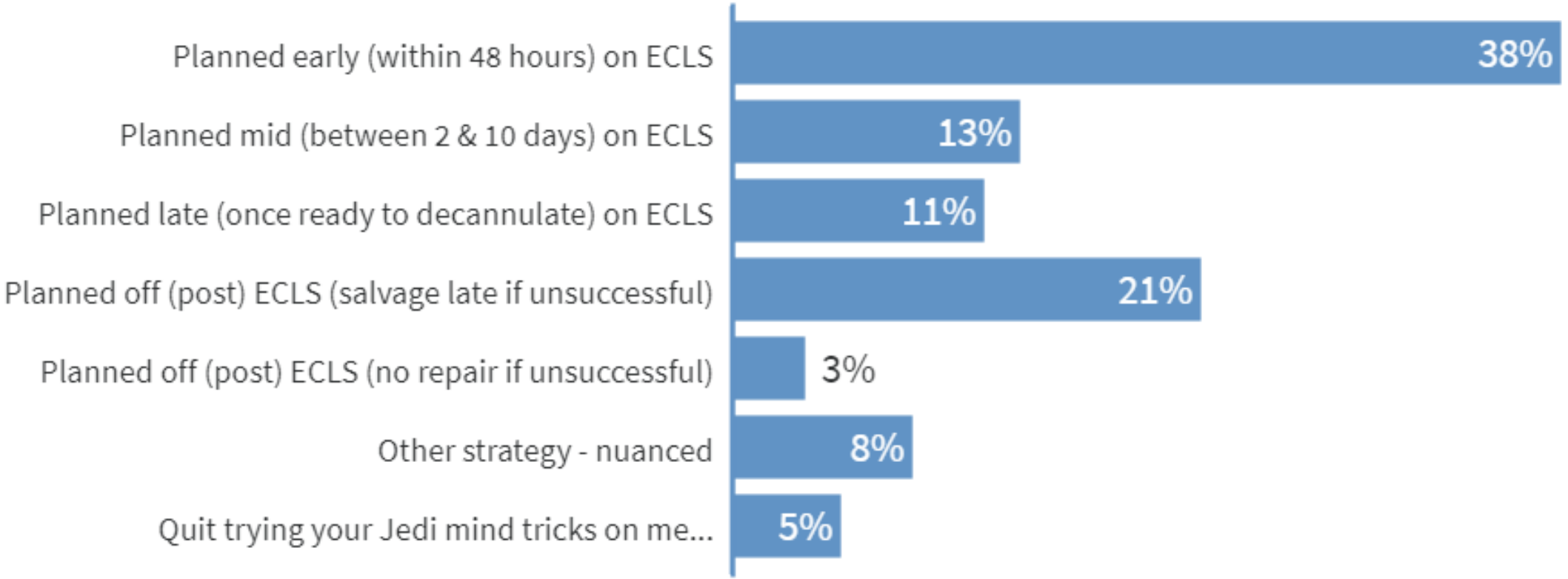




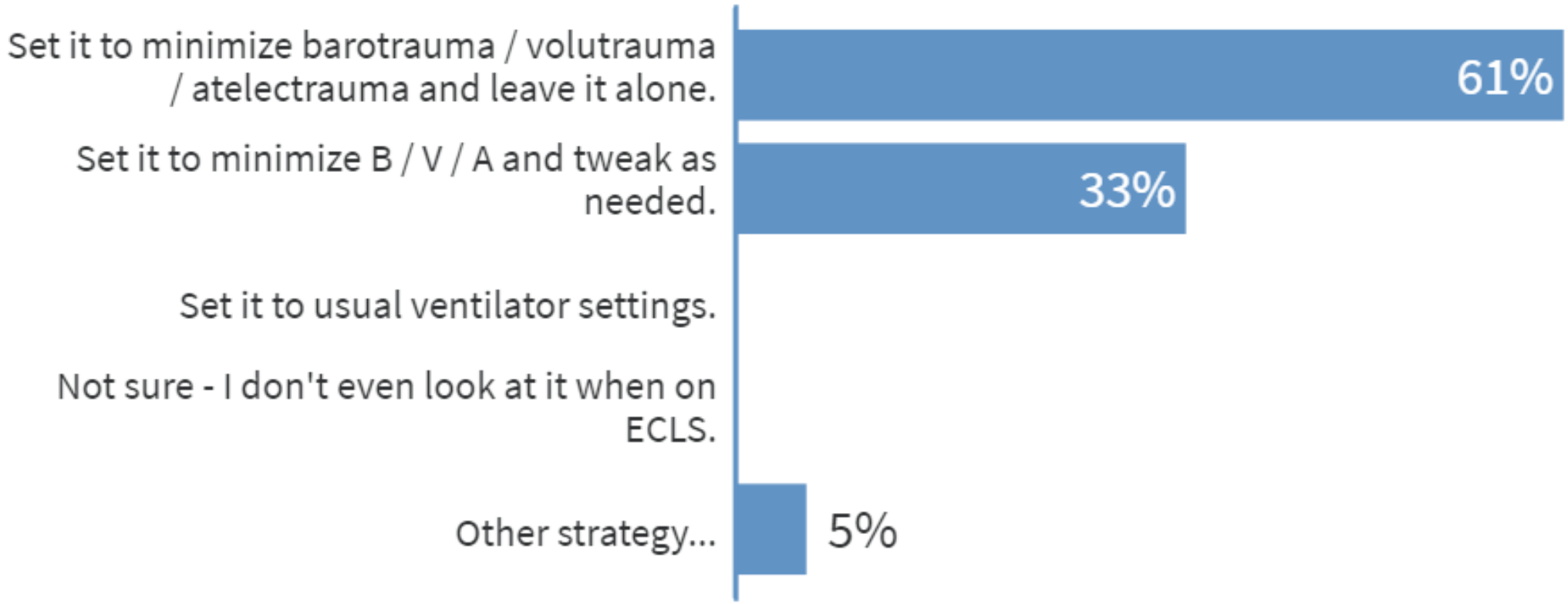
If you are to cannulate to ECLS secondary to not meeting goals and your hemodynamics are unstable – what mode would you try first?



Smooth cannulation… what is your preferred diaphragmatic repair strategy?



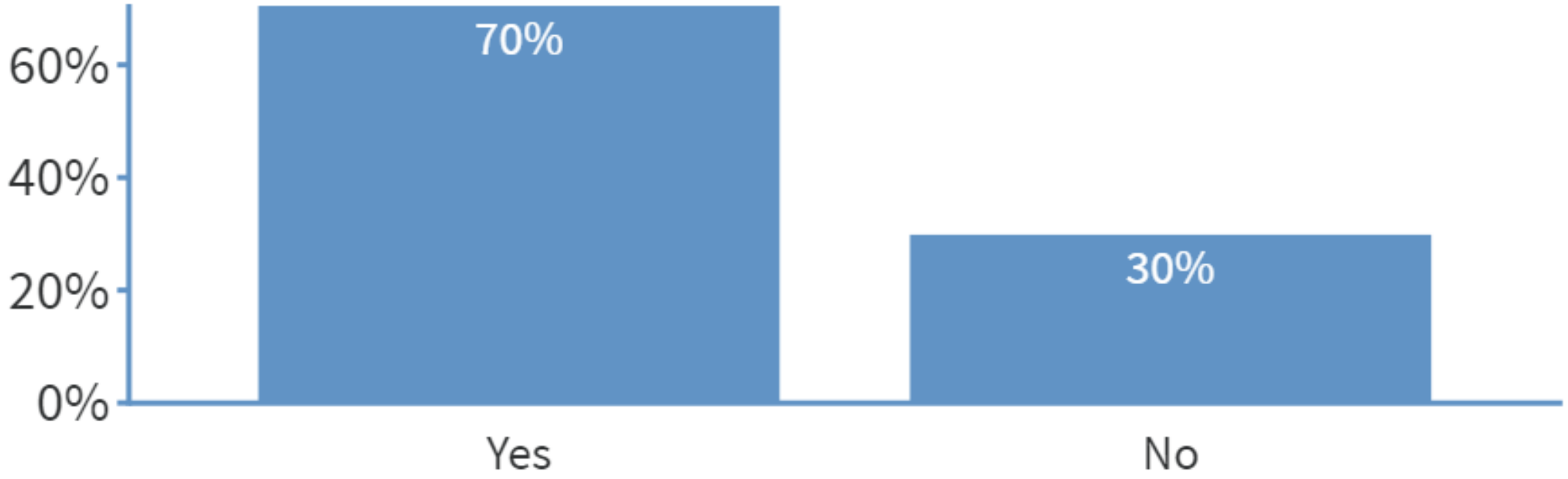
While on ECLS, what do you do with the ventilator?



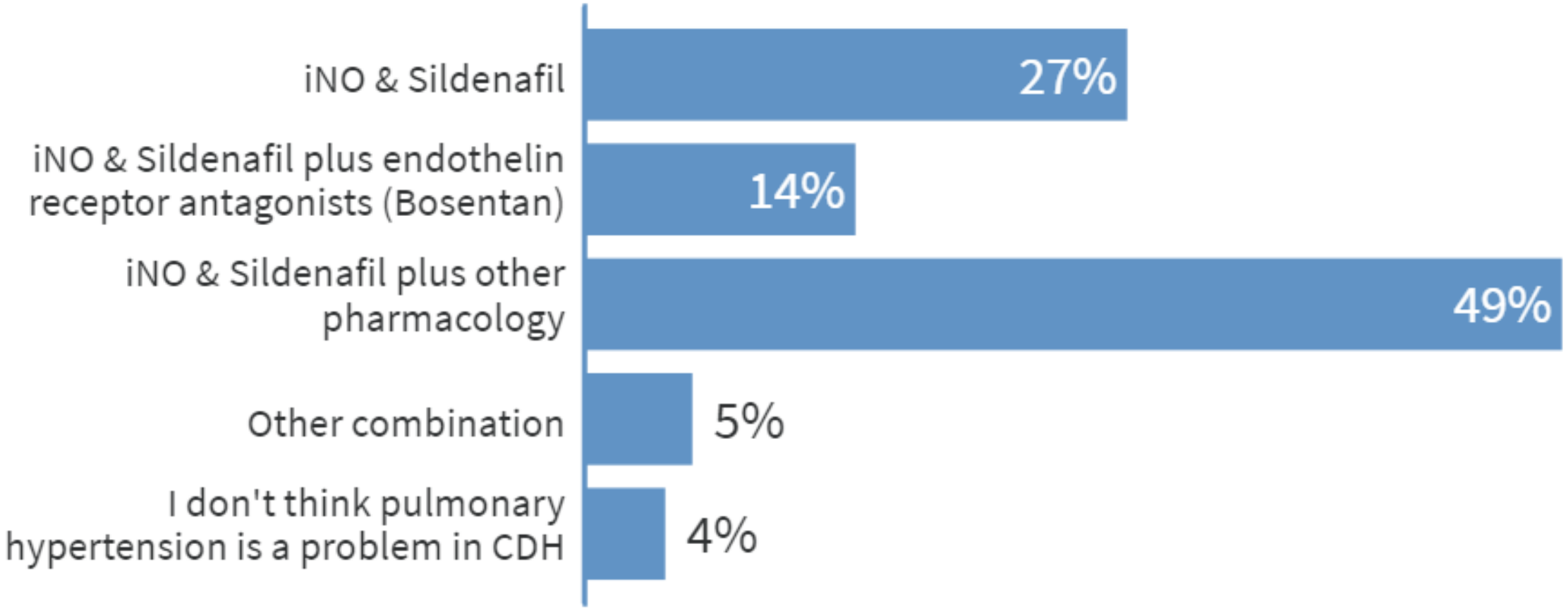
On ECLS

Weaning and liberation from ECLS is tricky…

Does pulmonary hypertension (assessed by echocardiogram) factor into your decision to proceed with repair?



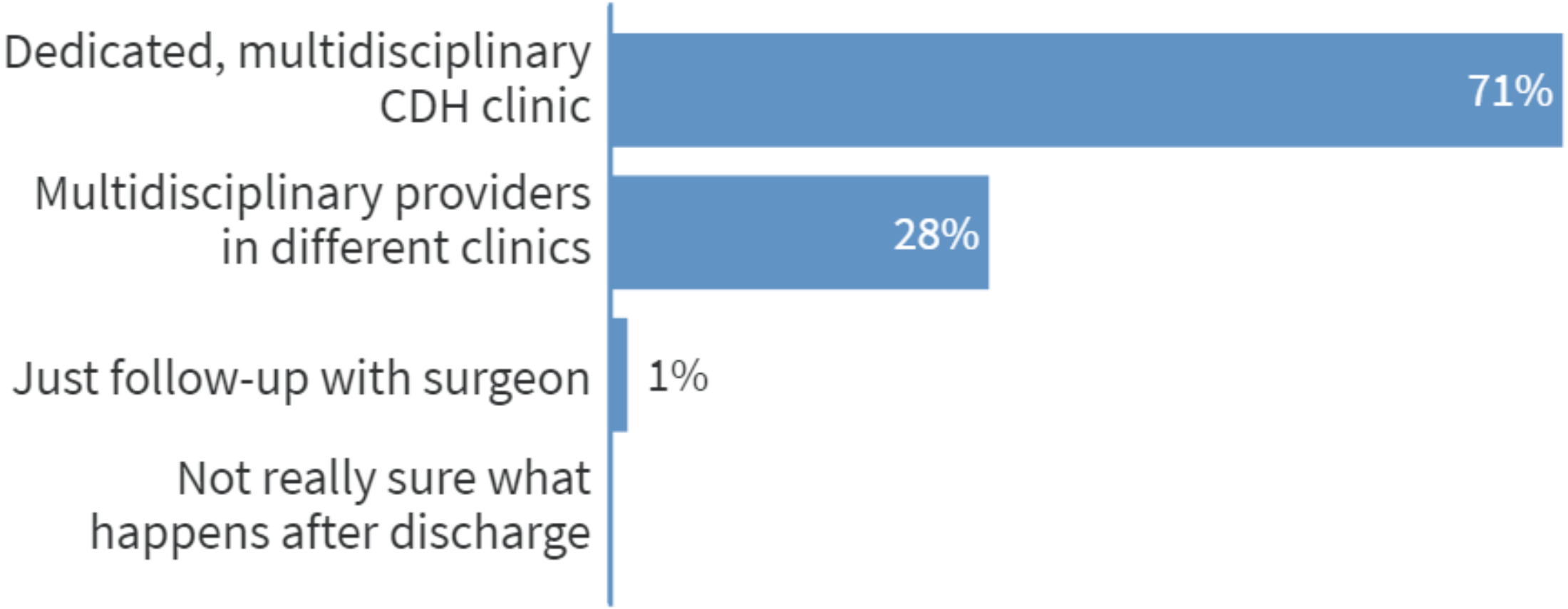
What do you prefer to try for pulmonary hypertension management?



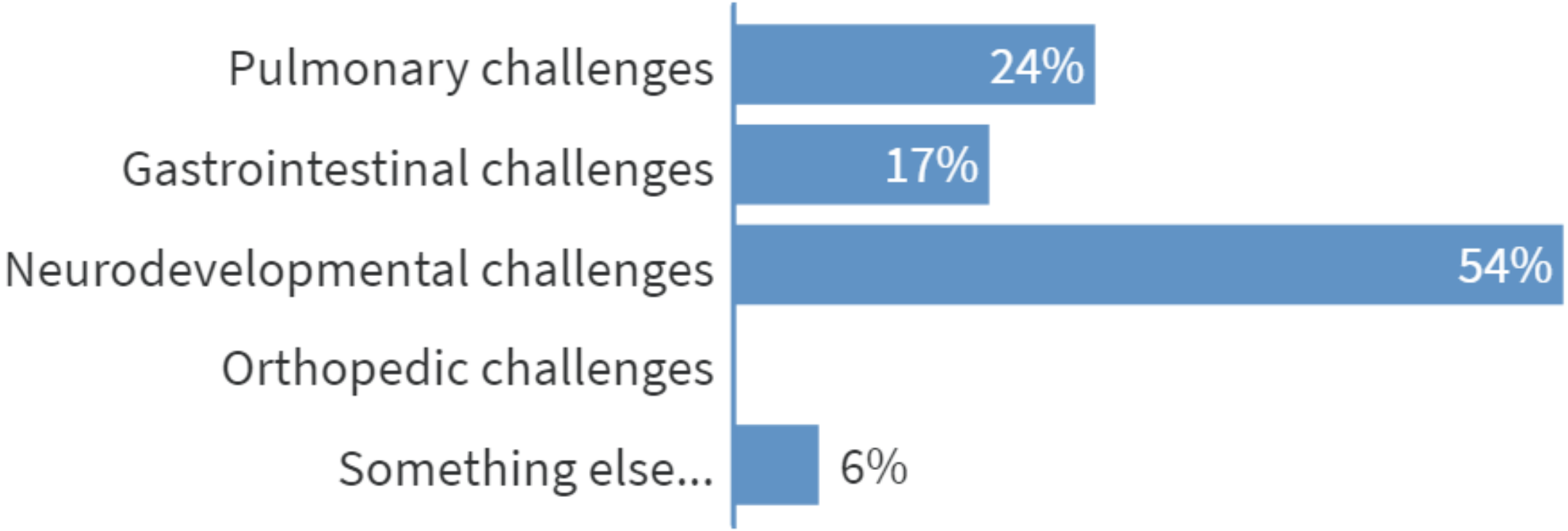
Ongoing CDH inpatient management

Thoughts on this window…

How is your post-discharge CDH care structured?



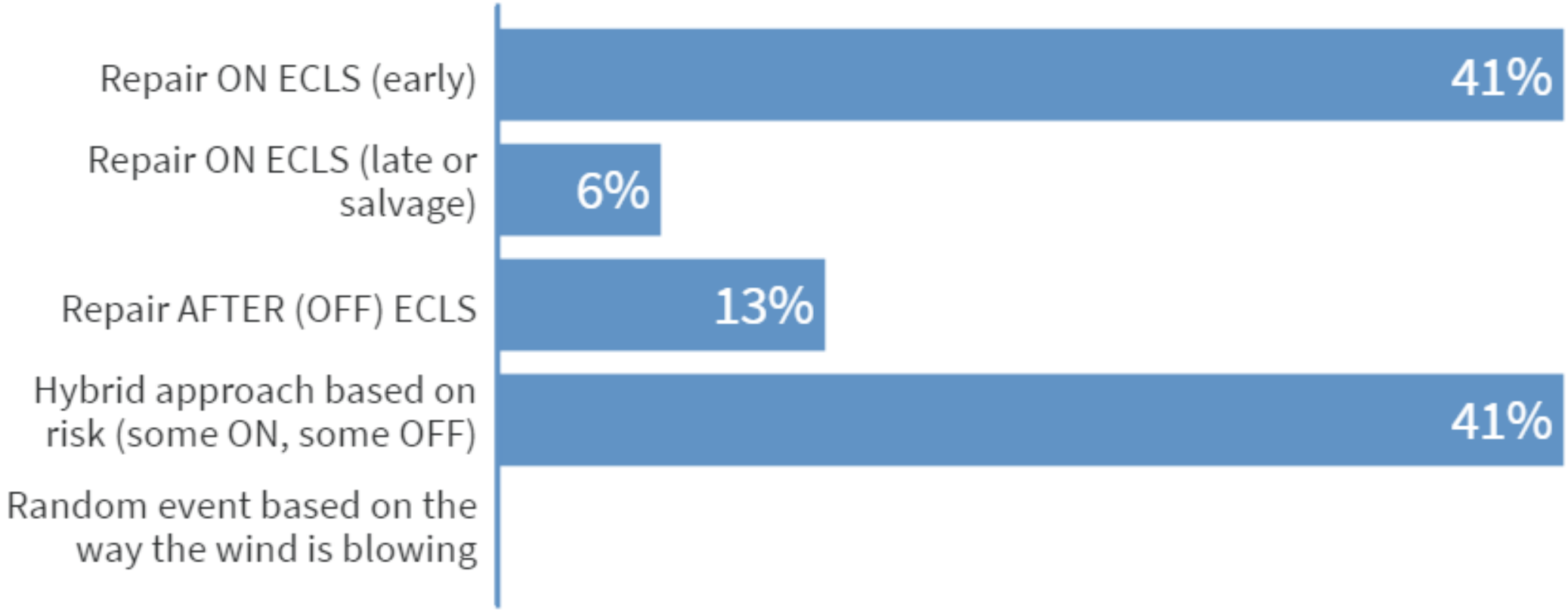
What do you see as the single greatest medical challenge facing CDH survivors?



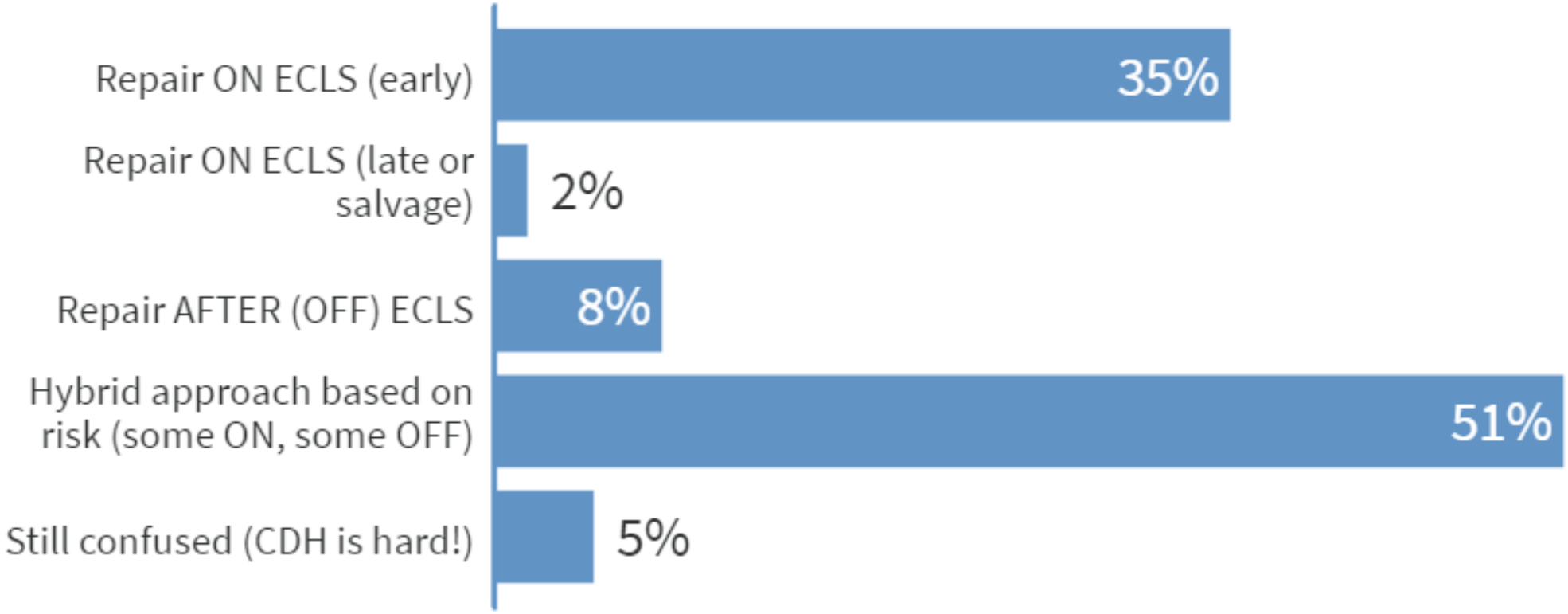
Post-discharge

Final thoughts…

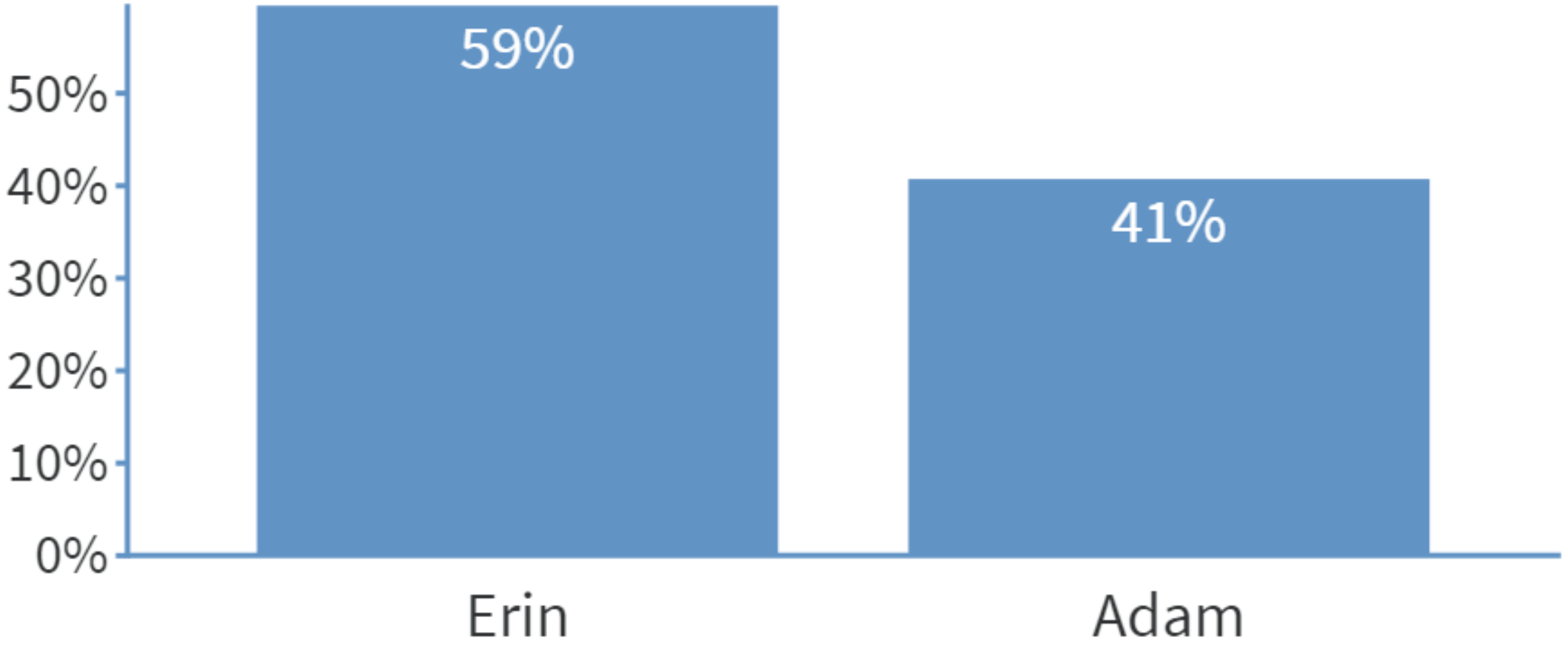
What is your current overarching institutional approach to diaphragmatic repair for CDH patients placed on ECLS?



After the debate, I feel like the best approach to diaphragmatic repair for CDH patients on ECLS is:



Who won the debate?



Please remain in *Live Oak*

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

CDH

Children's Memorial Hermann Hospital

What basic/ translational breakthroughs are going to change the way we understand CDH and care for these patients in the future?

Dick Tibboel; Robbert Rottier; Rene Wijnen

Departments of pediatric surgery; obstetrics; neonatology
cell biology and molecular/clinical genetics

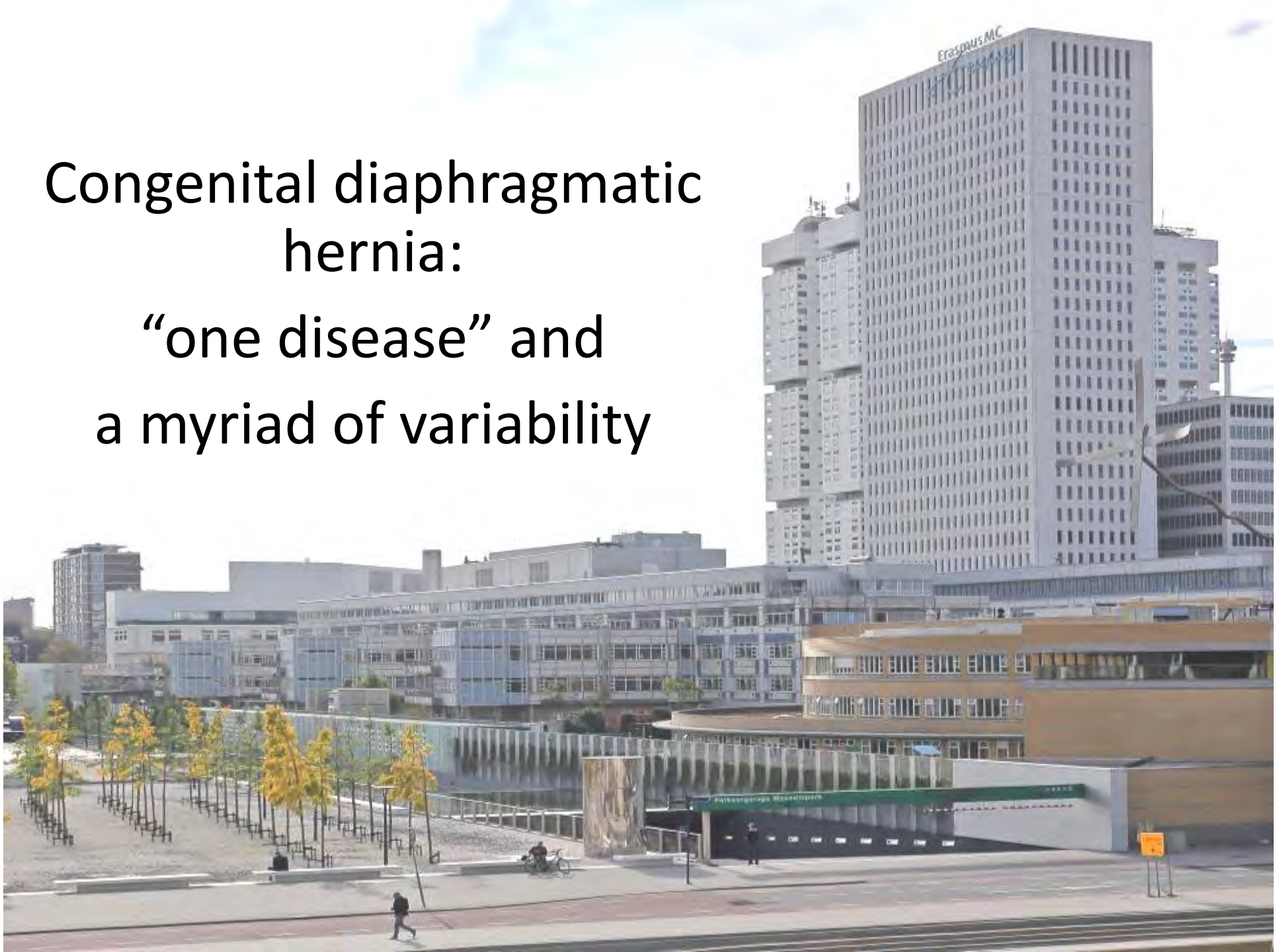
Erasmus MC – Sophia Children's Hospital
Rotterdam the Netherlands

d.tibboel@erasmusmc.nl

Congenital diaphragmatic hernia:

“one disease” and

a myriad of variability



Congenital diaphragmatic hernia:“one disease” and a myriad of variability

Variability in: (epi)genetics/ etiology

Natural history during fetal development

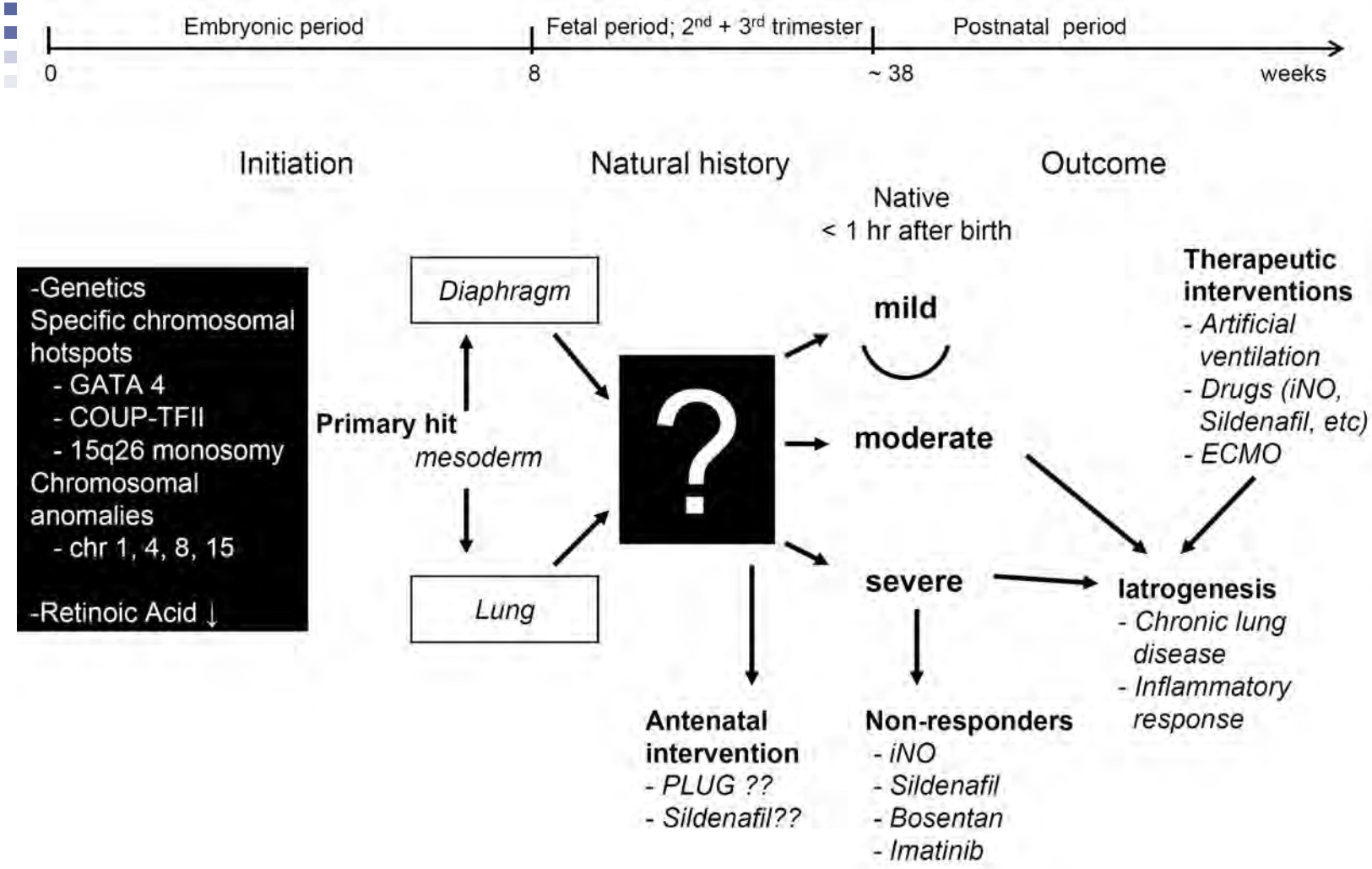
Births and the first hours

Treatment sequences in particular pharmacotherapy related

Iatrogenic insults and specific responses of the lung

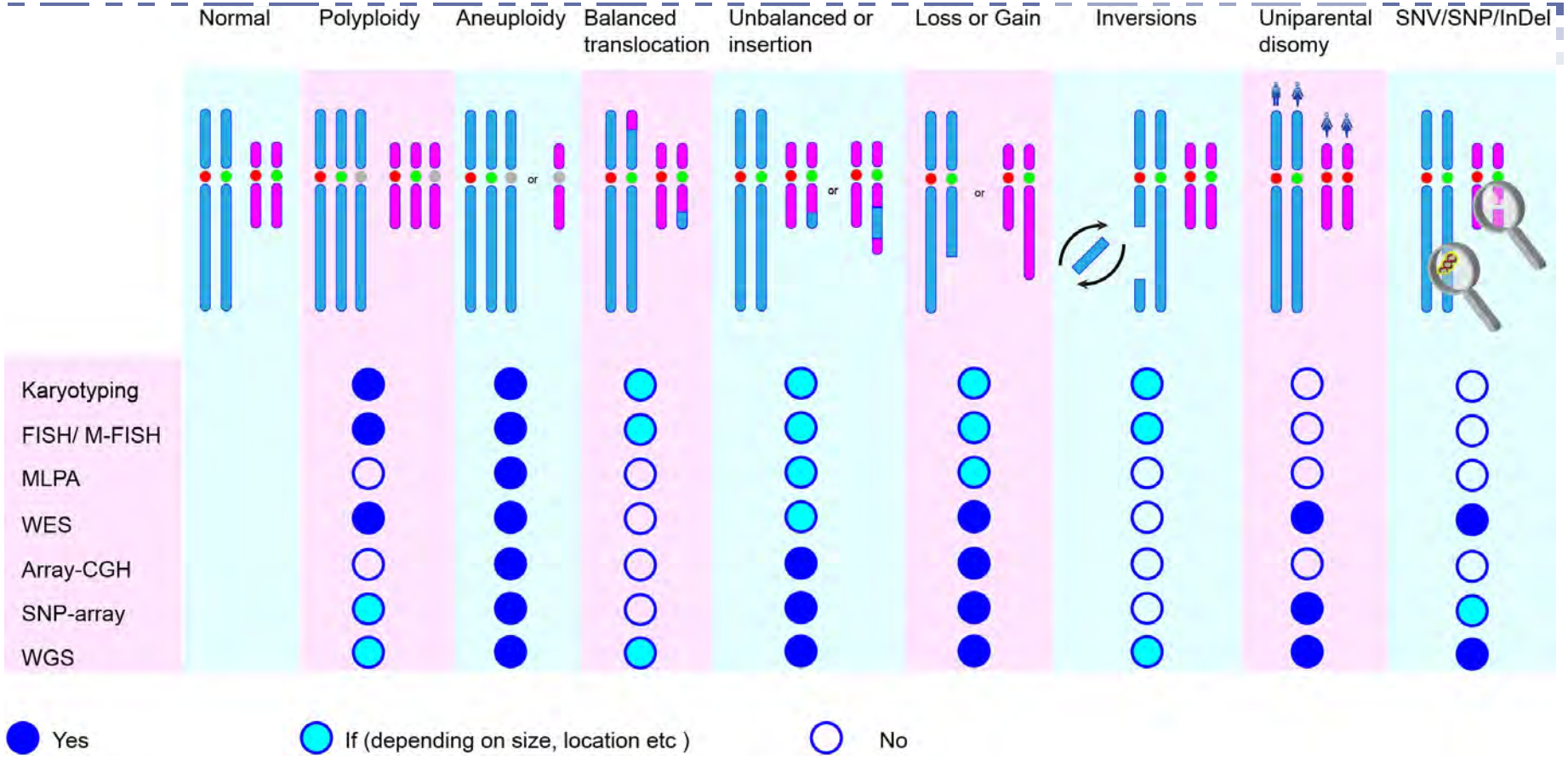
Microbiome effects

Insight in the black box of CDH



I. Sluiter, thesis 'CDH: A vascular disease'

Genetics: What do I want to detect?



Adapted from Speicher & Carter: **The new cytogenetics: blurring the boundaries with molecular biology**

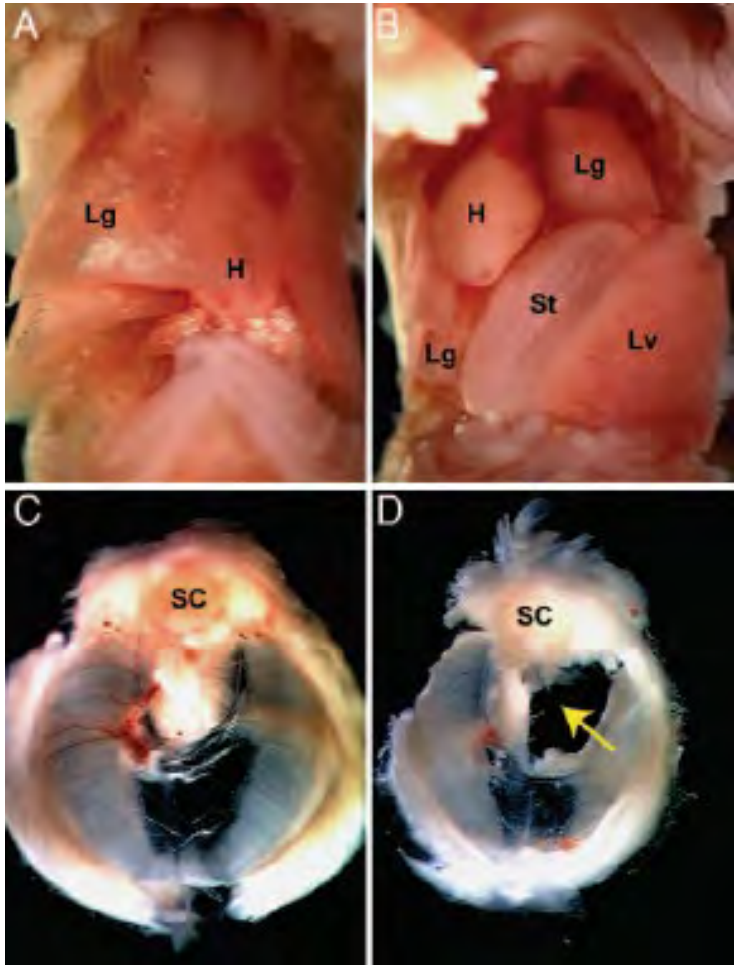
COUP-TF2 mouse model of CDH

- Tissue specific ablation

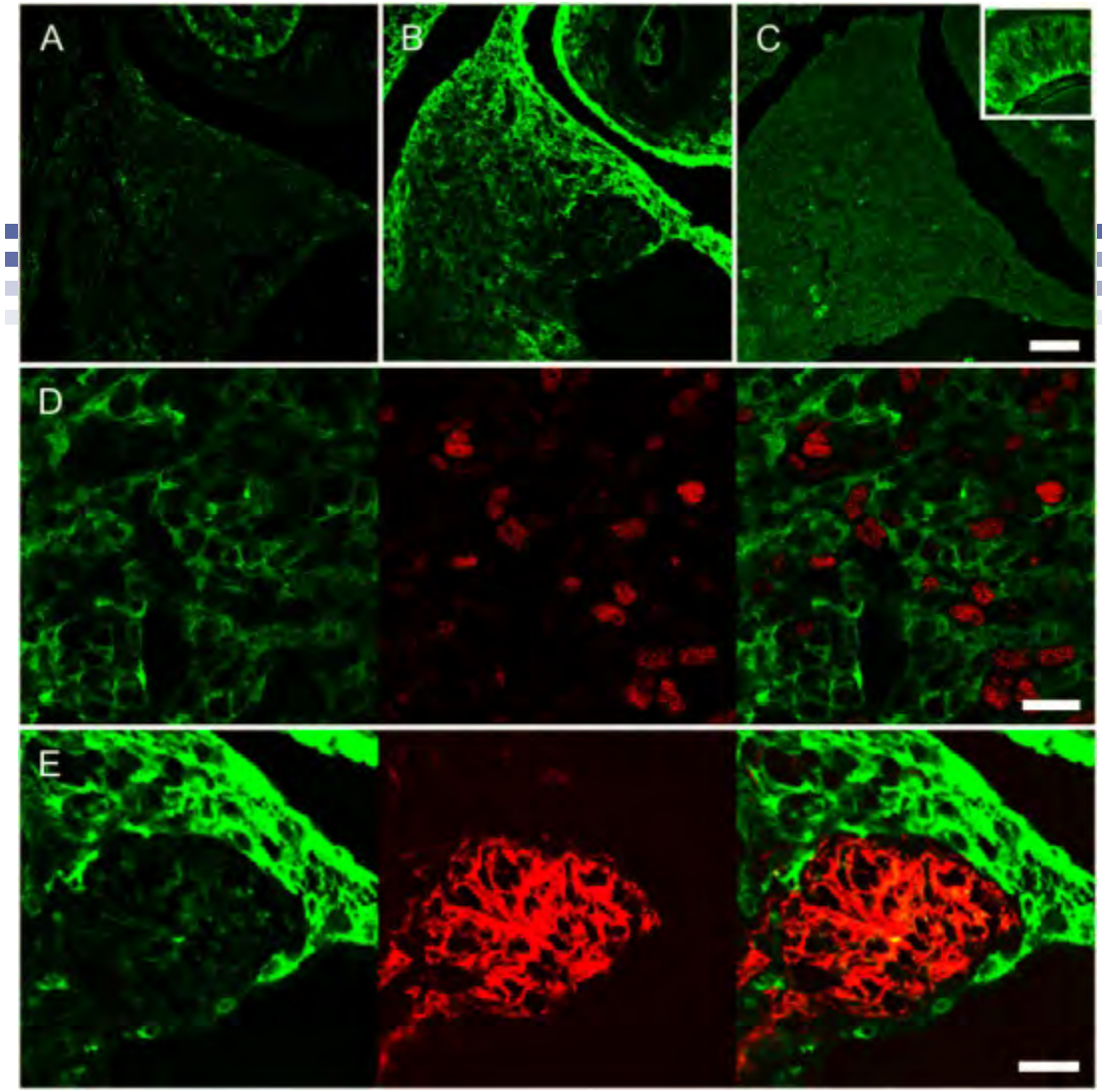
- Ablation in foregut mesoderm

  (incl. posthepatic mesenchymal plate)

  → left-sided CDH



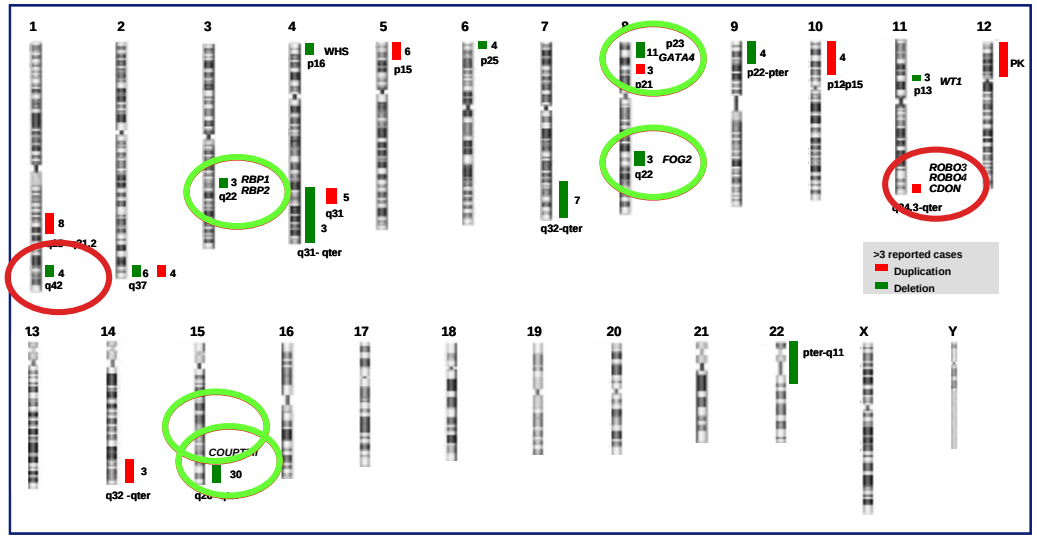
(You et al., PNAS, 2005)



Retinal dehydrogenase (Raldh2) expression in the developing diaphragm at E13.5 (A)

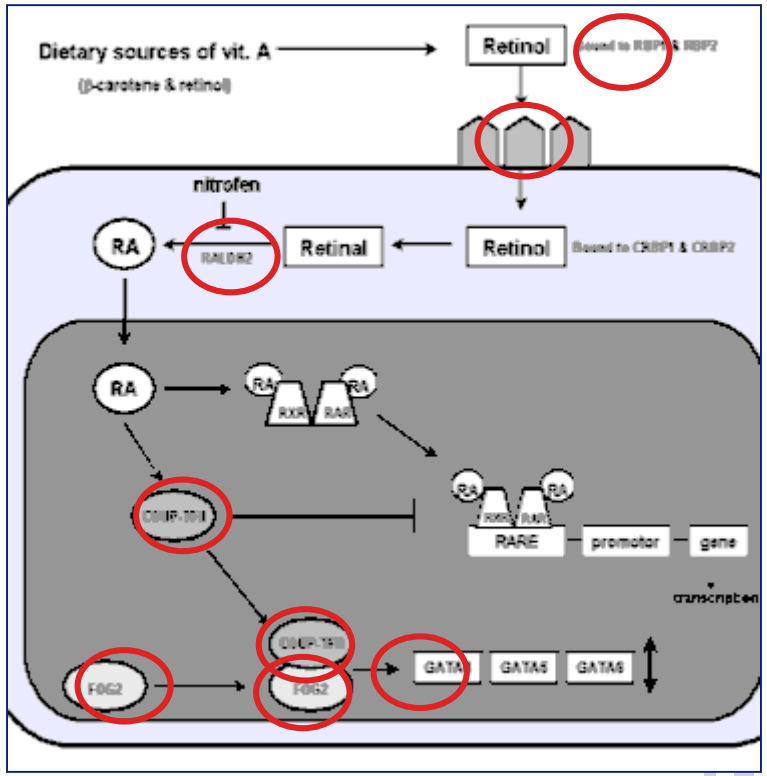
Robin D. Clugston, Wei Zhang, Susana Alvarez et al.
Am J Respir Cell Mol Biol 2010;42:276-285

Insights in molecular mechanisms



>450 chromosomal aberrations

Involved in RA pathway



Candidate genes??

Mutation analysis

COUPTF II (Tsai *etal*; KO mouse model)
-150 CDH pt for 15q gene *COUPTF* II
(total all research groups >500 pt for COUPTFII,*GATA4*, *FOG2*, *ROBO3*/4…)
(STRA6 (Donnai-Barrow) & *LRP2* (PDAC) : recessive mutation)

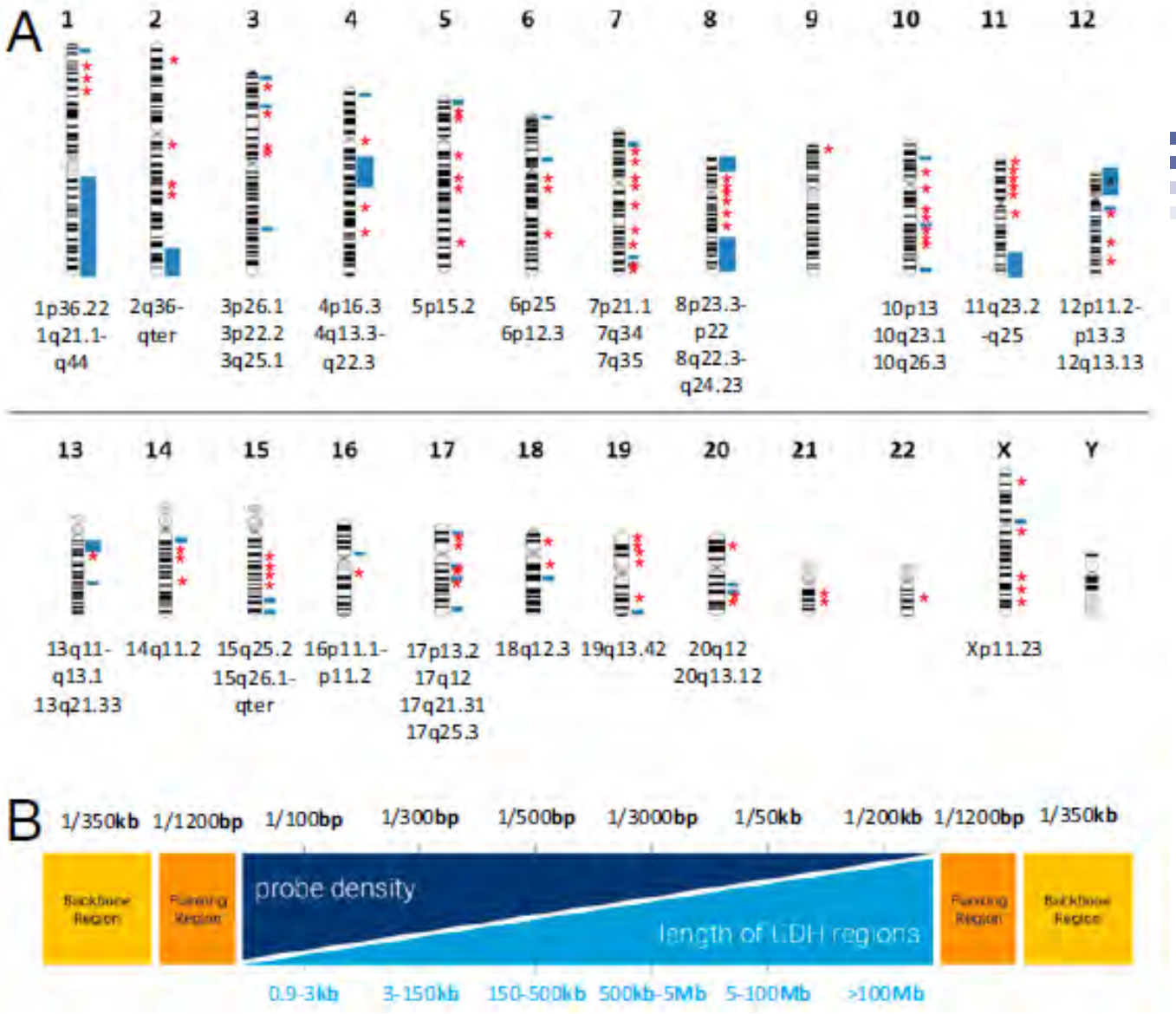
Only sporadic small (bp) changes!

Systematic analysis of copy number variation associated with congenital diaphragmatic hernia

Qihui Zhu[a,1], Frances A. High[b,c,d,1], Chengsheng Zhang[a,1], Eliza Cerveira[a], Meaghan K. Russell[b], Mauro Longoni[b,d], Maliackal P. Joy[b], Mallory Ryan[a], Adam Mil-homens[a], Lauren Bellfy[a], Caroline M. Coletti[b], Pooja Bhayani[b], Regis Hila[b], Jay M. Wilson[c,d], Patricia K. Donahoe[b,d,2,3], and Charles Lee[a,e,2,3]

Significance This study describes the results of a large-scale case control analysis of copy number variants (CNVs) in a cohort of patients with congenital diaphragmatic hernia (CDH) and a large number of healthy population-matched controls. Using a customized array comparative genomic hybridization system, we have identified six CNVs that are associated with CDH with statistical significance ($P < 0.05$). These regions validate several hypothesized CDH candidate genes and identify additional genes and pathways that contribute to the pathogenesis of CDH. The estimated frequency of pathogenic CNVs in this cohort is 13%, which underscores the critical contribution of CNVs in CDH. This study also provides a model approach that is broadly applicable to other structural birth defects and identifies candidates for future functional studies.

Proc Natl Acad Sci U S A. 2018;115(20):5247–5252.



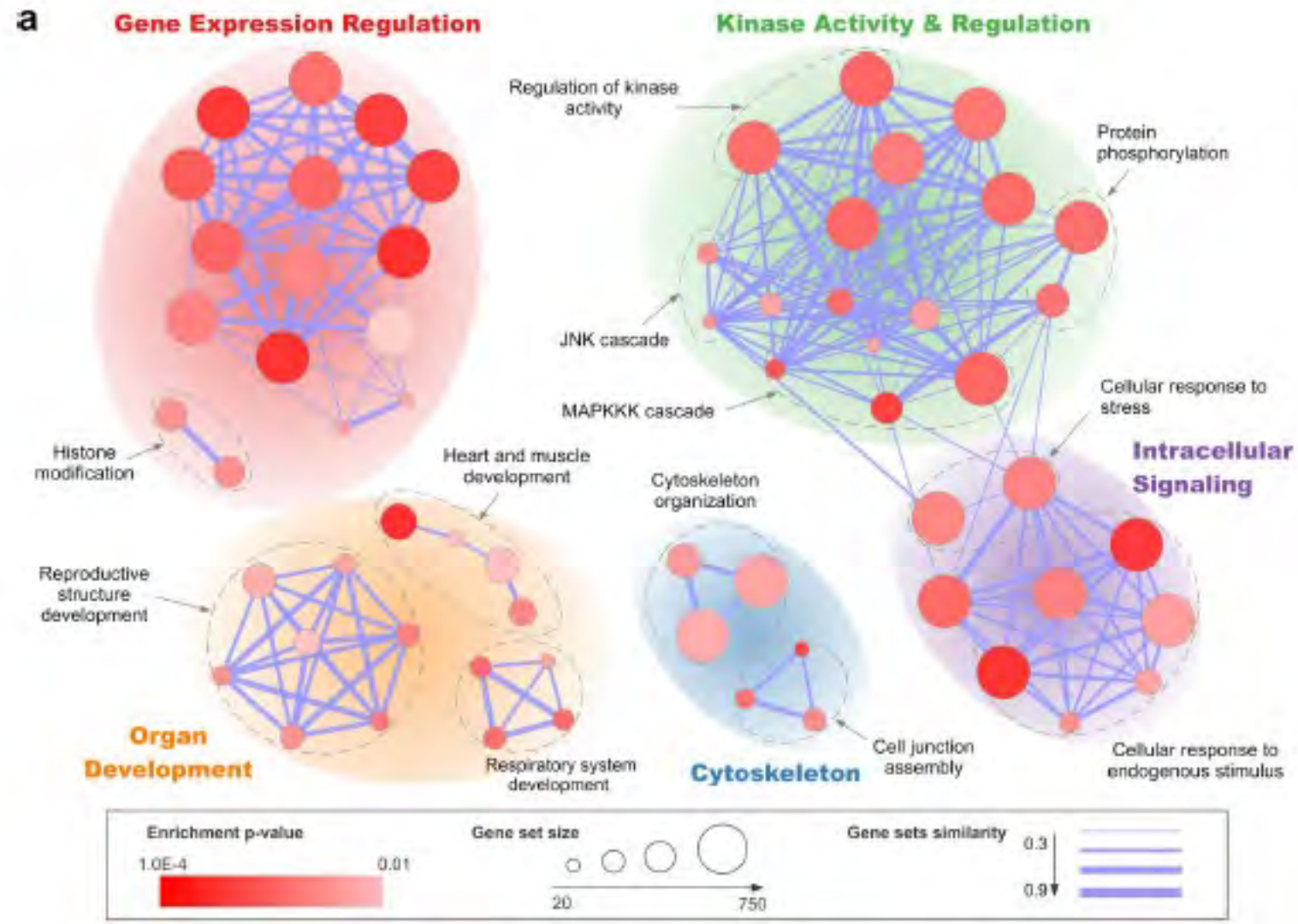
Zhu Q, High FA, Zhang C, et al. 2018

RESEARCH ARTICLE

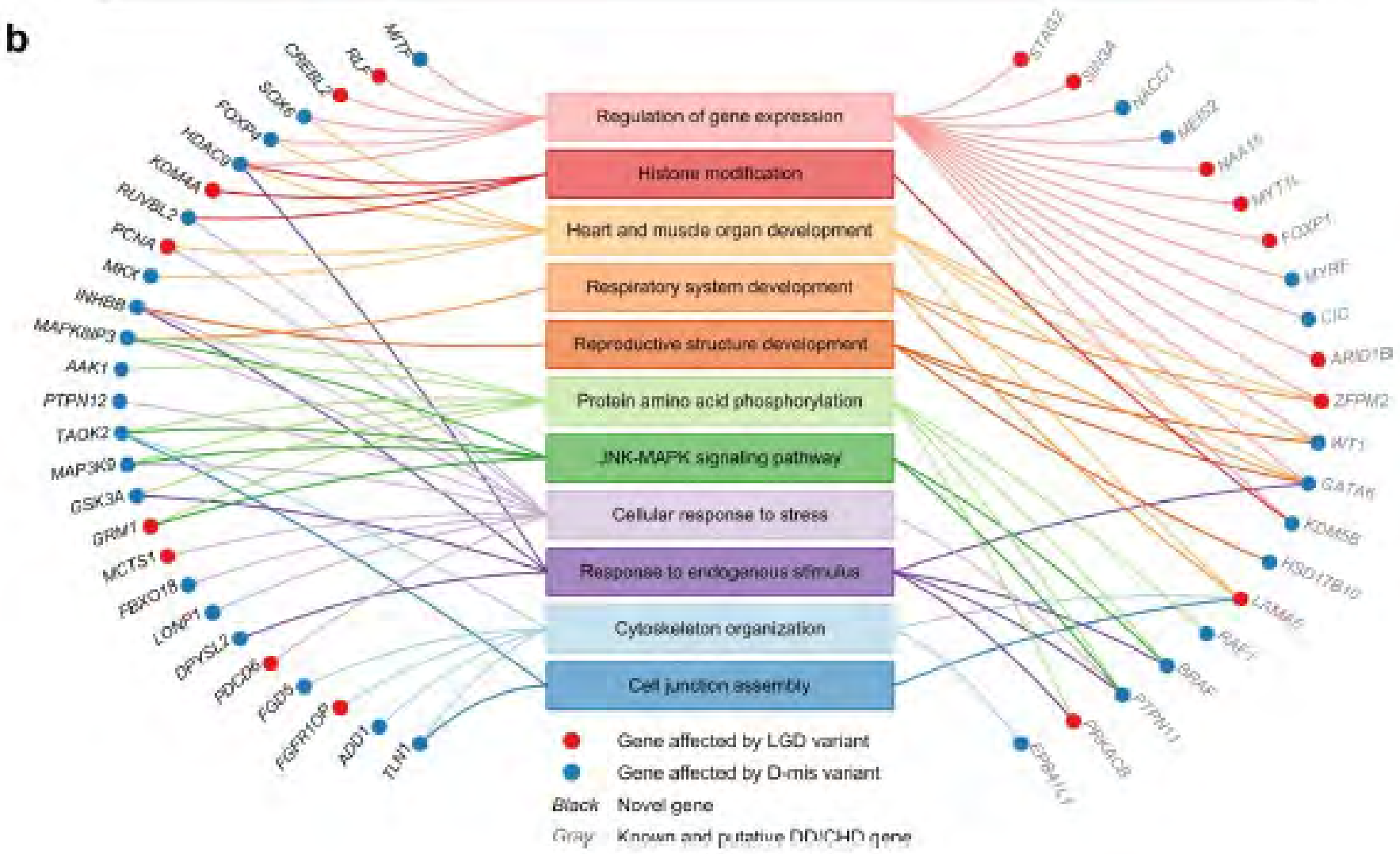
De novo variants in congenital diaphragmatic hernia identify *MYRF* as a new syndrome and reveal genetic overlaps with other developmental disorders

Hongjian Qi[1,2☯], Lan Yu[3☯], Xueya Zhou[1,3☯], Julia Wynn[3], Haoquan Zhao[1,4], Yicheng Guo[1], Na Zhu[1,3], Alexander Kitaygorodsky[1,4], Rebecca Hernan[3], Gudrun Aspelund[5], Foong-Yen Lim[6], Timothy Crombleholme[6], Robert Cusick[7], Kenneth Azarow[8], Melissa E. Danko[9], Dai Chung[9], Brad W. Warner[10], George B. Mychaliska[11], Douglas Potoka[12], Amy J. Wagner[13], Mahmoud ElFiky[14], Jay M. Wilson[15,16], Debbie Nickerson[17], Michael Bamshad[17], Frances A. High[15,16,18], Mauro Longoni[16,18], Patricia K. Donahoe[16,18], Wendy K. Chung[3,19,20]*, Yufeng Shen[1,4,21]*

PLOS genetics, 2018



Qi H, Yu L, Zhou X, Wynn J, Zhao H, Guo Y, et al. (2018)
PLoS Genet 14(12): e1007822



Qi H, Yu L, Zhou X, Wynn J, Zhao H, Guo Y, et al. (2018)
PLoS Genet 14(12): e1007822

Human Molecular Genetics, 2013, Vol. 22, No. 5 **1026–1038**
doi:10.1093/hmg/dds507
Advance Access published on December 5, 2012

Deficiency of FRAS1-related extracellular matrix 1 (FREM1) causes congenital diaphragmatic hernia in humans and mice

Tyler F. Beck[1], Danielle Veenma[3,4], Oleg A. Shchelochkov[5], Zhiyin Yu[1], Bum Jun Kim[1], Hitisha P. Zaveri[1], Yolande van Bever[4], Sunju Choi[6], Hannie Douben[4], Terry K. Bertin[1], Pragna I. Patel[6], Brendan Lee[1,7], Dick Tibboel[3], Annelies de Klein[4], David W. Stockton[8,9], Monica J. Justice[1] and Daryl A. Scott[1,2,*]

Human Molecular Genetics, 2012, Vol. 21, No. 18 **4115–4125**
doi:10.1093/hmg/dds241
Advance Access published on June 20, 2012

Mouse model reveals the role of SOX7 in the development of congenital diaphragmatic hernia associated with recurrent deletions of 8p23.1

Margaret J. Wat[1], Tyler F. Beck[1], Andrés Hernández-García[1,5], Zhiyin Yu[1], Danielle Veenma[6,7], Monica Garcia[2], Ashley M. Holder[8], Jeanette J. Wat[9], Yuqing Chen[1,3], Carrie A. Mohila[4], Kevin P. Lally[10], Mary Dickinson[2], Dick Tibboel[6], Annelies de Klein[7], Brendan Lee[1,3] and Daryl A. Scott[1,2,*]

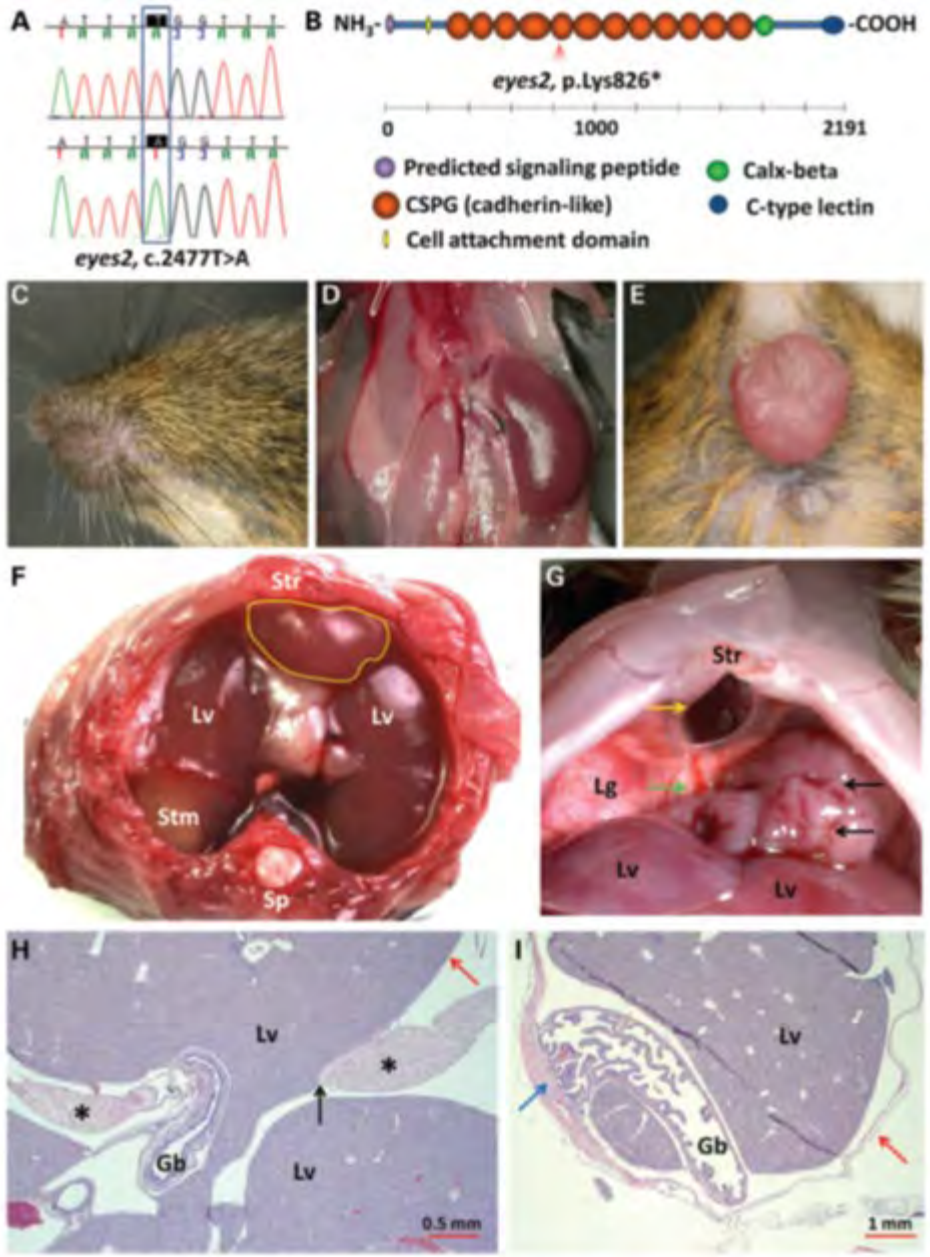


Figure 2. A homozygous truncating mutation in *Frem1* is responsible for the eye, kidney, anal, and diaphragmatic defects seen in *eyes2* mice.

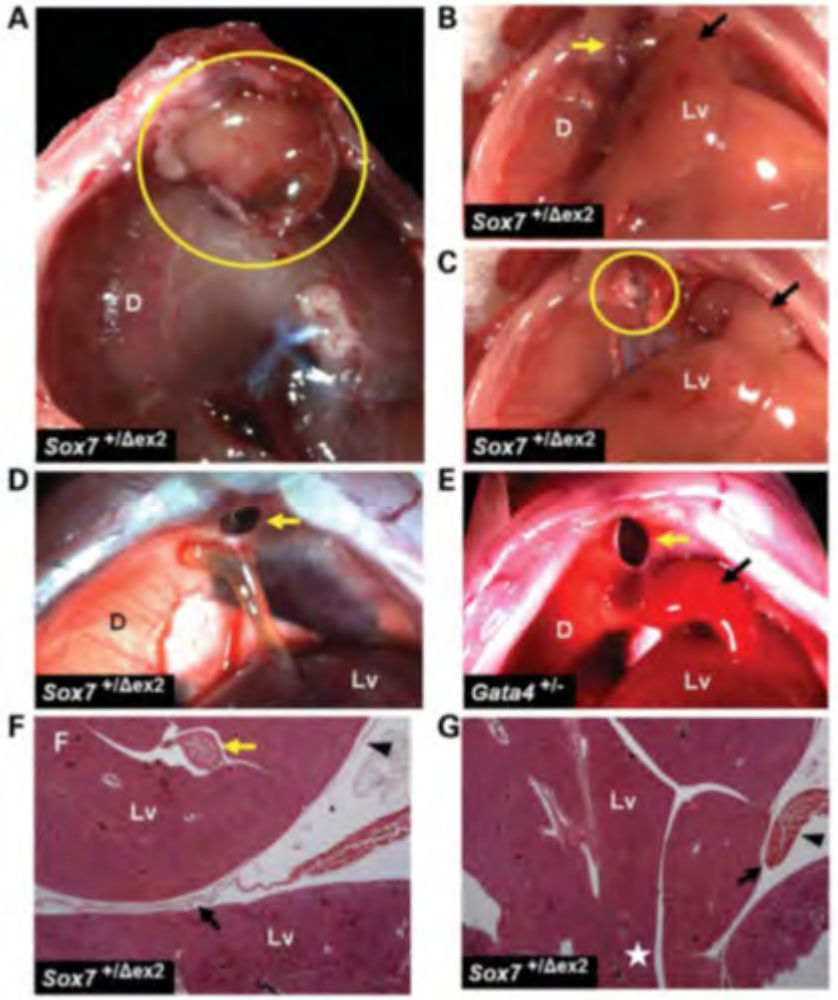
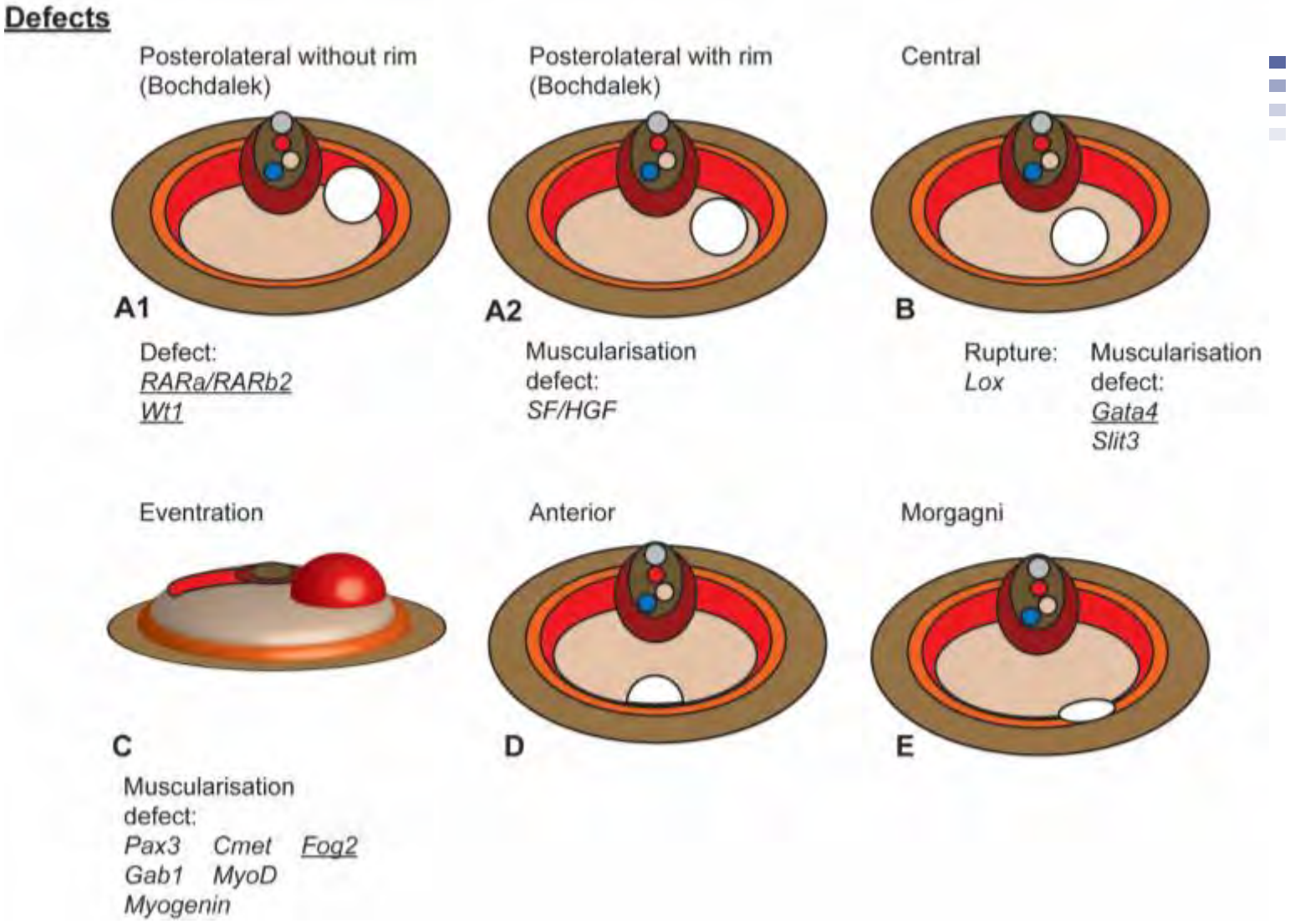


Figure 2. A portion of *Sox7*$^{+/\Delta ex2}$ mice develop retrosternal CDH that is similar to those seen in *Gata4*$^{+/-}$ mice.

Congenital Diaphragmatic Hernia



Adapted from Beurskens et al., 2009 Nutrition Reviews

REVIEW

Polygenic Causes of Congenital Diaphragmatic Hernia Produce Common Lung Pathologies

Patricia K. Donahoe,*†‡ Mauro Longoni,*† and Frances A. High*†§¶

From the Pediatric Surgical Research Laboratories and the Department of Pediatrics,§ Massachusetts General Hospital, Boston; the Department of Surgery,† Harvard Medical School, Boston; the Broad Institute of the Massachusetts Institute of Technology and Harvard,‡ Cambridge; and the Department of Surgery,¶ Boston Children's Hospital, Boston, Massachusetts*

The American Journal of PATHOLOGY

'Successful treatment of CDH is dependent on the integration of human genomic and genetic data with developmental expression profiling, mouse knockouts, and gene network and pathway modeling, which have generated a large number of candidate genes and pathways for follow-up studies.'

Am J Pathol 2016,186: 2532–2543

Table 1 Mouse Models with Both Diaphragm and Lung Abnormalities

Symbol	Name	Diaphragmatic phenotype	Lung phenotype
Atp2a1	ATPase, Ca^{++} transporting, cardiac muscle, fast twitch 1	Abnormal diaphragm muscle	Abnormal alveoli (failure to expand, hypercellularity)
Ctnnb1	Catenin (cadherin associated protein), β1	Diaphragmatic hernia (Wt1-Cre conditional knockout)	Absent lung buds (Shh-Cre conditional knockout)
Efemp2	Epidermal growth factor–containing fibulin-like extracellular matrix protein 2	Diaphragmatic hernia	Abnormal elastic fibers
Eya1	EYA transcriptional co-activator and phosphatase 1 and 2	Amuscular diaphragm (double Eya1; Eya2 knockout)	Lung hypoplasia, abnormal epithelium morphologic features
Eya2	EYA transcriptional co-activator and phosphatase 1 and 2	Amuscular diaphragm (double Eya1; Eya2 knockout)	Lung hypoplasia, abnormal epithelium morphologic features
Frem1	Fras1 related extracellular matrix protein 1	Diaphragmatic hernia	Fused pulmonary lobes
Frem2	Fras1-related extracellular matrix protein 2	Diaphragmatic hernia	Fused pulmonary lobes
Fuz	Fuzzy planar cell polarity protein	Diaphragmatic hernia	Lung hypoplasia
Gata4	GATA-binding protein 4	Diaphragmatic hernia	Abnormal saccule morphologic features, abnormal vasculature
Gli2, Gli3	GLI-Kruppel family member 2 and 3	Diaphragmatic hernia (double Gli2; Gli3 knockout)	Lung hypoplasia, absent right lung accessory lobe, thick mesenchyme
Hlx	H2.0-like homeobox	Diaphragmatic hernia	Enlarged lungs with normal structure
Igf2	Insulin-like growth factor 2	Thin diaphragm muscle (double Igf2; Myod1 knockout)	Abnormal epithelial proliferation/ differentiation (organ culture)
Kif7	Kinesin family member 7	Diaphragmatic hernia, thick diaphragm muscle	Lung hypoplasia
Lmnb1	Lamin B1	Thin diaphragm muscle, abnormal phrenic nerve	Abnormal alveoli
Lmnb2	Lamin B2	Thin diaphragm muscle, abnormal phrenic nerve (double Lmnb1; Lmnb2 knockout)	Abnormal alveoli
Lox	Lysyl oxidase	Diaphragmatic hernia, thin diaphragm muscle	Lung hypoplasia, abnormal acini, abnormal elastic fibers
Met	Met proto-oncogene	Diaphragmatic hernia, thin diaphragm muscle	Abnormal saccule morphologic features (conditional knockout in the respiratory epithelium)
Mmp2, Mmp14	Matrix metallopeptidase 2, and 14	Thin diaphragm muscle (double Mmp14; Mmp2 knockout)	Lung hypoplasia, abnormal alveoli, dilated alveolar ducts, abnormal elastic fibers
Myod1	Myogenic differentiation 1	Thin diaphragm muscle (MyoD:mdx)	Pulmonary hypoplasia (MyoD:mdx)
Myog	Myogenin	Thin diaphragm muscle	Lung hypoplasia
Msc	Musculin	Diaphragmatic hernia (double Msc; Tcf21 knockout)	Lung hypoplasia, abnormal branching, abnormal vasculature
Ndst1	*N*-deacetylase/*N*-sulfotransferase (heparan glucosaminyl) 1	Diaphragmatic hernia, thin diaphragm muscle (conditional knockout)	Lung hypoplasia, thick interalveolar septa
Pbx1	Pre–B-cell leukemia homeobox 1	Diaphragmatic hernia	Lung hypoplasia
Pdgfra	Platelet-derived growth factor receptor, α-polypeptide	Diaphragmatic hernia	Lung hypoplasia, abnormal alveoli, increased cell proliferation
Rara, Rarb	Retinoic acid receptor, α and β	Diaphragmatic hernia (double Rara; Rarb knockout)	Lung hypoplasia, abnormal alveoli (double Rara; Rarb knockout)
Robo1, Robo 2	Roundabout guidance receptor 1	Diaphragmatic hernia (double Robo1; Robo2 knockout)	Abnormal alveoli, thick septa
Six1	Sine oculis homeobox, *Drosophila*, homolog of, 1	Amuscular diaphragm (double Six1; Six4 knockout)	Lung hypoplasia
Tcf21	Transcription factor 21	Diaphragmatic hernia (double Msc; Tcf21 knockout)	Lung hypoplasia, abnormal branching, abnormal vasculature
Wdr35	WD repeat domain 35	Diaphragmatic hernia	Pulmonary hypoplasia
Wt1	Wilms tumor 1 homolog	Diaphragmatic hernia	Lung hypoplasia
Zfpm2	Zinc finger protein, multitype 2	Abnormal diaphragm morphologic features	Lung hypoplasia, absent right lung accessory lobe

The Mouse Genome Database Group 2015.[33]

Donahoe PK, Longoni M, High FA.
Am J Pathol 2016,186: 2532–2543

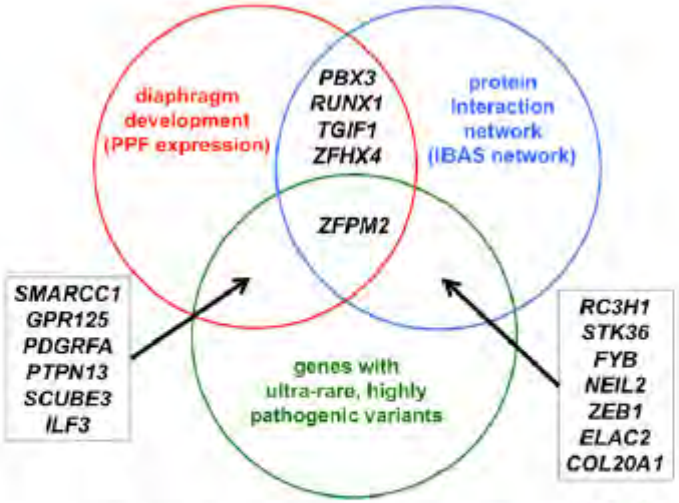
Molecular pathogenesis of congenital diaphragmatic hernia revealed by exome sequencing, developmental data, and bioinformatics

Mauro Longoni[a,b,1], Frances A. High[a,c,1], Meaghan K. Russell[a,b,1], Alireza Kashani[a,d,1], Adam A. Tracy[a], Caroline M. Coletti[a], Regis Hila[a], Ahmed Shamia[a], Julie Wells[e], Kate G. Ackerman[f], Jay M. Wilson[g], Carol J. Bult[e], Charles Lee[h], Kasper Lage[a,b,d], Barbara R. Pober[a,g,i], and Patricia K. Donahoe[a,b,d,2]

Significance Congenital diaphragmatic hernia (CDH) is a common birth defect associated with high morbidity and mortality. Focusing on the coding sequence of 51 genes, discovered in human studies and in mouse models, we studied 275 CDH patients and identified multiple variants in CDH-causing genes. Information on gene expression in embryonic mouse diaphragms and protein interactions allowed us to prioritize additional compelling CDHassociated genes. We believe that an improved understanding of the genetics of CDH will be important to design new therapeutic strategies for patients with diaphragmatic defects

Proc Natl Acad Sci U S A. 2014;111(34):12450–12455

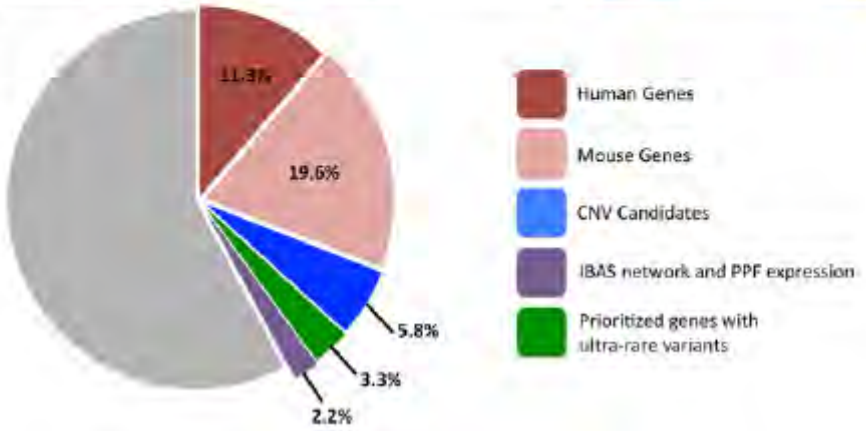
A



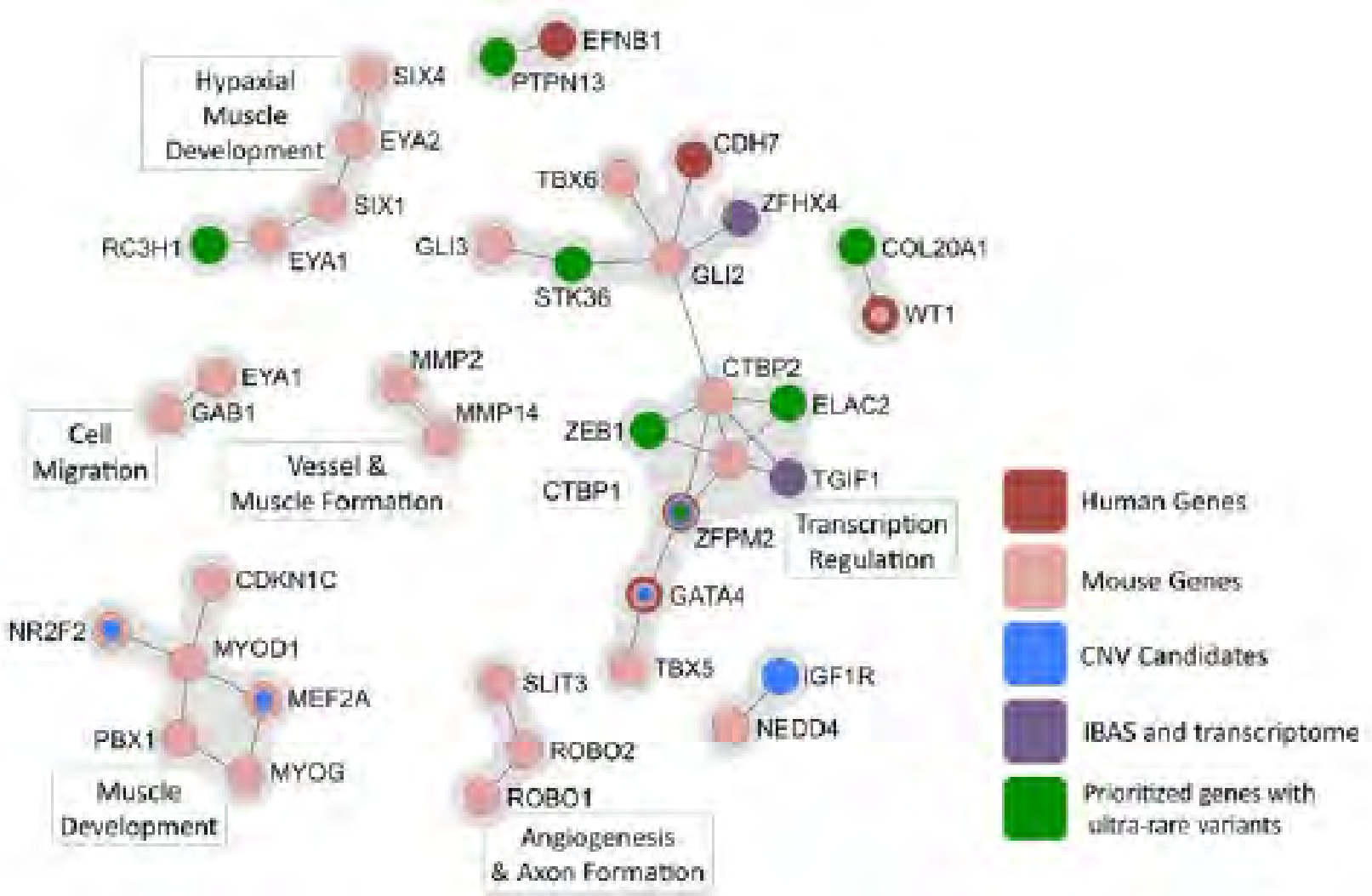
B

Chr	Position	Ref	Var	Protein Variant	Gene	Cases	Ph.	IBAS network	PPF expr.	ns	fs	sp
1	173910520	T	-	n/a	*RC3H1*	1	C					
2	219563908	C	G	p.S1193*	*STK36*	1	C					
3	47632201	G	-	p.P1057fs*5	*SMARCC1*	1	I					
4	22444439	G	A	p.Q252*	*GPR125*	1	C					
4	55151624	C	T	p.R804*	*PDGFRA*	1	I					
4	87614764	G	T	p.E191*	*PTPN13*	1	C					
5	39202090	-	C	p.P335fs*43	*FYB*	1	I					
6	35211445	GAGA	-	p.R663fs*37	*SCUBE3*	1	I					
8	11628978	A	-	p.R8fs*51	*NEIL2*	1	I					
8	106431503	G	T	p.E58*	*ZFPM2*	1	I					
8	106815496	C	-	p.N1062fs*23	*ZFPM2*	1	I					
10	31813042	G	A	n/a	*ZEB1*	1	I					
17	12901805	C	A	p.E442*	*ELAC2*	1	C					
19	10794414	-	C	p.G656fs*37	*ILF3*	1	C					
20	61947959	GG	-	p.G861fs*28	*COL20A1*	1	U					
20	61951722	T	C	n/a	*COL20A1*	1	I					

C



Longoni M et al. 2014



Longoni M et al. 2014

MicroRNA-200b regulates distal airway development by maintaining epithelial integrity

Naghmeh Khoshgoo[1,2,3], Robin Visser[1,2], Landon Falk[1,2], Chelsea A. Day[1,2], Dustin Ameis[1,2], Barbara M. Iwasiow[1,2], Fuqin Zhu[1,2], Arzu Öztürk[4,5], Sujata Basu[1,3], Molly Pind[4,5], Agnes Fresnosa[4,5], Mike Jackson[6], Vinaya Kumar Siragam[1,2], Gerald Stelmack[1,3], Geoffrey G. Hicks[4,5], Andrew J. Halayko[1,3] & Richard Keijzer[1,2,3]

MicroRNAs (miRNA) are small, non-coding RNAs that regulate gene expression through mRNA stability and translation[8–10]. They are essential for development and homeostasis of organs[11–14]. More than 1800 microRNAs have been identified in human[15]. Research focusing on the role of microRNAs in lung development and disease is limited. We recently discovered that miR-200b is elevated in abnormal lungs of human CDH babies. In the same study, we found that higher miR-200b expression in the fetal tracheal fluid of CDH fetus is associated with a better response to fetoscopic endoluminal tracheal occlusion (FETO, a prenatal therapy to promote lung growth)

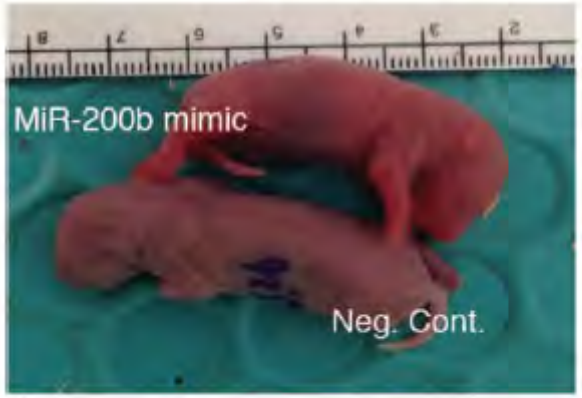
Scientific reports, 2017

Prenatal microRNA miR-200b Therapy Improves Nitrofen-induced Pulmonary Hypoplasia Associated With Congenital Diaphragmatic Hernia

Naghmeh Khoshgoo, MSc, Ramin Kholdebarin, MD, MSc,* Patricia Pereira-Terra, PhD,*† Thomas H. Mahood, MSc,* Landon Falk, BSc,* Chelsea A. Day, BSc,* Barbara M. Iwasiow, MSc,* Fuqin Zhu, BSc,* Drew Mulhall, BSc,* Carly Fraser, BSc,* Jorge Correia-Pinto, MD, PhD,†‡ and Richard Keijzer, MD, PhD, MSc, FACS**

‘**Conclusions**: Our data indicate that miR-200b improves PH and decreases the incidence of CDH. Future studies will further exploit this newly discovered prenatal therapy for lung hypoplasia and CDH.’

Annals of Surgery. 2019, 269(5):979–987,



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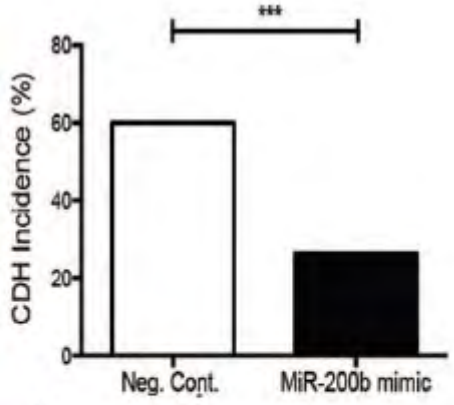

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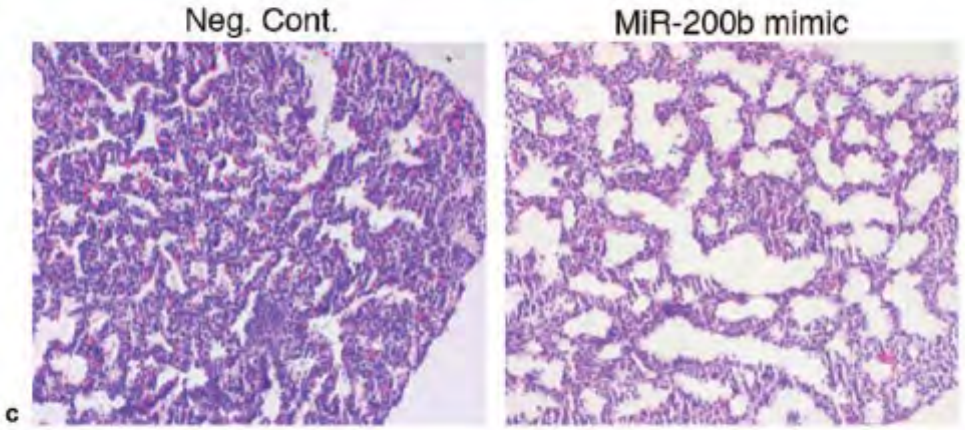

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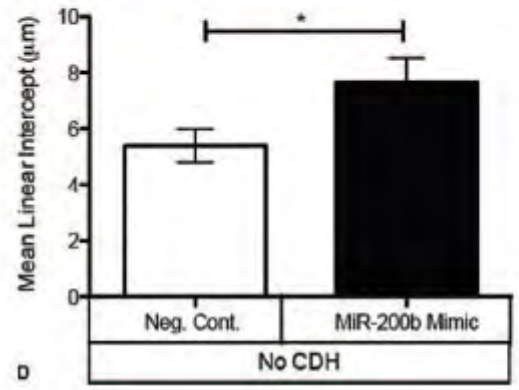

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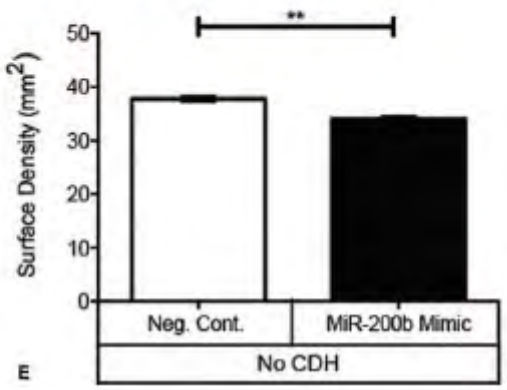


E

Koshgoo N, et al. 2019

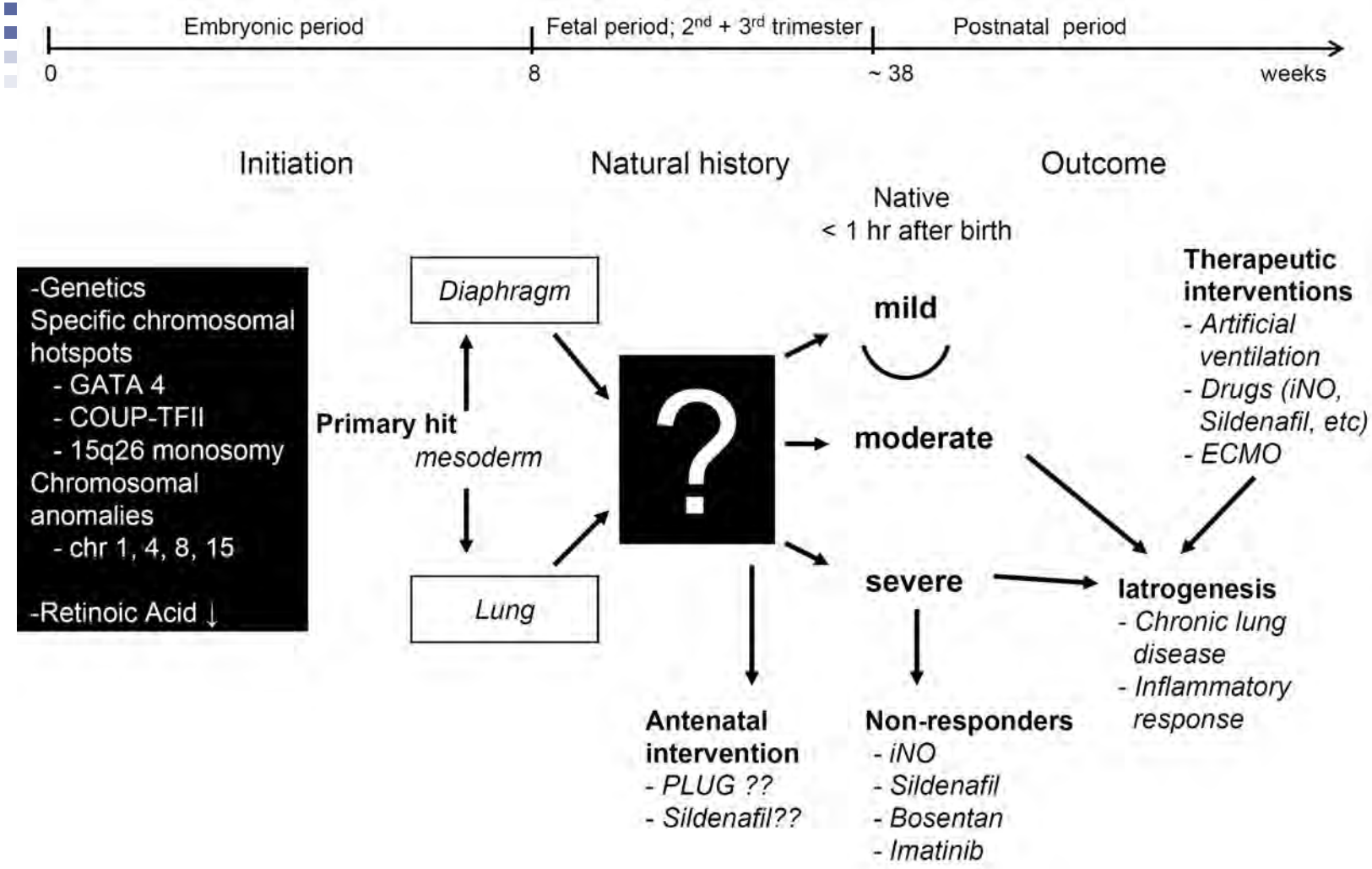
Unique Tracheal Fluid MicroRNA Signature Predicts Response to FETO in Patients With Congenital Diaphragmatic Hernia

Patrícia Pereira-Terra, MSc,† Jan A. Deprest, MD, PhD,‡ Ramin Kholdebarin, MD, MSc,* Naghmeh Khoshgoo, MS,* Philip DeKoninck, MD, PhD,‡ Anne A. Boerema-De Munck,§ Jinxia Wang,¶ Fuqin Zhu,* Robbert J. Rottier, PhD,§ Barbara M. Iwasiow, MSc,* Jorge Correia-Pinto, MD, PhD,† Dick Tibboel, MD, PhD,§ Martin Post, DVM, PhD,¶ and Richard Keijzer, PhD**

CONCLUSIONS: Human fetal hypoplastic CDH lungs have a specific miR-200/miR-10a signature. Survival after FETO is associated with increased miR-200 family expression. miR-200b overexpression in CDH lungs results in decreased TGF-β/SMAD signaling.

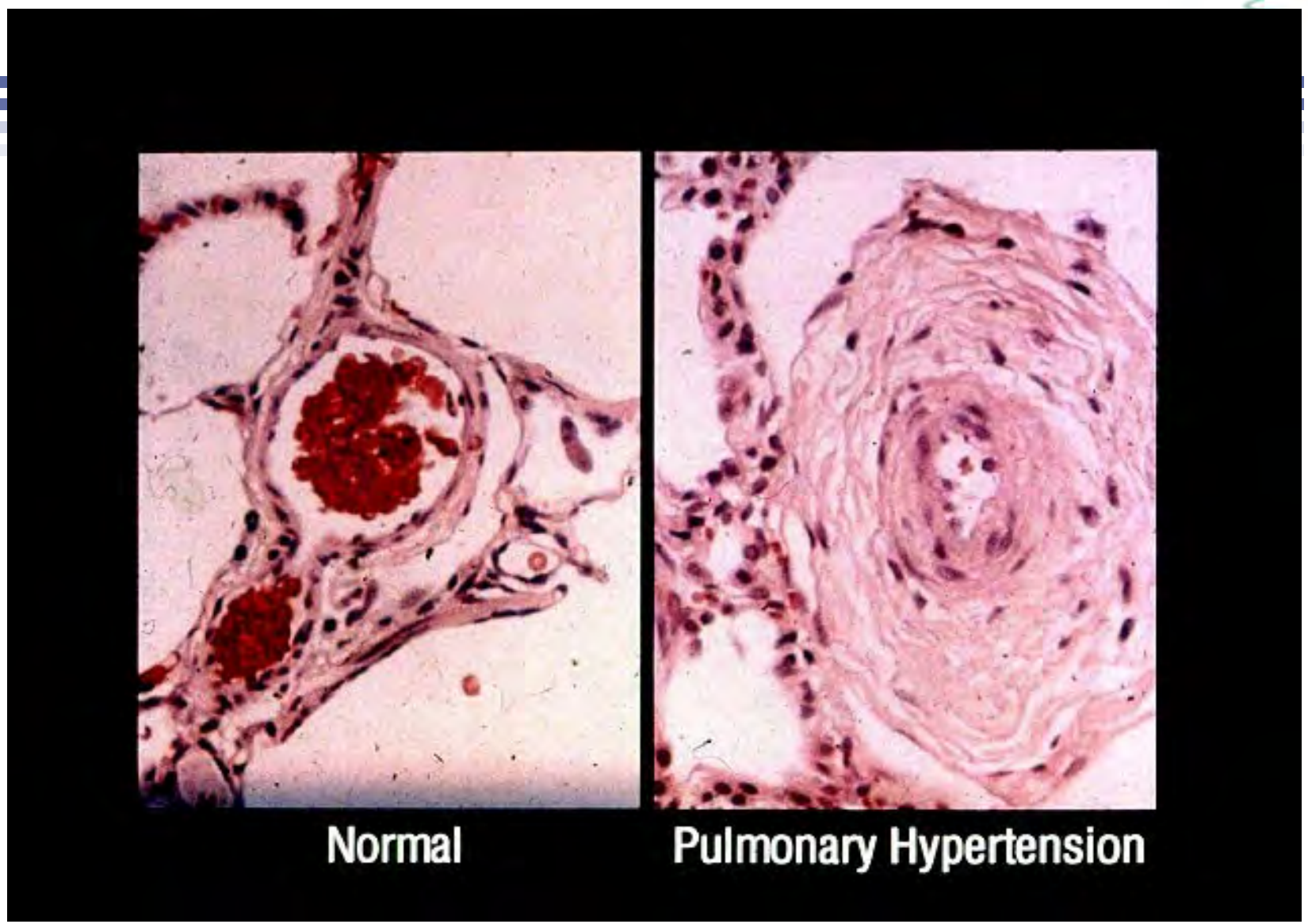
Annals of Surgery. 2015, 262(6):1130–1140,

Insight in the black box of CDH

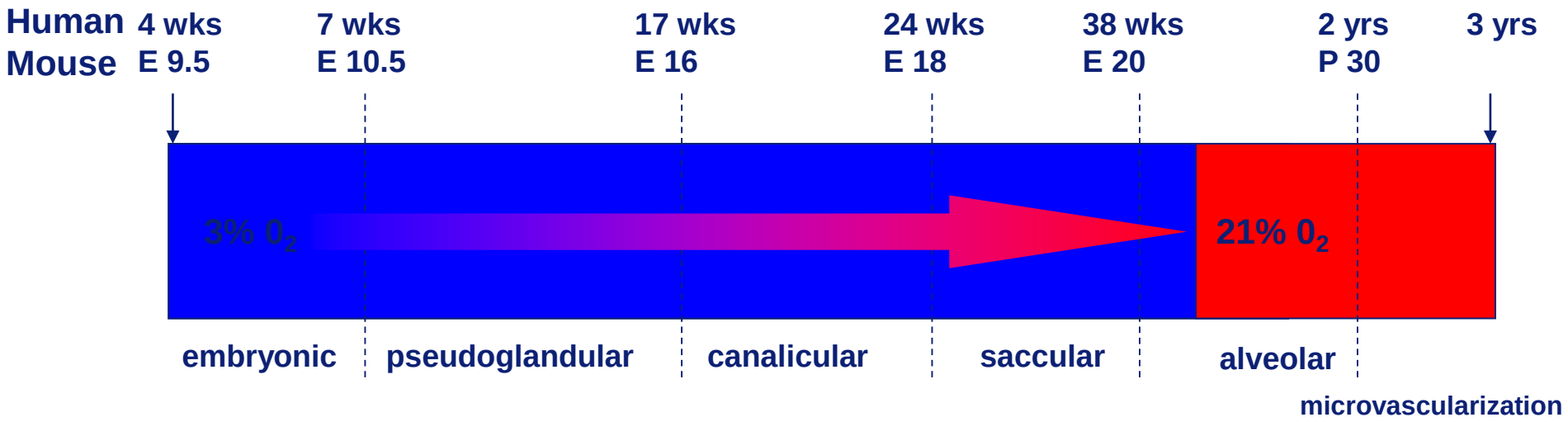


I. Sluiter, thesis 'CDH: A vascular disease'

Characteristic morphological findings

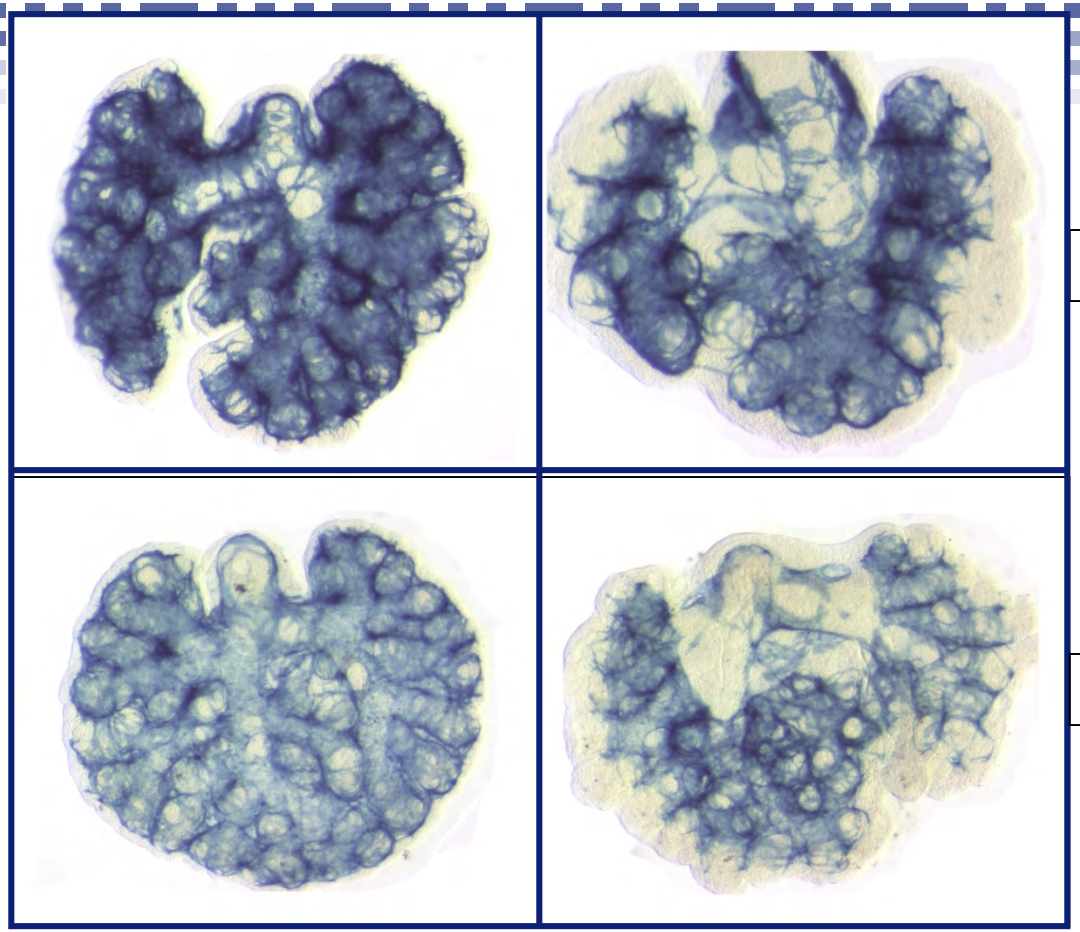


Oxygen and lung development



The master switch of life at birth?

Oxygen and lung development



48 hrs

72 hrs

3% O_2

21% O_2

M van Tuyl et al, Am J Physiol Lung Cell Mol 2005.

Neonatology
formerly Biology of the Neonate

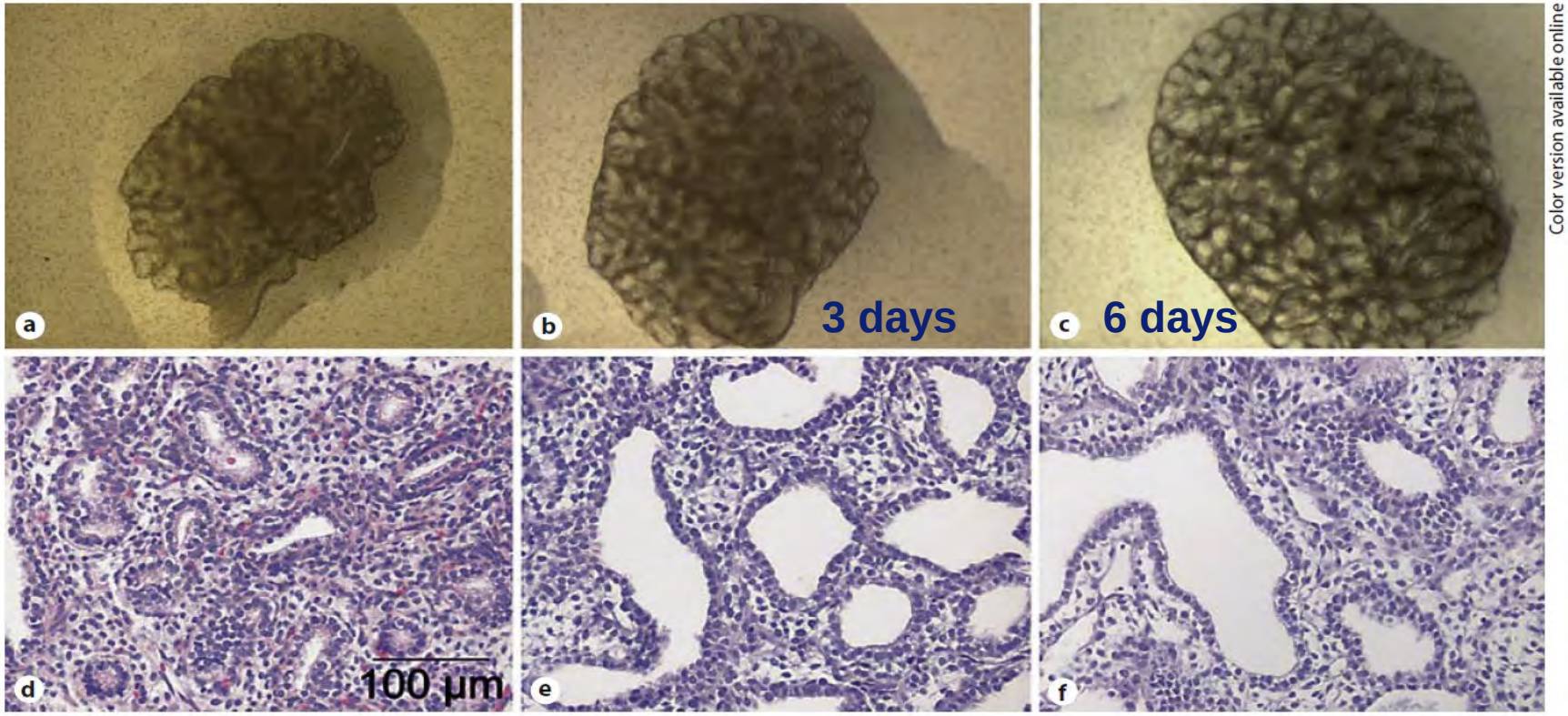
Neonatology 2010;97:346–354
DOI: 10.1159/000261018

Received: March 10, 2009
Accepted after revision: June 28, 2009
Published online: November 25, 2009

Erasmus MC

Effect of Oxygen on the Expression of Hypoxia-Inducible Factors in Human Fetal Lung Explants

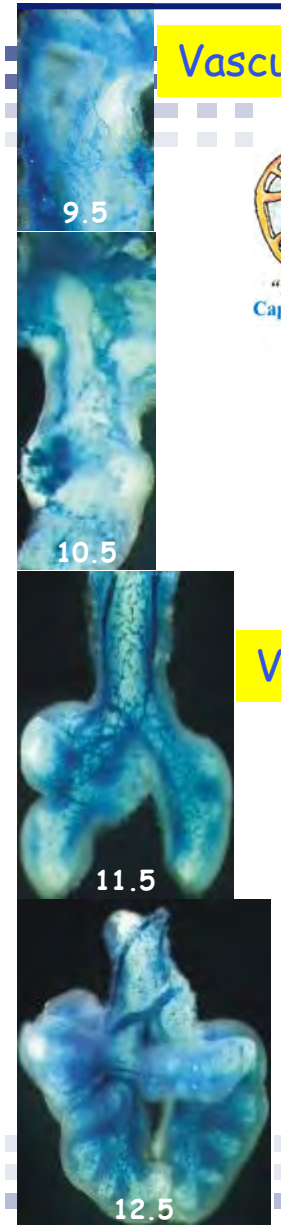
Prapapan Rajatapiti[a, d] Jessica D. de Rooij[a, b] Leonardus W.J.E. Beurskens[a, b]
Richard Keijzer[a] Dick Tibboel[a] Robbert J. Rottier[a, c] Ronald R. de Krijger[b]



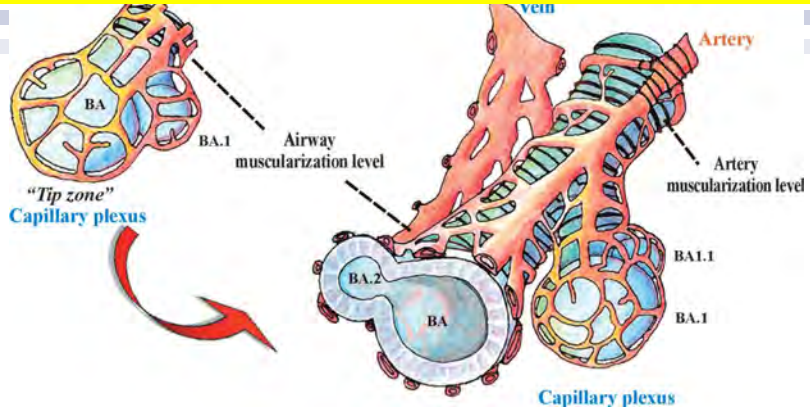
Color version available online

Representative images showing the morphology of human fetal lung explants (gestational age 16 weeks)

Lung Vascular Development

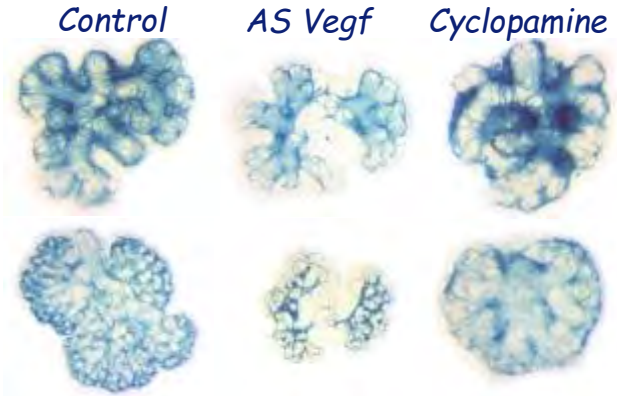


Vascular expansion through distal angiogenesis



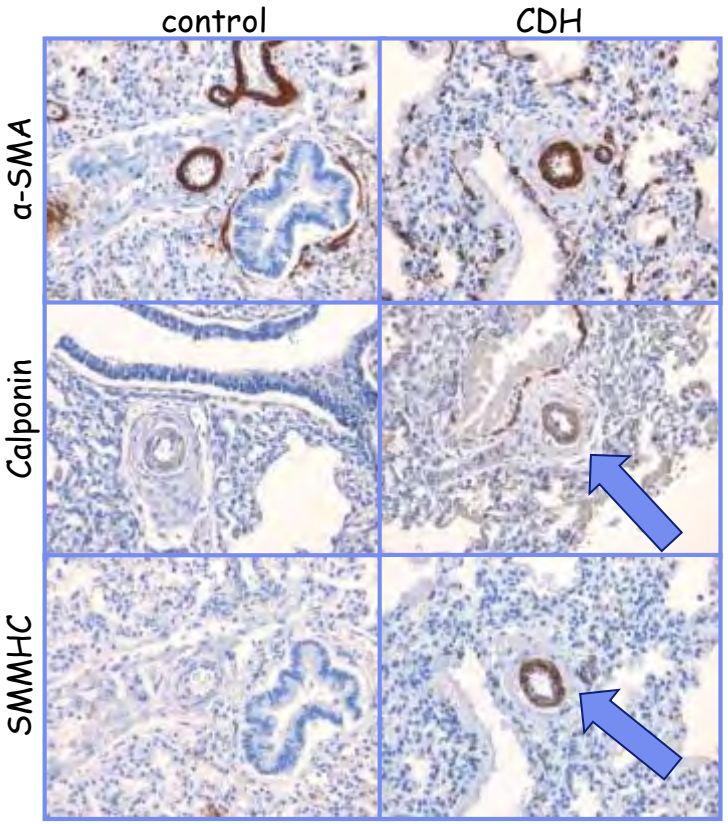
Parera *et al*, Am J Physiol L141-149, 2005

Vascular growth guides epithelial branching



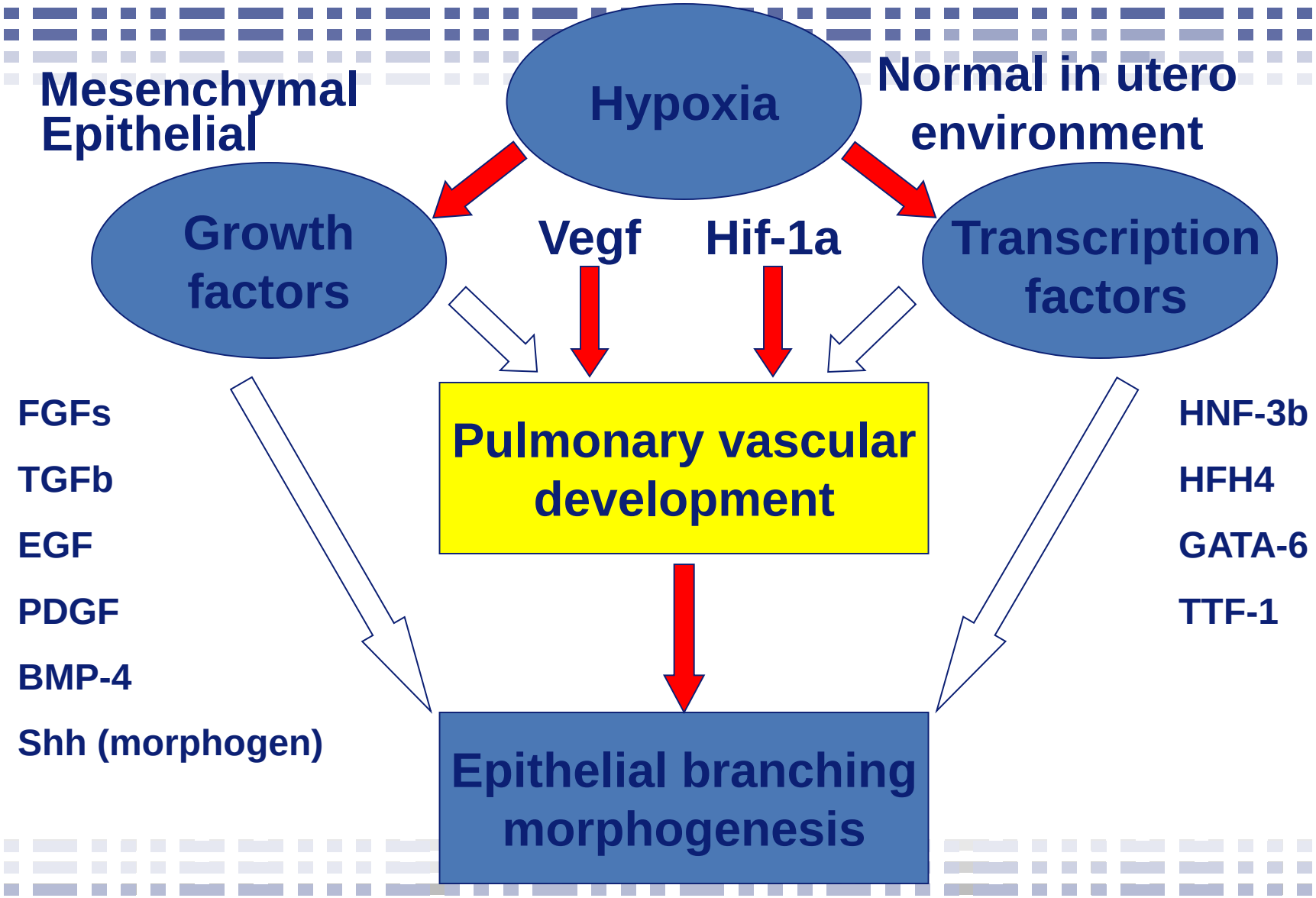
Van Tuyl et al, Am J Physiol 288, L167-L178, 2005

VSMCs are different in CDH



Sluiter et al., Exp Mol Pathol 94, 195-202, 2012

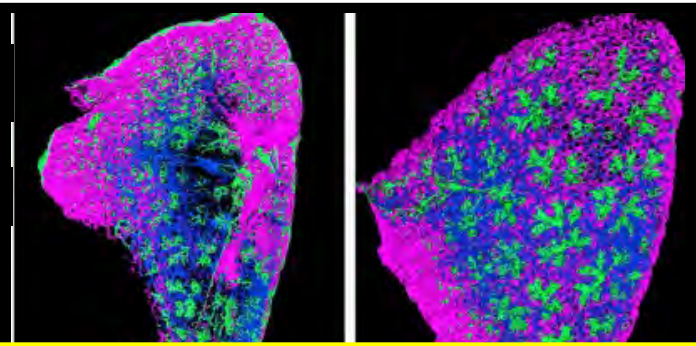
Working model



Whole mount analysis of pulmonary vasculature

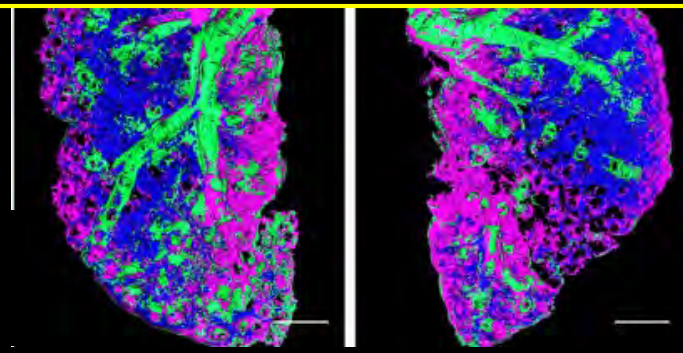
Lungs isolated at E15

Control



Capillaries in lungs of CDH pups appear less developed

CDH



NG2: pericytes
ACTA: smooth muscle cells
CD31: endothelial cells

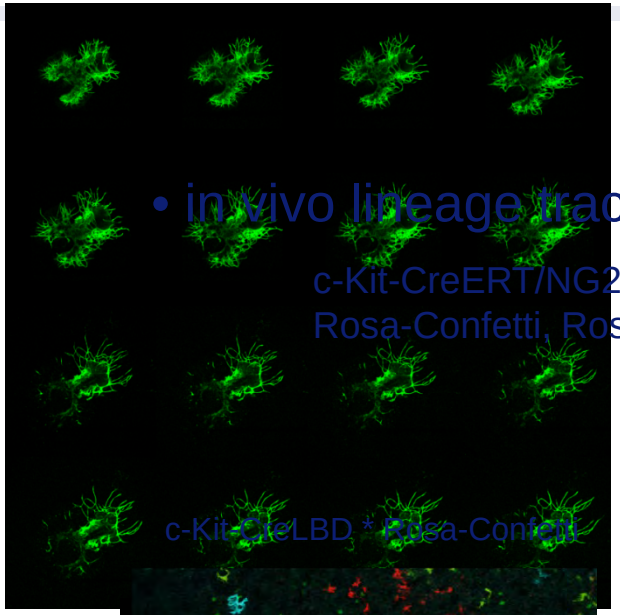
CD31: endothelial cells
NG2: pericytes
ACTA: smooth muscle cells

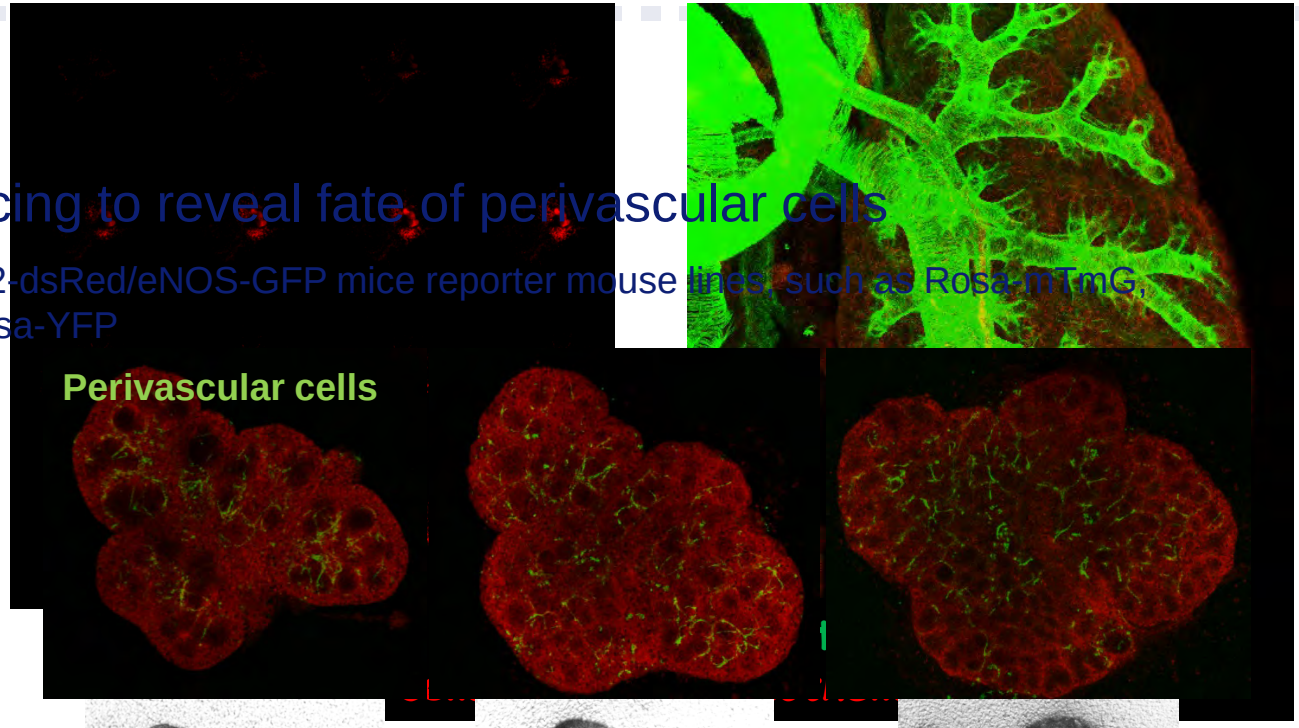
Origin pulmonary perivascular cells?

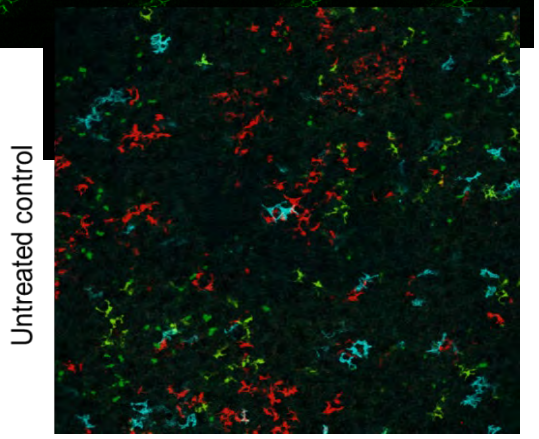
Lineage tracing of pericytes:

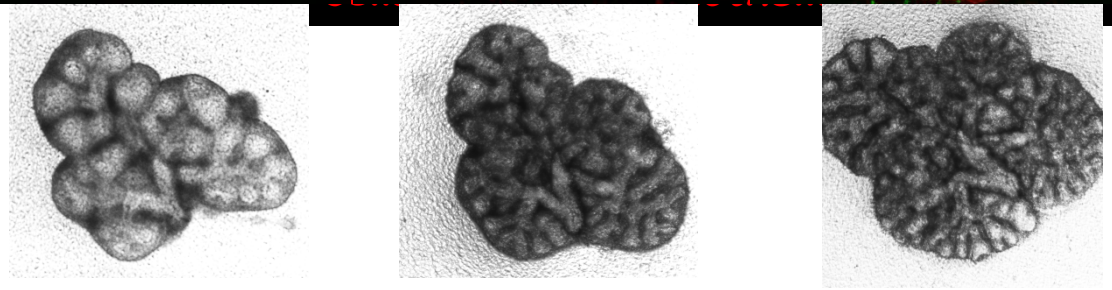
- ex vivo lung explants, whole mount immuno staining, …
- in vivo lineage tracing to reveal fate of perivascular cells

c-Kit-CreERT/NG2-dsRed/eNOS-GFP mice reporter mouse lines, such as Rosa-mTmG, Rosa-Confetti, Rosa-YFP





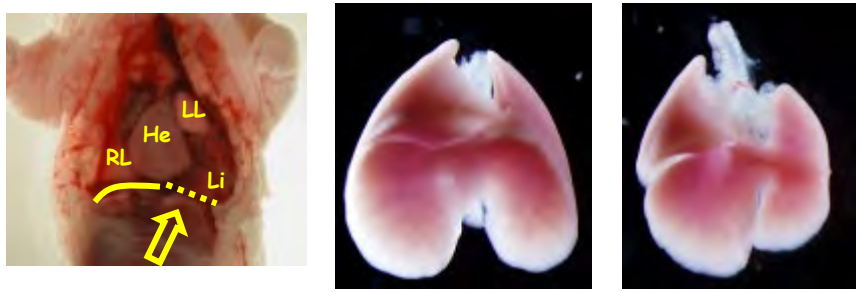




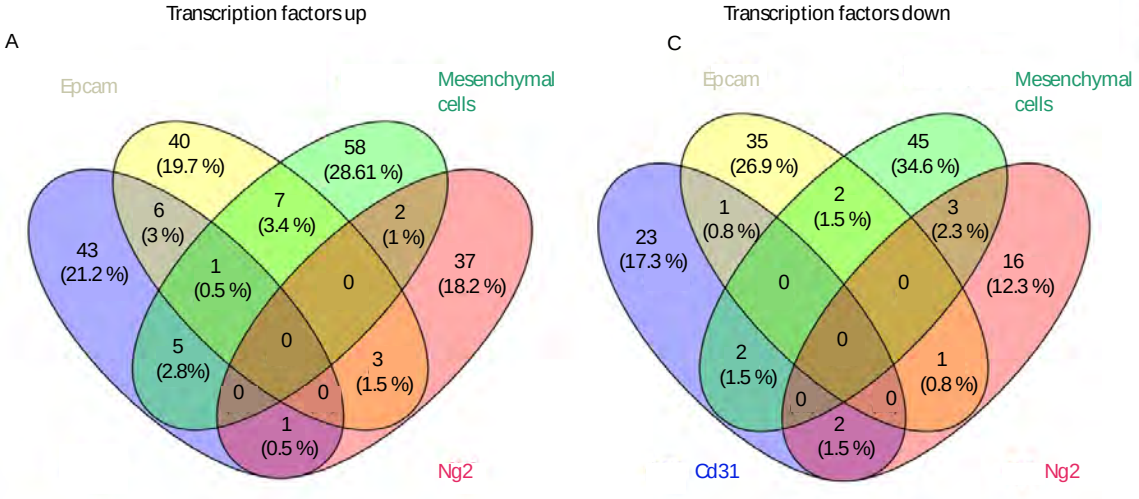
24 Hours 48 Hours 72 Hours

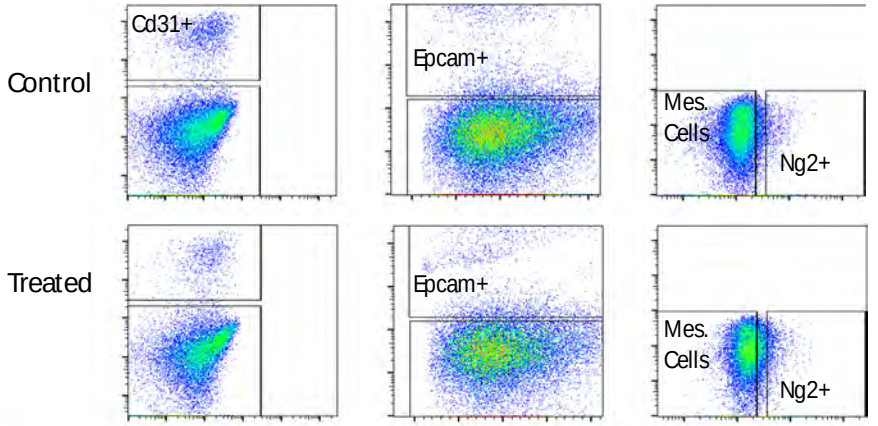
Origin pulmonary perivascular cells

Model of pulmonary vascular disease:



Mouse CDH model (SSWO project 678)

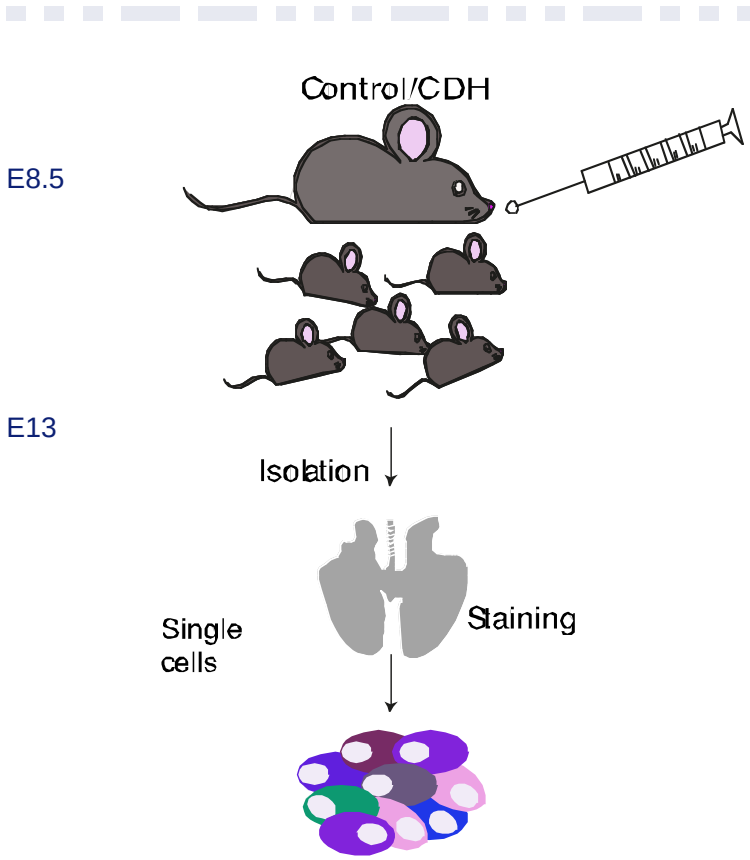


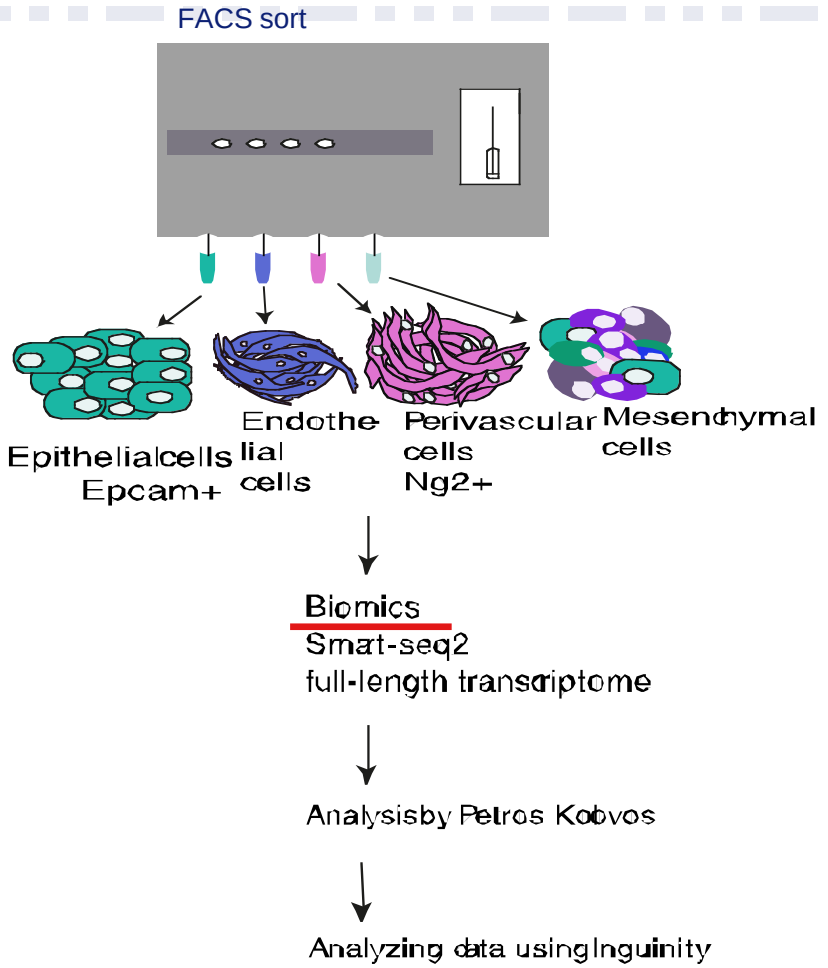


	Cd31+	Epcam+	Ng2+	Mes. Cells
Control	4.38	4.49	3.02	89.86
Treated	2.88	4.85	5.82	78.17

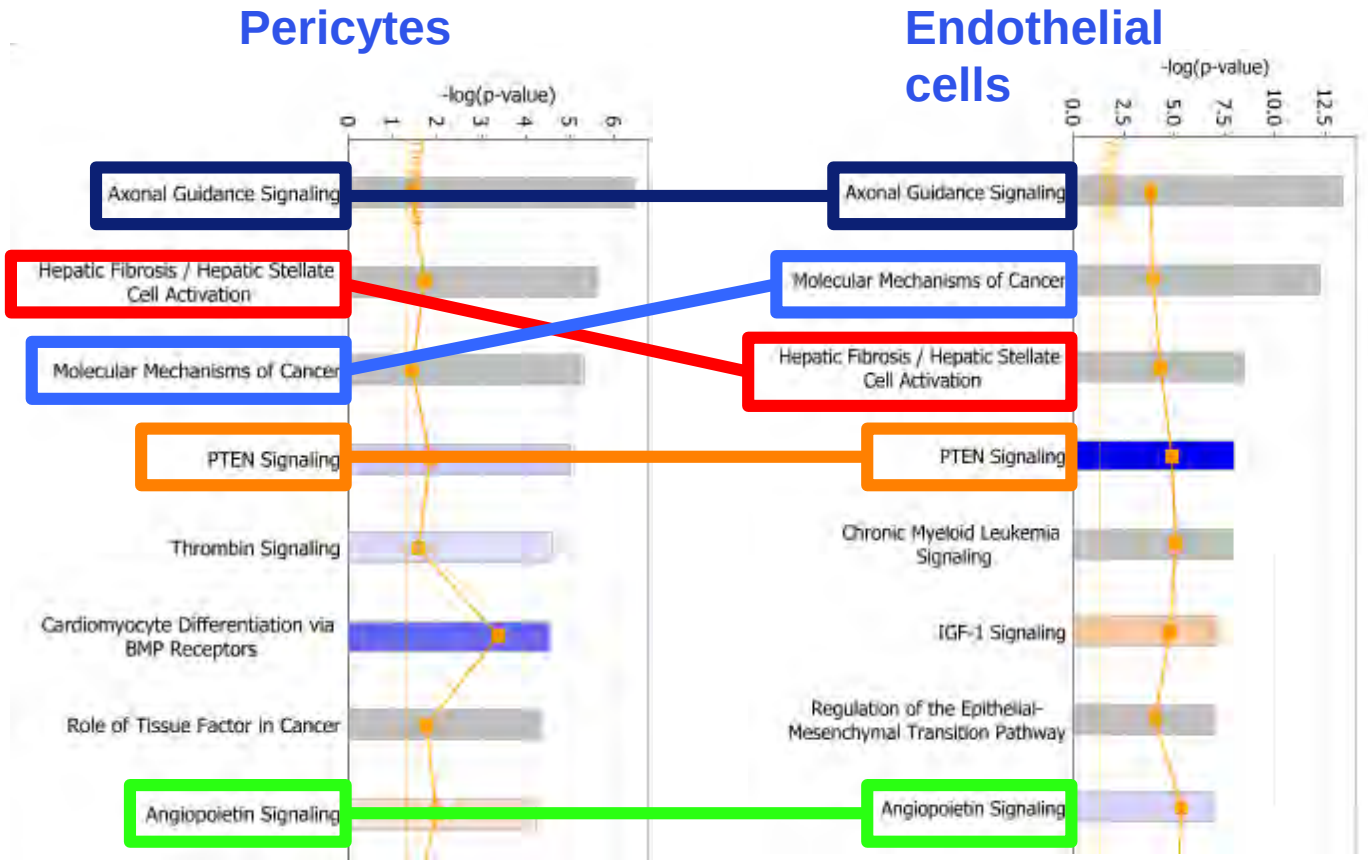
SSWO projects 678, S15-11

RNA sequencing of different cell populations





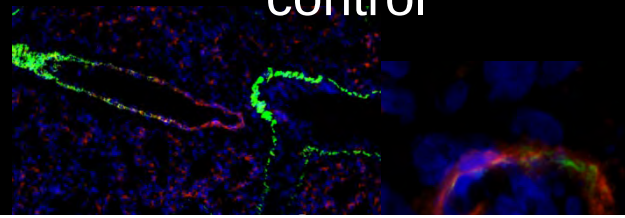
Top pathways overlap pericytes – endothelial cells



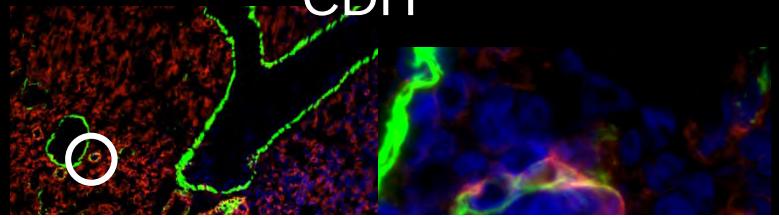
(Neo)-muscularization and perivascular cells?

Perivascular cells express differentiation markers in CDH

control

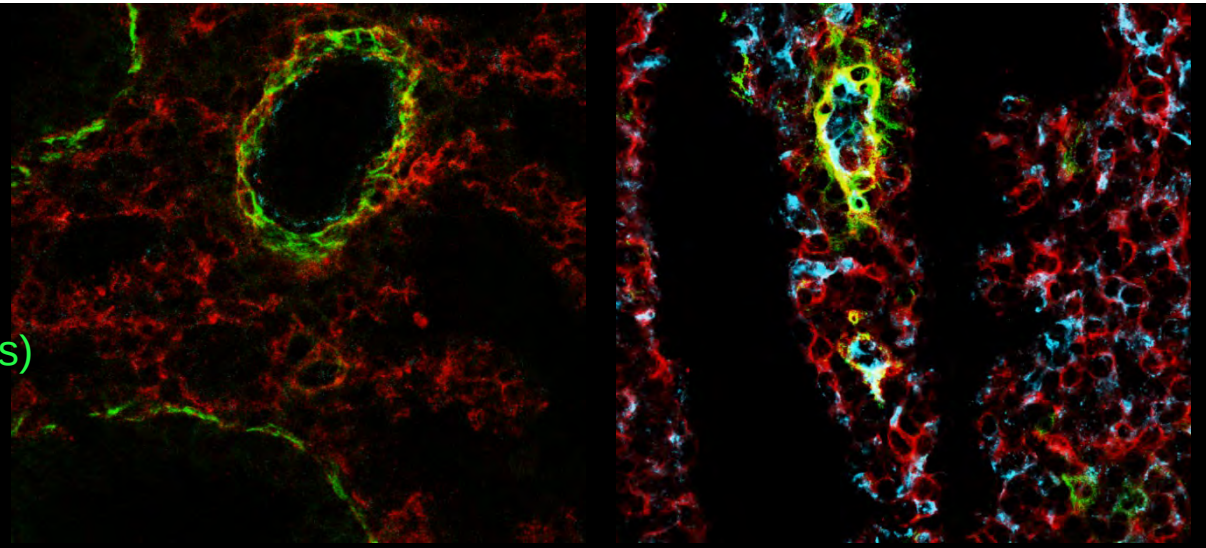


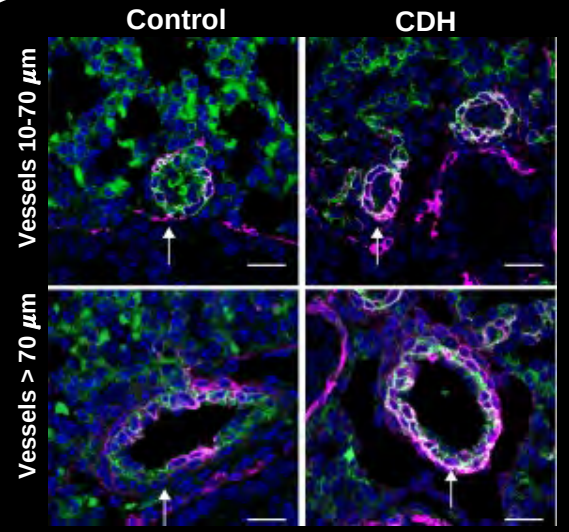
CDH



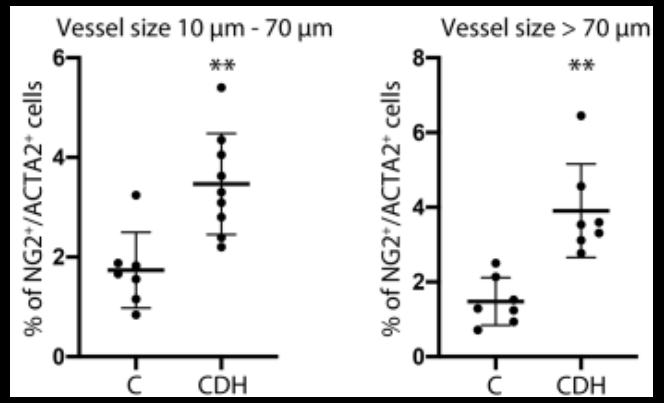
Premature or altered differentiation of pericytes in CDH

NG2
(perivascular cells)
SMA
(Smooth muscle cells)
CD31
(endothelial cells)

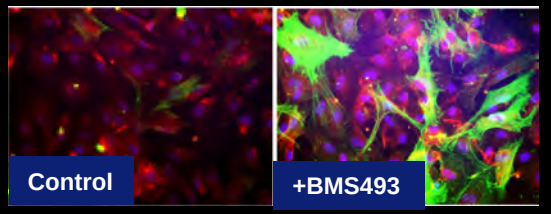


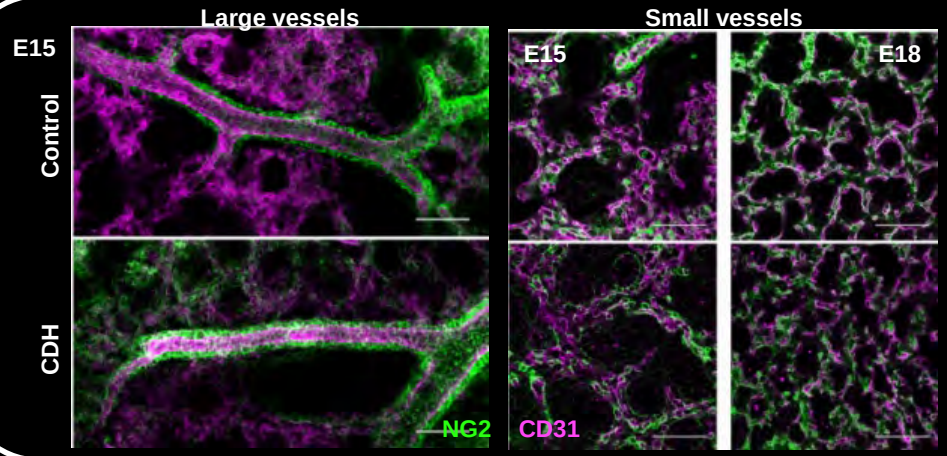


Pericytes express smooth muscle markers in CDH, independent of vessel size

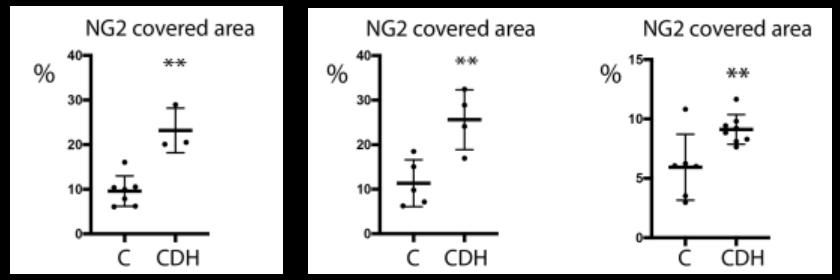


RA inhibition induces smooth muscle markers in vitro

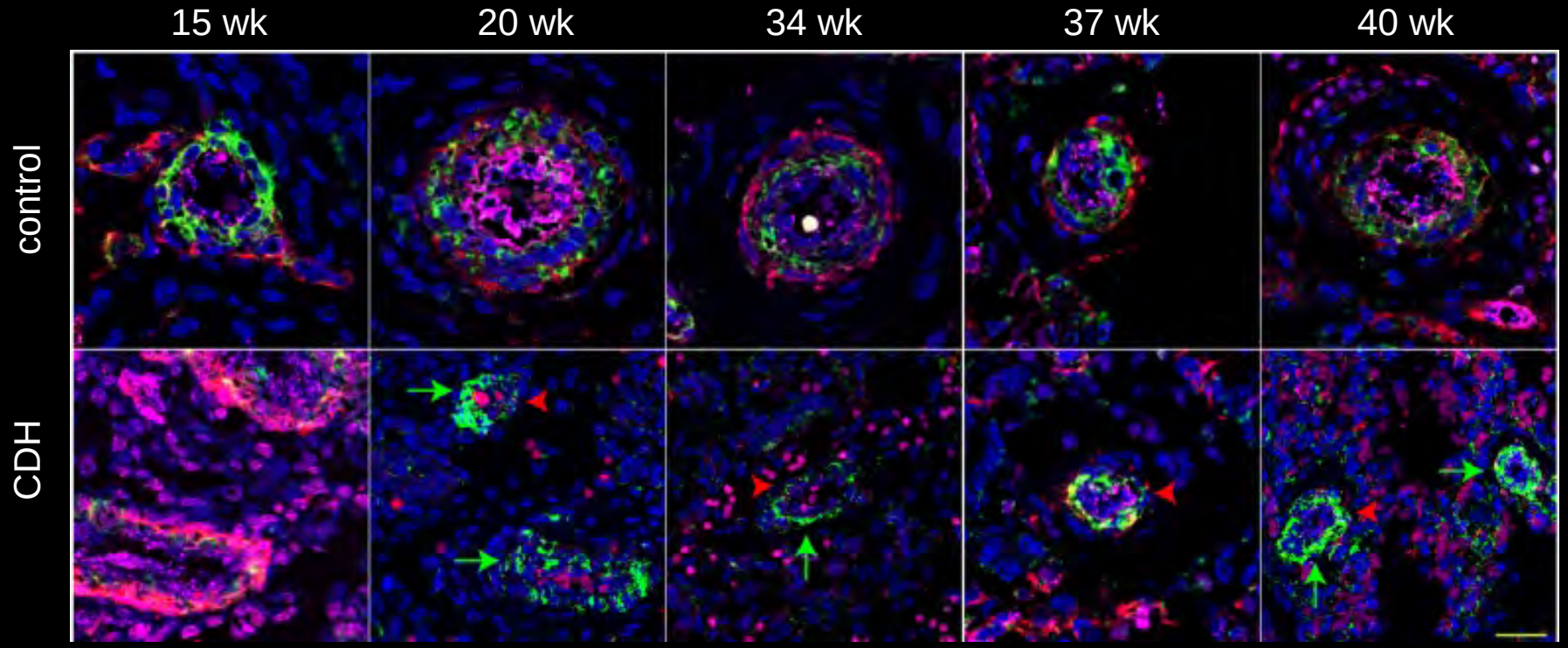




Increased pericyte coverage in CDH, and a reduced and impaired capillary bed

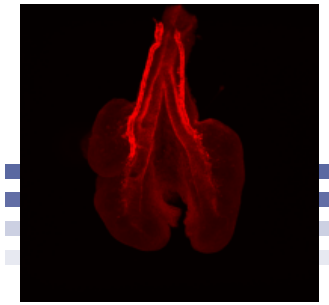


Vascular abnormalities in human CDH



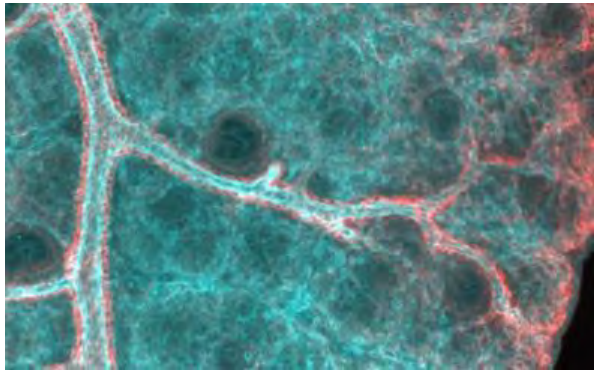
vWF
Collagen IV
NG2

Decreased collagen IV deposition (arrowheads)
Increased pericyte coverage (arrows)

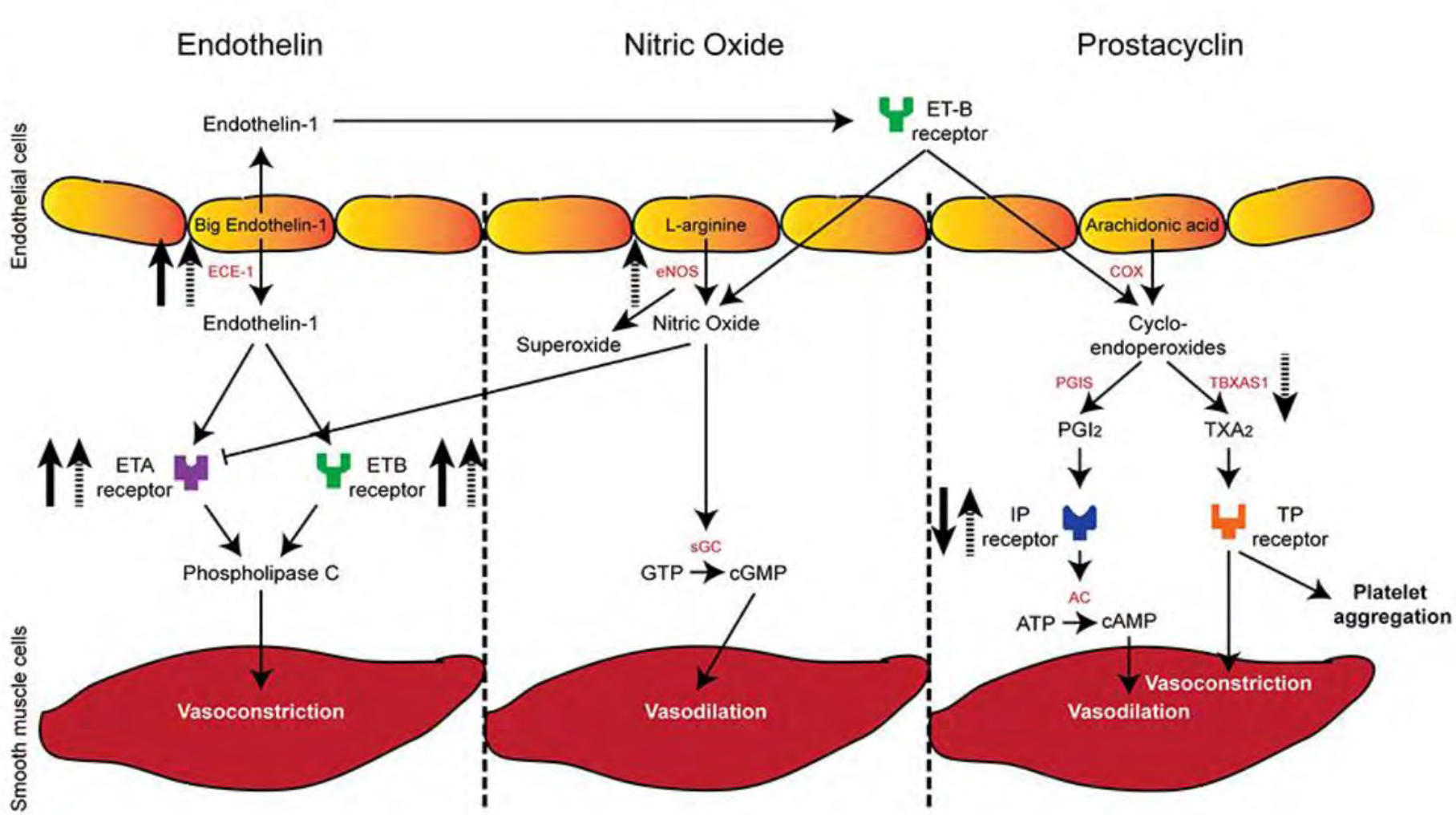


Thus……

- Pulmonary **vascular development** seems **accelerated** in CDH
- **Pericytes** are different in CDH and **may be the source** of extensive muscularisation
- **Pericytes** may be the **origin** of pulmonary hypertension in CDH
- **Increased** pericyte **coverage** in CDH



Metabolic pathways of vascular tone



Daphne S Mous; Marjon J Buscop-van Kempen MSc et al European Resp Review 2018

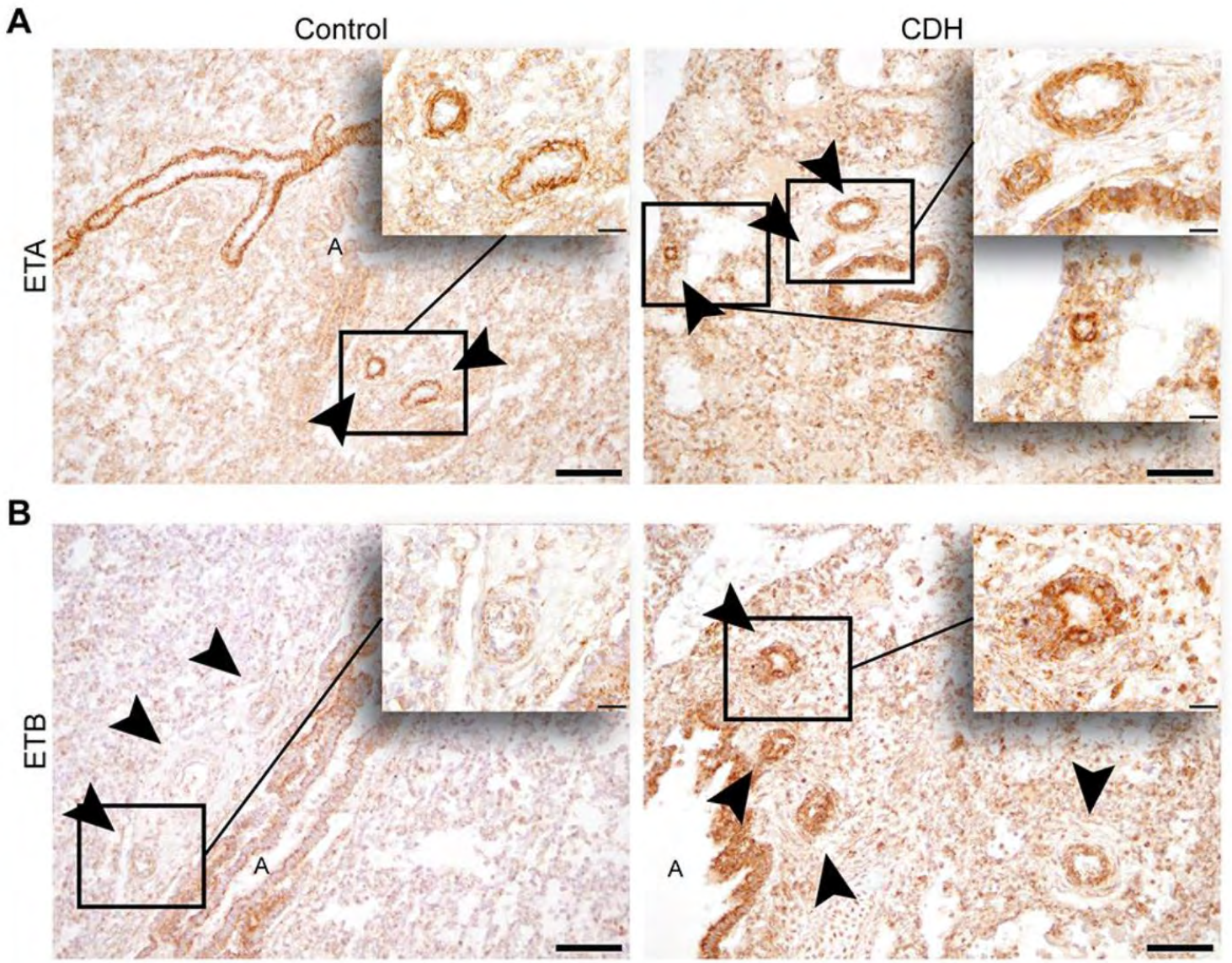


Figure 3: Increased expression of both the ETA and ETB receptor and endothelin converting enzyme in human CDH.

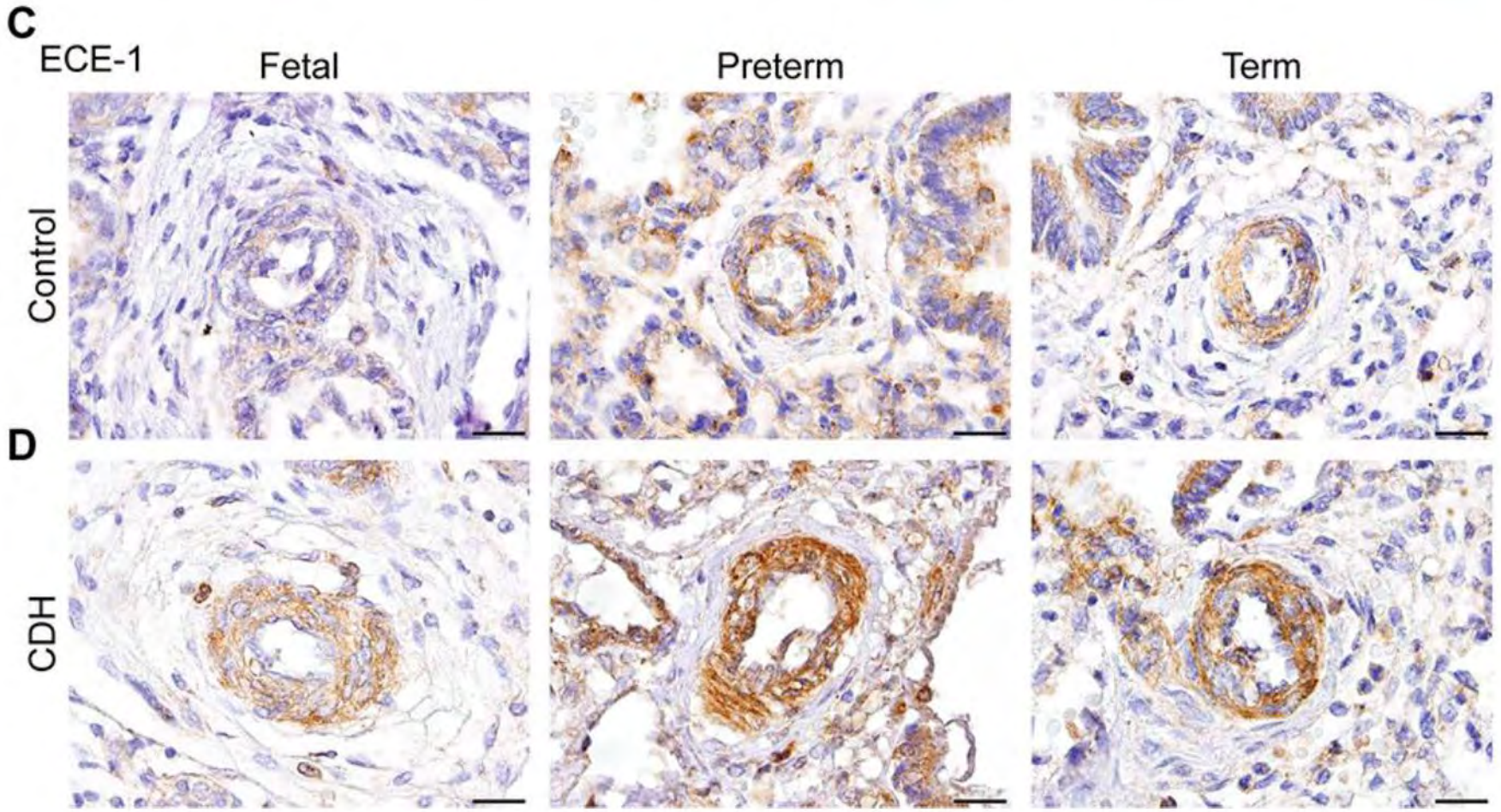


Figure 3: Increased expression of both the ETA and ETB receptor and endothelin converting enzyme in human CDH.

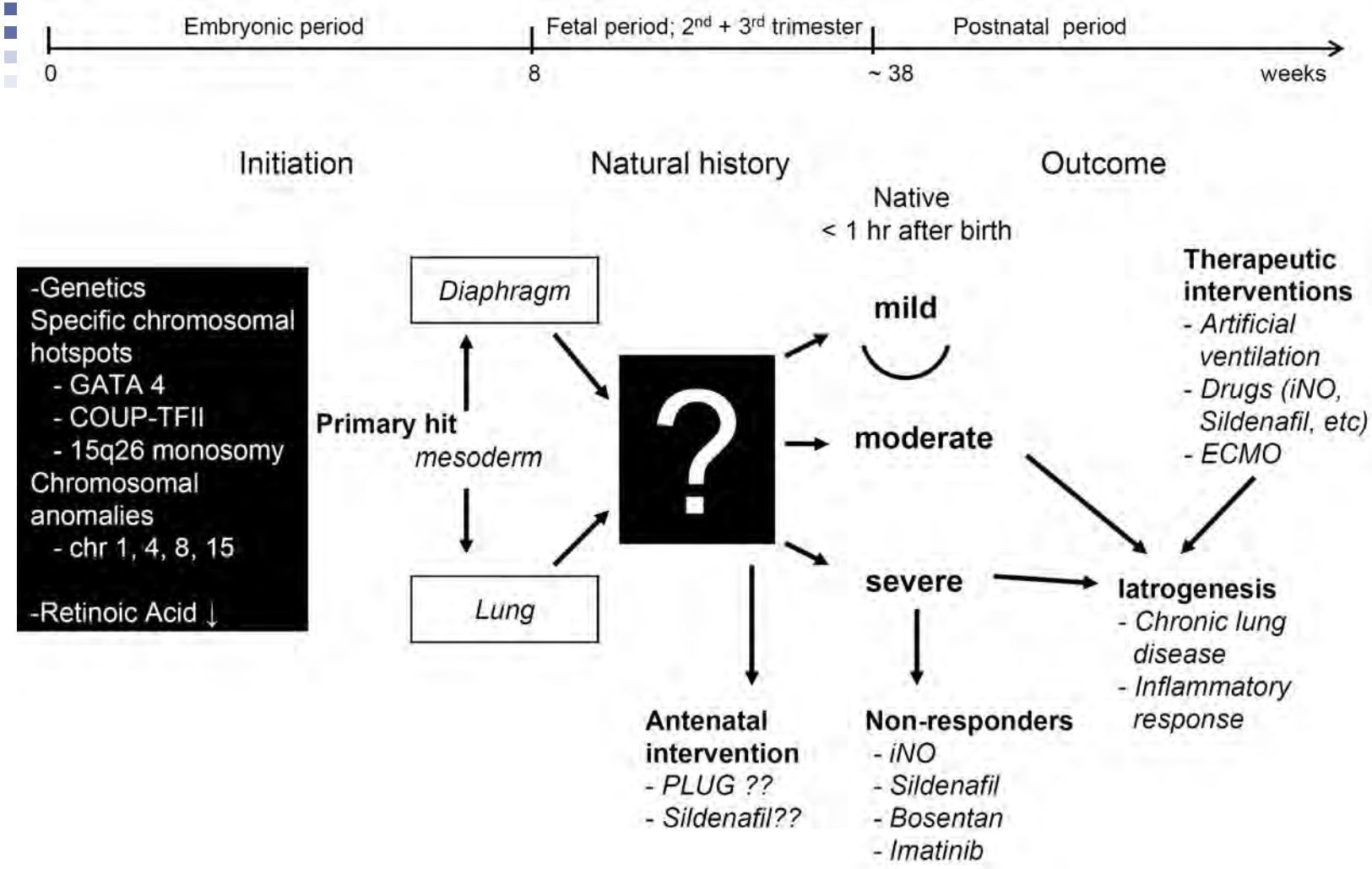
The next RCT on behalf of the CDH EURO consortium and supported by CDH-UK

Newborns with **Co**ngenital **Di**aphragmatic hernia: inhaled **N**itric **O**xide versus intravenous **S**ildenafil,

an international randomized controlled trial

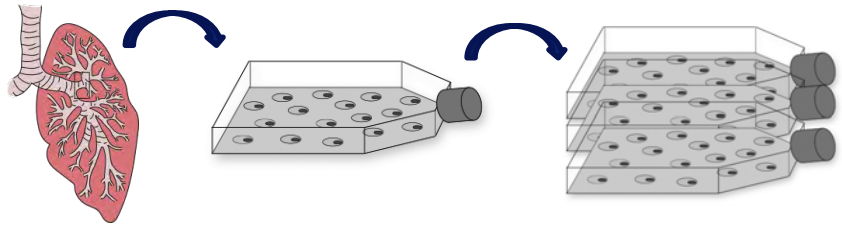
CoDiNOS Trial

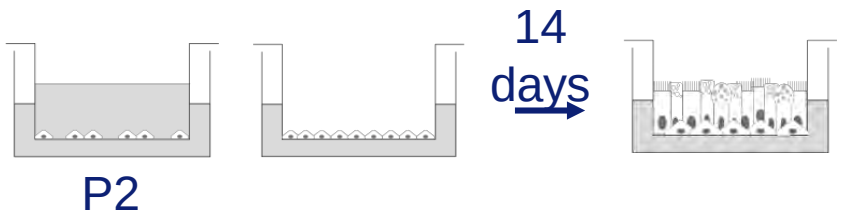
Insight in the black box of CDH



I. Sluiter, thesis 'CDH: A vascular disease'

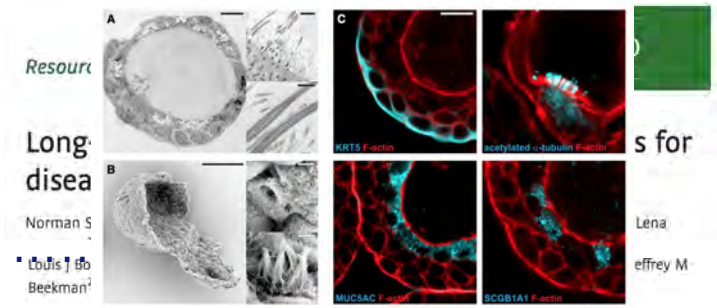
Study human diseases using *in vitro* cultures





- Sufficient starting material
- Limited expansion (passage 2) +

\+ Air Exposure -



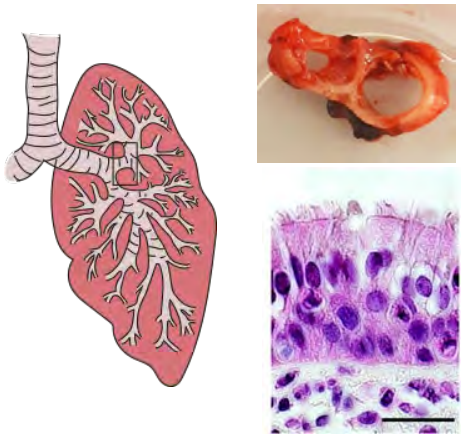
Need only 1 cell to form an organoid

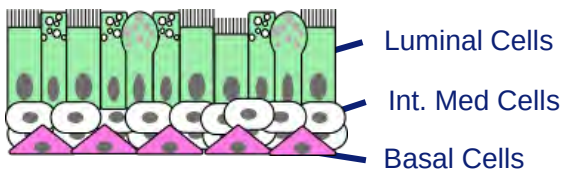
(Un)limited Expansion (Till P19)

No Air Exposure

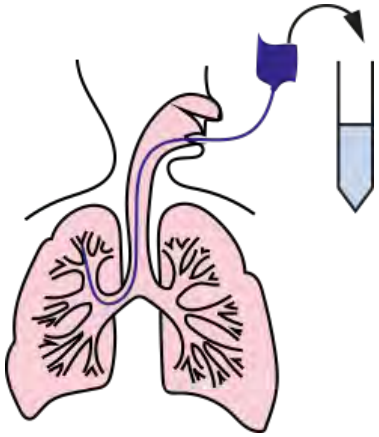
We obtained material from 3 different sources

Bronchial Tissue (BT)



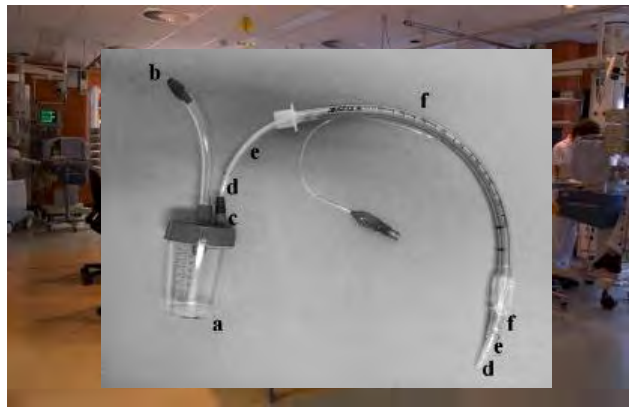


Broncho Alveolar Lavage (BAL)



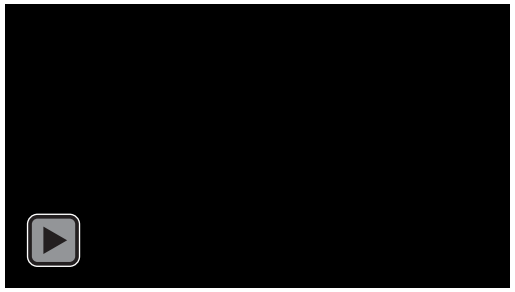
Department of Pulmonology
LUMC
Prof Hiemstra
Sander van Riet

Tracheal Aspirate (TA)

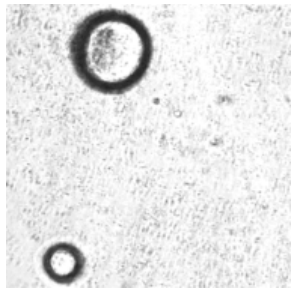


Department of Neonatology
Sophia Children's' hospital
Prof Reiss
Dr Kroon

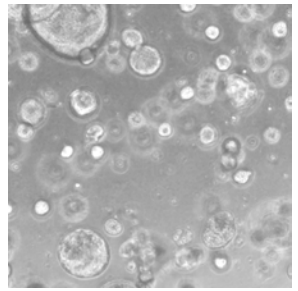
Tracheal aspirates are a good source for AEC differentiation

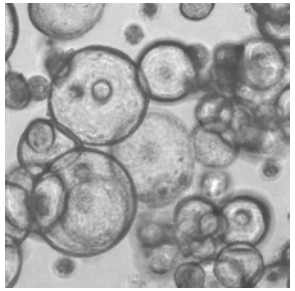


12 days →

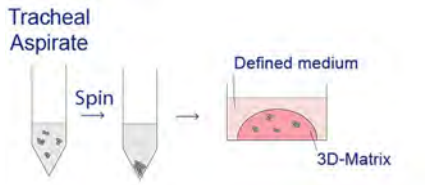


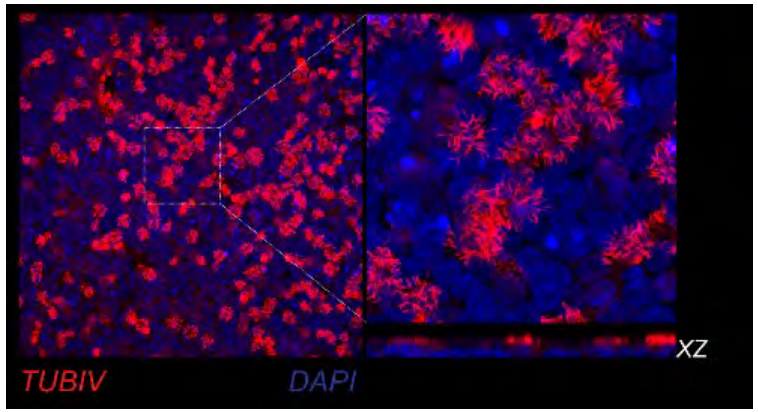
Expansion →





Disrupt ↓





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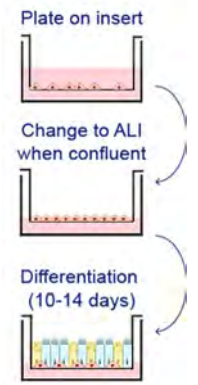
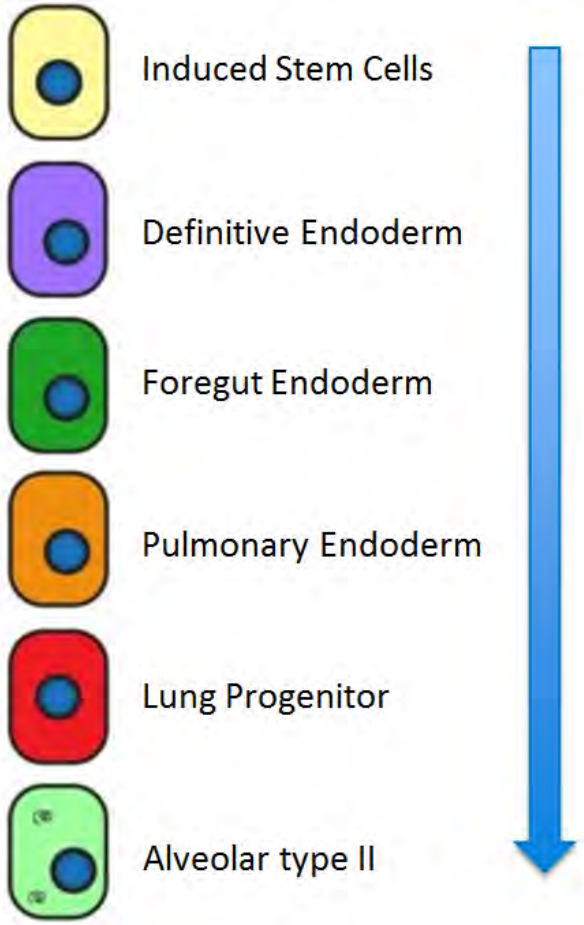
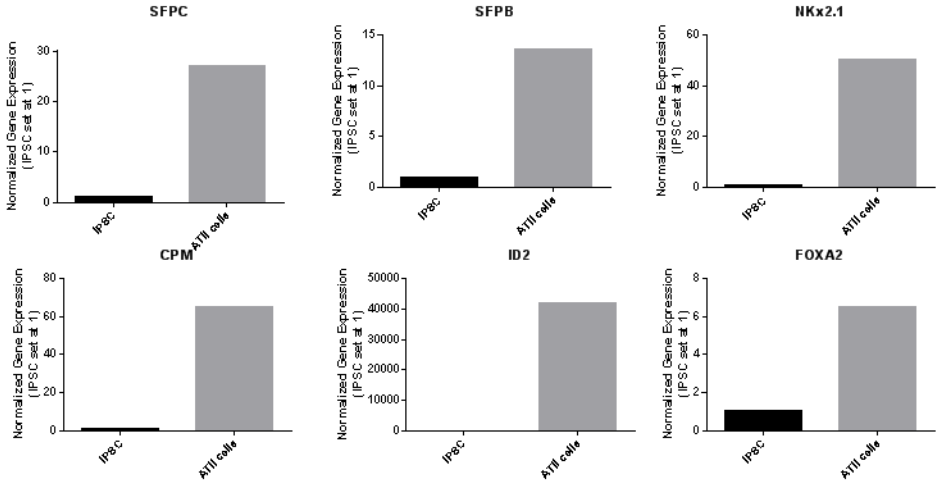


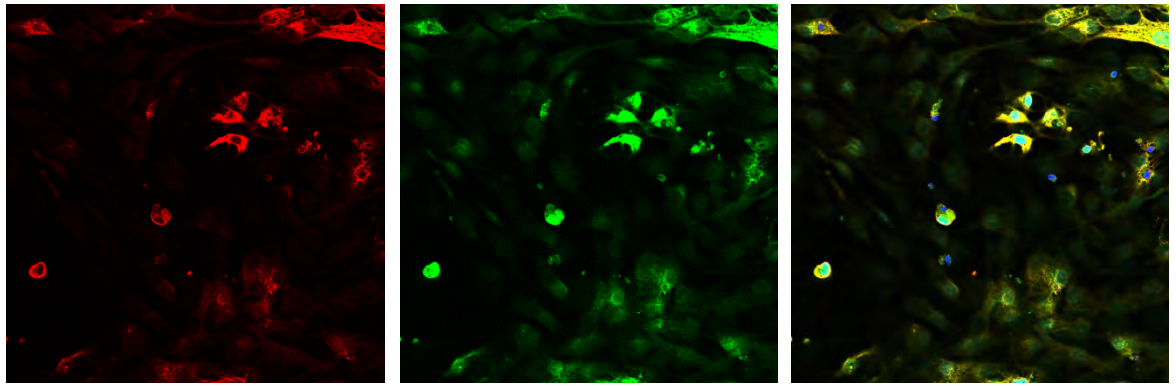
Generation of alveolar epithelial type 2 (ATII) cells from human induced pluripotent stems cells (hiPSC)



Stages of differentiation



Gene expression of iPSC compared to generated ATII cells

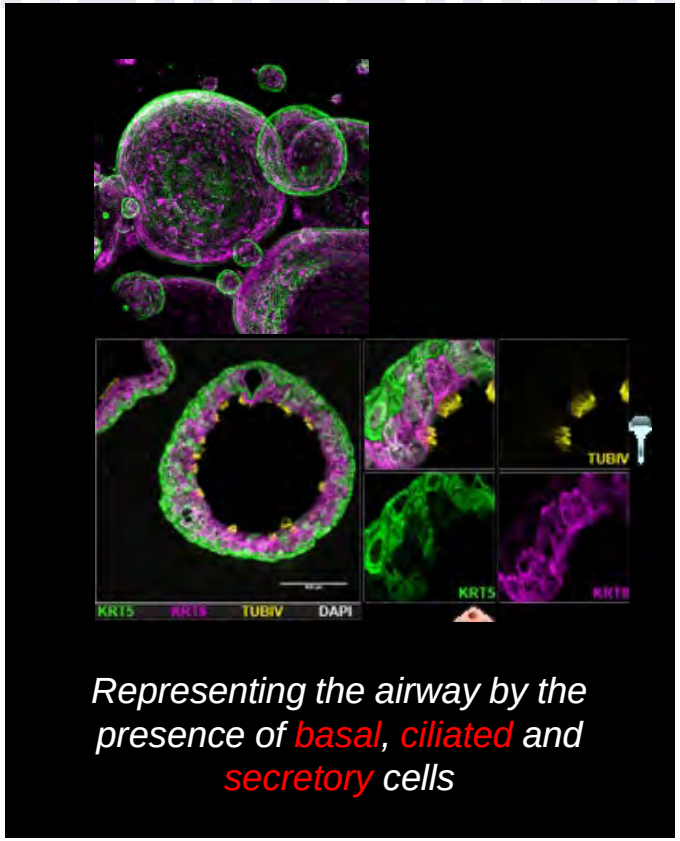


EpCAM SFTPC Merge

Staining of generated ATII cells

Sander van Riet, ms submitted

Airway organoids, an *in vitro* system to study airway diseases?



Representing the airway by the presence of basal, ciliated and secretory cells

- **The amount of primary tissue availability can be limited**
  - An Organoid can be obtained from one single cell

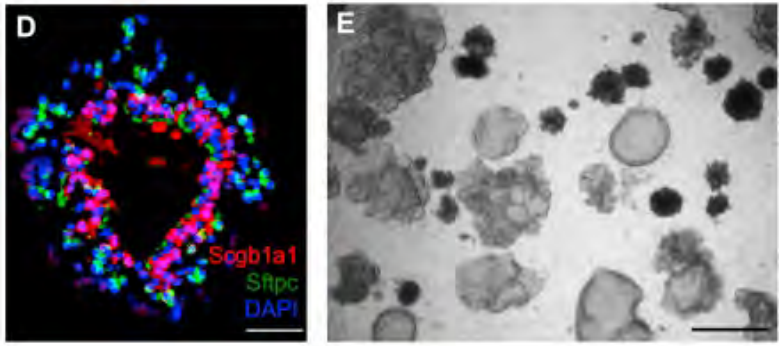
- **Can be obtained from**
  - Conducting airways
  - Tracheal aspirates
  - Nose swaps

Model and study disease using a small amount of patient material – Patient specific cultures

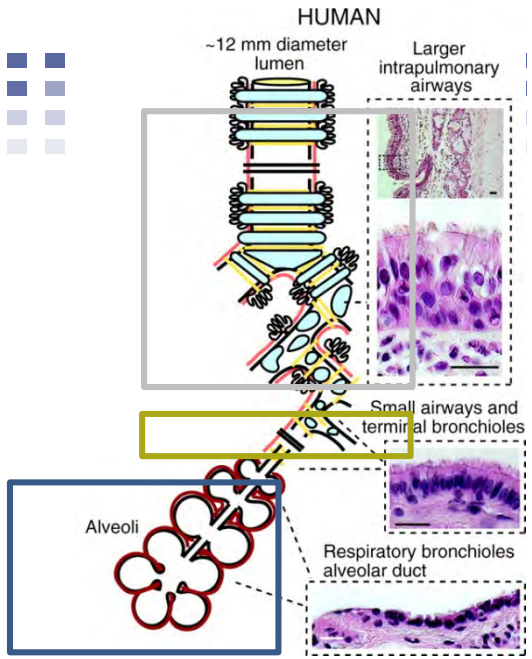
Congenital Pulmonary Airway Malformations

3 types of lung organoids: Bronchiolar, Bronchoalveolar, Alveolar

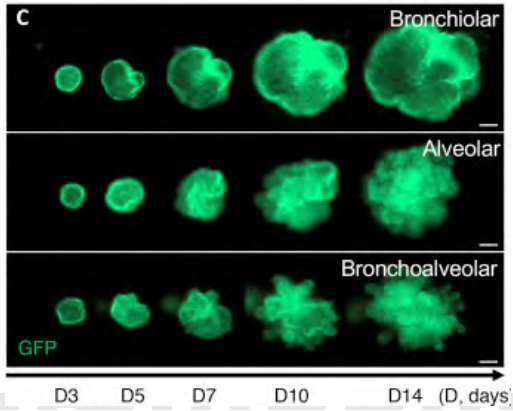
- **Alveolar organoids**
  - Formed from Alveolar type II cells
  - Show presence of both Alveolar type I and type II cells
- **Bronchoalveolar organoids**
  - Formed from Bronchoalveolar stem cells
  - Show presence of Alveolar and Airway cells
- **B**



Scgb1a1: Secretory cells
Sftpc: Alveolar type II cells



Rock et al., 2010 Dis Mod & Mech



Choi et al., 2016 Dev Biol

Chip requirements:

Mimic the organ of interest

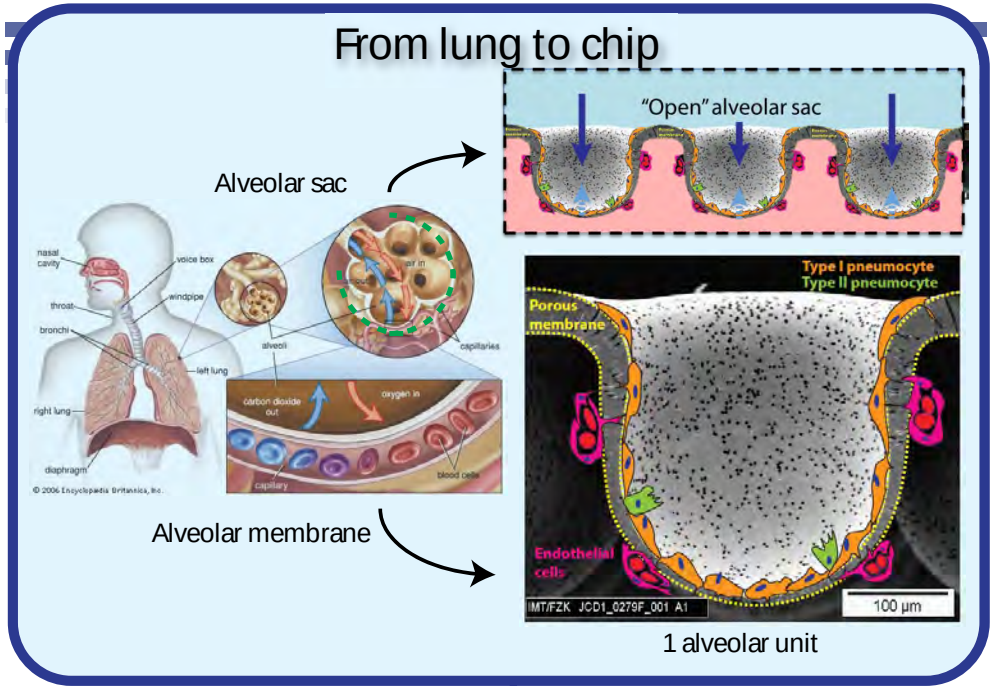
Recapitulate the organ's physiology

Attainable read-out system(s)

For the lung:

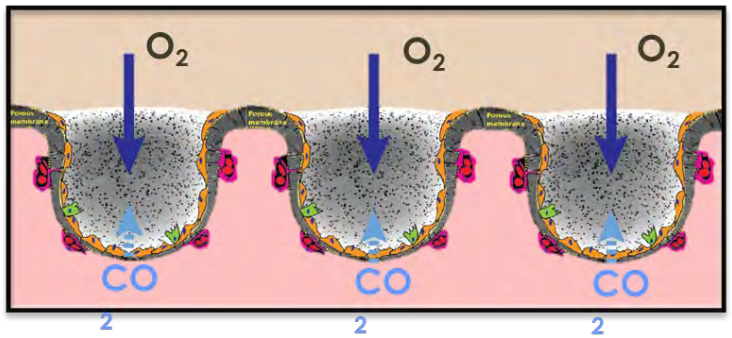
- Stretchable (breathing)
- Air - and blood compartment
- Read out of both compartments (microscopy, O_2 sensor, TEER measurement, etc)
- Collect air and "blood" from the chip for analysis
- Recovery of cells post-chip for analysis

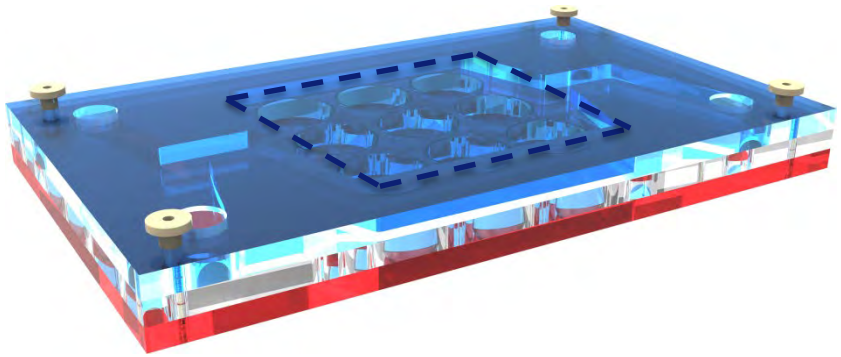
Epithelial differentiation - application

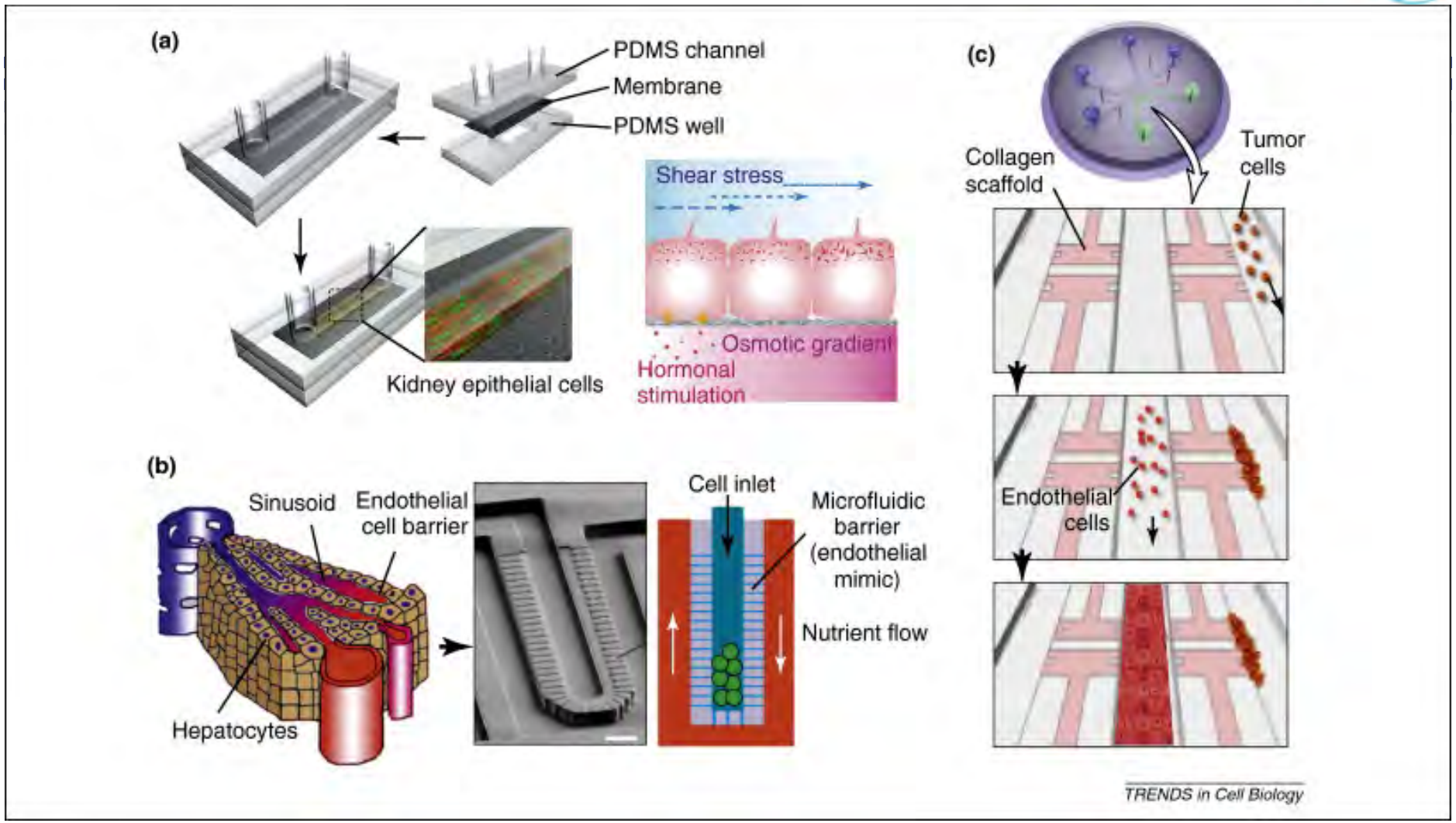


Dynamic 3D in vitro lung model :

- **Mimics micro-anatomy of lung**
- **Recapitulates alveolar physiology**



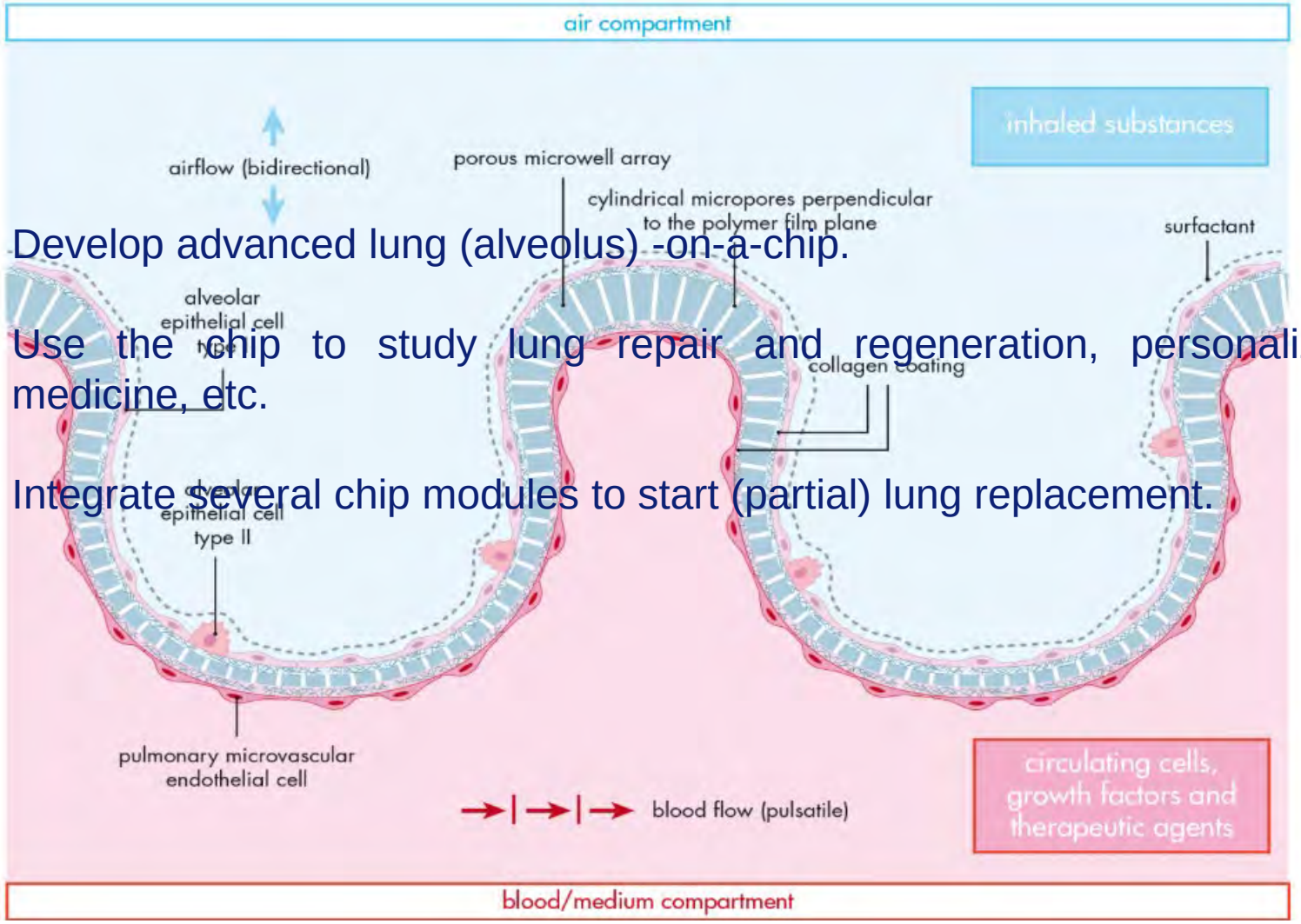




Huh et al, 2011

Lung-on-a-chip consortium

1. Develop advanced lung (alveolus) -on-a-chip.
2. Use the chip to study lung repair and regeneration, personalized medicine, etc.
3. Integrate several chip modules to start (partial) lung replacement.



microengineered 3D analogues of alveolar tissue for lung regeneration

What basic/ translational breakthroughs are going to change the way we understand CDH and care for these patients in the future?

d.tibboel@erasmusmc.nl

CDH in 2025: prenatal

High-risk CDH patient: new risk assessment score integrating both pre- and postnatal characteristics.

Molecular genetic analysis incorporating next generation sequencing and adding this info to the international genetic biobank of CDH.

iPS cells will be generated for further identification of factors known to predict chronic lung disease using organoids and organ on chip techniques.

Single cell sequencing after differentiation will be performed to elucidate developmental abnormalities.

New experimental studies, like the use of microRNAs or stem cell therapy +/- PLUG.

CDH in 2025: perinatal

At birth, umbilical cord cells will be harvested for endothelial cells responses on vasoactive drugs using vessel-on-a-chip perfusion models.

To investigate potential biomarkers to identify at an early stage patients at risk for developing chronic lung disease as well as adverse comorbidities

.

The best drug therapy for pulmonary hypertension based on in-vitro responses to a variety of drugs

Drug dosing will be tailored based on phenotypic knowledge of drug metabolism as well as known influence of the disease state.

CDH in 2025: first admission and beyond

All data will be integrated using the infrastructure of the CDH-EURO Consortium; the CDH-registry and ERNICA taking the FAIR principle into account

Markers of chronic lung disease extracted from tracheal aspirates during artificial ventilation will determine the ventilator settings and will be repeatedly re-evaluated.

Dense monitoring data are collected, notably with respect to brain-related parameters.

An MRI of the brain will be made with special attention for the hippocampus to predict dysfunction in executive functions enabling implementation in an intervention study.

The child and family are invited to join a tailor-made lifelong interdisciplinary follow-up program aiming to decrease long-term morbidity

CDH EURO CONSORTIUM 2017

Austria
Belgium
Canada
France
Germany
Ireland
Italy
Norway
Poland
Portugal
Scotland
Spain
Sweden
United Kingdom
The Netherlands

Acknowledgements

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Raymond Poot
Prof Huylebroeck

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Irene Heijink (UMCG)
Reinoud Gosens (UMCG)
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International collaborations

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Emma Rawlins (Cambridge)
Anne Hilgendorff (Munich)
Rory Morty (Bad Nauheim)
Jan DePrest (Leuven)
Richard Keijzer (Winnipeg)

Significant progress and shifts over time

- Prenatal risk stratification and trial design
- Improved survival and definition of standards of care

  Comparative effectiveness trials CDH-EURO Consortium

- Developmental biology of the pulmonary vasculature

Significant progress and shifts over time

- Establishment of parent support groups in many countries
- Delayed surgical repair
- Gentle ventilation
- International collaboration such as the CDH registry and the DHREAMS initiative

Erasmus MC

EUROPEAN CDH DATABASE

MISSION Better diagnosis, risk assessment and personalized treatment for CDH

GOAL Integration of clinical, molecular and cellular data, to understand the pulmonary vascularization in CDH

Collect Data/Material

European CDH database (WP1)

ANALYSIS Extract patient data/material for analysis:

Molecular: GWAS/NGS studies, expression studies (-omics based), image analysis (WP1,3,4)

Cellular: Isolate stem/progenitor cells, develop iPS cells, differentiation of cells, LCM (WP1,3)

Clinical: Prediction model, pathology, link prenatal imaging with postnatal management (WP1,2,4)

Designed by Richard Keijzer 2015

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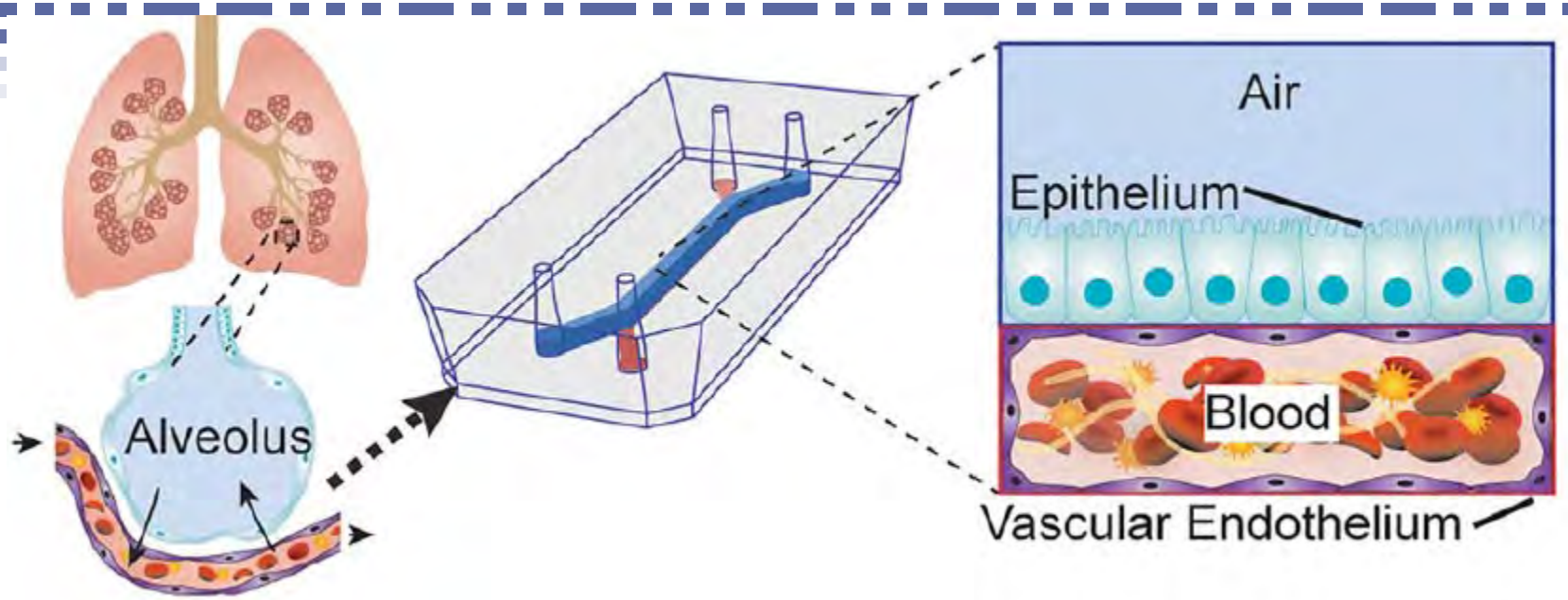
Maarten Brandt

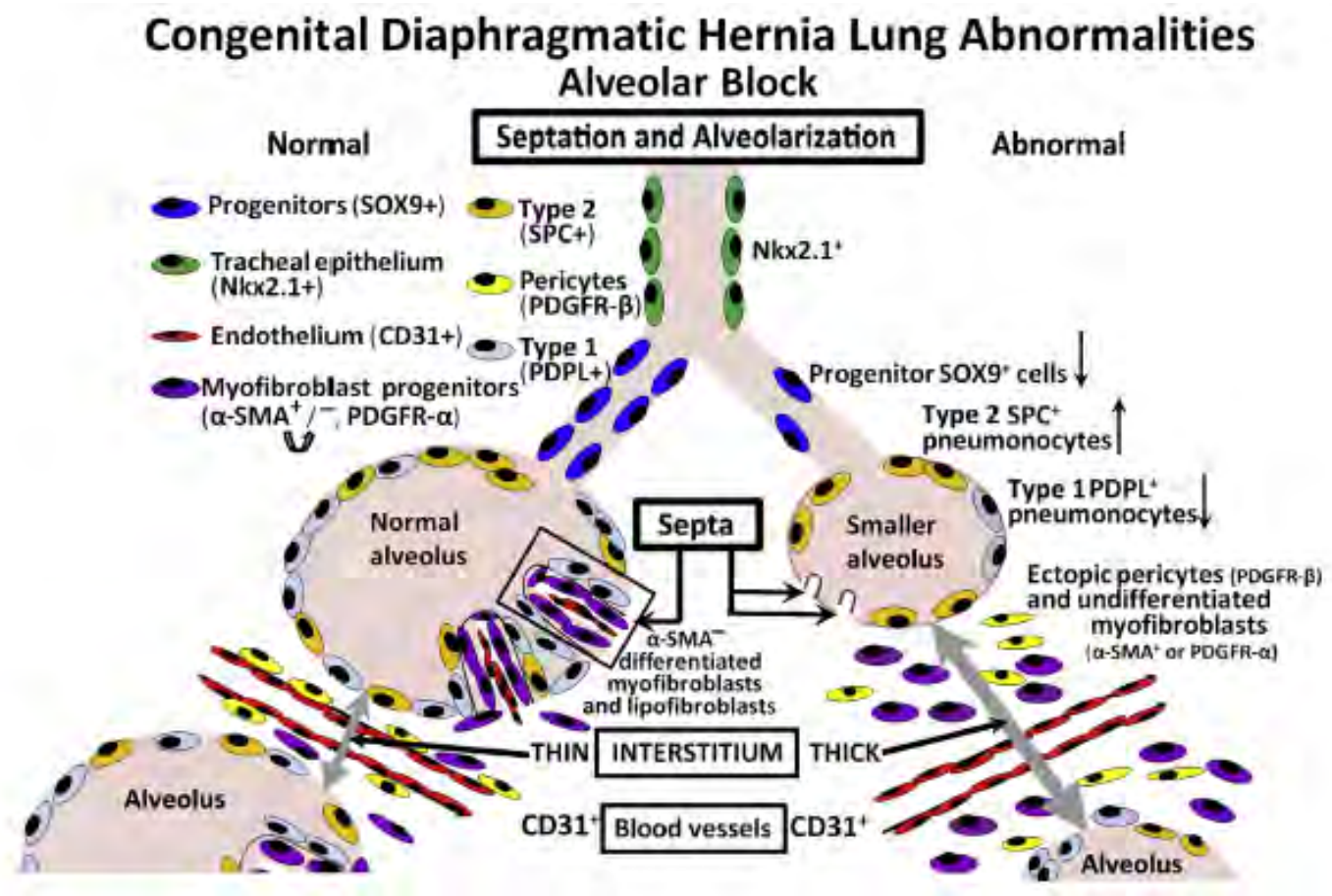
Pediatrics Erasmus MC

Isme de Kleer

Cell Biology Erasmus MC

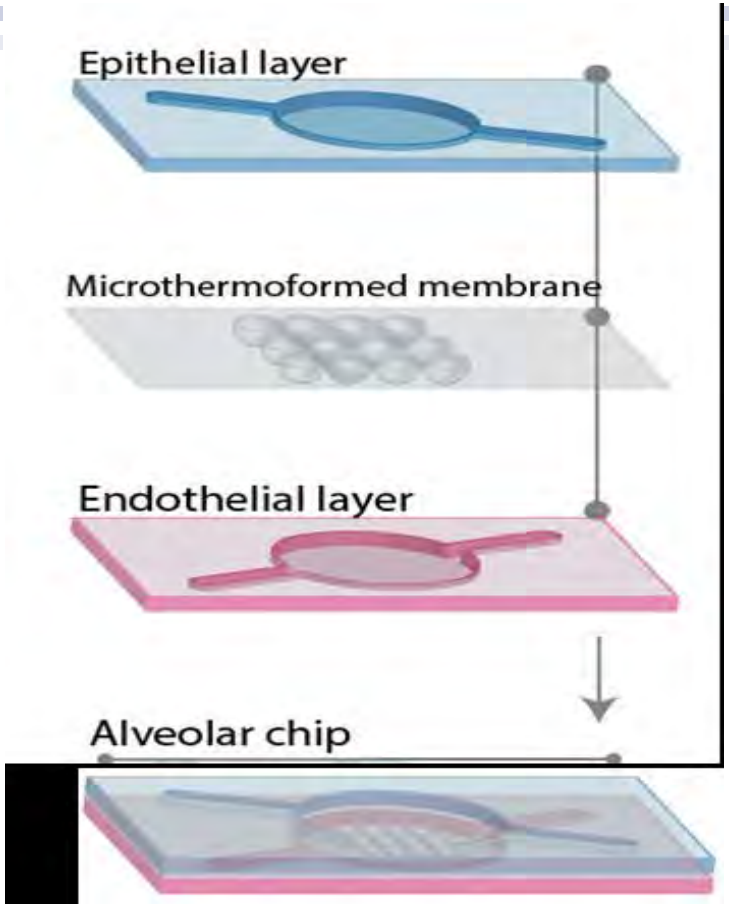
Frank Grosveld
Danny Huylebroeck

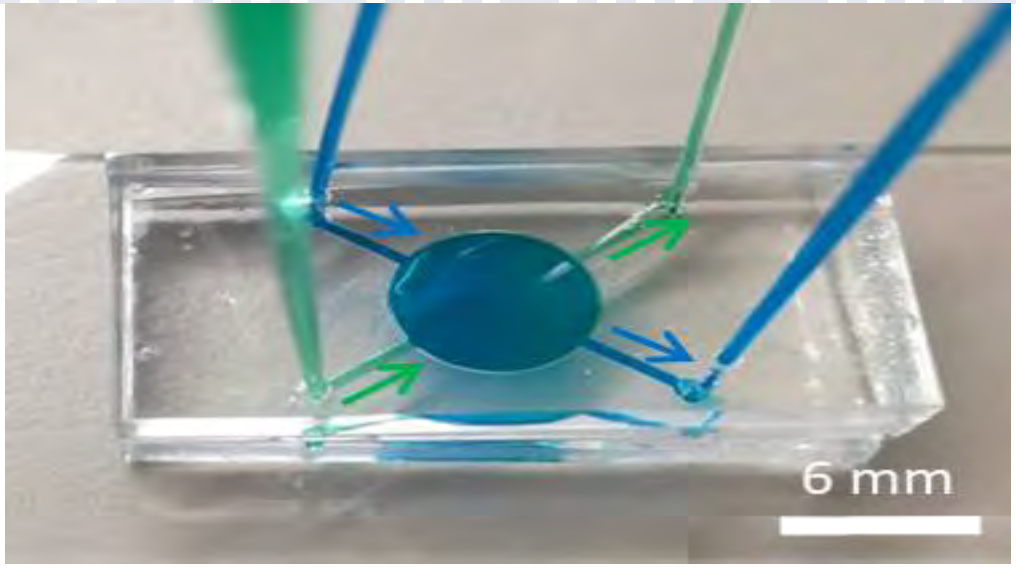

Air
Epithelium
Blood
Alveolus
Vascular Endothelium

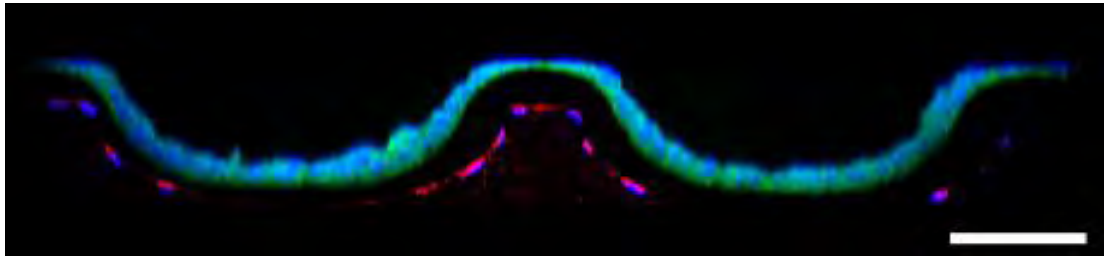


Donahoe PK, Longoni M, High FA.
Am J Pathol 2016,186: 2532–2543

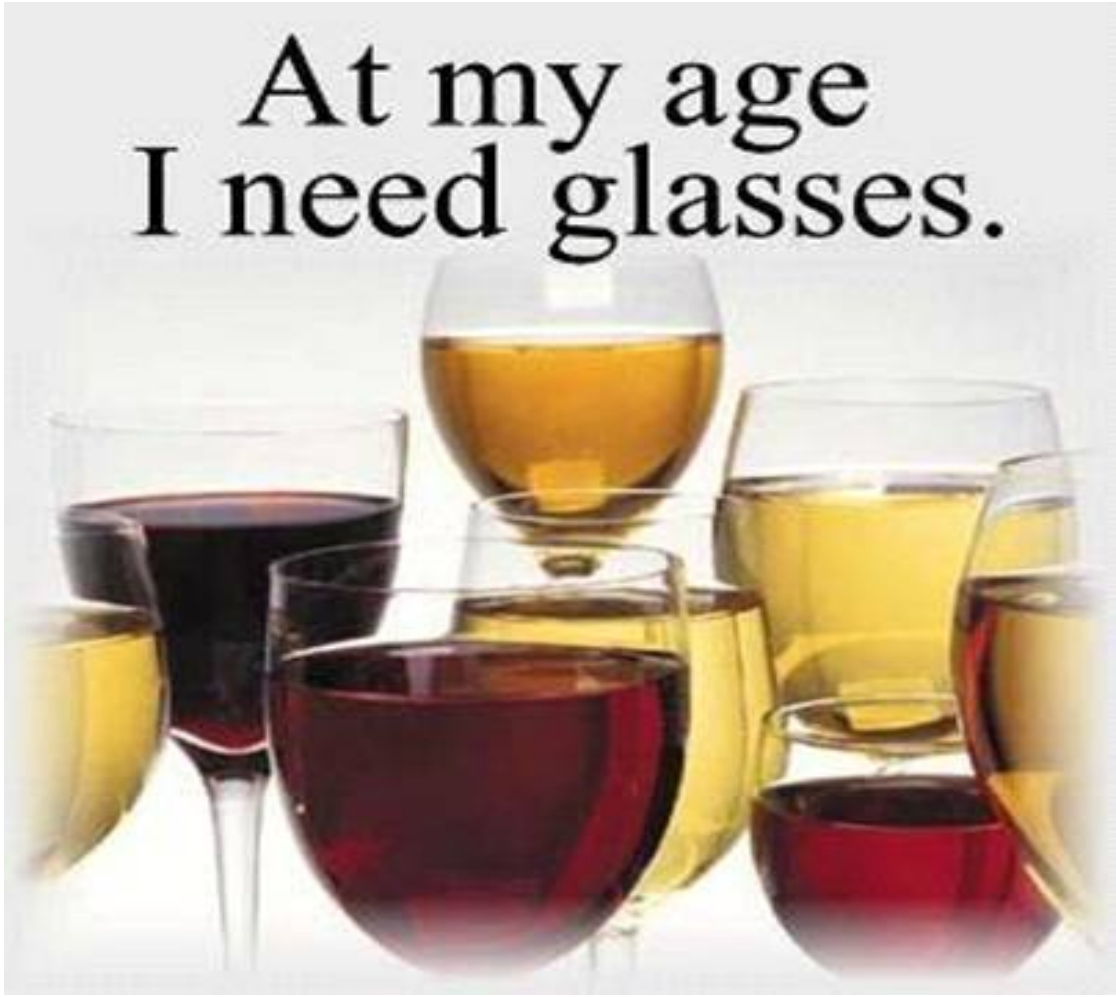
Epithelial differentiation - application







The CDH Registry and Study Group
Past, Present and Future


At my age
I need glasses.

CDH Registry

- Background of the Registry
- Current Status
- Major Publications
- Future Plans

EXTRACORPOREAL LIFE SUPPORT ORGANIZATION

Charter Meeting

October 1-3, 1989 **Ann Arbor, Michigan**

EXTRACORPOREAL LIFE SUPPORT ORGANIZATION

Charter Meeting

October 1-3, 1989 **Ann Arbor, Michigan**

Members in attendance:

9/12/91

NAME	CENTER
Lucienne Sanchez	CNMC, Washington, D.C.
Kevin Lally	Hermann Children's/Houston
Jim Atkinson	CHLA/Los Angeles
Charles Breaux, Jr.	Children's of Alabama
Karen West	Riley Hospital/Indpls IN
Billie Lou Short	CNMC, Washington, D.C.
William Engle	Riley Hospital/Indpls IN
Gail Kernaghan for W.P. Kanto	Med College of Georgia
Michele Walsh-Sukys	Rainbow Babies, Cleveland
David P. Meagher, Jr.	Children's Hospital, Denver
Gerald M. Haase	Children's Hospital, Denver
Jay Wilson	Boston Children's
Desmond Bohn	Hospital For Sick Children
Kyle Walker	Johns Hopkins Hospital
P. Pearl O'Rourke	Children's Hospital/Seattle

- 5 Neonatologists
- 7 Pediatric Surgeons
- 3 Intensivists

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

CDH The Comprehensive Center for CDH Care

Children's Memorial Hermann Hospital

CDH STUDY GROUP

MINUTES OF CHARTER MEETING 9/12/91

The meeting was scheduled to begin at 15:30, and began shortly thereafter. It lasted for approximately one hour. Items of import discussed were as follows:

* There was universal agreement of a need for such a study group. The goals of the group were not completely defined, however 2 main goals were cited:

1) **Universal data collection of CDH patients.**

2) **Collective attempt to answer questions regarding CDH patients.** There was universal agreement that no single individual or institution had found "the answer" to the ubiquitous problem of CDH infants. There were numerous expressions of willingness to work together and attempt to put aside previous biases and large egos to collectively address CDH patient management and outcome.

CDH STUDY GROUP

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CDH Registry

- Existing data forms collated and modified
- Voluntary collection
- A priori plan to limit total amount of data
- Data collection begun 1995
- Data in secure, anonymized database
- Some PHI – DOB, DOS

The Congenital Diaphragmatic Study Group

Versions of the CDH Registry

- Version 1 1995-2000
  - Defining the problem - medications, ventilator strategies, ECLS use

CONGENITAL DIAPHRAGMATIC HERNIA DATA FORM

Hospital:_____ DOB:____/____/____ Time of Birth:_____

Initials:_____Hosp. #_____Admission Date:____/____/____ Time:_____

Inborn Outborn **Group**(Circle one): No ECMO ECMO Pre-Repair ECMO Post-Repair

Sex: M F Race: Black White Hispanic Asian Other_____

Birthweight_____Kgs **EGA**(Exam)_____weeks

Prenatal Diagnosis: Yes No If Yes EGA@Dx(wks)___ Polyhydramnios Yes No

Stomach in Chest Yes No Left Ventricular mass index(if known) _____

Liver in Chest Yes No Prenatal Repair Yes No Pregnancy terminated: Yes No

Delivery Data: Apgars (1/5/10) ____/____/____ Early death (<24 hrs) Yes No

Immediate Distress: Yes No CPR: Yes No Age at Dx:Date____/____/____Time____

Age at Intubation:Date___/___/___ Time_____

Associated Anomalies

Cardiac: Yes No If Yes: Hypoplastic Heart/TOF/TAPVR/VSD/ASD/Other_____

Chromosomal: Yes No If Yes:_____ Neural tube Anomaly: Yes No

Omphalocele: Yes No Other:_____

PHARMACOLOGIC DATA

Surfactant given: Yes No If Yes: Hours of Life: ____/____/____/____

If Yes: Survanta Exosurf Infrasurf Other

Drug Strategy(Circle)				Complications
Vasopressors	Yes	No		_____
Intravenous Vasodilators	Yes	No		_____
Inhaled Vasodilators	Yes	No	Don't Know	_____
Hyperoxia	Yes	No		_____
Sedation	Yes	No		_____
Alkalinization Yes	No			_____
Neuromuscular Blockade	Yes	No		_____

Version 1

Repair Data:

Side : Left Right Bilateral Repair Done Yes No

Type Repair: 1º: Yes No Patch: Yes No Material: PTFE Dura Other____

Size of Defect: 1/4 1/2 Agenesis

Approach:Subcostal Thoracic Other_____Abdomen Closure: 1º Fascia Silo Expander

Chest Tube: Yes No Suction Yes No Malrotation Procedure: Yes No

Appendectomy: Yes No Other procedure:_____

Repair on ECMO: Yes No If Yes: Hours of ECMO when Repair _____Fibrin glue: Yes No

Date of Operation:____/____/____ Time:_____

Length of Operation (mins.)_____ EBL:_____ Introp Probs:_____

Operation Indication: ABG's Age ECHO PFT's Can Wean from ECMO Inability to Wean

Complications: Yes No If Yes: Bleeding Infection

Describe_____

_____

ECMO DATA

ECMO Criteria: OI>_____ x ____Hrs $AaDO_2$ > _____ x ___Hrs

Acute Deterioration_____It's Time____

Date on ECMO: ____/____/____ Time on ECMO:_____

Date off ECMO: ____/____/____ Time off ECMO:_____

ECMO Mode: - VA VA(+V) VV(DL) VV to VA

Amicar: Yes No Second Run: Yes No If Y(Duration of 2nd run hrs)_____

Complications: ICH Renal Failure Other_____

Bleeding: Neck Amount(Total)_____
Wound Amount(Total)_____
GI Tract Amount(Total)_____
Other Amount(Total)_____(Site)_____

Version 1

Versions of the CDH Registry

- Version 1 1995-2000
  - Defining the problem - medications, ventilator strategies, ECLS use
- Version 2 2001-2006
  - Understanding the details - delivery, oxygen/carbon dioxide, discharge status, cardiac anomalies

CDH Registry – Why it has worked

Management (2000 – 2019)

CONGENITAL DIAPHRAGMATIC HERNIA FORM
(To be used for patients born 10/1/2000 – 12/31/2006)

Year of Birth: _____ Center #: _____ Patient #: _____
Patient *Date of Birth*: ___/___/___ Time of Birth: _____
☐ Inborn
☐ Outborn: *Admission Date* : ___/___/___ Time: _____
Sex: M / F
Race: Black / White / Hispanic / Asian / Native American / Other: _____
Birthweight: _____ kg Head Circ: _____ cm Length: _____ cm
EGA (at birth): _____ wks APGAR (1/5/10): ___/___/___
Method of delivery: Vaginal (Spontaneous) Vaginal (Induced)
C-Section (Elective) C-Section (Urgent or Non-Elective))
If C-S, indication:_____
Immediate Distress: Yes / No CPR Given: Yes / No
Prenatal diagnosis of CDH: Yes / No If Yes, diagnosis made at ___ weeks gestation
Prenatal steroids given: Yes / No / Unknown
If Yes, steroids given at gestational ages (in wks): ___/___/___/___

Associated Non-Cardiac Anomalies (Check all that apply and please provide DX if known):
☐ Chromosomal – If Yes, please describe: _____
☐ Neural Tube Defect – If Yes, please describe: _____
☐ Omphalocele
☐ Other Anomalies – If Yes, please describe: _____

Associated Structural Cardiac Anomalies (Check all that apply):
☐ ASD
☐ VSD
☐ AVSD (AV Canal)
☐ Pulmonic Stenosis
☐ Pulmonary Atresia
☐ TOF (Tetralogy of Fallot)
☐ Coarctation of Aorta
☐ TOGV (Transposition of Great Vessels or Transposition of Great Arteries)
☐ Truncus Arteriosus
☐ Complex Biventricular anatomy (i.e. heterotaxy syndrome)
☐ Anomalous Pulmonary Venous Return: please describe: _____
☐ Single Ventricle Variant (hypoplastic left heart syndrome):
please describe: _____
☐ Other: please describe: _____

Treatment of Cardiac Anomaly (Check all that apply):
☐ Prostaglandins required
☐ Cardiac Surgery performed
If Yes, type of procedure(s) and date(s) performed: _____
_____
☐ ECMO needed post Cardiac Surgery

Version 2

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

CDH The Comprehensive Center for CDH Care

Children's Memorial Hermann Hospital

Versions of the CDH Registry

- Version 1 1995-2000
  - Defining the problem - medications, ventilator strategies, ECLS use
- Version 2 2001-2006
  - Understanding the details - delivery, oxygen/carbon dioxide, discharge status, cardiac anomalies
- Version 3 2007-2014
  - Staging - classifying defect size, pulmonary hypertension

Pulmonary Hypertension (PHTN):
First Echo on date: ___/___/___
PHTN: ☐None ☐ < 2/3 systemic ☐ between 2/3 and systemic ☐ > systemic
Ductus: ☐ Open ☐ Closed
Ductal Shunt: ☐ L to R ☐ Bidirectional ☐ R to L
Atrial Shunt: ☐Yes ☐No
Tricuspid regurgitation: ☐Yes ☐No

Last Echo on date: ___/___/___
PHTN: ☐None ☐ < 2/3 systemic ☐ between 2/3 and systemic ☐ > systemic
Ductus: ☐ Open ☐ Closed
Ductal Shunt: ☐ L to R ☐ Bidirectional ☐ R to L
Atrial Shunt: ☐Yes ☐No
Tricuspid regurgitation: ☐Yes ☐No

Treatment of Pulmonary Hypertension:

Check if used		Date Started	Date Ended
☐	Inhaled Nitric Oxide – Maximum dose: __ ppm	__/__/__	__/__/__
☐	Sildenafil ☐ Oral ☐ iv	__/__/__	__/__/__
☐	Endothelial Receptor Blockade	__/__/__	__/__/__
☐	Prostacyclin	__/__/__	__/__/__
☐	Alprostadil (PGE1)	__/__/__	__/__/__
☐	Milrinone	__/__/__	__/__/__
☐	Other (specify): _____	__/__/__	__/__/__

Ventilation:
Intubated at: date: ___/___/___, time: ____
Extubated at date: ___/___/___ (☐ Never extubated)

Actual Values in the first 24 hours of life (pre-ECMO):

Highest **pre**-ductal PaO_2: ____ mm Hg O_2 sat: _____% ☐ Not available	Highest **post**-ductal PaO_2: ____ mm Hg O_2 sat: _____% ☐ Not available
Highest $PaCO_2$: ____ mm Hg ☐ Not available	Lowest $PaCO_2$: ____ mm Hg ☐ Not available
Highest Lactate in first 24 hours: ____ mmol/L)	Highest Lactate in first 72 hours: ____mmol/L)

Version 3

Side of Diaphragmatic Hernia: ☐Left ☐Right ☐Bilateral/Central

☐ **No Repair:**
Reasons repair not done (select best):
- ☐ Unable to stabilize patient
- ☐ Patient felt to be non-survivable / not candidate for ECMO:
  - ☐ PaO_2 never greater than _____
  - ☐ $PaCO_2$ never lower than _____
  - ☐ Anomaly: Cardiac / Chromosomal / Other
  - ☐ Parents requested no further therapy
  - ☐ Other: _____
- ☐ Patient felt to be survivable / not candidate for ECMO:
  - ☐ Prematurity / low birth weight
  - ☐ IVH or cerebral hemorrhage pre-ECMO
  - ☐ Parents requested no further therapy
  - ☐ Other: _____
- ☐ Patient felt to be survivable / placed on ECMO but no repair done:
  - ☐ IVH or cerebral hemorrhage on ECMO
  - ☐ Other ECMO complication: _____
  - ☐ Parents requested no further therapy
  - ☐ Unable to wean off ECMO
  - ☐ Late diagnosis of anomaly: Cardiac / Chromosomal / Other
  - ☐ Other: _____
- ☐ Patient came off ECMO but was not repaired:
  - ☐ Refractory hypoxia
  - ☐ Refractory hypercarbia
  - ☐ Anomaly: Cardiac / Chromosomal / Other
  - ☐ Parents requested no further therapy
  - ☐ Multisystem organ failure
  - ☐ Sepsis
  - ☐ Other: _____

☐ **Repair Done:**
Repair done on date: ___/___/___ time: _____
Diaphragm Defect: ☐A ☐B ☐C ☐D

(Have surgeon identify which diagram (A, B, C, D) most closely approximates defect noted intra-operatively. Orientation: diagrams drawn with the diaphragm (defect) on the patient's left and you are looking up from the abdomen towards the chest)

Type Repair: ☐Primary ☐Patch
If Patch, type patch: ☐PTFE ☐Surgisis ☐Mesh plug ☐Alloderm ☐Other
Hernia Sac: ☐Yes ☐No
Liver: ☐Chest ☐Abdomen
Approach: ☐Subcostal ☐Thoracic ☐Both ☐Thoracoscopic ☐Laparoscopic
☐Other: _____
Abdominal Closure: ☐Primary ☐Ventral hernia ☐Silo ☐Patch ☐Other: _____
Chest Tube: ☐Yes ☐No

Version 3

Versions of the CDH Registry

- Version 1 1995-2000
  - Defining the problem - medications, ventilator strategies, ECLS use
- Version 2 2001-2006
  - Understanding the details - delivery, oxygen/carbon dioxide, discharge status, cardiac anomalies
- Version 3 2007-2014
  - Staging - classifying defect size
- Version 4 2015-present
  - The role of the heart and PH, prenatal dx

Issues addressed by version 4

- Timing of surgical repair when receiving ECLS
- Cardiac dysfunction in CDH
- CDH-associated pulmonary hypertension
- Prenatal diagnosis / prediction in CDH

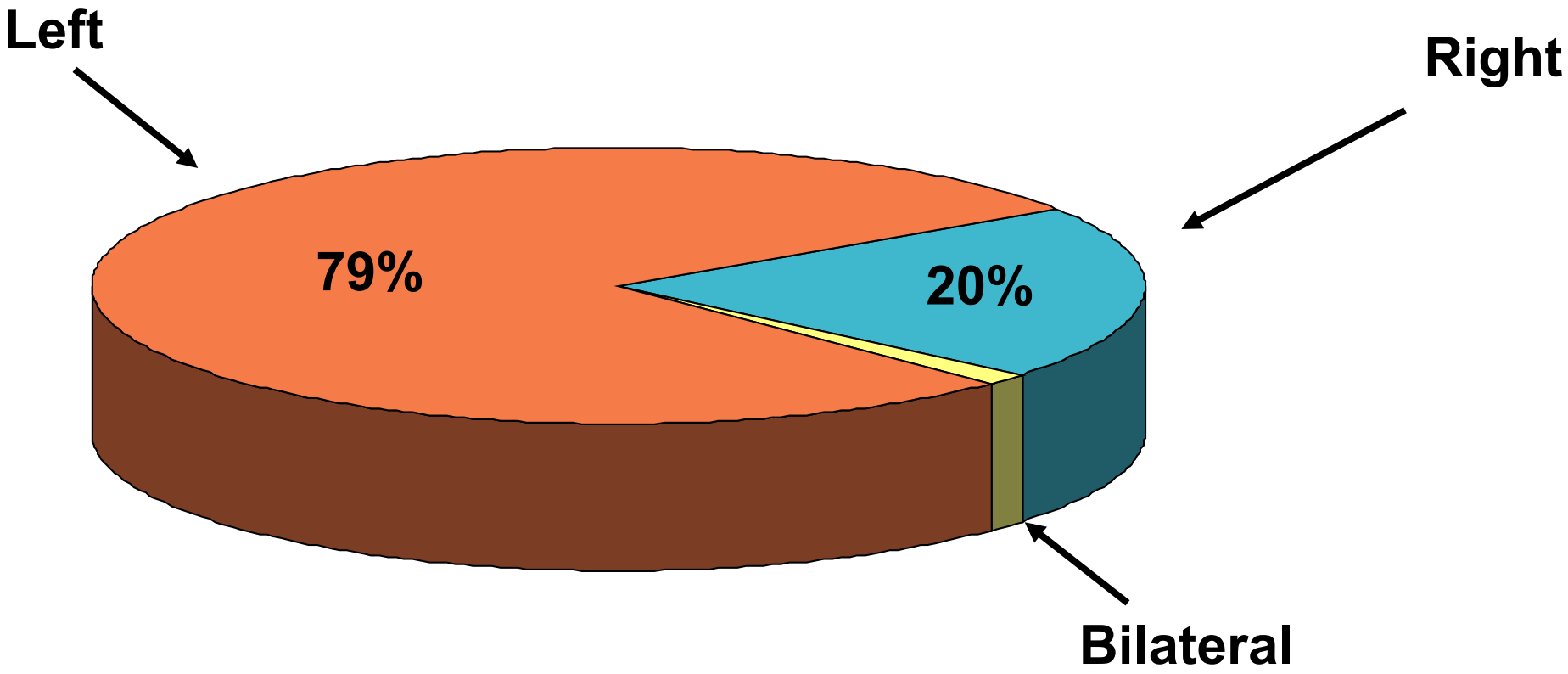
85 Centers/17 countries/12,000 Patients

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

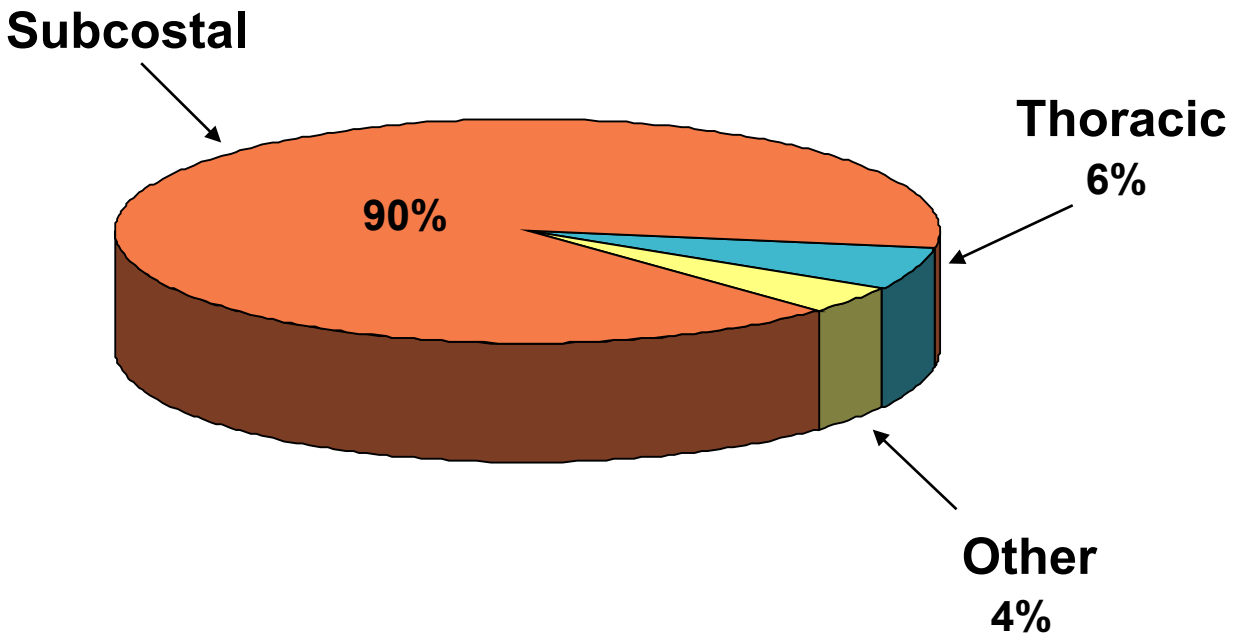
CDH The Comprehensive Center for CDH Care

Children's Memorial Hermann Hospital

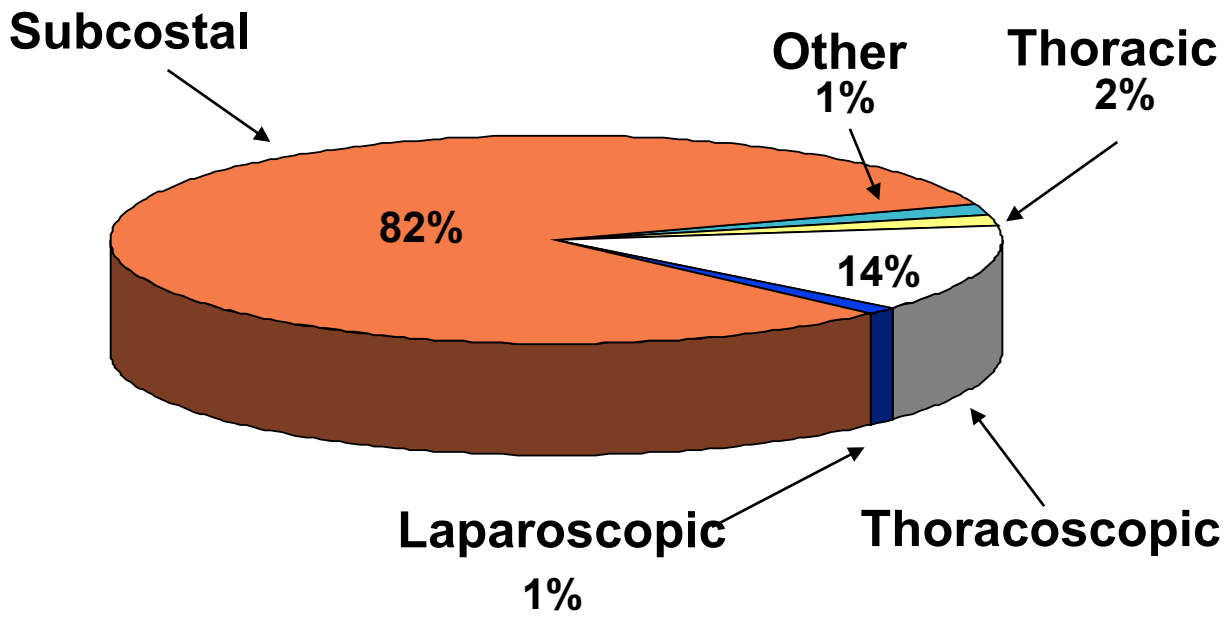
Hernia Side



Operative Approach

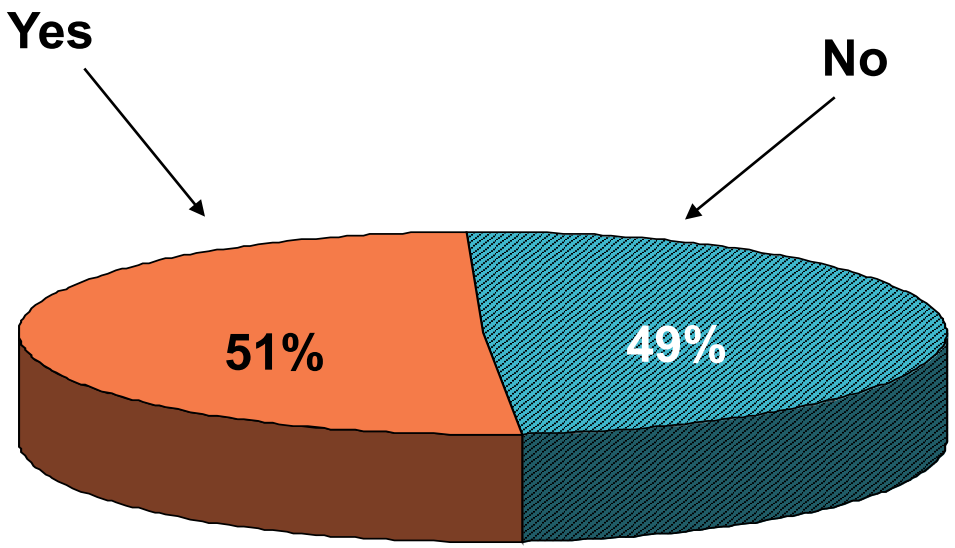


1995-1996

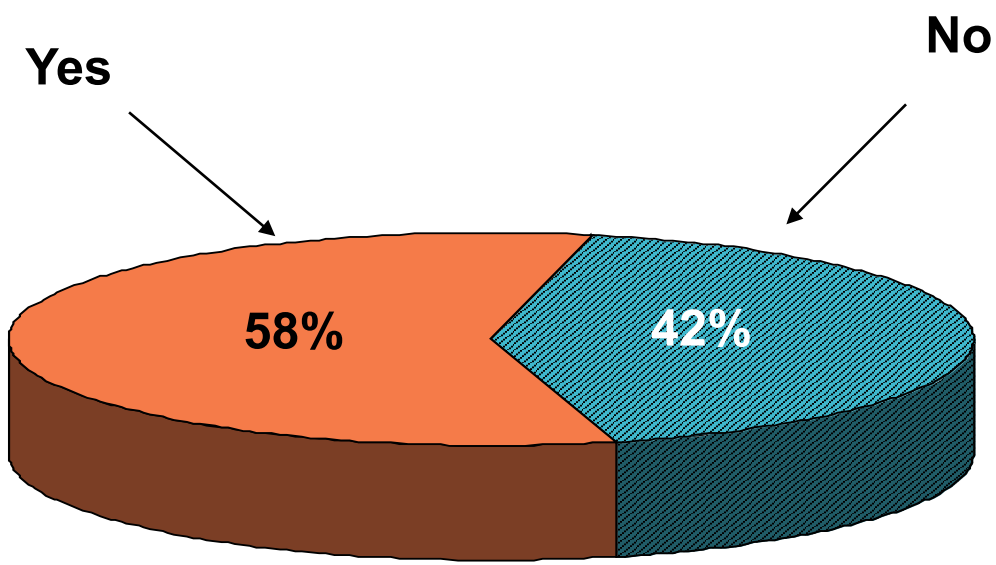


2017-2018

Patch Used In Repair

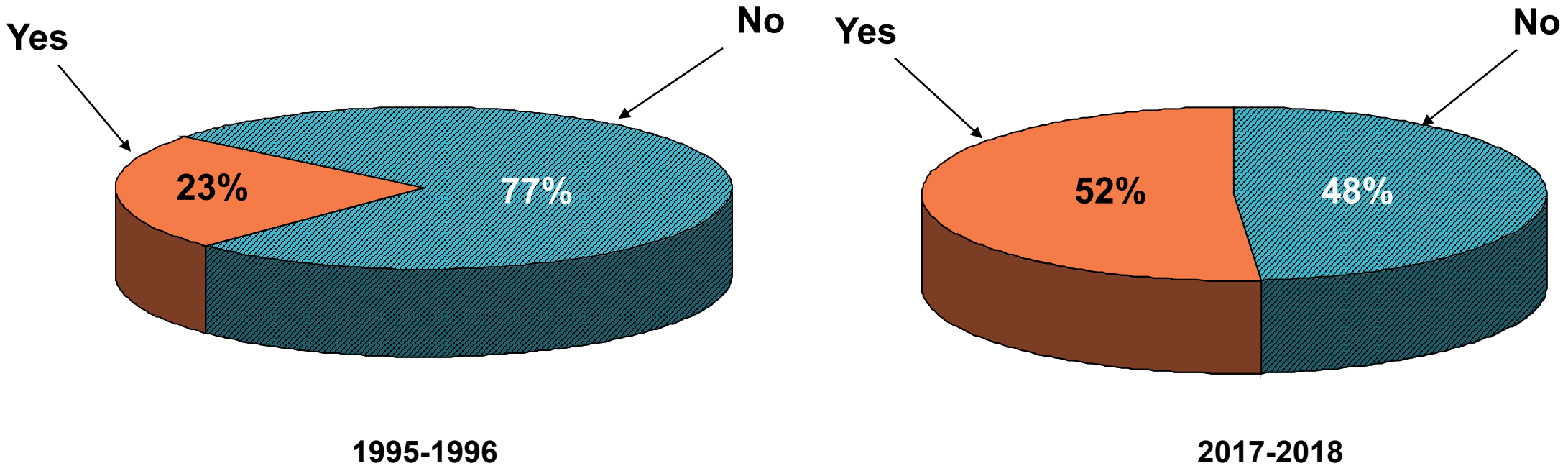


1995-1996

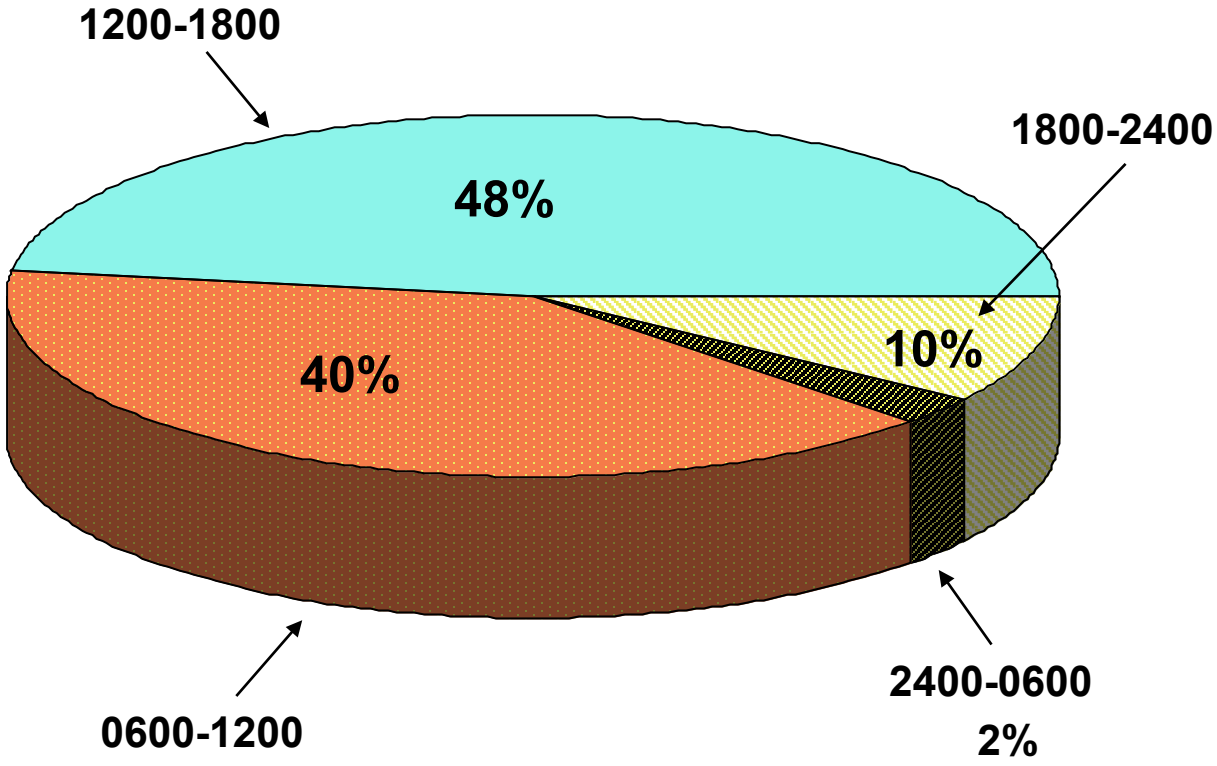


2017-2018

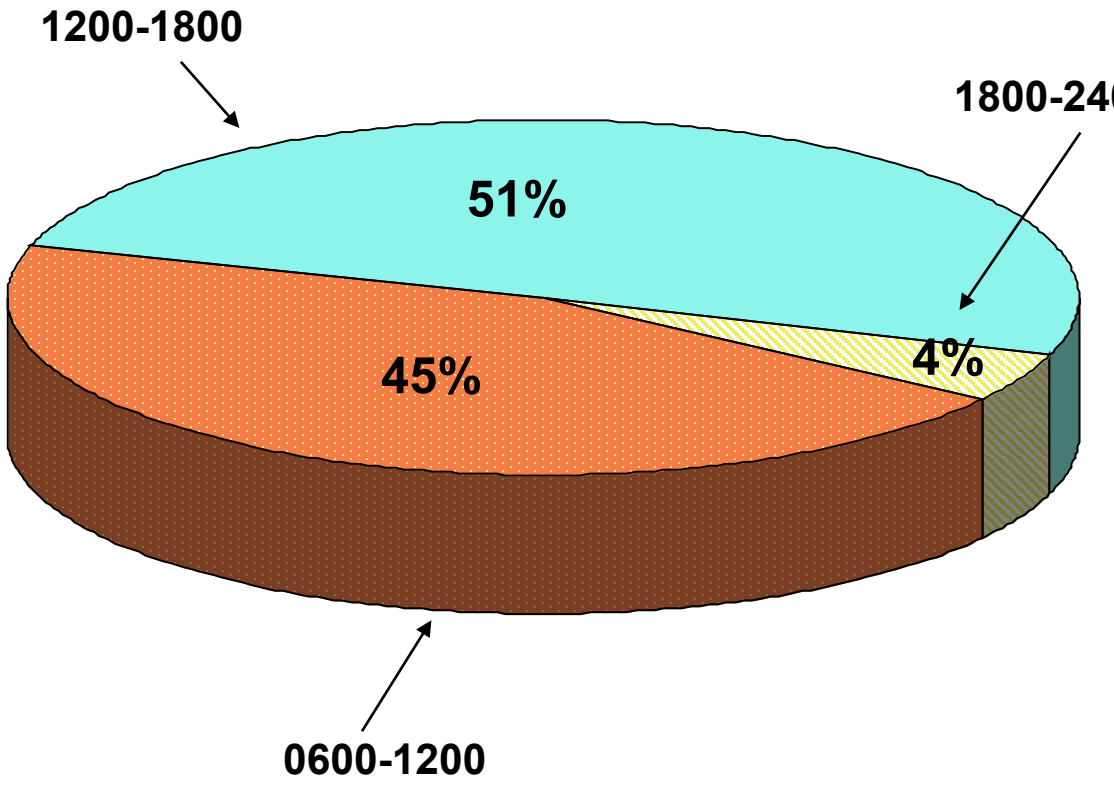
Repair On ECMO (Of all ECMO)



Time of Day For Repair



1995-1996



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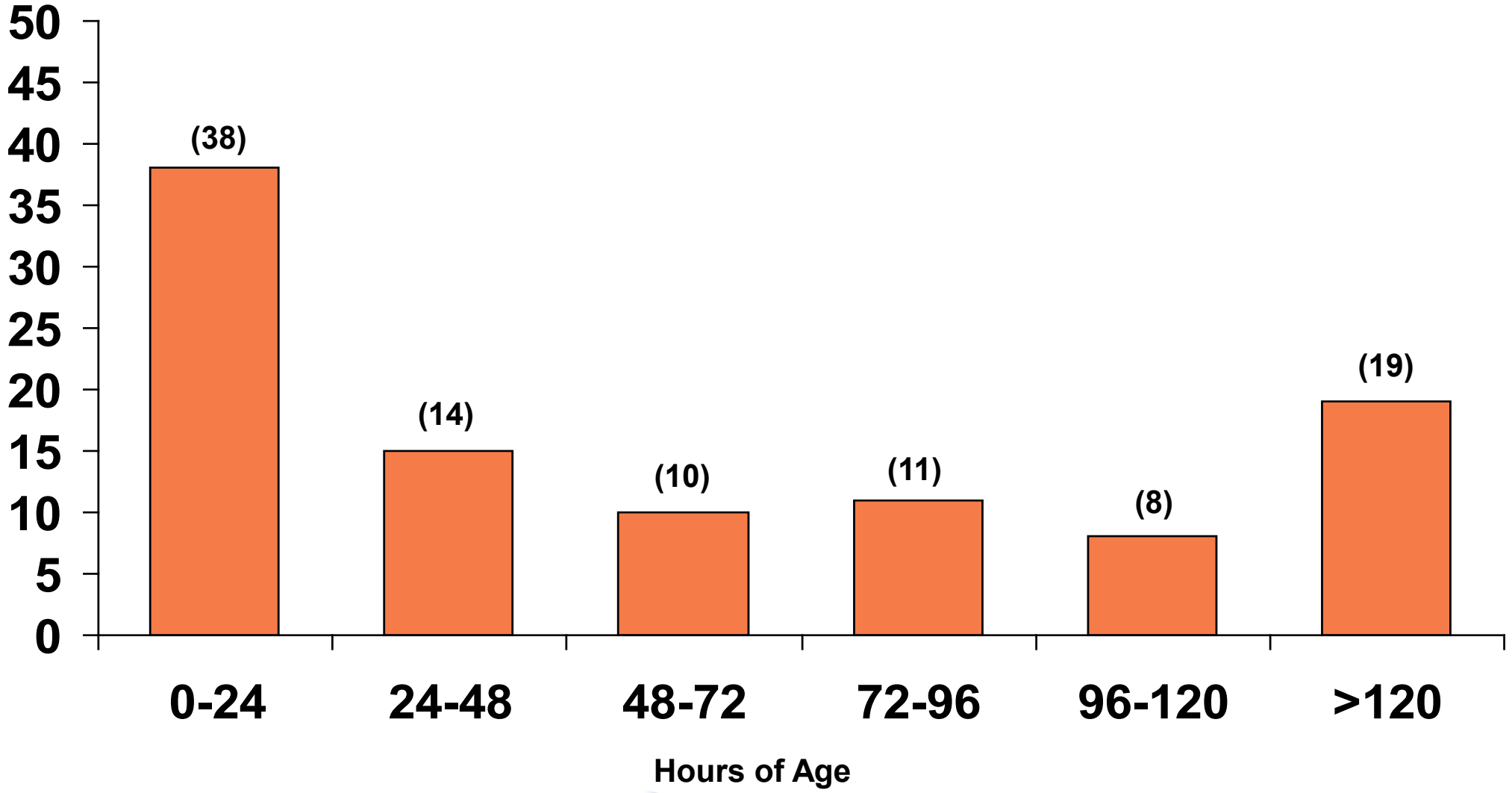
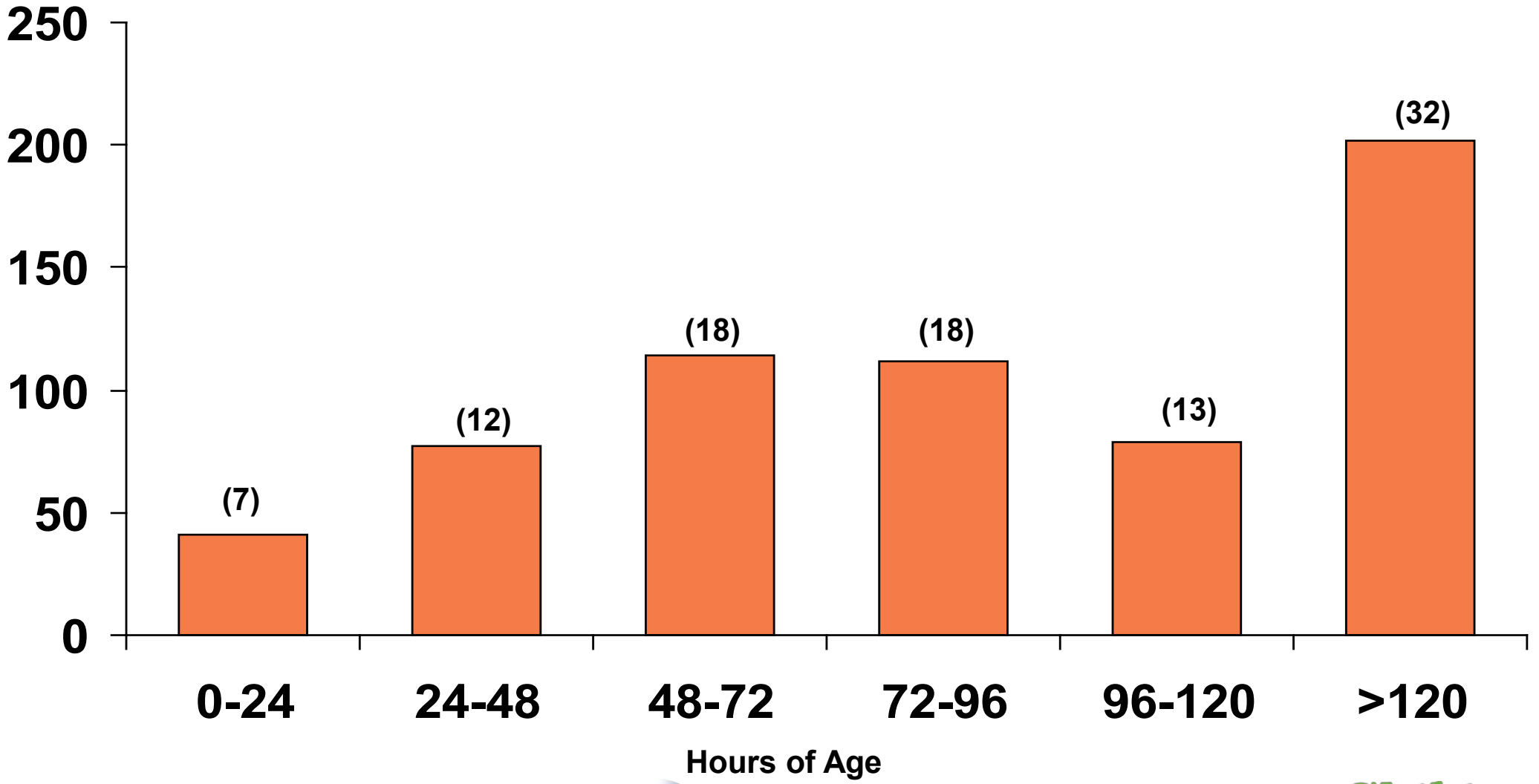
Timing of Operation (No ECMO)



1995-1996

Timing of Operation (No ECMO)



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2017-2018

Children's Memorial Hermann Hospital

Publications

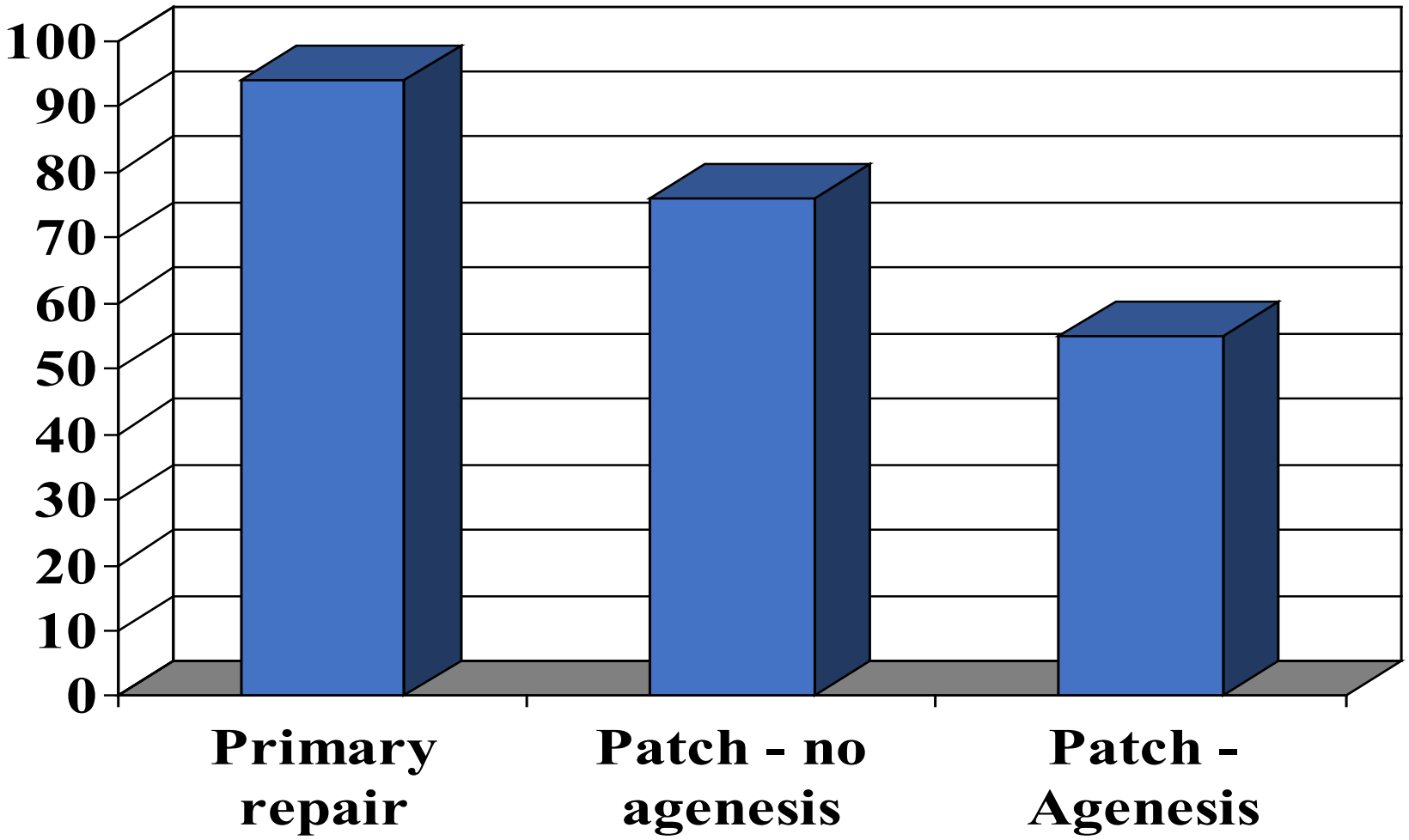
- Data available only to CDHSG members
- Authored by writing committee on behalf of CDHSG
- 55 publications
- Multiple studies in progress

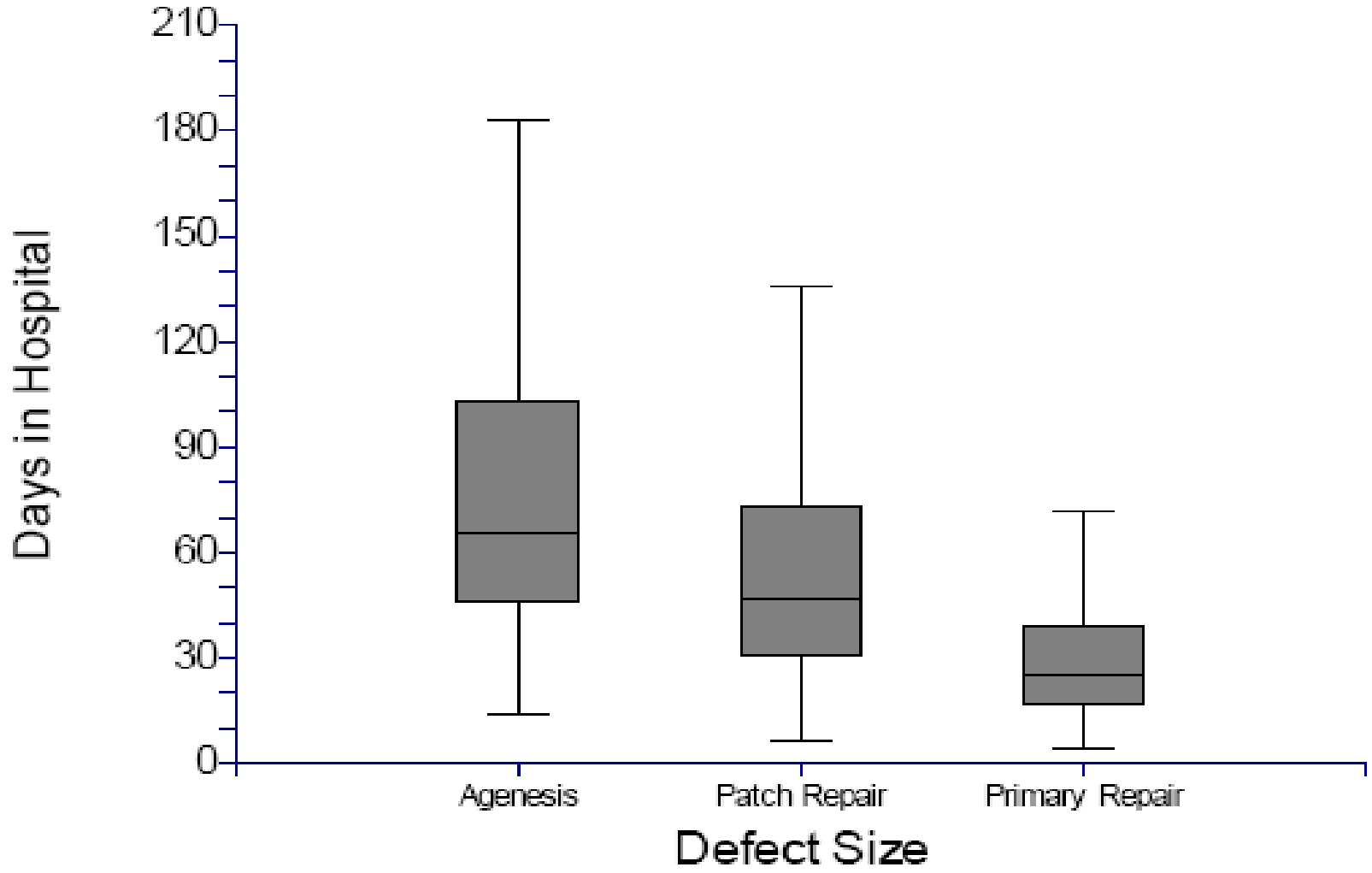
Defect Size Determines Survival in Infants With Congenital Diaphragmatic Hernia

The Congenital Diaphragmatic Hernia Study Group

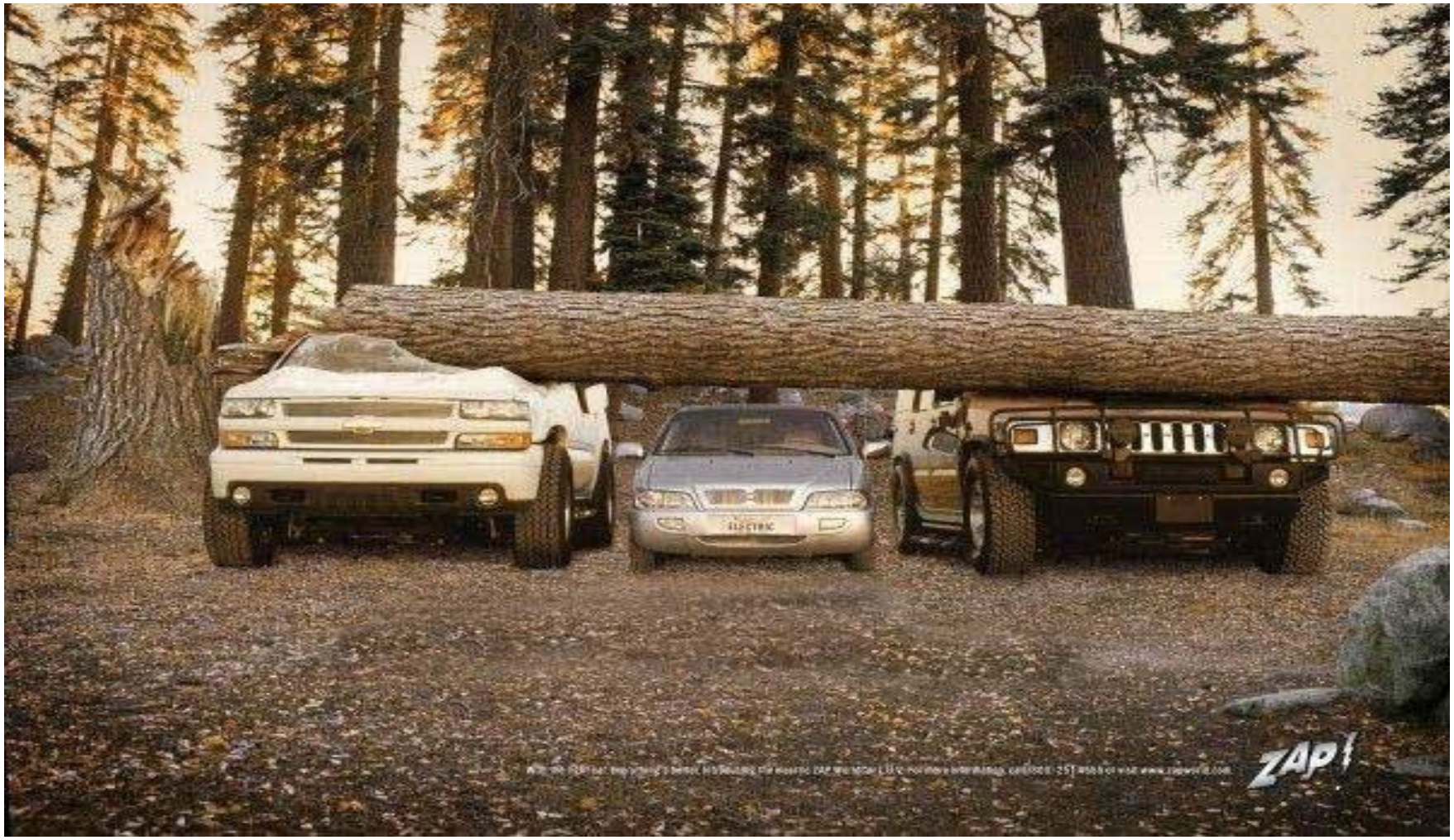
Pediatrics 2007;120;e651-e657
DOI: 10.1542/peds.2006-3040

Defect Size


100
90
80
70
60
50
40
30
20
10
0
Primary repair
Patch - no agenesis
Patch - Agenesis


210
180
150
120
90
60
30
0
Days in Hospital
Agenesis
Patch Repair
Primary Repair
Defect Size

Size Does Matter!



Defect Size

It became apparent that not all CDH were created equal and that size of defect was important

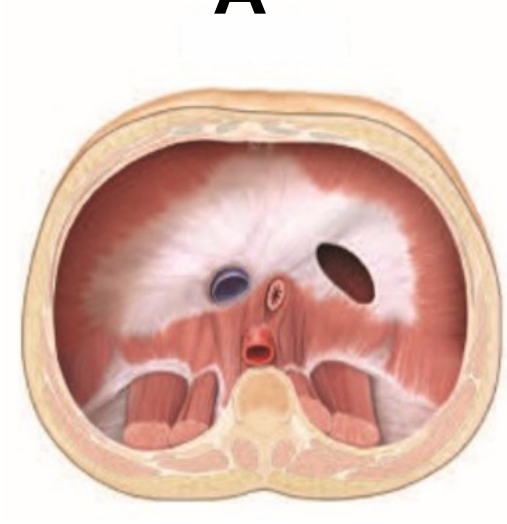
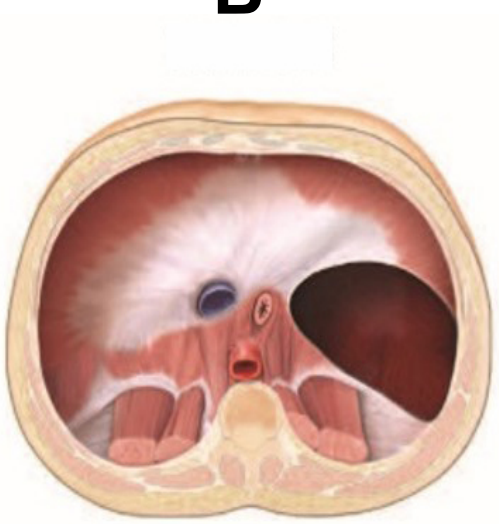
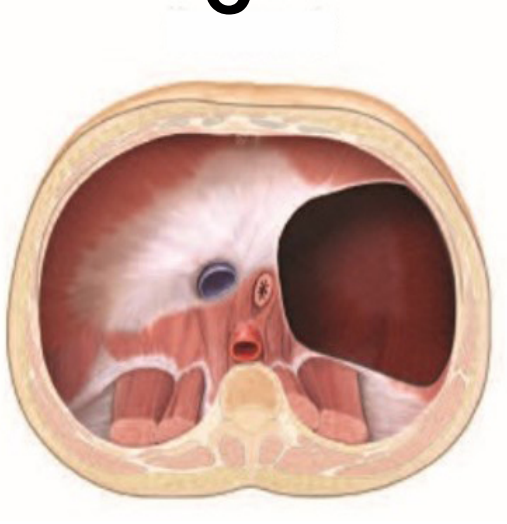
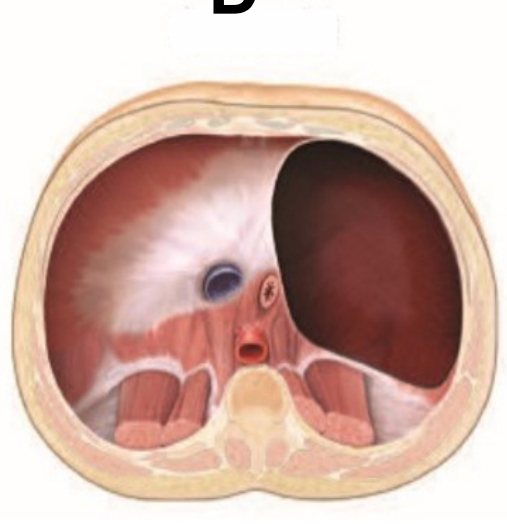
Version III designed to quantitate size of defect

Standardized Reporting for Congenital Diaphragmatic Hernia
An International Consensus

Methods
Factors Evaluated

- Defect class
- Cardiac anomalies
- Chromosomal anomalies
- Birthweight /Gestational age
- Apgar Scores

CDHSG Staging

	A	B	C	D
				
Frequency	13%	44%	30%	13%
Survival	99%	96%	78%	58%

Lally, et al, *J Pediatr Surg*, 2013

Congenital diaphragmatic hernia: Defect size correlates with developmental defect

The Congenital Diaphragmatic Hernia Study Group [1]

Journal of Pediatric Surgery (2013) **48**, 1177–1182

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

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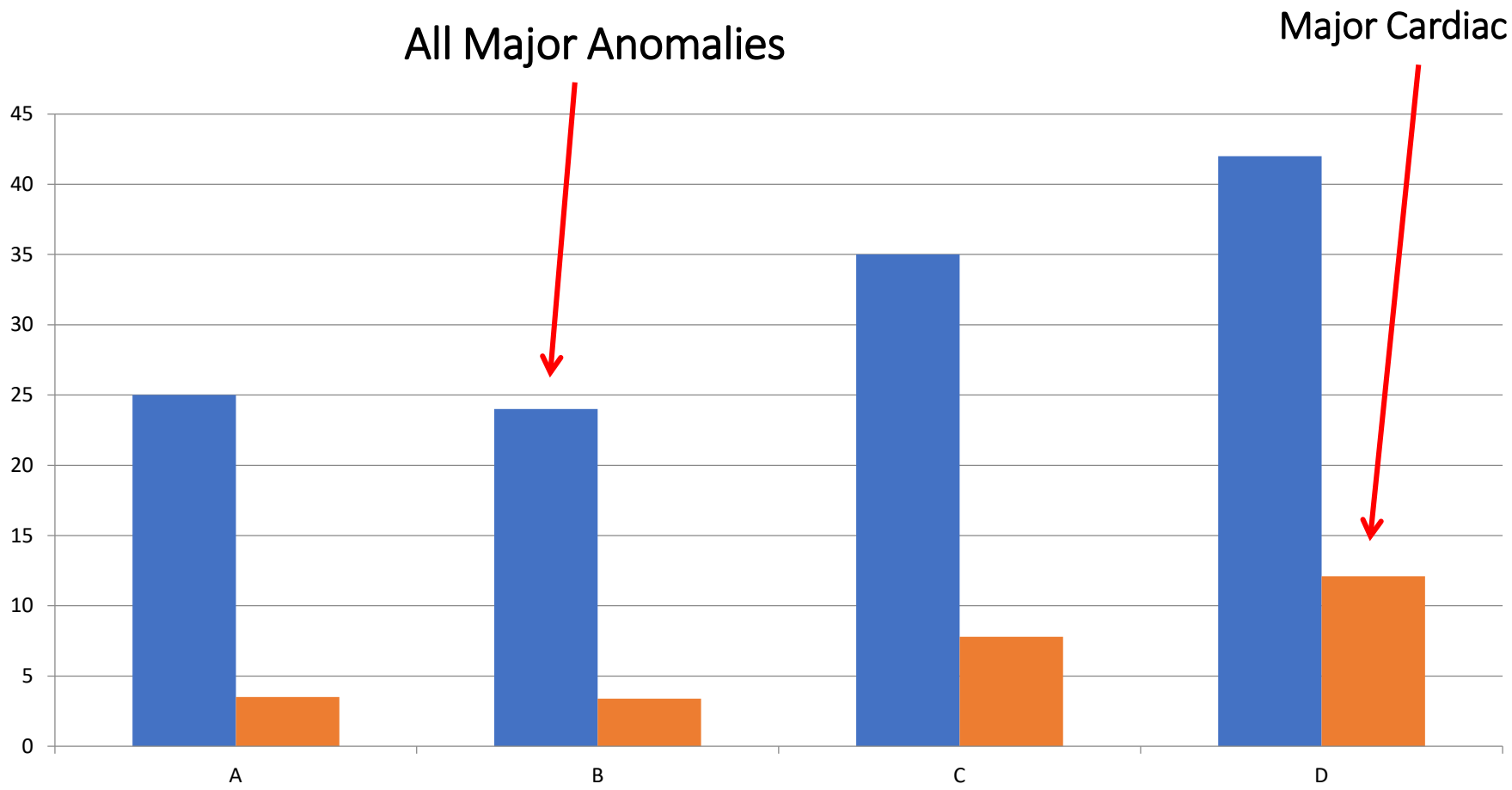
Children's Memorial Hermann Hospital

Methods

- V. 3 of Registry
- Grouped by defect size
- Compared for associated anomalies

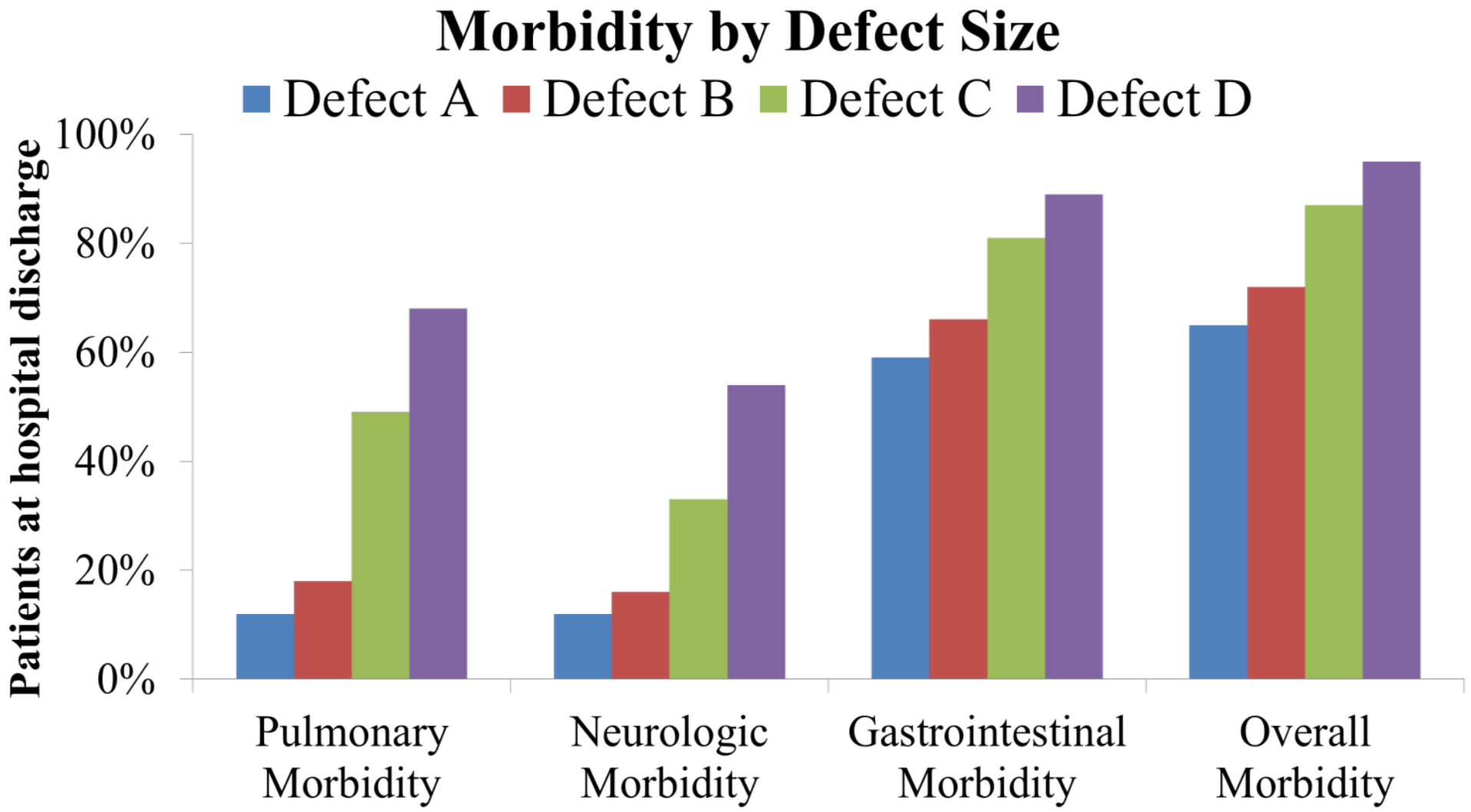

All Major Anomalies
Major Cardiac
45
40
35
30
25
20
15
10
5
0
A
B
C
D

Congenital Diaphragmatic Hernia Defect Size and Infant Morbidity at Discharge

PEDIATRICS Volume 138: 2016:e2016204

Methods

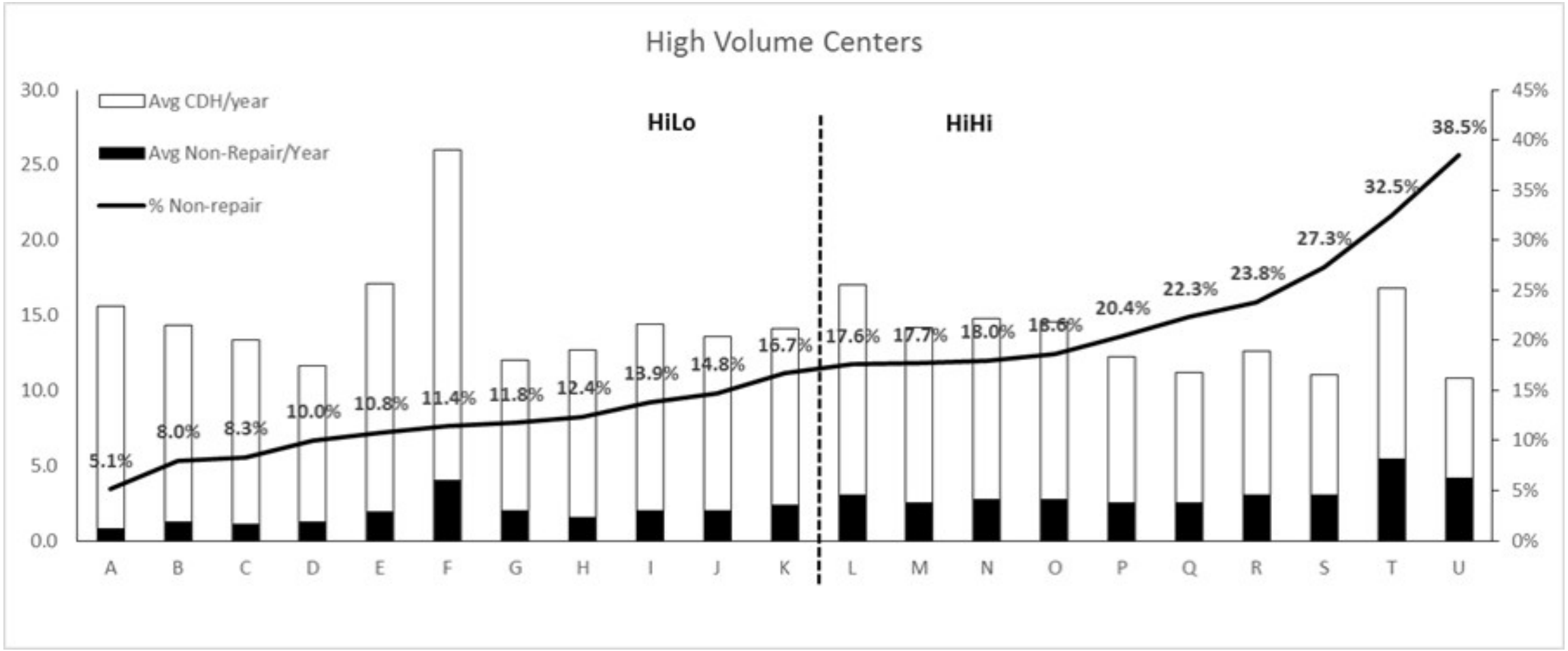
- V. 3 of Registry
- Evaluated recorded morbidity at d/c
- Correlated degree of morbidity to defect
- Analysis between groups and time


Morbidity by Defect Size
Defect A
Defect B
Defect C
Defect D
Patients at hospital discharge
100%
80%
60%
40%
20%
0%
Pulmonary Morbidity
Neurologic Morbidity
Gastrointestinal Morbidity
Overall Morbidity

Conclusions

- Defect correlated with morbidity as well as mortality
- Overall improving morbidity
- No major changes in large defect patients

Is aggressive surgical management worth it?



Harting et al, *Ann Surg*, 2018

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

CDH The Comprehensive Center for CDH Care

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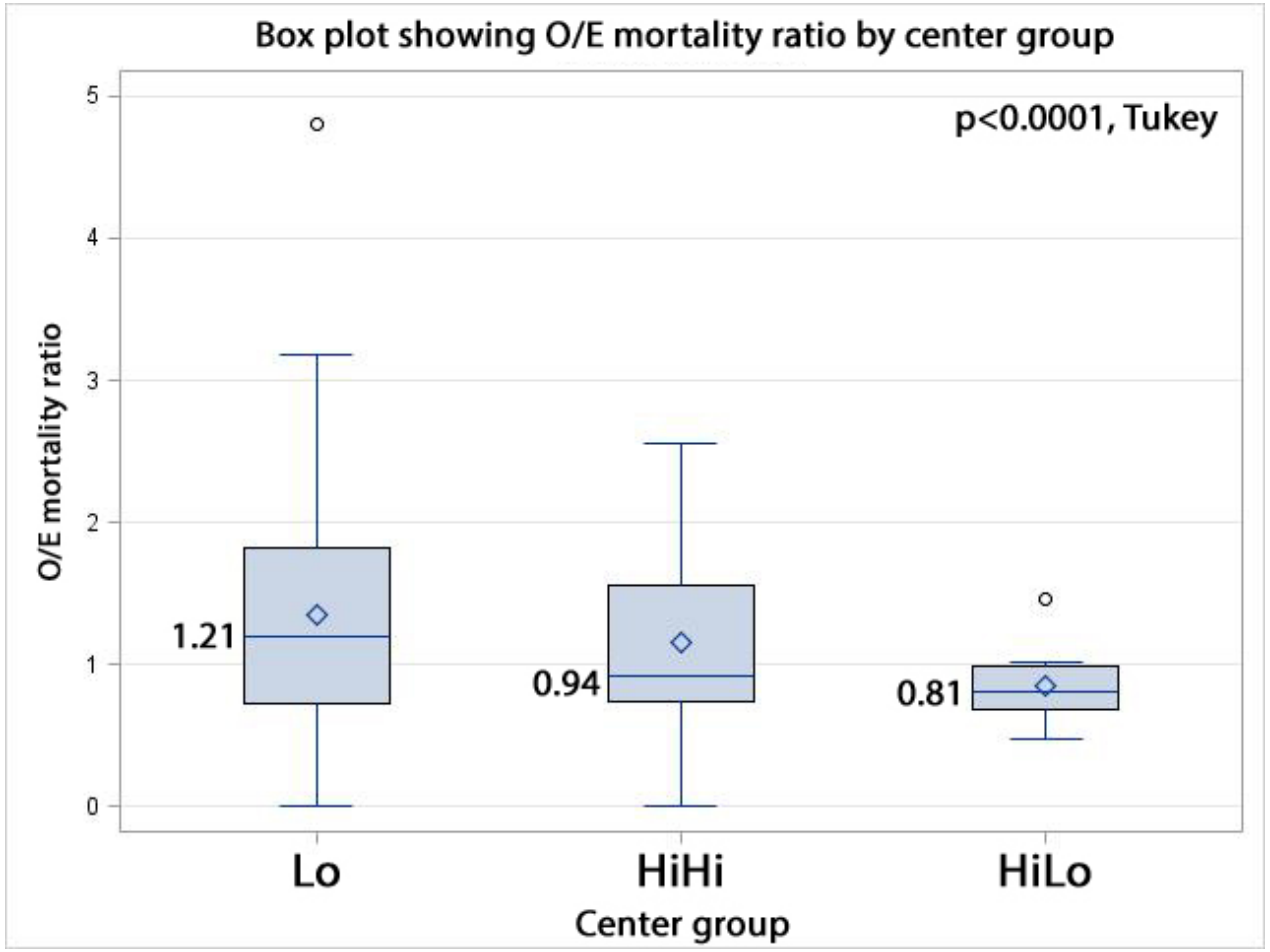
Is aggressive surgical management worth it?



Harting et al, *Ann Surg*, 2018

Conclusions

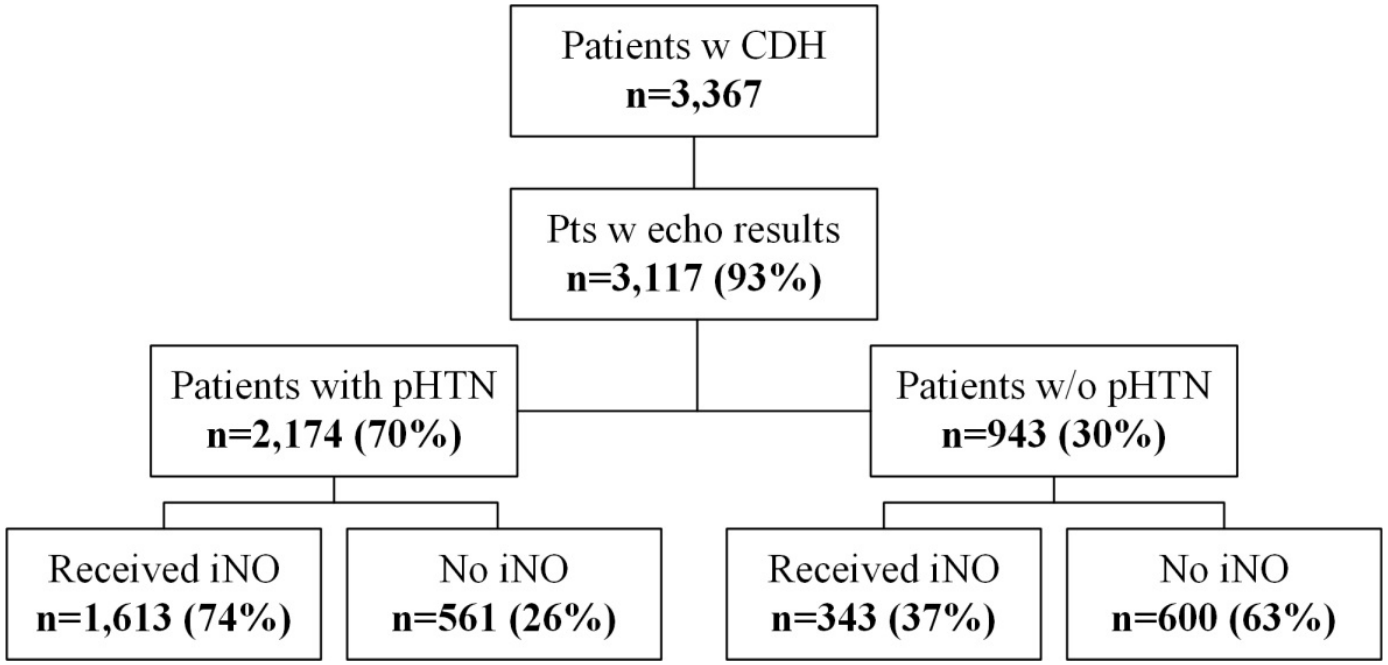
- Aggressive approach leads to highest survival
- It is costly
- Morbidity is high

JAMA Pediatrics | Original Investigation

Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia

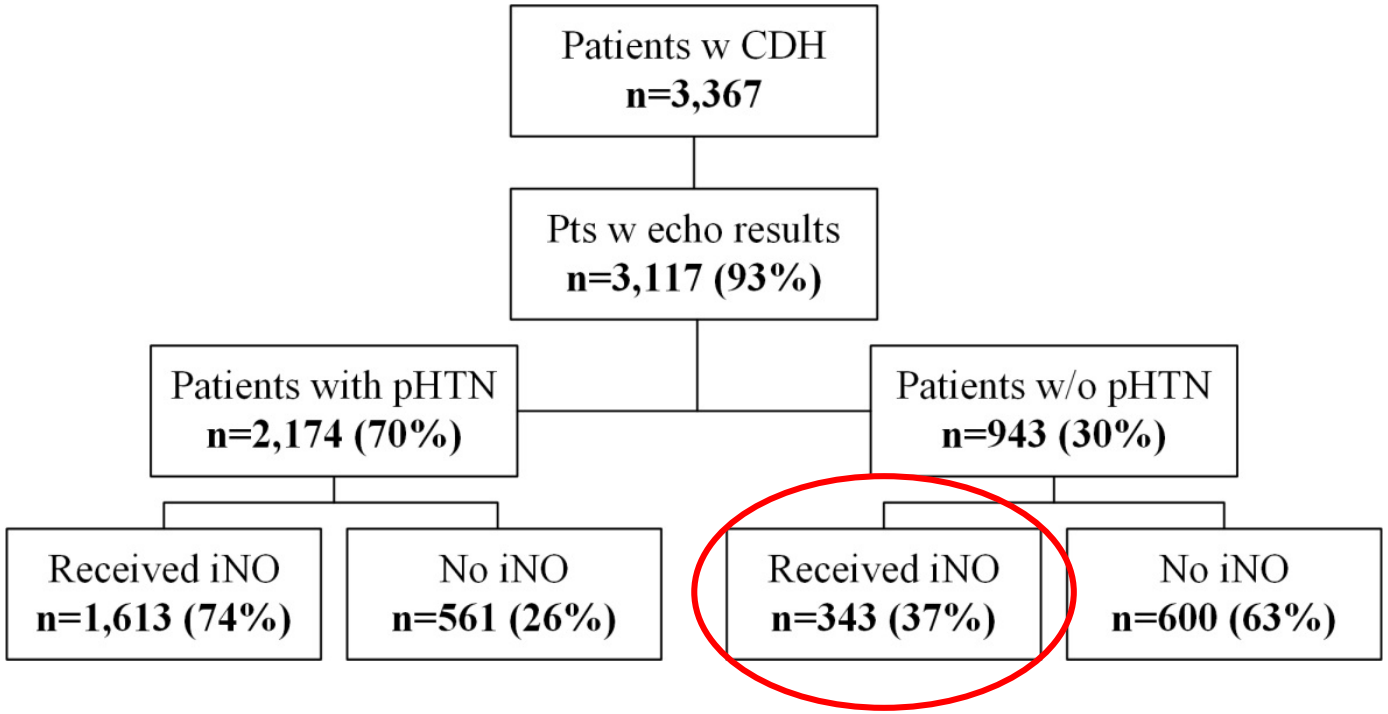
JAMA Pediatr. 2016;170(12):1188-1194. doi:10.1001/jamapediatrics.2016.2023
Published online October 10, 2016.

What about Nitric Oxide ?



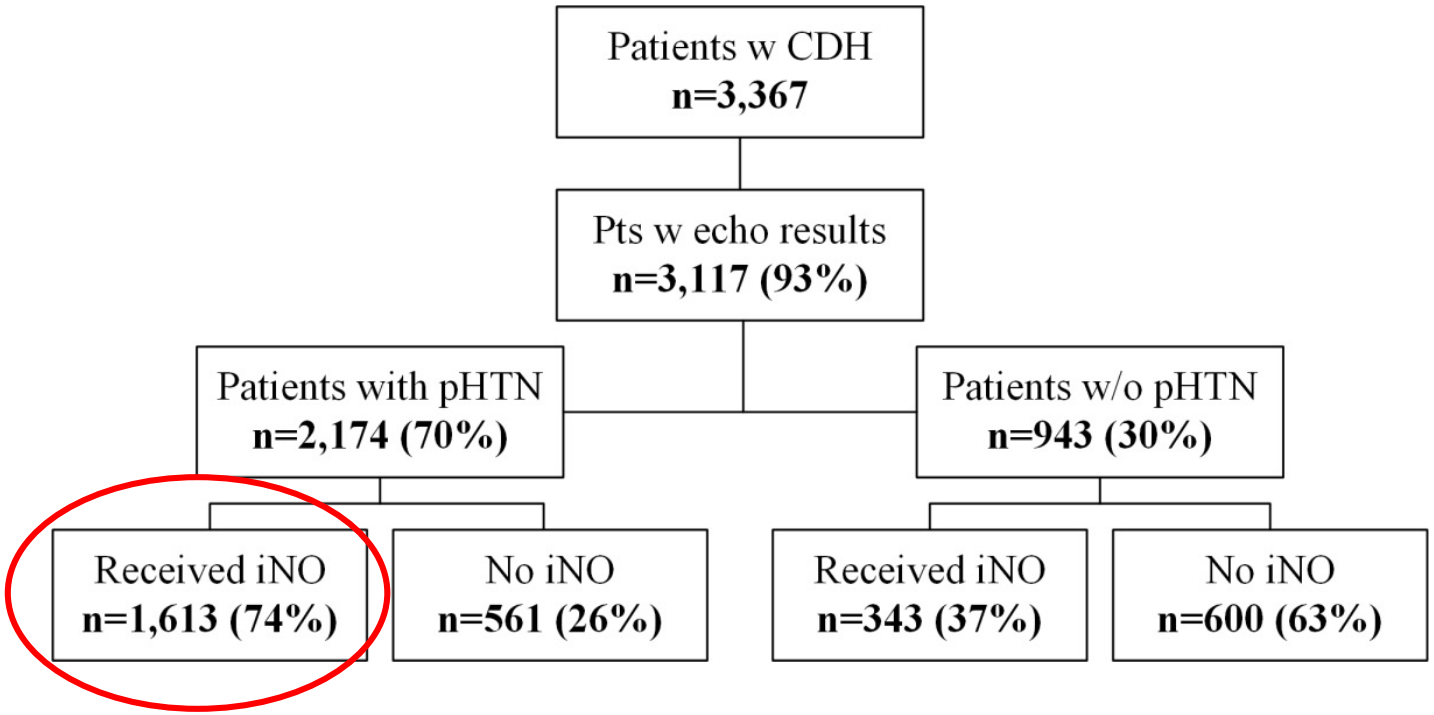
Putnam et al, *JAMA Pediatrics*, 2017

What about Nitric Oxide ?



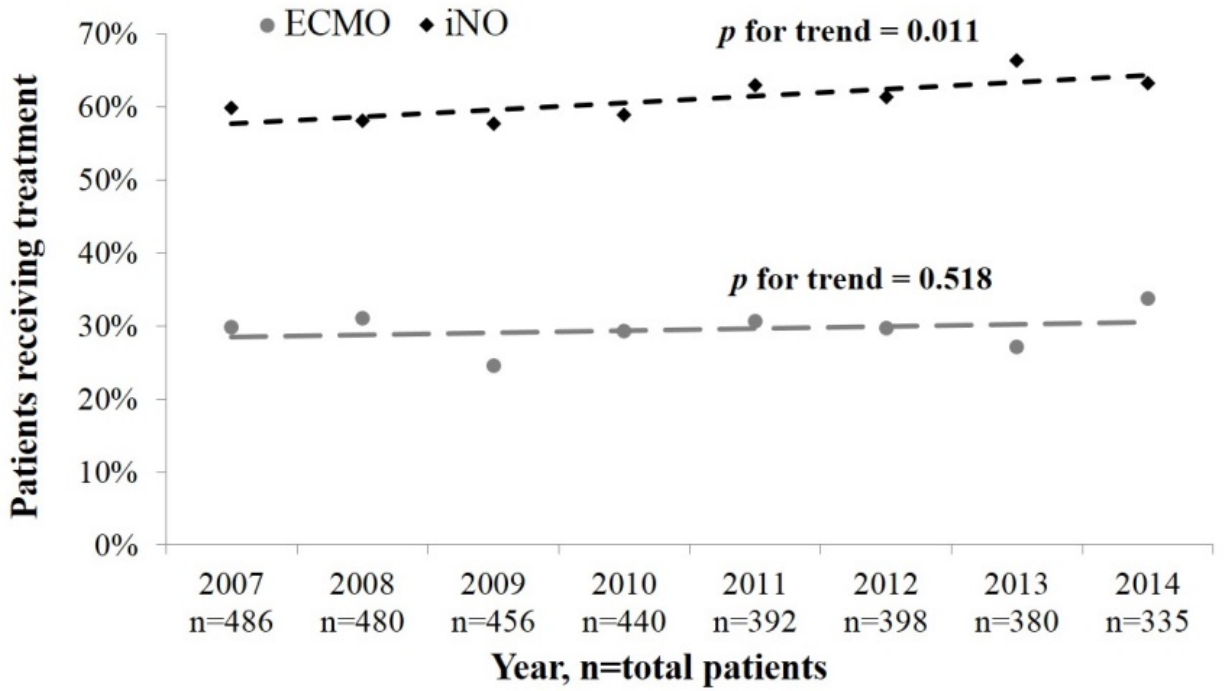
Putnam et al, *JAMA Pediatrics*, 2017

What about Nitric Oxide ?



Putnam et al, *JAMA Pediatrics*, 2017

What about Nitric Oxide ?

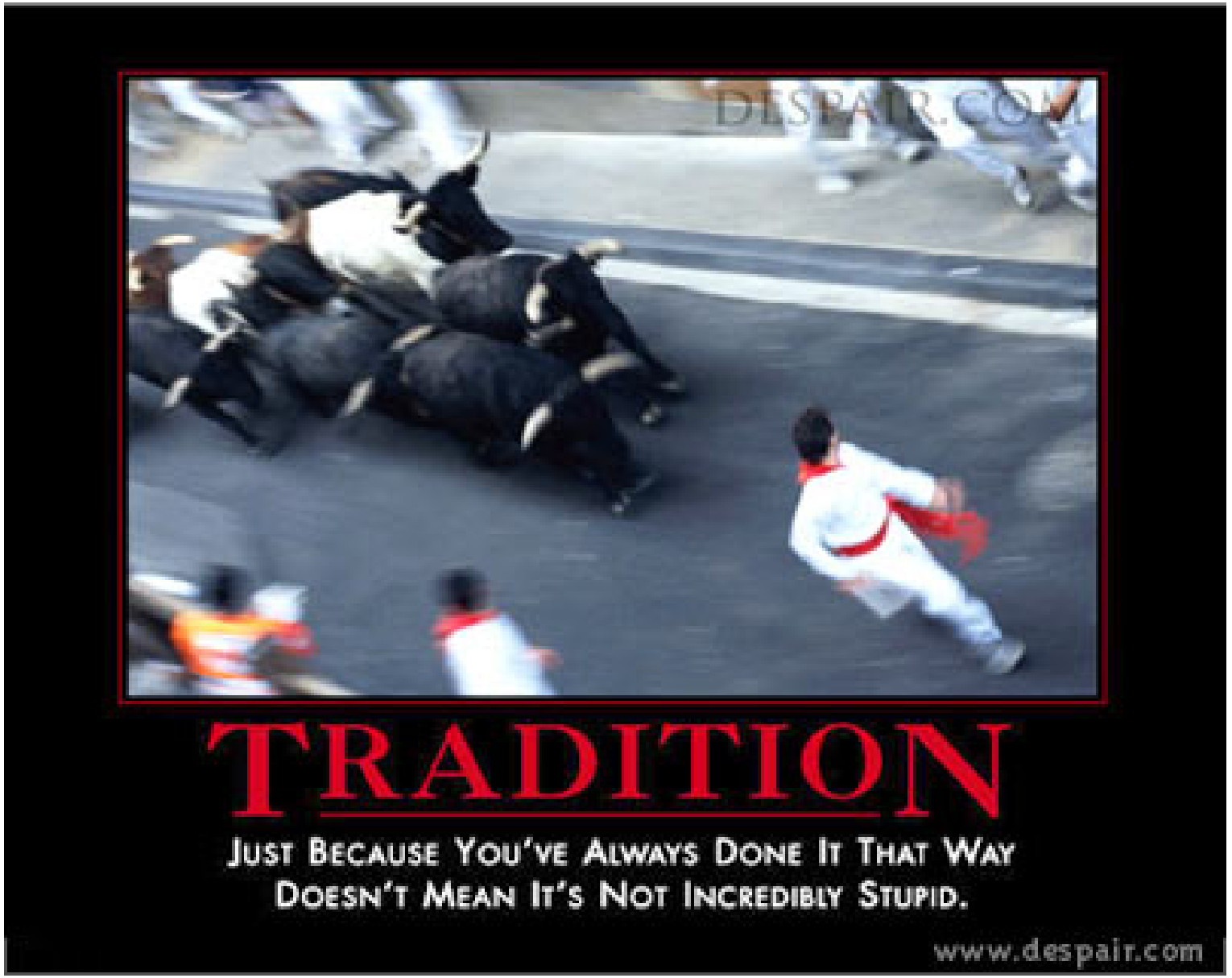


Putnam et al, *JAMA Pediatrics*, 2017

Treatment with iNO was associated with a 15% higher absolute mortality

Conclusions

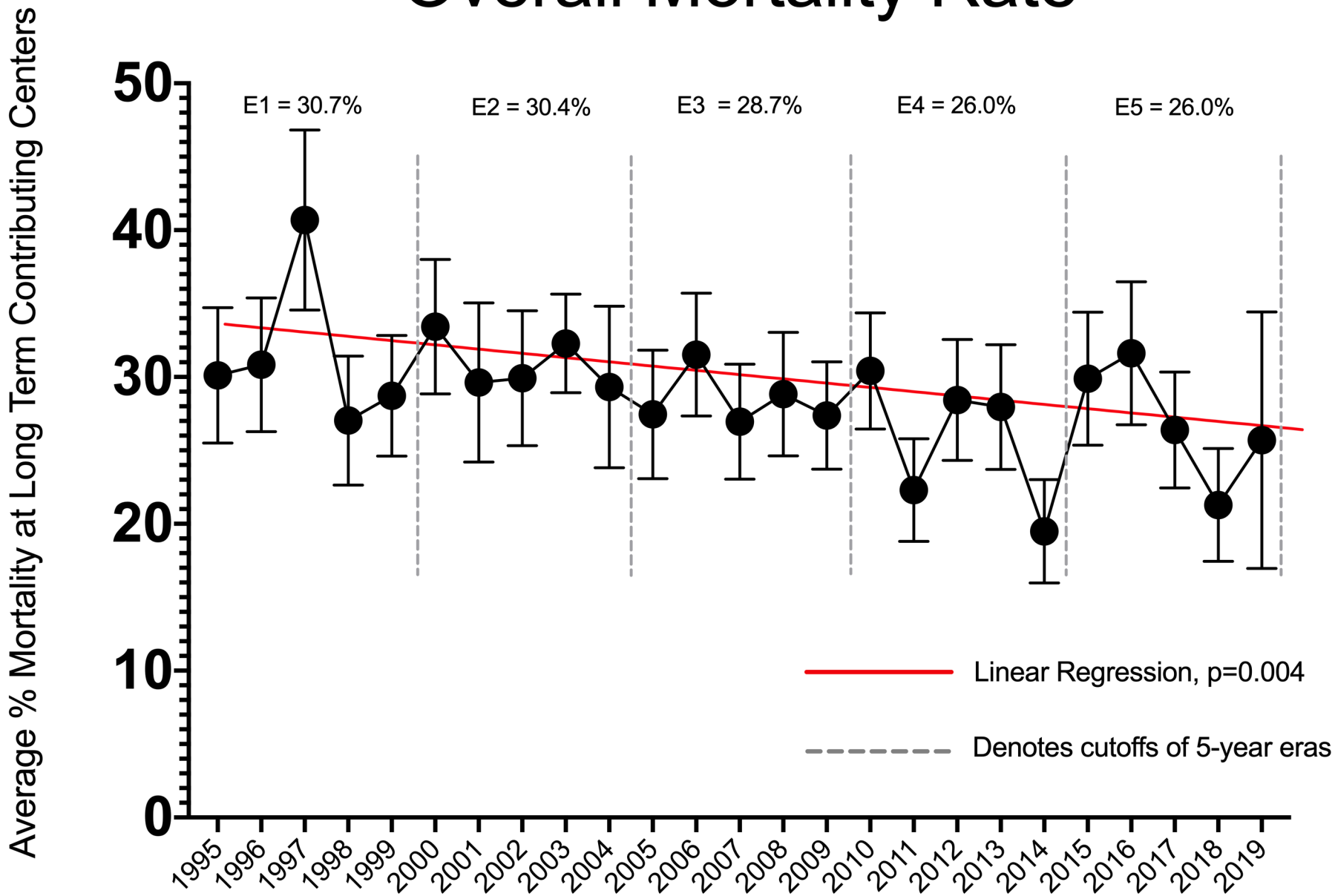
- iNO use highly variable between centers
- > 1/3 patients w/o CDH-PHTN received iNO
- Little data to support iNO benefit in CDH
- iNO use is *associated* with worse outcome
- iNO use in patients with CDH needs re-evaluation

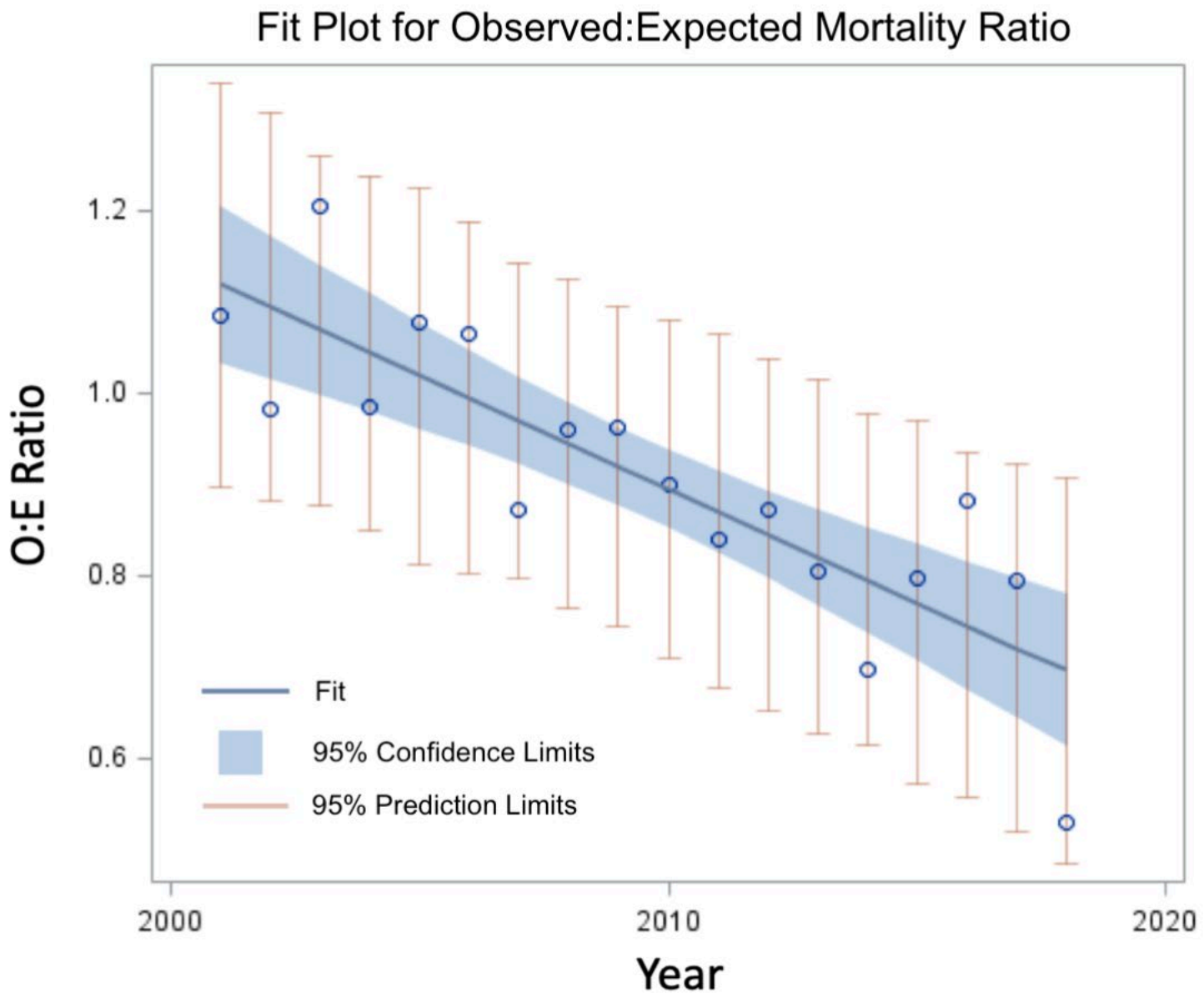

TRADITION
Just Because You've Always Done It That Way
Doesn't Mean It's Not Incredibly Stupid.
www.despair.com

25 Years – Any Progress?

- Centers with at least 22 years of continual participation
- Grouped by 5 year intervals
- Evaluated Overall Survival
- Looked at O:E survival

Overall Mortality Rate




Fit Plot for Observed:Expected Mortality Ratio
O:E Ratio
1.2
1.0
0.8
0.6
2000
2010
2020
Year
Fit
95% Confidence Limits
95% Prediction Limits

25 Years – Any Progress?

- Significant increase in survival over years
- Current overall survival is 73% for all comers
- Surgical survival is 85%
- Remains a large variation amongst centers

The CDH Study Registry

PROs

- Ability to study infrequent problems
- Data on very large number of patients
- Individual centers can compare themselves with others
- Demonstrate changes over time of management and outcome

The CDH Study Registry

CONs

- Observational data
- Inability to evaluate long-term sequelae
- Difficult to collect complicated information
- Wide spectrum of patients and treatment philosophies


The Future
NEXT EXIT

The “Gold Standard”

Randomized Clinical Trial

- Expensive ($500k-$3 million+)
- Labor intensive
- Takes a long time (5-10 years)
- Requires consent / challenges of recruitment
- Requires multi-institutional cooperation
- Answers a single question
- Nearly impossible to achieve appropriate sample size in CDH

The future of the CDHSG

- Ongoing evolution of versions to address current questions
  - Version 5 – Breakout session this meeting
- Management standardization
- Long term data collection
- Novel statistical analysis


Samford University
Commencement Ceremony
May 14, 2011
ZAP

John Roesler – DOB 11/26/2019

The secret of enjoying a good wine:

1. Open the bottle to allow it to breathe.

2. If it does not look like it's breathing, give it mouth-to-mouth.

Congenital diaphragmatic hernia

Long term follow-up

Francesco Morini
Department of Medical and Surgical Neonatology
Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

CDH

- ✓ Prenatal diagnosis & treatment
- ✓ Mechanical ventilation
- ✓ Drugs
- ✓ Surgery
- ✓ +/- ECMO
- ✓ DISCHARGE

francesco.morini@opbg.net

CDH: long term sequelae

"Now this is not the end. It is not even the beginning of the end.

But it is, perhaps, the end of the beginning."

Sir Winston Churchill, El Alamein, November 1942

francesco.morini@opbg.net

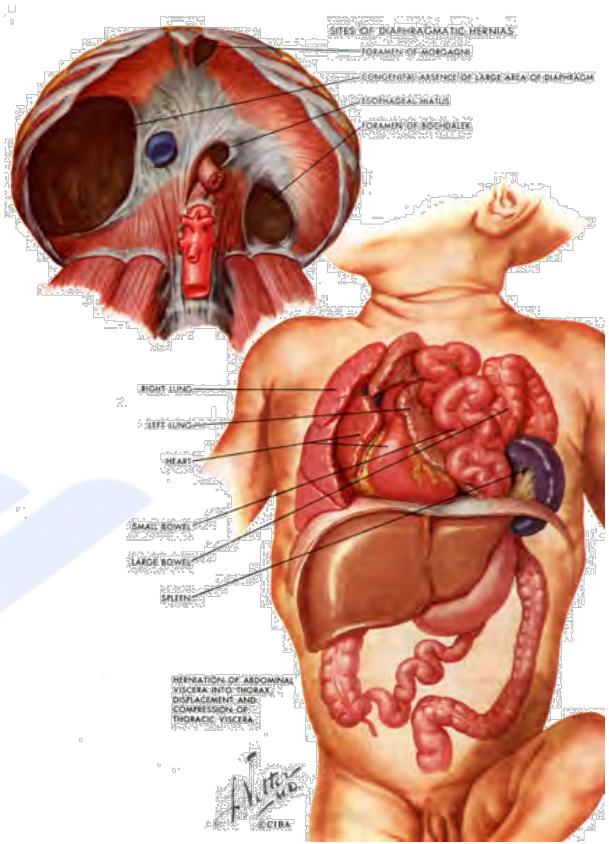
CDH: long term sequelae

Auxological	Up to 70%
Cardio-pulmonary	Up to 60%
Gastrointestinal	Up to 70%
NDO	Up to 40%
Orthopedic	Up to 30%
Surgical	Up to 50%

francesco.morini@opbg.net

CDH

- ✓ Diaphragmatic defect
- ✓ Pulmonary hypoplasia
- ✓ Pulmonary hypertension



francesco.morini@opbg.net

CDH

GENETIC COUNSELING, Vol. 26, No 3, 2015, pp 281-298

ASSOCIATED NON DIAPHRAGMATIC ANOMALIES AMONG CASES WITH CONGENITAL DIAPHRAGMATIC HERNIA

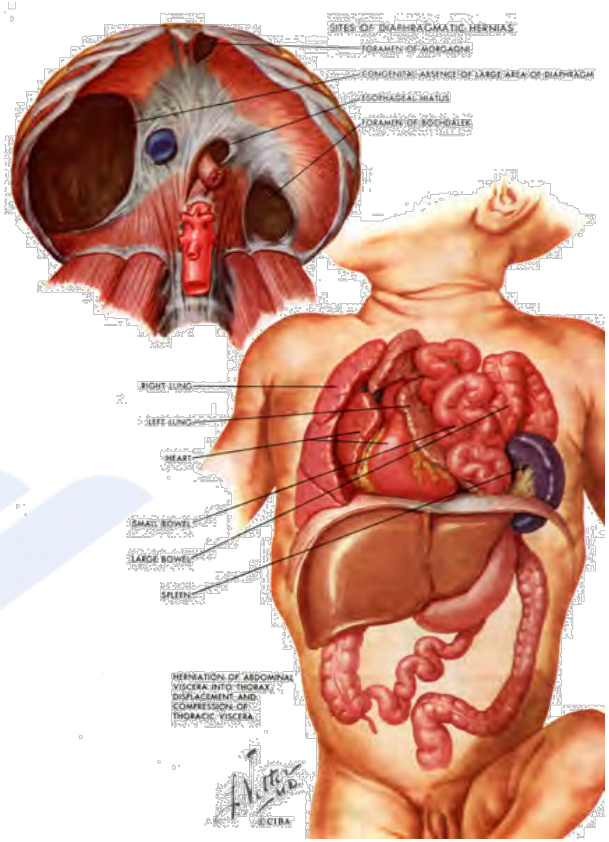
BY C. STOLL, Y. ALEMBIK, B. DOTT AND M.-P. ROTH

Table I: Isolated and associated anomalies in 139 cases with congenital diaphragmatic hernia (CDH) ascertained from 1979 to 2007 in 386,088 consecutive pregnancies in Northeastern France

	Number	%	P[c]
CDH with associated anomalies			
Nonchromosomal			
Recognized conditions[a]	24	17.3	
MCA[b]	36	25.9	
Chromosomal	25	18.0	
Total Associated	85	61.2	2.20
Isolated CDH	54	38.8	1.39
Total	139		3.60

[a]Included syndromes, associations, sequences, and complexes
[b]MCA: multiple congenital anomalies
[c]Prevalence per 10,000 pregnancies.

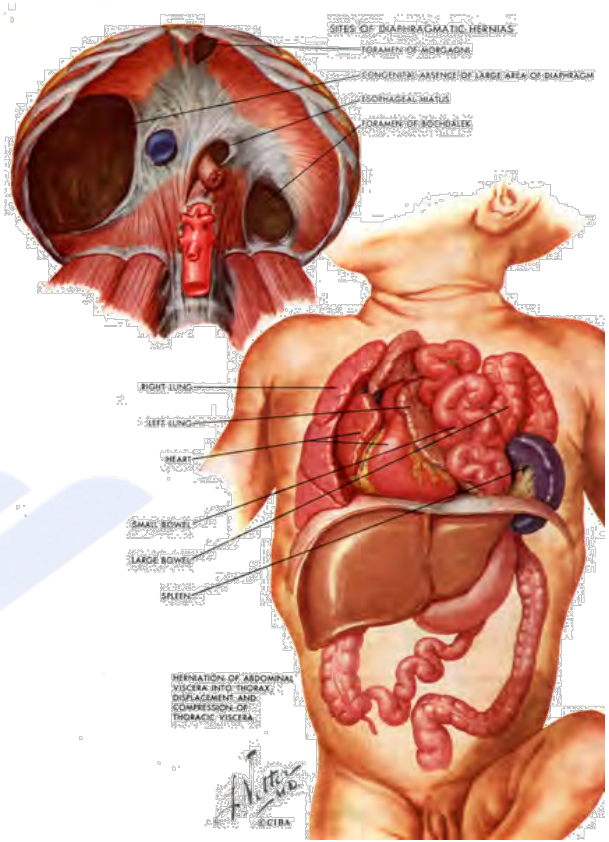
Stoll C et al., Genet Couns, 2015



francesco.morini@opbg.net

CDH

- ✓ Prenatal treatment
- ✓ Mechanical ventilation
  - ✓ FiO2
  - ✓ Pressure
- ✓ Drugs
- ✓ ECMO
- ✓ Minimal access surgery
- ✓ Patch repair

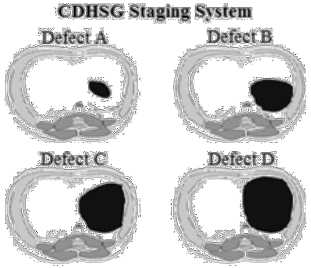


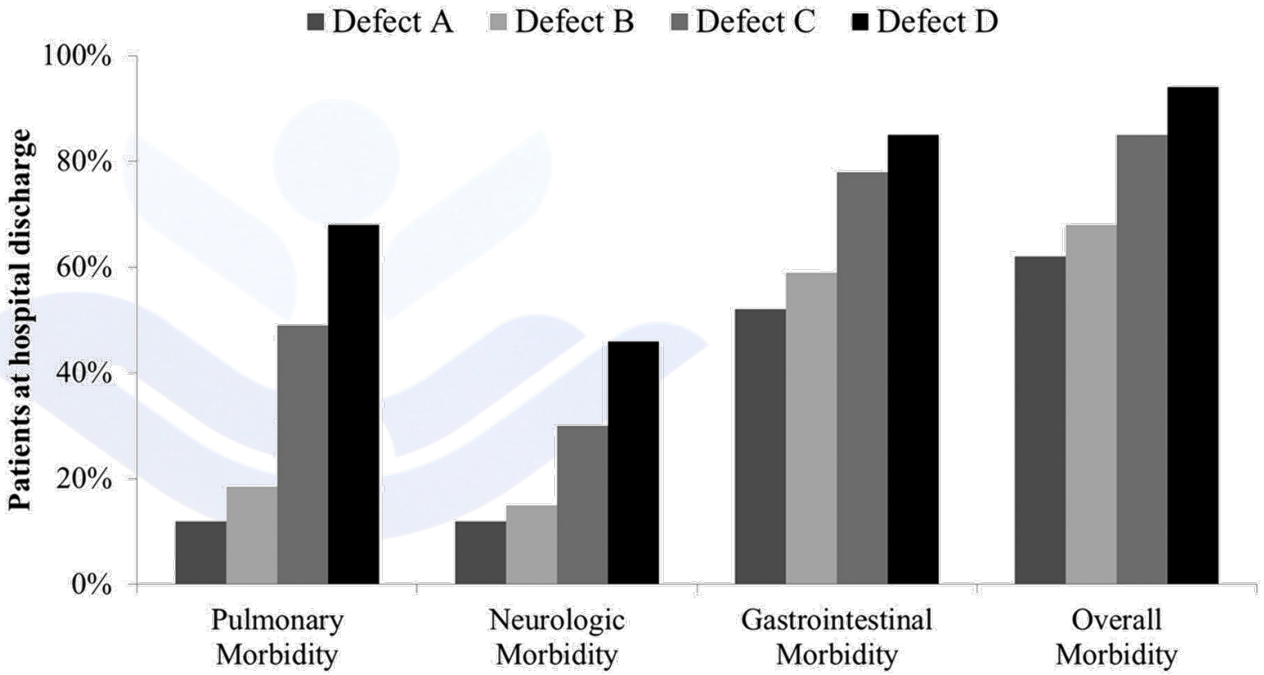
francesco.morini@opbg.net

CDH sequelae

Congenital Diaphragmatic Hernia Defect Size and Infant Morbidity at Discharge

Luke R. Putnam, MD, MS,[a] Matthew T. Harting, MD, MS,[a] Kuojen Tsao, MD,[a] Francesco Morini, MD,[b] Bradley A. Yoder, MD,[c] Matias Luco, MD,[d] Pamela A. Lally, MD,[a] Kevin P. Lally, MD, MS,[a] on behalf of the Congenital Diaphragmatic Hernia Study Group





Putnam LR et al., Pediatrics, 2016

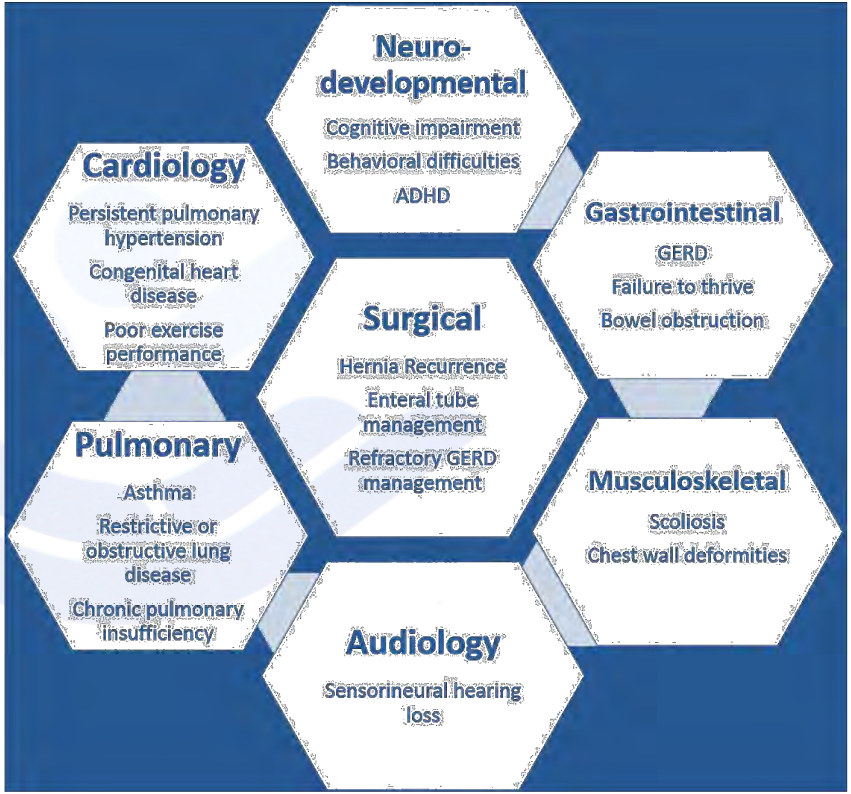
francesco.morini@opbg.net

CDH: long term sequelae

Long term follow-up in congenital diaphragmatic hernia

Laura E. Hollinger[a,*], *and Terry L. Buchmiller*[b]

[a]*Department of Surgery, Medical University of South Carolina, 96 Jonathan Lucas Street, MSC 613/CSB 417, Charleston SC 29425, USA*
[b]*Department of Surgery, Boston Children's Hospital, Boston MA, USA*



Hollinger LE & Buchmiller TL, Semin Perinatol, 2019

francesco.morini@opbg.net

Giorgia

Lung Transplantation for Late-Onset Pulmonary Hypertension in a Patient with Congenital Diaphragmatic Hernia

Chiara Iacusso[1] Francesco Morini[1] Irma Capolupo[1] Andrea Dotta[1] Stefania Sgrò[2] Francesco Parisi[3] Adriano Carotti[4] Pietro Bagolan[1]

- GA 33 wks; BW 1.6 kg
- STABILZATION: 72 h
- LEFT CDH (Type D defect, Liver up, Stomach up)
- REPAIR: Patch
- PO COURSE: Uneventful (O2 dependent at 30 days)
- DISCHARGE: 60 days after birth
- No O2-support

Iacusso C et al., Eur J Pediatr Surg Rep, 2018

francesco.morini@opbg.net

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Francesco Parisi[3] Adriano Carotti[4] Pietro Bagolan[1]

4 years-old…climbing!

- Regular follow up check-visits
- Unremarkable first 9 years of life…

JANUARY 21st, 2007
Abdominal pain, vomiting… Emergency admission…

Iacusso C et al., Eur J Pediatr Surg Rep, 2018

francesco.morini@opbg.net

Giorgia

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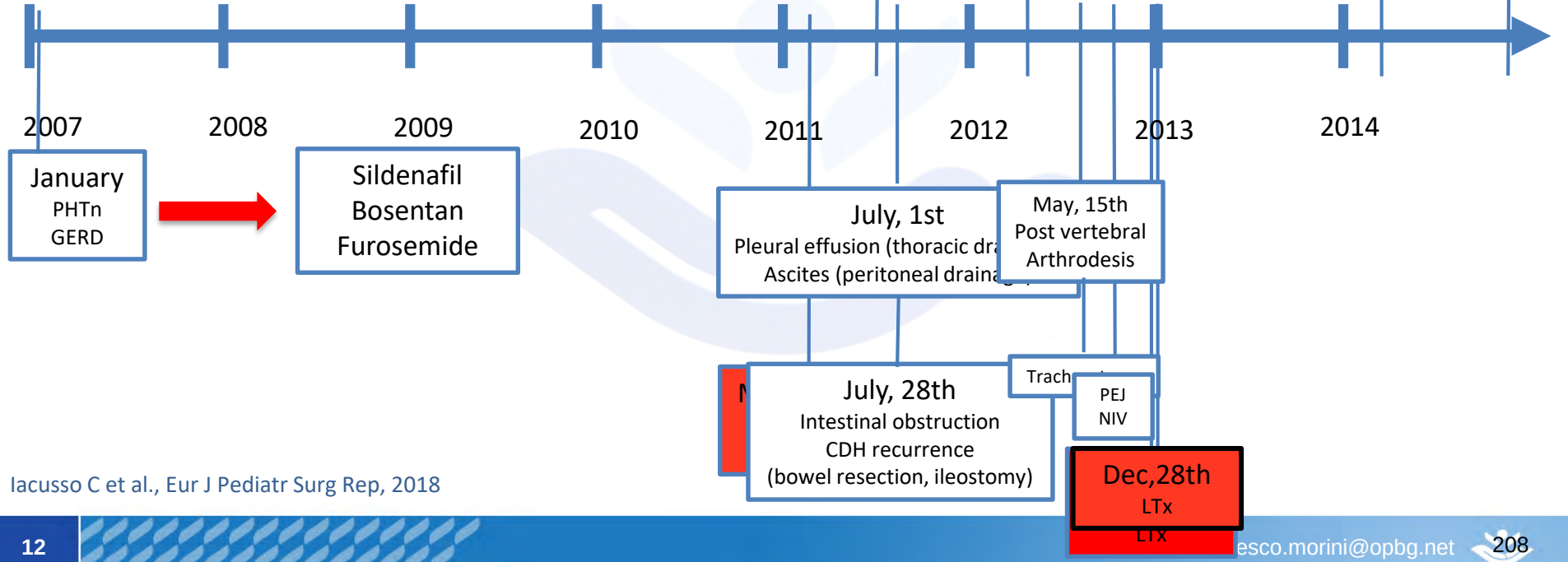

Iacusso C et al., Eur J Pediatr Surg Rep, 2018

esco.morini@opbg.net

CDH & Persistent/recurrent PHTn

Addressing the causes of late mortality in infants with congenital diaphragmatic hernia

Carmen Mesas Burgos *, Agnes Modée, Elin Öst, Björn Frenckner

Department of Pediatric Surgery, Karolinska Institutet, Stockholm, Sweden

sidered. One of the patients dying from persistent pulmonary hypertension was treated during the newborn period, but had been free from medication and symptoms during several years until a new onset of pulmonary hypertension occurred, which at this time not responded to treatment. One patient died because of respiratory insuf-

Patient	4
Age at death	9 yr. 4 mo
Cause of death	PPH
Gender	Female
Intubated <6 h	Yes
Patch repair	Yes
Liver up	Yes
ECMO	Yes
Other GI surgery	Yes (GT)
Recurrence	No
Side	Left
Failure to thrive	Yes

Mesas Burgos C et al., J Pediatr Surg, 2017

CDH & lung transplantation

Lung Transplantation for Late-Onset Pulmonary Hypertension in a Patient with Congenital Diaphragmatic Hernia

Chiara Iacusso[1] Francesco Morini[1] Irma Capolupo[1] Andrea Dotta[1] Stefania Sgrò[2]
Francesco Parisi[3] Adriano Carotti[4] Pietro Bagolan[1]

Author	Year	No. of patients	Prenatal diagnosis	ECMO	CDH side	Type of Tx	Age at Tx	Outcome	Follow-up
Van Meurs et al	1994	1	No	Yes	R	Lung	17 d	Alive	4 y
Lee et al	2002	1	18 wk	Yes	L	Lung	36 d	Died 51 d post-Tx	–
Lee et al	2002	2	27 wk	Yes	L	Lung	105 d	Alive	3 y
Lee et al	2002	3	18 wk	Yes	L	Heart–lung	19 d	Died 84 d post-Tx	–
Rama et al	2010	1	ns	ns	ns	Lung	ns	ns	ns
Rama et al	2010	2	ns	ns	ns	Lung	ns	ns	ns
Schmidt et al	2013	1	ns	Yes	L	Lung	10 y	Died 109 d post-Tx	–
Iacusso et al (this study)	2017	1	31 wk	No	L	Heart–lung Lung	12 y 17 y	Died 4 y after first Tx	–

Iacusso C et al., Eur J Pediatr Surg Rep, 2018

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CDH & PHTn

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CDH & gastroesophageal reflux

Long-term follow up of infants with congenital diaphragmatic hernia

Pietro Bagolan, MD, Francesco Morini, MD

From the Department of Medical and Surgical Neonatology, "Bambino Gesù" Children's Hospital, Rome, Italy.

Author	Pts	Follow-up (mos)	GER (%)	Surgery for GER (%)
Stolar et al, 1990[67]	17	32	17	0
Koot et al, 1993[72]	31	6	52	16
Van Meurs et al, 1993[30]	18	8–72	17	0
Nagaya et al, 1994[74]	86	6–120	12	8
Lund et al, 1994[11]	33	5–72	—	18
D'Agostino et al, 1995[15]	16	0.6–12	81	12
Kieffer et al, 1995[73]	74	36	62	32
Rais-Bahrami et al, 1995[70]	33	24	76	—
Stolar et al, 1995[50]	25	31	—	—
Wischermann et al, 1995[34]	45	7–360	13	—
Vanamo et al, 1996[16]	60	355	63	18
Naik et al, 1996[77]	15	6–36	13	13
McGahren et al, 1997[47]	37	3–120	—	22
Schoeman et al, 1999[71]	8	2–32	67	62
Huddy et al, 1999[92]	13	24–84	23	15
Muratore et al, 2001[18]	121	12–120	60	21
Bétrémieux et al, 2002[78]	12	12–72	50	—
Jaillard et al, 2003[19]	51	24	27	6
Davis et al, 2004[25]	27	>12	52	15
Hedrick et al, 2004[27]	19	0.7–88	47	11
Cortes et al, 2005[23]	16	24	62	60
Colvin et al, 2005[84]	37	24–156	27	5
Crankson et al, 2006[28]	31	6–108	26	6
Chiu et al, 2006[10]	38	36	45	32
TOTAL	863		39	19

Bagolan P & Morini F, Semin Pediatr Surg, 2007

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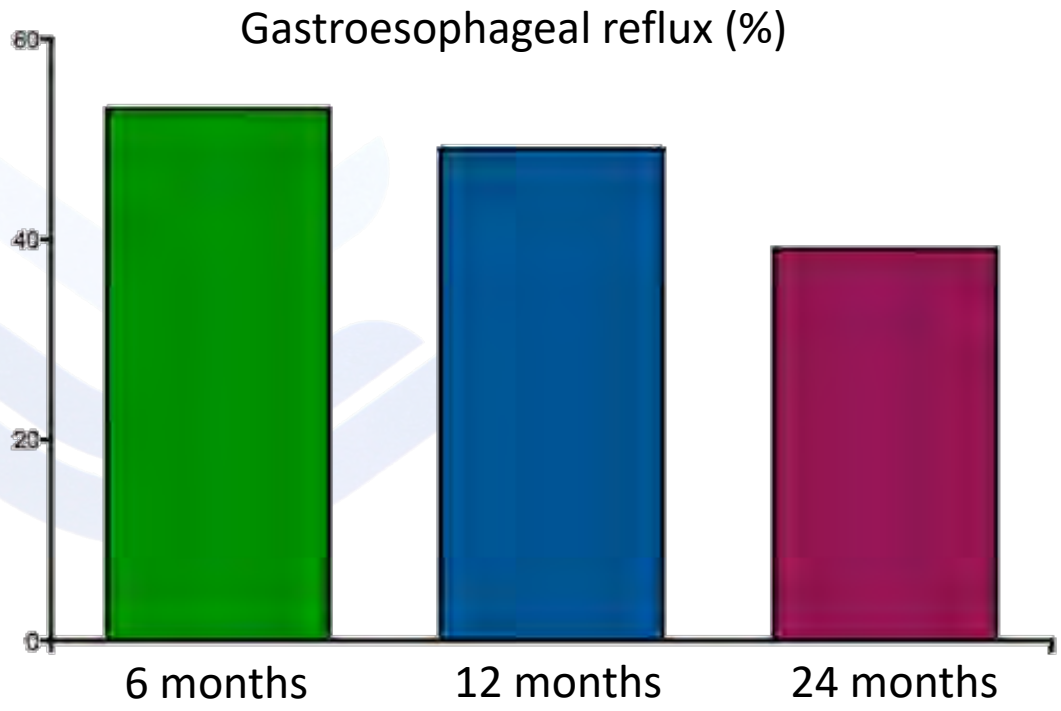
CDH & gastroesophageal reflux

Long term follow-up in high-risk congenital diaphragmatic hernia survivors: patching the diaphragm affects the outcome

Laura Valfrè*, Annabella Braguglia, Andrea Conforti, Francesco Morini, Alessandro Trucchi, Barbara Daniela Iacobelli, Antonella Nahom, Natalia Chukhlantseva, Andrea Dotta, Carlo Corchia, Pietro Bagolan

Neonatal Surgery Unit, Department of Medical and Surgical Neonatology, Bambino Gesù Children's Research Hospital, 00165 Rome, Italy

- ✓ 61 CDH survivors
  - ✓ 61 @ 6 mos
  - ✓ 49 @ 12 mos
  - ✓ 43 @ 24 mos



Valfrè L et al., J Pediatr Surg, 2011

CDH & gastroesophageal reflux

Endoscopic Surveillance for Congenital Diaphragmatic Hernia: Unexpected Prevalence of Silent Esophagitis

Anna Morandi[1] Francesco Macchini[1] Andrea Zanini[1] Noemi Pasqua[1] Giorgio Farris[1]
Lorena Canazza[1] Valerio Gentilino[1] Antonio Di Cesare[1] Ernesto Leva[1]

[1]Department of Pediatric Surgery, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

Eur J Pediatr Surg 2016;26:291–295.

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Grade 0	No mucosal abnormalities
Grade I	No macroscopic erosions but erythema, hyperemia, or mucosal friability
Grade II	Superficial erosions, involving < 10% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade III	Superficial erosions or ulceration involving 10 to 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade IV	Deep peptic ulceration anywhere in the esophagus or confluent erosion of > 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa

Materials and Methods Patients operated on for posterolateral CDH and undergoing general anesthesia for concomitant pathologies between January and October 2013 were included in the study. GERD was investigated both clinically (Manterola questionnaire) and endoscopically. The severity of esophagitis was evaluated according to the Hetzel–Dent classification and multiple biopsies were performed. The correlation between clinical score and severity of esophagitis was evaluated.

Results Twelve patients were included in the study (mean age: 14.5 years; range, 9–18 years). Only three children (25%) had a pathological questionnaire. At endoscopy, three children (25%) were affected by grade 1 esophagitis, six (50%) by grade 2, two (17%) by grade 3, and one (8%) by grade 4. One of the children presented Barrett esophagus. A moderate negative correlation was found between clinical data and endoscopic findings (r: −0.54 and *p*: 0.067).

- ✓ 12 CDH survivors
- ✓ Mean age 14.5 yrs
- ✓ 75% asymptomatic

Morando A et al., Eur J Pediatr Surg, 2016

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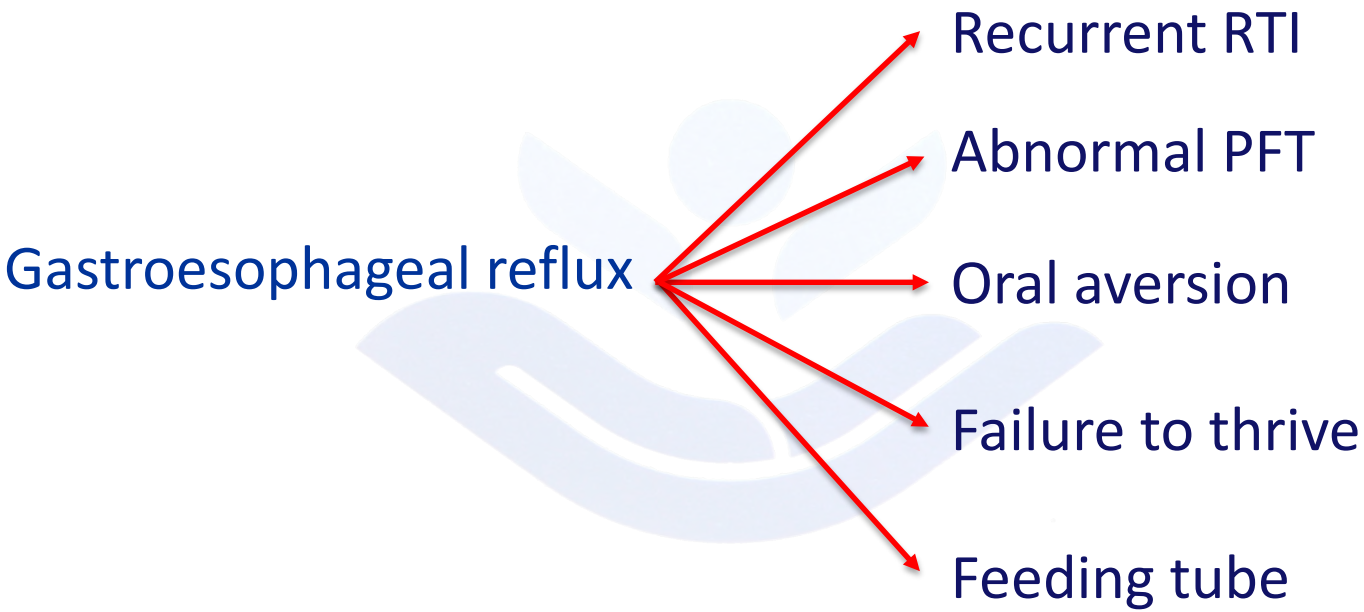
CDH & gastroesophageal reflux



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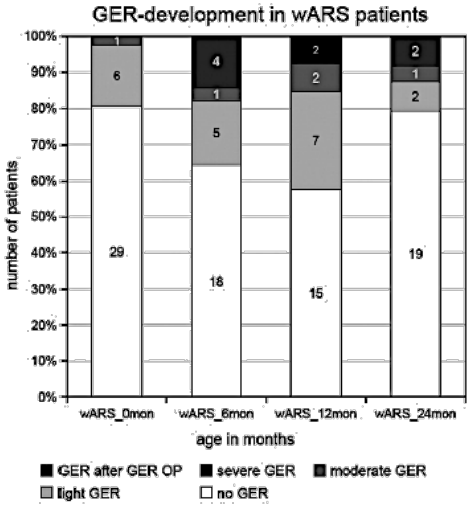
CDH & gastroesophageal reflux

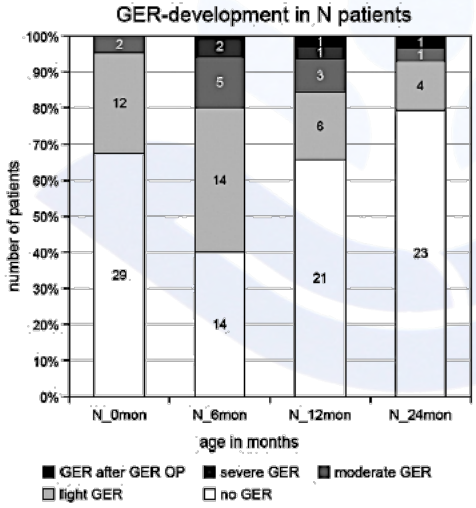
Preventive antireflux surgery in neonates with congenital diaphragmatic hernia: a single-blinded prospective study☆

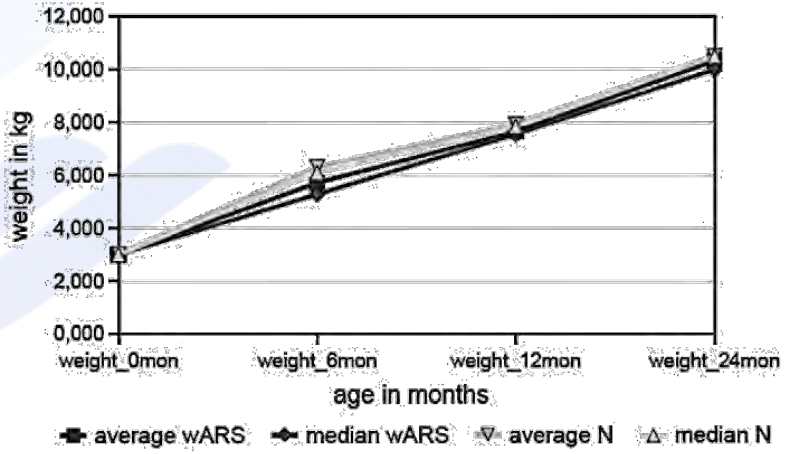
Susanne Maier[a,*,1], Katrin Zahn[a,1], Lucas M. Wessel[a], Thomas Schaible[b], Joachim Brade[c], Konrad Reinshagen[a]

[a]Department of Pediatric Surgery, Universitätsklinikum Mannheim, University of Heidelberg, Mannheim 68167, Germany
[b]Department of Neonatology, Universitätsklinikum Mannheim, University of Heidelberg, Mannheim 68167, Germany
[c]Department of Statistics, Universitätsklinikum Mannheim, University of Heidelberg, Mannheim 68167, Germany

- ✓ 79 L-CDH survivors
- ✓ 36 wARS
- ✓ 43 controls







Maier S et al., J Pediatr Surg, 2011

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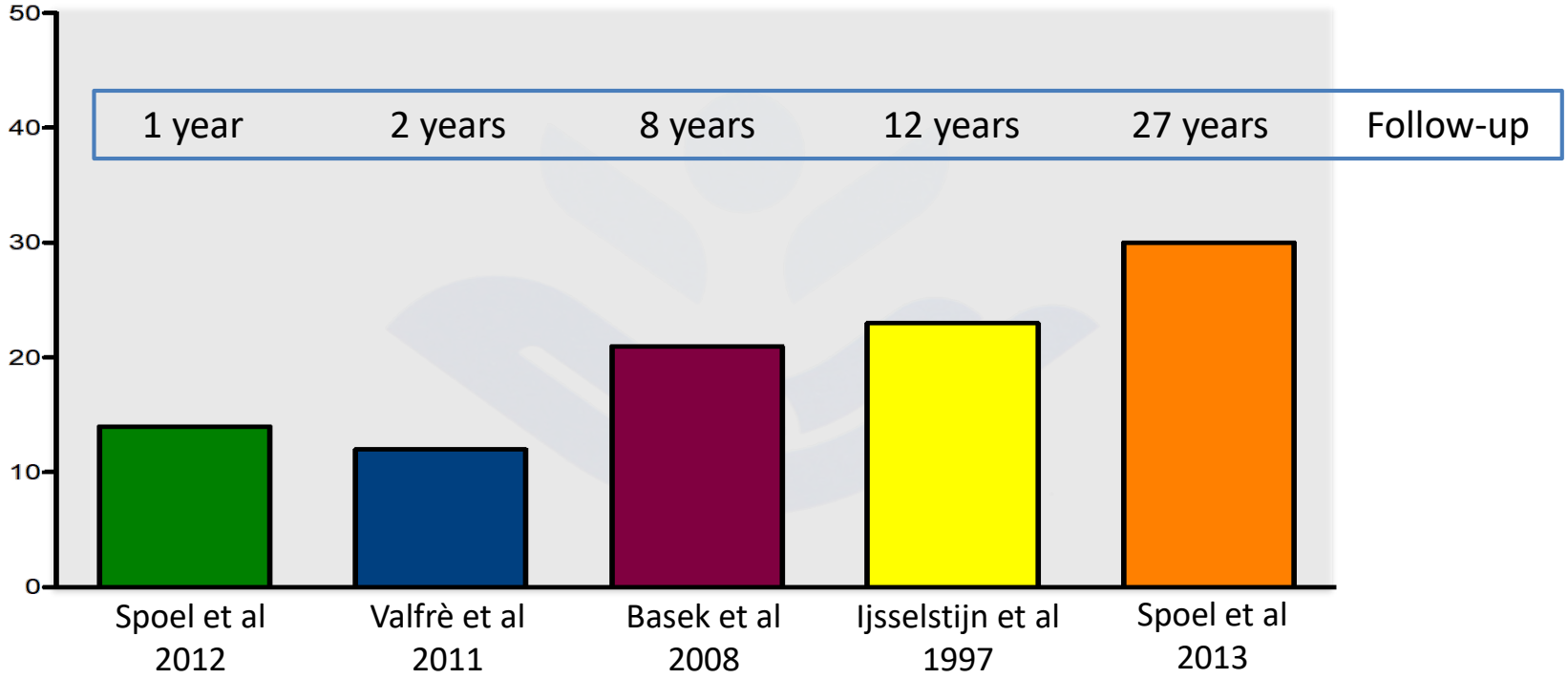
CDH & obstructive manifestations



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CDH & obstructive manifestations

Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia

M.G. Peetsold*, H.A. Heij#, A.F. Nagelkerke*, H. IJsselstijn*, D. Tibboel*, P.H. Quanjer* and R.J.B.J. Gemke*

- ✓ 53 CDH survivors
- ✓ Mean age 12 yrs
- ✓ Asthma 28%

	CDH		Controls		p-value	95% CI of the difference
	Mean±SD	Range	Mean±SD	Range		
Before bronchodilation						
Spirometry						
Subjects n	48		48			
FEV_1	-1.63±1.78	-7.14–1.45	0.08±0.90	-1.53–2.38	<0.001	-2.28– -1.14
FVC	-1.28±1.62	-6.33–1.93	0.05±0.87	-1.57–2.76	<0.001	-1.85– -0.80
FEV_1/FVC	-0.84±1.27	-4.03–1.07	0.05±0.90	-2.04–1.90	<0.001	-1.33– -0.44
MMEF	-1.57±1.70	-6.18–1.08	0.16±1.03	-2.31–2.27	<0.001	-2.30– -1.16
PEF $L \cdot s^{-1}$	4.89±1.79	1.42–8.23	6.45±2.10	3.16–10.34	<0.001	-2.34– -0.78
After bronchodilation						
Spirometry						
Subjects n	38					
FEV_1	-1.45±1.51	-6.22–1.43				
FVC	-1.45±1.46	-5.67–2.05				
FEV_1/FVC	-0.22±1.30	-2.83–1.77				
MMEF	-0.22±1.30	-5.54–2.19				
PEF $L \cdot s^{-1}$	5.38±1.80	2.36–9.02				
Lung volumes						
Subjects n	48		29			
TLC	0.16±1.91	-4.16–1.55	0.03±1.04	-1.86–1.93	0.70	-0.54–0.80
RV	0.98±2.06	-5.37–2.44	-0.24±0.84	-2.17–0.98	0.001	0.55–1.89
RV/TLC %	26.7±9.0	6–47	20.4±3.0	14–25	<0.001	3.50–9.13

Data are expressed as z-scores calculated from a reference population [20], unless otherwise stated. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow; PEF: peak expiratory flow; TLC: total lung capacity; RV: residual volume.

Peetsold MG et al., Eur Respir J, 2009

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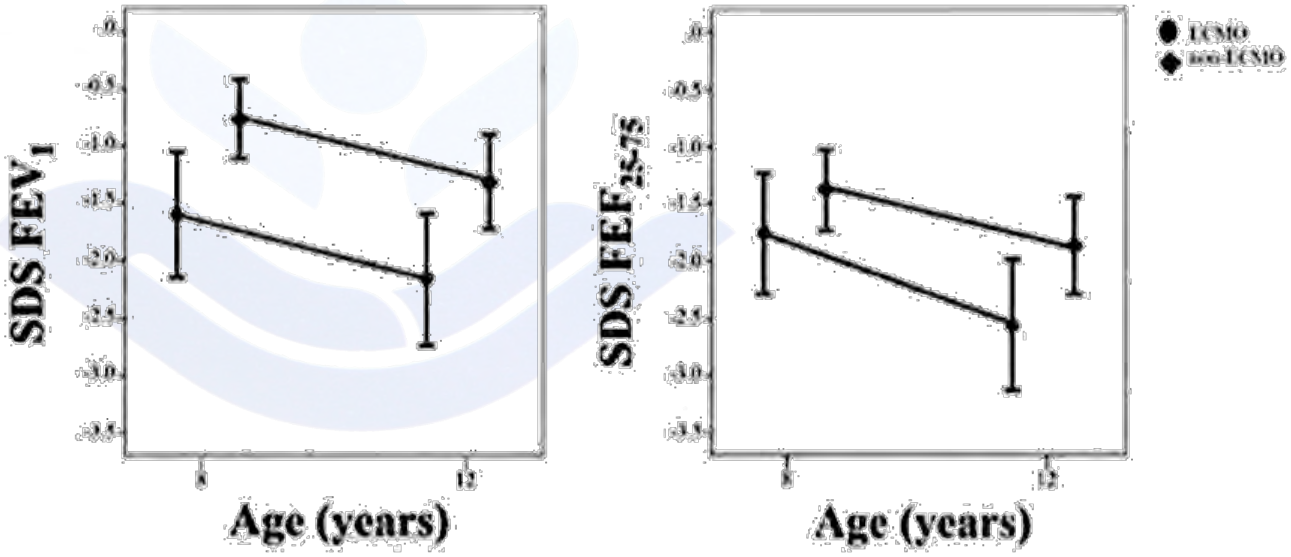
CDH & obstructive manifestations

Congenital diaphragmatic hernia and exercise capacity, a longitudinal evaluation

Leontien C.C. Toussaint-Duyster MPPT[1,2] |
Monique H.M. van der Cammen-van Zijp PhD[1,2] | Johan C. de Jongste MD, PhD[3] |
Dick Tibboel MD, PhD[1] | Rene M.H. Wijnen MD, PhD[1] |
Saskia J. Gischler MD, PhD[1] | Joost van Rosmalen PhD[4] |
Hanneke IJsselstijn MD, PhD[1]



Toussaint-Duyster LCC et al., Pediatr Pulmonol, 2019

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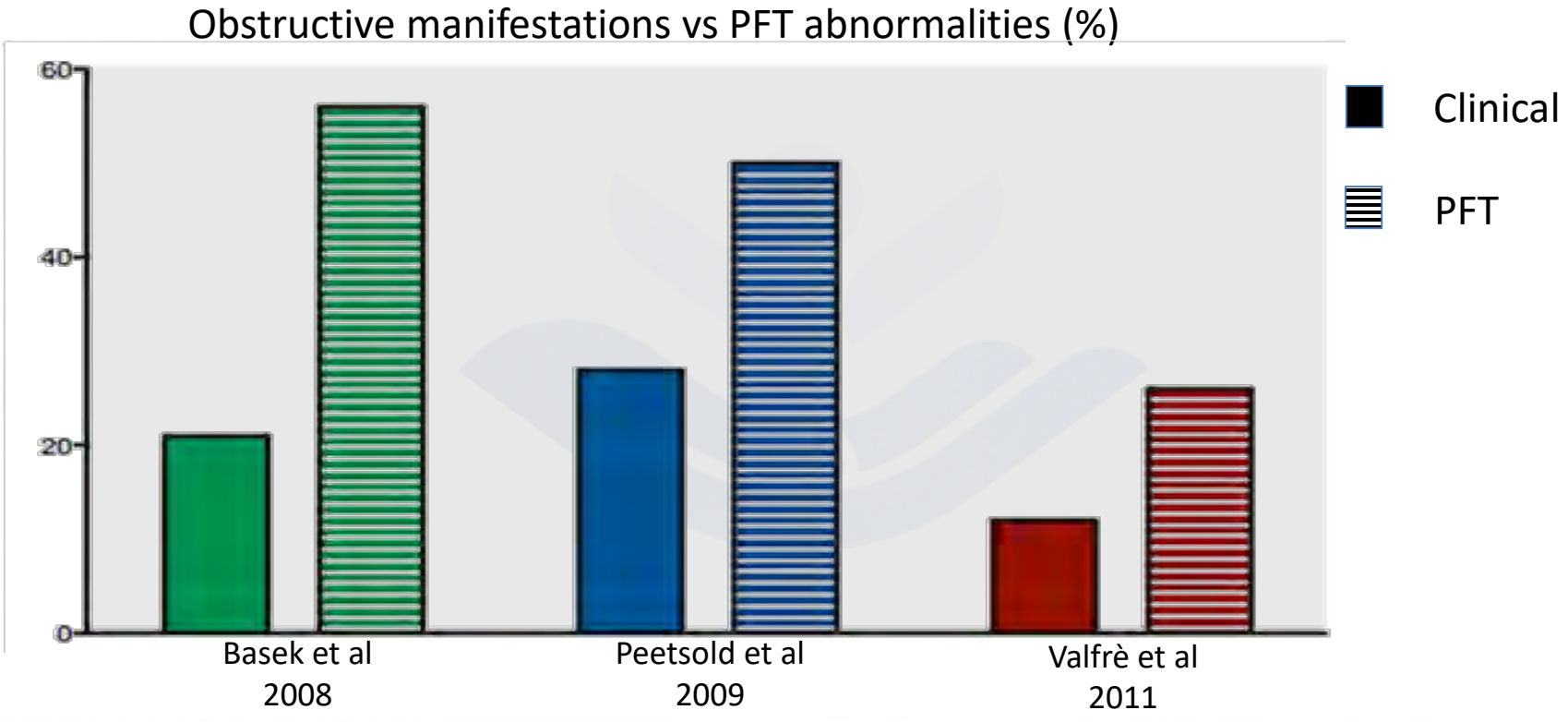
CDH & obstructive manifestations



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CDH & Fitness

Resting and Exercise Cardiorespiratory Function in Survivors of Congenital Diaphragmatic Hernia

Daniel Trachsel, MD,[1] Hiran Selvadurai, MD, PhD,[1]* Ian Adatia, MD,[2] Desmond Bohn, MD,[3] Jane Schneiderman-Walker, MSc,[1] Donna Wilkes, MSc,[1] and Allan L. Coates, MD[1]

1.2 ± 1.6, $P < 0.01$). Exercise capacity was mildly reduced in CDH compared to controls and predictive data (maximum workload, 77% ± 12% vs. 91% ± 16% of predicted, $P < 0.01$). Cardiorespiratory response to exertion was not significantly different between groups. In conclusion, most adolescent CDH survivors have nearly normal exercise capacity and cardiorespiratory response to exertion. This study may prove useful in comparisons with future cohorts comprising more severely affected individuals now surviving due to improved neonatal care.

		CDH	Controls	*P*-value
Wmax (percent predicted for height)		77 ± 12	91 ± 16	<0.01
Wmax (watts)		116 ± 37	149 ± 53	<0.02
Wmax/weight (watts/kg)		2.5 ± 0.6	2.8 ± 0.6	NS (0.08)
Wmax/LBM (watts/kg)		3.2 ± 0.6	3.7 ± 0.6	<0.01
Heart rate maximum (min^{-1})		189 ± 11	191 ± 9	NS
Respiratory rate maximum (min^{-1})		50 ± 7	54 ± 7	0.02
$V_E$max (l/min)		68 ± 21	84 ± 22	0.01
$V_E$max/MVV*100 (%)		81 ± 19	83 ± 16	NS
V_{O2}max (percent predicted for height)		88 ± 17	99 ± 17	0.03
V_{O2}max (l/min)		1.8 ± 0.6	2.2 ± 0.8	NS (0.06)
V_{O2}max/Wmax (ml/min/watts)		0.016 ± 0.002	0.015 ± 0.002	NS
V_{CO2}max (l/min)		2.0 ± 0.7	2.5 ± 0.9	NS (0.07)
V_{CO2}max/Wmax (l/min/watts)		0.017 ± 0.002	0.017 ± 0.002	NS
V_E/V_{O2} at Wmax		38 ± 6	39 ± 5	NS
V_E/V_{CO2} at Wmax		34 ± 5	35 ± 5	NS
$V_T$max (l)		1.4 ± 0.45	1.6 ± 0.49	NS
$V_T$max/weight (ml/kg)		29 ± 5	30 ± 5	NS
	Watts	CDH	Controls	*P*-value
Cardiac output (l/min)	75	10.5 ± 3.1	10.9 ± 1.8	NS
	110	13.0 ± 2.7	12.5 ± 2.5	NS
	135	14.5 ± 3.3	13.2 ± 1.8	NS
Cardiac index (l/min/m^2)	75	7.3 ± 1.3	7.3 ± 1.1	NS
	110	8.2 ± 1.4	8.2 ± 1.5	NS
	135	8.7 ± 1.4	8.5 ± 0.9	NS
Stroke-volume index (ml/m^2)	75	45 ± 11	48 ± 9	NS
	110	47 ± 10	48 ± 10	NS
	135	47 ± 9	48 ± 7	NS

Trachsel D et al., Pediatr Pulmonol, 2006

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CDH & Fitness

Physical Activity, Fitness, and Dyspnea Perception in Children With Congenital Diaphragmatic Hernia

Attilio Turchetta,[1]* Danilo Fintini,[1] Giulia Cafiero,[1] Armando Calzolari,[1] Ugo Giordano,[1] Renato Cutrera,[2] Francesco Morini,[3] Annabella Braguglia,[3] and Pietro Bagolan[3]

difference in CDH severity between the two groups. Group A had a statistically significant lower duration of exercise ($P < 0.01$), maximal oxygen consumption (VO_2 max $P < 0.0001$), VO_2 ml/kg/min ($P < 0.001$), higher throat closing feeling ($P < 0.004$), chest dyspnea ($P < 0.001$), and effort perception ($P < 0.04$) compared to group B. No differences were found in lung function tests. In conclusion, our data may suggest that children with a history of CDH who are active maintain a higher level of performance with less perception of dyspnea and effort. **Pediatr**

Turchetta A et al., Pediatr Pulmonol, 2011

	Total (n = 18) (M/F = 11/7)	No sport, Group A (n = 11; M/F = 7/4)	Sport, Group B (n = 7; M/F = 4/3)	*P*
Age	6.6 ± 2.6	6.5 ± 3.5	6.6 ± 1.1	NS
Weight (kg)	22.7 ± 12.2	25.6 ± 15.1	18.8 ± 6.2	NS
Height (cm)	120.9 ± 19.5	121 ± 26.1	120.8 ± 6.7	NS
BMI	14.6 ± 3.5	16.1 ± 2.3	12.8 ± 4.0	NS
GA (weeks)	38.1 ± 2	38.2 ± 2.2	38.0 ± 1.9	NS
Surgery (days)	7.0 ± 7.3	9 ± 9.4	4.4 ± 0.8	NS
Vent (days)	18.6 ± 12.3	14.3 ± 9.9	24 ± 13.5	NS
Patch (yes/no)	6/12	3/8	3/4	NS
TE%	68.4 ± 12.9	62.3 ± 10.4	78.1 ± 10.5	<0.01
HR%	96.4 ± 10.8	97.8 ± 12.0	94.7 ± 9.7	NS
BP%	97.4 ± 6.8	96.9 ± 7.7	98.0 ± 5.9	NS
VO_2 max %	68.6 ± 14.4	59.9 ± 4.8	83.7 ± 10.5	≤0.0001
VO_2/kg/min	28.2 ± 7.4	23.3 ± 2.9	35.7 ± 5.8	≤0.001
SaO2 max	95.8 ± 1.1	95.8 ± 1.0	95.7 ± 1.3	NS
FEV_1%	78.7 ± 19.3	75.5 ± 18.9	82.7 ± 20.5	NS
FVC%	75.5 ± 15	74.7 ± 18	76.2 ± 13	NS
PEF%	74.9 ± 22	73.6 ± 21	76.1 ± 22	NS
MVV	35.5 ± 14.7	34.3 ± 8.9	36.7 ± 20.5	NS
VE	25.9 ± 9.8	25.2 ± 4.9	24.7 ± 14.7	NS
VE/MVV	0.71 ± 0.1	0.75 ± 0.1	0.67 ± 0.1	NS
Throat	5.2 ± 1	5.7 ± 0.8	4.4 ± 0.8	≤0.004
Chest	4.5 ± 1.0	5.3 ± 0.6	3.6 ± 0.5	≤0.001
Effort	5.3 ± 0.8	5.8 ± 0.9	4.9 ± 0.7	≤0.04

Physical, respiratory, and treadmill parameters and Dalhousie Scale results are shown. All data were divided between sedentary children (Group A) and active children (Group B). Data are expressed as mean ± SD (M, males; F, females; BMI, body mass index; GA, gestational Age; Surgery, day of surgery after birth; Vent, ventilation days; TE%, time of exercise during treadmill test expressed as percentage of normal value for age and sex; HR%, maximal heart rate during treadmill test expressed as percentage of normal value for age and sex; BP%, maximal BP during treadmill test expressed as percentage of normal value for age and sex; VO_2, maximal oxygen consumption; MVV, maximal voluntary ventilation; VE, ventilation (L/m); Throat, Chest, Effort, parameters of Dalhousie Dyspnea Scale collected from children at the end of treadmill test).

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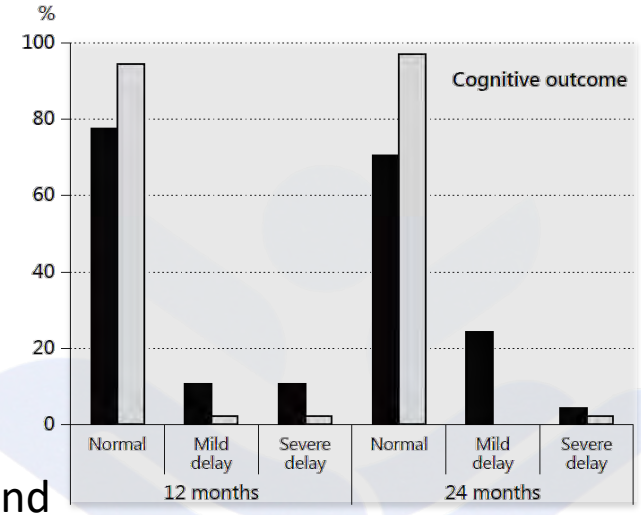
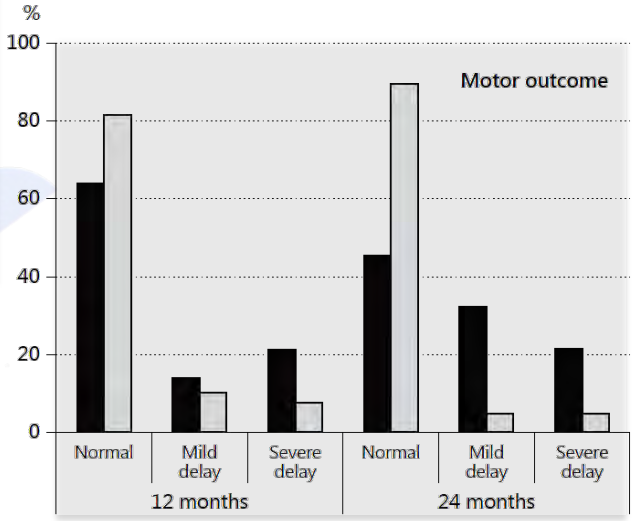
CDH & Neurodevelopmental outcome

Neurodevelopmental Outcome in High-Risk Congenital Diaphragmatic Hernia Patients: An Appeal for International Standardization

Kitty G. Snoek[a] Irma Capolupo[c] Annabella Braguglia[c] Lucia Aite[c]
Joost van Rosmalen[b] Laura Valfrè[c] René M. Wijnen[a] Pietro Bagolan[c]
Dick Tibboel[a] Hanneke IJsselstijn[a]

[a]Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, and [b]Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands; [c]Department of Medical and Surgical Neonatology, Bambino Gesu Children's Hospital, Rome, Italy





Different diagnostic tool (Bayley II vs III)
Different professional background (physical therapist vs developmental psychologist)
Different patients' population

Snoek KG et al., Neonatology, 2016

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CDH & Neurodevelopmental outcome

Does Ventilatory Time Retain Its Validity in Predicting Neurodevelopmental Outcome at Two Years of Age in High-Risk Congenital Diaphragmatic Hernia Survivors?

Francesca Bevilacqua, PsD[1] Francesco Morini, MD[2] Antonio Zaccara, PhD[3] Laura Valfrè, MD[2]
Lelia Rotondi Aufiero, MD[4] Simonetta Gentile, PsD[1] Pietro Bagolan, MD[2] Lucia Aite, PsD[1]

[1] Unit of Clinical Psychology, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children's Hospital, Rome, Italy
[2] Department of Neonatal Medicine and Surgery, Bambino Gesù Children's Hospital, Rome, Italy
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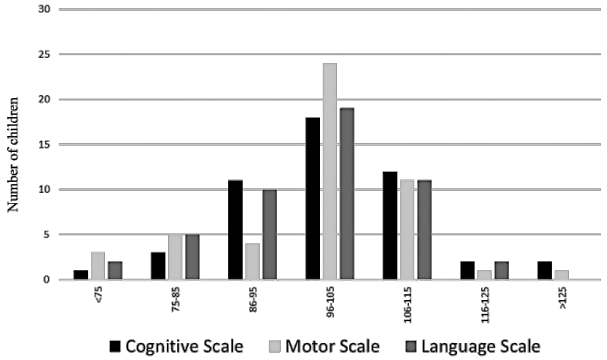
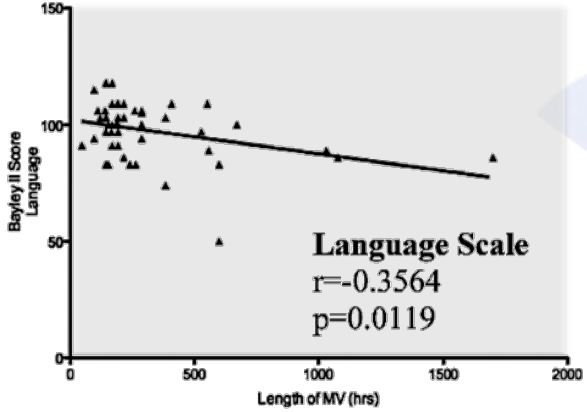
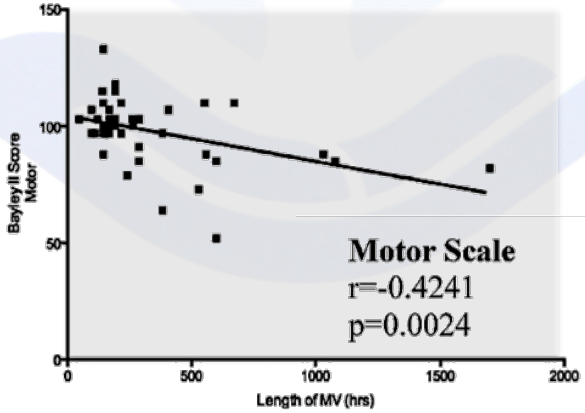
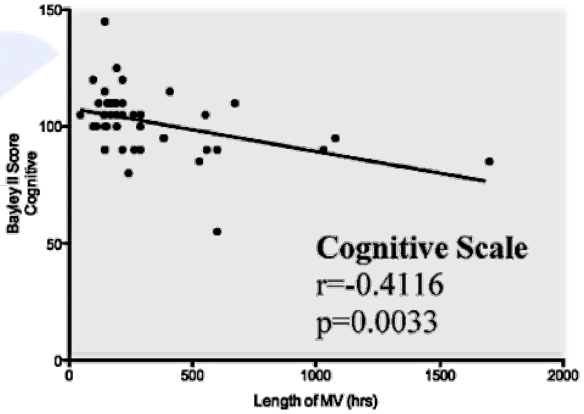
Address for correspondence Lucia Aite, PsD, Bambino Gesù Children's Hospital, P.zza S. Onofrio, 4, 00165 Rome, Italy (e-mail: lucia.aite@opbg.net).

22% delay









Bevilacqua F et al., Am J Perinatol, 2017

CDH & Neurodevelopmental outcome

Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia

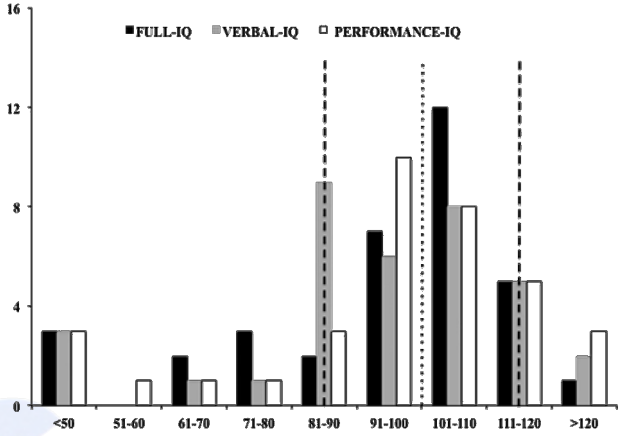
Enrico Danzer *, Casey Hoffman, Jo Ann D'Agostino, Marsha Gerdes, Judy Bernbaum, Ryan M. Antiel, Natalie E. Rintoul, Lisa M. Herkert, Alan W. Flake, N. Scott Adzick, Holly L. Hedrick

The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Table 5
OLS regression modeling of the relationship between adverse developmental and functional outcomes and clinical important predictors.

	WPPSI-III Full IQ		WPPSI-III Verbal IQ		WPPSI-III Visual–spatial IQ		VMI	
	b (95% CI)	*P* value	b (95% CI)	*P* value	B (95% CI)	*P* value	b (95% CI)	*P* value
Low LHR	−13.4 (−25.1 to −1.8)	**<0.03**	−12.6 (−24.2 to −0.9)	**<0.04**	−6.9 (−19.3 to 5.5)	0.26	−6.4 (−18.6 to 5.9)	0.26
Prolonged ventilatory support	−0.2 (−0.4 to −0.02)	**0.02**	−0.2 (−0.4 to −0.02)	**0.03**	−0.2 (−0.4 to −0.04)	**0.02**	−0.1 (−0.2 to 0.1)	0.36
HFOV	−13.2 (−26.3 to −0.3)	**0.05**	−10.2 (−22.9 to 2.4)	0.11	−14.2 (−28.1 to −0.3)	**<0.05**	−3.4 (−16.3 to 9.5)	0.60
Tracheostomy	−20.4 (−38.3 to −2.4)	**<0.03**	−14.6 (−32.2 to 2.9)	0.10	−26.3 (−44.6 to −7.9)	**0.006**	−18.1 (−36.6 to 0.4	0.06
Need for supplemental O2 at DOL 30	−13.7 (−16.1 to −1.2)	**0.03**	−11.8 (−23.7 to 0.2)	0.053	−14.6 (−27.8 to −1.3)	**0.03**	−5.5 (−17.9 to 6.9)	0.37
pHTN	−15.4 (−30.5 to −0.2)	**0.05**	−18.5 (32.3 to −4.7)	**0.01**	−20.1 (−35.6 to −4.5)	**0.01**	−7.3 (−21.9 to 7.4)	0.32
Need for fundoplication	−13.5 (−27.2 to 0.2)	**0.05**	12.6 (−25.6 to 0.4)	0.06	−15.2 (−29.7 to −0.9)	**<0.04**	−13.1 (−26.5 to 0.4)	0.06
Prolonged LOS	−0.1 (−0.1 to −0.4)	**<0.0001**	−0.1 (−0.1 to −0.03)	**<0.0001**	−0.1 (−0.1 to −0.04)	**<0.0001**	−0.1 (−0.1 to −0.01)	**<0.02**
Below average BSID-III scores during infancy	−14.9 (−21.3 to −8.7)	**<0.0001**	−12.3 (−19.0 to −5.6)	**0.001**	−13.8 (−20.8 to −6.7)	**<0.0001**	−11.9 (−18.5 to −5.3)	**0.001**
Abnormal BAERs	−35.0 (−49.9 to −20.0)	**<0.0001**	−28.3 (−43.7 to −12.9)	**0.001**	−37.4 (−53.2 to −21.6)	**<0.0001**	−25.7 (−40.9 to −10.9)	**0.002**
Below average length percentile at follow-up	0.3 (0.1 to 0.6)	**0.006**	0.2 (−0.04 to 0.5)	0.105	0.4 (0.1 to 0.6)	**0.007**	0.3 (0.01 to 0.5)	**<0.05**
Autism	−30.0 (−48.5 to −11.5)	**0.002**	−25.5 (−43.5 to −7.4)	**0.007**	−28.7 (−48.8 to −8.5)	**0.007**	−22.9 (−40.7 to −5.1)	**0.01**
Need for g-tube or j-tube or nutritional support	−16.1 (−33.1 to 0.9)	0.06	−22.7 (−37.7 to −7.6)	**0.004**	−18.1 (−35.9 to −0.2)	**<0.05**	−17.3 (−32.6 to −1.9)	**<0.03**
Microcephaly	−15.3 (−43.9 to 13.4)	0.29	−13.1 (−40.4 to 14.1)	0.34	−19.8 (−49.9 to 10.3)	0.19	−25.9 (−51.1 to −0.8)	**0.04**

LHR, lung-to-head ratio; LOS, length of stay; HFOV, high frequency oscillatory ventilation; pHTN, pulmonary hypertension; DOL, day of life; BSID-III, Bayley Scales of Infant Development 3rd Edition; BAERs, brainstem auditory evoked responses; g-tube, gastrostomy tube; j-tube; jejunostomy tube; f/u, follow-up.



Danzer E et al., J Pediatr Surg, 2017

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CDH & Psychiatric problems

Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia

Enrico Danzer *, Casey Hoffman, Jo Ann D'Agostino, Marsha Gerdes, Judy Bernbaum, Ryan M. Antiel, Natalie E. Rintoul, Lisa M. Herkert, Alan W. Flake, N. Scott Adzick, Holly L. Hedrick

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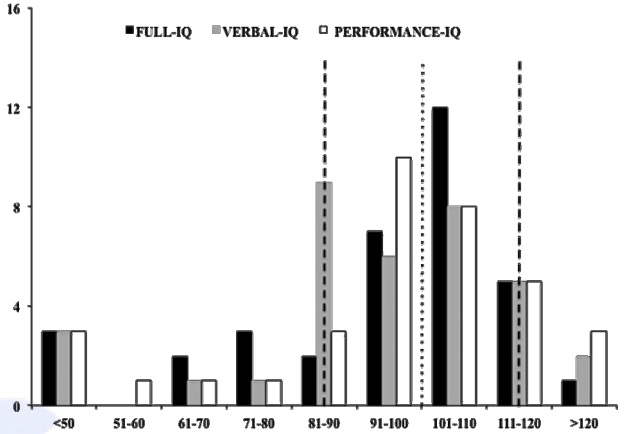
Table 4
CDH CBCL scores in comparison to normative data.

	Prevalence of at risk or clinical significant CBCL/1.5–5 normative data [23]	Prevalence of at risk or clinical significant CBCL results of CDH patients	*P*-value*
Total problems	18%	23%	0.48
Externalizing problems	17%	12%	0.42
Internalizing problems	21%	31%	0.15
Emotionally reactive	10%	23%	**0.02**
Anxious/depressed	8%	15%	0.18
Somatic problems	9%	12%	0.65
Withdrawn	7%	8%	1.00
Sleep problems	5%	0%	0.06
Attention problems	7%	12%	0.34
Aggressive behavior	7%	12%	0.34
DSM-affective	7%	12%	0.34
DSM-anxiety	8%	15%	0.18
DSM-pervasive	7%	27%	**0.0003**
DSM-ADHD	9%	4%	0.25
DSM-oppositional defiant	7%	8%	1.00

* The *P*-values were calculated using chi-square statistics.



Autism was diagnosed in 11% of female and 11% of male patients, which is significantly higher than the general population (0.5% and 2.4% respectively, $P < 0.01$) [25].

Danzer E et al., J Pediatr Surg, 2017

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CDH: long term sequelae

- ✓ May be severe
- ✓ May be smoldering
- ✓ Tend to worsen over time

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CDH: long term sequelae

Long term follow-up in congenital diaphragmatic hernia

Laura E. Hollinger[a,*], *and Terry L. Buchmiller*[b]

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[b]*Department of Surgery, Boston Children's Hospital, Boston MA, USA*

Hollinger LE & Buchmiller TL, Semin Perinatol, 2019

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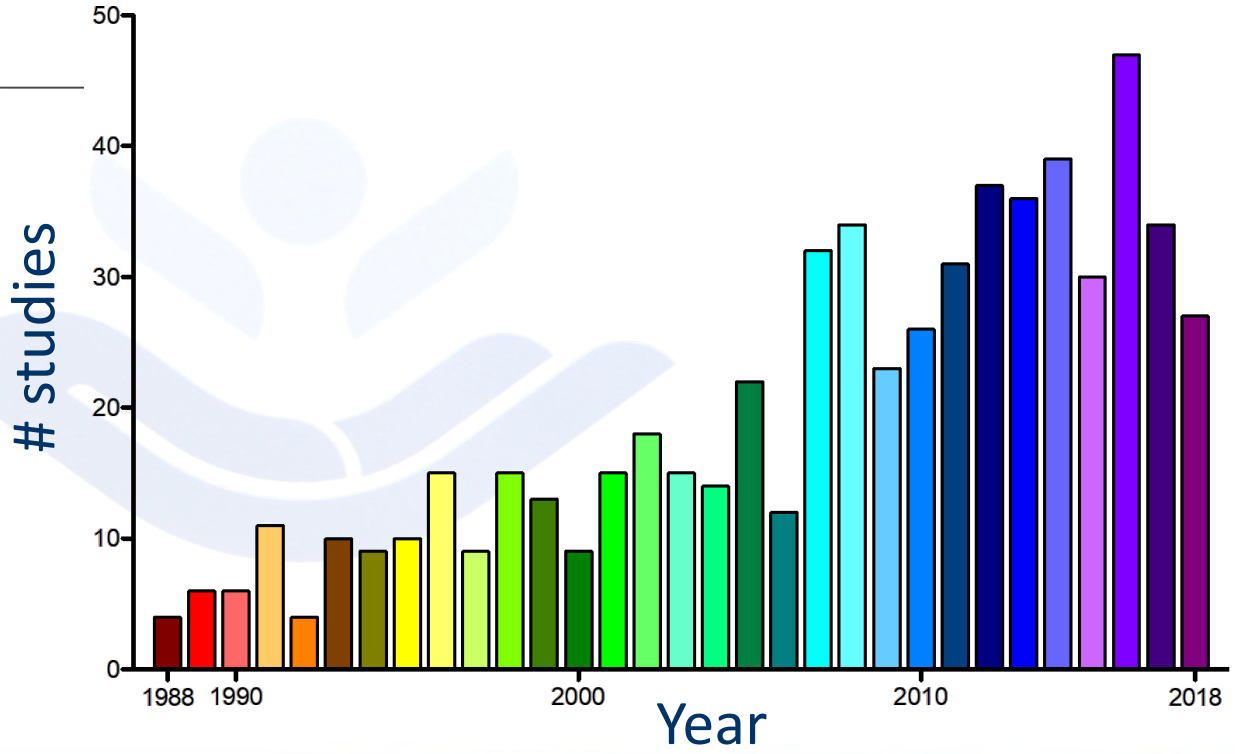
CDH: long term follow-up

Long-term morbidity of congenital diaphragmatic hernia: A plea for standardization

Francesco Morini, Laura Valfrè, Pietro Bagolan*

Neonatal Surgery Unit, Department of Medical and Surgical Neonatology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy



Morini F et al., Semin Pediatr Surg, 2017

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CDH follow-up

CLINICAL REPORT

Postdischarge Follow-up of Infants With Congenital Diaphragmatic Hernia

Section on Surgery and the Committee on Fetus and Newborn

TABLE 1 Recommended Schedule of Follow-up for Infants With CDH

	Before Discharge	1–3 mo After Birth	4–6 mo After Birth	9–12 mo After Birth	15–18 mo After Birth	Annual Through 16 y
Weight, length, occipital-frontal circumference	X	X	X	X	X	X
Chest radiograph	X	If patched	If patched If indicated	If patched	If patched If indicated	If patched If indicated
Pulmonary function testing						
Childhood immunizations	As indicated throughout childhood	X	X	X	X	X
RSV prophylaxis	RSV season during first 2 years after birth (if evidence of chronic lung disease)	X	X	X	X	X
Echocardiogram and cardiology follow-up	X	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen
Head computed tomography or MRI	If (1) abnormal finding on head ultrasound; (2) seizures/abnormal neurologic findings*; or (3) ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
Hearing evaluation[44]	Auditory brainstem evoked response or otoacoustic emissions screen	X	X	X	X	Every 6 mo to age 3 y, then annually to age 5 y
Developmental screening evaluation	X	X	X	X		Annually to age 5 y
Neurodevelopmental evaluation	X			X		Annually to age 5 y
Assessment for oral feeding problems	X	X	If oral feeding problems	If oral feeding problems	If oral feeding problems	If oral feeding problems
Upper gastrointestinal study, pH probe, and/or gastric scintiscan	Consider for all patients	If symptoms	If symptoms	Consider for all patients	If symptoms	If symptoms
Esophagoscopy		If symptoms	If symptoms	If symptoms or if abnormal gastrointestinal evaluations	If symptoms	If symptoms
Scoliosis and chest wall deformity screening (physical examination, chest radiograph, and/or computed tomography of the chest)				X		X

AAP Section on Surgery and Committee on Fetus and Newborn, Pediatrics, 2007

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CDH sequelae: our long term follow-up

Multidisciplinary follow-up clinic:

Pediatrician

Pediatric surgeon

Psychologist

Nurse

& physiotherapist, neurologist, radiologist, ENT, …

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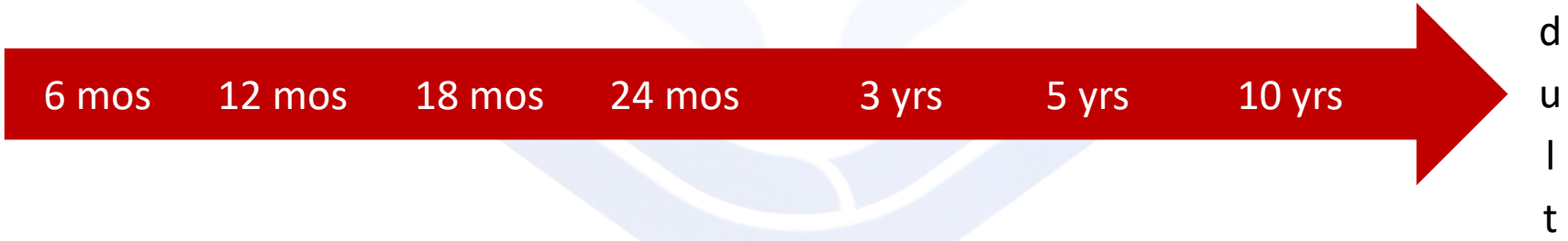
CDH sequelae: our long term follow-up

Multidisciplinary follow-up clinic:



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CDH follow-up: the tale of three cities

Long-term morbidity of congenital diaphragmatic hernia: A plea for standardization

Francesco Morini, Laura Valfrè, Pietro Bagolan*

Neonatal Surgery Unit, Department of Medical and Surgical Neonatology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

	Hospital for sick children Toronto	Sophia children's hospital Rotterdam	Bambino Gesù Chiuldren's Hospital Rome
4 wks	General surgical clinic + CXR	Pediatric surgeon	Pediatric surgeon
3–4 mos	CXR, neonatal FU (AIMS, PFMA-I), hearing test	–	Neonatologist, pediatric surgeon, developmental psychologist (parental emotional assesment)
6 mos	–	Pediatric surgeon, pediatrician, clinical geneticist, cardiologist (ECHO, ECG), PFT (LCI), pH-metry	Neonatologist, pediatric surgeon, clinical geneticist, developmental psychologist (Bayley III + parental emotional assesment), PFT (LCI), hearing test
8 mos	CXR, neonatal FU (AIMS, PFMA-I, CSBS if concerns), cardiologist if PTHN/PDA/PFO	–	–
12 mos	CXR, neonatal FU (AIMS, PFMA-I, CSBS), hearing test	Pediatric surgeon, pediatrician, cardiologist (ECHO, ECG), PFT (LCI), developmental psychologist (Bayley II)	Neonatologist, pediatric surgeon, developmental psychologist (Bayley III+ parental emotional assesment), PFT (LCI), cardiologist (ECHO), upper GI contrast study, pH-metry, hearing test
18 mos	CXR, neonatal FU (Bayley III, M.CHAT, REEL III)	–	Neonatologist, pediatric surgeon, developmental psychologist (parental emotional assessment), PFT (LCI), hearing test, orthopedic surgeon
2 yrs	CXR, cardiologist if no PTHN/PDA/PFO at first assessment	Pediatric surgeon, pediatrician, developmental psychologist (Bayley II-Dutch version, mental scale), physiotherapist (Bayley II, motor scale)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist (Bayley III + parental emotional assessment), CXR, PFT (LCI), orthopedic, hearing test
3 yrs	Neonatal FU (Bayley III, BRIEF-P, CBCL, Vineland II)	–	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, orthopedic surgeon, cardiologist, hearing test
5 yrs	CXR, PFT (spirometry), neonatal FU clinic	Pediatric surgeon, pediatrician, psychologist (QoL and social emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist (Leiter-R), PFT (spirometry and CPET), cardiologist (ECHO), orthopedic surgeon, hearing test
7 yrs	CXR, PFT (spirometry + lung volumes), neonatal FU clinic (if not assessed at 5 years)		–
8 yrs	–	Pediatric surgeon, pediatrician, psychologist (intelligence, neuropsychological assessment, QoL, social emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (spirometry, body pletismography, diffusion capacity, LCI), pH-metry	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, orthopedic surgeon, hearing test
10 yrs	CXR, PFT (complete with MIPS/MEPS), cardiologist (ECHO, ECG, CT scan, VO_2 exercise test)	–	–
12 yrs	–	Pediatric surgeon, pediatrician, cardiologist (ECHO, ECG), pulmonologist (MRI diaphragm, lungs and vessels), psychologist [neuropsychological assessment, QoL, social-emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (spirometry, body pletismography, diffusion capacity, LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist (ECHO), orthopedic, hearing test
15 yrs			Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist, orthopedic, hearing test
17 yrs	Cardiology (ECHO, ECG)	Pediatric surgeon, pediatrician, clinical geneticist, psychologist [neuropsychological assessment, QoL, social-emotional assessment), physiotherapist (movement ABC, maximal exercise test), PFT (spirometry, body pletismography, diffusion capacity, LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist, orthopedic, hearing test

Morini F et al., Semin Pediatr Surg, 2017

CDH follow-up

Multi-institutional follow-up of patients with congenital diaphragmatic hernia reveals severe disability and variations in practice☆

Arash Safavi[a], Anne R. Synnes[b], Karel O'Brien[c], Monping Chiang[d], Erik D. Skarsgard[a], Priscilla P.L. Chiu[d,*]
Canadian Pediatric Surgery Network

[a]*Division of Pediatric General Surgery, BC Children's Hospital and University of British Columbia, Vancouver, British Columbia, Canada*
[b]*Division of Neonatology, BC Children's Hospital and University of British Columbia, Vancouver, British Columbia, Canada*
[c]*Division of Neonatology, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada*
[d]*Division of Pediatric General and Thoracic Surgery, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada*

Table 1 Characteristics of surveyed CAPSNet centers

Center		Where			Who					When	What							
		Community based	Center-based multiple clinics	Center-based multidisciplinary CDH clinic	Pediatric surgeon	General pediatrician	Subspecialty pediatrician	Other health care providers[a]	Audiologist	Duration (y)	Neurodevelopmental	Hearing	Nutritional	Chest x-ray	PFT	Echo	GER	Neuroimaging
A	▲		✓		✓		✓✪	✓		2-4	✓	✓	✓	✓		✓		
B	▲			✓	✓✪		✓	✓		>10	✓	✓	✓	✓	✓	✓		HR
C	▲				✓✪	✓	✓			2-4	HR			✓				HR
D	▲	✓			✓	✓✪	✓			6-10	HR	✓		✓		✓		HR
E		✓			✓	✓✪	✓			2-4	HR	✓		✓				HR
F		✓			✓	✓✪	✓	✓	✓	VAR	HR	✓		✓				
G		✓			✓	✓✪	✓	✓	✓	2-4	✓	✓	✓	✓		✓	✓	HR
H	▲				✓	✓	✓✪			1-2	HR	✓		✓				HR
I					✓✪					2-4	HR	✓		✓				HR
J					✓✪	✓	✓	✓		2-4	HR	✓	✓	✓		✓		HR
K	▲	✓				✓✪	✓	✓	✓	2-4	✓	✓	✓	✓			✓	HR
L		VAR					✓	✓	✓	<1	HR	HR	✓	✓		✓		HR

Safavi A et al., J Pediatr Surg, 2012

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CDH follow-up

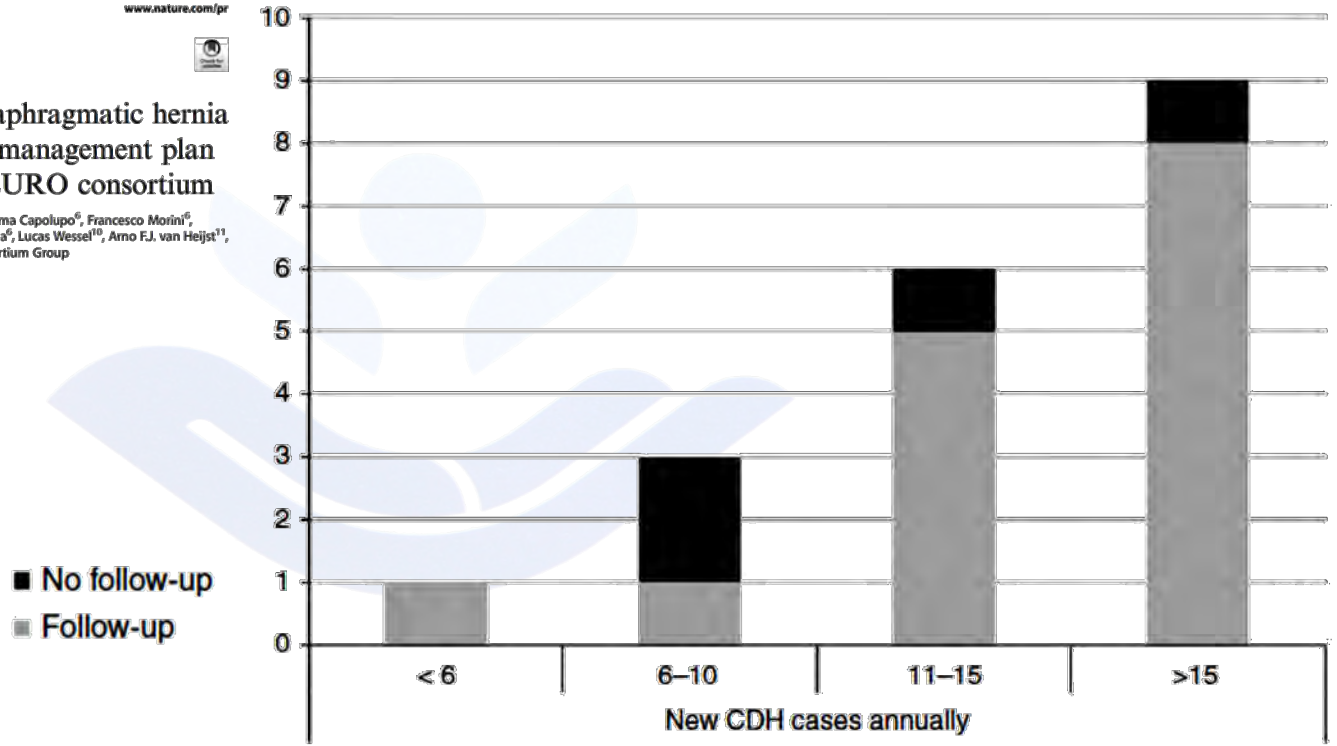
Pediatric RESEARCH

www.nature.com/pr

REVIEW ARTICLE

Defining outcomes following congenital diaphragmatic hernia using standardised clinical assessment and management plan (SCAMP) methodology within the CDH EURO consortium

Hanneke IJsselstijn[1], Cormac Breatnach[2], Aparna Hoskote[3], Anne Greenough[4], Neil Patel[5], Irma Capolupo[6], Francesco Morini[6], Horst Scharbatke[7], Florian Kipfmueller[8], Kjetil Ertresvag[9], Ulrike Kraemer[1], Annabella Braguglia[6], Lucas Wessel[10], Arno F.J. van Heijst[11], Inger Moinichen[9], Raghnild Emblem[9] and Dick Tibboel[1] on behalf of the CDH EURO Consortium Group



Ijsselstijn A et al., Pediatr Res, 2018

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CDH follow-up

Pediatric RESEARCH

www.nature.com/pr

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Table 2. Follow-up programs provided within the CDH EURO consortium centers

Age of follow-up	Infancy	15 (100%)	Assessments performed	Anthropometry (height, weight)	15 (100%)
	Toddler	13 (87%)		Chest radiograph	11 (73%)
	(Pre)school	13 (87%)		Gastroesophageal reflux	11 (73%)
	Adolescence (>12 yrs)	8 (53%)		Pulmonary function	10 (67%)
	Up till 20 yrs	1 (7%)		Mental development	8 (53%)
Disciplines involved	Pediatric surgeon	14 (93%)		Motor-function development	8 (53%)
	Pediatrician	11 (73%)		Audiometry	8 (53%)
	Pulmonologist	11 (73%)		Echocardiography	6 (40%)
	Pediatric physical therapist	6 (40%)		Maximal exercise test	5 (33%)
	Dietician	5 (33%)		Social–emotional well-being	4 (27%)
	Pediatric cardiologist	5 (33%)		Extensive neuropsychological testing	3 (20%)
	Speech-language pathologist	4 (27%)		Electrocardiogram	3 (20%)
	Psychologist	3 (20%)		Quality-of-life assessment	3 (20%)
	Neonatologist	2 (13%)		Intracranial imaging ultrasound	3 (20%)
	Orthopedic surgeon	1 (7%)		Orthopedic assessment	2 (13%)
	Clinical geneticist	1 (7%)		CT chest	1 (7%)
				Ventilation/perfusion scan	1 (7%)
				Intracranial imaging MRI	1 (7%)
				Thoracic MRI	1 (7%)
				Genetic assessment	1 (7%)
				Cardiac catheterization	0

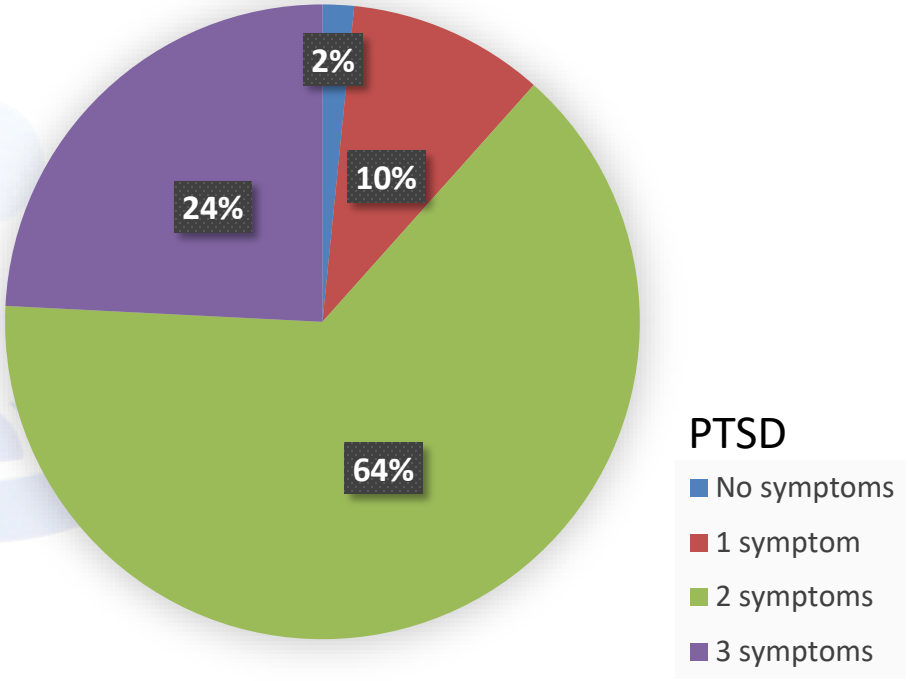
Ijsselstijn A et al., Pediatr Res, 2018

CDH parents: who cares?

Seeing Their Children in Pain: Symptoms of Posttraumatic Stress Disorder in Mothers of Children with an Anomaly Requiring Surgery at Birth

Lucia Aite, PsD[1] Francesca Bevilacqua, PsD[1] Antonio Zaccara, MD[2] Edoardo La Sala, MS[3]
Simonetta Gentile, PsD[1] Pietro Bagolan, PhD[4]

- ✓Failed project
- ✓Uncertainty for the future
- ✓Fear for loss
- ✓Change of familial routine



Aite L et al., Am J Perinatol, 2016

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CDH parents: who cares?

Couples Facing the Birth of a Newborn with a Congenital Anomaly: PTSD Symptoms in the First Year

Francesca Bevilacqua, PsD[1] Francesco Morini, MD[2] Antonio Zaccara, MD[3] Chiara De Marchis, MD[2]
Annabella Braguglia, MD[2] Simonetta Gentile, PsD[1] Pietro Bagolan, MD[2] Lucia Aite, PsD[1]

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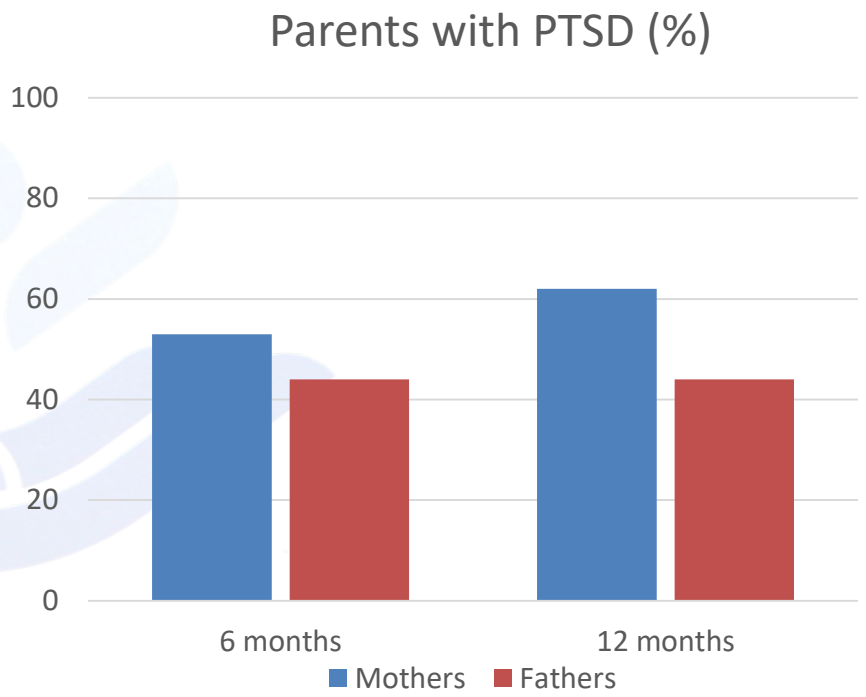
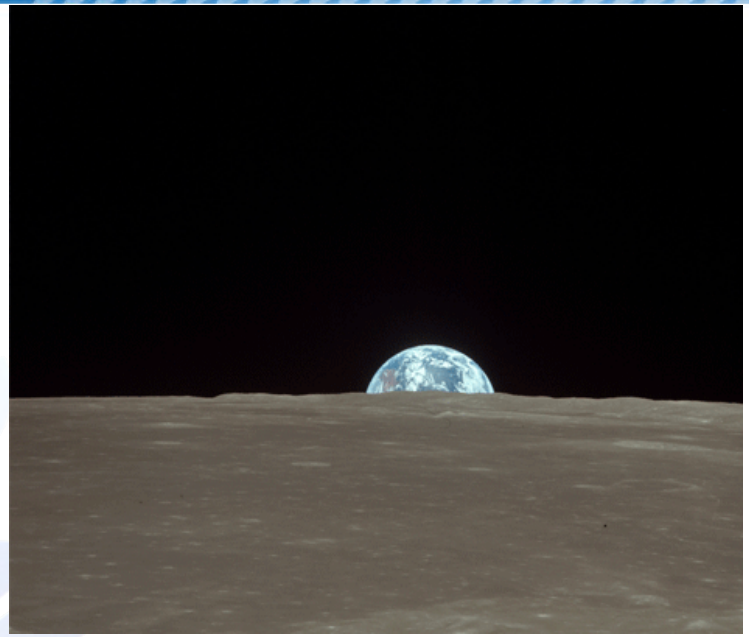


Bevilacqua F et al., Am J Perinatol, 2018

Take home messages



- ✓ CDH patients may have serious long term sequelae
- ✓ In CDH patients long term sequelae may be smoldering
- ✓ Long term, family-centered follow-up programs are needed
- ✓ Standardization of follow-up programs is desirable
- ✓ Future: TRANSITION

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Thank you

MiRacles for babies with abnormal lung development and Congenital Diaphragmatic Hernia

Richard Keijzer, MD, MSc, PhD, FACS

Thorlakson Chair in Surgical Research

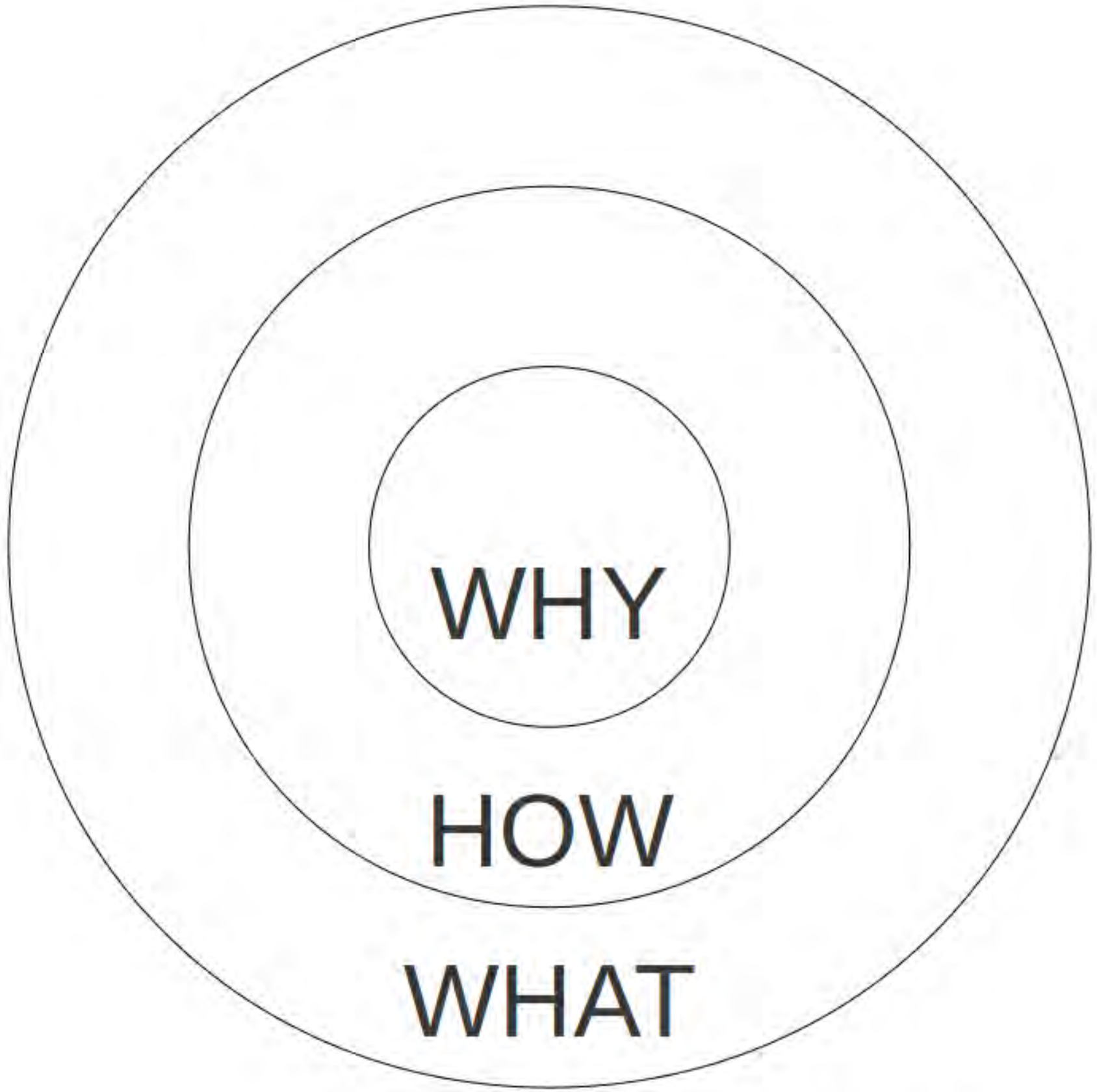
Conflict of Interest Disclosure

I hold a patent application (PCT/CA2015/051028) containing technology described in the presentation

I have filed for a patent to use circular RNAs as biomarkers for abnormal lung development and CDH

How it began

We don’t do chart reviews here, why don’t you go in the lab for the next few months.



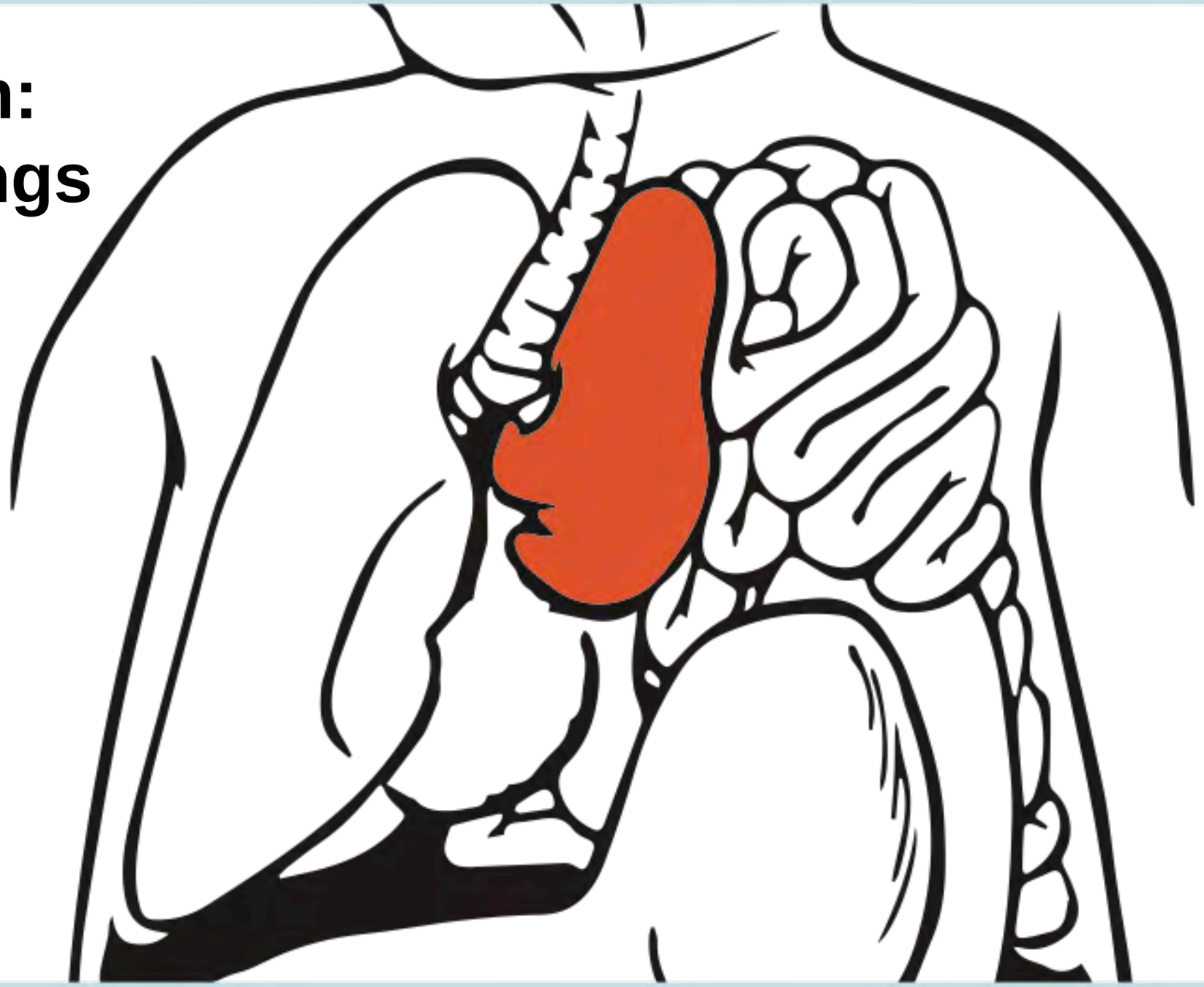
The 'golden circle' from Simon Sinek

http://store.winnipegfreepress.com/photostore/details/139975/

Mortality: >400,000 since 2000

Image: Shutterstock

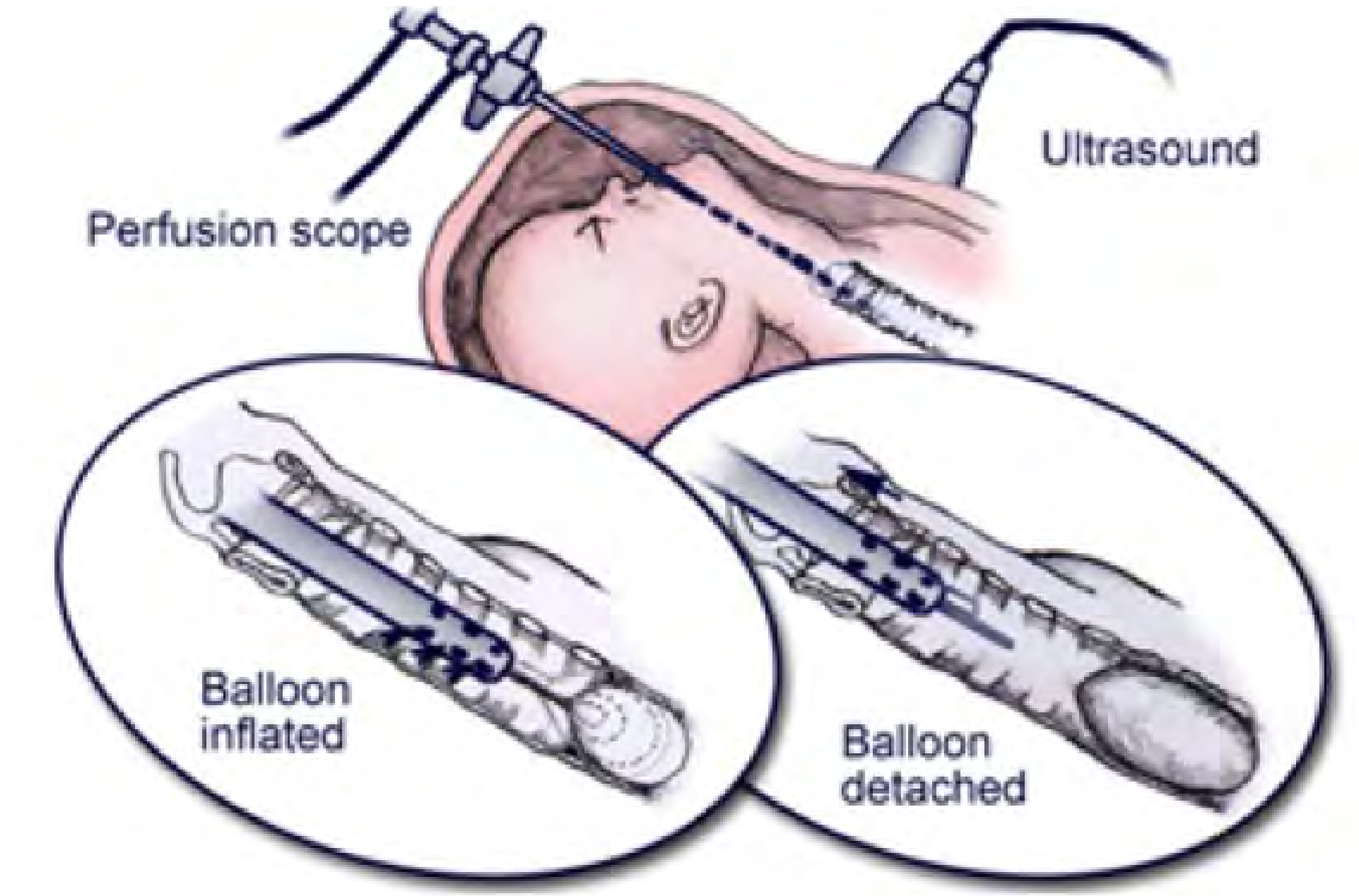
Main problem:
Abnormal lungs




MiRACLA
MicroRNAs • And • Congenital • Lung • Anomalies

What is wrong with CDH lungs?

Can we fix the lungs before birth?



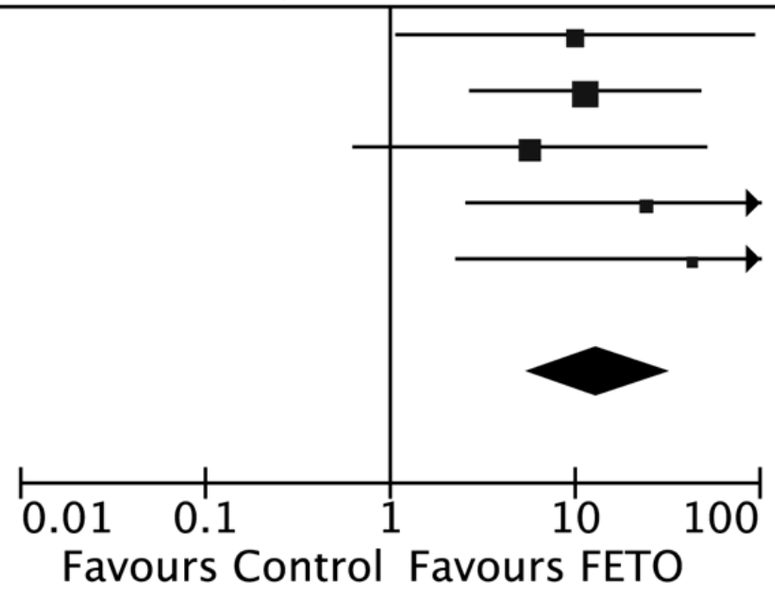
totaltrial.eu

Meta-analysis FETO improves survival in isolated CDH

Study or Subgroup	FETO Events	FETO Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Deprest 2004	10	21	1	12	19.5%	10.00 [1.09, 91.98]
Deprest 2006	12	24	3	37	34.5%	11.33 [2.72, 47.17]
Peralta 2011	9	28	1	13	27.1%	5.68 [0.64, 50.73]
Ruano 2011	10	17	1	18	11.7%	24.29 [2.60, 227.25]
Ruano 2012	10	20	0	21	7.1%	43.00 [2.29, 806.44]
Total (95% CI)		**110**		**101**	**100.0%**	**13.32 [5.40, 32.87]**
Total events	51		6			

Heterogeneity: $Chi^2 = 1.59$, $df = 4$ ($P = 0.81$); $I^2 = 0\%$

Test for overall effect: $Z = 5.62$ ($P < 0.00001$)



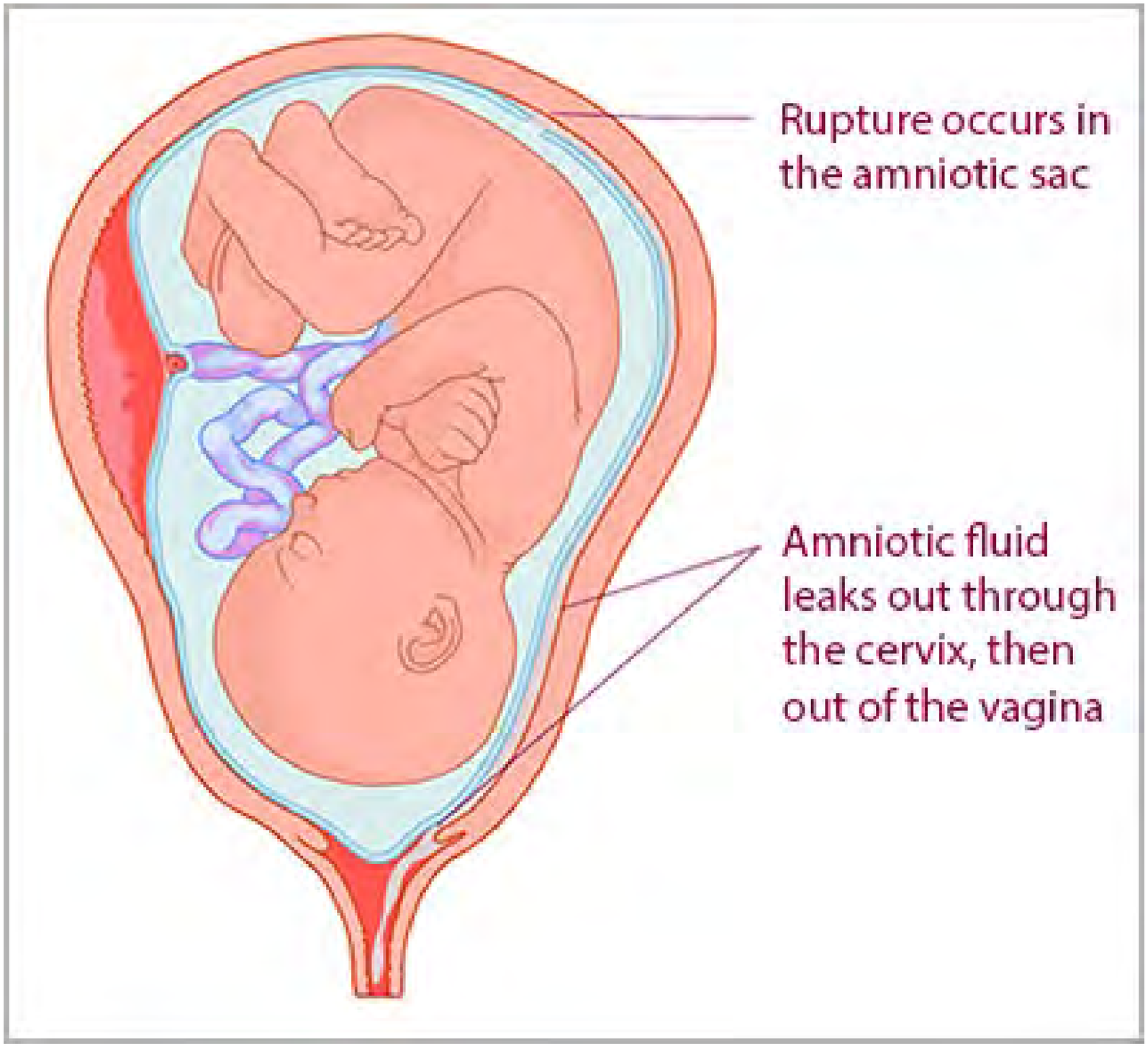
META-ANALYSIS

Fetal Tracheal Occlusion for Severe Pulmonary Hypoplasia in Isolated Congenital Diaphragmatic Hernia

A Systematic Review and Meta-analysis of Survival

Jamila Al-Maary, MD, Mary P. Eastwood, MBChB,† Francesca Maria Russo, MD,†*
Jan A. Deprest, PhD,†§ and Richard Keijzer, PhD‡*

But, negative side effects!



https://www.tommys.org/pregnancy-information/pregnancy-complications/waters-breaking-early-pprom

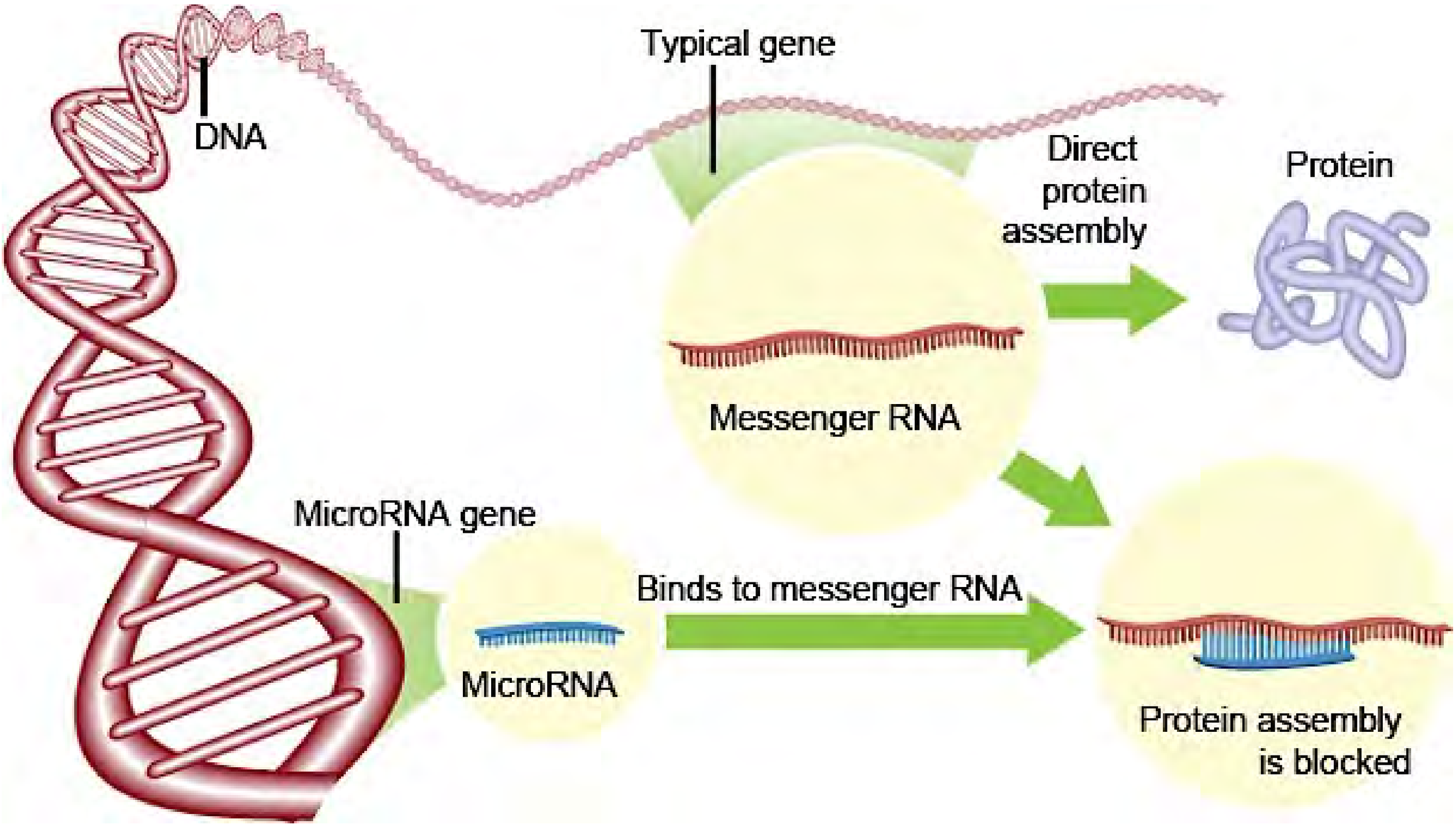
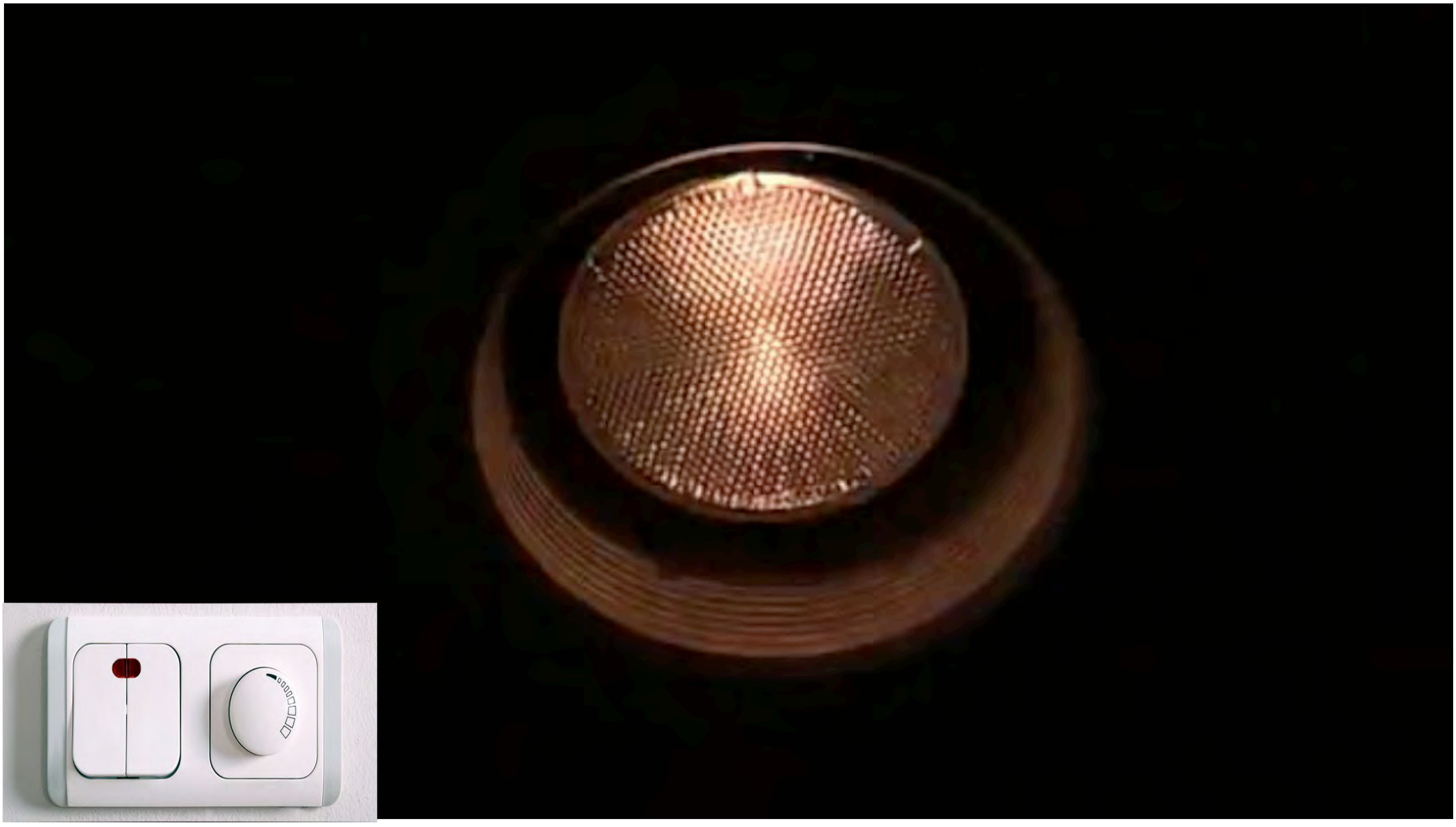
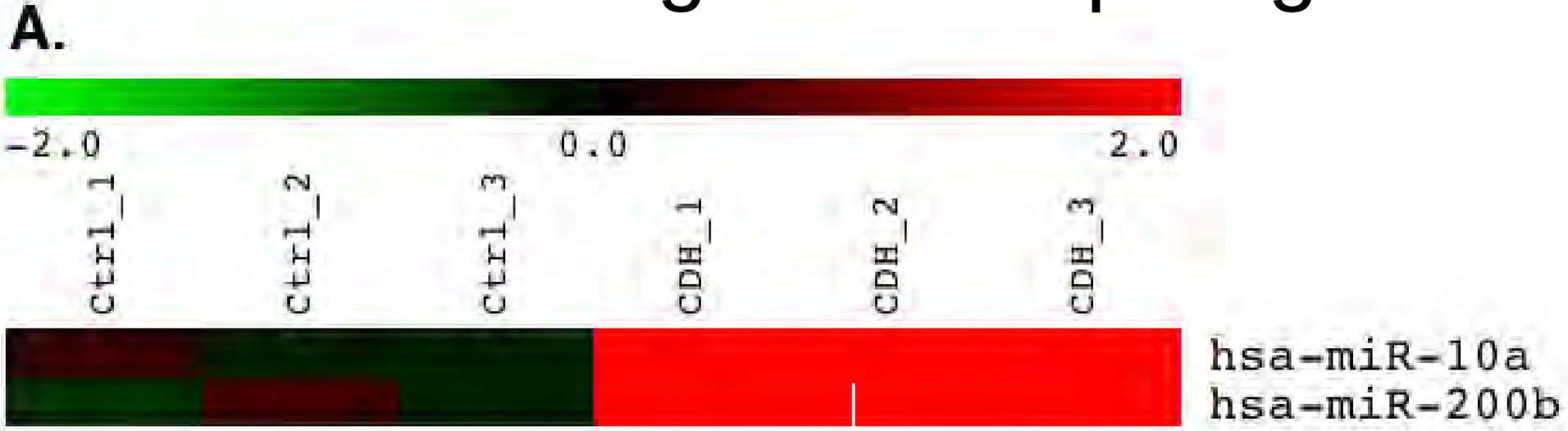
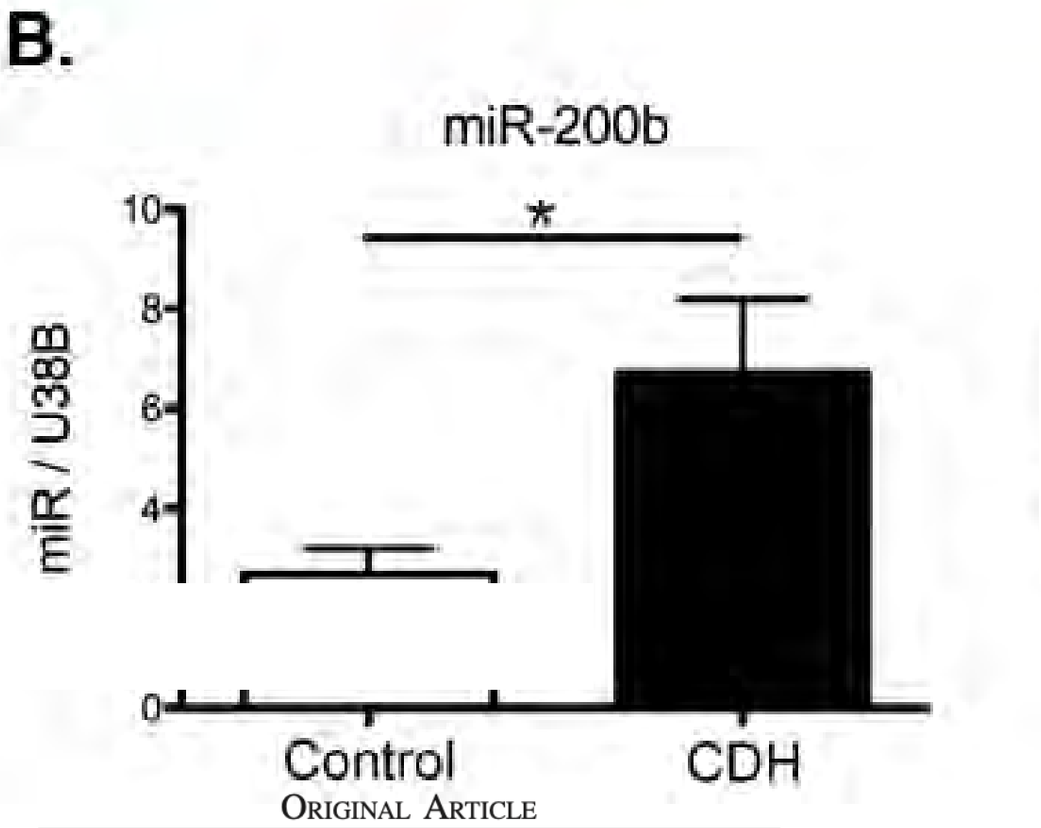


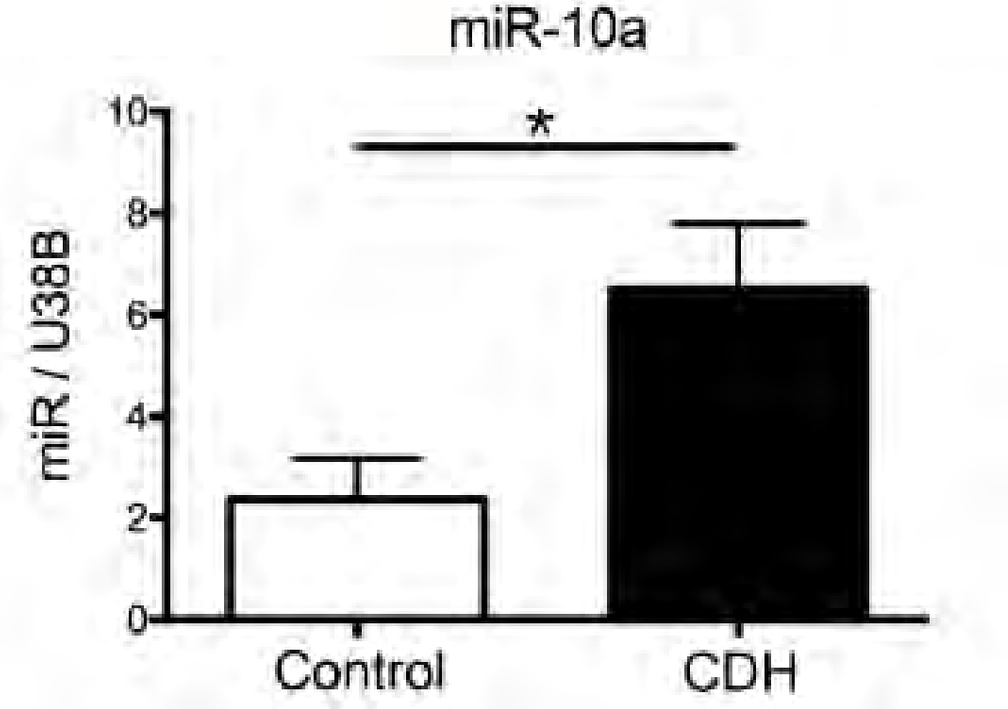
Image: Steve Karp, Discover Magazine



MicroRNAs and Congenital Diaphragmatic Hernia



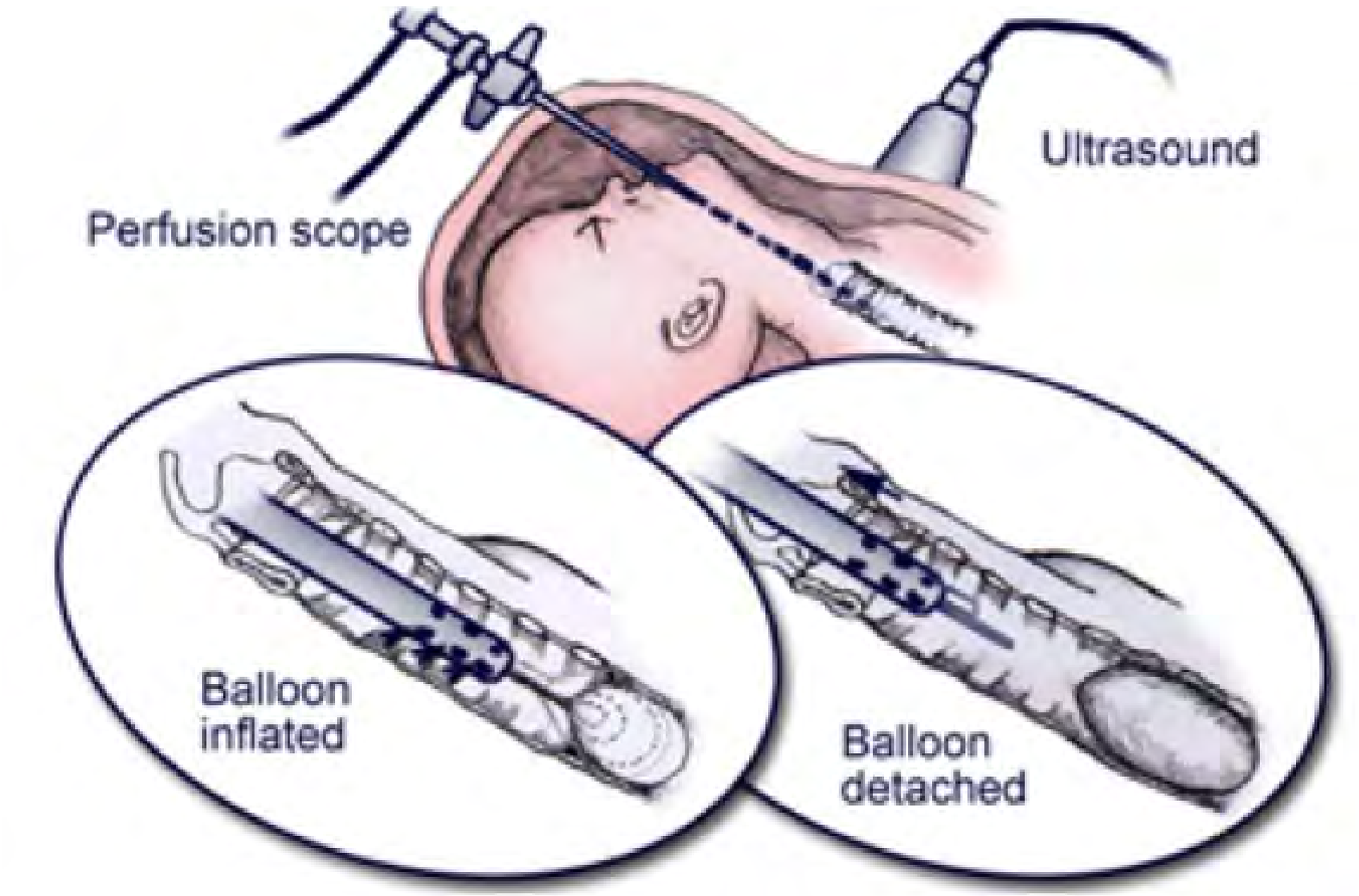




ORIGINAL ARTICLE

Unique Tracheal Fluid MicroRNA Signature Predicts Response to FETO in Patients With Congenital Diaphragmatic Hernia

Patrícia Pereira-Terra, MSc,† Jan A. Deprest, MD, PhD,‡ Ramin Kholdebarin, MD, MSc,* Naghmeh Khoshgoo, MS,* Philip DeKoninck, MD, PhD,‡ Anne A. Boerema-De Munck,§ Jinxia Wang,¶ Fuqin Zhu,* Robbert J. Rottier, PhD,§ Barbara M. Iwasiow, MSc,* Jorge Correia-Pinto, MD, PhD,† Dick Tibboel, MD, PhD,§ Martin Post, DVM, PhD,¶ and Richard Keijzer, PhD**



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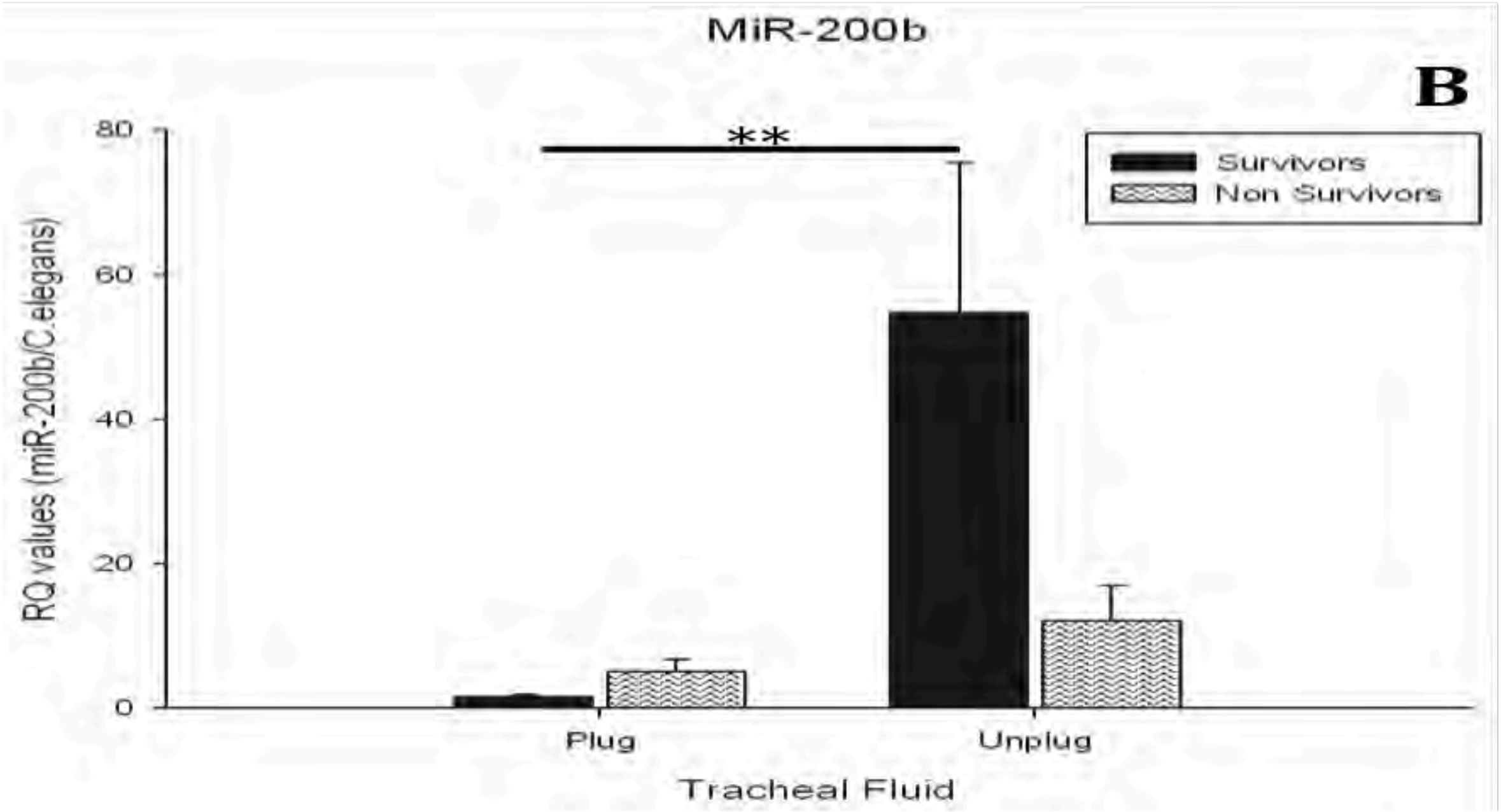
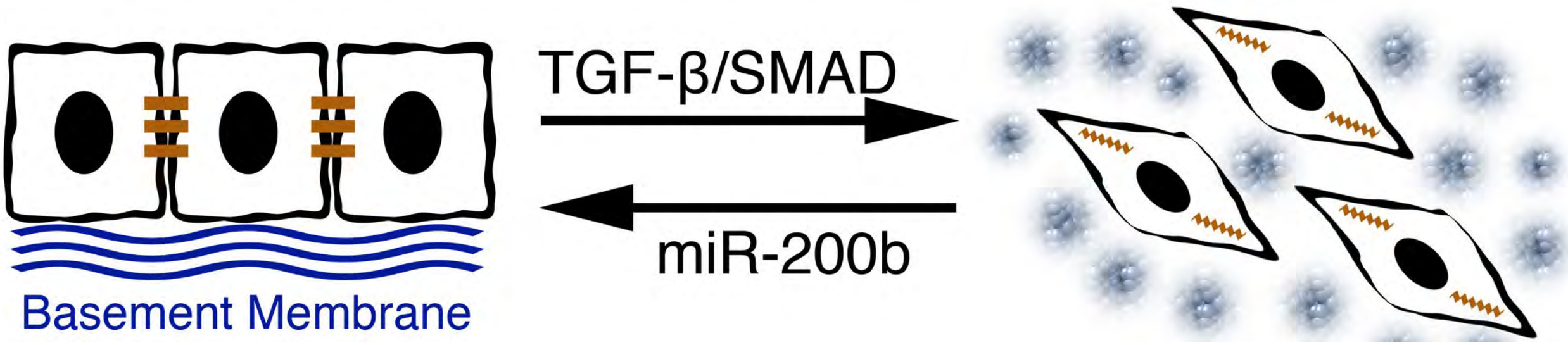
Higher miR-200b has better outcomes



Epithelial-to-Mesenchymal Transition (EMT)



Epithelial cells

Mesenchymal cells

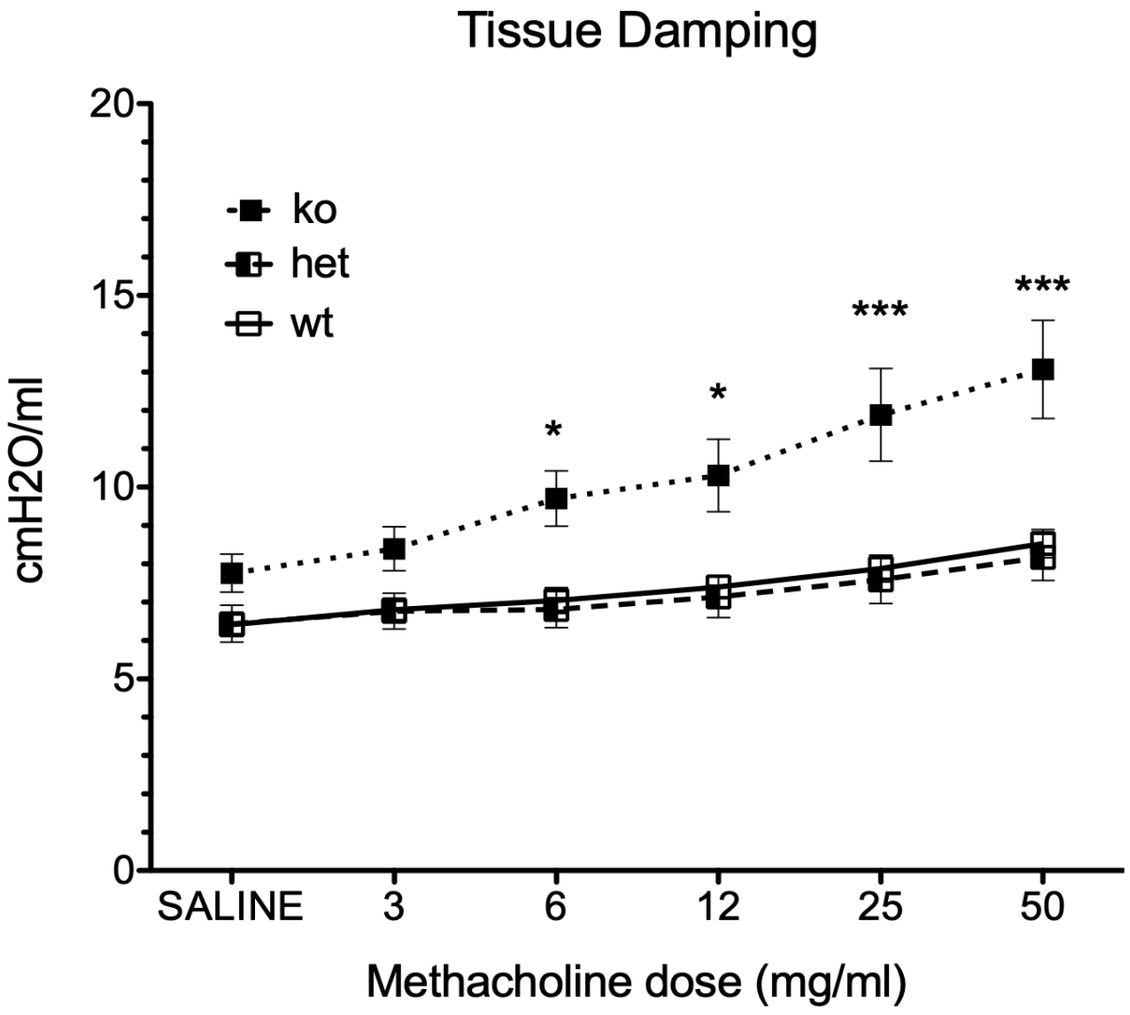
SCIENTIFIC REPORTS

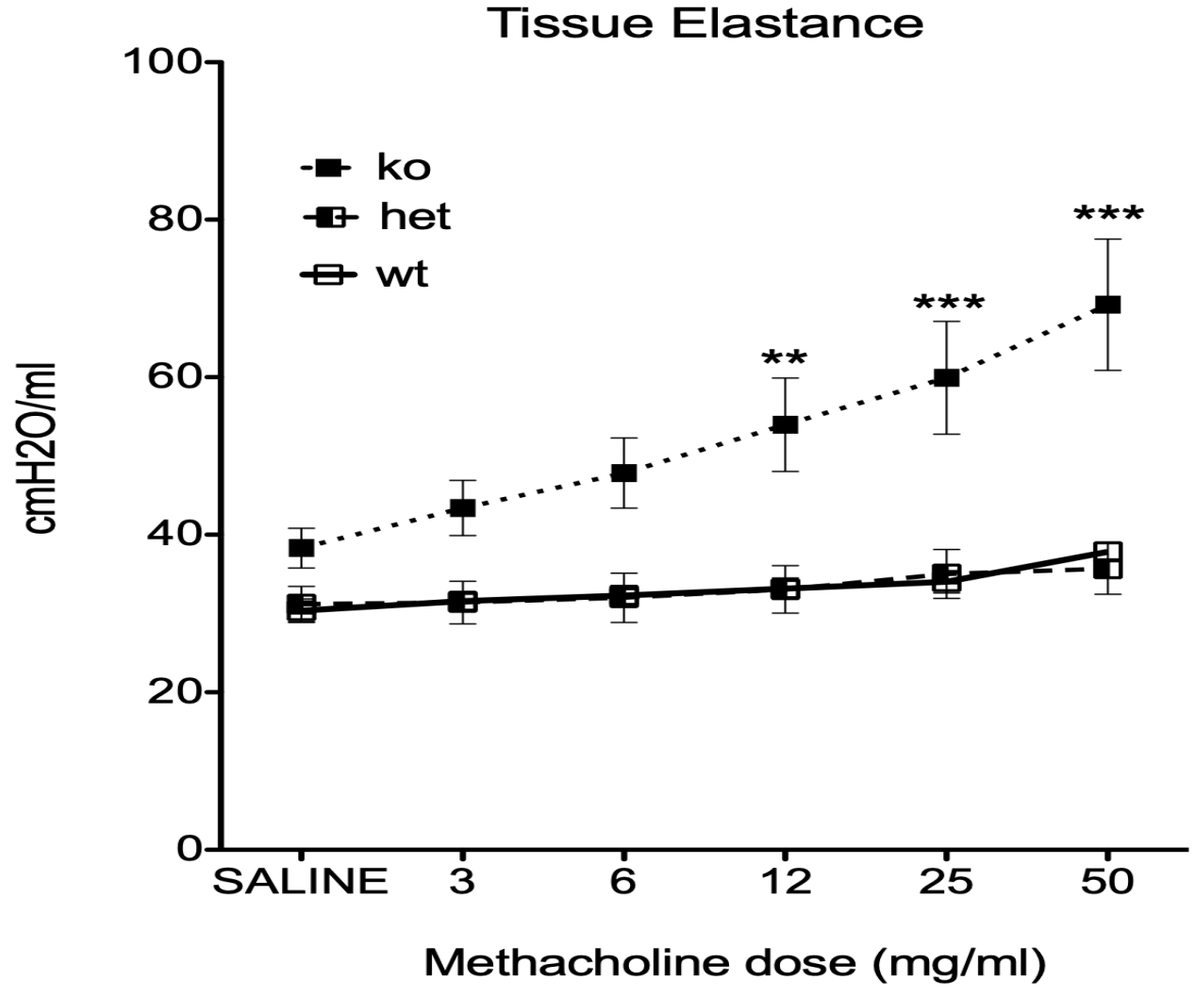
OPEN

MicroRNA-200b regulates distal airway development by maintaining epithelial integrity

Naghmeh Khoshgoo[1,2,3], Robin Visser[1,2], Landon Falk[1,2], Chelsea A. Day[1,2], Dustin Ameis[1,2], Barbara M. Iwasiow[1,2], Fuqin Zhu[1,2], Arzu Öztürk[4,5], Sujata Basu[1,3], Molly Pind[4,5], Agnes Fresnosa[4,5], Mike Jackson[6], Vinaya Kumar Siragam[1,2], Gerald Stelmack[1,3], Geoffrey G. Hicks[4,5], Andrew J. Halayko[1,3] & Richard Keijzer[1,2,3]

miR-200b -/- mice have higher lung tissue damping and elasticity

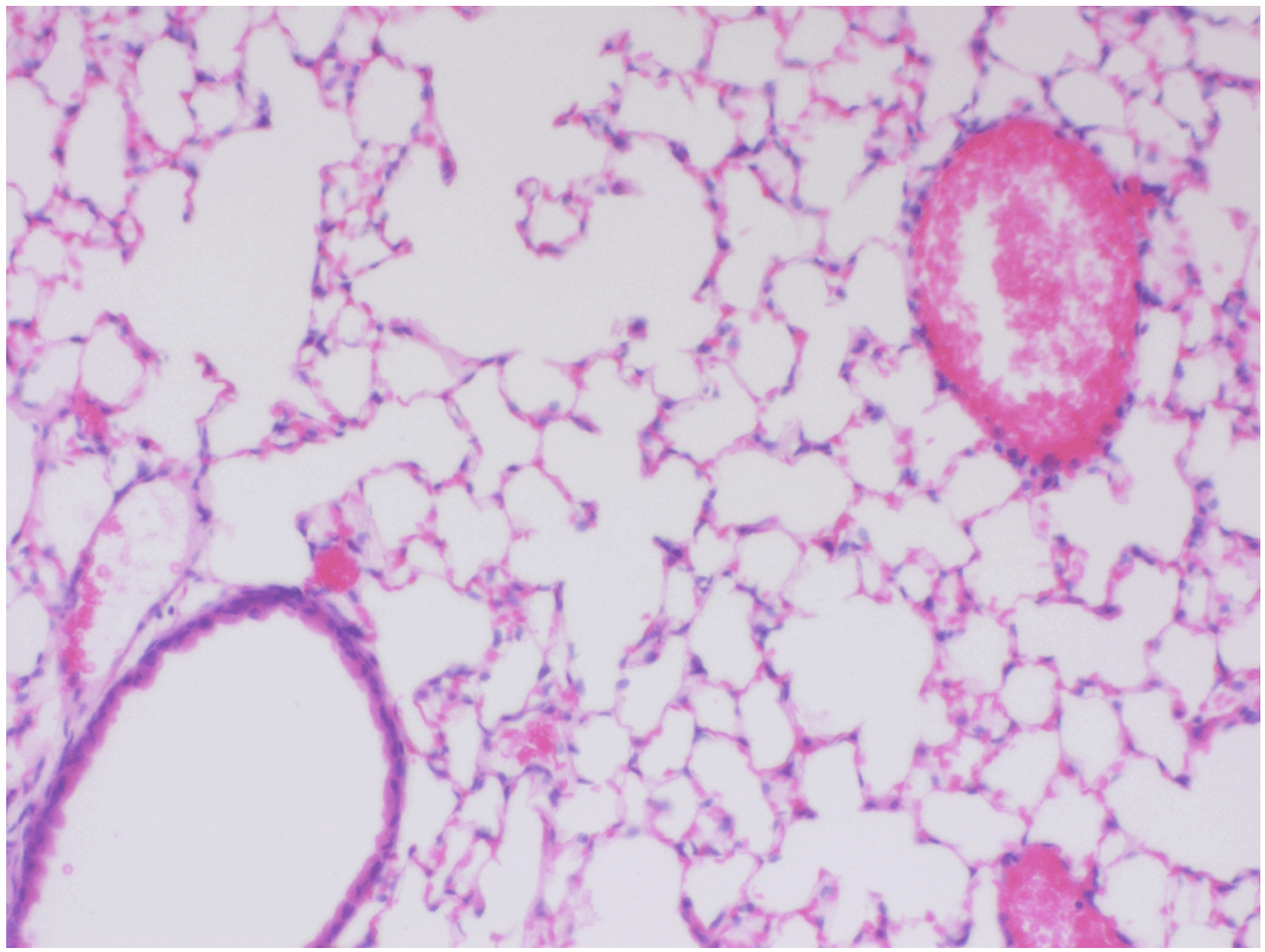




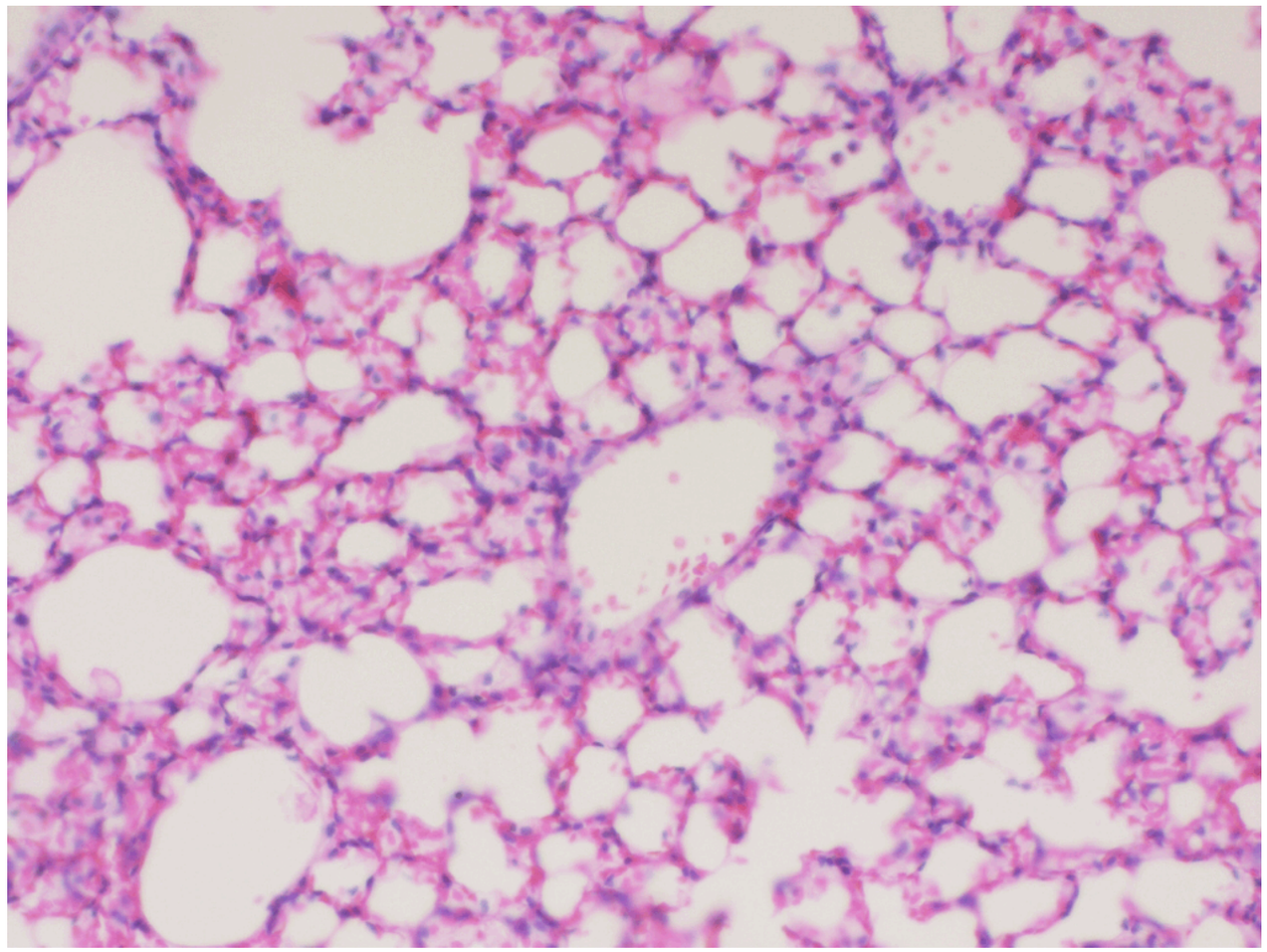
* P< 0.05, ** P< 0.01, *** P< 0.001

miR-200b -/- lungs are hypoplastic

wt

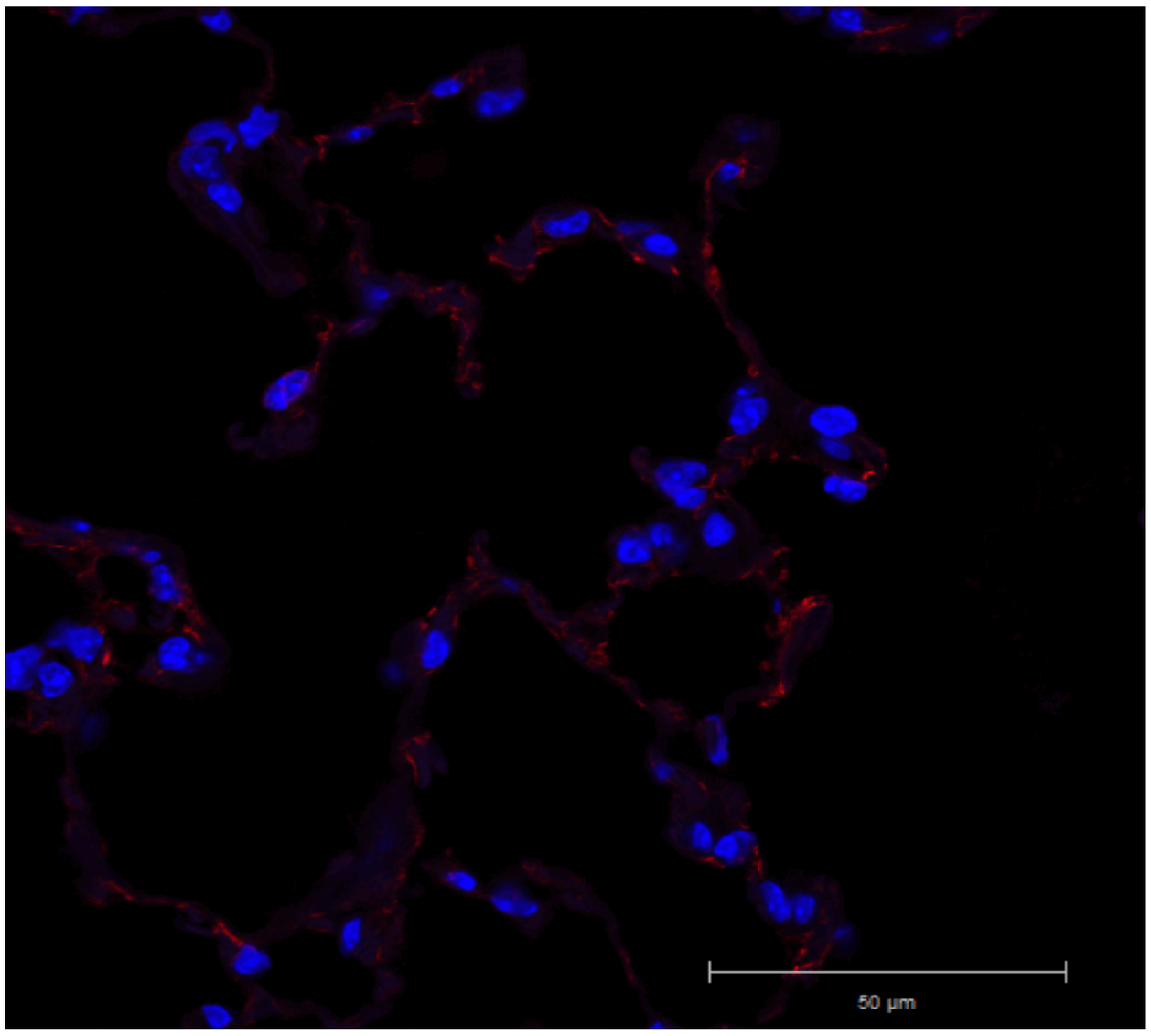


miR-200b -/-

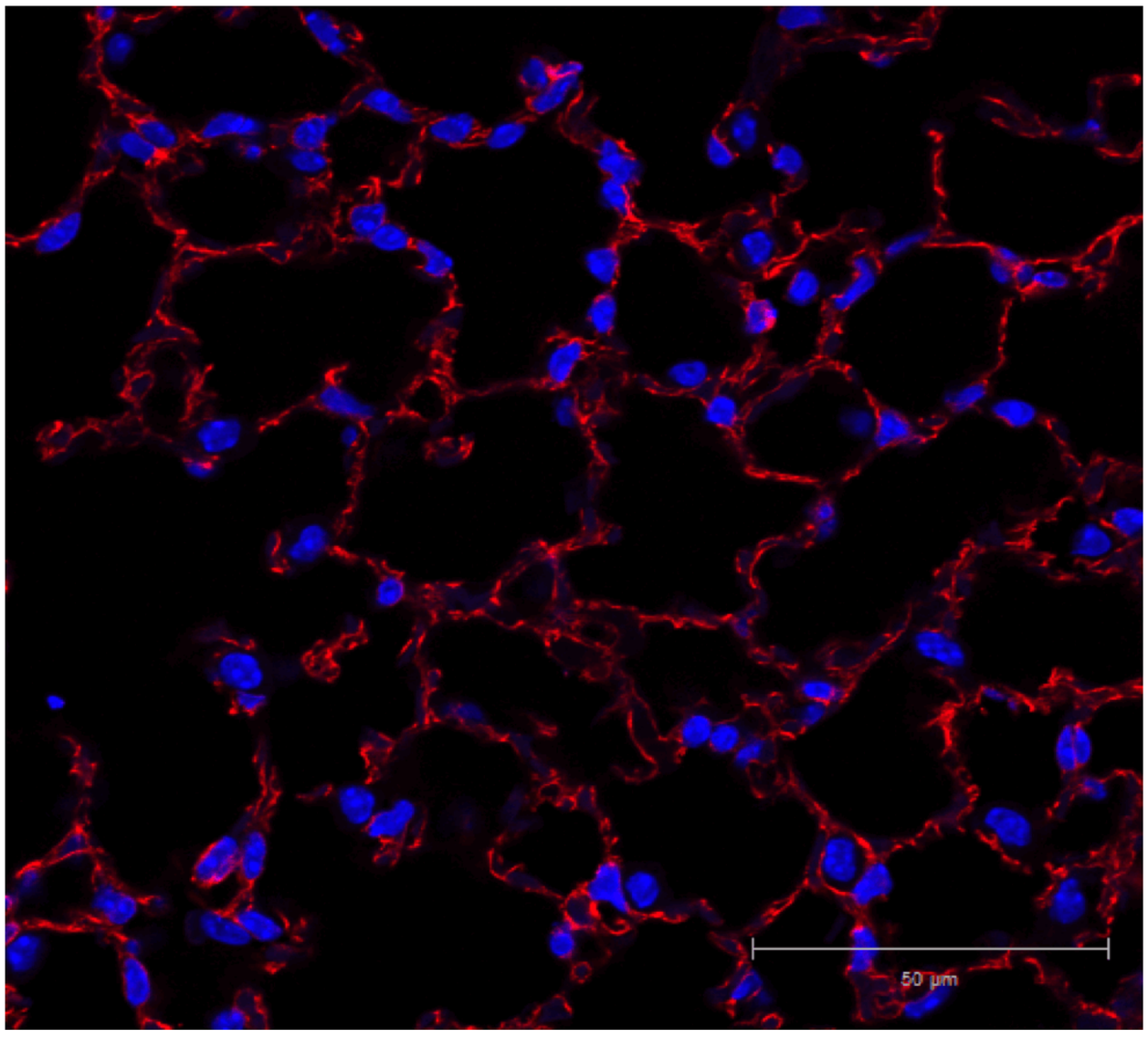


miR-200b -/- lungs have more vimentin

wt



miR-200b -/-

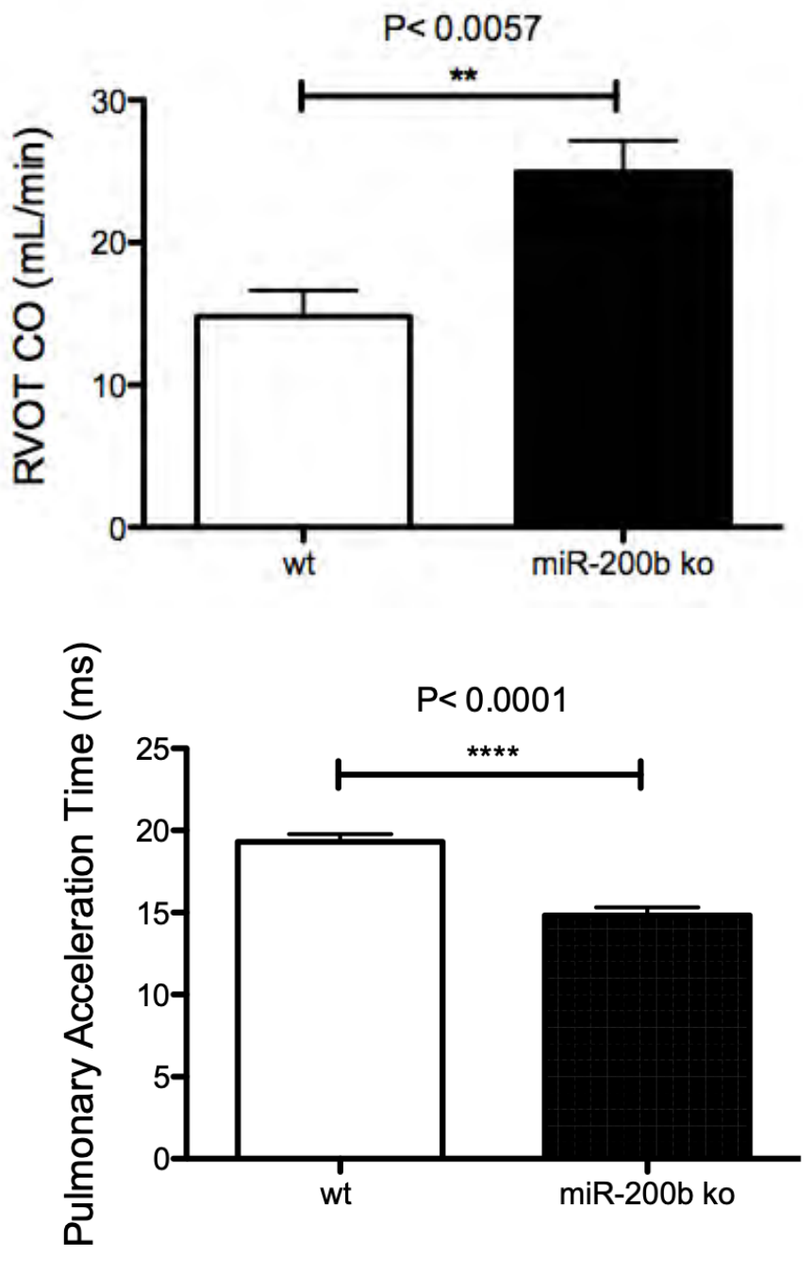


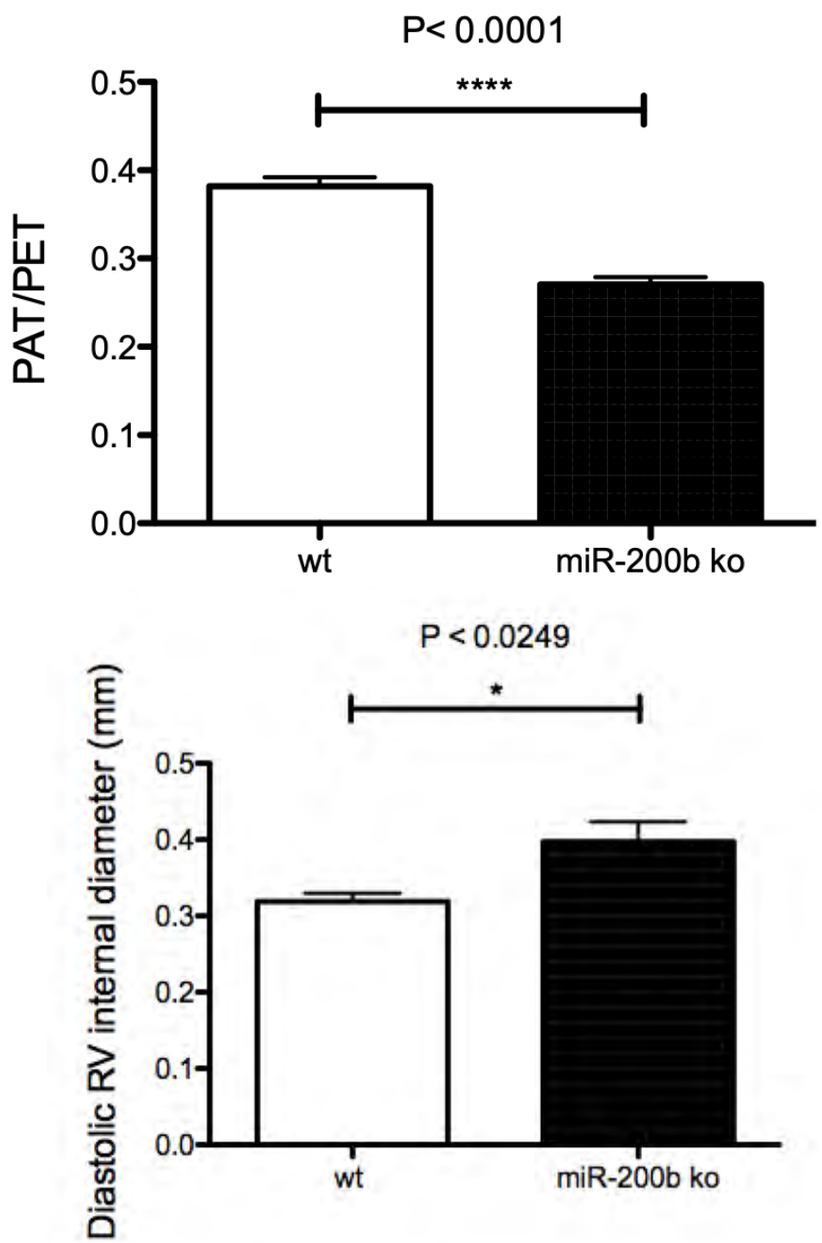
Wildtype

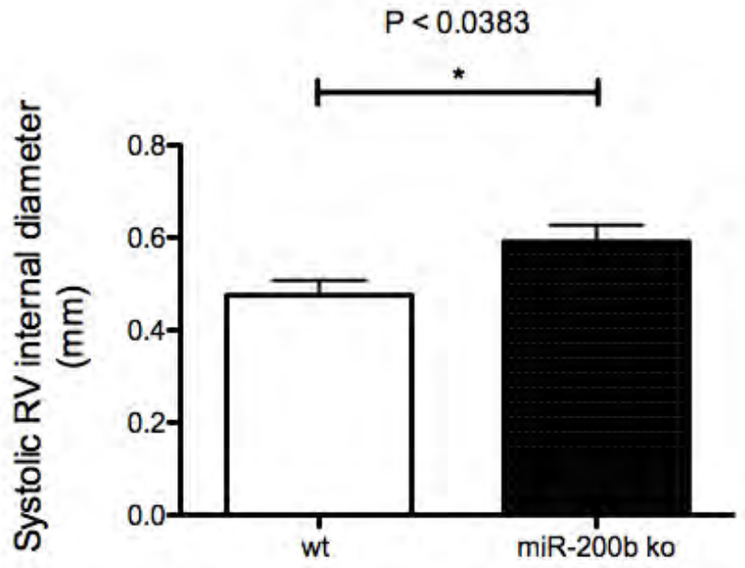
miR-200b -/-

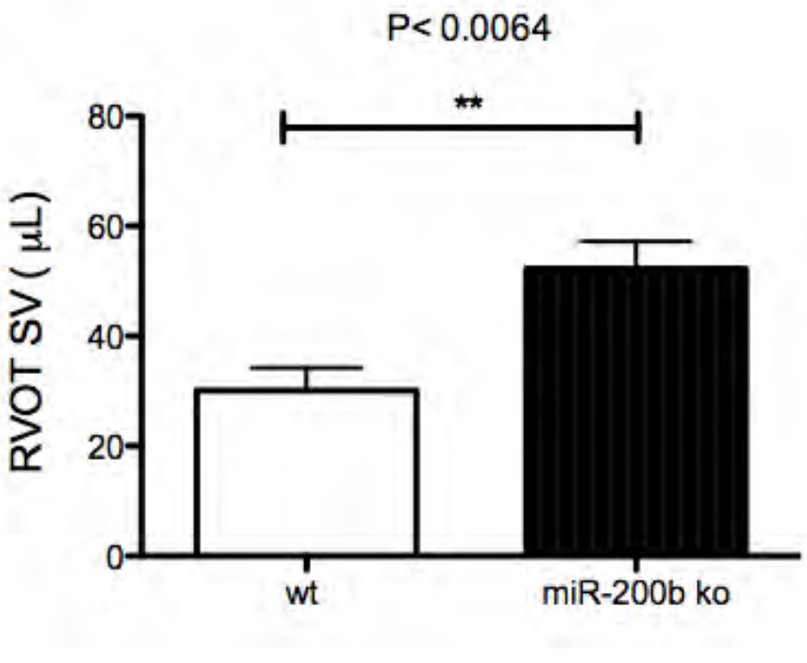
Unpublished results

miR-200b knockout mice have pulmonary hypertension on cardiac echography



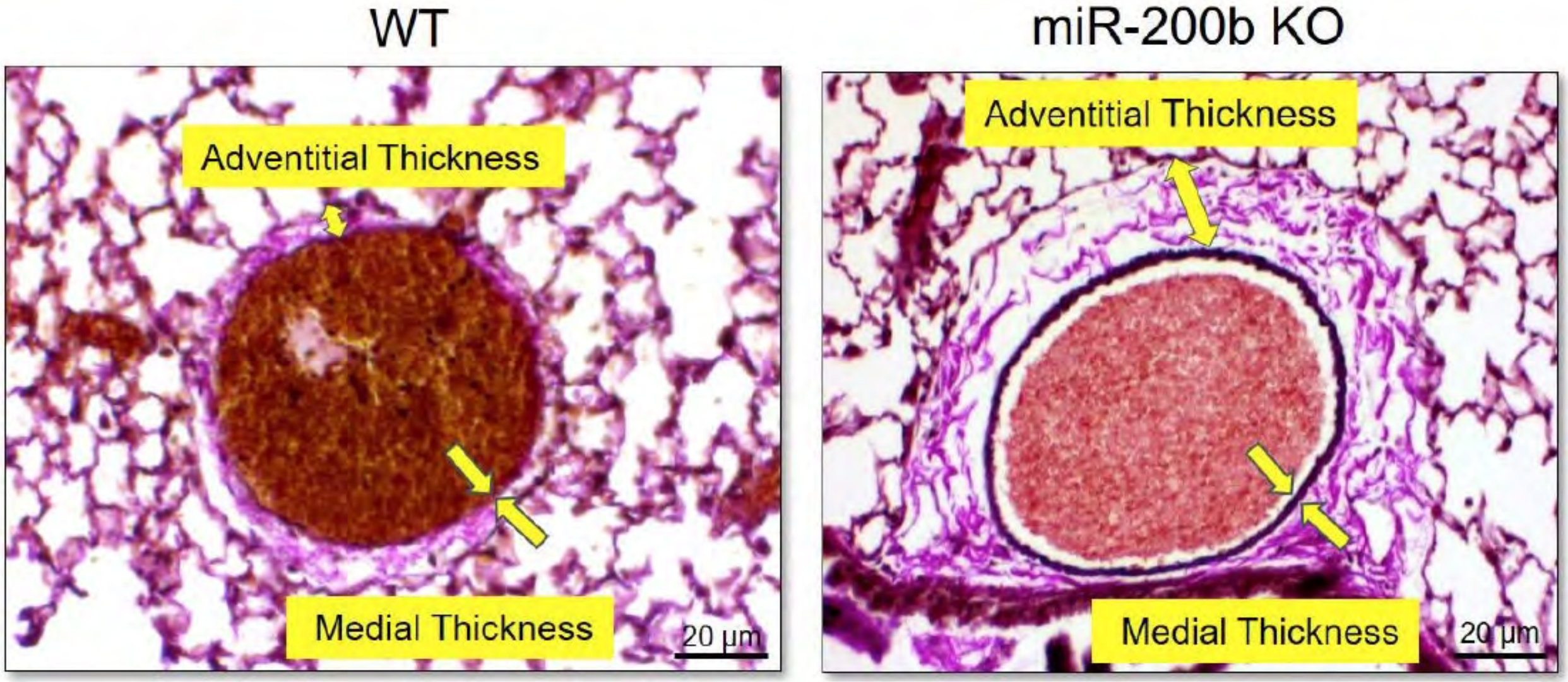






Unpublished results

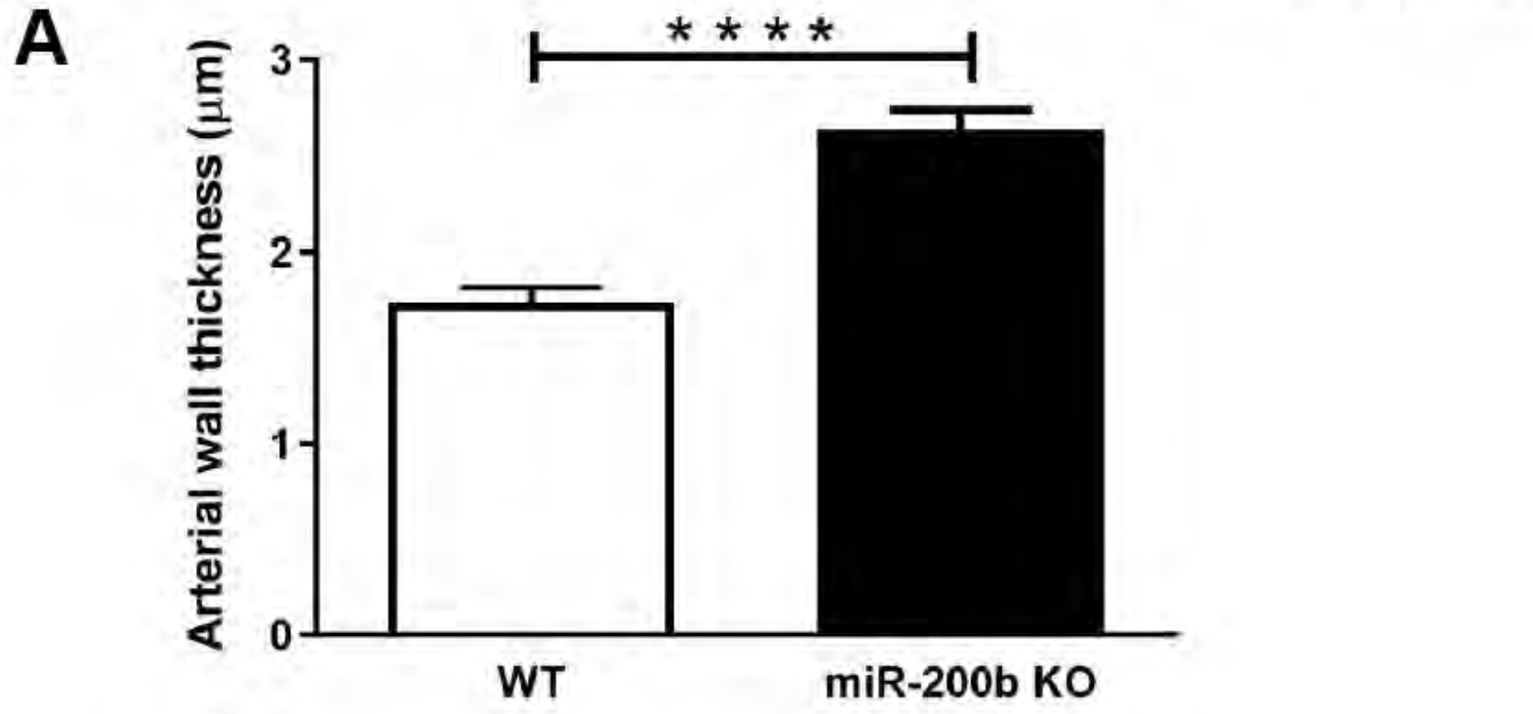
miR-200b-/- lungs have thicker vessel walls

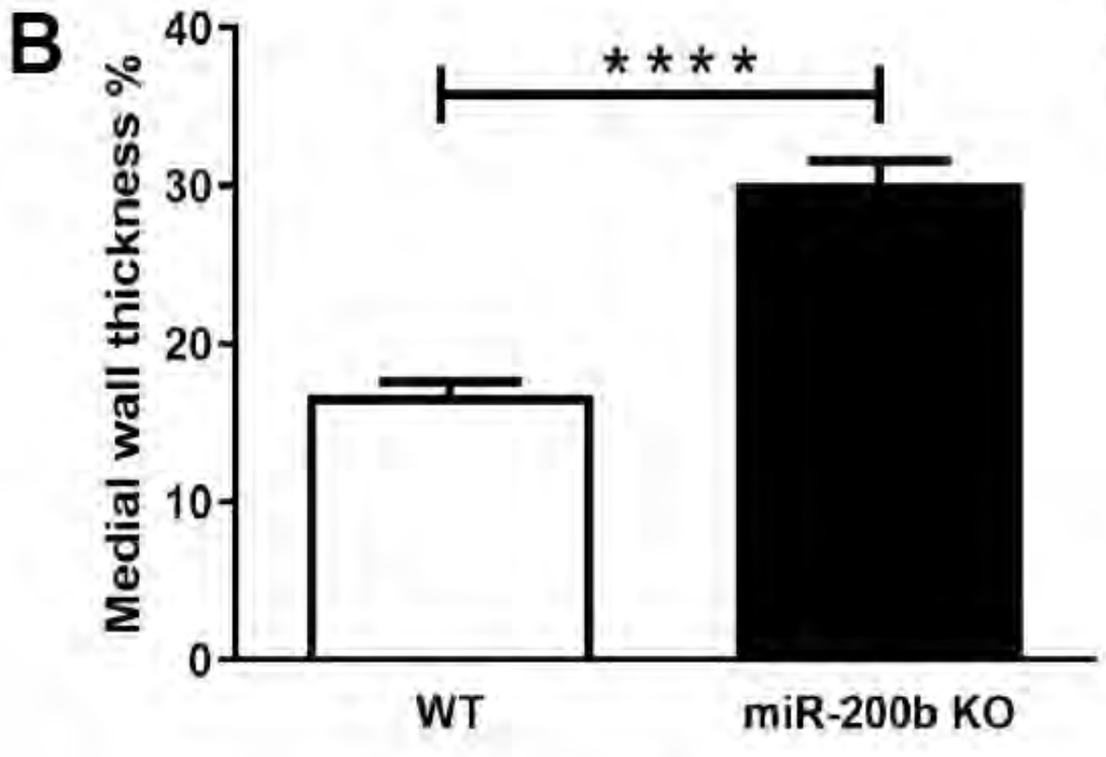


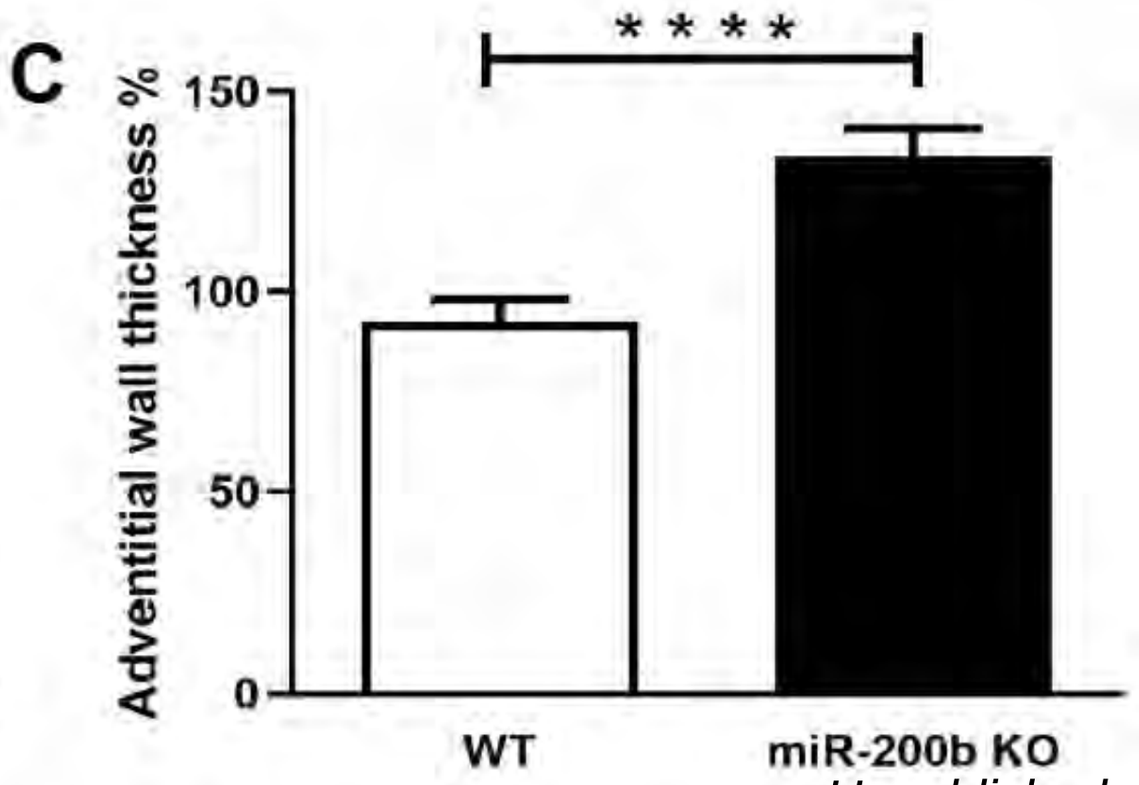
Unpublished results

miR-200b-/- lungs have thicker vessel walls

**** $P < 0.0001$

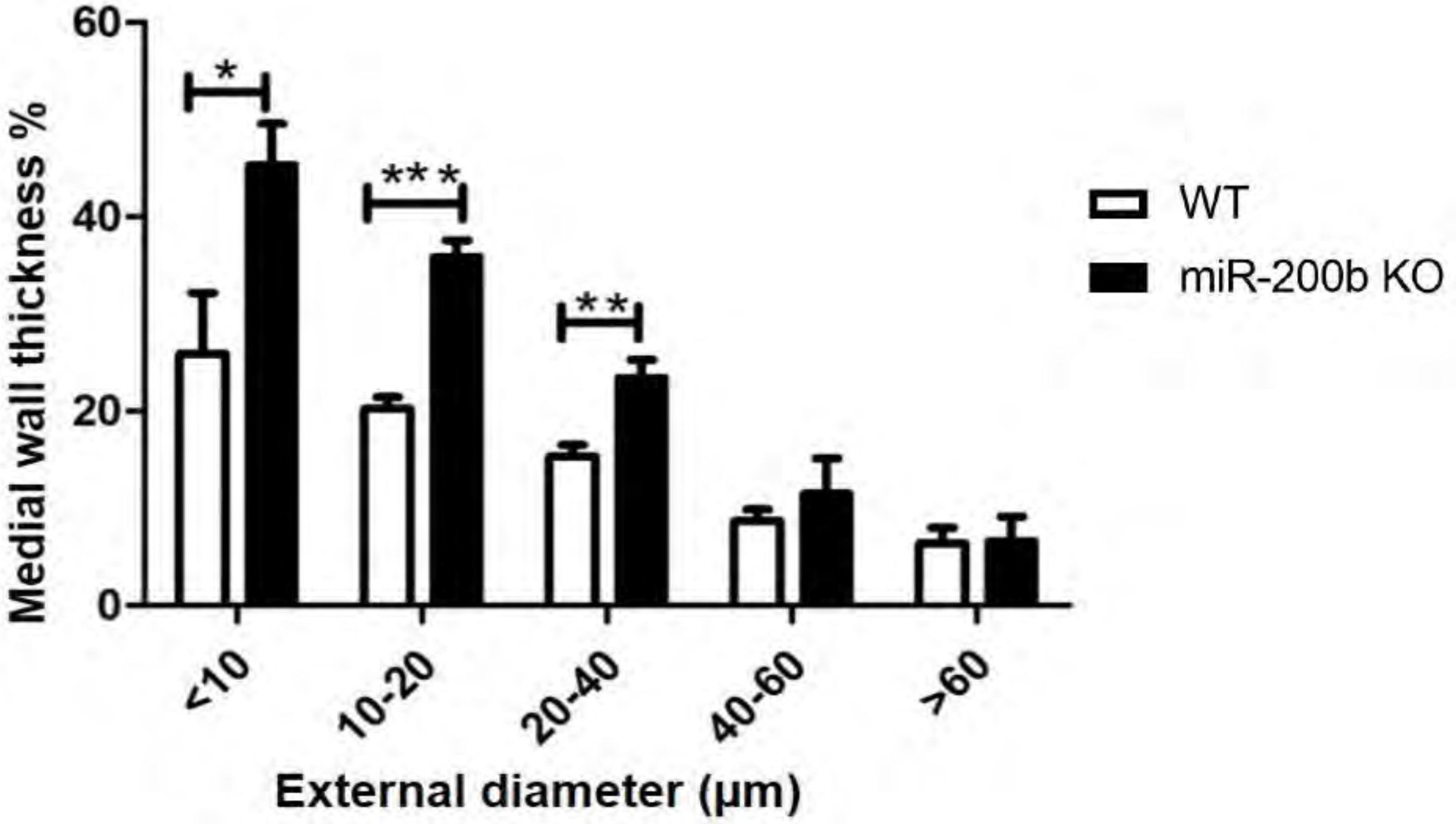






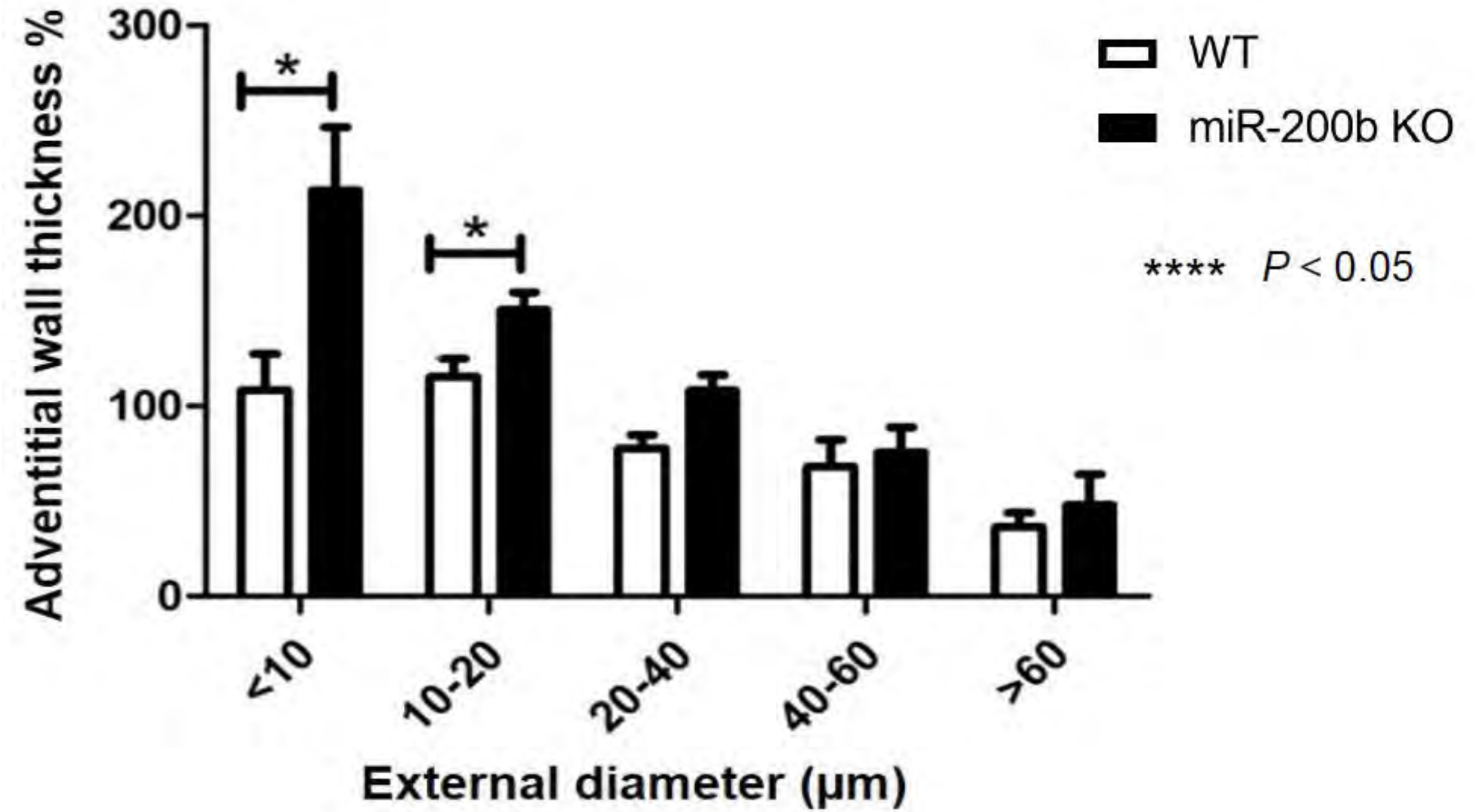
Unpublished results

miR-200b-/- lungs have thicker vessel walls



Unpublished results

miR-200b-/- lungs have thicker vessel walls



Unpublished results

NITROFEN MODEL OF CDH

Lung

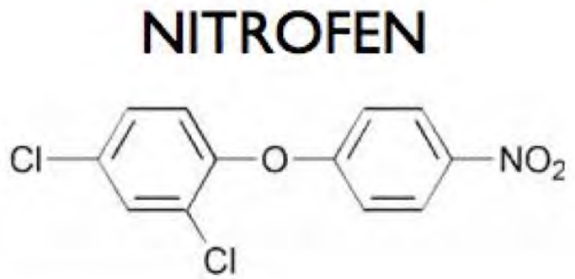
Diaphragm

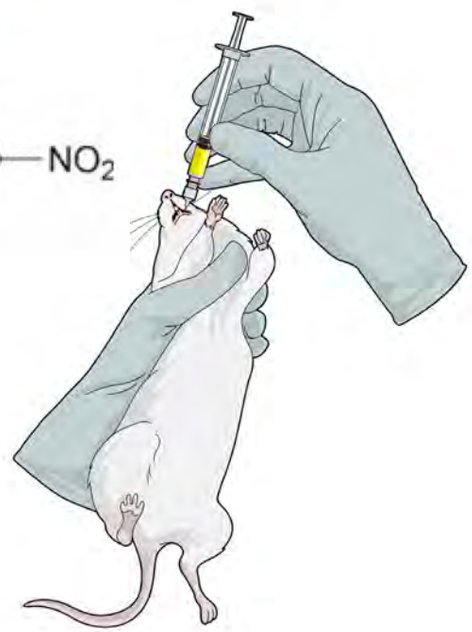
Fetal breathing

Birth

E0 E9 E11 E14 E17 E22

NITROFEN





80% CDH

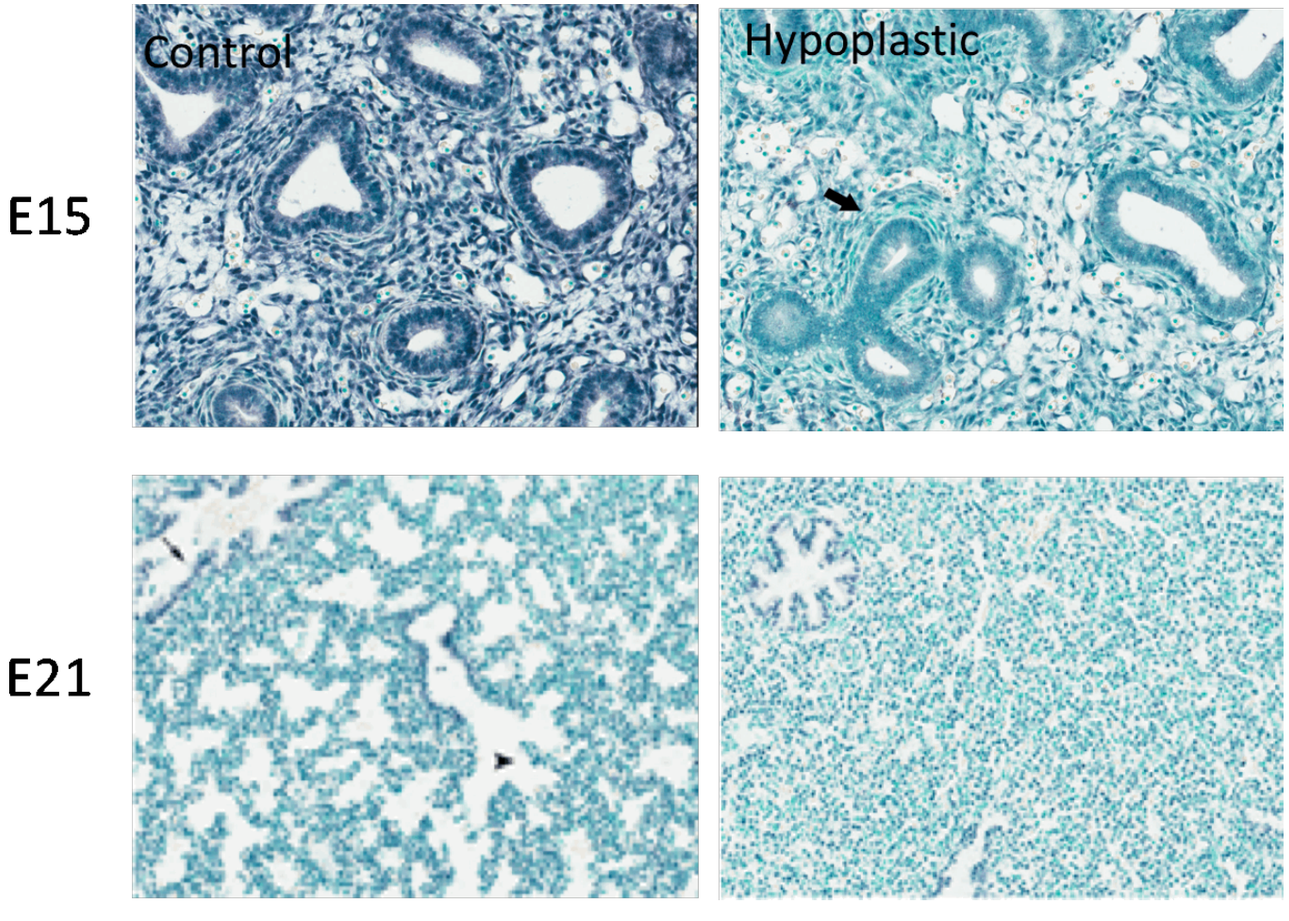
100% PH

Prenatal microRNA miR-200b Therapy Improves Nitrofen-induced Pulmonary Hypoplasia Associated With Congenital Diaphragmatic Hernia

Naghmeh Khoshgoo, MSc, Ramin Kholdebarin, MD, MSc,* Patricia Pereira-Terra, PhD,*† Thomas H. Mahood, MSc,* Landon Falk, BSc,* Chelsea A. Day, BSc,* Barbara M. Iwasiow, MSc,* Fuqin Zhu, BSc,* Drew Mulhall, BSc,* Carly Fraser, BSc,* Jorge Correia-Pinto, MD, PhD,†‡ and Richard Keijzer, MD, PhD, MSc, FACS**

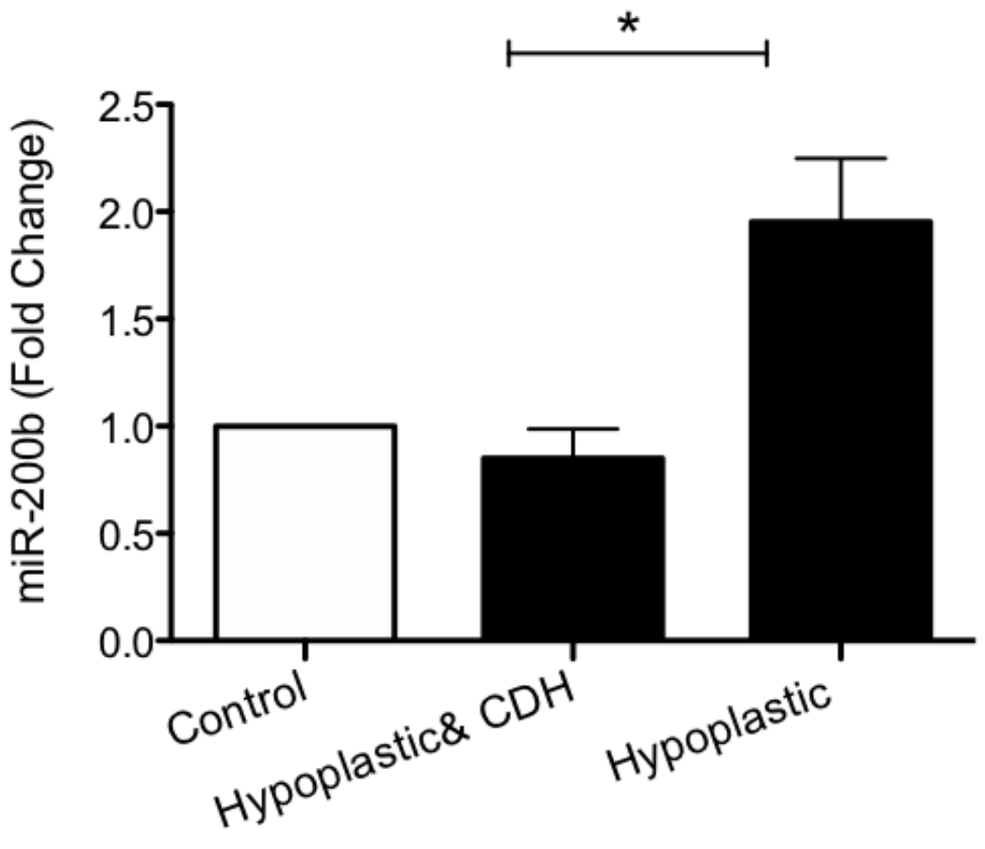
In Situ Hybridization

Control Hypoplastic+ CDH



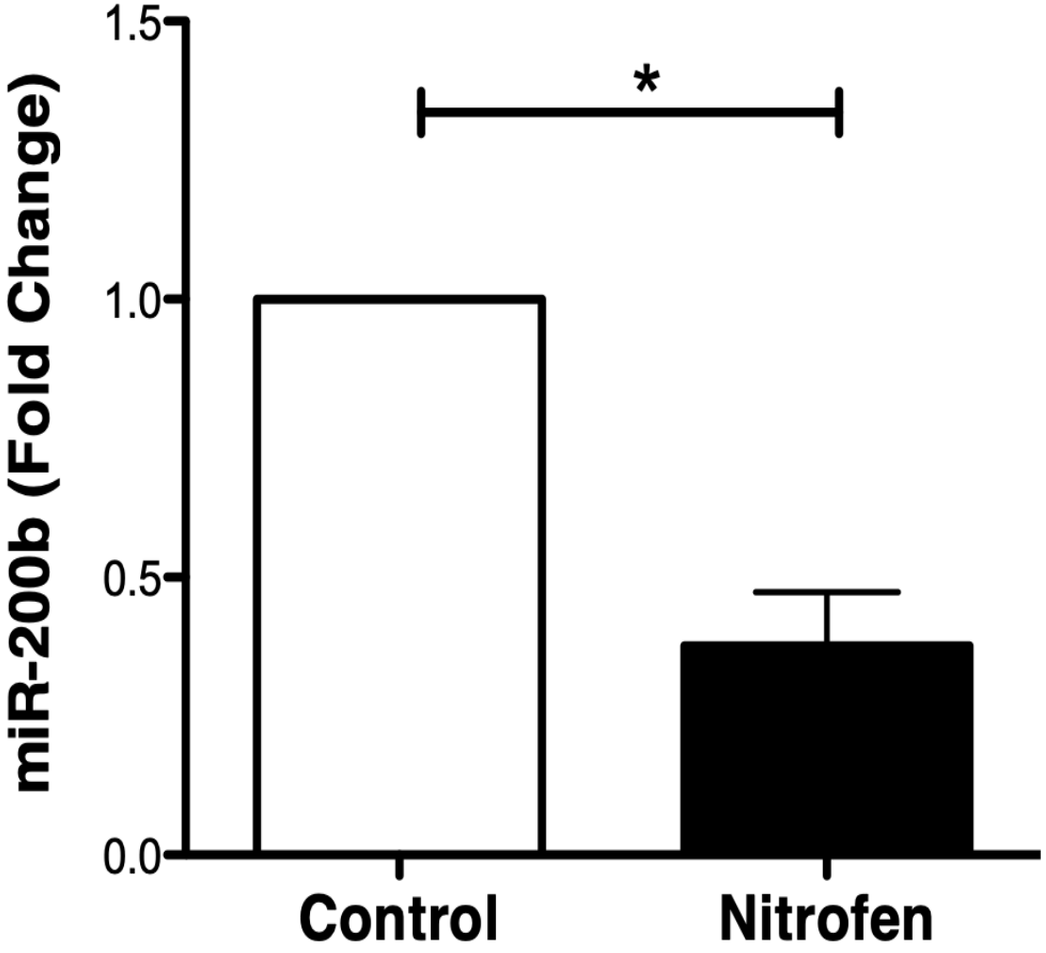
Blue staining: miR-200b

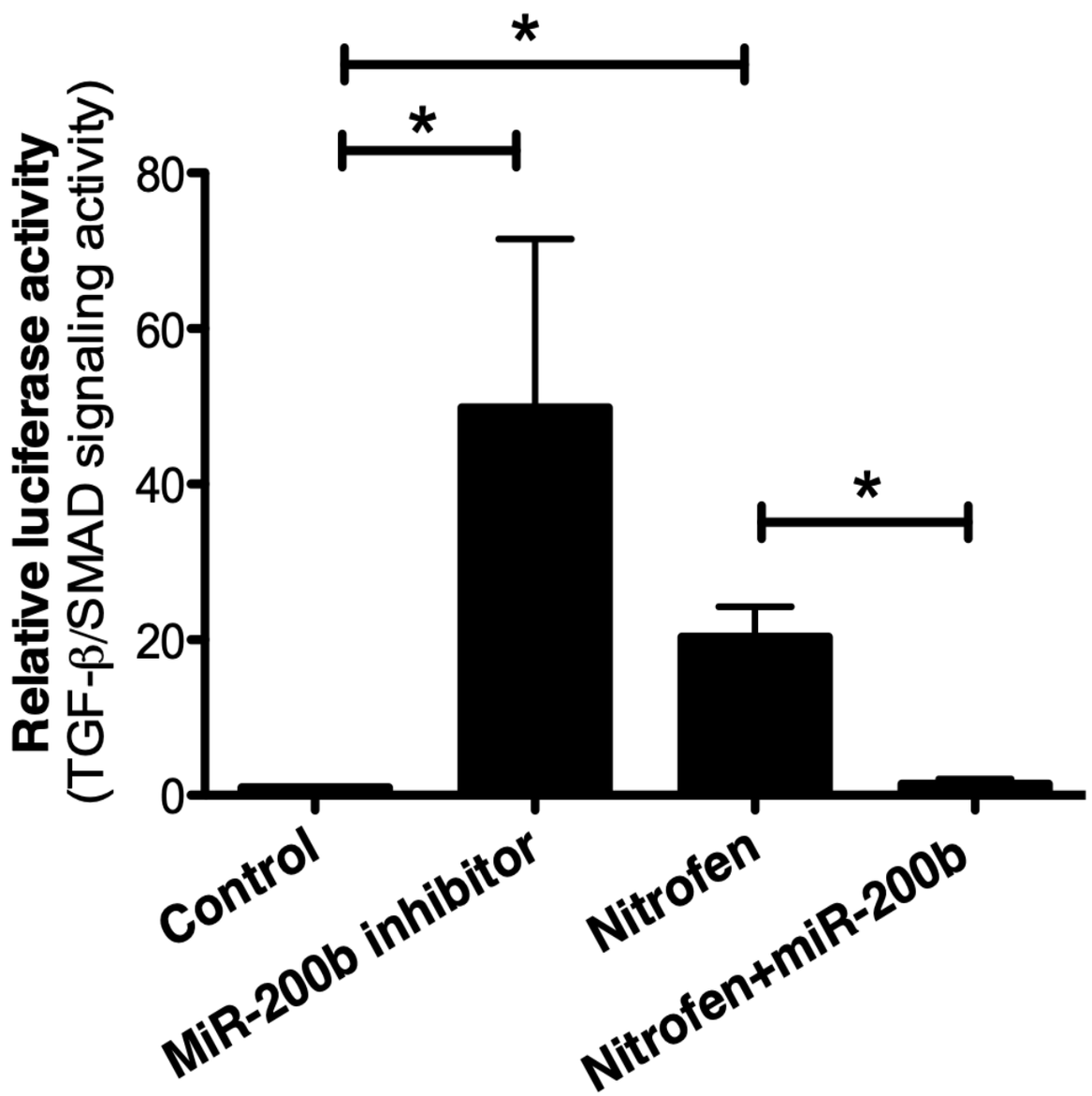
PCR (E21)



* P< 0.05

MiR-200b & Human Bronchial Epithelial Cells



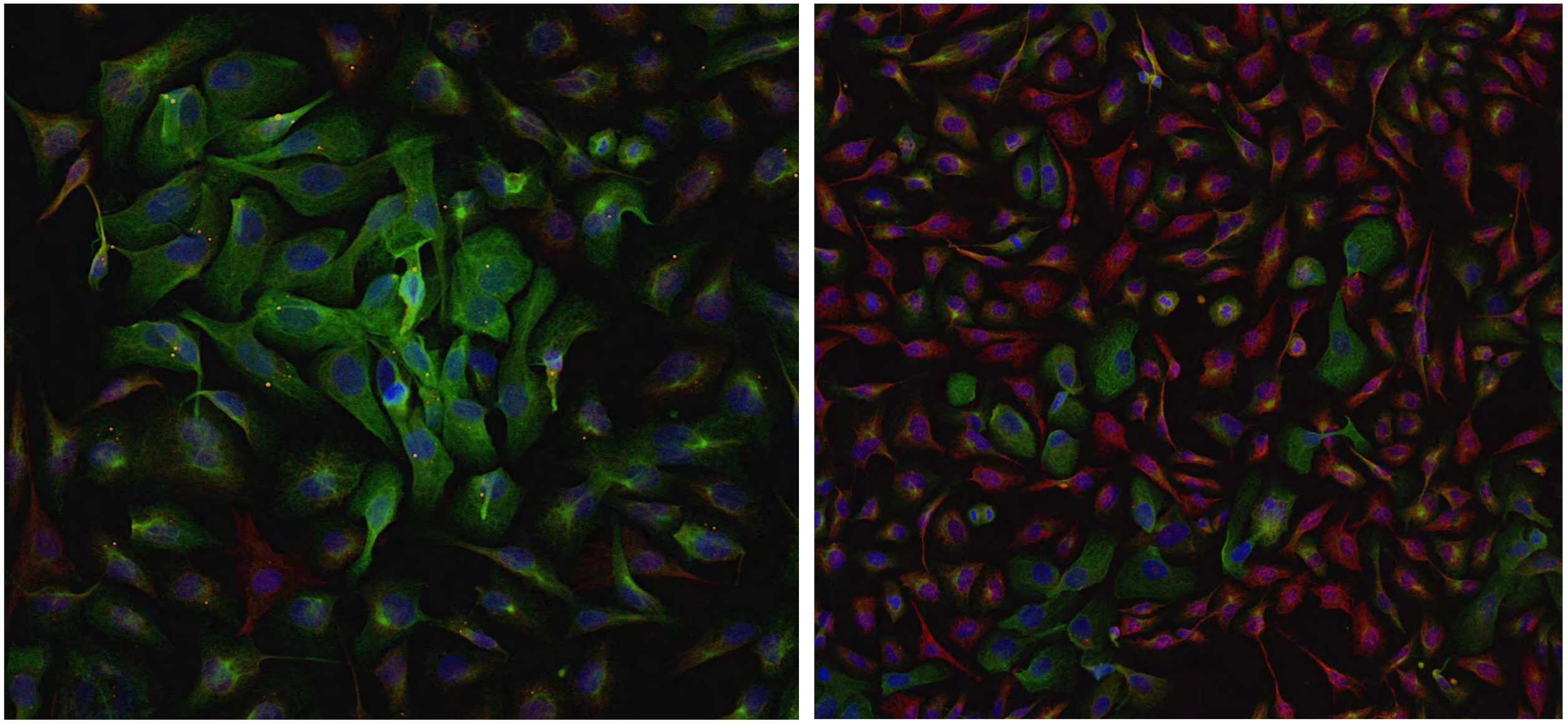


* P< 0.05

miR-200b maintained epithelial cell phenotype in bronchial epithelial cells

Control

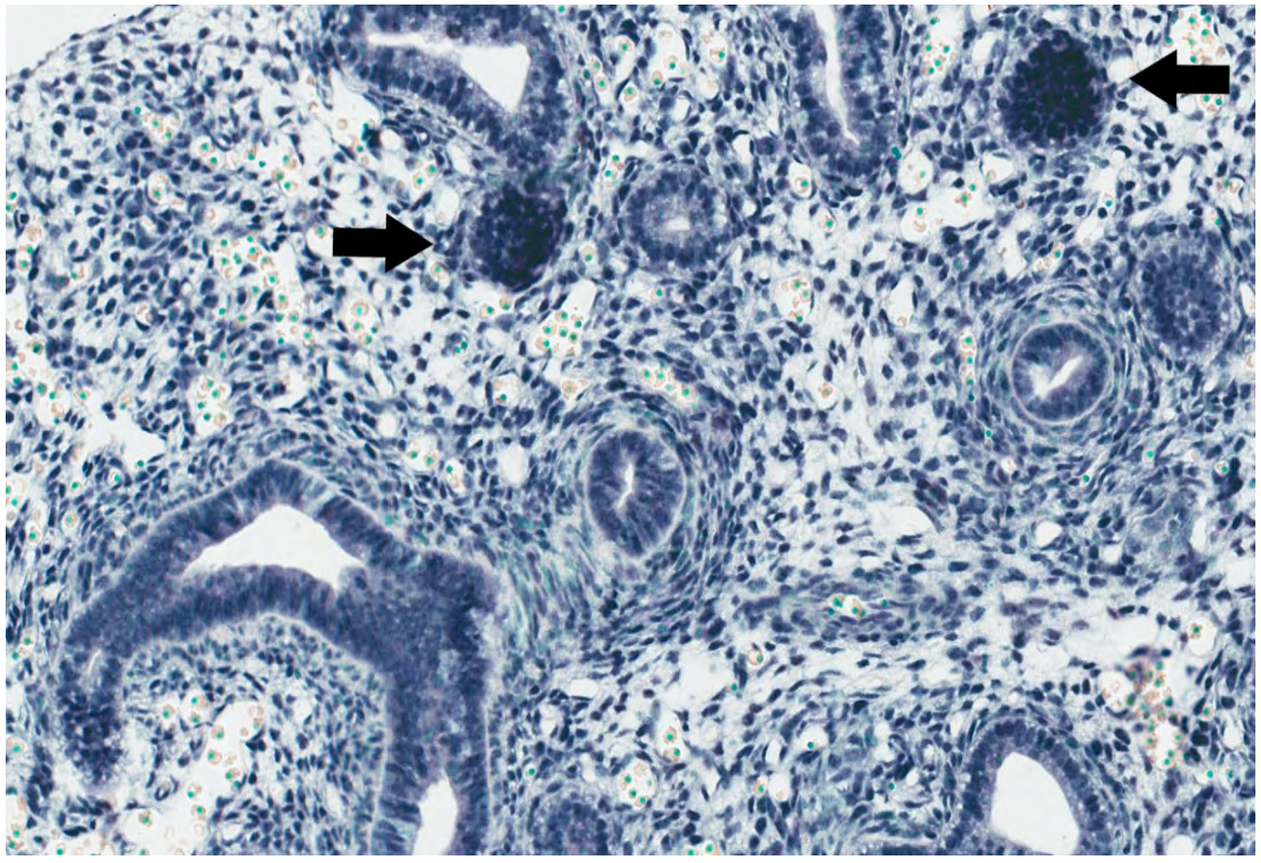
MiR-200b inhibitor

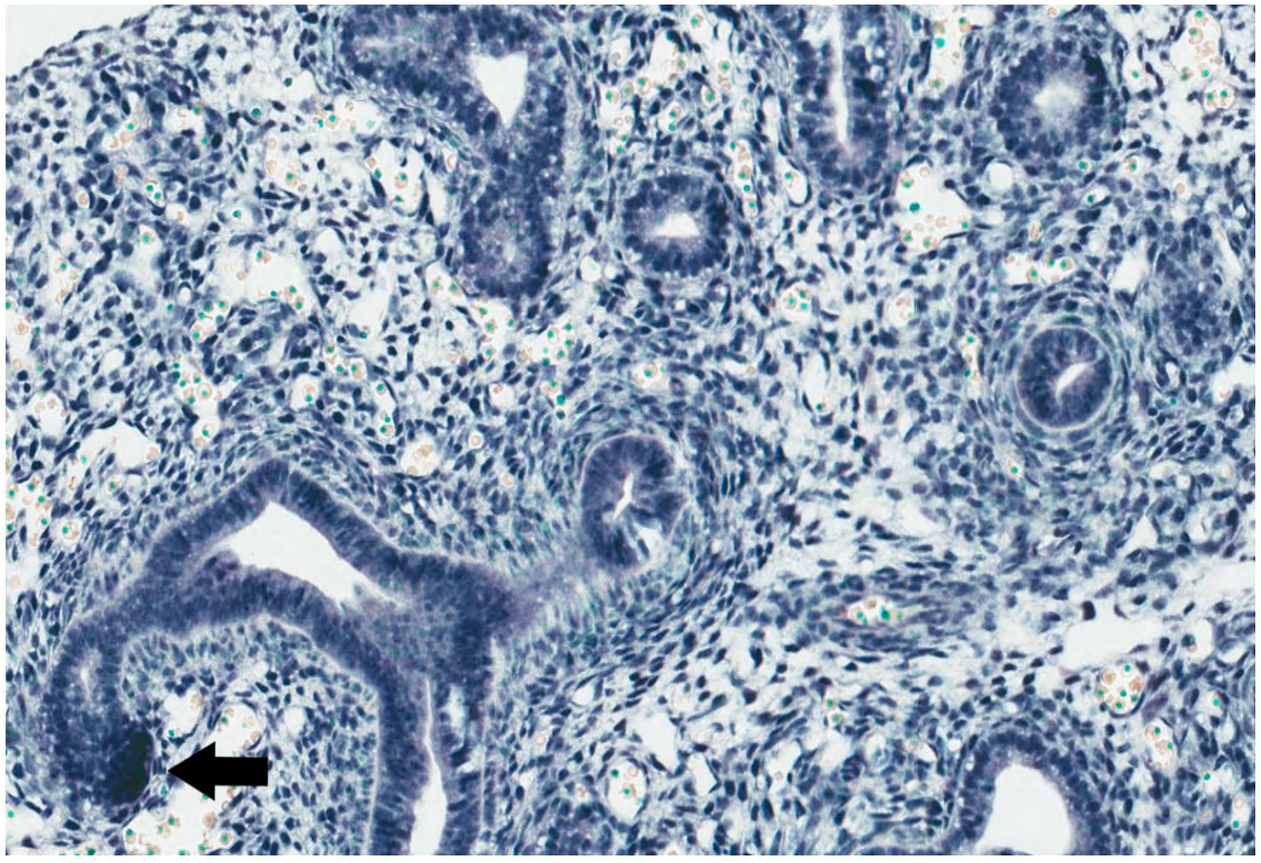


Green : Epithelial Marker (cytokeratin)
Red: Mesenchymal Marker (Vimentin)

Annals of Surgery • Volume 269, Number 5, May 2019

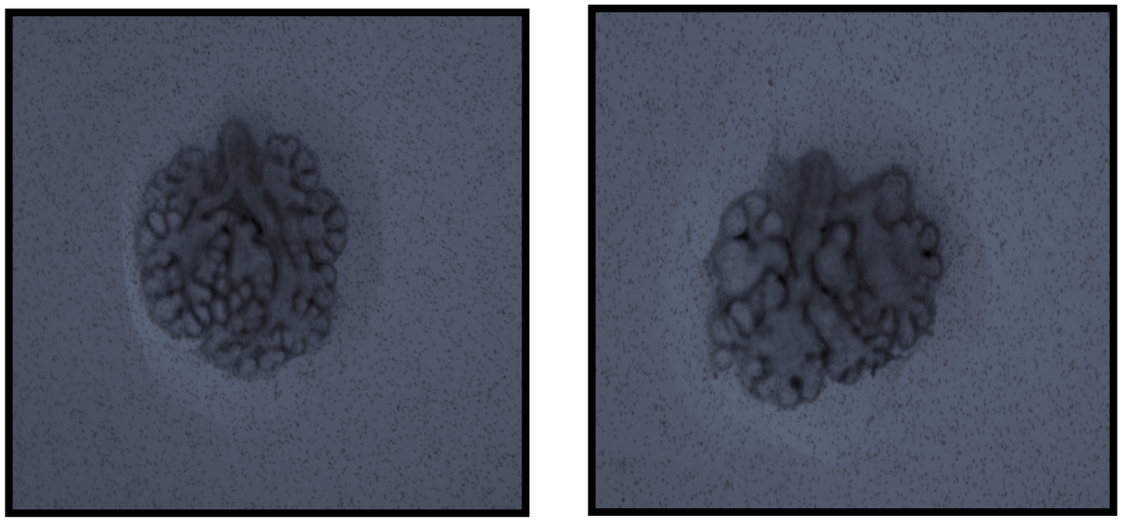
miR-200b expression is high at branching lung tips



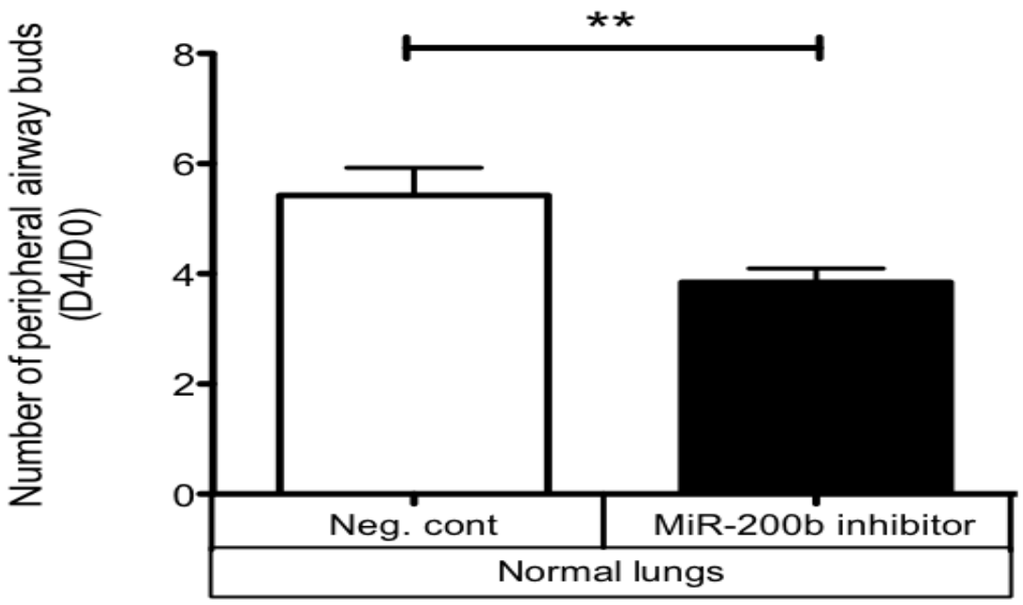


miR-200b improves branching hypoplastic lungs

Normal lungs

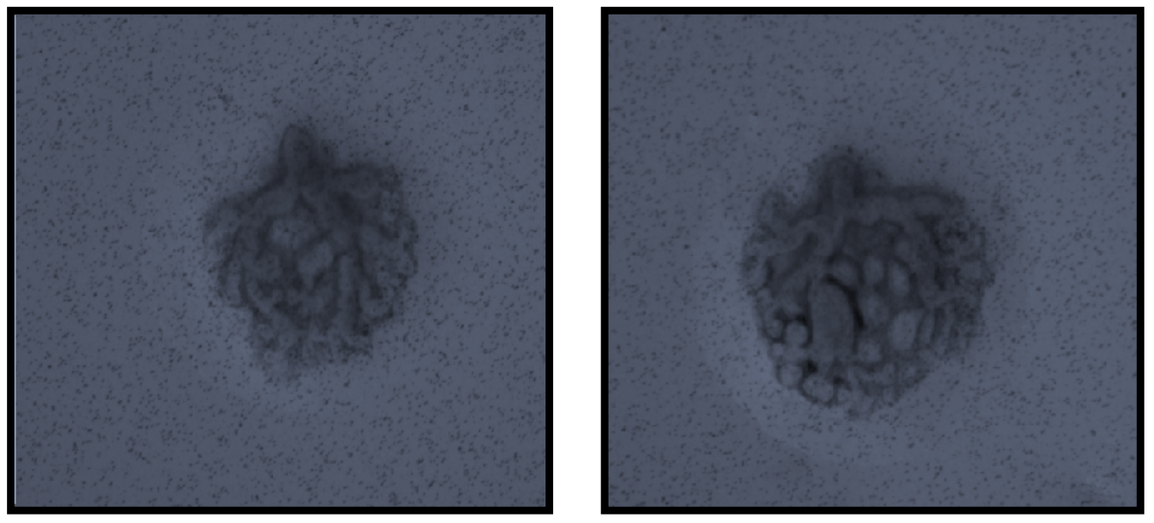


Control 200b inhibitor

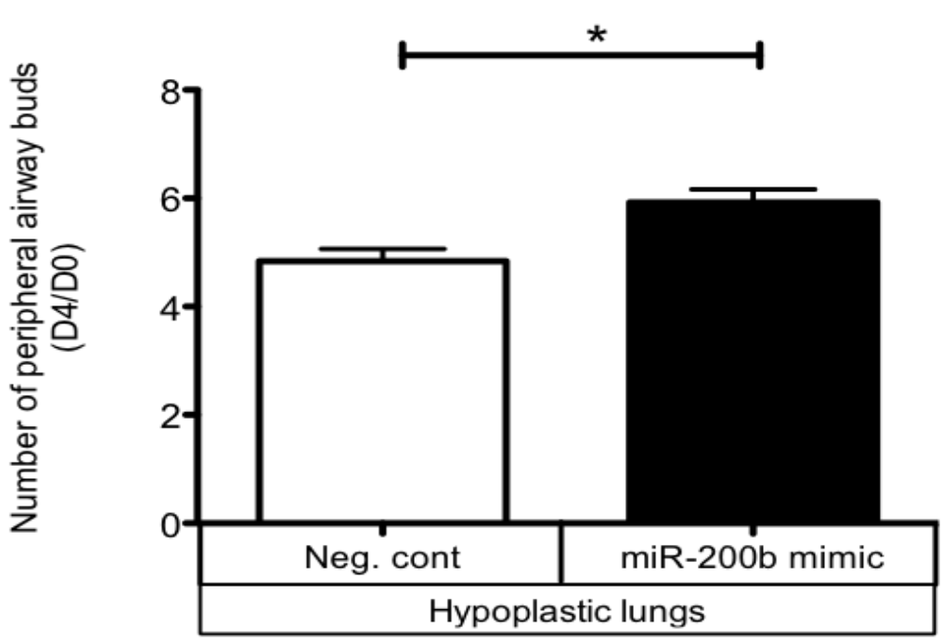


* P< 0.05, ** P< 0.01

Hypoplastic lungs



Hypoplastic Hypoplastic+ miR-200b



Annals of Surgery • Volume 269, Number 5, May 2019

NITROFEN MODEL OF CDH

Lung

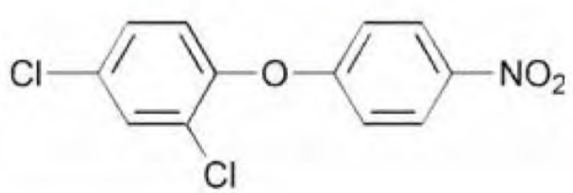
Diaphragm

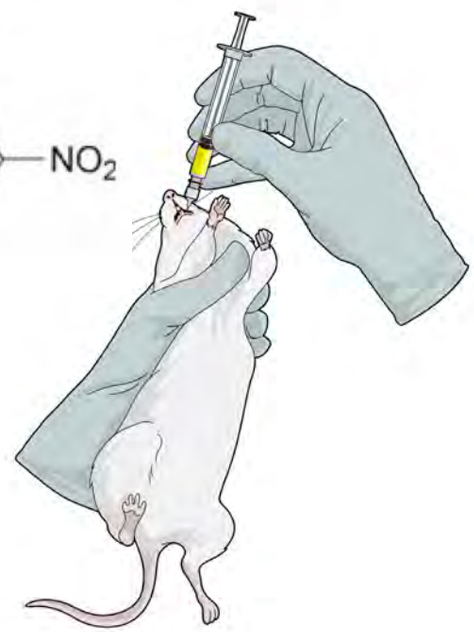
Fetal breathing

Birth

E0 E9 E11 E14 E17 E22

NITROFEN





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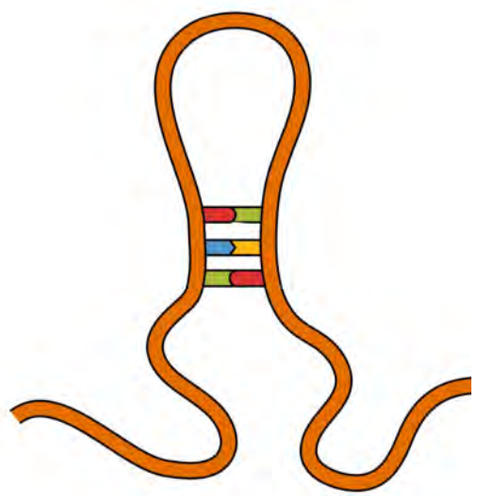
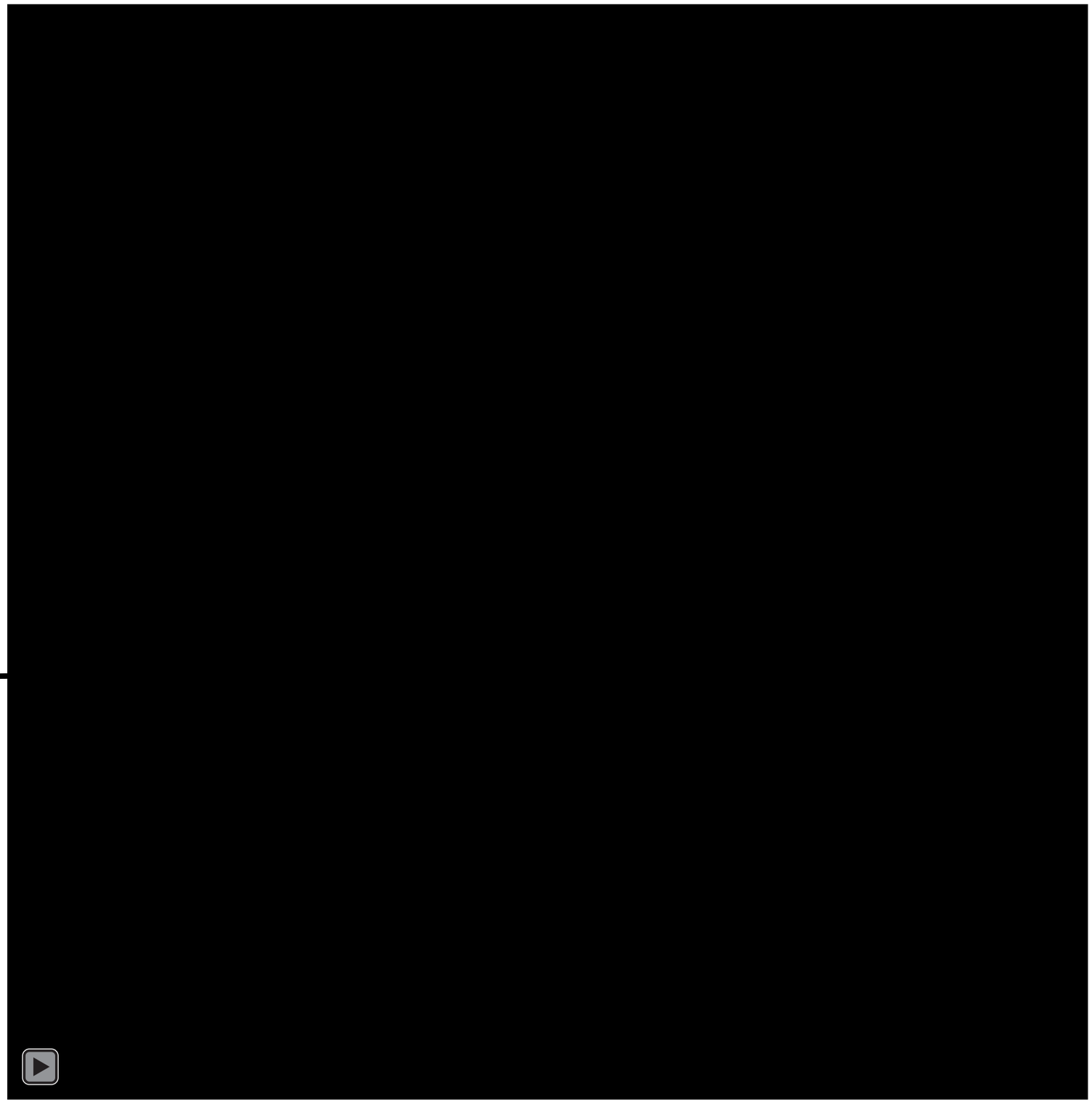


?

Prenatal miR-200b improves lung hypoplasia

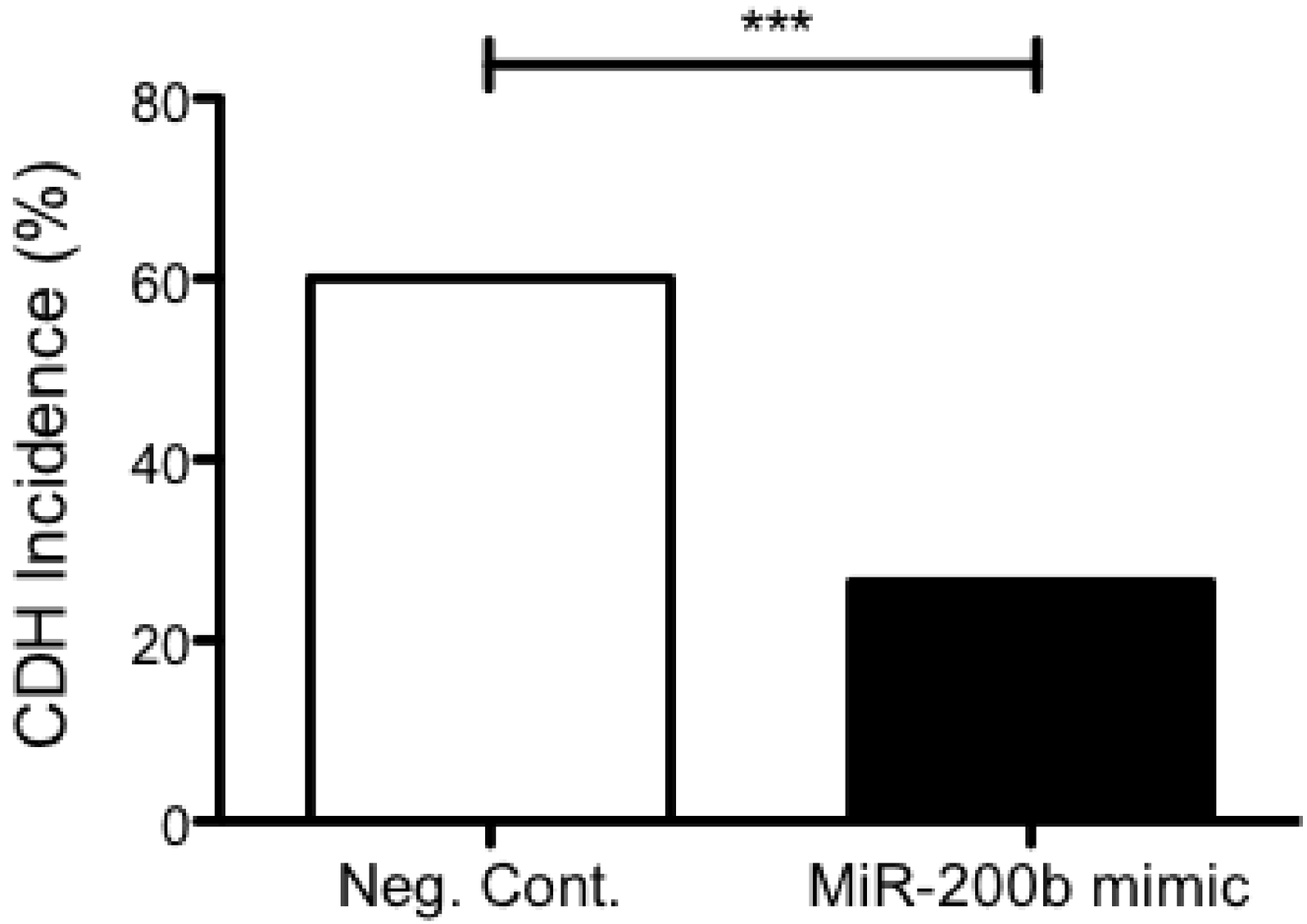


hypoplastic
(80% CDH)

hypoplastic +
miR-200b
(15% CDH)

Annals of Surgery • Volume 269, Number 5, May 2019

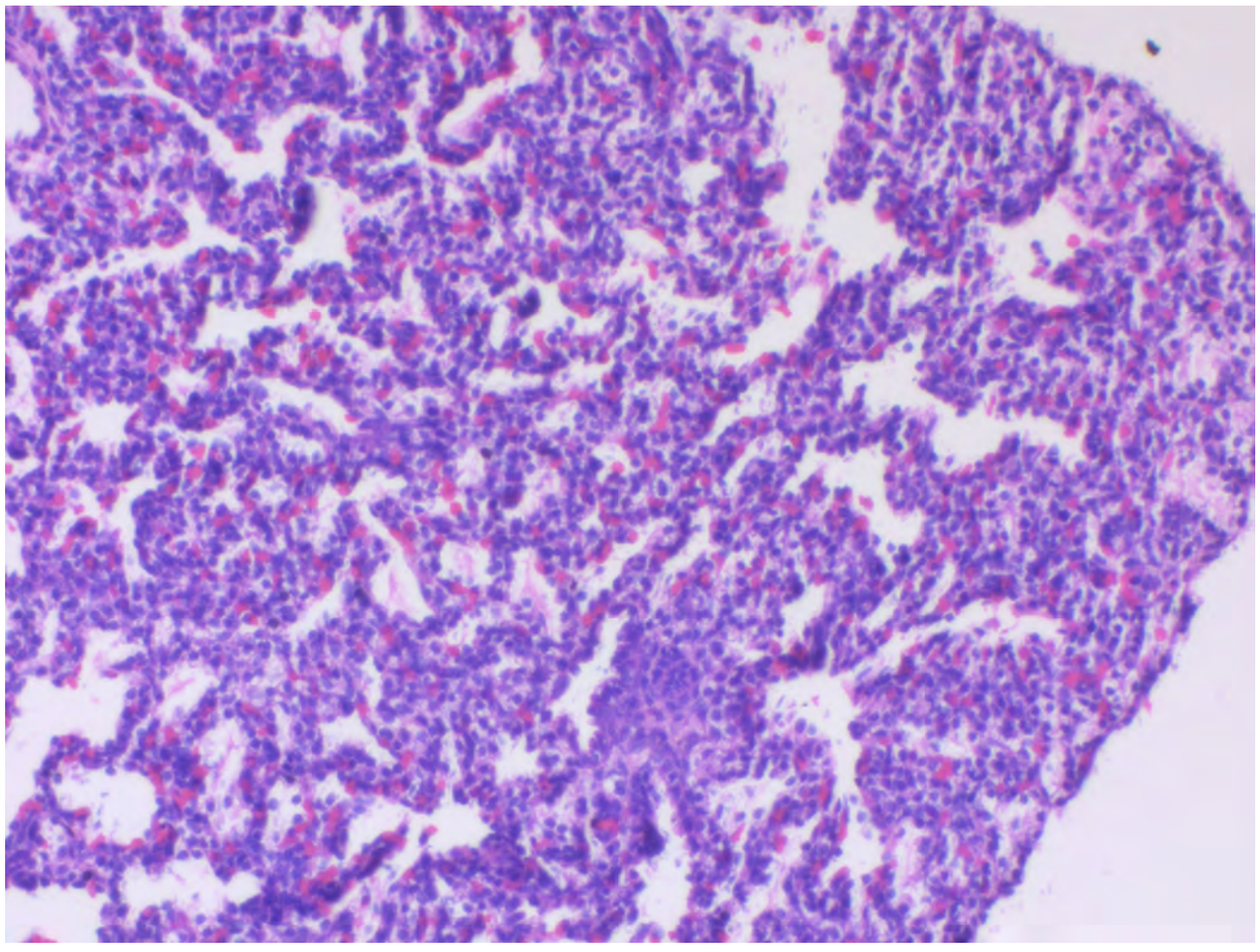
Prenatal miR-200b reduces CDH incidence

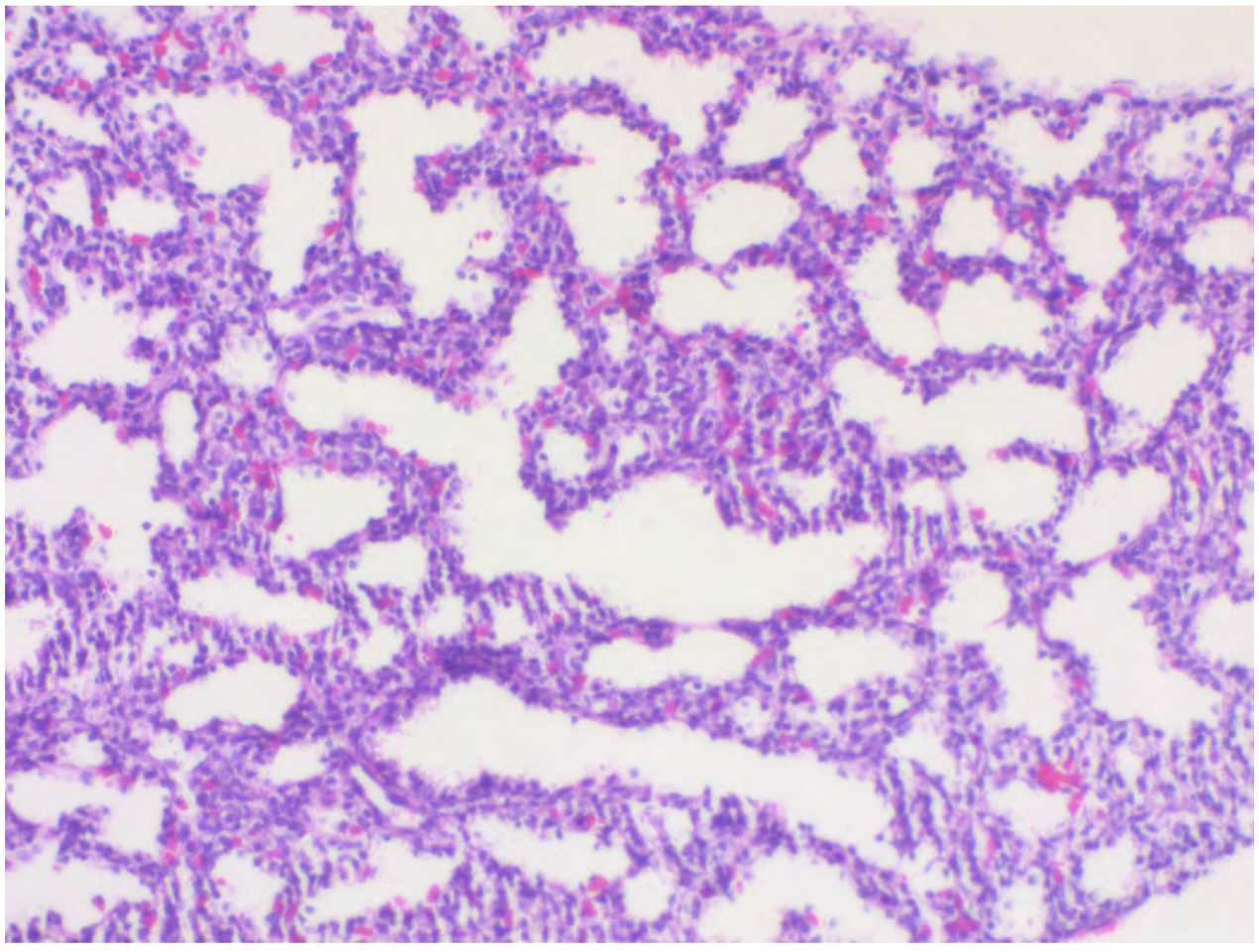


Prenatal miR-200b improves lung hypoplasia

Negative Control

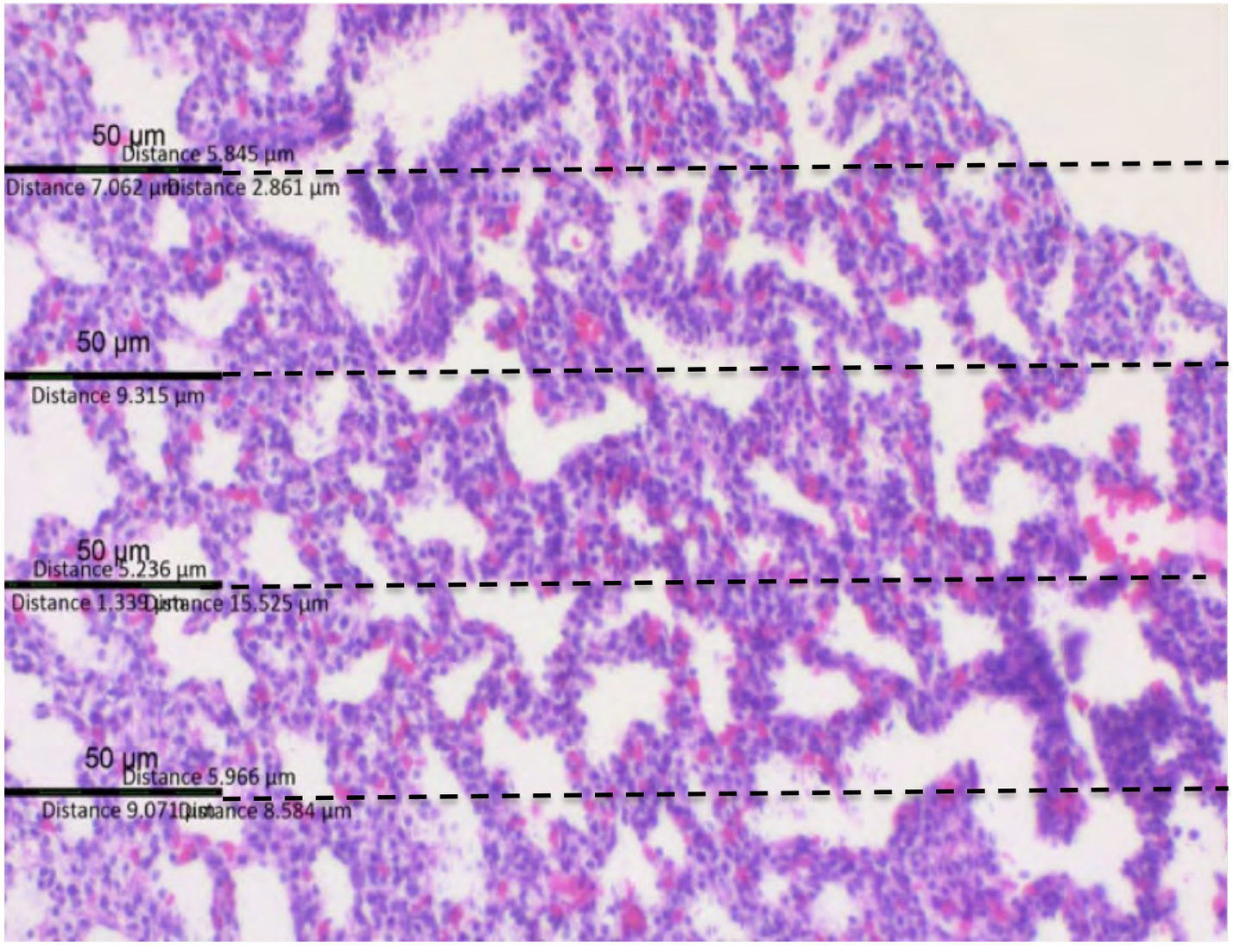
MiR-200b

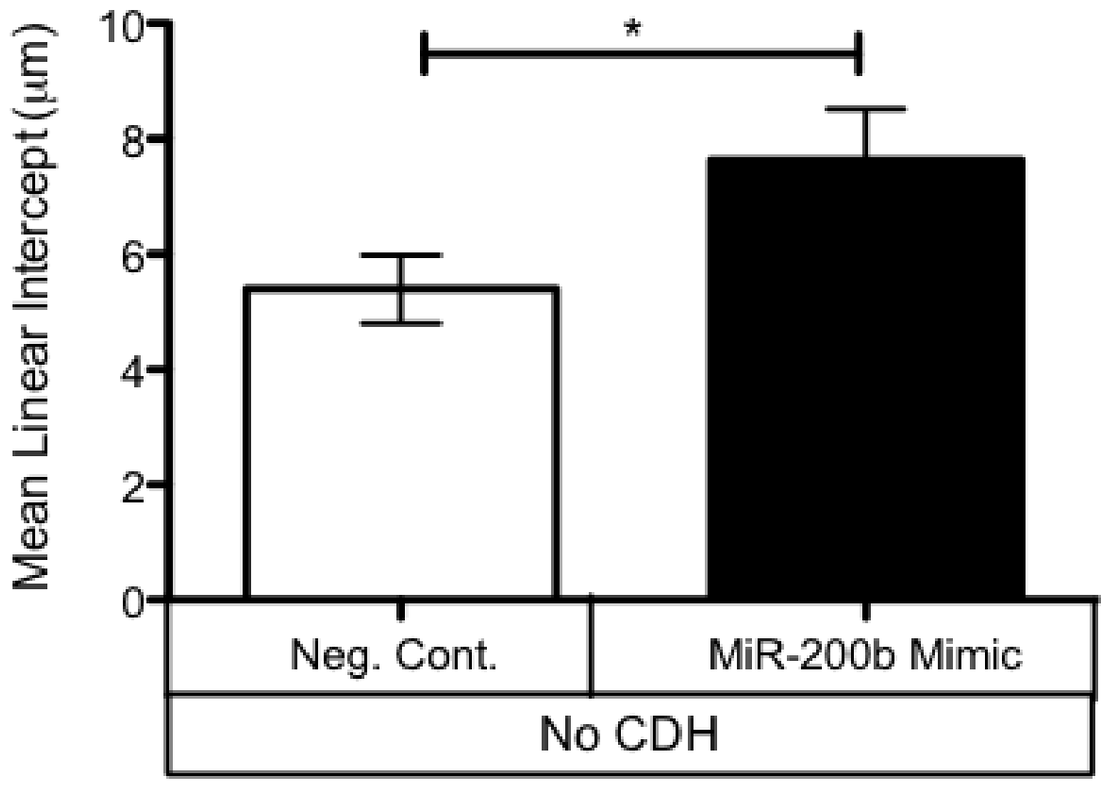




Prenatal miR-200b improves lung hypoplasia

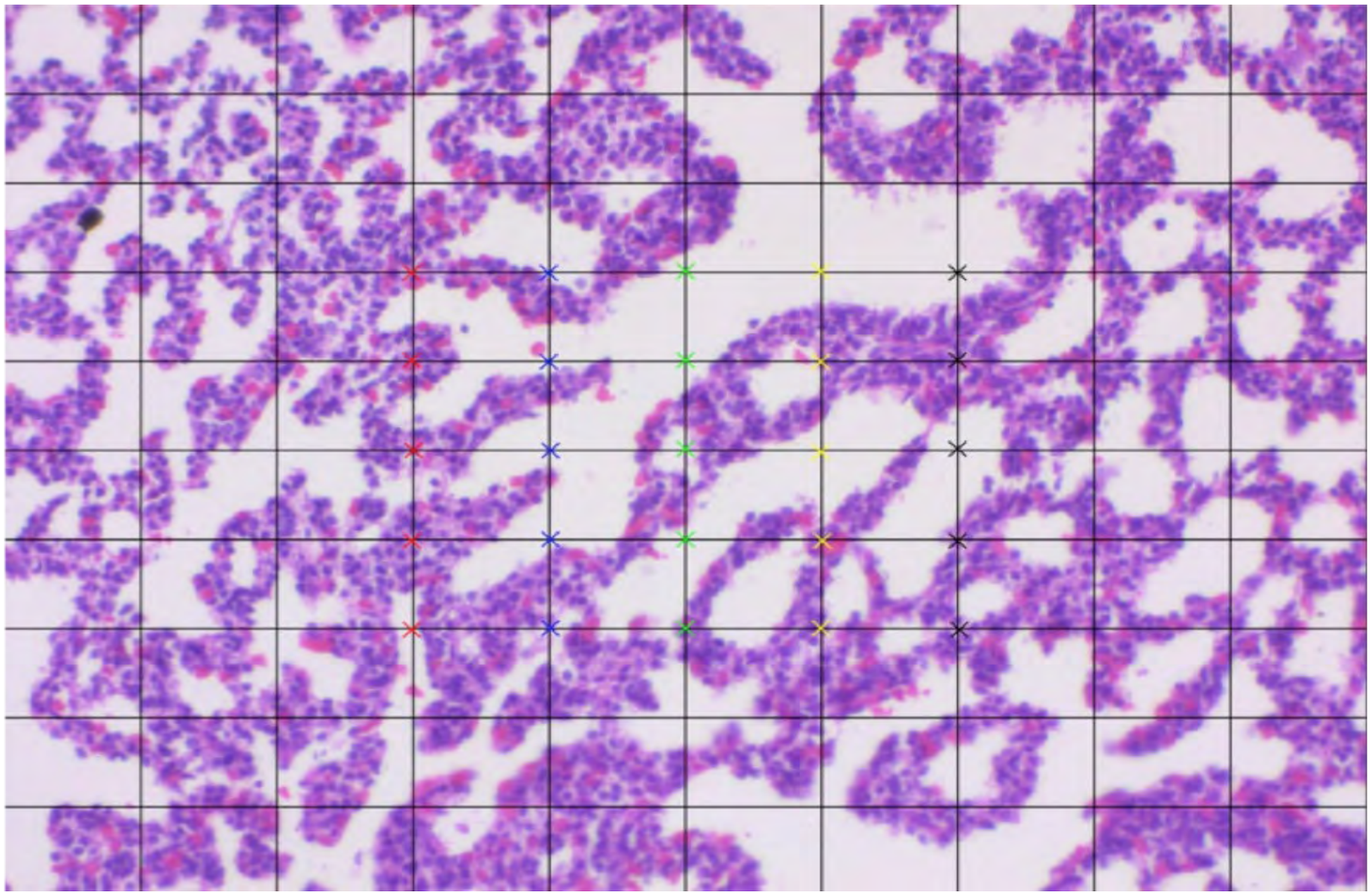
Mean Linear Intercept

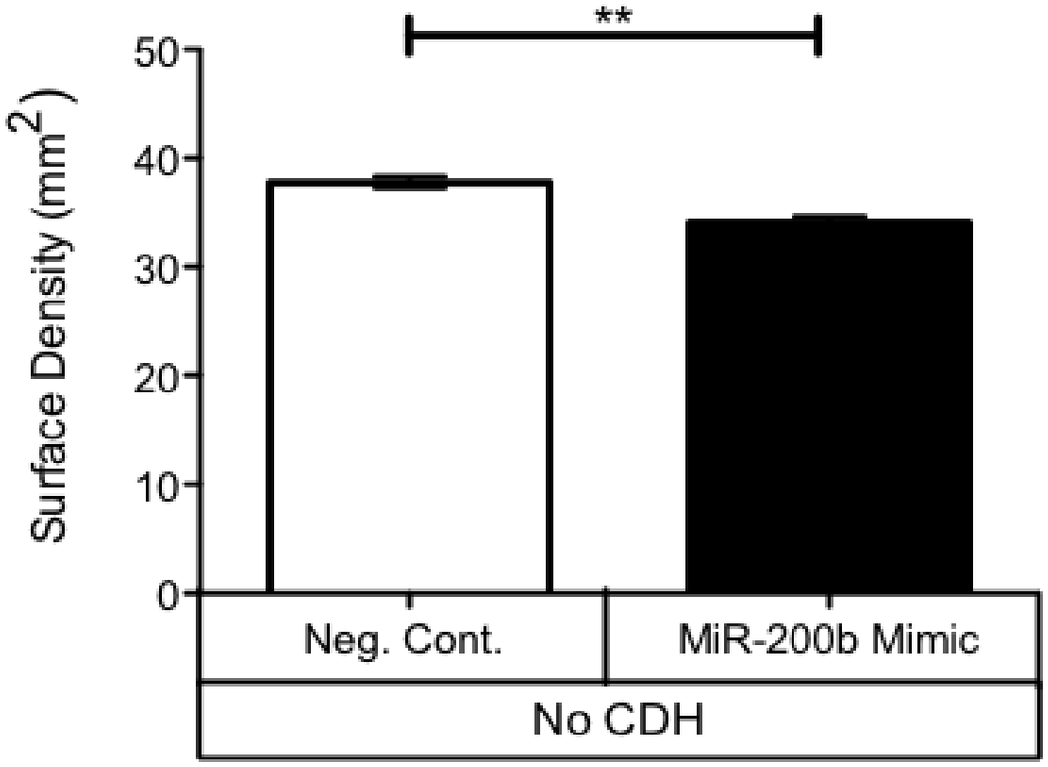




Prenatal miR-200b improves lung hypoplasia

Surface Density





control lung

CDH lung

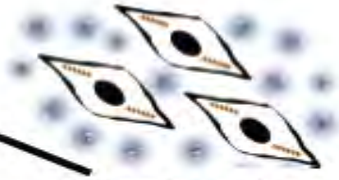
miR-200b ↓

fibroblasts

epithelial cells

epithelial cells

TGF-beta ↑



fibroblasts

E-cadherin ↑

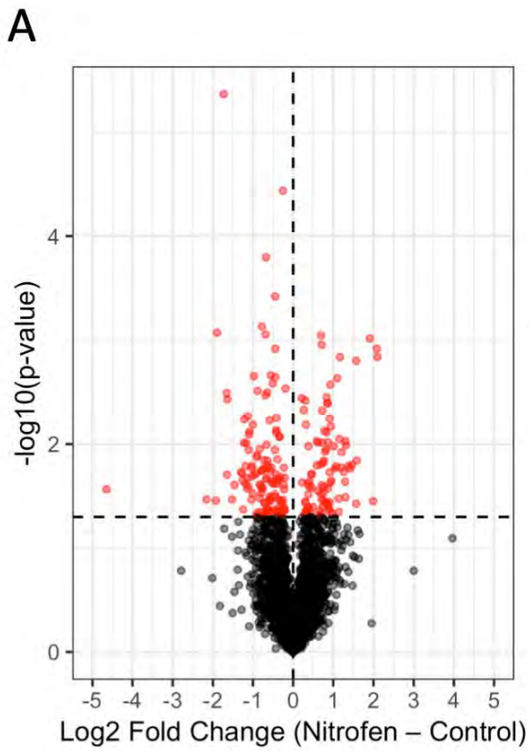
ZEB ↓

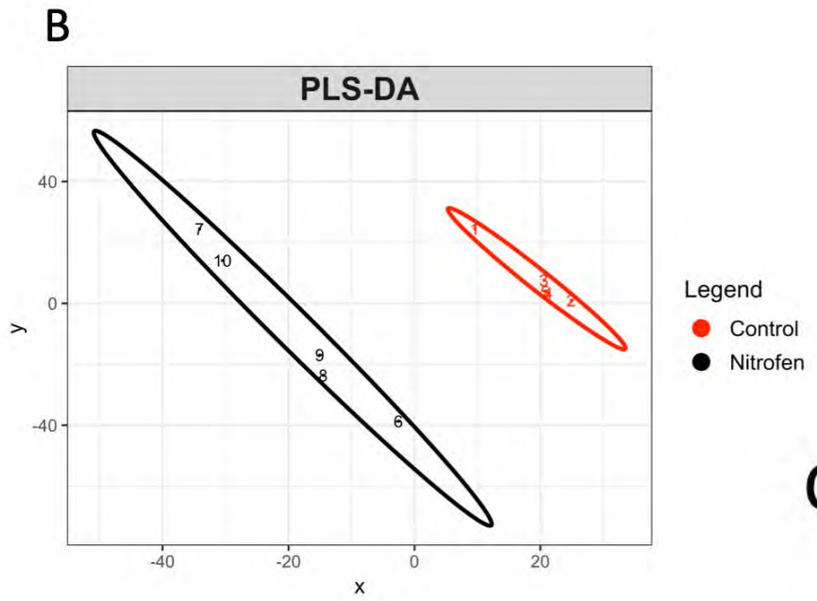
normal lung development

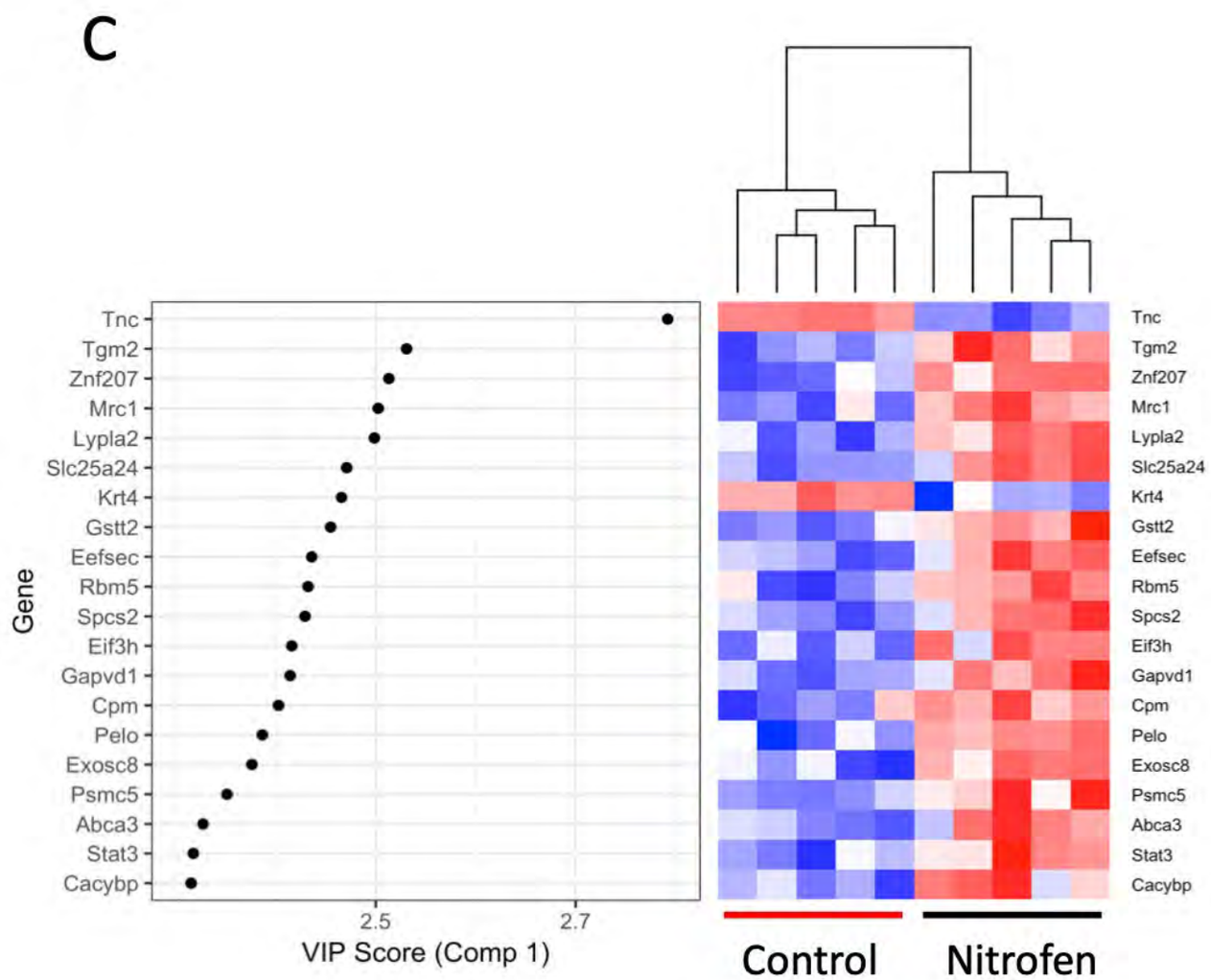
miR-200b ↑

lung hypoplasia

Proteome suggests that nitrofen-induced abnormal lung development is an immune disease?



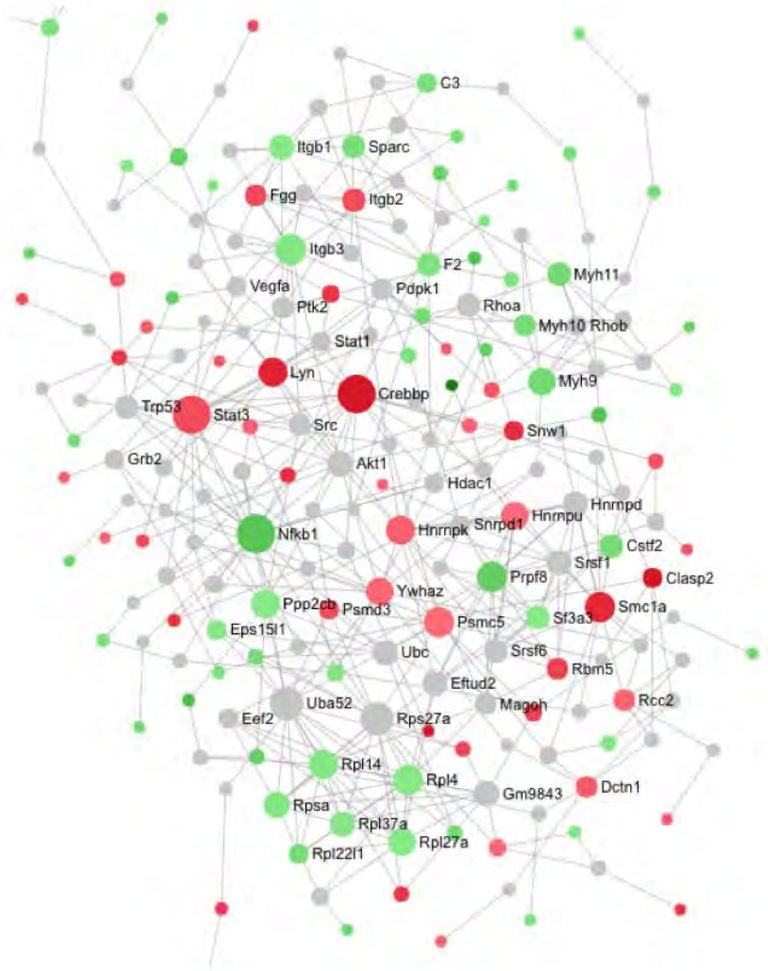




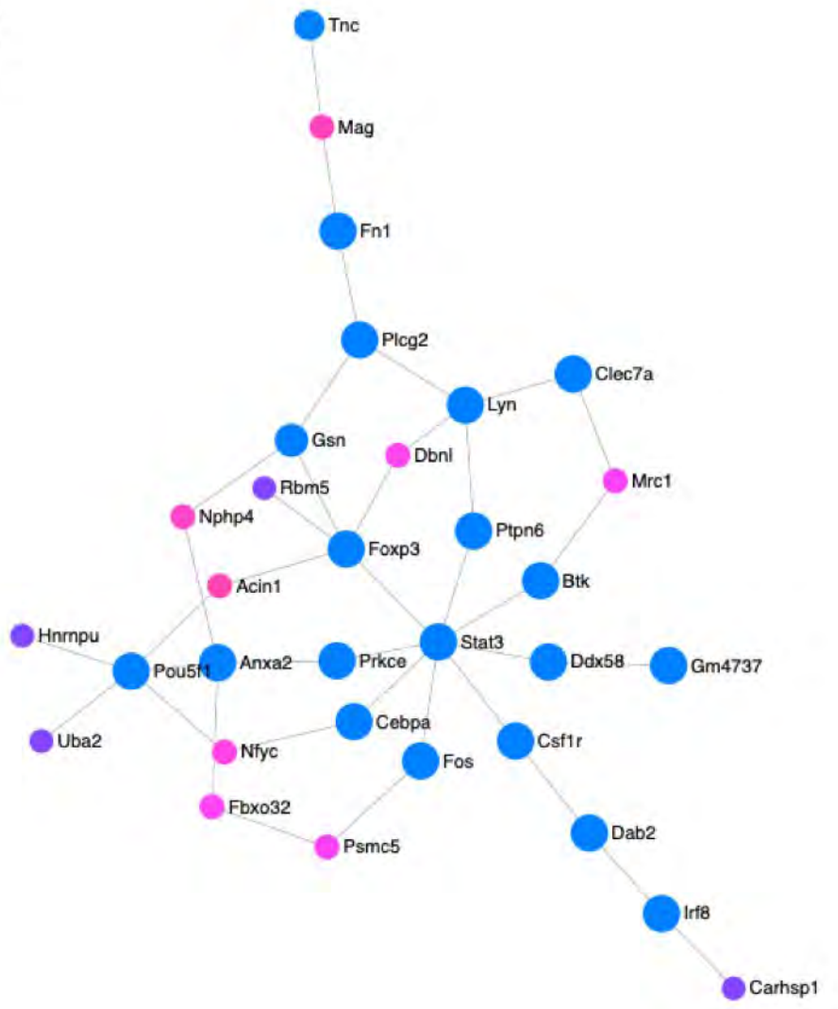
Unpublished results

Proteome suggests that nitrofen-induced abnormal lung development is an immune disease?

A



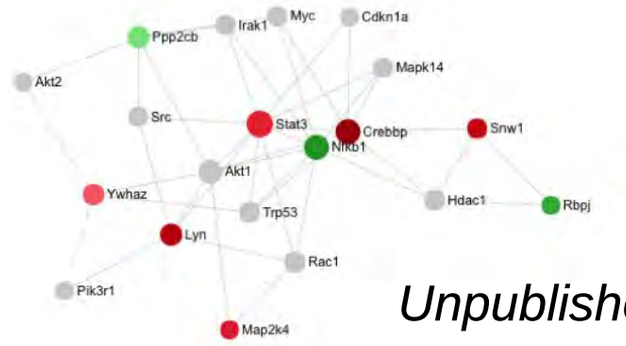
B



C

Pathway	Total	Expected	Hits	P.Value	FDR
Immune System	1110	27.3	62	4.25E-11	3.33E-08
Signaling by Interleukins	118	2.91	19	5.09E-11	3.33E-08
Cytokine Signaling in Immune system	270	6.66	26	1.62E-09	7.09E-07

D



Unpublished results

Upregulated nodes KEGG

Pathway	Total	Expected	Hits	P.Value	FDR
Epstein-Barr virus infection	114	0.458	4	0.000973	0.207
Cell cycle	127	0.51	3	0.0136	0.75
Phagosome	49	0.197	2	0.0161	0.75
Notch signaling pathway	49	0.197	2	0.0161	0.75
Wnt signaling pathway	147	0.59	3	0.02	0.75
Tuberculosis	170	0.682	3	0.0293	0.75
Salmonella infection	68	0.273	2	0.0299	0.75
Long-term potentiation	69	0.277	2	0.0307	0.75
Phenylalanine, tyrosine and tryptophan biosynthesis	8	0.0321	1	0.0317	0.75
Fc epsilon RI signaling pathway	75	0.301	2	0.0358	0.762
ErbB signaling pathway	87	0.349	2	0.0469	0.829
Malaria	12	0.0482	1	0.0472	0.829

Unpublished results

Does EBV cause CDH?????

JOURNAL OF VIROLOGY, Oct. 2010, p. 10329–10343 Vol. 84, No. 19
0022-538X/10/$12.00 doi:10.1128/JVI.00923-10

Cellular MicroRNAs 200b and 429 Regulate the Epstein-Barr Virus Switch between Latency and Lytic Replication[▽]

Amy L. Ellis-Connell,† Tawin Iempridee, Iris Xu, and Janet E. Mertz*

Tumor and Stem Cell Biology

Cancer Research

Downregulation of MicroRNA-200 in EBV-Associated Gastric Carcinoma

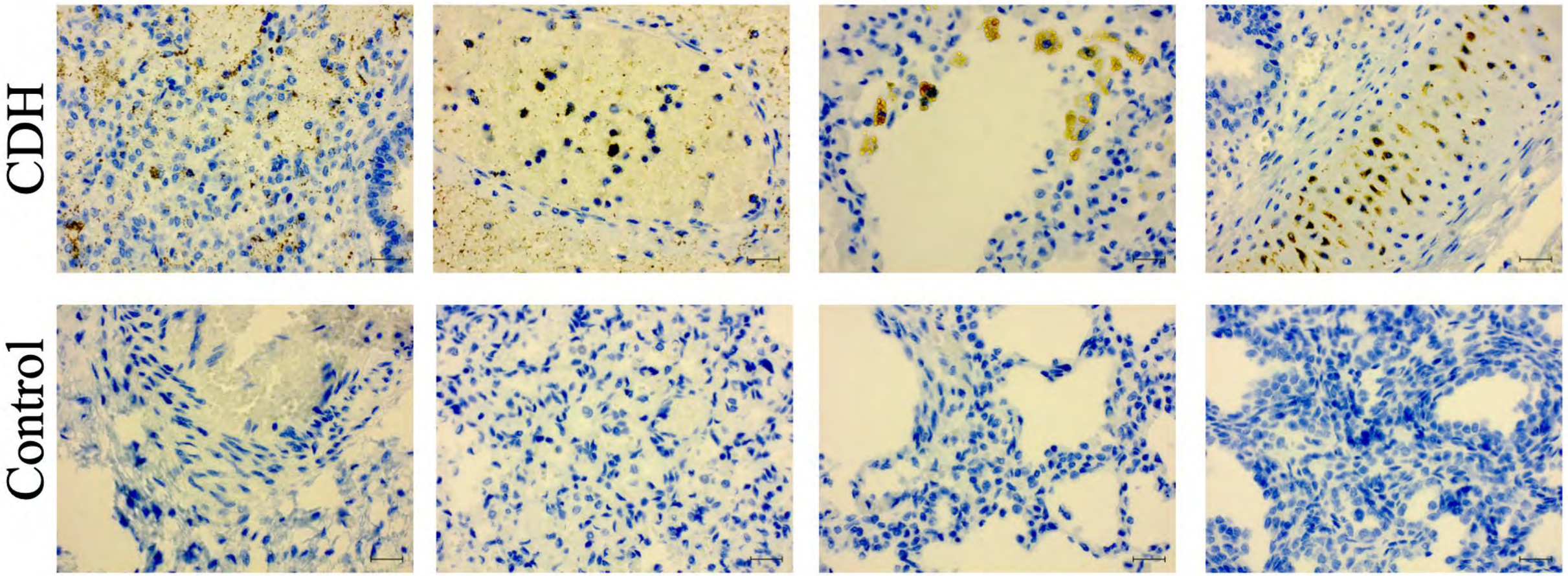
Aya Shinozaki[1], Takashi Sakatani[1], Tetsuo Ushiku[1], Rumi Hino[1], Maya Isogai[1], Shunpei Ishikawa[1], Hiroshi Uozaki[1], Kenzo Takada[2], and Masashi Fukayama[1]

JOURNAL OF VIROLOGY, Aug. 2010, p. 7892–7897 Vol. 84, No. 15
0022-538X/10/$12.00 doi:10.1128/JVI.00379-10

Differential Expression of the miR-200 Family MicroRNAs in Epithelial and B Cells and Regulation of Epstein-Barr Virus Reactivation by the miR-200 Family Member miR-429[▽]

Zhen Lin, Xia Wang, Claire Fewell, Jennifer Cameron, Qinyan Yin, and Erik K. Flemington*

Does EBV cause CDH?????



WiSDOM:

WINNIPEG'S SURGICAL DATABASE & OUTCOMES MANAGEMENT

DEVOTION Legacy Project

Drs. Richard Kaplan, Suyin Lum Min, Melinda Morris, Anna Shawyer, Chelsea Ruth, Manji Brownell, Fiamaccia Rieti, and Robert Bellshaw

ABOUT WiSDOM:

WiSDOM is all about children with congenital anomalies. A congenital anomaly is a birth defect. Some babies are born with a congenital anomaly that requires surgery immediately after birth. Until a few decades ago, most of these babies died. Recent improved surgical and intensive care techniques have resulted in better survival. Currently, we do not know how these babies do later in life when they grow up. To find out, we created a database of almost 800 surgical congenital anomaly patients, recording birth and surgery details. We plan to link our surgical database to population data managed by the Manitoba Centre for Health Policy (MCHP). MCHP databases contain unique information about healthcare, education, and social service utilization for all Manitobans. This linkage will allow us to answer the following questions:

1. **Who** is at greatest risk of giving birth to a baby with a congenital anomaly requiring surgery?
2. **How** do children with surgical congenital anomalies do at school and in life compared to children without a defect?
3. **Why** do some children with surgical congenital anomalies do better than other children with surgical congenital anomalies?

The answers to these questions will help us understand the causes and long-term outcomes of surgical birth defects and improve the care of babies born with surgical congenital anomalies.

OBJECTIVES:

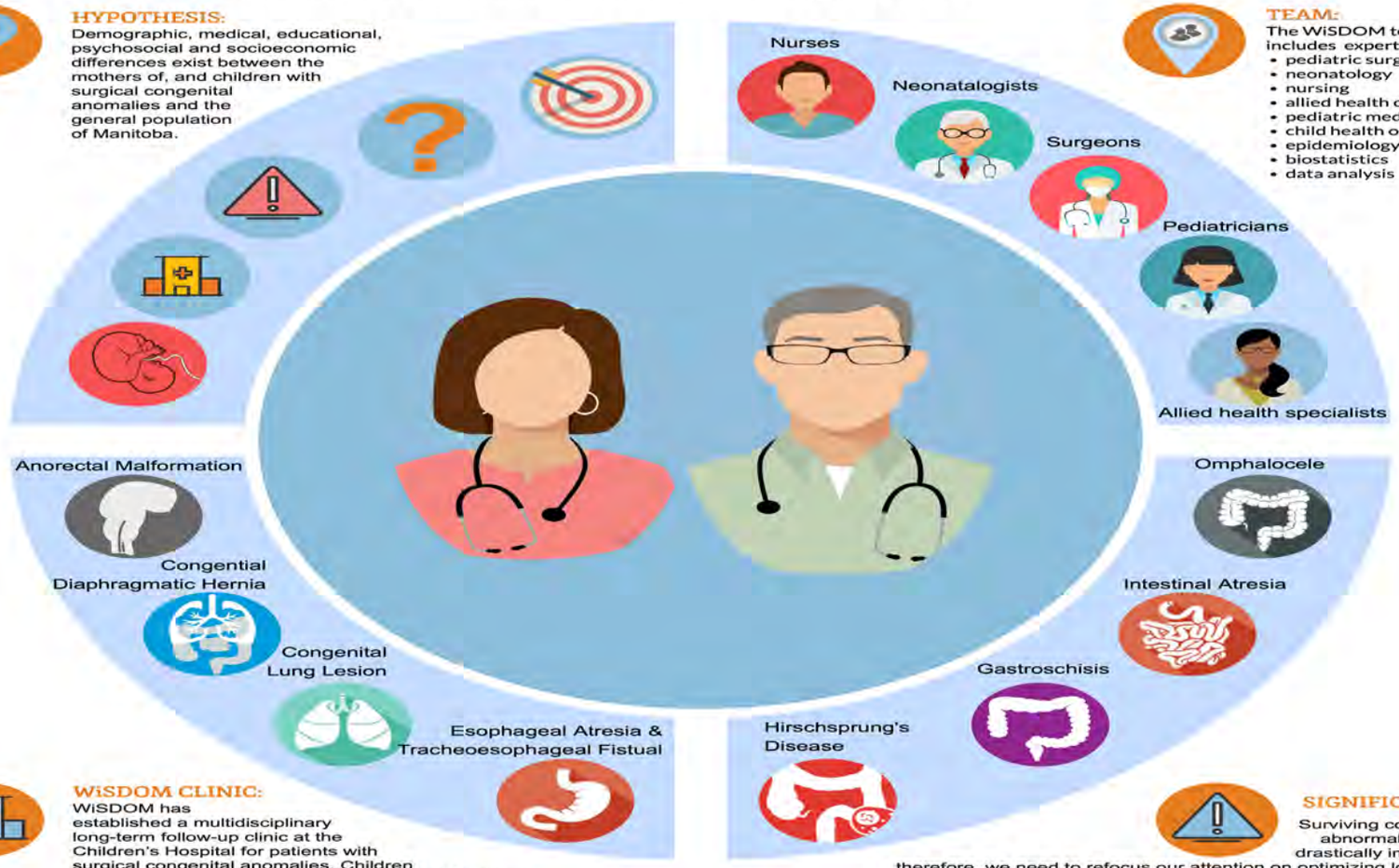
1. WHO is at risk: Identify maternal factors associated with surgical congenital anomalies: Maternal demographic information will be identified using MCHP databases to determine the populations with highest risk of having a baby with surgical congenital anomalies.

2. HOW are children doing: Compare the long-term outcomes of patients with surgical congenital anomalies to those of age-matched controls: Virtual long-term follow-up of each patient in WiSDOM using MCHP linkages to determine their medical, educational, psychosocial, socioeconomic outcomes and comparing them with an age-matched control from MCHP.

3. WHY do some children do better: Determine patient and maternal factors that affect long-term patient outcomes: After defining the maternal risk factors and long-term outcomes for the WiSDOM patient-cohort, subgroups who have the highest risk of poor outcomes will be identified, as well as as the demographic, medical, educational, psychosocial and socioeconomic determinants of favourable long-term outcomes.

HYPOTHESIS:

Demographic, medical, educational, psychosocial and socioeconomic differences exist between the mothers of, and children with surgical congenital anomalies and the general population of Manitoba.



TEAM:

The WiSDOM team includes expertise in:

- pediatric surgery
- neonatology
- nursing
- allied health care
- pediatric medicine
- child health outcomes
- epidemiology
- biostatistics
- data analysis

WiSDOM CLINIC:

WiSDOM has established a multidisciplinary long-term follow-up clinic at the Children's Hospital for patients with surgical congenital anomalies. Children attending the clinic receive evidence-based follow-up for early indentification and intervention for patients and families. Other advantages of the WiSDOM clinic include improved and coordinated care, ongoing education, increased quality of life, and ease of access to health care professionals.

SIGNIFICANCE:

Surviving congenital abnormalities has drastically improved, therefore, we need to refocus our attention on optimizing long-term medical, educational, psychosocial and socioeconomic outcomes. By linking our surgical congenital anomalies patient cohort with the comprehensive information in the MCHP databases we will be able to begin this optimization. Linking databases will provide the opportunity for virtual long-term follow-up for the first time in this patient population. This virtual follow-up will identify the risk factors and outcomes of surgical congenital anomalies. This information will guide the development of preventative strategies to provide better care to babies born with surgical congenital anomalies.

DEVOTION:

1. Provides support for prospective data collection and entry for babies born with surgical congenital anomalies after 2016
2. Facilitates consent and enrollment of participants into the WiSDOM study and collection of research data in the WiSDOM Clinic
3. Helps to distribute information to high-risk populations, healthcare providers and stakeholders using research findings from the WiSDOM database.
4. Aids in developing policies to direct risk mitigation strategies
5. Assists in developing a plan to establish a multidisciplinary, long-term follow-up clinic for WiSDOM children born in Manitoba within the next 5 years
6. DEVOTION provided initial funding for the retrospective data collection for all babies born in Manitoba from 1991 - 2016 in addition to the funding for prospective data collection and linkages to MCHP.

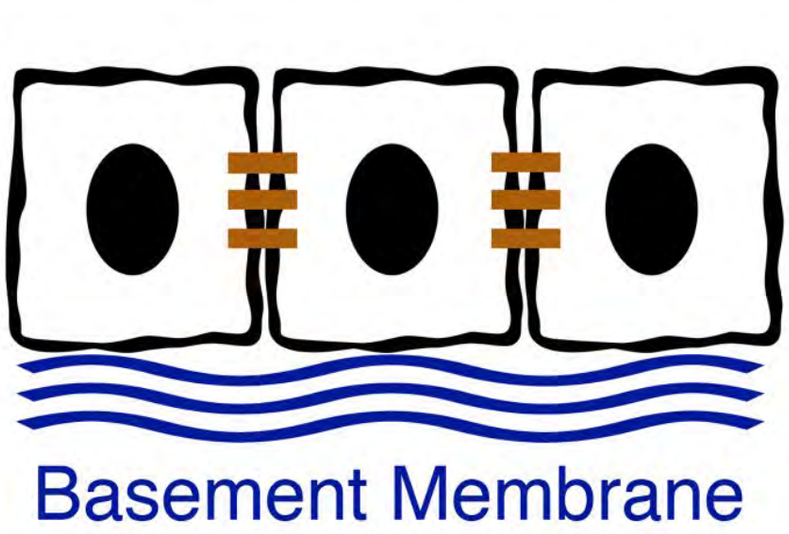
Does EBV cause CDH?????_WiSDOM

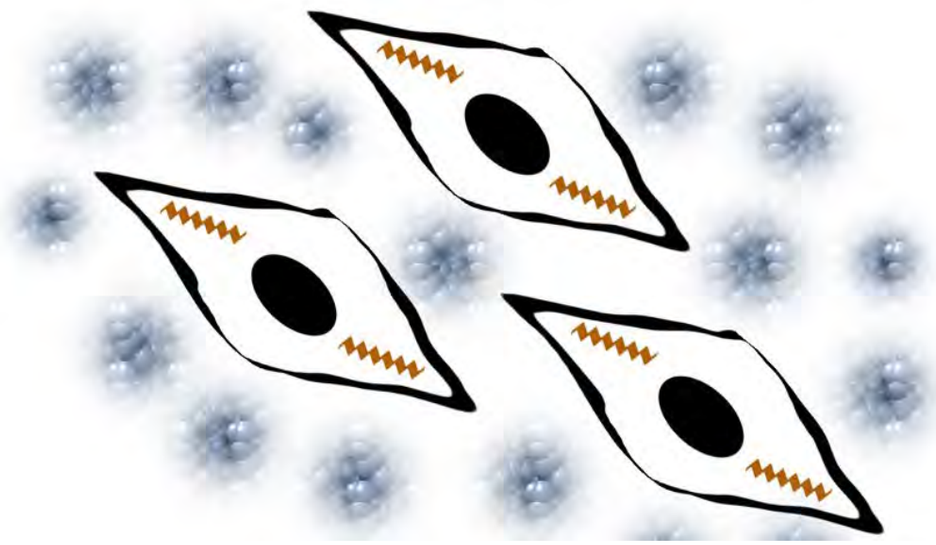
Infectious Mononucleosis (ICD-9:075)

Odds ratio = 0.49 for mothers with CDH baby compared to controls from the general population

95% CI = 0.12-1.36
P-value = 0.2371

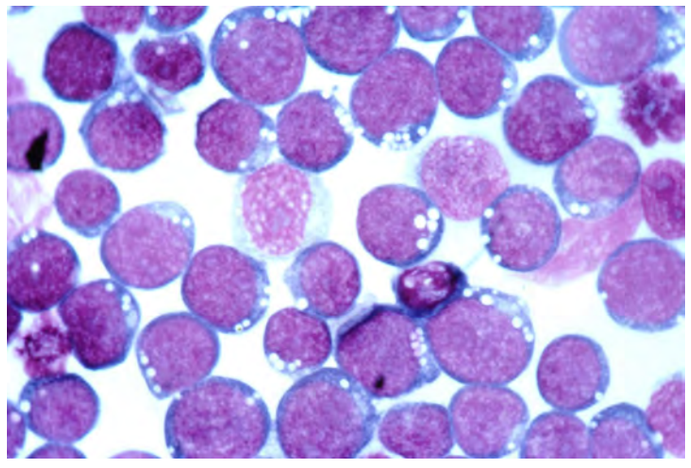
Epithelial-to-Mesenchymal Transition, CDH and EBV





Epithelial cells

Mesenchymal cells



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Prenatal treatment

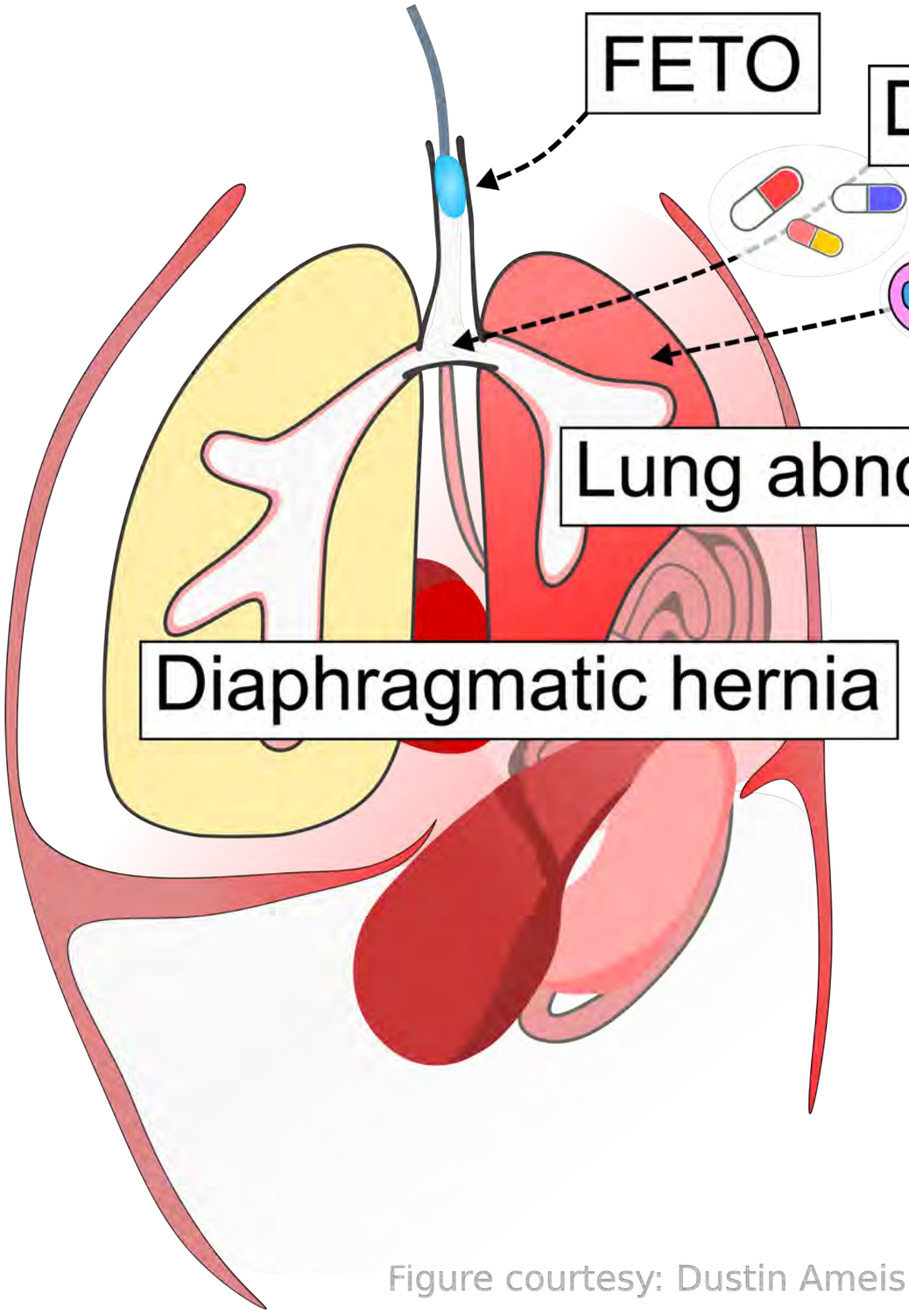
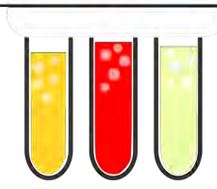


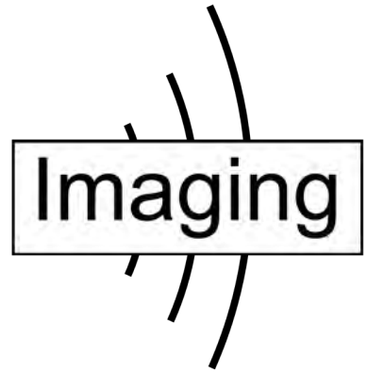
Figure courtesy: Dustin Ameis

Pathogenesis

Prenatal diagnosis

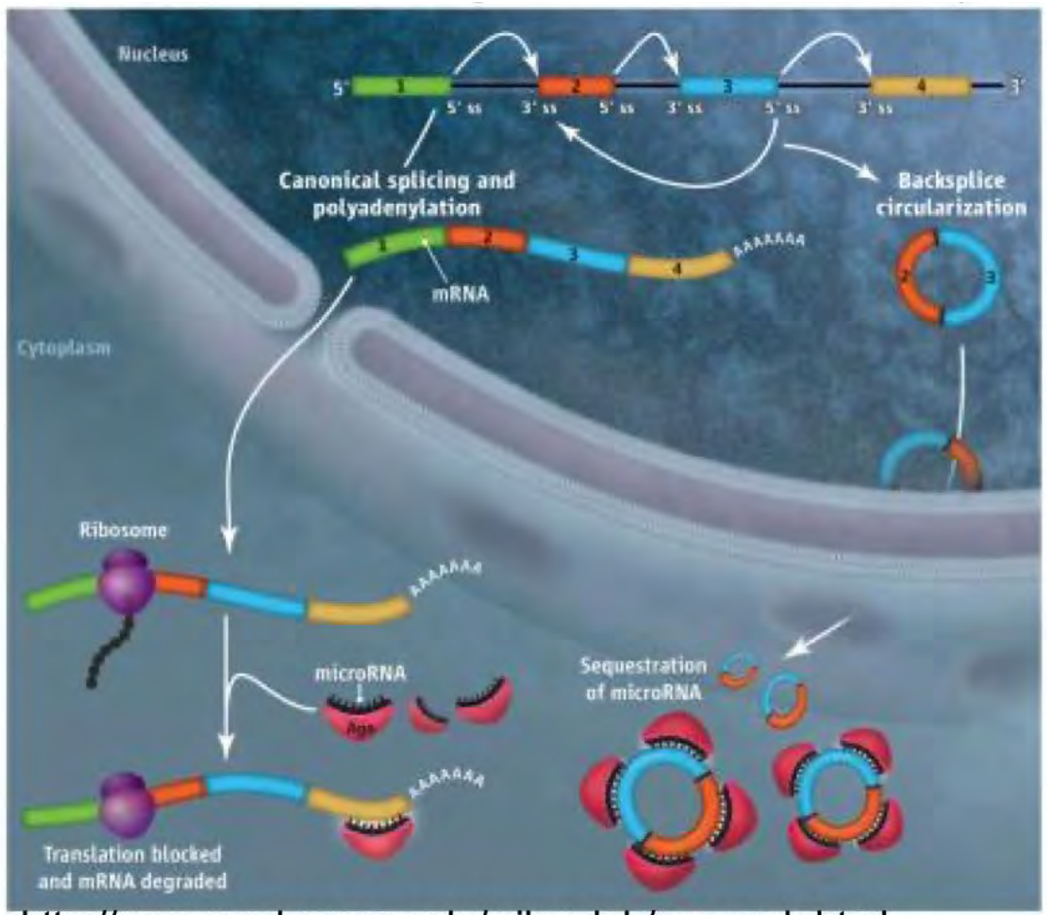
Biomarkers





CircularRNA

- More stable, more abundant and specific than linear RNAs.
- Regulate gene expression at transcriptional and post-transcriptional level by serving as **microRNA sponges** and interacting with mRNA and proteins.

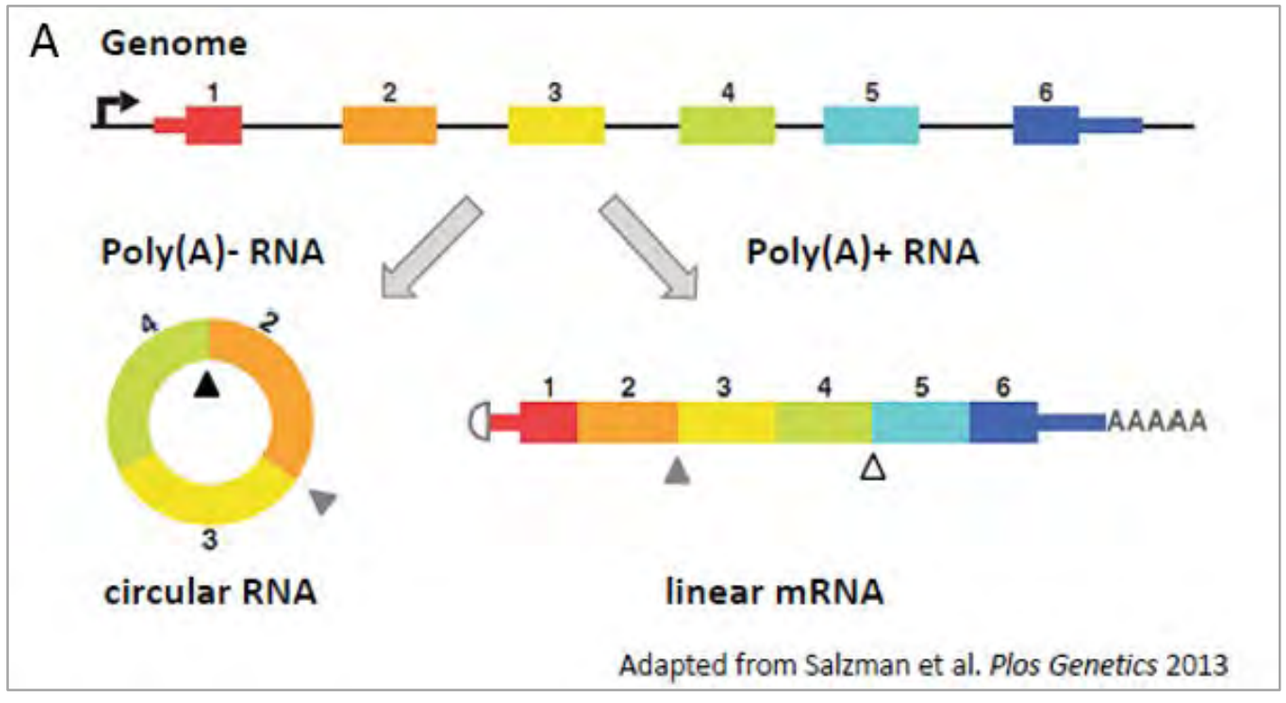


http://www.med.upenn.edu/wiluszlab/research.html

http://www.epibeat.com/developmental-biology-stem-cells/circular-rnas-as-molecular-sponges-for-mirnas/518/

Circular RNAs

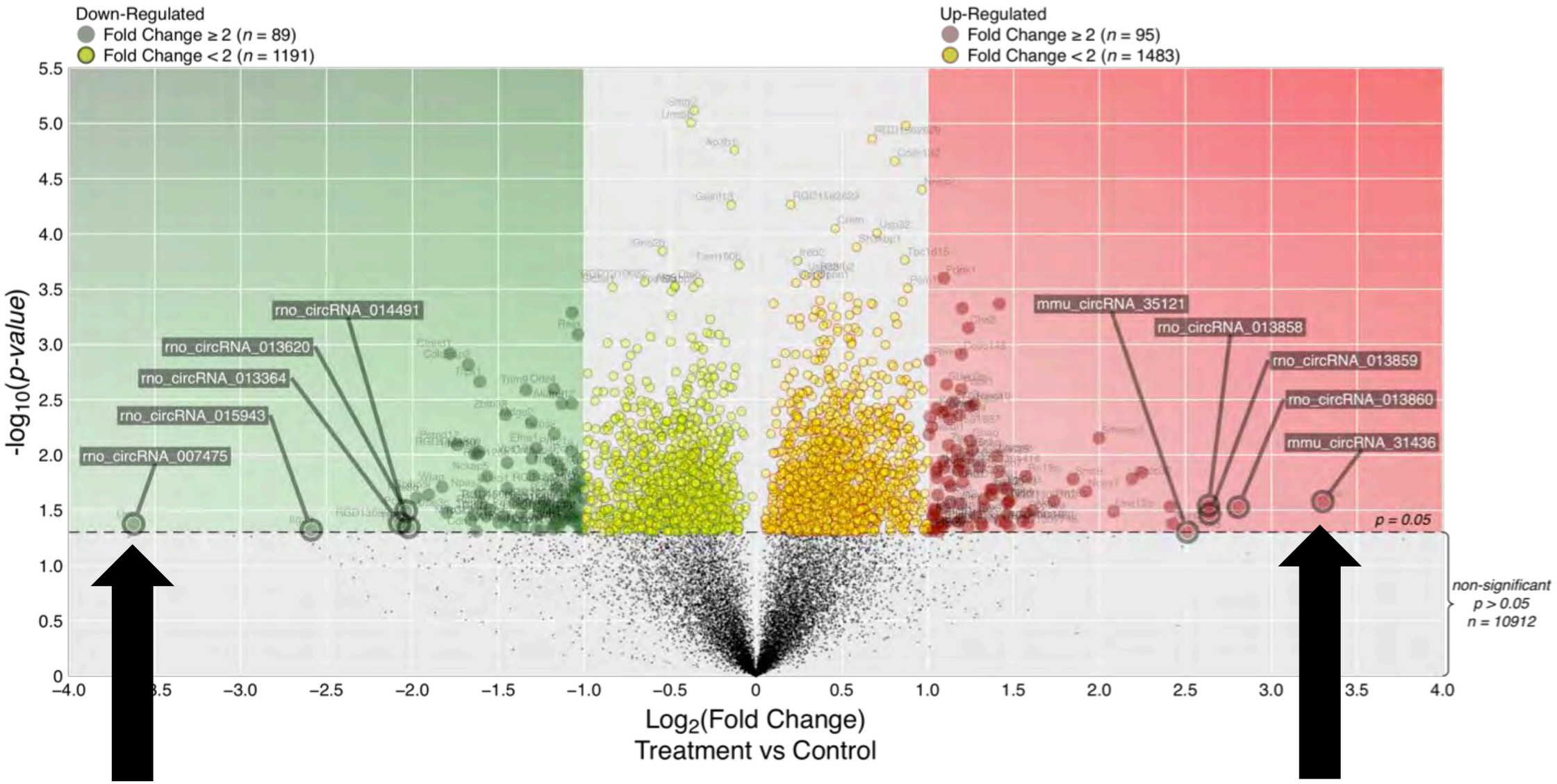
- Upstream regulators of miRNAs (epigenetic regulation)
- “Head-to-tail” splicing



Ideal Biomarkers:

- Stable
- Conserved
- Tissue- and development stage-specific expression
- High abundance in extracellular compartments

Circular RNA profile is dysregulated in E21 nitrofen-induced hypoplastic lungs



BaseScope™ ISH

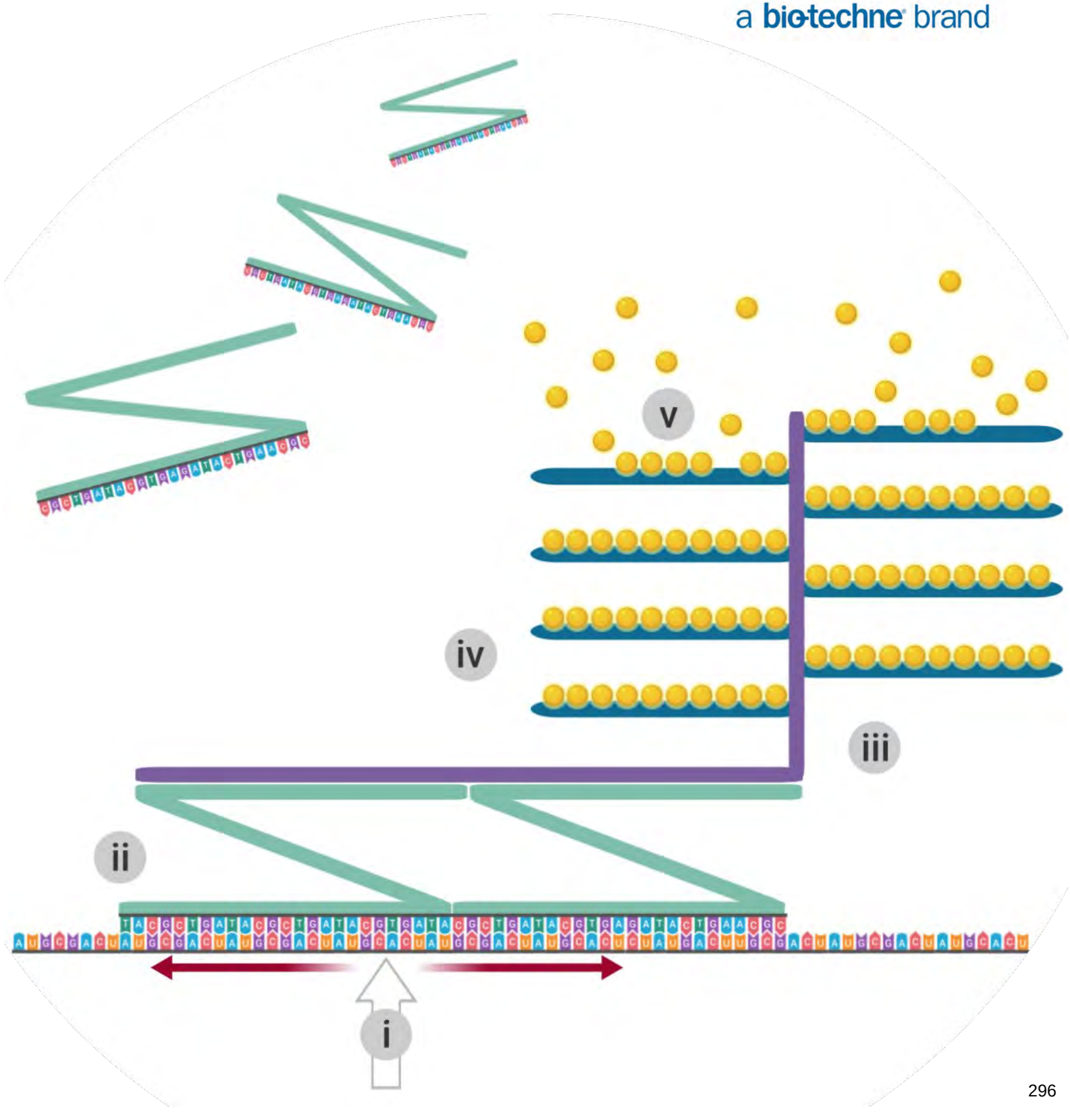
i. Backsplice-specific probe

ii. Adjacent hybridization of probes to circular RNA

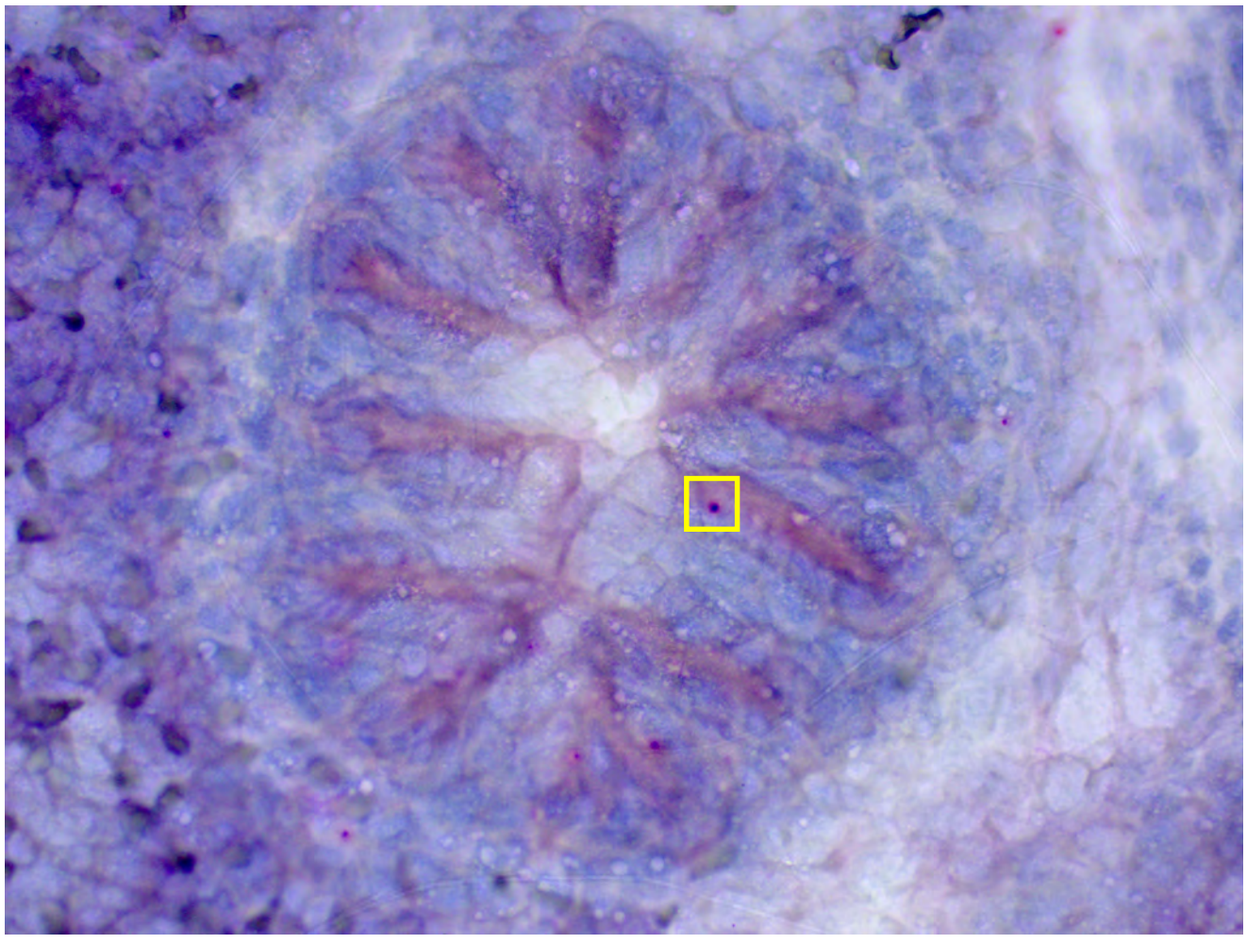
iii. Preamplifier binding

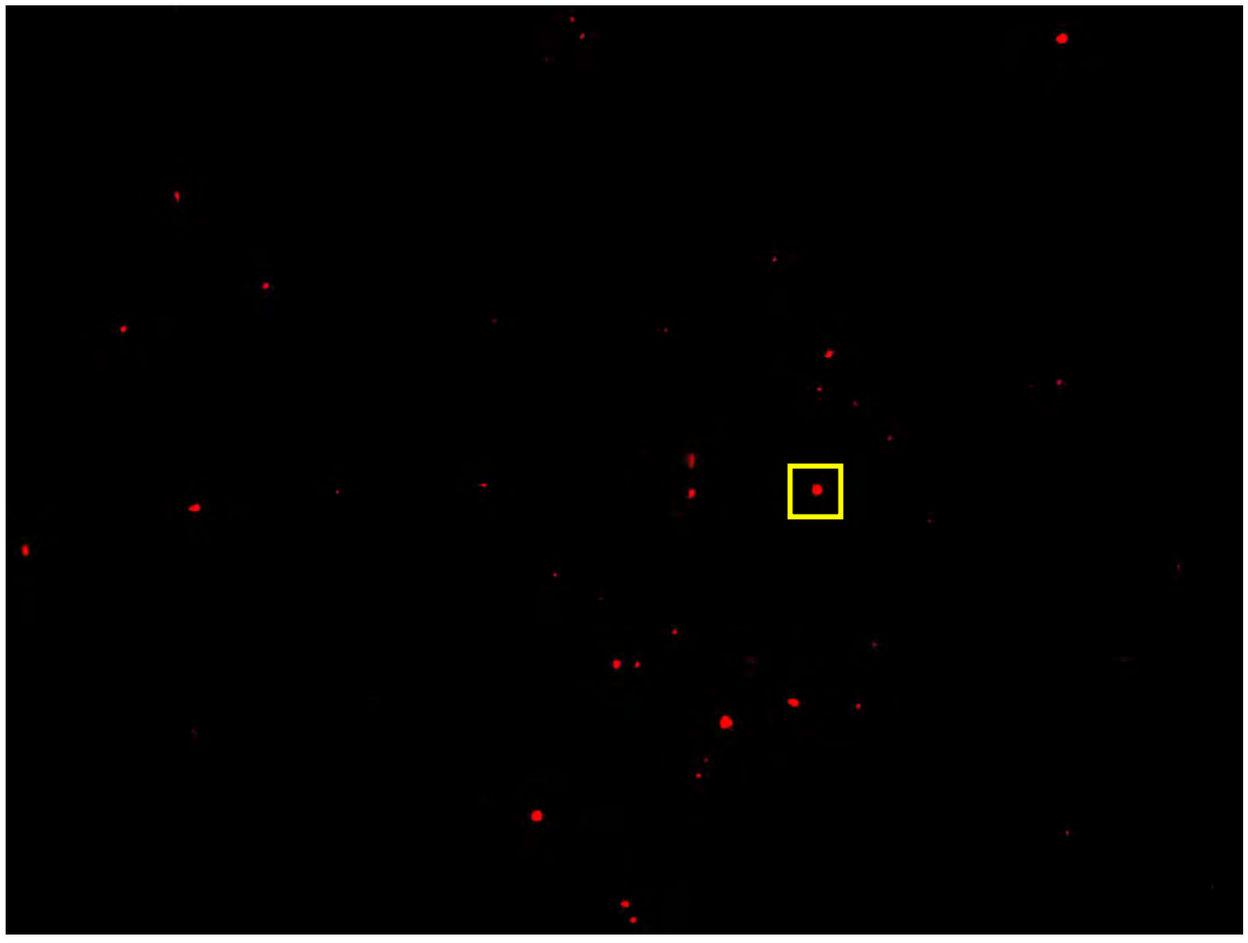
iv. Amplification cascade

v. Label probe binding for fluorescent / chromogenic readout



BaseScope™ E21 Rat Lung





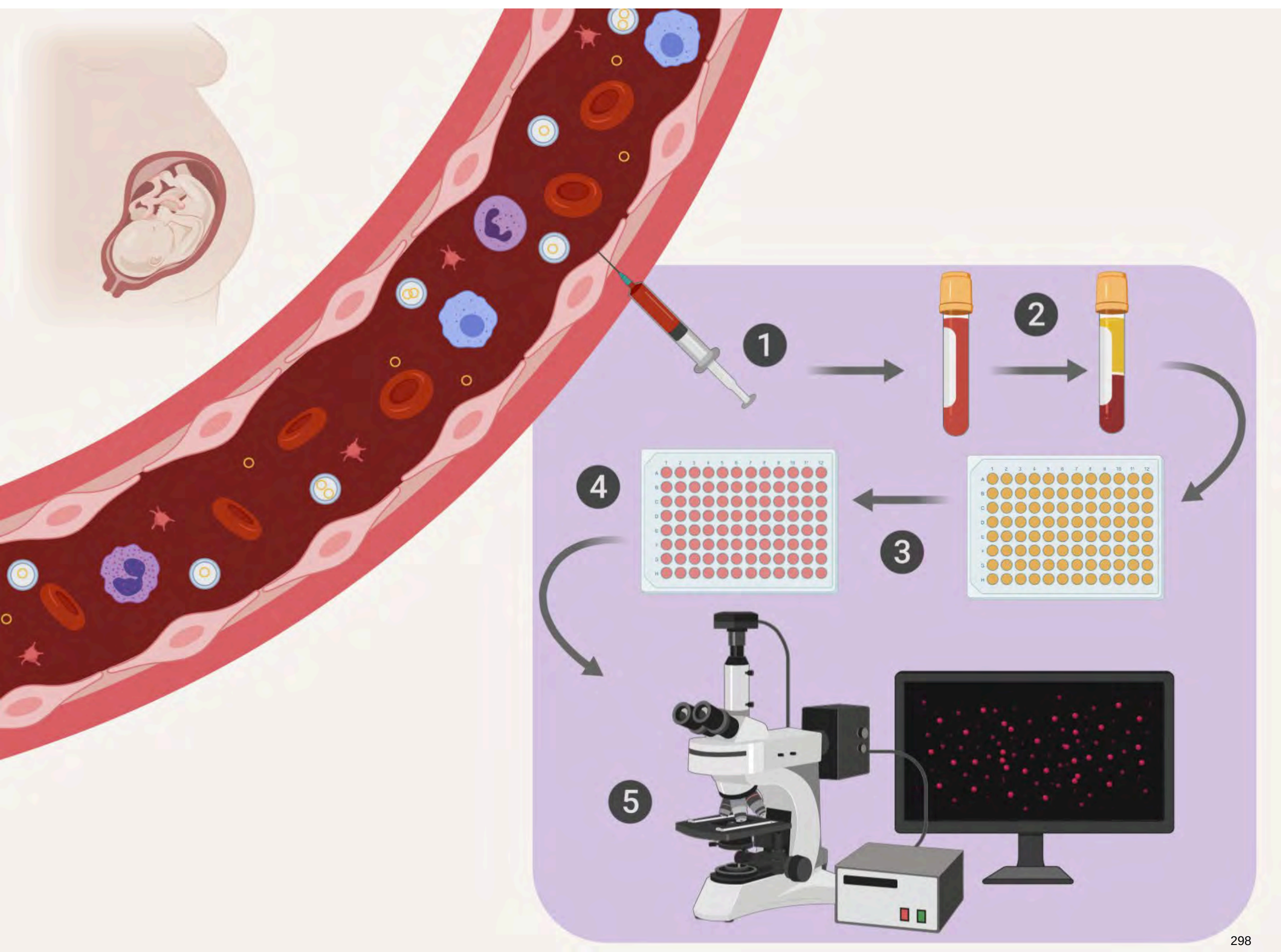
(rno_circRNA_007475)

Pediatric Surgery International
https://doi.org/10.1007/s00383-019-04558-2

ORIGINAL ARTICLE

Check for updates

First steps in the development of a liquid biopsy in situ hybridization protocol to determine circular RNA biomarkers in rat biofluids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2
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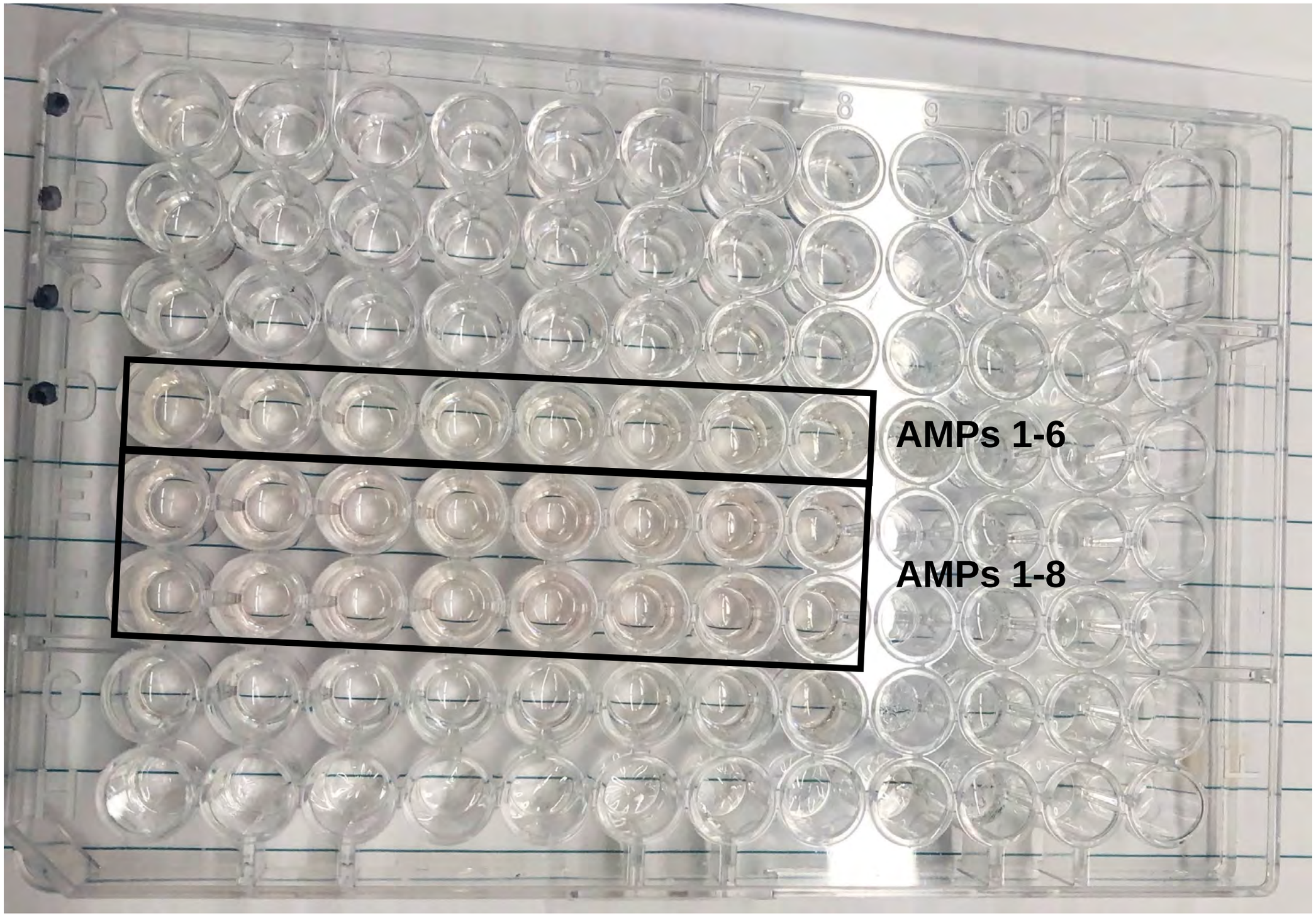
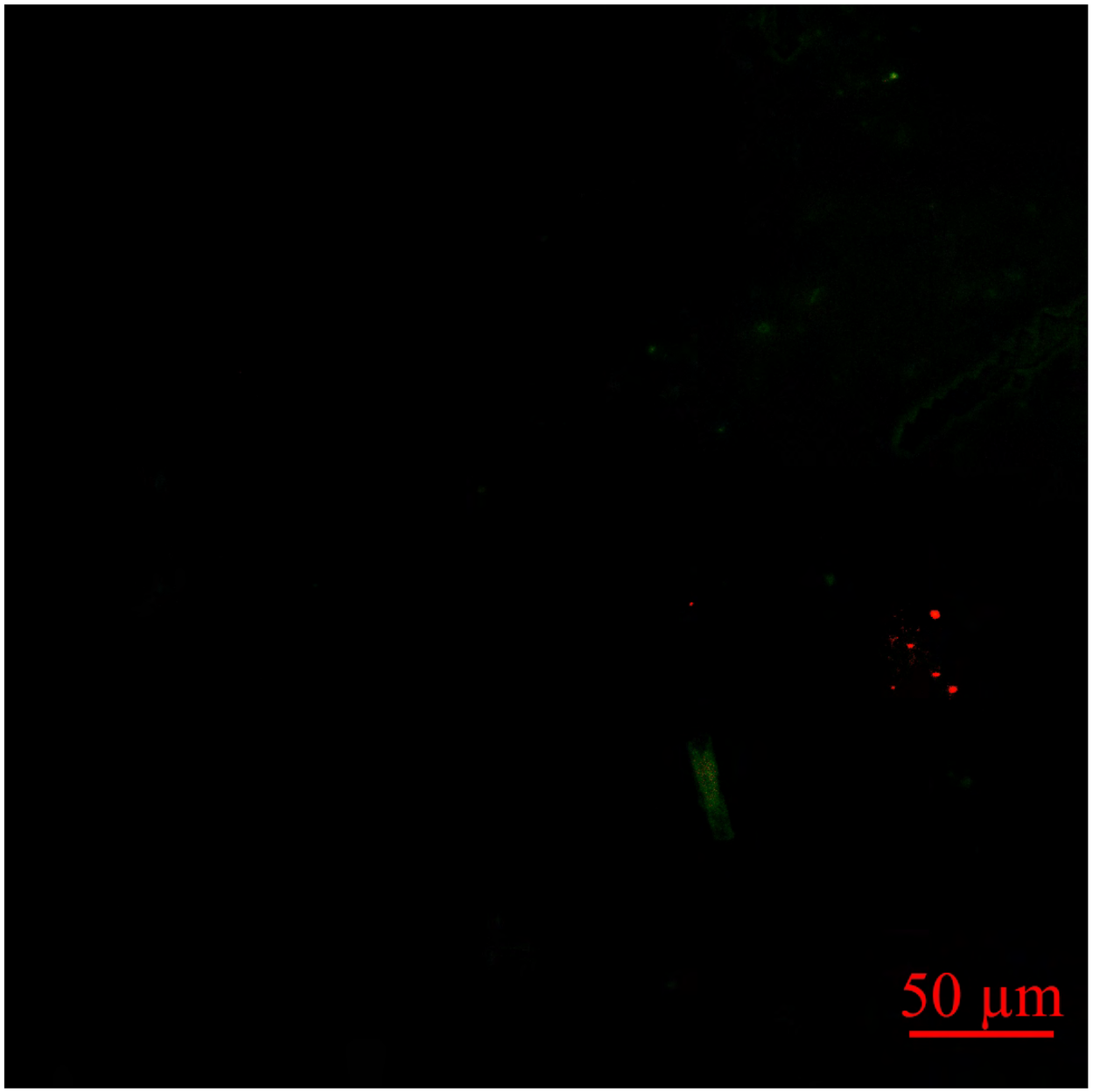
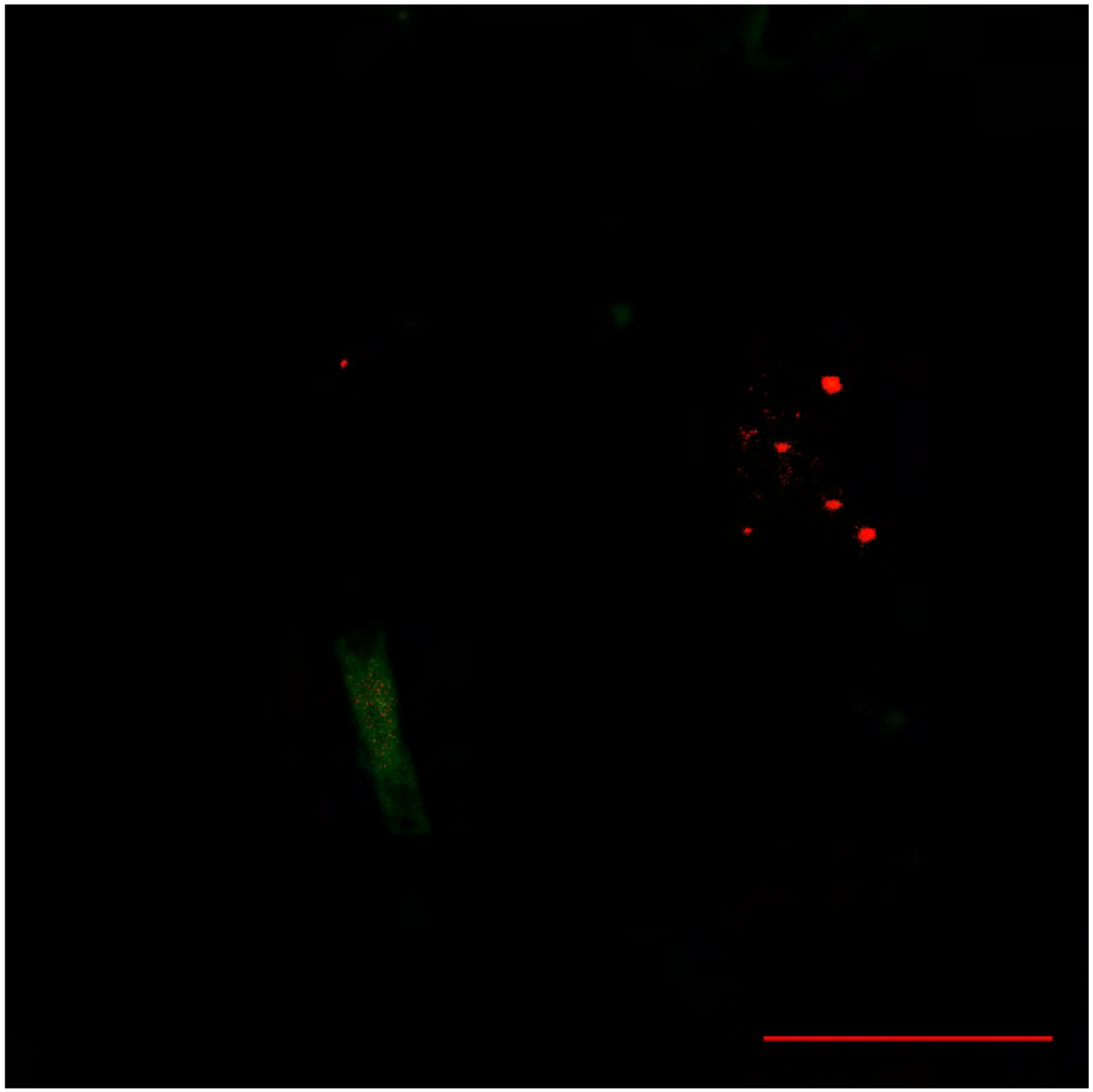
4
5


AMPs 1-6
AMPs 1-8

Control Adult Rat Serum: rno_circRNA_007475





Pregnant mother

CDH baby at diagnosis (>20 weeks)

Potential biomarker and predictor?

Validate circRNAs

circ_002131

circ_405159

Extract maternal blood circRNAs

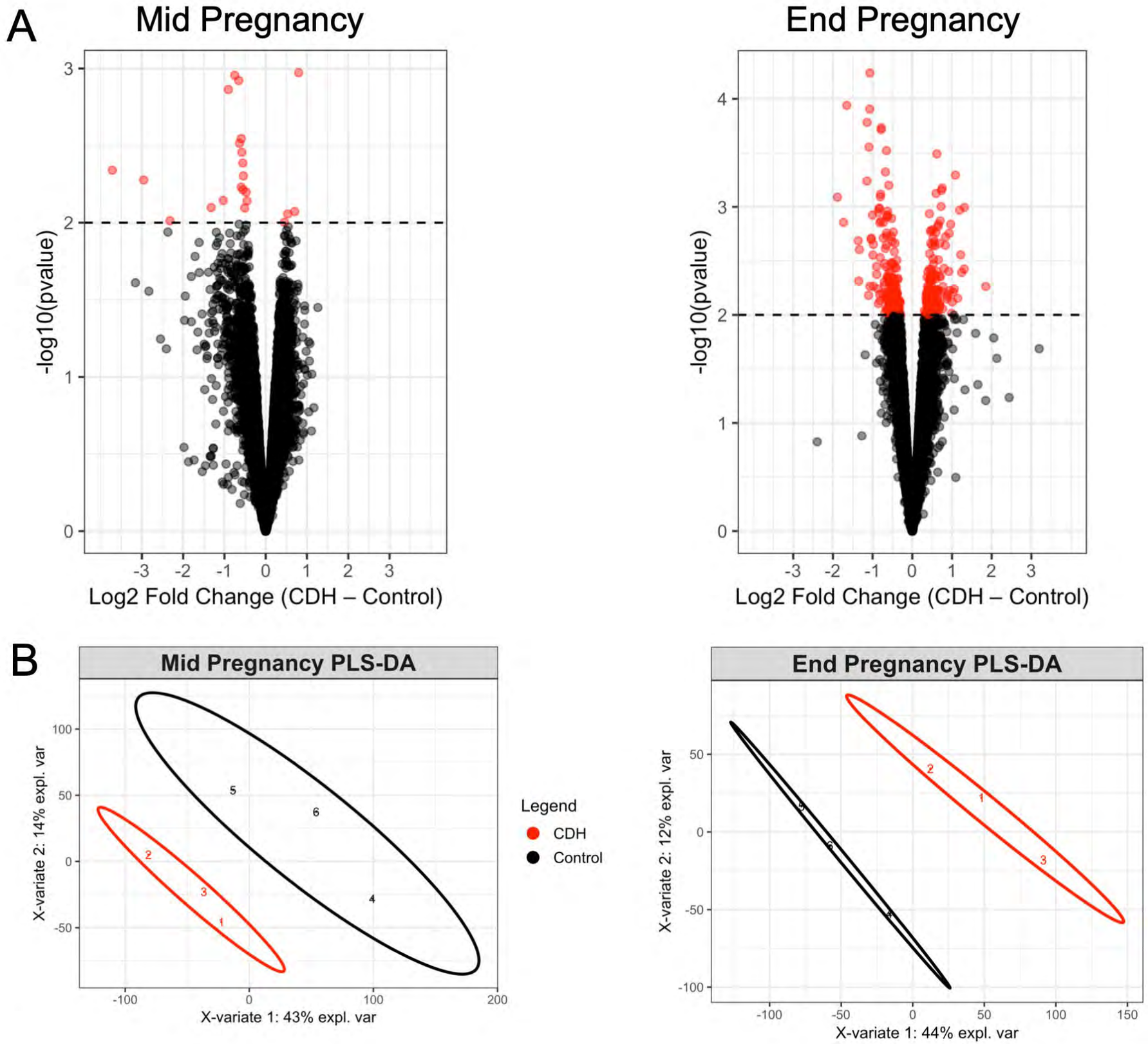
circRNA microarray

Bioinformatics

Screen for differentially regulated circRNAs

Figure courtesy: Dustin Ameis

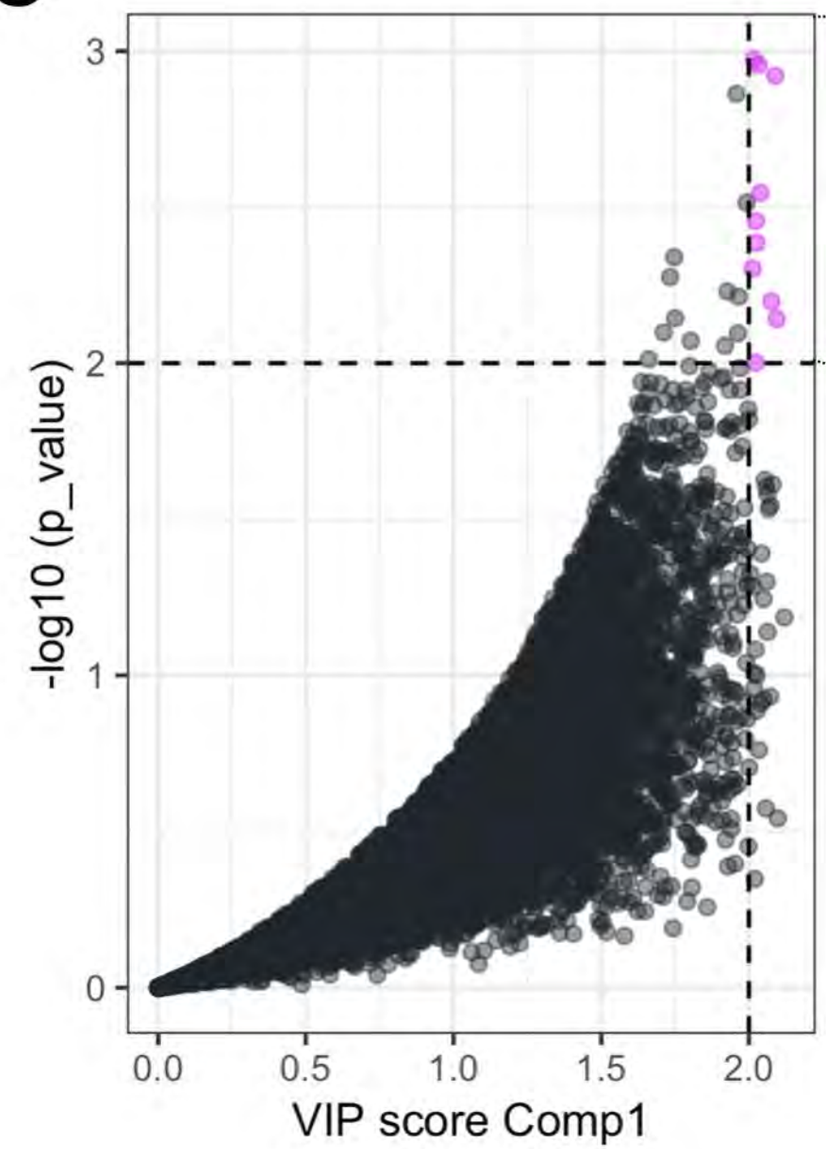
CircRNA profile distinguishes CDH lung from control



Eur Respir J 2020; in press (https://doi.org/10.1183/13993003.00514-2019)

CircRNA profile distinguishes CDH lung from control

C



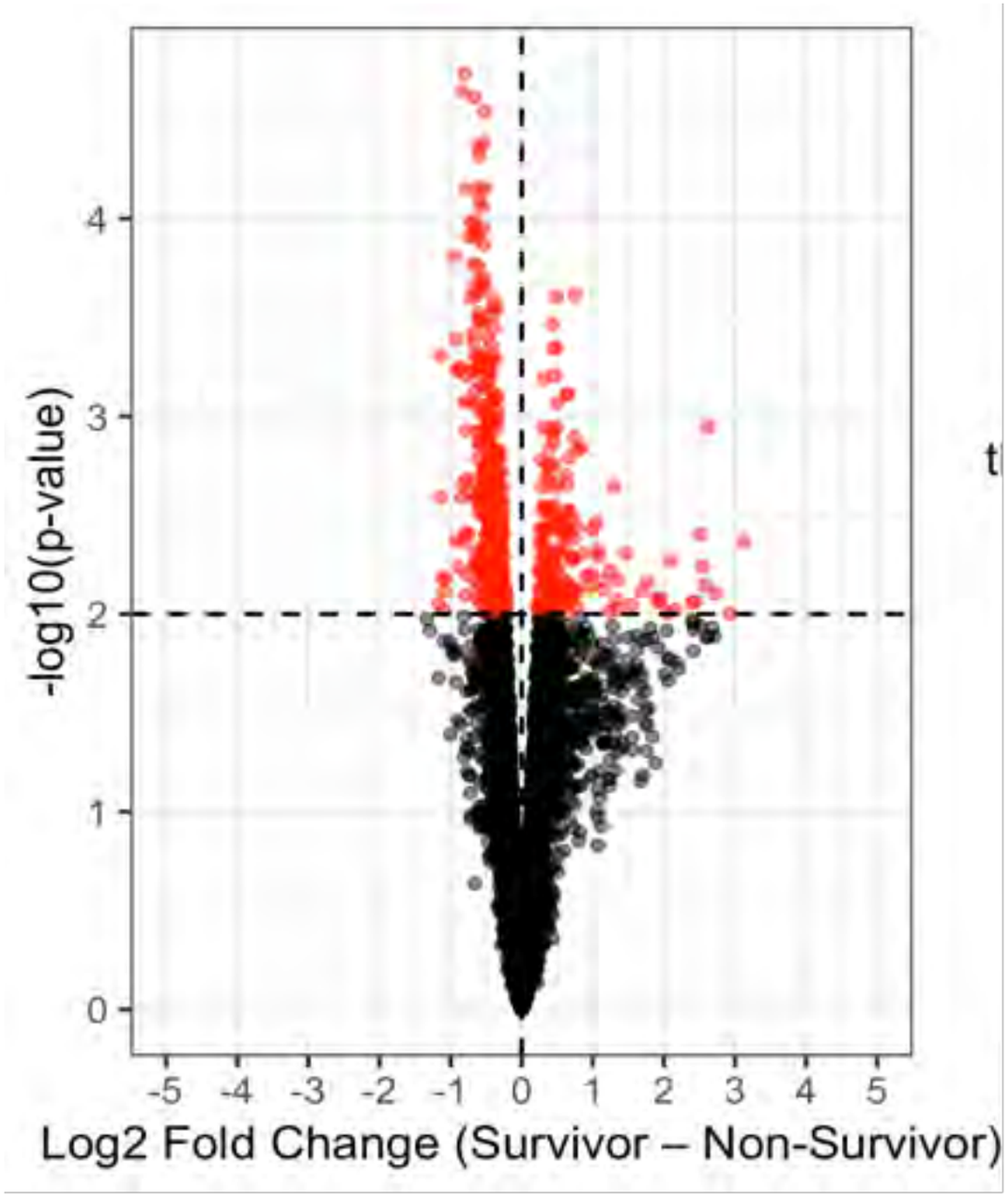
circRNA	VIP Comp1	logFC	P value
hsa_circRNA_001609	2.024	-0.579	0.003
hsa_circRNA_001632	2.089	-0.654	0.001
hsa_circRNA_002074	2.076	-0.475	0.006
hsa_circRNA_002131	2.012	-0.541	0.005
hsa_circRNA_007586	2.023	0.451	0.010
hsa_circRNA_054339	2.094	-0.454	0.007
hsa_circRNA_102068	2.039	-0.593	0.003
hsa_circRNA_103742	2.026	-0.556	0.004
hsa_circRNA_405159	2.016	0.797	0.001
hsa_circRNA_406350	2.033	-0.752	0.001

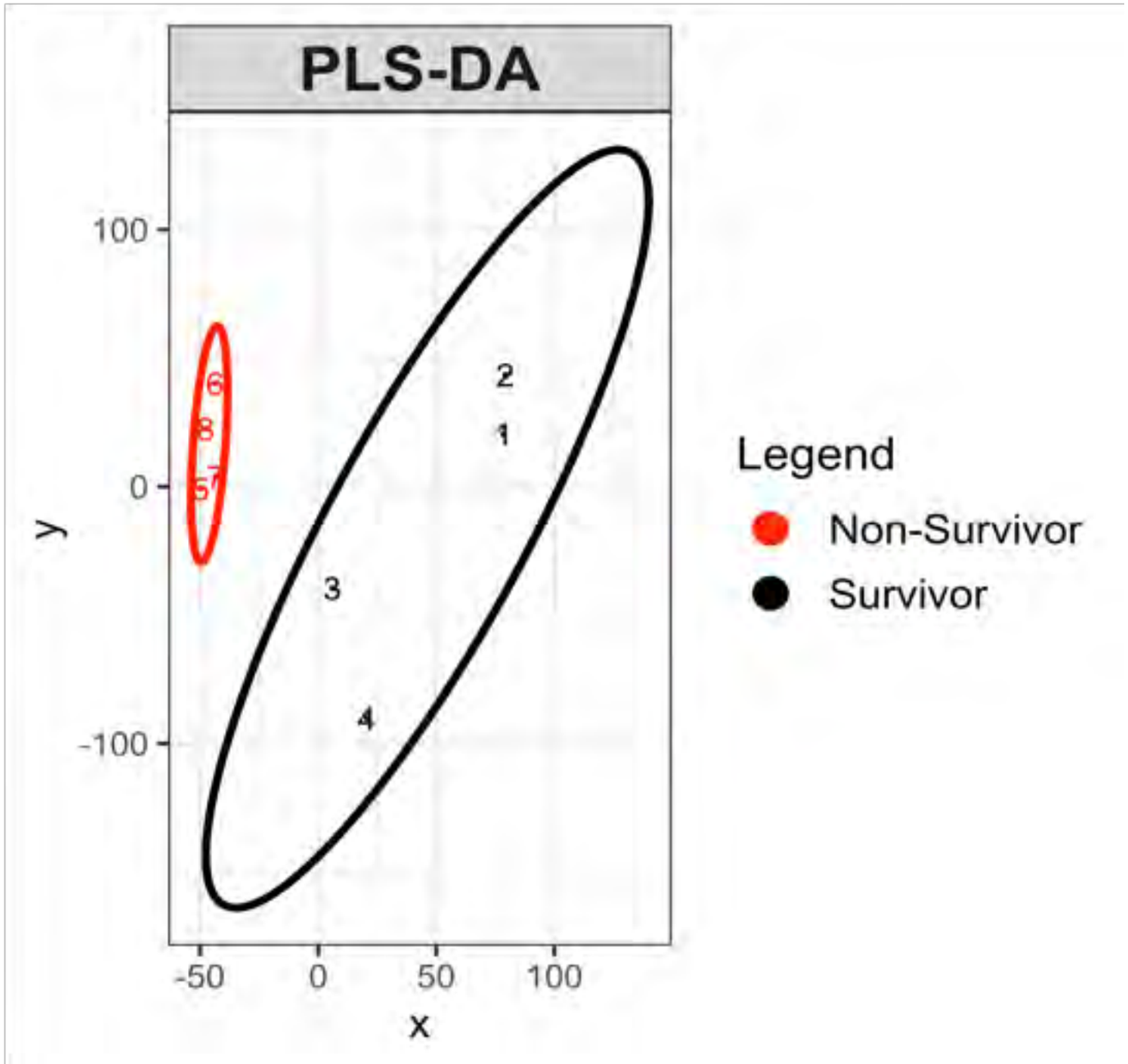
Eur Respir J 2020; in press (https://doi.org/10.1183/13993003.00514-2019)

CircRNA profile can distinguish FETO survivors from non-survivors

	Survivors	**Non-Survivors**	**P-value**
Gestational Age at Plug (weeks)	28.1 (28.7 - 27.1)	27.9 (29.1 - 27.0)	0.84
Observed/ Expected Lung to Head Ratio (%)	22.5 (23.6 - 17.5)	21.6 (24.0 - 15.9)	0.87
Liver herniated	10 (91%)	9 (100%)	1.00
Fetal gender	7 male/ 4 female	4 male/ 5 female	0.65
Birth weight (g)	2780 (3180 - 2160)	3195 (3278 - 2650)	0.3

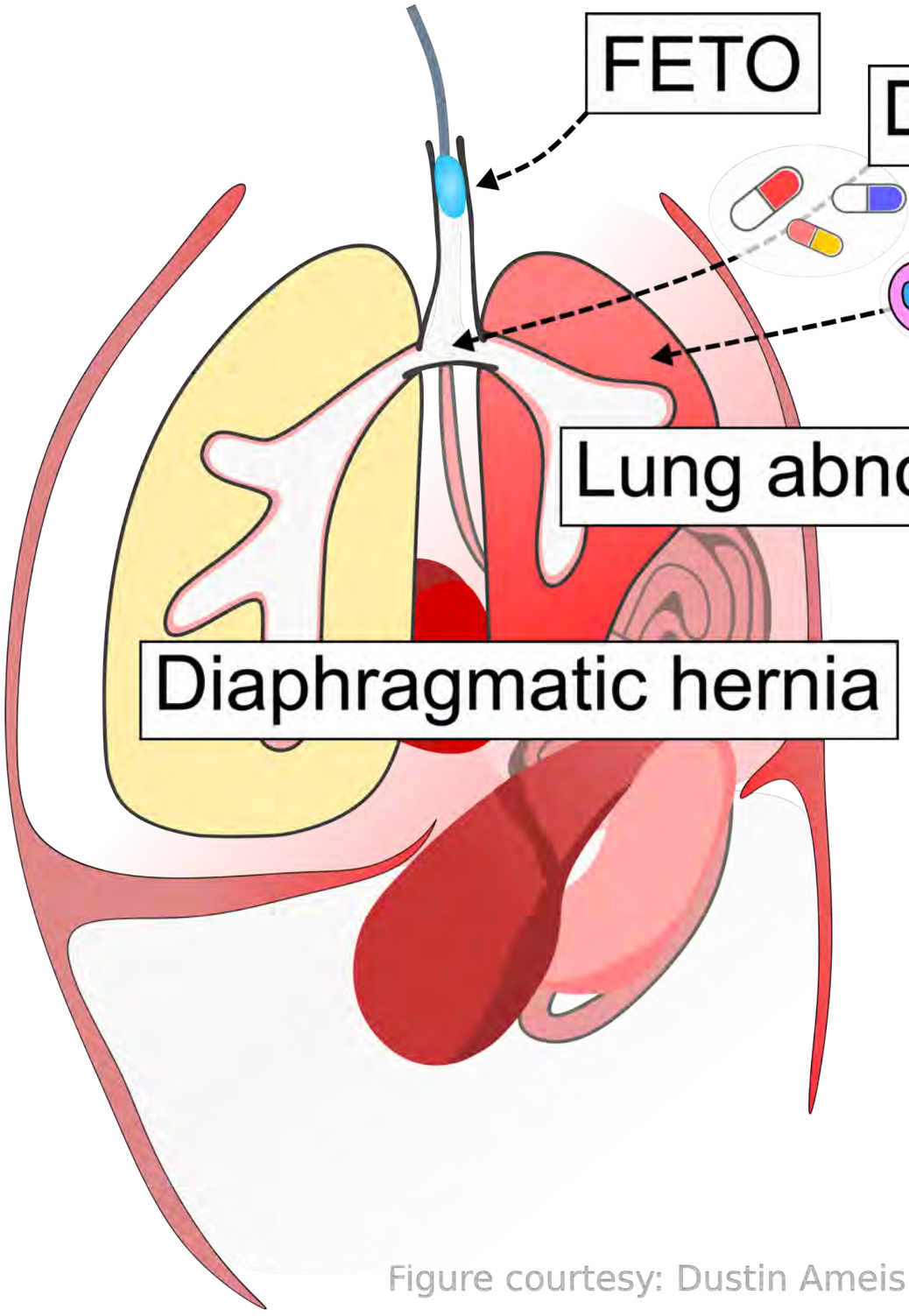
CircRNA profile can distinguish FETO survivors from non-survivors





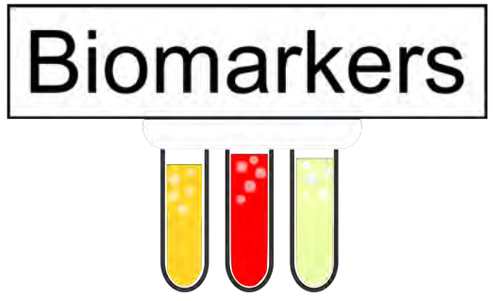
Unpublished results

Prenatal treatment



Pathogenesis

Prenatal diagnosis



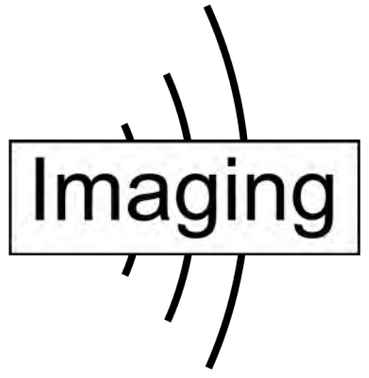


Figure courtesy: Dustin Ameis

http://store.winnipegfreepress.com/photostore/details/139975/

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Barbara Iwasiow
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GFT Group Academic Surgeons Winnipeg

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Canada Foundation for Innovation
Fondation canadienne pour l'innovation

DEVOTION
Developmental Origins of Chronic Diseases in Children Network

EXIQON

CCHCSP PCCSE

Research Manitoba

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

The Children's Hospital Research Institute of Manitoba

Thorlakson Chair in Surgical Research

The Children's Hospital Research Institute of Manitoba

BIOLOGY OF BREATHING

Shared health Soins communs Manitoba

Health Sciences Centre Winnipeg

University of Manitoba

ADVENTURER TRAILBLAZER CHALLENGER DEFENDER VISIONARY INNOVATOR

TRAILBLAZER CHALLENGER DEFENDER VISIONARY INNOVATOR EXPLORER TRAILBLAZER CHALLENGER DEFENDER VISIONARY INNOVATOR EXPLORER

The Children's Hospital Research Institute of Manitoba

BIOLOGY OF BREATHING

Shared health Soins communs Manitoba

Health Sciences Centre Winnipeg

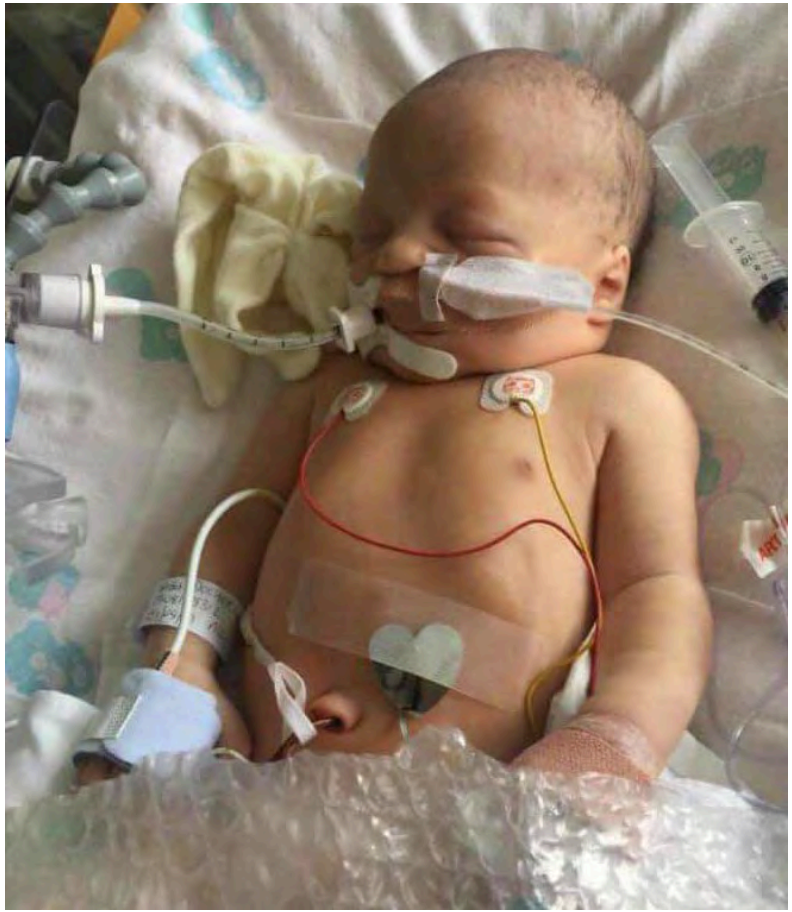
University of Manitoba

The Role of the Heart in Congenital Diaphragmatic Hernia

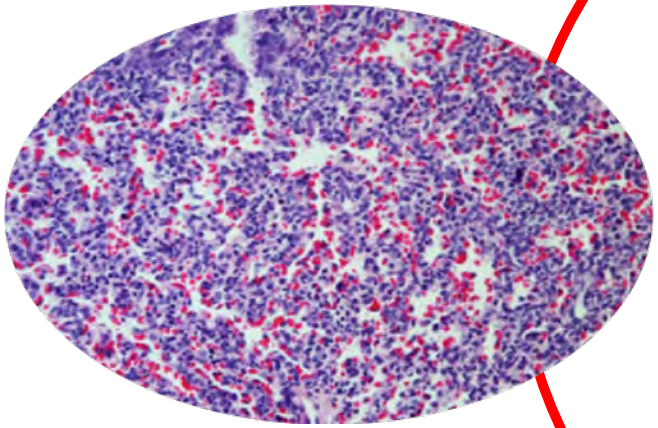
Neil Patel
Royal Hospital for Children
Glasgow, UK

PEOPLE MAKE GLASGOW

NHS Greater Glasgow and Clyde

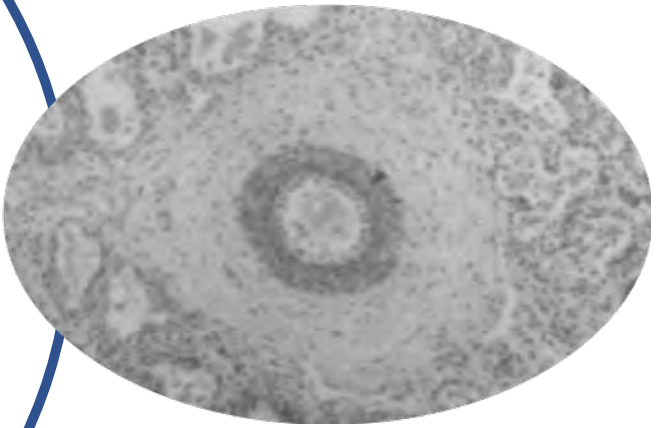


Pulmonary hypoplasia

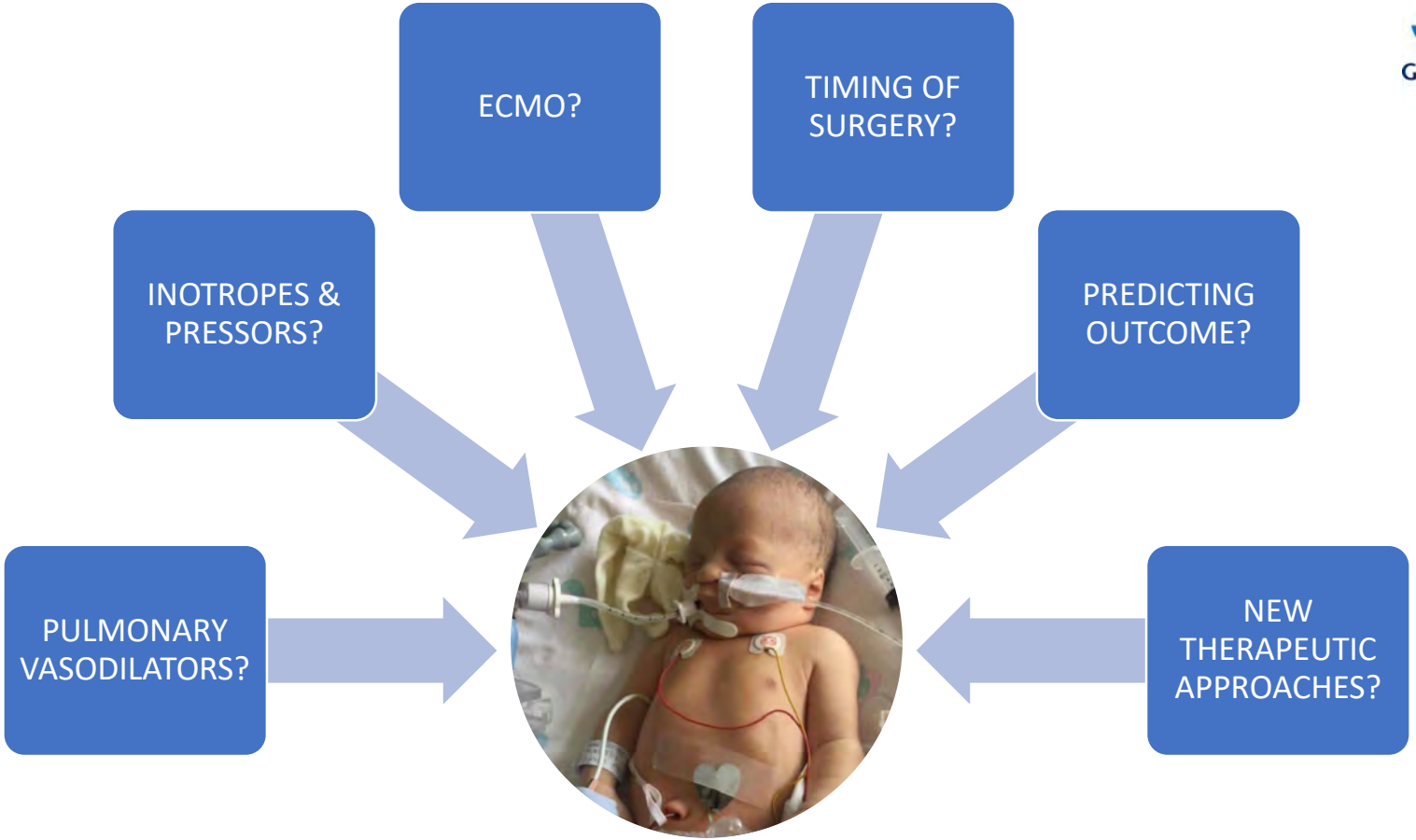


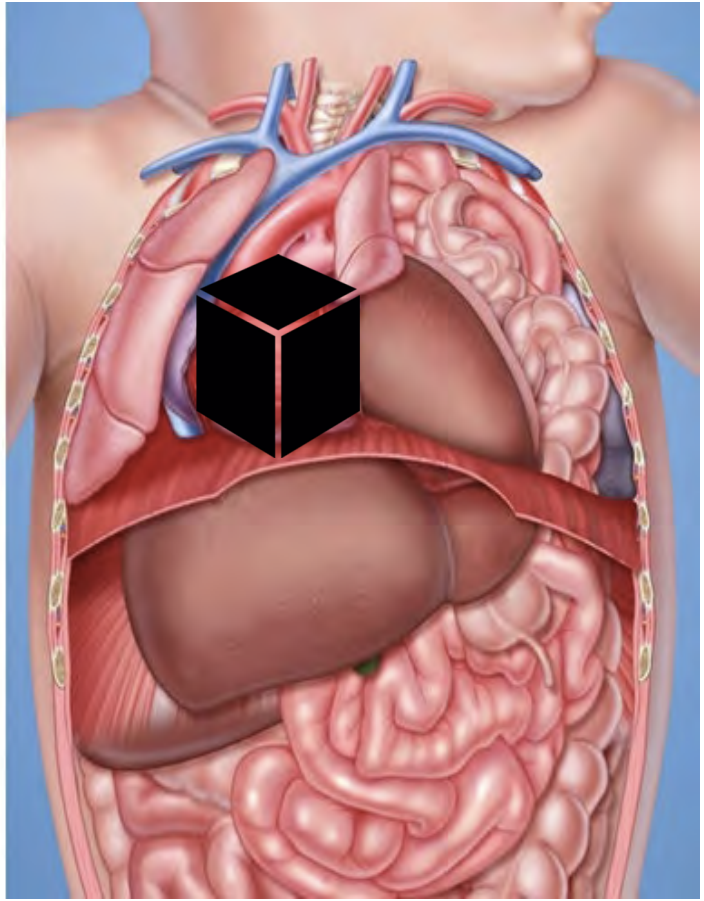
Schmidt et al, 2012

Pulmonary hypertension



Yamataka and Puri, 1997


ECMO?
TIMING OF SURGERY?
INOTROPES & PRESSORS?
PREDICTING OUTCOME?
PULMONARY VASODILATORS?
NEW THERAPEUTIC APPROACHES?



Cardiac function in CDH

What?

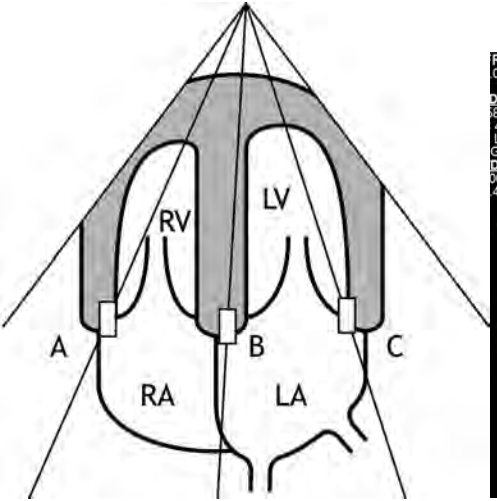
Why?

When?

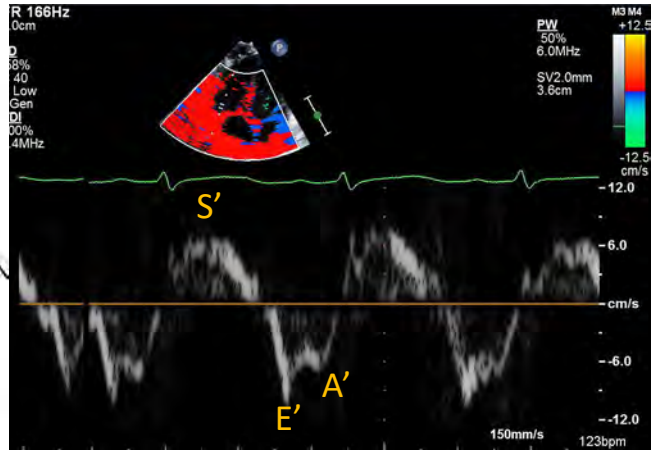
How often?

(Who cares?)

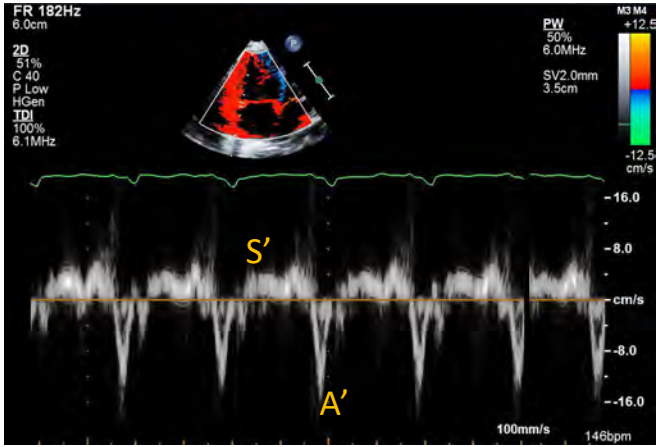
Tissue Doppler Imaging of RV in CDH



Control

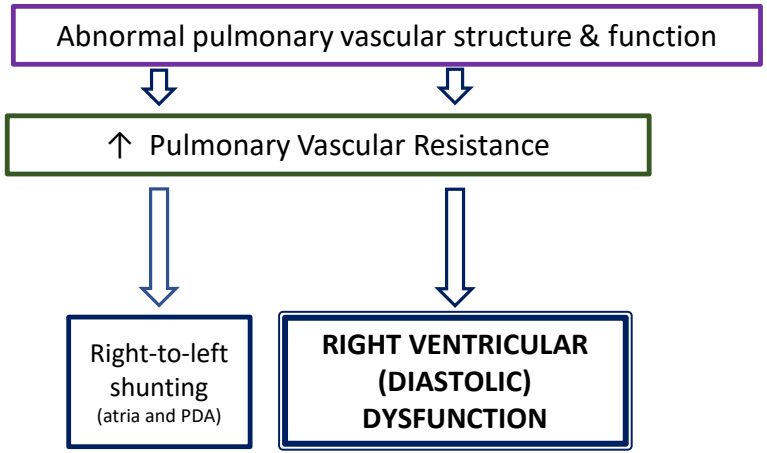


CDH



- Reduced systolic velocities (S')
- **Loss of diastolic (e') velocity**

Patel et al, Neonatology 2009

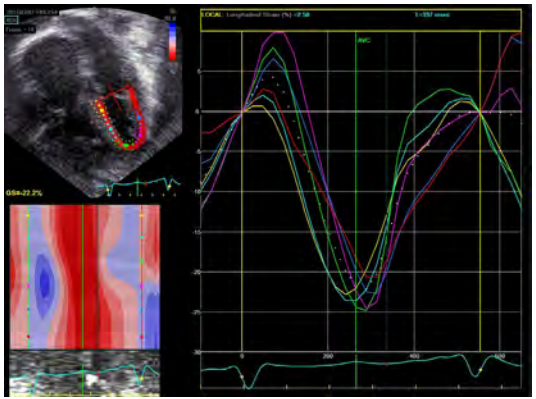

Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
RIGHT VENTRICULAR (DIASTOLIC) DYSFUNCTION

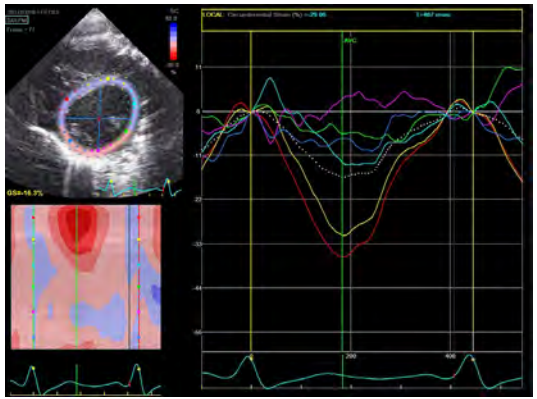
Speckle tracking echocardiography in CDH

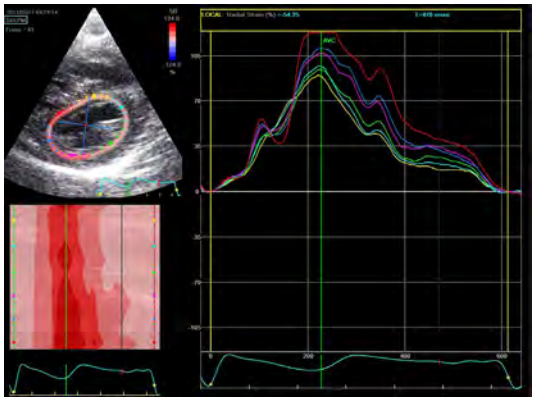
Longitudinal strain (LS)

Circumferential strain (CS)

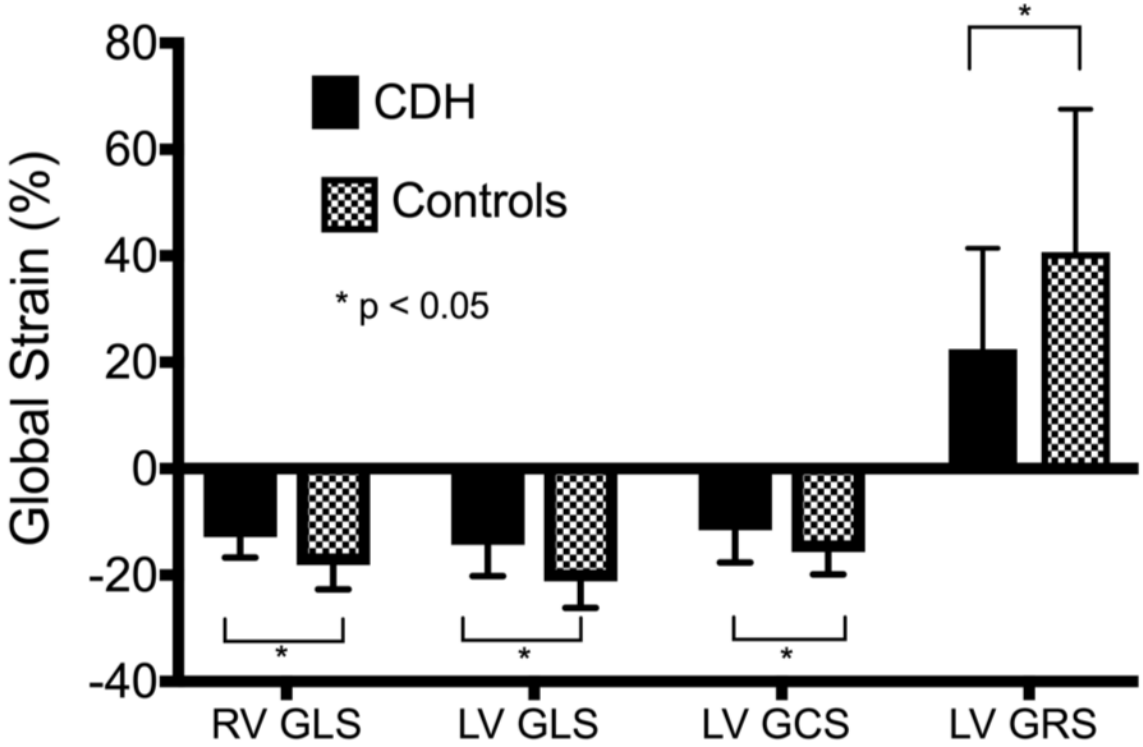
Radial strain(RS)



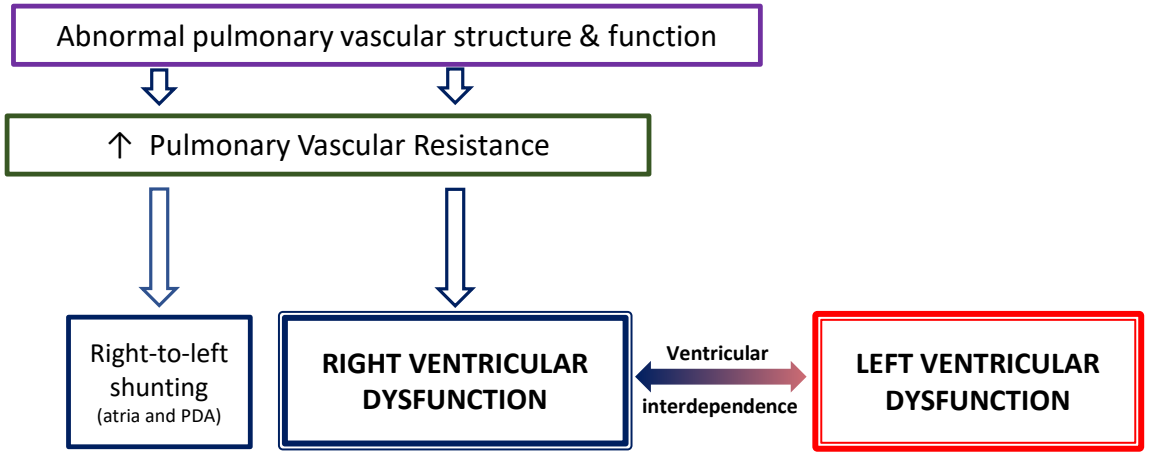




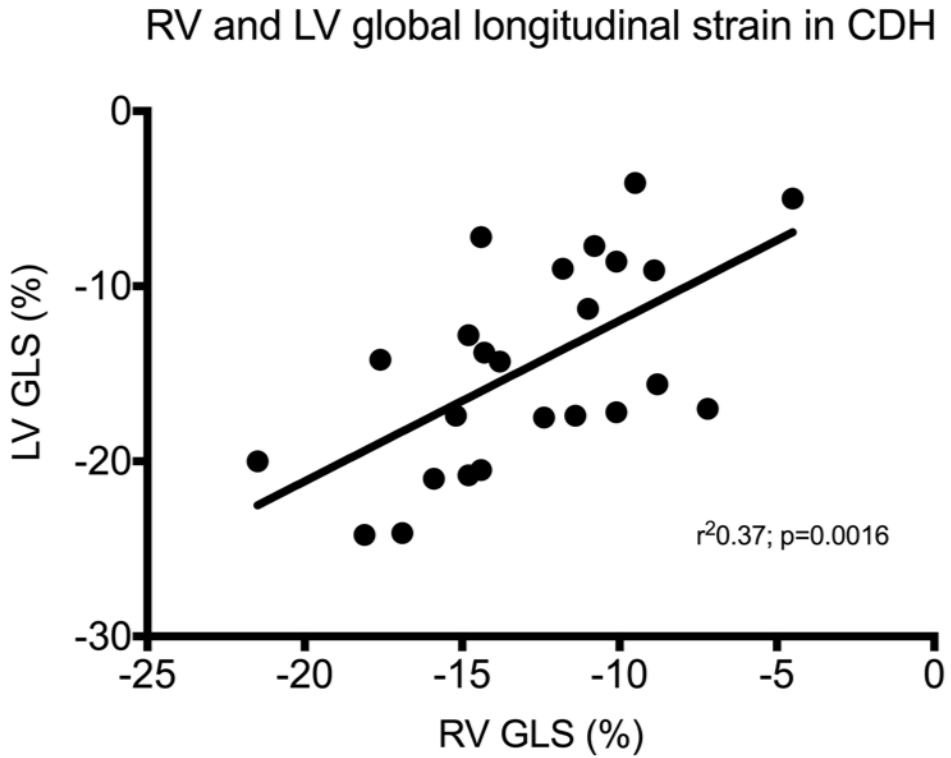
Ventricular strain in CDH (first 48h of life)



Patel et al, J Peds 2018


Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION

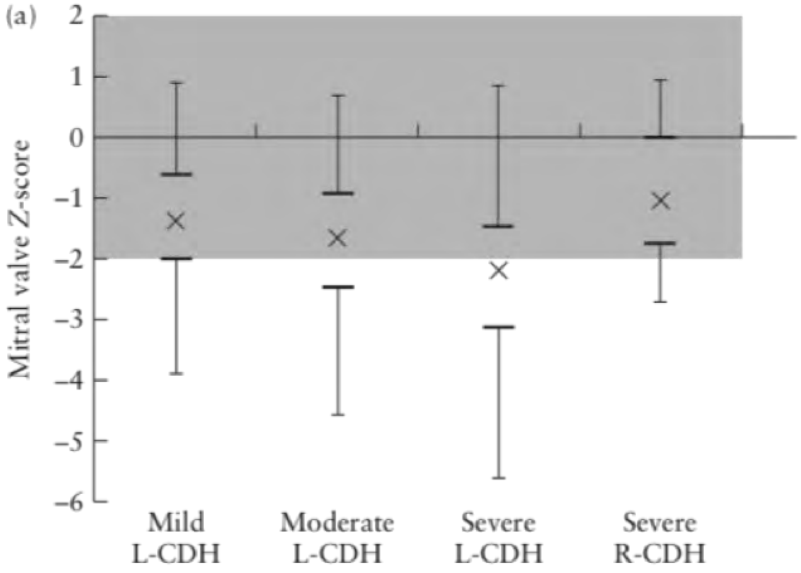
Ventricular inter-dependence in CDH

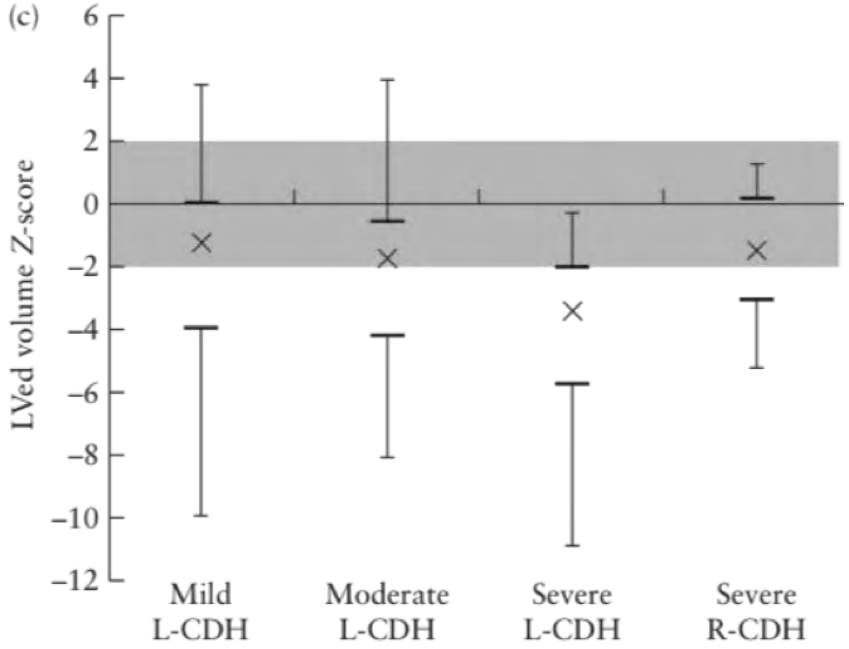


Massolo et al, Neonatology 2019

Severe left diaphragmatic hernia limits size of fetal left heart more than does right diaphragmatic hernia

F. A. BYRNE*, R. L. KELLER†, J. MEADOWS*, D. MINIATI‡§, M. M. BROOK*, N. H. SILVERMAN* and A. J. MOON-GRADY*§





Ultrasound Obstet Gynecol 2015; **46**: 688–694

Possible mechanisms of fetal LV hypoplasia

- Reduced pulmonary blood flow
- Altered ductus venosus streaming
- Mechanical compression

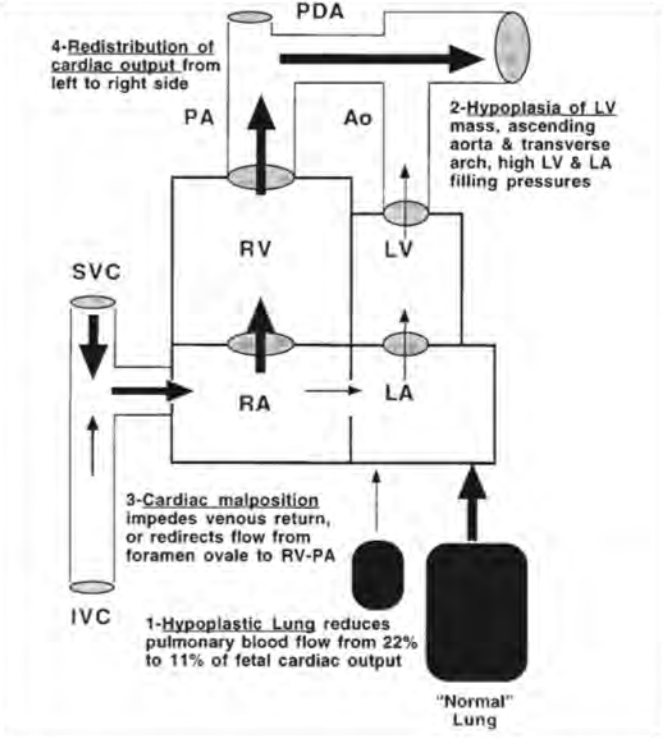
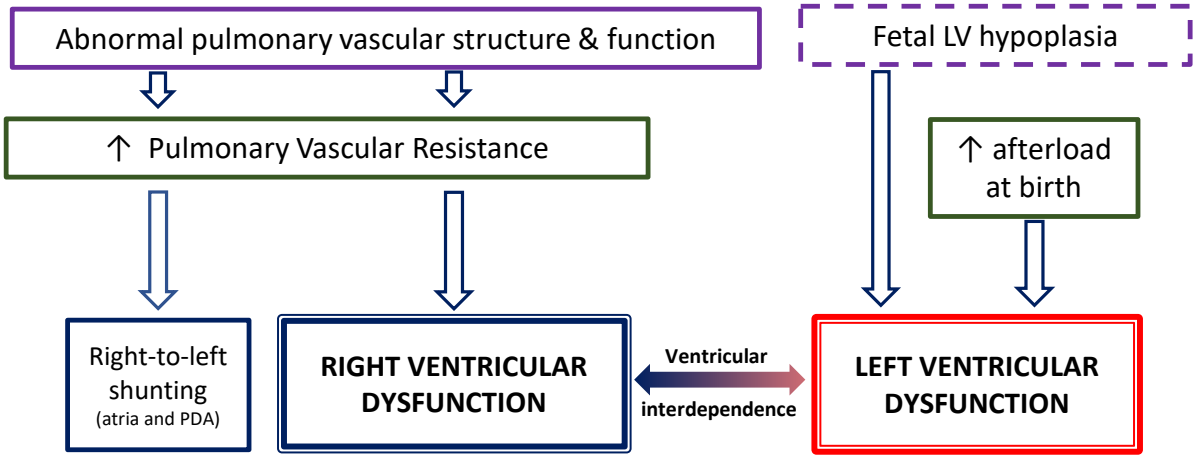
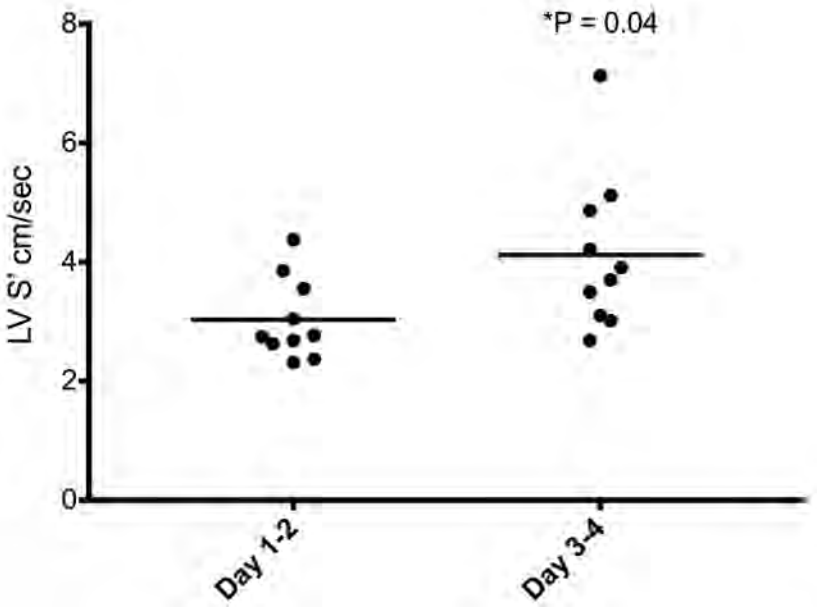


Fig. 2. Diagram summarizing four mechanisms for cardiovascular compromise during fetal life with severe CDH. (Adapted with permission from WB Saunders, Katz AL, Wiswell TE, Baumgart S. Clin Perinatol 1994.)[1]

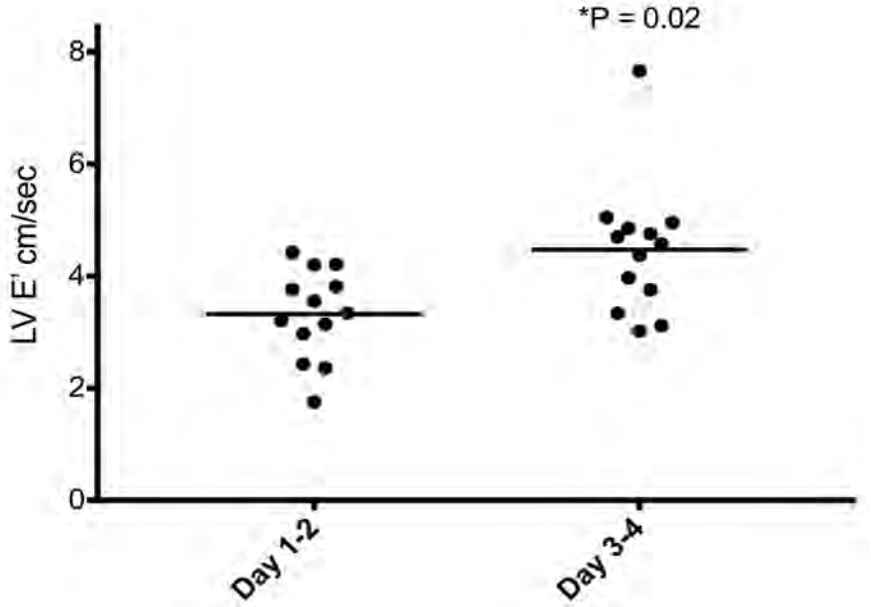

Abnormal pulmonary vascular structure & function
Fetal LV hypoplasia
↑ Pulmonary Vascular Resistance
↑ afterload at birth
Right-to-left shunting (atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION

LV function improves in first days of life

Systolic TDI velocities (LV S')

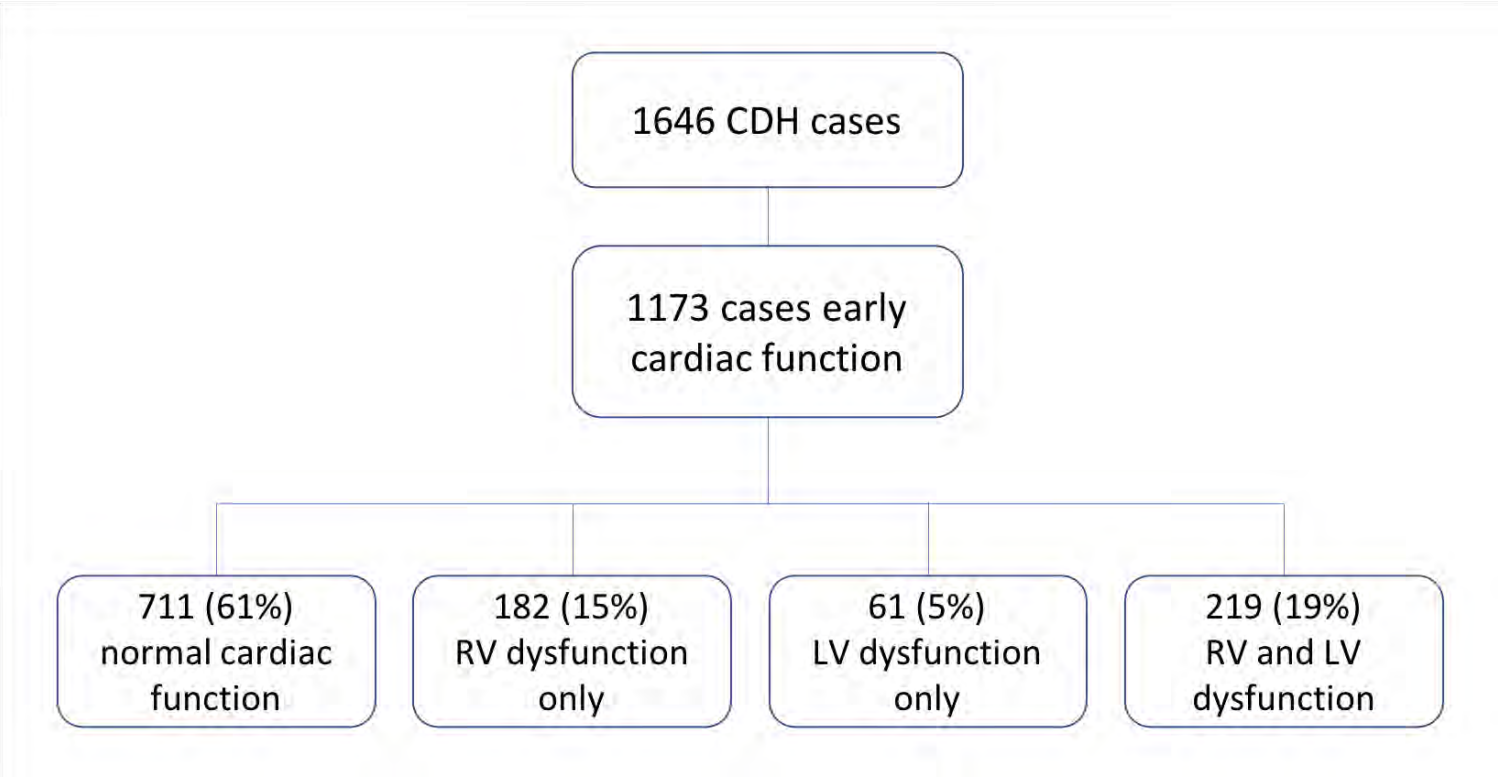


Diastolic TDI velocities (LV E')



N. Patel, F. Kipfmueller / Seminars in Pediatric Surgery 26 (2017)

Early ventricular function: CDH Study Group Registry Analysis 2015-2018

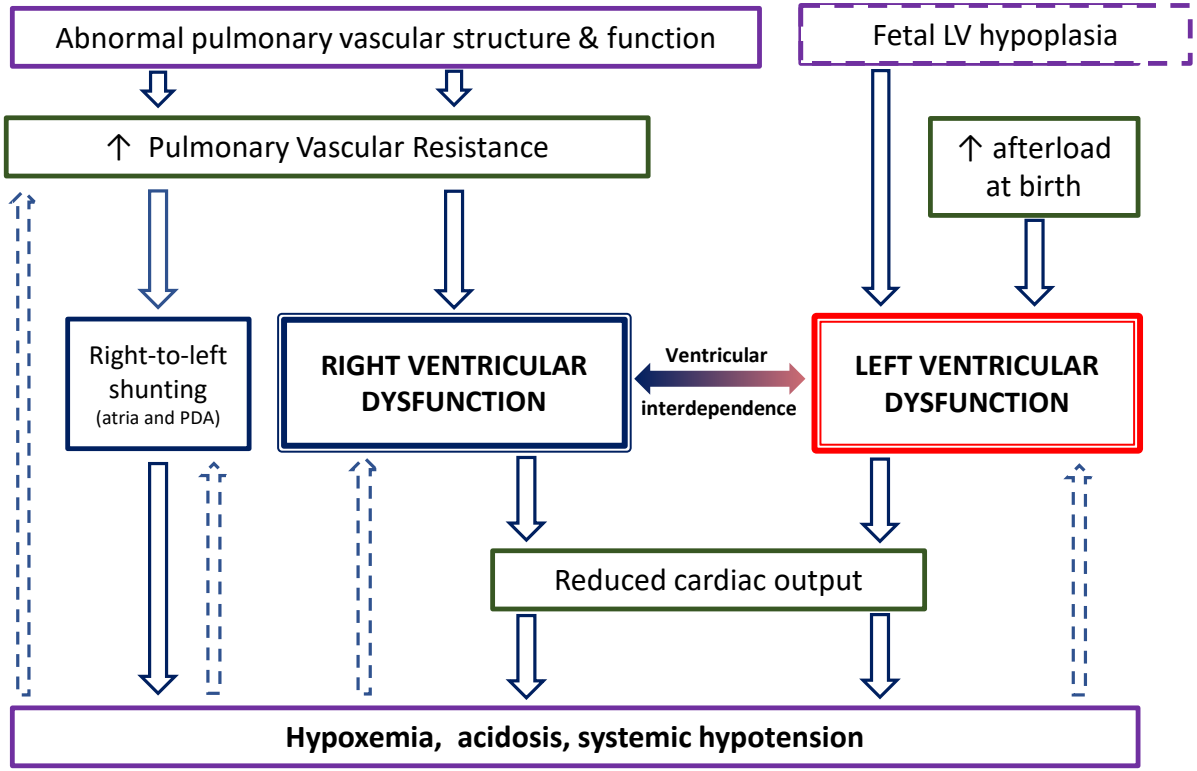


AJRCCM 2019

Variable		Cardiac Function Category				
		Normal function	RV dysfunction only	LV dysfunction only	RV & LV dysfunction	P value
N (%)		711 (61)	182 (15)	61 (5)	219 (19)	-
Birth weight, median (SD), kg		2.93 (0.63)	3.02 (0.61)	3.00 (0.48)	2.96 (0.56)	0.489
Gestational age, median (SD), weeks		37.4 (2.33)	37.5 (2.11)	37.8 (1.80)	37.6 (1.85)	0.928
Male n (%)		410/709 (58)	91/182 (50)	36/61 (59)	121/219 (55)	0.275
Inborn n (%)		**437/710 (62)**	**122/181 (67)**	**34/61 (56)**	**159/219 (73)**	**0.009**
Prenatal diagnosis n (%)		**534/708 (25)**	**150/182 (82)**	**44/61 (72)**	**186/219 (85)**	**0.007**
Left sided CDH n (%)		599/710 (84)	155/182 (85)	50/59 (85)	167/214 (78)	0.145
Major Cardiac anomaly n (%)		49/711 (7)	13 /180 (7)	10/61 (16)	20/219 (9)	0.054
Chromosomal anomaly n (%)		57/710 (8)	13/181 (7)	4/61 (6)	22/219 (10)	0.685
Other anomaly n (%)		79/711 (11)	20/180 (11)	9 /61 (15)	28/219 (13)	0.778
CDHSG Stage group	A/B n (%)	335 (52)	60 (37)	19 (36)	40 (25)	**<0.001**
	C/D n (%)	307 (48)	103 (63)	33 (64)	122 (75)	
Liver in chest n (%)		294/642 (46)	92/163 (56)	32/51 (63)	105/161 (65)	**<0.001**
Patch Repair n (%)		345/645 (53)	111/163 (68)	35/511 (69)	130/161 (81)	**<0.001**

Patel et al, AJRCCM 2019

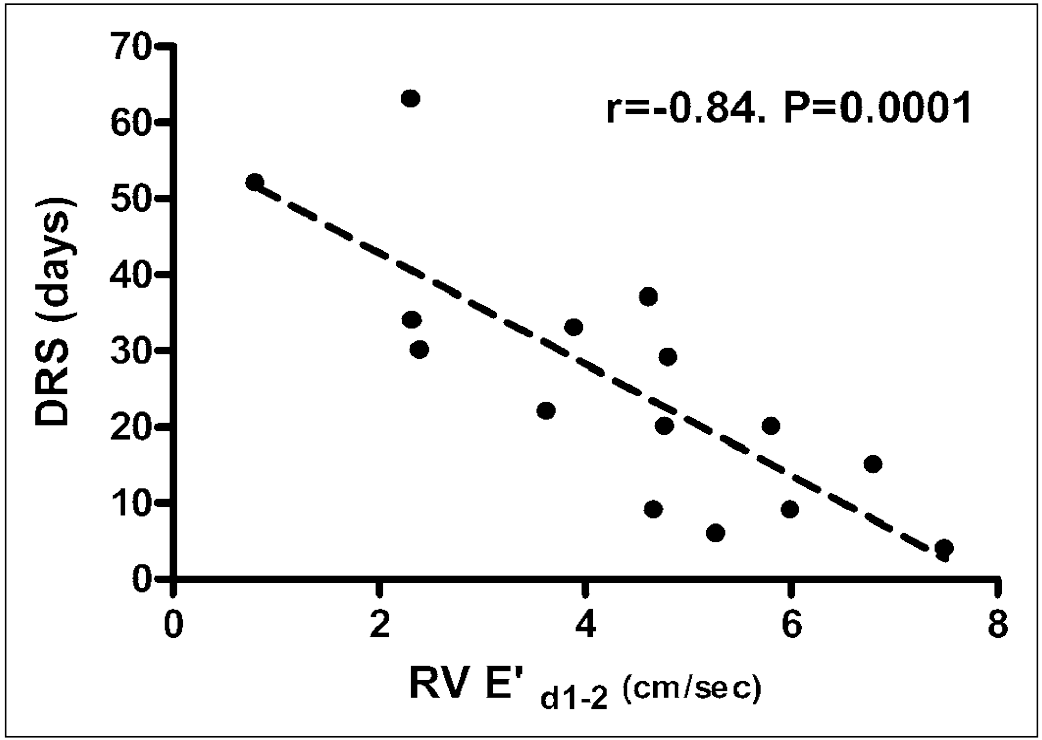

Mmmm, Tastes
like a combination
of Who Cares?
&
So What?



Patel et al, Sem Perinatol 2019

Right Ventricular Diastolic Function Measured by Tissue Doppler Imaging Predicts Early Outcome in Congenital Diaphragmatic Hernia

Florian Moenkemeyer, MD; Neil Patel, MD



Ped Crit Care Med 2013

Ventricular Performance is Associated with Need for Extracorporeal Membrane Oxygenation in Newborns with Congenital Diaphragmatic Hernia

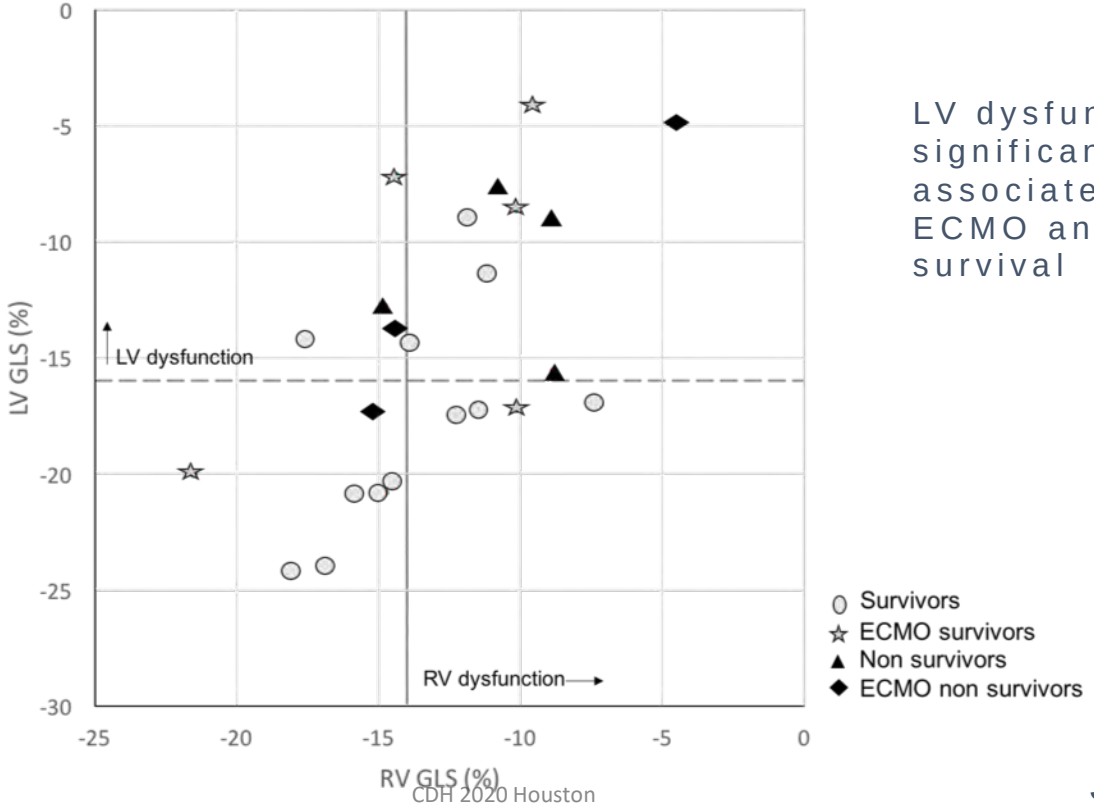
Gabriel Altit, MDCM, FRCPC, FAAP[1,2,3], Shazia Bhombal, MD, FAAP[2,3], Krisa Van Meurs, MD, FAAP[2,3], and Theresa A. Tacy, MD, FAAP[1,3]

	ECMO (n = 15)	Non-ECMO (n = 29)	*P* value
RV pGLS (%)	–5.2 (3.9)	–10.7 (5.0)	.001
LV pGLS (%)	–9.1 (4.9)	–14.9 (5.3)	.002

J Peds, 2017

Early Postnatal Ventricular Dysfunction Is Associated with Disease Severity in Patients with Congenital Diaphragmatic Hernia

Neil Patel, MD[1], Anna Claudia Massolo, MD[2], Anshuman Paria, MBBS[1], Emily J. Stenhouse, MBChB[3], Lindsey Hunter, MRCPCH[4], Emma Finlay, BSE[4], and Carl F. Davis, FRCS[5]

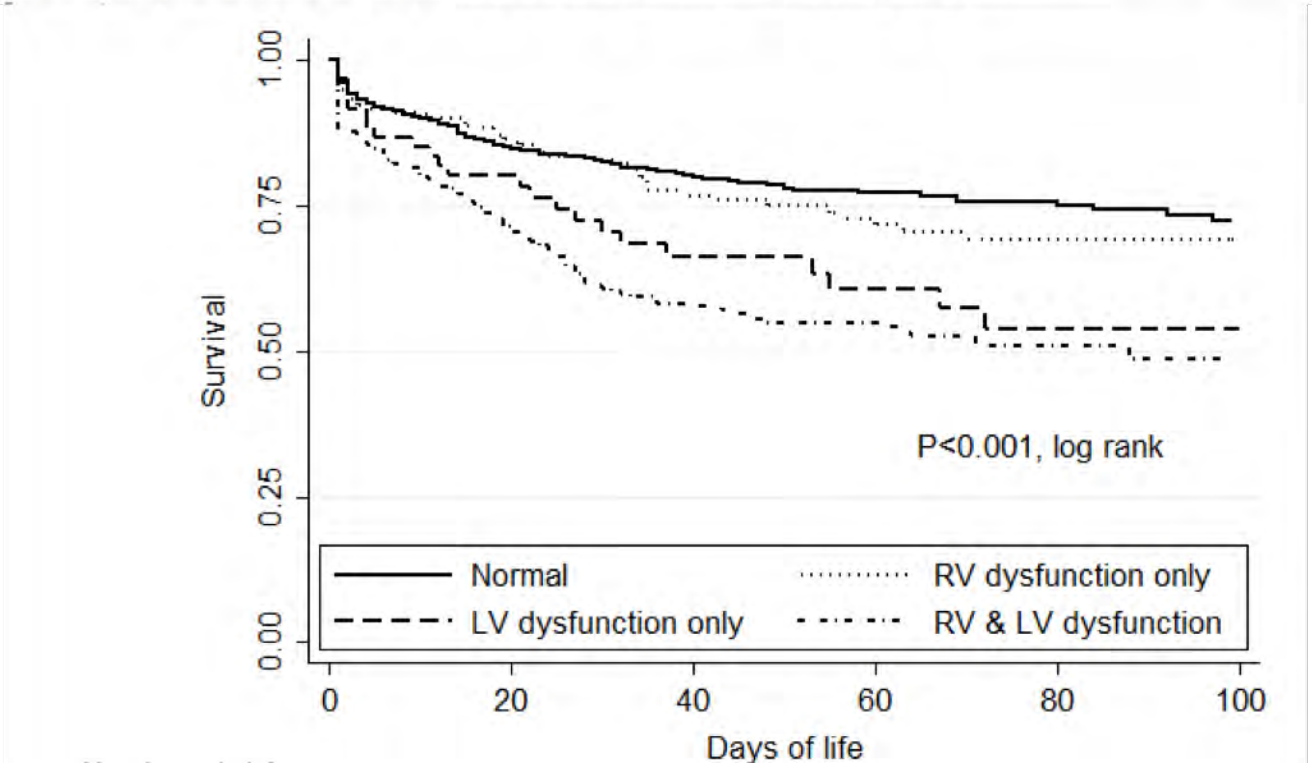


LV dysfunction significantly associated with ECMO and non-survival

J Peds, 2018

Ventricular Dysfunction is a Critical Determinant of Mortality in Congenital Diaphragmatic Hernia

Neil Patel , Pamela A Lally , Florian Kipfmueller , Anna Claudia Massolo , Matias Luco , Krisa P Van Meurs , Kevin P Lally , Matthew T Harting , and , for the Congenital Diaphragmatic Hernia Study Group



AJRCCM 2019

Ventricular Dysfunction is a Critical Determinant of Mortality in Congenital Diaphragmatic Hernia

Neil Patel , Pamela A Lally , Florian Kipfmueller , Anna Claudia Massolo , Matias Luco , Krisa P Van Meurs , Kevin P Lally , Matthew T Harting , and , for the Congenital Diaphragmatic Hernia Study Group

NHS Greater Glasgow and Clyde

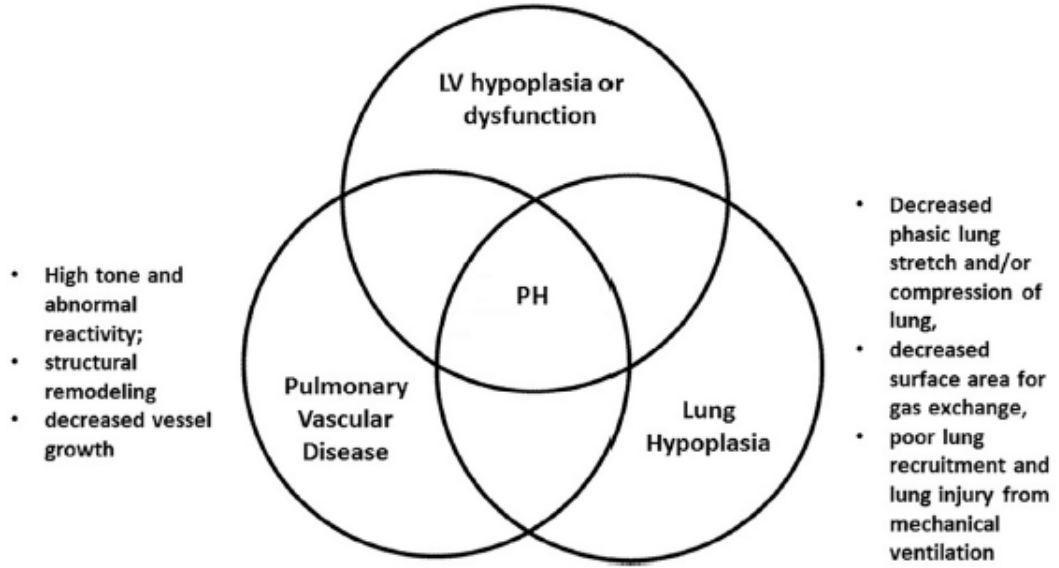
Variable		Multivariate analysis			
		HR	SE	P	95% CI
Birth weight <3kg		1.44	0.22	0.020	1.06 – 1.95
Defect Stage C/D		3.37	0.92	<0.001	1.97 – 5.77
Liver in chest		1.63	0.34	0.018	1.09 – 2.46
Cardiac Dysfunction	RV only	1.02	0.23	0.92	0.66 – 1.58
	LV only	1.90	0.52	0.020	1.11 – 3.26
	RV & LV	1.59	0.29	0.011	1.11 – 2.27

AJRCCM 2019

The Left Ventricle in Congenital Diaphragmatic Hernia: Implications for the Management of Pulmonary Hypertension

John P. Kinsella, MD[1], Robin H. Steinhorn, MD[2], Mary P. Mullen, MD[3], Rachel K. Hopper, MD[4], Roberta L. Keller, MD[5], D. Dunbar Ivy, MD[6], Eric D. Austin, MD[7], Usha S. Krishnan, MD[8], Erika B. Rosenzweig, MD[8], Jeffrey R. Fineman, MD[9], Allen D. Everett, MD[10], Brian D. Hanna, MD[11], Tilman Humpl, MD[12], J. Usha Raj, MD[13], and Steven H. Abman, MD[14], on behalf of the Pediatric Pulmonary Hypertension Network (PPHNet)

- Pulmonary Venous Hypertension
- Decreased cardiac output
- Pulmonary edema, worsened with PH drug therapy



J Peds, 2018

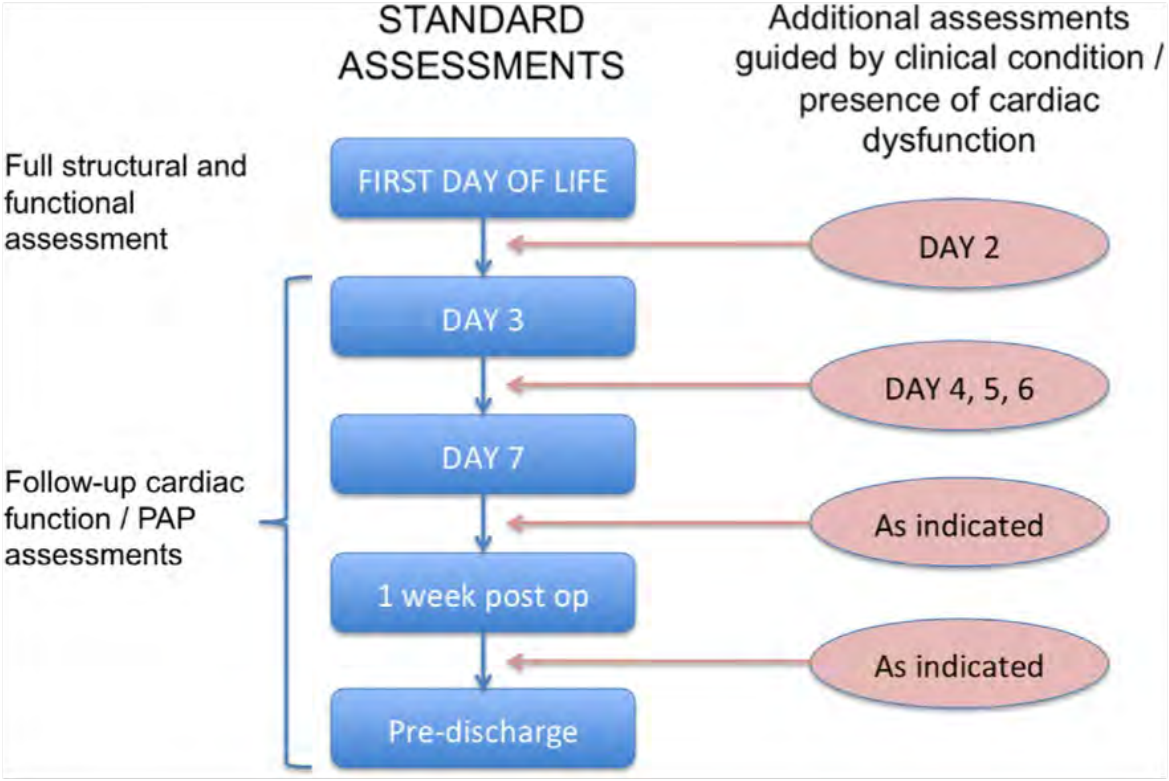
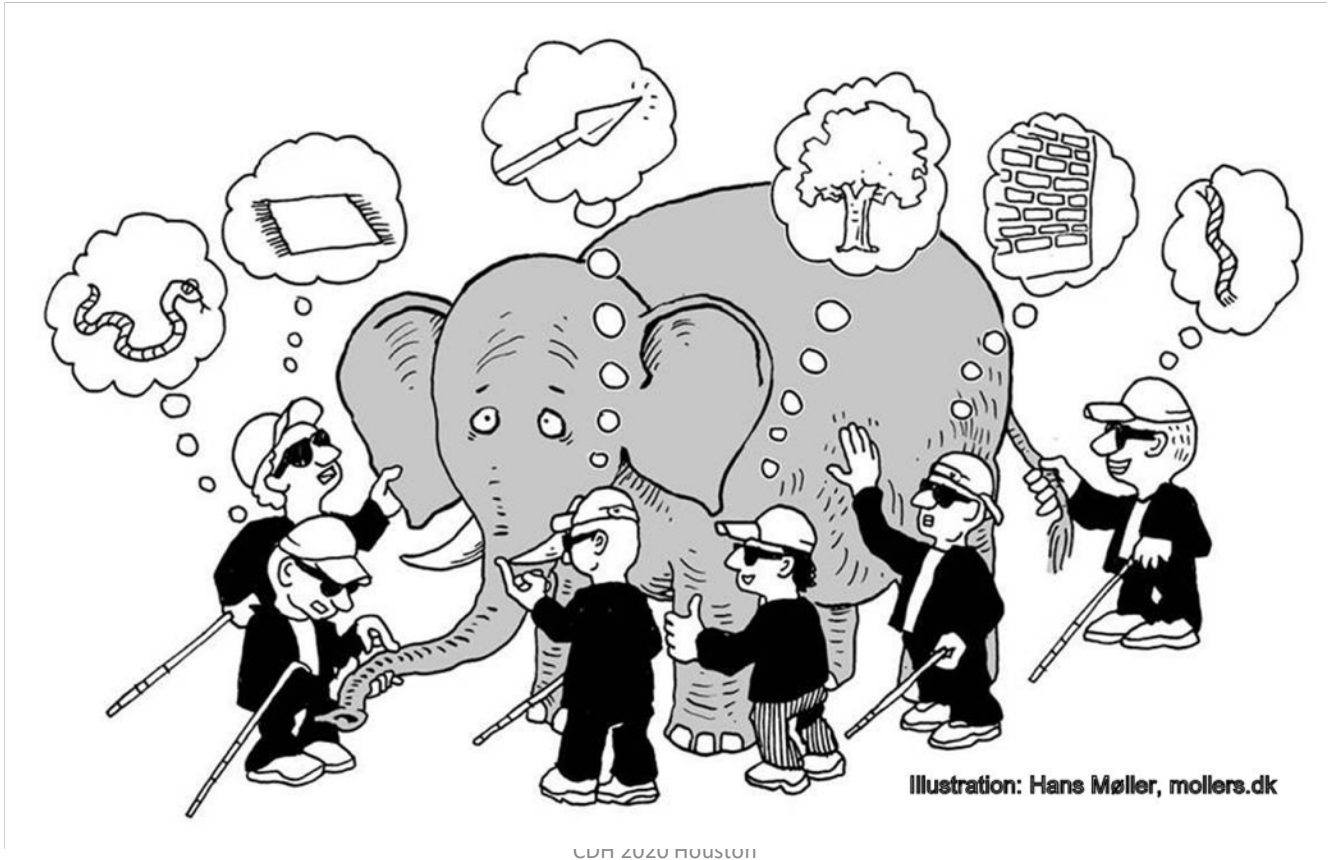
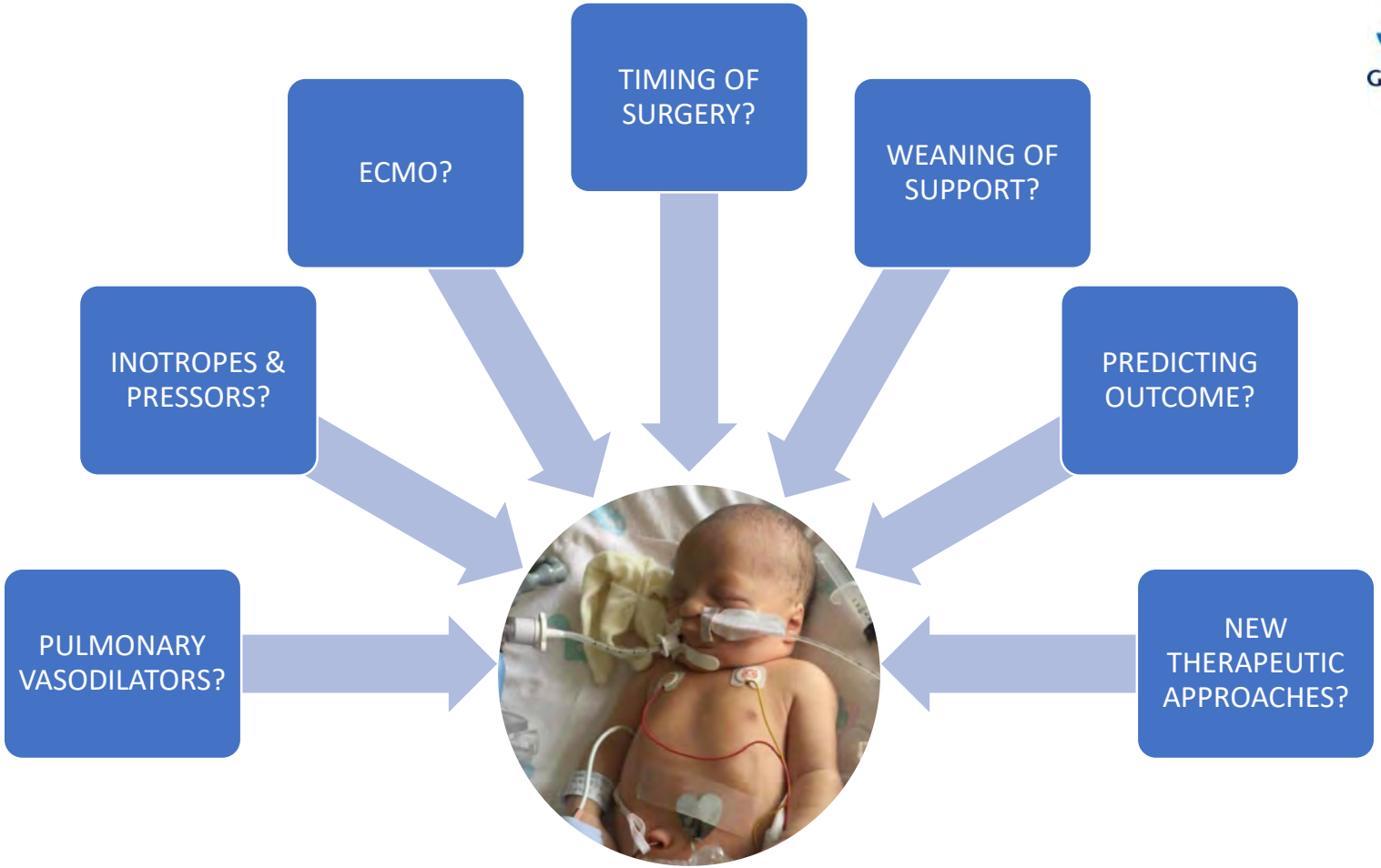


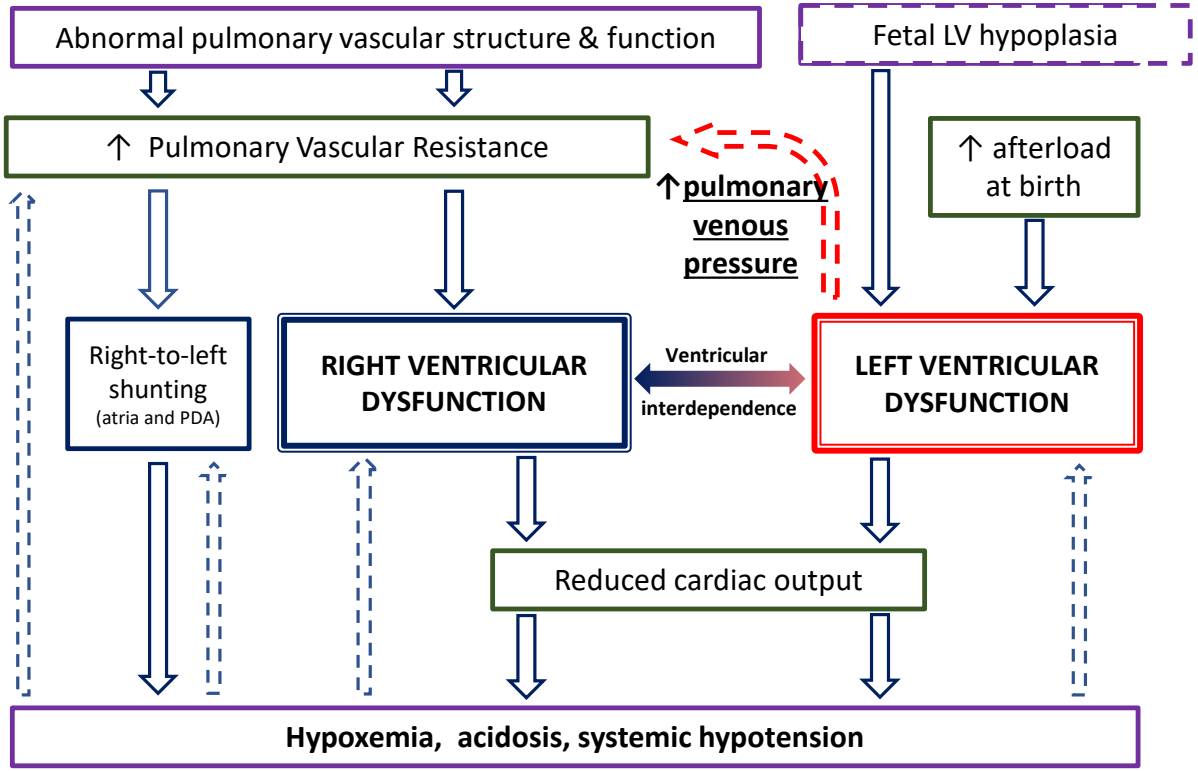
Fig. 3. Example protocol for timing of cardiac function assessment in CDH.

The Blind Men of Indostan and the Elephant in the Echo Lab

Lawrence G. Rudski, MDCM, FACC, FASE, and Jonathan Afilalo, MD, MSc, FRCPC, *Montreal, Quebec, Canada*




TIMING OF SURGERY?
ECMO?
WEANING OF SUPPORT?
INOTROPES & PRESSORS?
PREDICTING OUTCOME?
PULMONARY VASODILATORS?
NEW THERAPEUTIC APPROACHES?


Abnormal pulmonary vascular structure & function
Fetal LV hypoplasia
↑ Pulmonary Vascular Resistance
↑pulmonary venous pressure
↑ afterload at birth
Right-to-left shunting (atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION
Reduced cardiac output
Hypoxemia, acidosis, systemic hypotension

Implications of Atrial-Level Shunting by Echocardiography in Newborns with Congenital Diaphragmatic Hernia

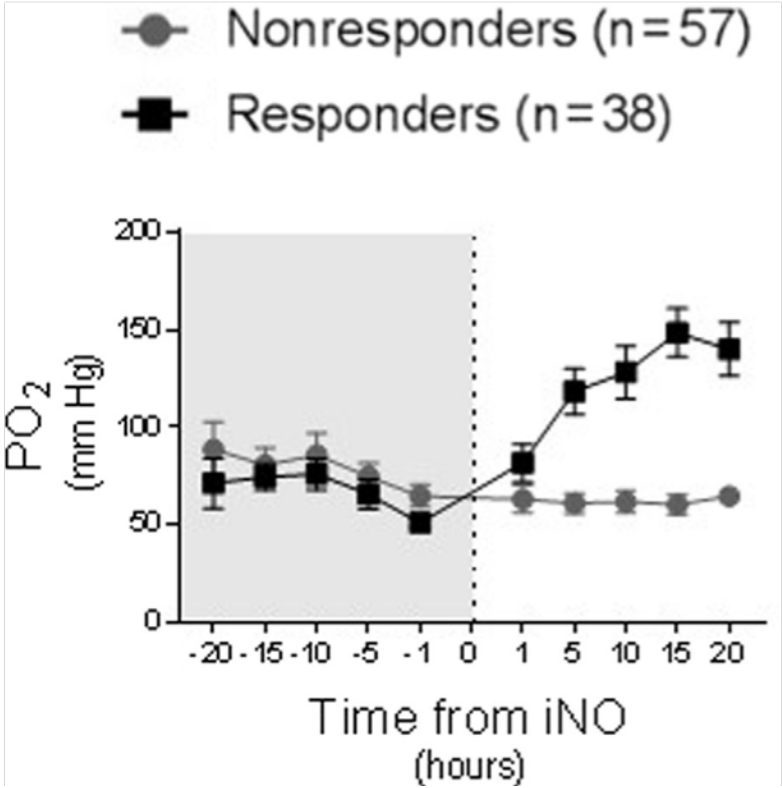
Melissa Wehrmann, MD[1], Sonali S. Patel, MD, PhD[1], Caitlin Haxel, MD[1,2], Courtney Cassidy, RDCS[1], Lisa Howley, MD[1,3], Bettina Cuneo, MD[1], Jason Gien, MD[4], and John P. Kinsella, MD[4]

NHS Greater Glasgow and Clyde

Table II. Characteristics, outcomes, and echocardiographic measurements grouped by atrial-level shunt direction

Variables	Right-to-left n	Right-to-left Value	Left-to-right n	Left-to-right Value	*P* value
Characteristics and outcomes					
Percent predicted lung volume, %, mean ± SD	7	14.71 ± 8.30	24	24.63 ± 8.23	.0091
Liver up, n (%)	9	9 (100)	42	23 (54.8)	.0109
ECMO during hospitalization, n (%)	9	4 (44.4)	42	9 (21.4)	.1505
Survival to discharge, n (%)	9	6 (66.7)	42	38 (90.5)	.0596
Echocardiographic measurements					
LV 2D area (diastole) *z*-score, mean ± SD	9	−1.89 ± 0.71	37	−1.38 ± 0.90	.1179
LV 2D area (systole) *z*-score, mean ± SD	9	−1.42 ± 0.95	37	−0.49 ± 1.24	.0415
LV myocardial performance index, mean ± SD	5	0.18 ± 0.08	36	0.50 ± 0.66	.0088
RV myocardial performance index, mean ± SD	4	0.49 ± 0.03	28	0.54 ± 0.24	.3719
Ductus arteriosus direction, n (%)*	9		39		.0002
Right-to-left		6 (66.7)		3 (7.7)	
Left-to-right		0		5 (12.8)	
Bidirectional		3 (33.3)		31 (79.5)	

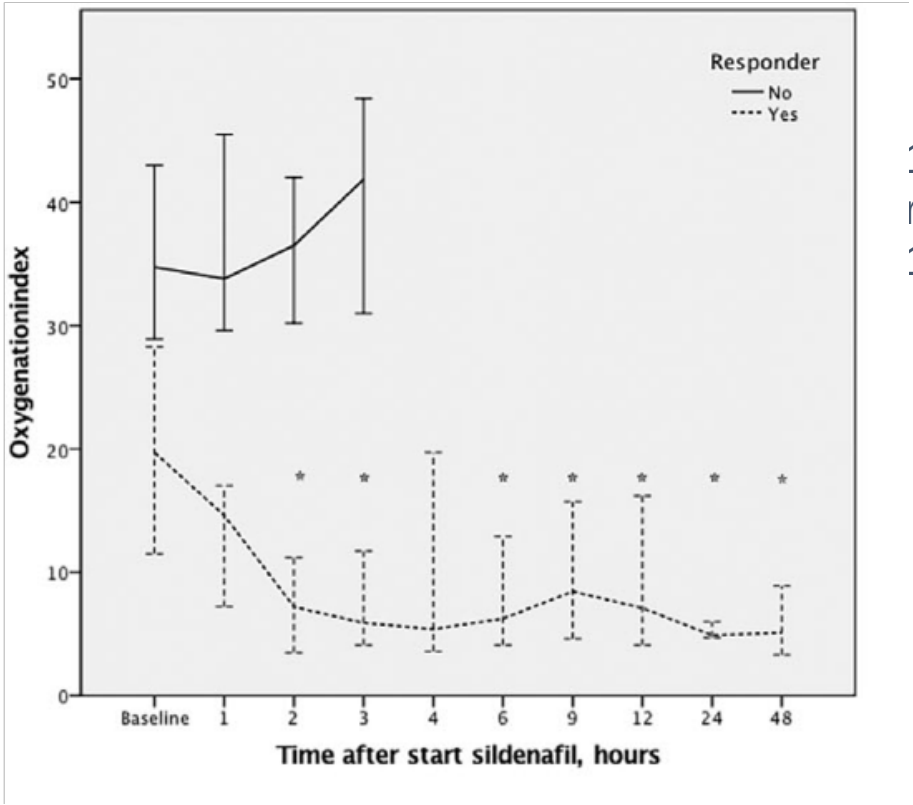
Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension



Lawrence et al, J Peds 2019

Continuous intravenous sildenafil as an early treatment in neonates with congenital diaphragmatic hernia

Florian Kipfmueller MD[1] | Lukas Schroeder MD[1] | Christoph Berg MD[2] | Katrin Heindel MD[1] | Peter Bartmann MD, PhD[1] | Andreas Mueller MD[1]



15 non-responders
11 responders

Ped Pulmonol 2018

Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension

NHS Greater Glasgow and Clyde

Table I. Characteristics of initial responders and nonresponders to iNO therapy

Patient characteristics	Nonresponder to iNO therapy (n = 57)	Responder to iNO therapy (n = 38)	*P* value
Male sex (n, %)	28 (49%)	23 (61%)	.30
Gestational age (wk)	38.0 ± 0.2	38.4 ± 0.2	.43
Birthweight (kg)	3.2 ± 0.1	3.2 ± 0.1	.57
LHR	0.97 ± 0.05	1.01 ± 0.04	.07
LHR (observed to expected lung to head ratio)	0.37 ± 0.02	0.34 ± 0.02	.59
Liver up position CDH (n, %)	37 (65%)	25 (66%)	>.99
Right sided CDH (n, %)	10 (18%)	2 (7%)	.32
PaO_2 at initiation (mm Hg)	65 ± 6	51 ± 3	.27
FiO_2 at initiation (%)	76 ± 4	78 ± 4	.71
P/F at initiation (mm Hg)	121 ± 16	82 ± 10	.45
A-a gradient at initiation (mm Hg)	397 ± 28	422 ± 30	.77
pH at initiation	7.18 ± 0.02	7.20 ± 0.02	.63
All right to left shunting on echo (n, %)	19 (37%) (n = 52)	8 (22%) (n = 37)	.16
Bowing ventricular septum (n, %)	50 (56%)	15 (43%)	.14
LV dysfunction (n, %)	14 (27%) (n = 52)	3 (8%)	.03

Lawrence et al, J Peds 2019

Use of Milrinone to Treat Cardiac Dysfunction in Infants with Pulmonary Hypertension Secondary to Congenital Diaphragmatic Hernia:

		Duration of milrinone therapy		
		pre	12–24 h post	48–72 h post
PDA flow velocity, m/s	left to right	0.8 (1.1)	0.8 (0.4)	0.5 (0.13)
	right to left	1.9 (0.6)	1.3 (0.1)	1.1 (0.3)
FiO_2		0.55 (0.19)	0.47 (0.25)	0.47 (0.43)
Mean airway pressure, cm H_2O		11.8 (4.1)	10.3 (5.8)	8.6 (1.7)
OI		10.6 (5.6)	7.9 (6.2) *	5.1 (2.6)*, **
Mean BP, mm Hg		52.7 (4.3)	53.7 (11.5)	51 (7.3)
Systolic BP, mm Hg		72.6 (6.3)	75 (20.7)	67 (9.9)
Diastolic BP, mm Hg		42.8 (4.2)	43 (6.9)	43 (6.3)

Fig. 1. Early diastolic velocities (E′) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI. * $p < 0.05$.

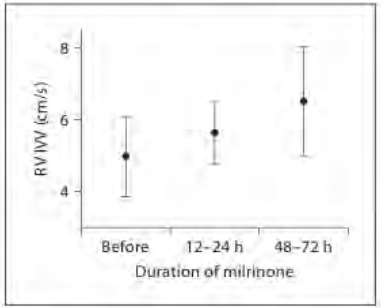


Fig. 2. Isovolumic contraction velocities (IVV) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.

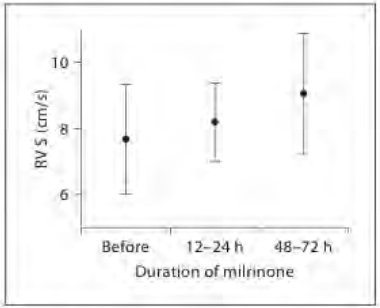
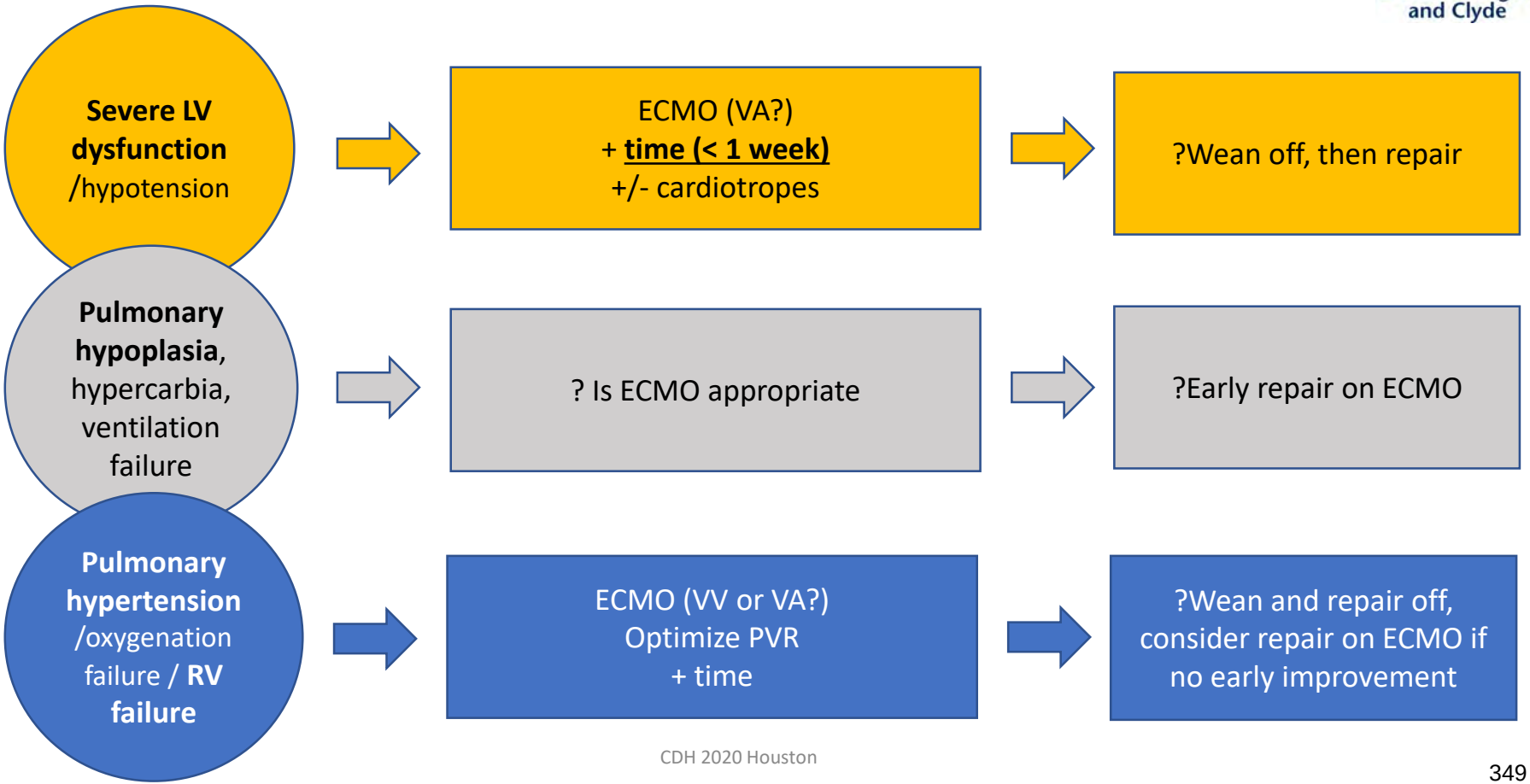


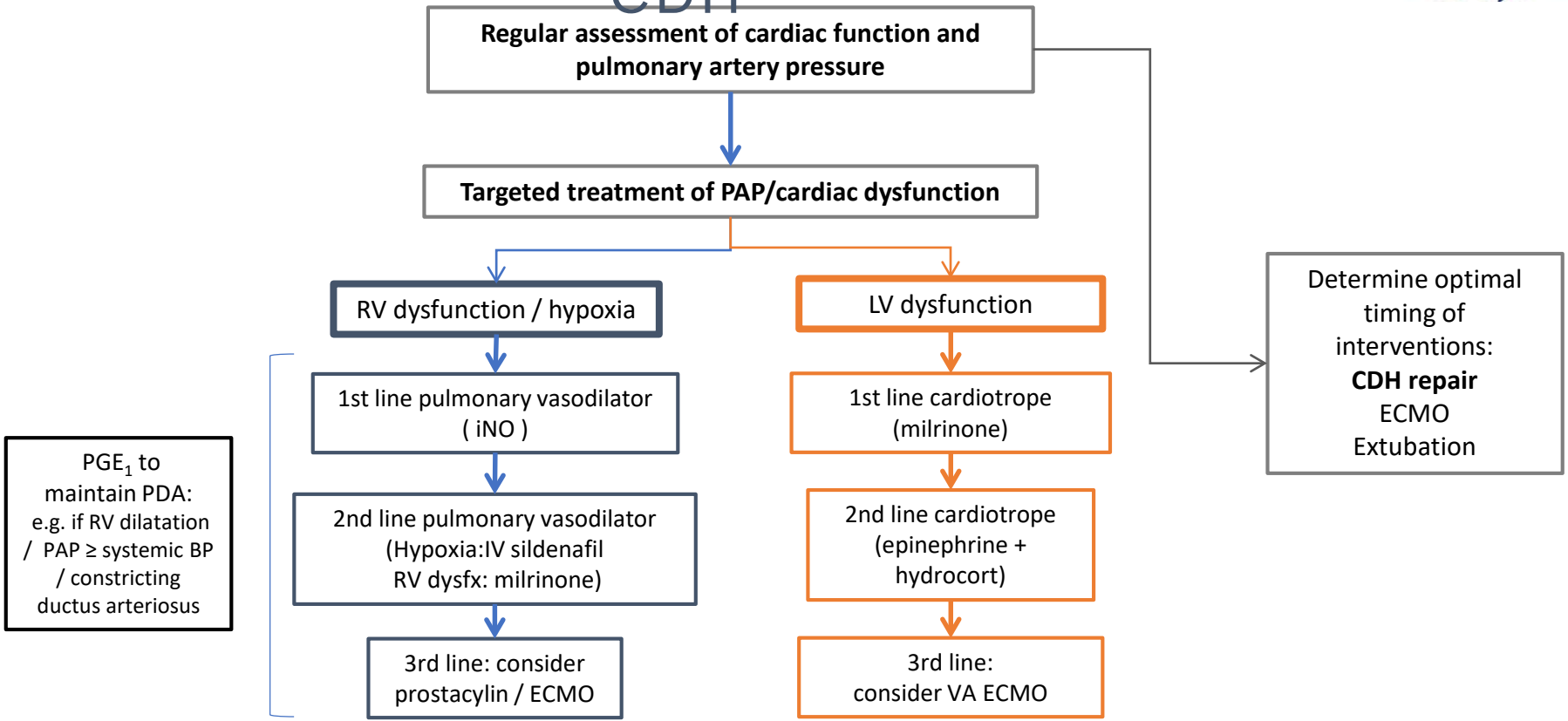
Fig. 3. Systolic ejection velocities (S) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.

Patel Neonatology 2012;102:130–136

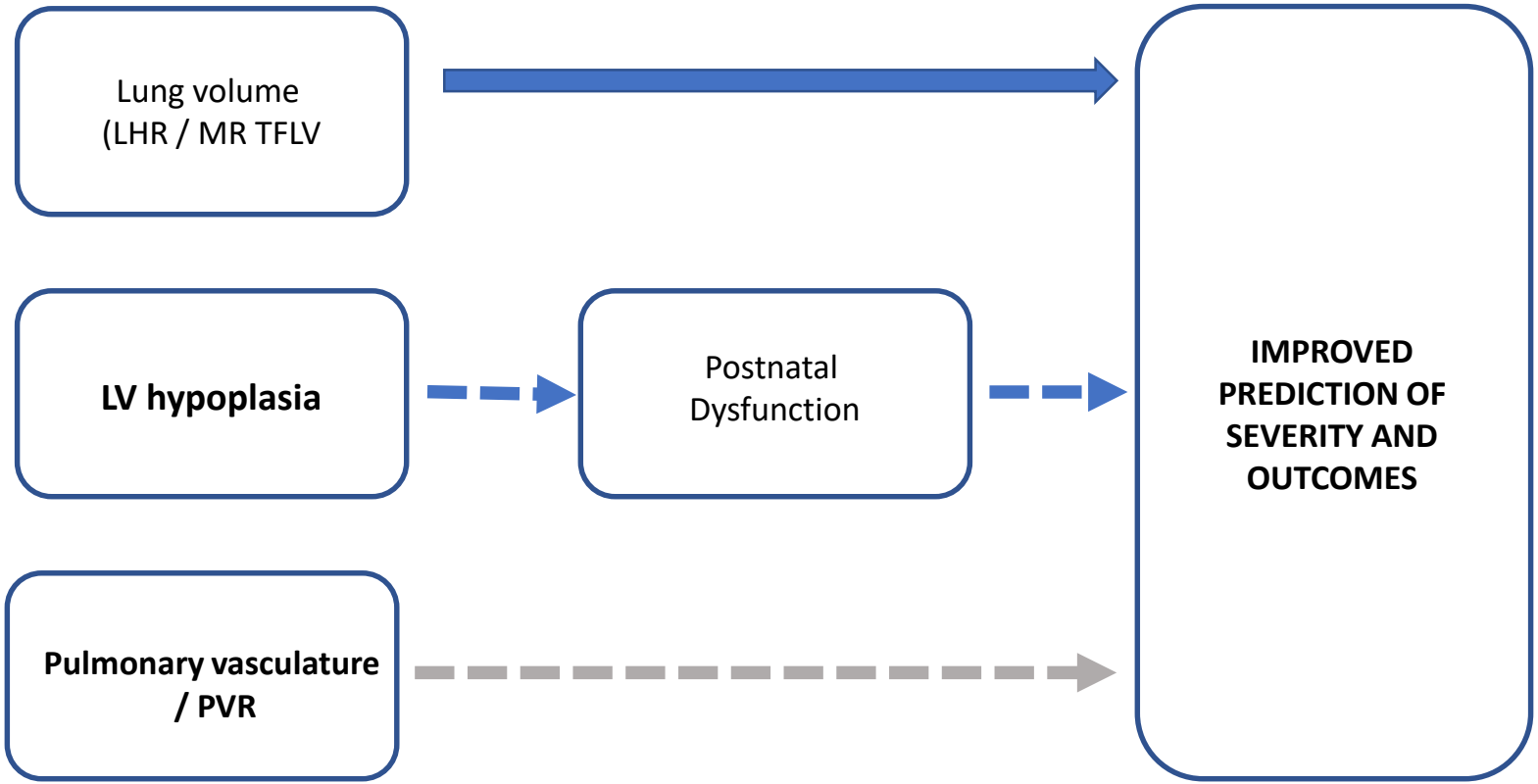
Informing ECMO strategy:



Targeted therapy of PH and cardiac function in CDH



?Improved pre-natal prognostication



Initiating resuscitation before umbilical cord clamping in infants with congenital diaphragmatic hernia: a pilot feasibility trial

NHS Greater Glasgow and Clyde

Table 3 Physiological outcomes

	Trial participants (n=19)	Historical controls (n=19)	P value
Apgar score at 1 min, median (IQR)	5 (3–7)	7 (3–8)	0.51
Apgar score at 5 min, median (IQR)	8 (5–8)	8 (5–9)	0.72
First Haemoglobin, g/dL; mean (SD)	17.6 (1.3)	16.3 (1.9)	0.02
Mean blood pressure 1 hour after birth; mean (SD)*	51.1 (8.5)	44.3 (6.3)	0.008
First blood gas after birth*			
pH, mean (SD)	7.02 (0.15)	7.03 (0.13)	0.74
CO_2, mean (SD)	90 (26)	88 (25)	0.82
Base deficit, mean (SD)	8.9 (3.3)	9.8 (3.8)	0.51
Oxygenation index with first blood gas, median (IQR)	17.5 (12.8–25.5)	16.3 (12.2–22.8)	0.74
Vasopressors (first 48 hours), n (%)	13 (68)	16 (84)	0.45
iNO (first 48 hours), n (%)	9 (47)	11 (58)	0.52
ECMO (first 7 days), n (%)	7 (37)	4 (21)	0.48
Mortality (first 7 days), n (%)	0	1 (5)	>0.99

Foglia EE, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2019;

Thanks to

Staff and patients of the:
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Royal Children's Hospital Melbourne

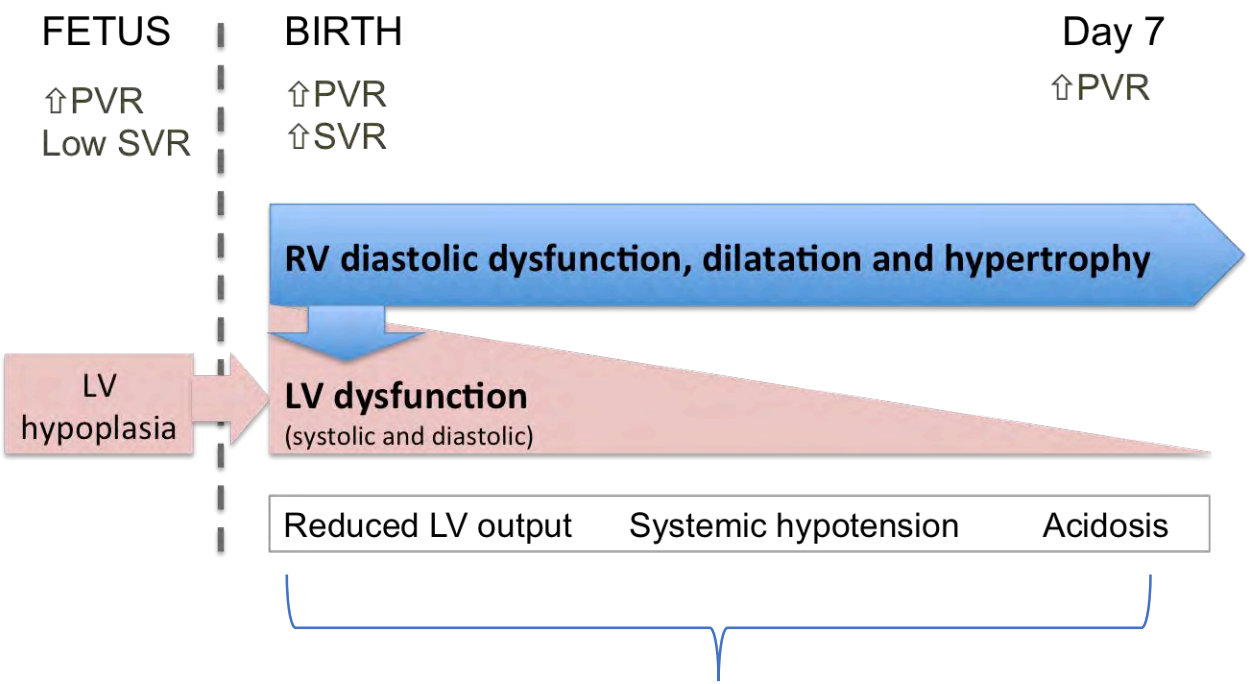
Claudia Massolo
Florian Moenkemeyer
Florian Kipfmueller
Lindsey Hunter
Carl Davis, Morag Liddell
Kevin Lally, Pam Lally, Matt Harting
CDH Study Group and Registry
CDH Euroconsortium
CDH UK







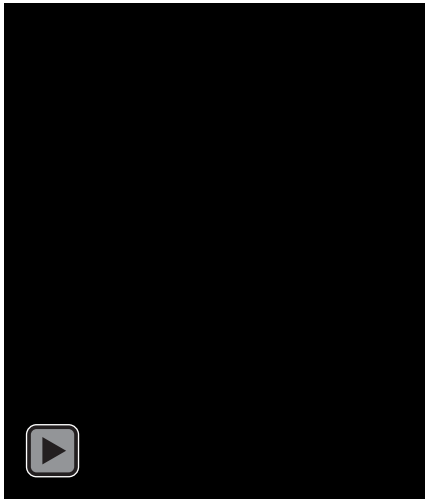
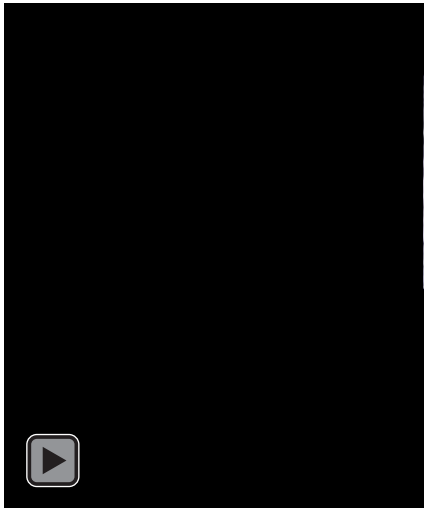
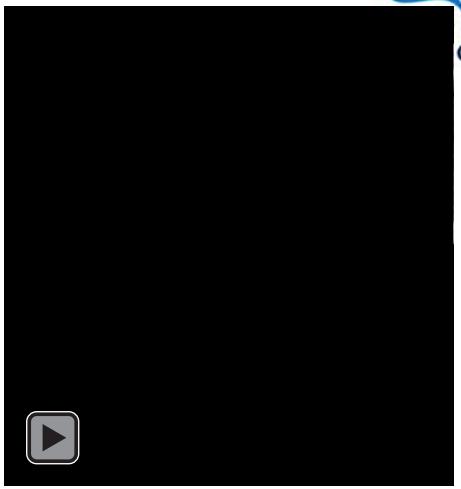
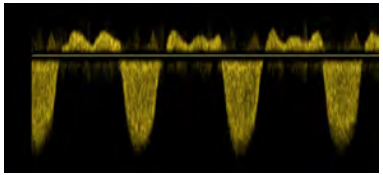
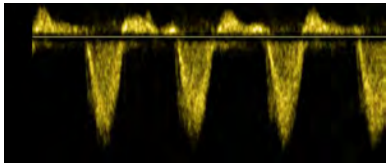
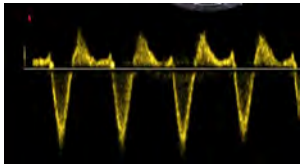




Associated with outcomes:

- Duration ventilation
- Length of stay
- Survival
- ECMO

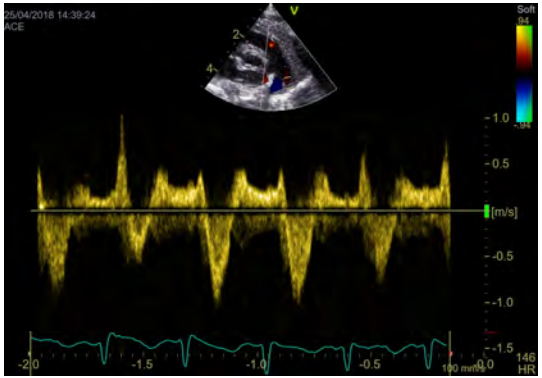
N. Patel, F. Kipfmueller / Seminars in Pediatric Surgery 26 (2017)

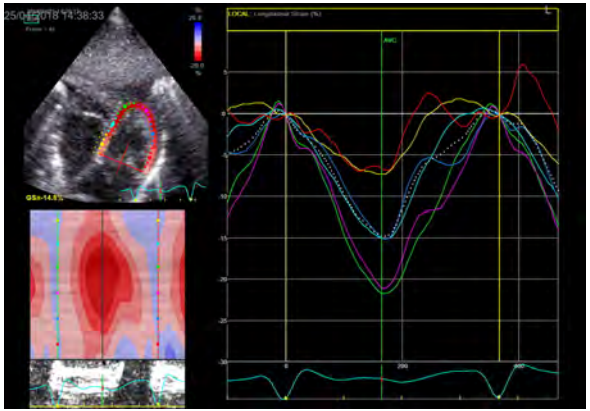
	Day 1	Day 3	Day 5
4 chamber view			
PDA flow			
STE Strain	RV GLS -12% LV GLS [illegible]%	RV GLS -12% [illegible]	RV GLS -16% [illegible]S -20%

Milrinone and epinephrine

IV sildenafil

Cardiac function and timing of repair?



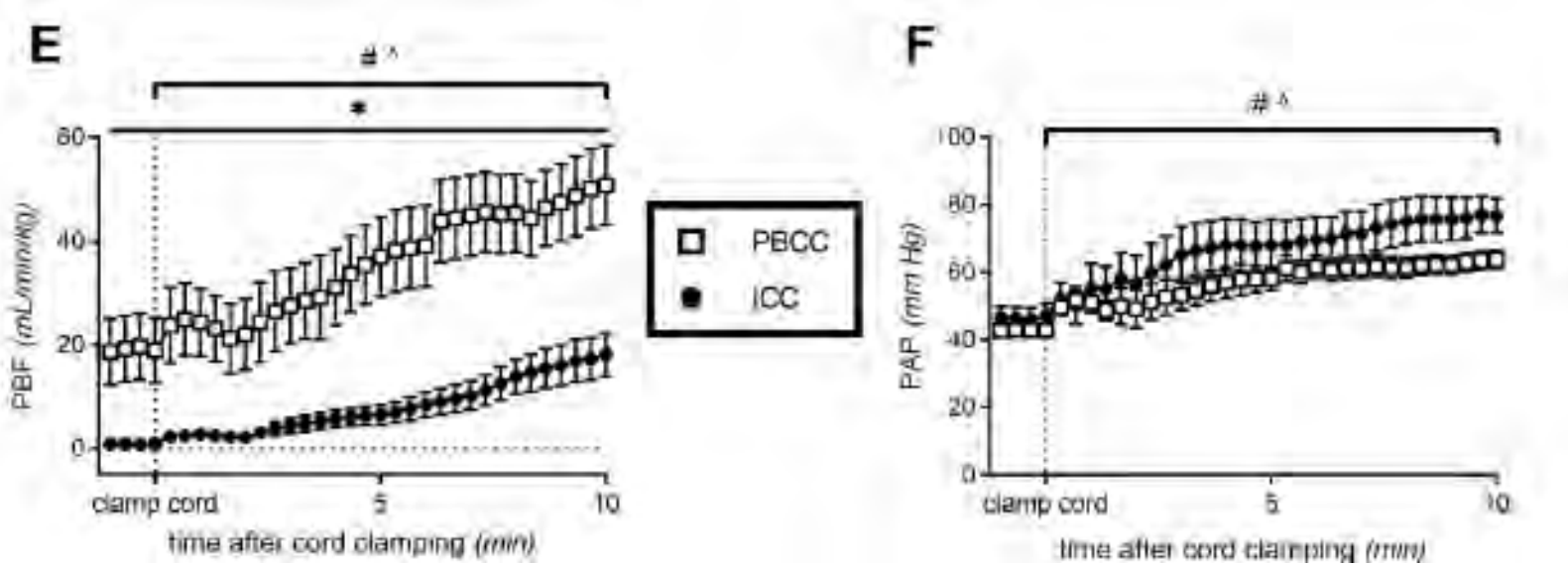


- 38/40. 3kg. L CDH. Day 1 of life
- Conventional ventilation: 22/5, FiO_2 0.35. Sats 96/97%. BP 45/32 (36)
- Cardiac function improved spontaneously by day 3 of life
- Primary repair, day 3. Stage “A” defect

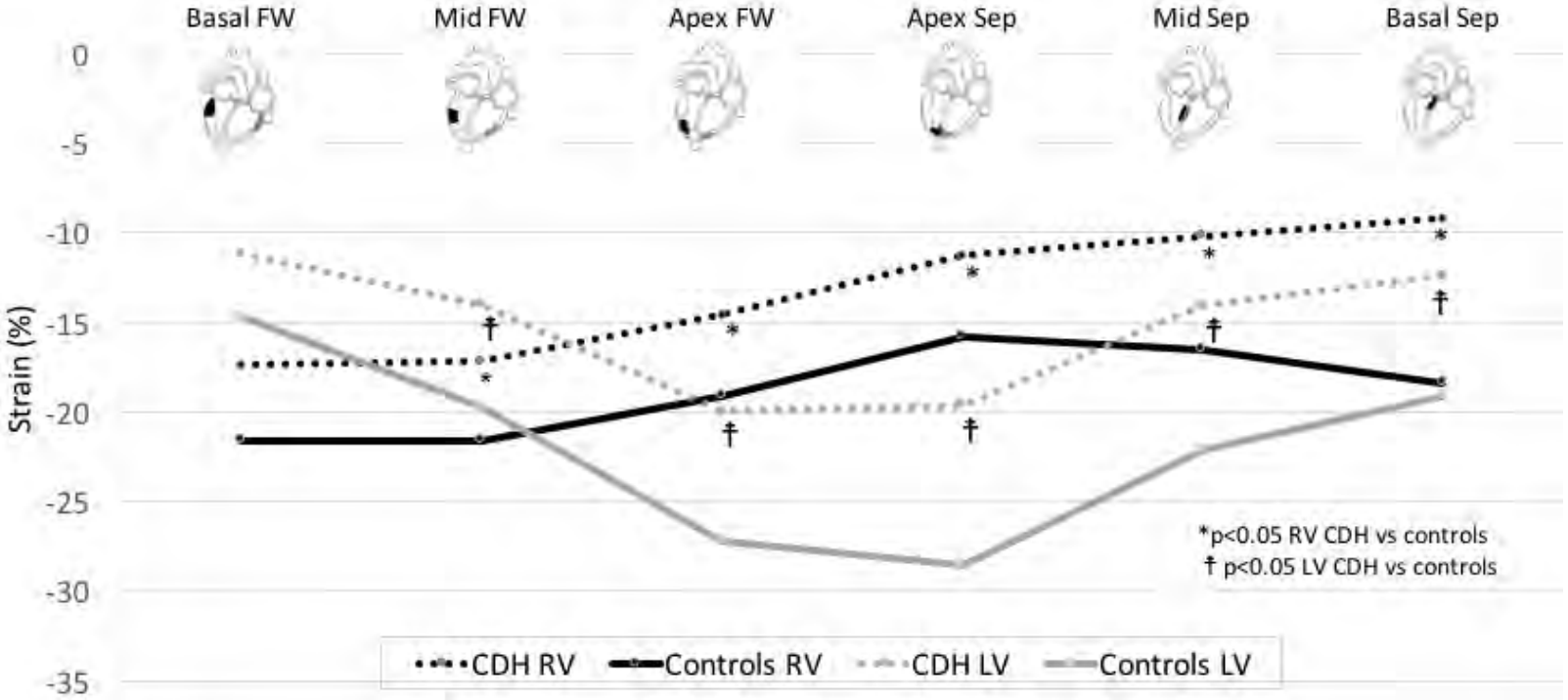
New therapies in CDH: Physiological based cord clamping?

Physiologically based cord clamping improves cardiopulmonary haemodynamics in lambs with a diaphragmatic hernia

Aidan J Kashyap,[1,2] Ryan J Hodges,[1,3] Marta Thio,[4,5] Karyn A Rodgers,[1,2] Ben J Amberg,[1,2] Erin V McGillick,[1,2] Stuart B Hooper,[2,6] Kelly J Crossley,[1,2] Philip L J DeKoninck[6,7]



Segmental longitudinal strain in the RV and LV, in CDH and controls



Massolo et al, Neonatology 2019

CDH Treatment and Outcomes: What we've learned.

David W. Kays, MD
Director Center for Congenital Diaphragmatic Hernia
Director Extracorporeal Life Support
Johns Hopkins All Children's Hospital

JOHNS HOPKINS
All Children's Hospital

Background

- Trained in Pediatric Surgery at Columbia University
  - Credit Charlie Stolar
  - Credit Jen Wung
  - Credit Jay Wilson
  - Credit Kevin Lally
  - Thank Matt Harting and the CDH community for asking me to speak

I have no disclosures

- >450 CDH patients
- 321 at University of Florida
  - 1992 - 2015
- > 140 patients at Johns Hopkins All Children's Hospital
  2016 - present

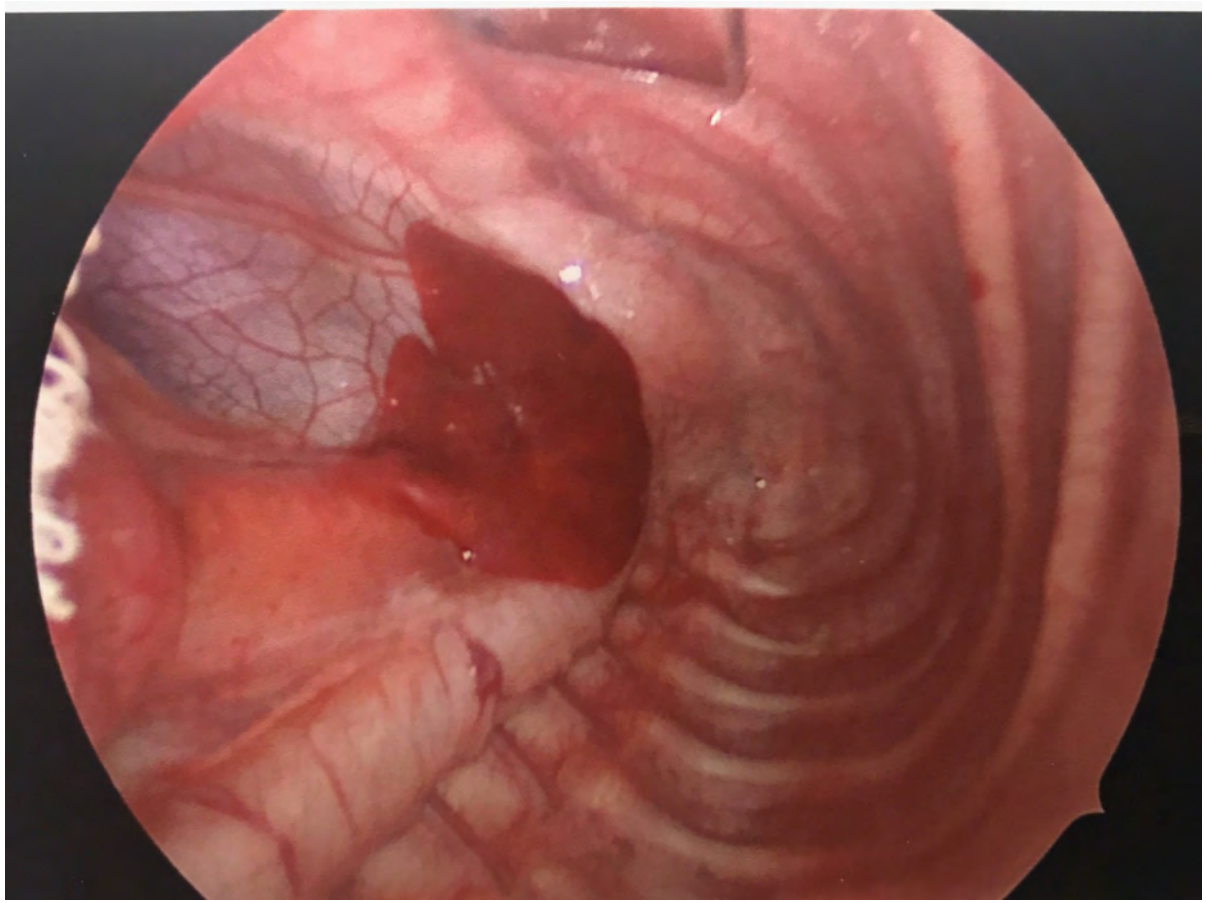
Outline

- Describe our population
  - 101 consecutive CDH cases at JHACH
  - Describe them by risk stratifiers
    - Anatomy, lung volumes, physiology, associated anomalies
- Describe the care paradigm
  - Foundational principles
  - Ventilation
  - **Focus on ECMO**
  - **Focus on Repair**

Describe Outcomes

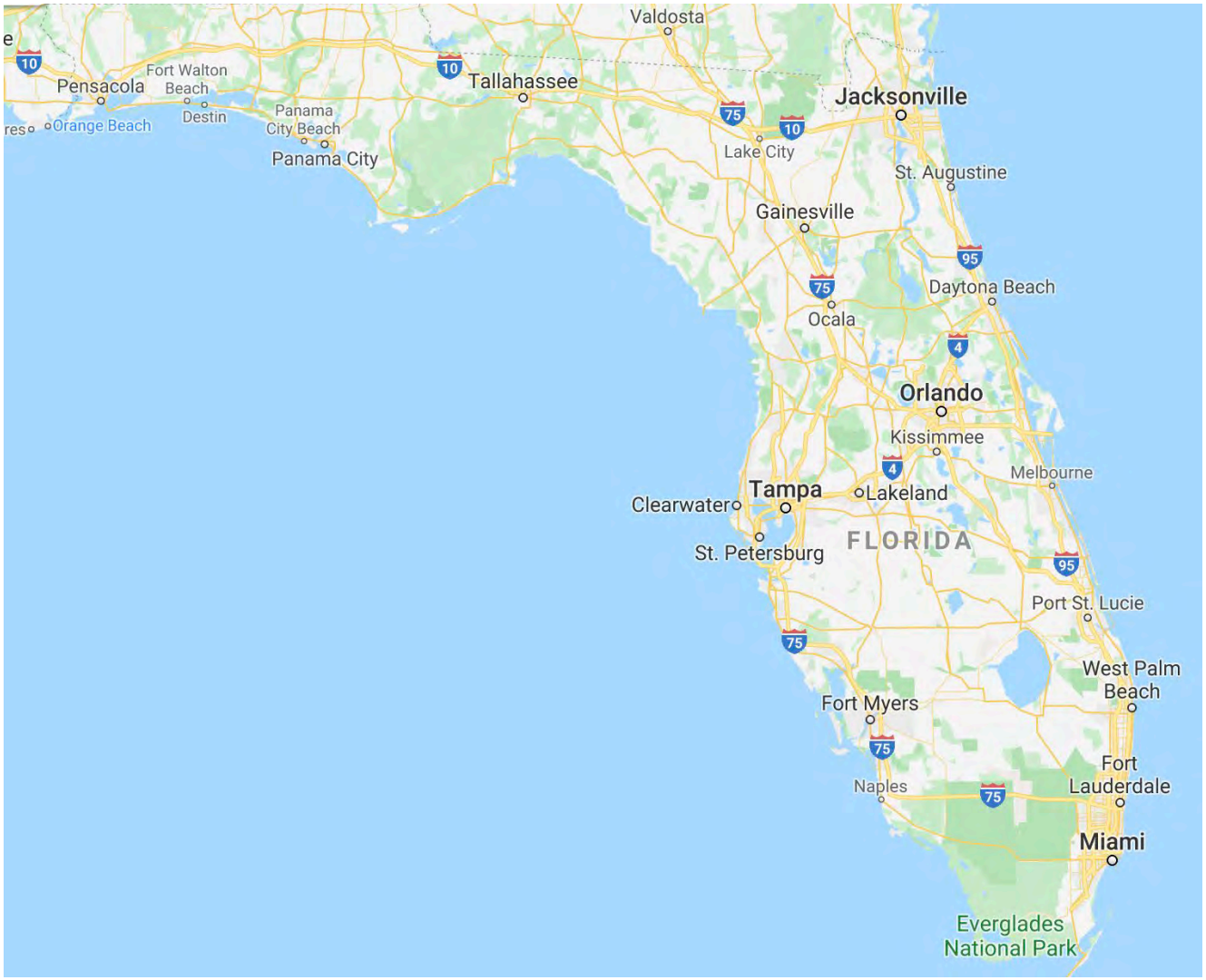
- Survival
- Time in hospital
- Outcomes
  - Neuro imaging outcomes (gross)
- Conclusions

This is the disease: Pulmonary Hypoplasia (highly severe)



CDH Referral Pattern

High volume Referral Center
High percentage of prenatally diagnosed and evaluated patients
Increased Severity


Valdosta
Pensacola
Fort Walton Beach
Destin
Orange Beach
Panama City Beach
Panama City
Tallahassee
Jacksonville
Lake City
St. Augustine
Gainesville
Daytona Beach
Ocala
Orlando
Kissimmee
Melbourne
Tampa
Lakeland
Clearwater
St. Petersburg
FLORIDA
Port St. Lucie
West Palm Beach
Fort Myers
Naples
Fort Lauderdale
Miami
Everglades National Park

Johns Hopkins All Children's St Petersburg, FL

Lessons Learned, treatments refined

- >450 CDH patients
- 321 at University of Florida
  - 1992 - 2015
- > 140 patients at Johns Hopkins All Children's Hospital
  2016 - present

Analogy: Golf

- Golf is a HARD game
- To succeed: ALL ASPECTS of your game need to be good
  - Drives
  - Long irons
  - Short irons
  - Chipping
  - Putting
  - Rescue

  - One bad shot can ruin any hole

CDH care is hard.

To succeed at CDH care, it's not just one thing.
There is no single "secret"

5 major lessons learned

-Lungs: the primary key to survival
-Repair: the second key to survival
-ECMO: Critical to save the worst
-Must do Better ECMO
-Risk stratification: know your patient
-Offer your best therapy to your sickest patients
-Belief: they do have enough lung to survive

Detrimental Effects of Standard Medical Therapy in Congenital Diaphragmatic Hernia

David W. Kays, MD, Max R. Langham, Jr., MD, Daniel J. Ledbetter, MD, and James L. Talbert, MD

From the Department of Surgery, Division of Pediatric Surgery, University of Florida, and The Shands Children's Hospital at the University of Florida, Gainesville, Florida

Hypothesis:

- Hyperventilation/alkalosis is harmful to CDH patients
- Elimination of this therapy will result in improved survival
- Prospective change in therapy in August, 1992

Annals of Surgery. 1999. 230(3) 340-351
Kays, Langham, Ledbetter, and Talbert

CDH: Treatment Strategy

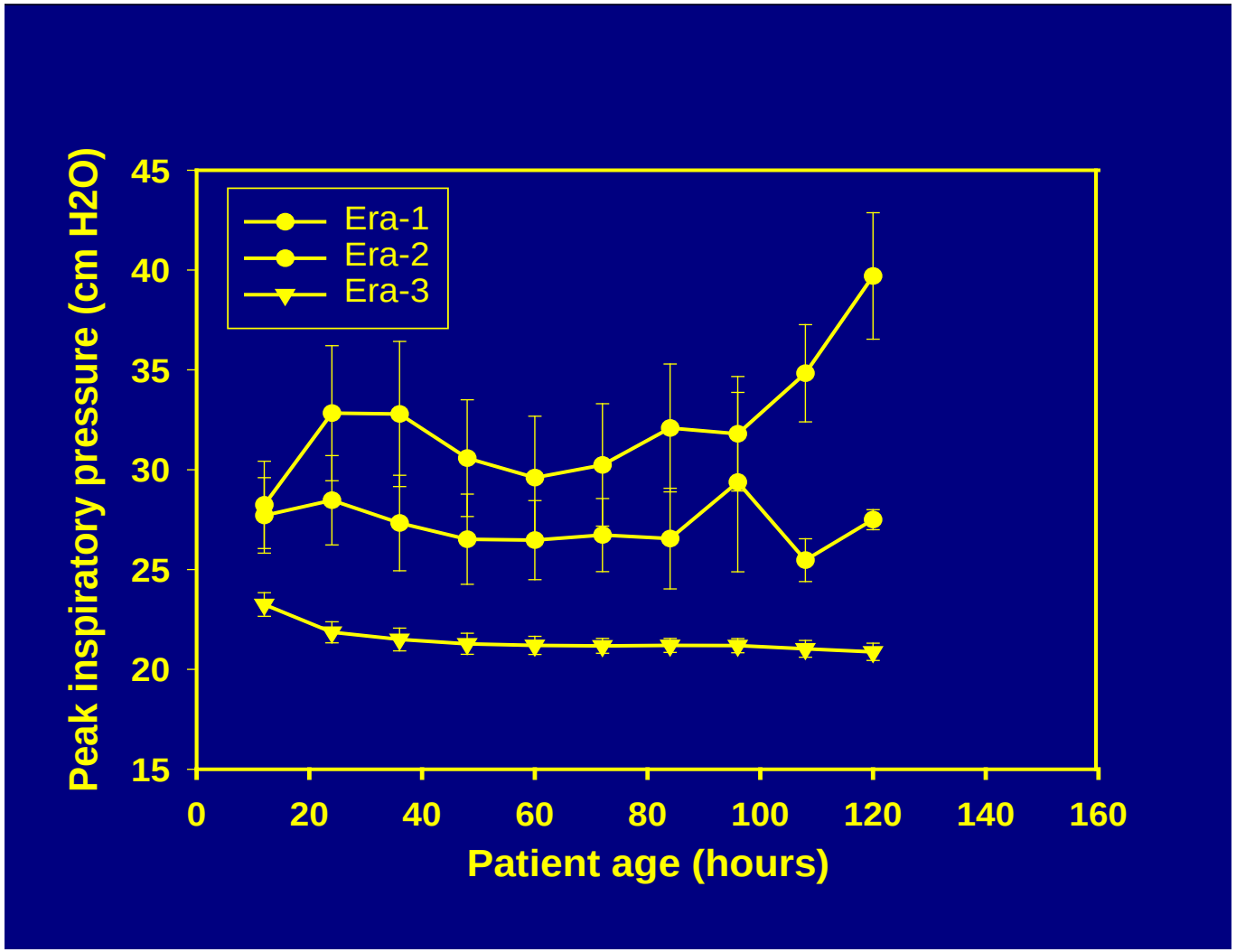
- Light to moderate sedation (no paralysis)
- Conventional SIMV pressure-limited ventilation with rate set to patient comfort and clinical state
- Lowest pressure which provides adequate chest movement (usually 20 - 24 cm H2O)
- Hyperventilation and alkalosis are strictly avoided

Annals of Surgery. 1999. 230(3) 340-351

Indications for ECMO

- Inability to maintain and insure adequate oxygen delivery to the brain
  - Pre-ductal sats < 85%
  - NIRS < 50%
  - Despite optimal support

Mean PIP over 120 hours



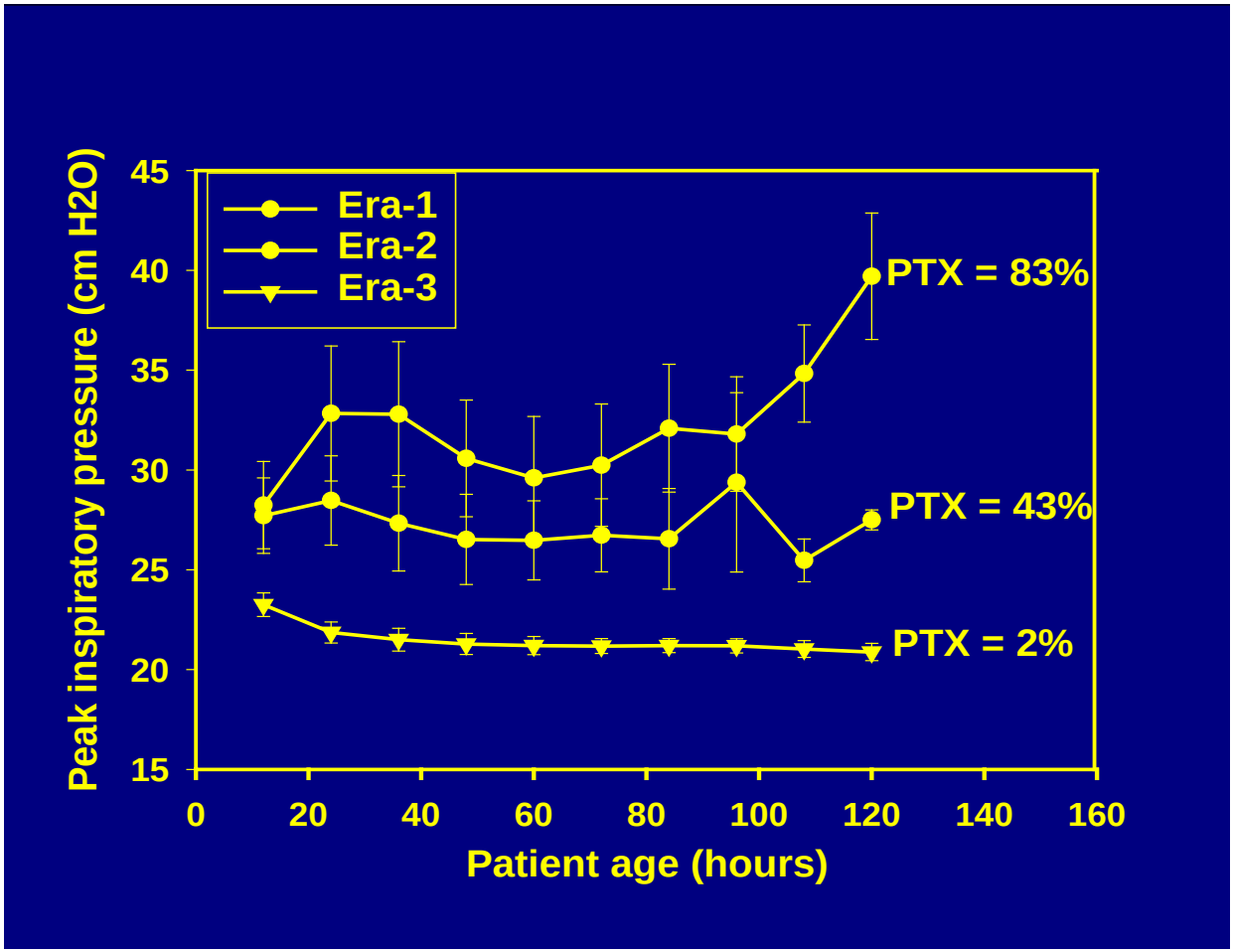
Mean +/- SEM

p<0.05 at all time points

p=0.00001

Time*Era effect

Mean PIP over 120 hours



Mean +/- SEM

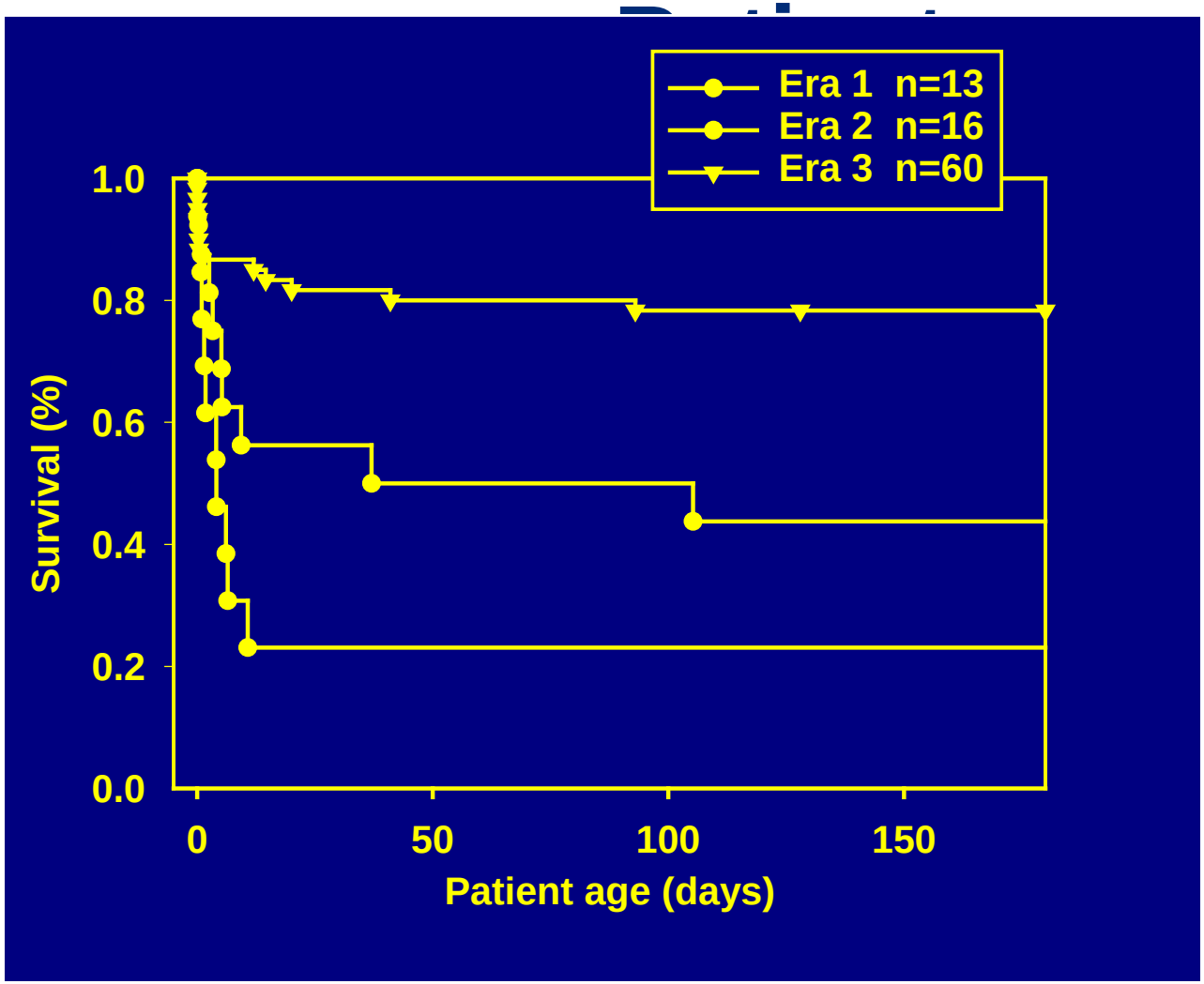
p<0.05 at all time points

p=0.00001

Time*Era effect

Annals of Surgery. 1999. 230(3) 340-351

Survival Curve by Era, All Patients



Survival Graph
p<0.0001

Annals of Surgery. 1999. 230(3) 340-351

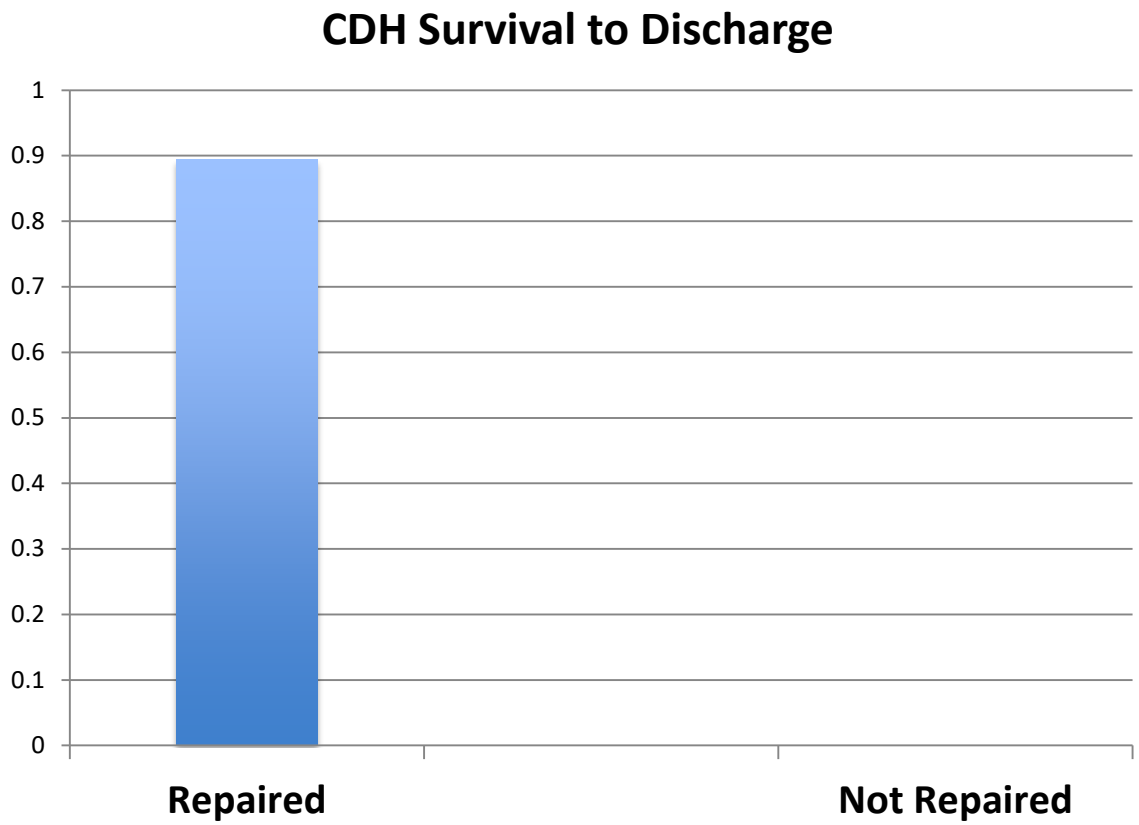
CDH Treatment Fundamental #1

Must eliminate any iatrogenic lung injury:

The number of CDH patients that survive is all about how well we take care of their lungs

CDH Treatment Fundamental #2

- (2) Repair the Hernia (CDH) (n=268)



UF Data: Unpublished

When to repair

- Avoided ECMO:
  - Follow clinical course. When improvement plateaus, repair
  - Day 4 – 7 (mean 118 (+/- 27) hrs

Early repair before ECMO vs Delay and arrive to ECMO unrepaired (w/ opportunity)

	ECMO 1st n=20	Repair first n=22	P= (Mann-Whit)
Survived	**13 (65%)**	**21 (96%)**	**0.018**
Apgar-5	5.9	6.0	.610
CDH SG Surv	52.4	58.2	.364
1st LHR	1.1	1.1	.791
LHR o/e	30.6	28.5	.868
pH-1	7.1	7.1	.319
PO2-1	46.1	46.9	.705
PCO2-1	85.8	77.1	.307
Surv Eq 1	**.79**	**.77**	**.537**
ECMO risk-1	**.81**	**.83**	**.811**
ECMO risk-2	**.77**	**.80**	**.734**
Pred Surv w/o ECMO	**.20**	**.16**	**.801**

Pros and Cons of "Repair before ECMO"

- Pros
  - It works. ECMO runs are easier, cleaner, better.
  - Minimal risk of bleeding
  - New comfort going to ECMO.
  - **Everyone gets repaired.**

- Cons
  - Repair becomes time sensitive:
  - Still concern could increase risk of ECMO

  - BUT WHY ALL THIS EFFORT???

In early 2016, we transitioned from early repair “BEFORE ECMO”, to early repair ON ECMO

- Repair next am
- Ave time to ECMO: 30 hrs (+/- 33)
- Ave time to Repair: 65 hrs (+/- 69)
- Next morning is most common time for repair after initiating ECMO

Principle #3
Do Better ECMO

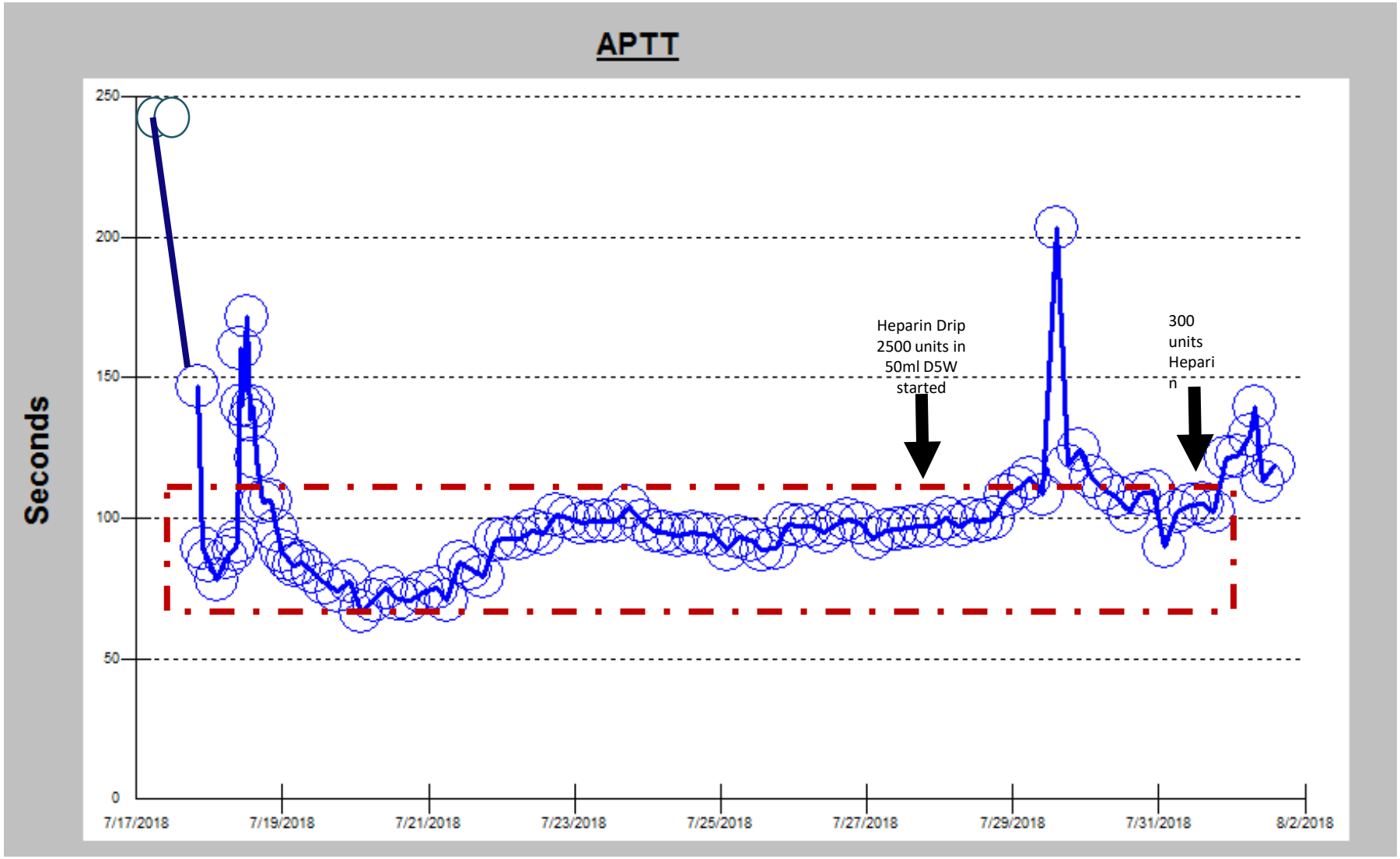
- Decision making and timing
- Better Circuits
- Better anticoagulation
- Better concepts
  - Support and weaning

Better ECMO:

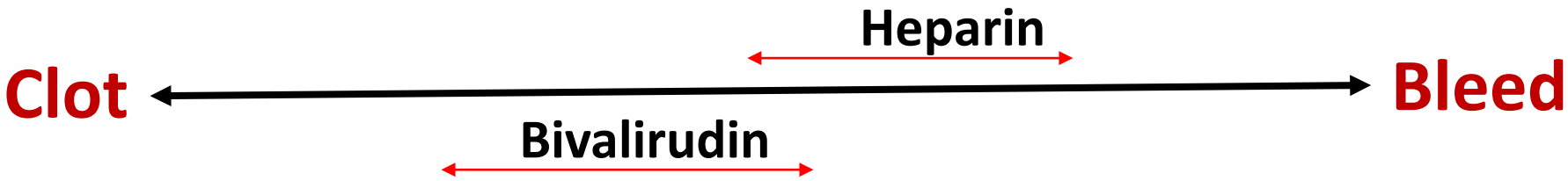
- All VA. (VV doesn’t unload RV nor PA’s)
- Repair early on ECMO. 24 hours
- Better anticoagulation:
  - Bivalirudin

Bivalirudin

- Direct thrombin inhibitor
- Clean
- Predictable
- Efficacy?
  - Bleeding vs clotting?
- Pharmacokinetics
  - 20% renal excretion
  - **80% proteolytic degredation**
    - ? Where ? (important)


APTT
Seconds
250
200
150
100
50
0
7/17/2018
7/19/2018
7/21/2018
7/23/2018
7/25/2018
7/27/2018
7/29/2018
7/31/2018
8/2/2018
Heparin Drip 2500 units in 50ml D5W started
300 units Heparin

Anticoagulant Properties (?)



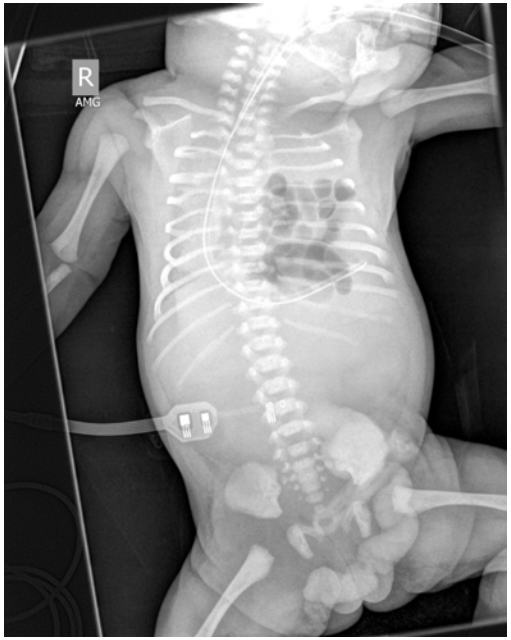
ECMO Pumps

- Roller vs Centrifugal?
- Below 10 kg, not all centrifugal are created equal

Offer your best treatment to your sickest patients. Believe they can survive.

- What are the outcomes in ”the worst” CDH patients?
  - (Buckets A&B)

J Pediatr Surg. 2015 Jun;50(6):893-7
Kays DW, Islam S, Perkins JM, Larson SD, Taylor JA, Talbert JL

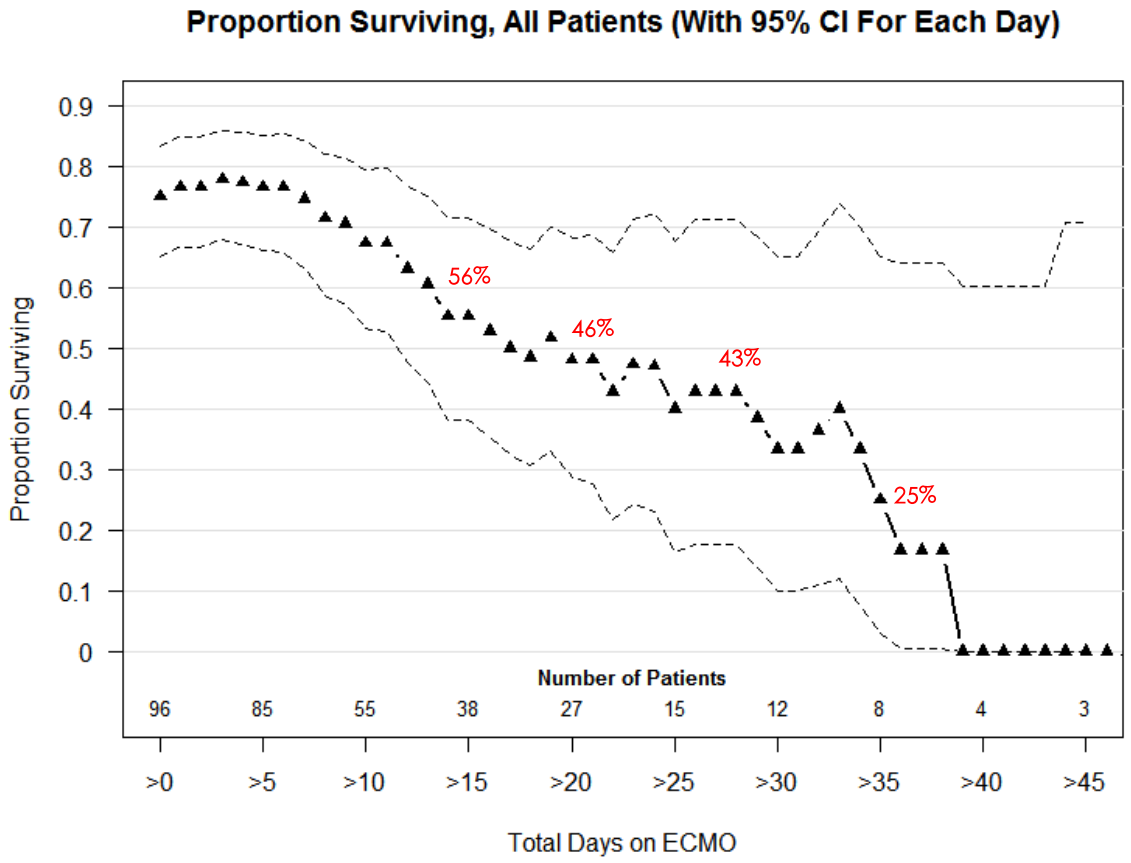


6.64 / >130 / 15

	GA	BW	Ap-1	Ap-5	Pred %	Side	pH-1	PCO2	PO2	ECMO	Surv	d/c-m	Resp d/c
1	28	1053	1	2	4	Left	6.59	> 100	16	No	No	*	*
2	39	2000	0	1	6	Left	6.75	> 100	41	Yes	Yes	3.2	100 cc NC
3	38	3200	1	2	23	Right	6.67	> 100	75	Yes	No	*	*
4	36	3939	1	2	38	Left	6.64	> 130	15	Yes	Yes	3.4	400 cc NC
5	35	2645	0	4	31	Left	6.75	106	59	Yes	No	*	*
6	37	2400	2	1	9	Left	6.76	> 100	41	Yes	Yes	2.9	100 cc NC
7	35	2040	1	4	21	Left	6.81	145	46	Yes	No	*	*
8	27	988	3	1	2	Left	6.8	> 100	8	No	No	*	*
9	37	2500	1	3	20	Left	6.88	> 100	33	Yes	Yes	3.7	300 cc NC
10	37	2212	1	3	16	Left	6.95	> 100	62	Yes	No	*	*
11	33	1250	3	4	11	Left	6.86	96	49	No	No	*	*
12	39	2450	1	1	9	Left	7.04	79	37	Yes	Yes	3.4	100 cc NC
13	34	2595	2	5	40	Left	6.85	> 130	37	Yes	No	*	*
14	35	1880	3	4	18	Left	6.93	> 100	21	Yes	Yes	3.6	100 cc NC
15	38	2750	1	2	17	Left	7.07	67	44	Yes	No	*	*
16	37	3590	0	4	52	Right	6.93	> 100	48	Yes	Yes	1.6	400 cc NC
17	38	3030	2	4	39	Right	6.88	> 100	33	Yes	Yes	4.2	100 cc NC

Most Severe 10%: (N=172) Survival 8/17 = 47%.

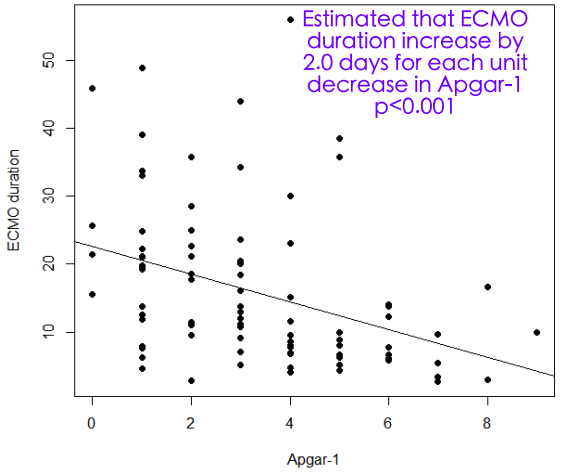
Survival vs Time on ECMO

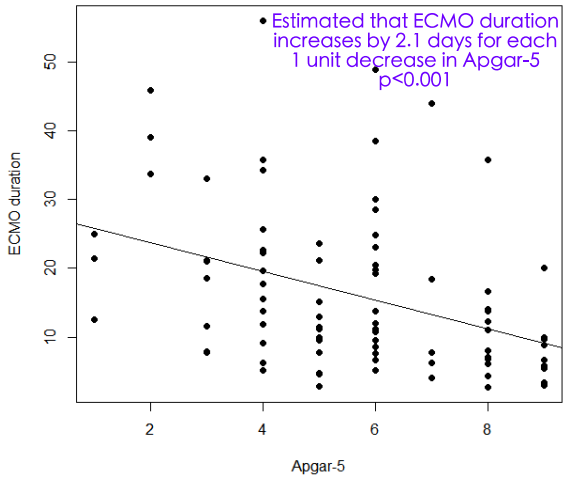


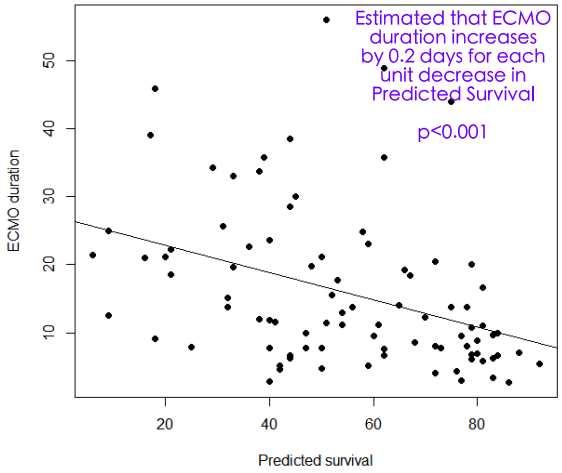
J American College of Surgeons, 2014

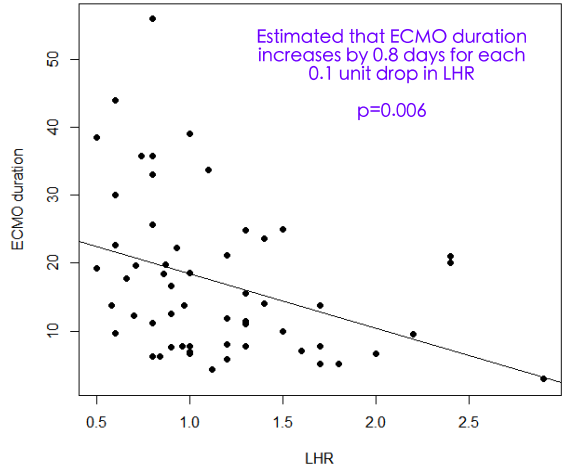
Kays, Islam, Larson, Perkins, Talbert

Association of risk factors with Duration



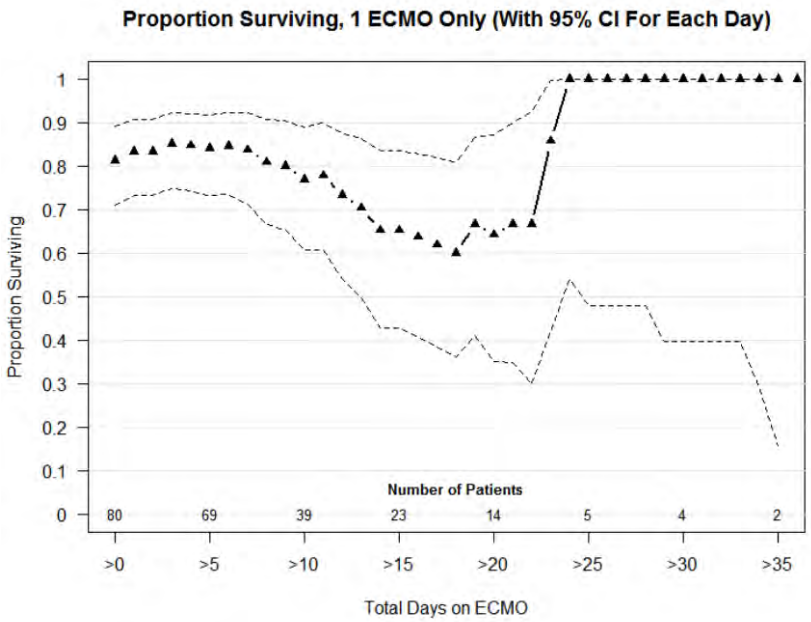




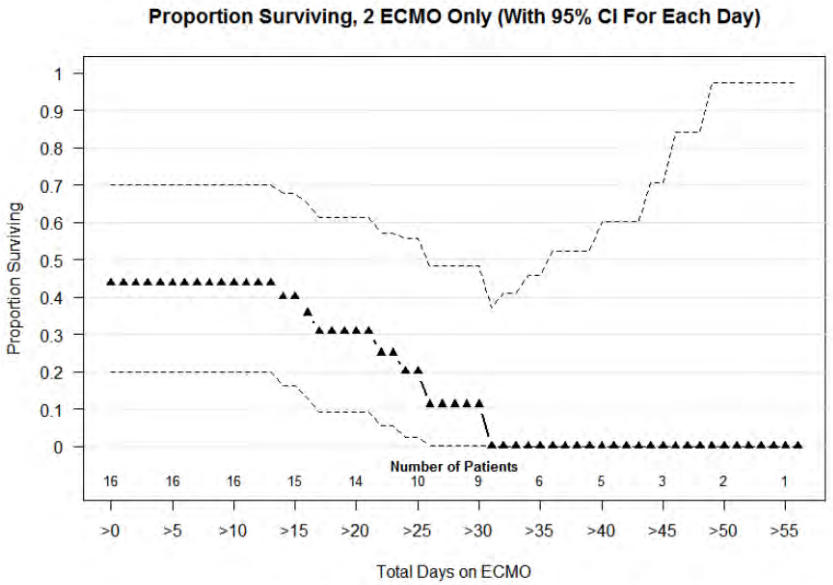


1St Run ECMO vs 2nd Run ECMO for CDH

1st Run ECMO



2nd Run ECMO



What if we put it all together?

- Protect lungs
- Risk Stratify Repair timing
- Get Everyone Repaired
- Do Great ECMO
  - Good decision making
  - Minimize errors
- Believe they can Survive
- What If ?

CDH Program @ JHACH

- 101 Consecutive patients
- Unselected. All-comers*
  - *2 patients seen at our program chose to deliver at their home hospital. Both FDIU
    - Bilateral CDH with 2% o/e TFLV
    - Trisomy 15 mosaic with hydrops

Our Paradigm

- CDH is about lung hypoplasia
  - All treatment decisions are about gas exchange and about helping little lungs work as well as they can.
  - Pulmonary Hypertension is a secondary issue, and does not drive management

Treatment Specifics

- Prenatally evaluation including
  - LHR, Echo, and MRI (o/e TFLV)
  - Counseling
- Inborn Delivery at 38 weeks or so
- Resuscitation in Delivery Room by CDH Team
  - CDH surgeon, CDH neonatologist, CDH RT, CDH nurses
  - (Roles meld and titles fade)
- Conventional ventilation,
  - PIP 25 or less
  - Pre-ductal sats most important
  - Nitric Oxide started for near ECMO level hypoxemia
    - Pre-ductal sats less than 85, PO2 less than 35
  - ECMO when unable to maintain pre-ductal sats at or near 80 - 85 despite optimization of support (brain protection)

Treatment Paradigm

- Risk stratify repair timing to minimize risk of ECMO
- Delay repair for 4 – 6 days (as long as improving)
- If goes to ECMO, repair within 24 hrs
  - Pediatric specific centrifugal or rollerhead pump
  - Bivalirudin probably better than heparin
  - Do GREAT ECMO: good decisions, good supportive care, time
  - Develop exceptional surgical technique and expertise
- Focus on lung function and gas exchange
  - Pulmonary hypertension is the symptom, not the disease
- Believe they can survive
  - Minimize Errors
  - Learn from mistakes
  - Simplify care

ECMO Management

- VA ECMO
- Pump:
  - Sorin Revolution at JHACH (3 patients then changed)
  - Pedi-Mag for all subsequent ECMO (14 cc prime)
- Anticoagulation
  - Changed to Bivalirudin (3/1/2016)

ECMO Weaning

- Athletic Training Paradigm
  - Wean ECMO at a (slow) rate that allows the heart and pulmonary vasculature to develop work capacity over time.
  - All ECMO patients started on sildenafil at 0.8 mg/kg/d when start wean phase (to help stabilize pulm vasc)
  - All patients successfully weaned and none required a second ECMO run.

Second Axis of Severity: CDH Groups (Buckets)

The full spectrum of CDH:

-Associated anomalies**: None**

-"**Isolated CDH**"

The full spectrum of CDH

-Associated anomalies**: less severe, not life threatening**

-ie. Small to moderate VSD, partial renal obstruction

-less severe genetic defects

The full spectrum of CDH

-Associated anomalies**: severe to life-threatening**

-**major chromosomal** (trisomy 13, 15, 18, others)

-**major heart defects. (STAT 3 or higher?)**

single ventricle physiology (HLHS, pulm atresia-VSD)

-bilateral CDH

-major abd wall defect: Giant Omphalocele

-major CNS anomaly

101 Consecutive patients

- Bucket A
- (Isolated)
- 71

- Full spectrum of disease

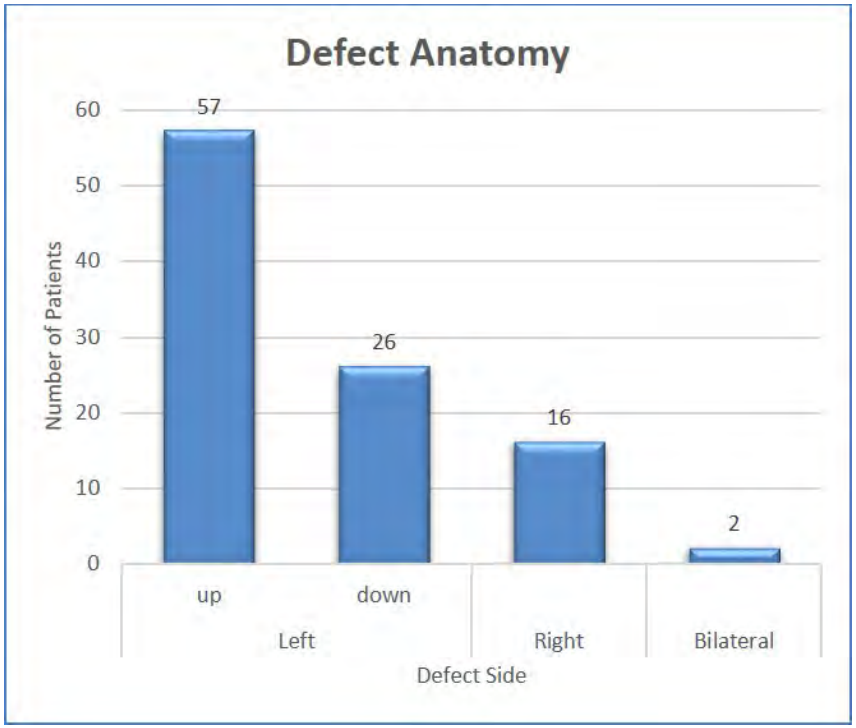
- Bucket B
- Assoc. Anomalies
- 20

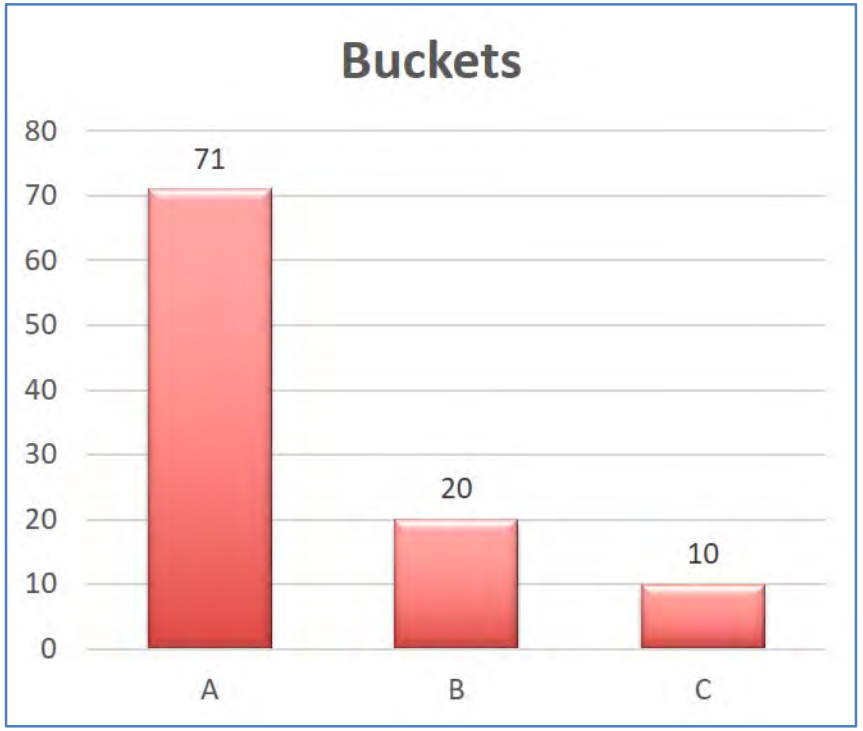
- Large VSD: 2
- DiGeorge Syndrome
- Neonatal Diabetes
- Kleinfelter
- Obstructive Uropathy
- Serious but non-lethal chromosomal abnormalities

- Bucket C
- Severe Assoc
- 10

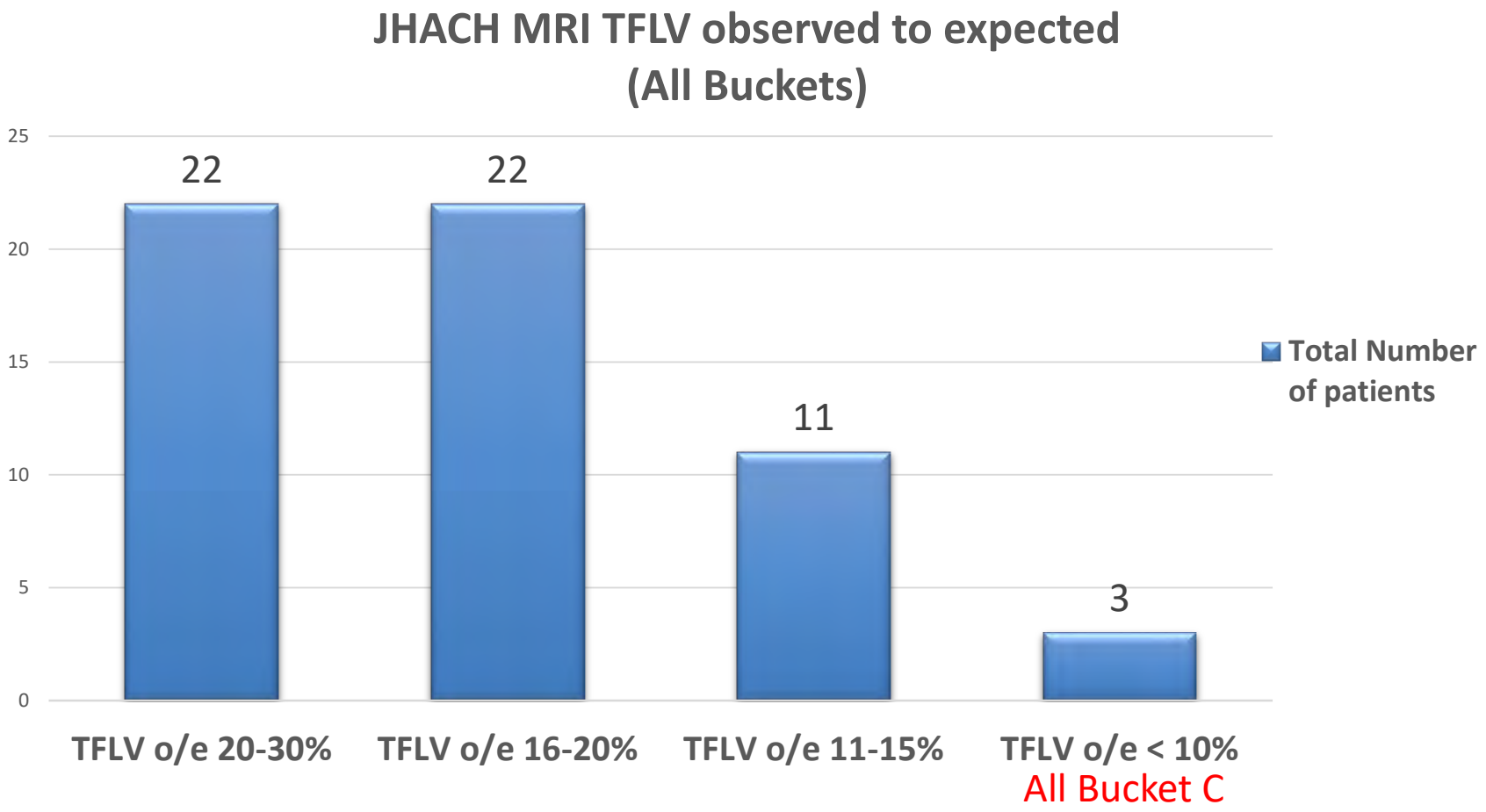
- Bilat CDH-2
  - TFLV 6% and 8%
- Complex Card-4
  - Single vent
  - Pulm atresia/VSD
  - TA w/ IAA
  - TAPVR w/ Em. Syn
- Giant Omph.-2
- Massive hydrocephalus

JHACH Patient Distribution





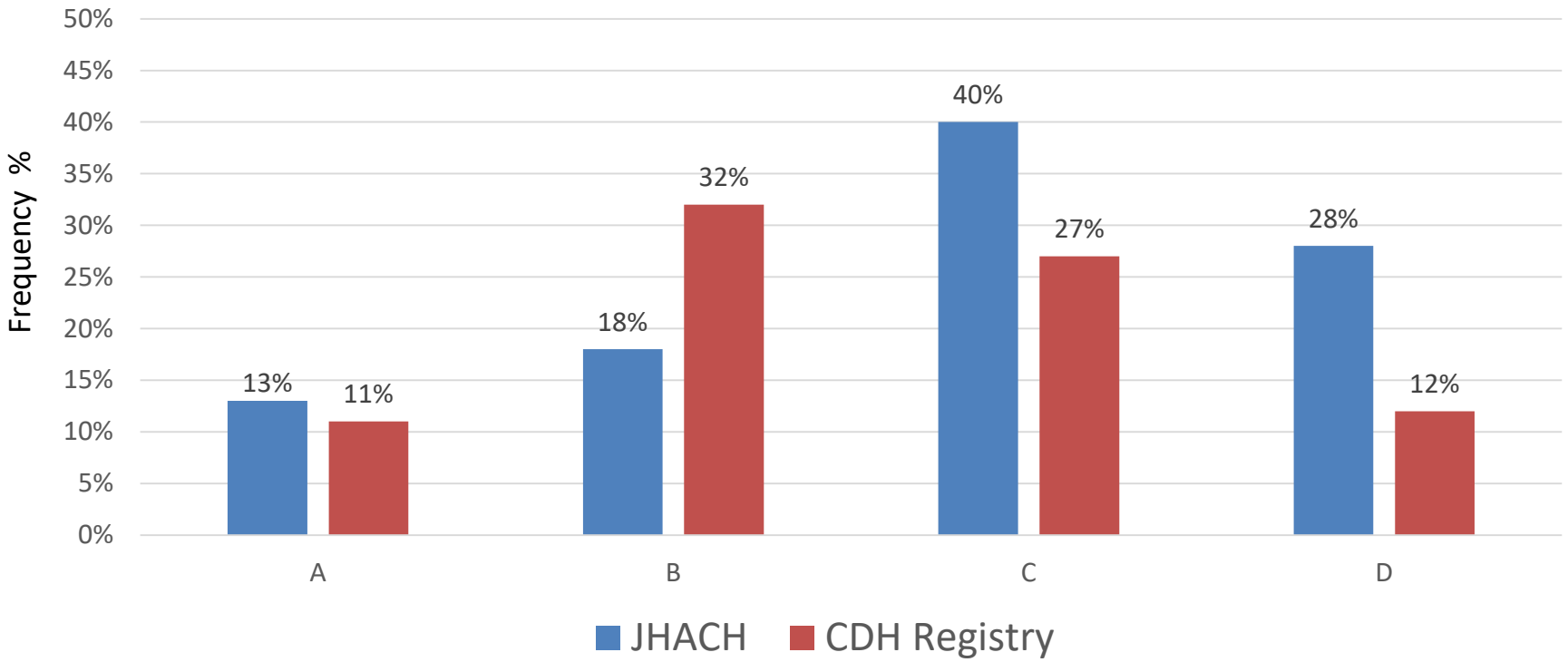
58 of 101 had TFLV o/e less than 30%. (58%)



9 worst patients by 1 hour ABG

Patient	pH @ 1 hour	PCO2 @ 1 hours	PO2 2 1 hour
1	**< 6.80**	**> 134**	50
2	**< 6.80**	**> 112**	46
3	**6.83**	**> 112**	64
4	**6.85**	**> 122**	29
5	**6.91**	**91**	43
6	**6.94**	**> 134**	32
7	**6.96**	**116**	31
8	**6.96**	**119**	51
9	**6.99**	**103**	49

Figure 1: Distribution by Severity by Defect Size

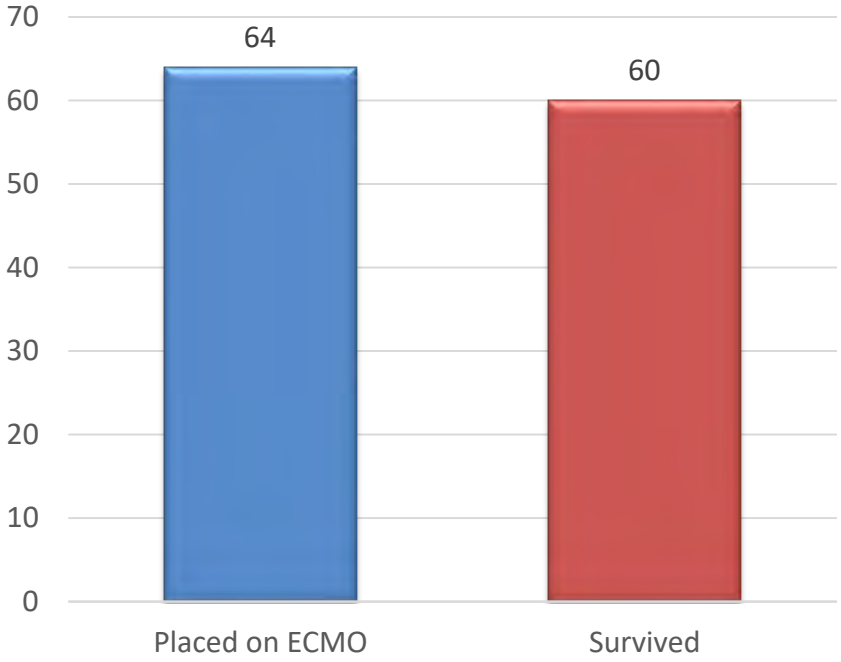


Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)		
APGAR 5min	5.94 (2)		
CDH SG Predicted Survival	60.7 (21)		
LHR	1.06 (0.4)		
o/e LHR	36 (15)		
MRI-1 TFLV o/e	27 (13)		
MRI-2 TFLV o/e	24.5 (9)		
PH	7.07 (0.19)		
PCO2	91 (36)		
PO2	77 (101)		
Lactate	3.3 (3.65)		

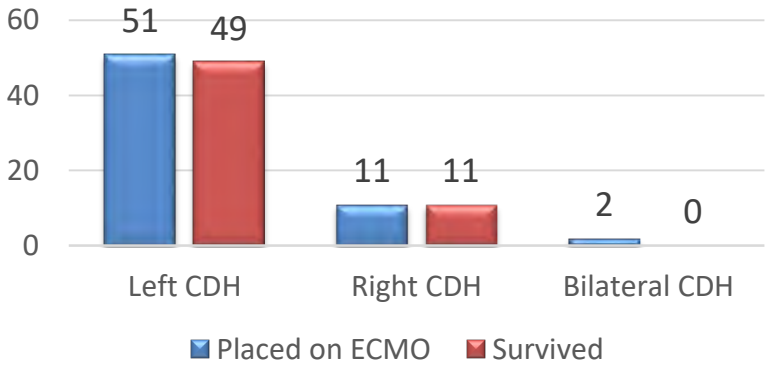
Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)	4.8 (2)	
APGAR 5min	5.94 (2)	7.1 (1.7)	
CDH SG Predicted Survival	60.7 (21)	76.5 (12)	
LHR	1.06 (0.4)	1.36 (0.54)	
o/e LHR	36 (15)	47 (18)	
MRI-1 TFLV o/e	27 (13)	40.4 (12)	
MRI-2 TFLV o/e	24.5 (9)	28.8 (6.8)	
PH	7.07 (0.19)	7.24 (0.13)	
PCO2	91 (36)	61.5 (24)	
PO2	77 (101)	131 (146)	
Lactate	3.3 (3.65)	1.8 (0.8)	

Risk Stratifier	All CDH (n=101) Mean (SD)	No ECMO (n=37) Mean (SD)	ECMO (n=66) Mean (SD)
APGAR 1 min	3.35 (2)	4.8 (2)	2.5 (1.5)
APGAR 5min	5.94 (2)	7.1 (1.7)	5.2 (1.8)
CDH SG Predicted Survival	60.7 (21)	76.5 (12)	51.6 (19.8)
LHR	1.06 (0.4)	1.36 (0.54)	0.93 (0.28)
o/e LHR	36 (15)	47 (18)	31 (10)
MRI-1 TFLV o/e	27 (13)	40.4 (12)	22 (8)
MRI-2 TFLV o/e	24.5 (9)	28.8 (6.8)	23 (9)
PH	7.07 (0.19)	7.24 (0.13)	6.97 (0.14)
PCO2	91 (36)	61.5 (24)	108 (30)
PO2	77 (101)	131 (146)	45 (32)
Lactate	3.3 (3.65)	1.8 (0.8)	4.0 (4.2)

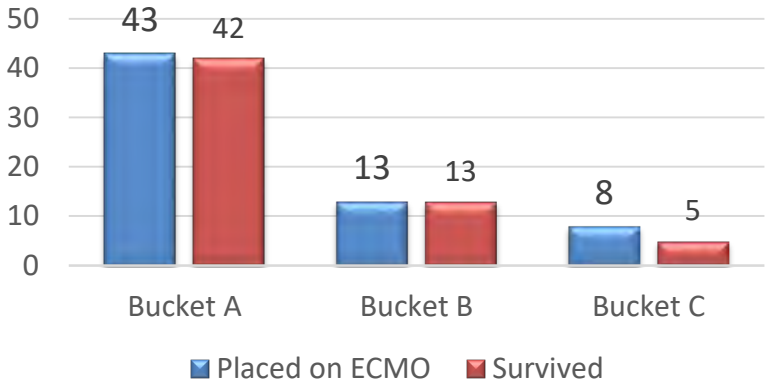
ECMO Survival to D/C



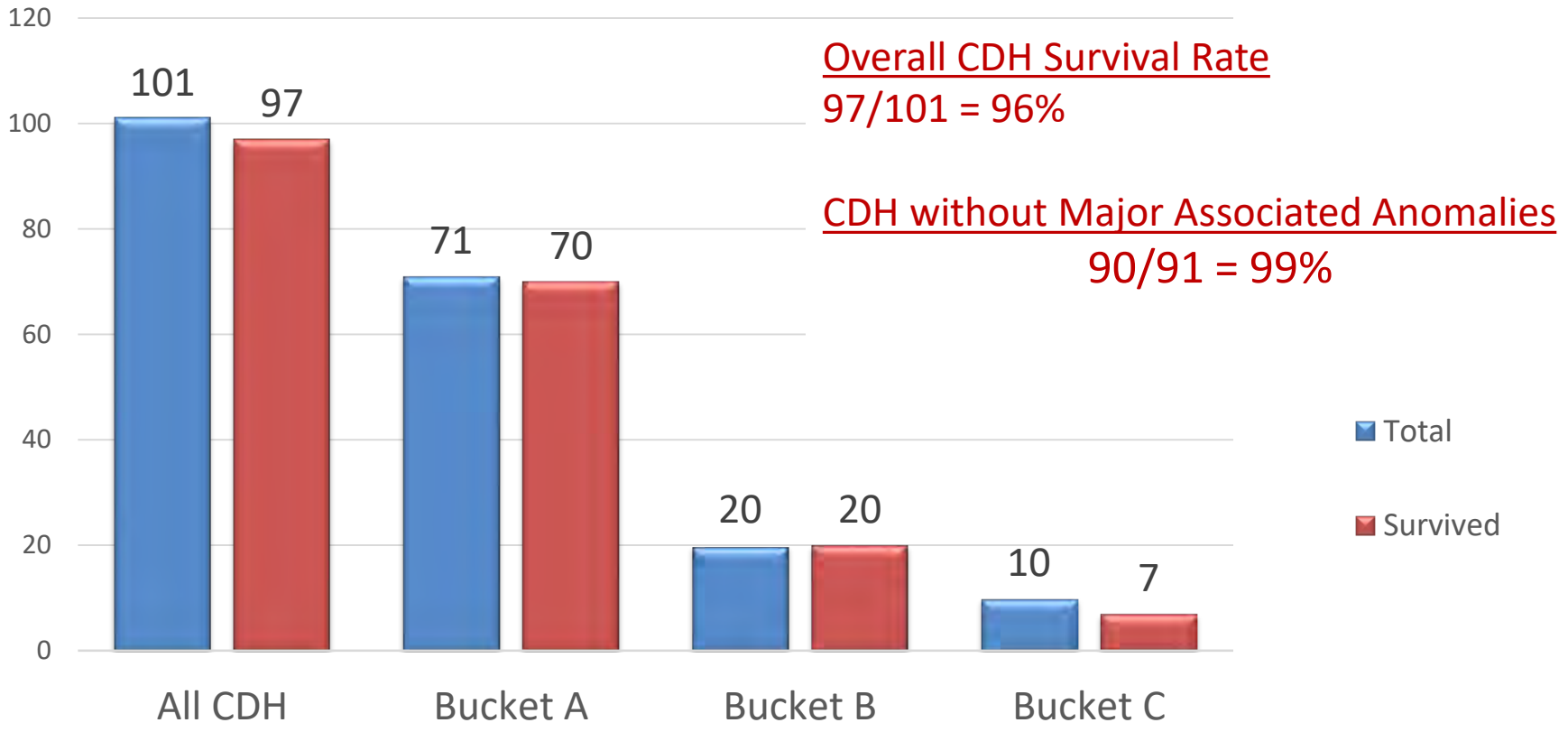
CDH-ECMO Anatomy



Buckets

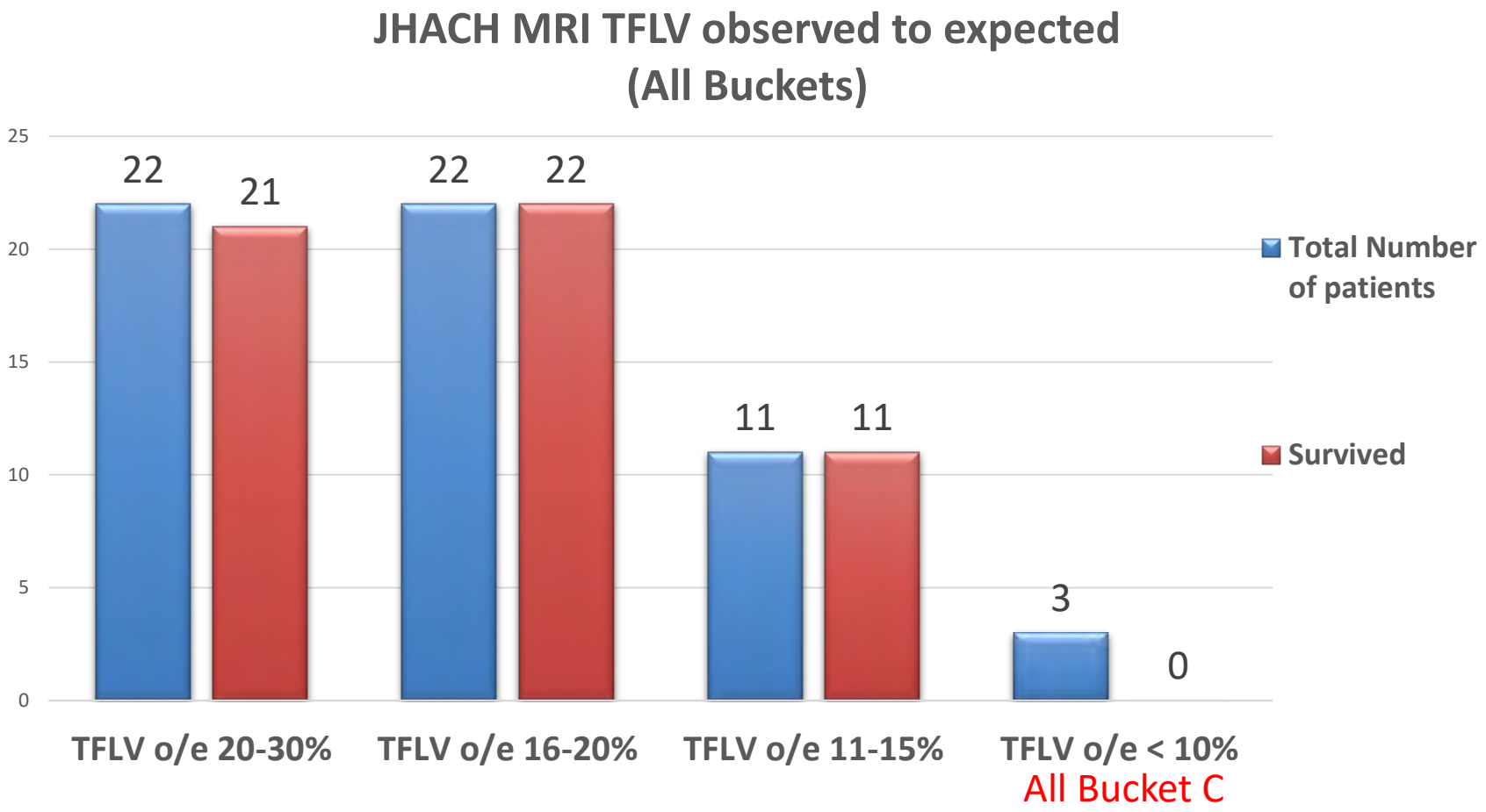


JHACH CDH Survival



Overall CDH Survival Rate
97/101 = 96%

CDH without Major Associated Anomalies
90/91 = 99%


JHACH MRI TFLV observed to expected
(All Buckets)
25
20
15
10
5
0
22
21
22
22
11
11
3
0
Total Number of patients
Survived
TFLV o/e 20-30%
TFLV o/e 16-20%
TFLV o/e 11-15%
TFLV o/e < 10%
All Bucket C

Time in Hospital

- No ECMO
- Extubation: 12.7 (+/- 6 days)
- Discharge: 1.5 mos (+/- 0.9)

- ECMO
- Extubation: 32 (+/- 33) days
- Discharge: 2.42 (+/- 2.2) mos

95/ 97 went home breathing spontaneously

2 tracheostomies, both from Bucket C

What we've learned

- Focus on the lungs
- Repair the CDH
- Do exceptional ECMO
- Believe they can survive

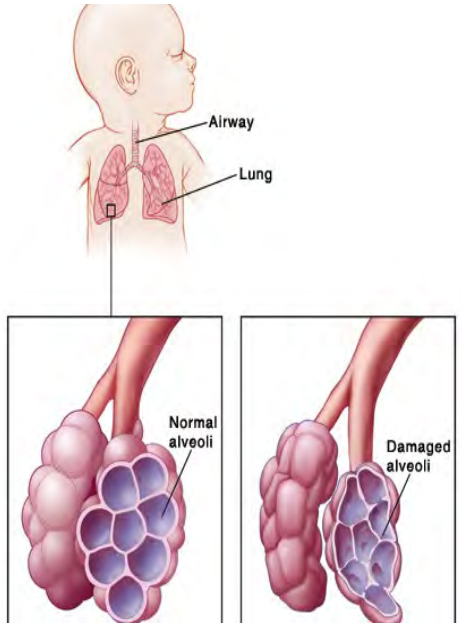
What we've learned

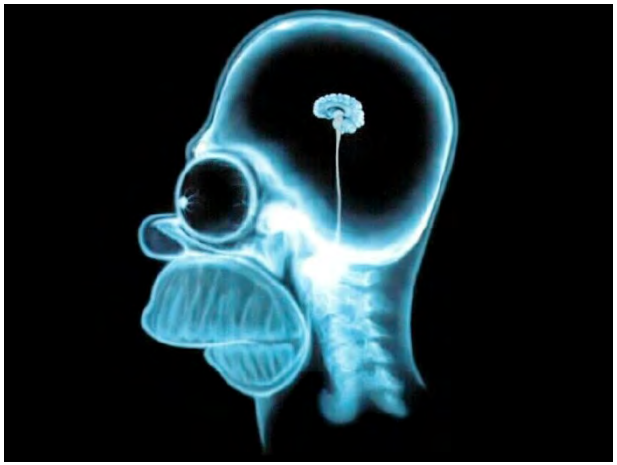
- Pulmonary hypoplasia in CDH needs not be lethal
- We currently have the tools necessary for exceptional outcomes.
- Survival in CDH without major associated anomalies can approach **100%**

- We can look prenatal patients in the eye and quote 95% predicted survival

CDH

- **Quantity of Survival**
  - **Care of lungs**
- **Quality of Survival**
  - **Care of brain**
- **(Another talk)**






Welcome to the CDH Family Reunion
all we do for kids


D.O.N.T.
FLOCK WITH THE FILTHY FLAMINGOS


BEACH
Sun, Sand & CDH
Help us Capture the fun!
#Leston
Hope starts here!
all we do for kids

JOHNS HOPKINS

All Children's Hospital

all we do. all for kids.™

Care Standardization and Clinical Guidelines: The future is now for CDH

Pramod S. Puligandla, MD MSc FRCSC FACS FAAP

Professor of Pediatric Surgery, Pediatrics and Surgery

Pediatric Surgeon and Pediatric Intensivist

Harvey E. Beardmore Division of Pediatric Surgery

Montreal Children's Hospital

Quebec, Canada

McGill

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Montreal Children's Hospital
McGill University Health Centre

I have no financial disclosures

Optimal Health Care Delivery

- The optimal delivery of health care is guided by the following principles:
  - People are treated safely
  - The treating environment is suitable to a patient's needs
  - There is shared decision-making
  - Care providers are suitably trained and supported
  - The optimal quality of care is being provided

Standardization

- Process of developing, agreeing upon and implementing uniform technical specifications, criteria, methods, processes, designs or practices that can increase compatibility, interoperability, safety, repeatability and quality

Standardization

- Widely used for decades in non-health care industry
- Assumes failure from start to end of process
- Creates a system that proactively attempts to mitigate risk, provide surveillance while enacting barriers to potential hazards

Standardization in Surgery

VOLUME LXIII
NUMBER 9

JAMA (1914)

STANDARDIZATION OF SURGERY

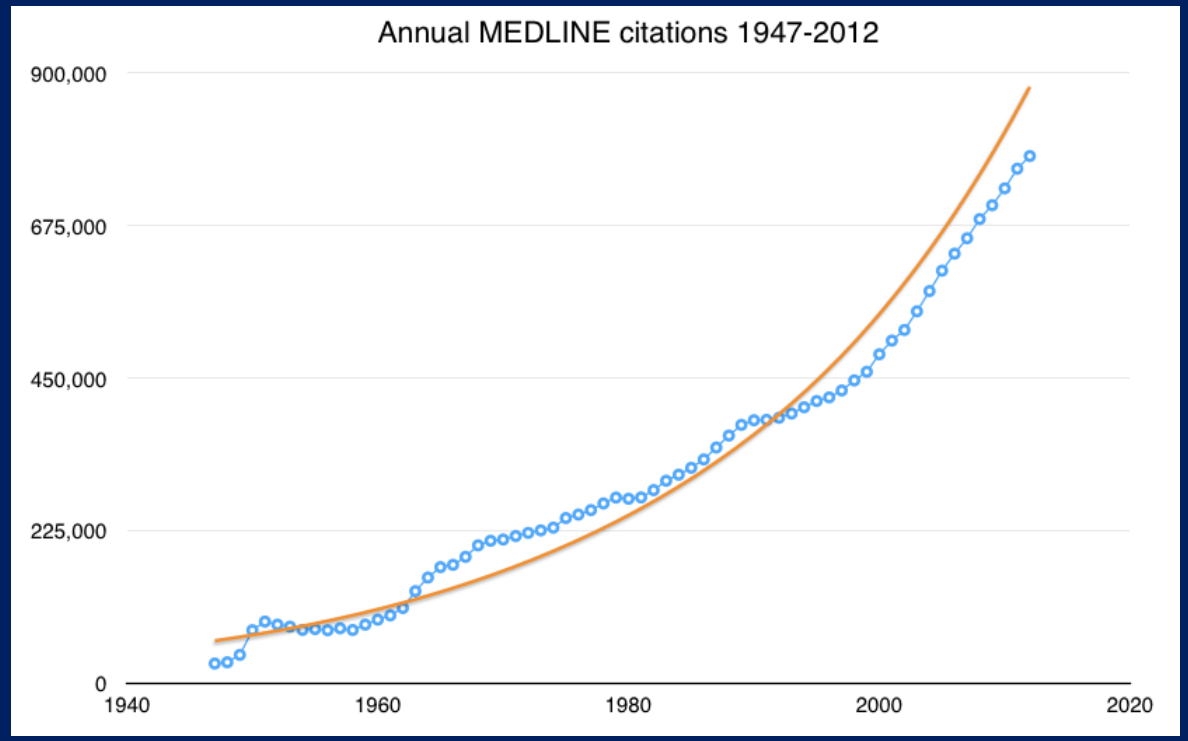
AN ATTACK ON THE PROBLEM *

ROBERT L. DICKINSON, M.D.
BROOKLYN

the management of industries. Some of these are new adjustments of "function" (responsibilities and duties) clarified, charted, defined; regular instruction, such as drill in technic and manual dexterity and correct form; practice in team work; the printing on instruction cards of the best standard practice covering all ordinary acts and activities; constant inspection by one delegated to this duty; record of successes and errors like a ball-player's fielding average or a government office tally of character of work done; promotion by rating, and finally, a series of studies, undertaken as in the other mechanical crafts, by measurement of motion, speed, fatigue and efficiency.

Why Standardize in Health Care?

- Knowledge transfer has occurred through mentorship for generations
- Exponential growth in medical evidence over the last 50 years
  - Hard for clinicians to keep abreast of rapidly evolving treatment paradigms
  - Increasing complexity of medical conditions



Why Standardize in Health Care?

- High level evidence supports routine clinical decision making only 20% of the time [1]
- Even when evidence-based guidelines are available, only 2/3 of patients receive recommended care and 25% receive unnecessary or harmful care [2]
- Successful outcomes are assumed as the baseline (contrary to non-healthcare industry)

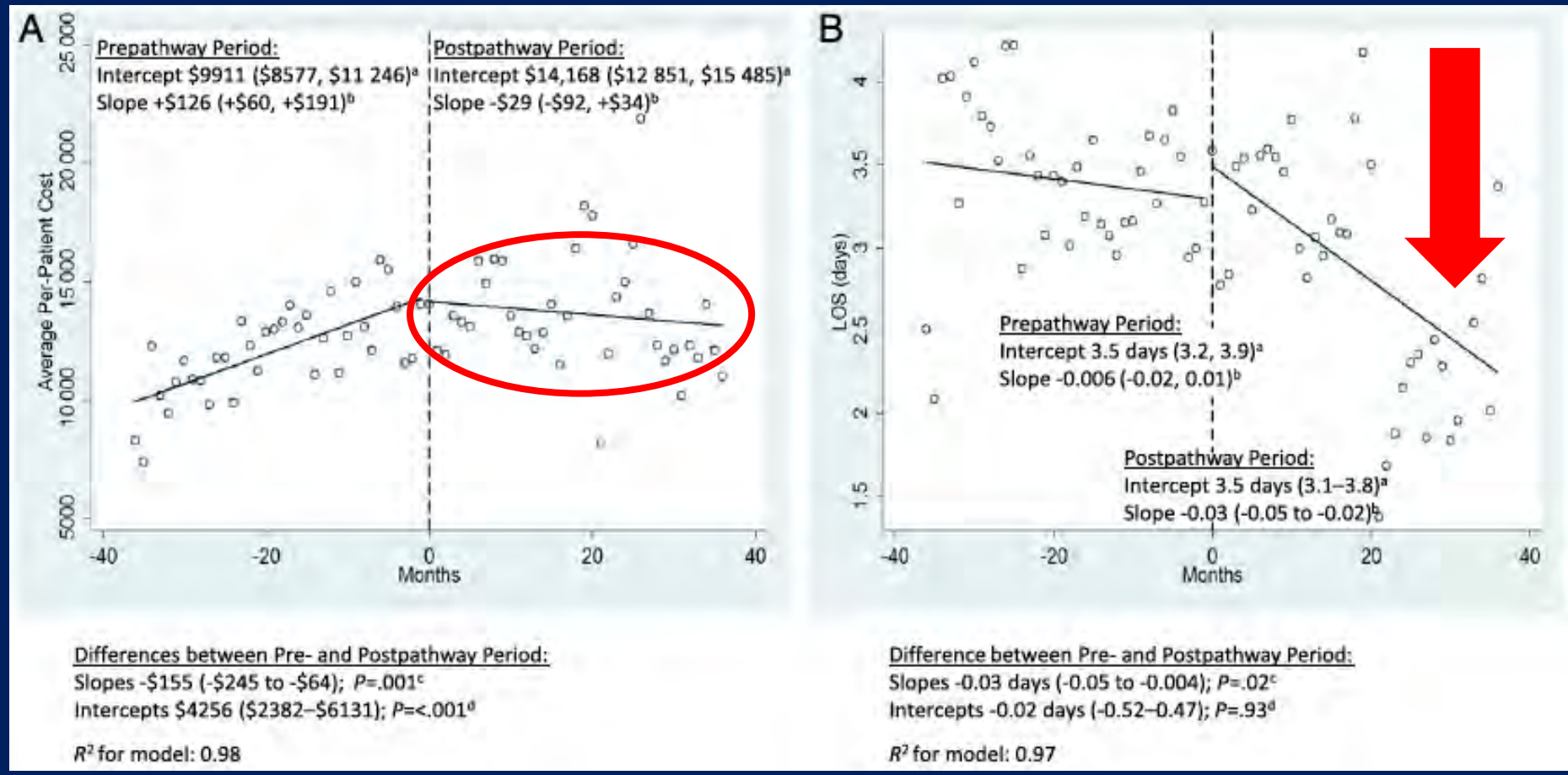
- Development of "standard operating procedures"
  - Guidelines, clinical pathways, protocols

[1]Health Aff (2013): 32(5):911-20; [2]JAMA (2012):307(14)1513-1516

Clinical Practice Guidelines

- High quality, evidence-informed clinical practice guidelines (CPGs) can provide a way to bridge the gap between
  - Health policy
  - Best practices
  - Local clinical contexts
  - Patient choice

Clinical Standard Work Pathways in Pediatrics



Standardization in LMIC's

Surgical Safety Checklist

World Health Organization | Patient Safety

Before induction of anaesthesia	Before skin incision	Before patient leaves operating room
(with at least nurse and anaesthetist)	(with nurse, anaesthetist and surgeon)	(with nurse, anaesthetist and surgeon)
Has the patient confirmed his/her identity, site, procedure, and consent? ☐ Yes	☐ **Confirm all team members have introduced themselves by name and role.**	**Nurse Verbally Confirms:** ☐ The name of the procedure
Is the site marked? ☐ Yes ☐ Not applicable	☐ **Confirm the patient's name, procedure, and where the incision will be made.**	☐ Completion of instrument, sponge and needle counts
Is the anaesthesia machine and medication check complete? ☐ Yes	**Has antibiotic prophylaxis been given within the last 60 minutes?** ☐ Yes ☐ Not applicable	☐ Specimen labelling (read specimen labels aloud, including patient name)
Is the pulse oximeter on the patient and functioning? ☐ Yes	**Anticipated Critical Events**	☐ Whether there are any equipment problems to be addressed
Does the patient have a:	**To Surgeon:** ☐ What are the critical or non-routine steps? ☐ How long will the case take? ☐ What is the anticipated blood loss?	**To Surgeon, Anaesthetist and Nurse:** ☐ What are the key concerns for recovery and management of this patient?
Known allergy? ☐ No ☐ Yes	**To Anaesthetist:** ☐ Are there any patient-specific concerns?	
Difficult airway or aspiration risk? ☐ No ☐ Yes, and equipment/assistance available	**To Nursing Team:** ☐ Has sterility (including indicator results) been confirmed? ☐ Are there equipment issues or any concerns?	
Risk of >500ml blood loss (7ml/kg in children)? ☐ No ☐ Yes, and two IVs/central access and fluids planned	**Is essential imaging displayed?** ☐ Yes ☐ Not applicable	

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged.

Revised 1 / 2009 © WHO, 2009

Standardization in pat
High 5s project

AGNÈS LEOTSAKOS[1]*, HAO ZHENG[1], RICK CROTE/
CAROLYN HOFFMAN[4], LOUISE MORGANSTEIN[5], D
MARGARET DUGUID[8], CHRISTIAN THOMECZEK[9], E
BILL MUNIER[11]

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International Journal for Quality in Health Care 2014; Volume 26, Number 2: pp. 109–116

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Definition of CPG

Institute of Medicine – systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances

Current guidelines are a convenient way of packaging evidence and presenting recommendations to health care decision makers

2011 – statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and the assessment of the benefits and harms of alternative care options

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What are the goals of guidelines and pathways?

- Provide consistent care
- Provide efficient care
- Remove *unwanted* variation in care
- Use evidence to guide clinical decision-making

- Many consider CPGs as an essential component of quality care delivery

Terminology

- Guidelines – generally relate to broader systems with a primary care focus (e.g. food security, water and air quality)
  - Developed and used by policy makers, service organizations, funders, regulatory authorities
- Care pathways – series of evidence-informed steps which can include a multidisciplinary team at various care levels
  - More details on the sequence, timing and provision of care
- Protocols – pertain to explicit rules or instructions on how to perform a process or task without error

Potential Benefits of Clinical Guidelines?

Patients

- Improved outcomes
- Reduced morbidity and mortality
- Consistency of care
- Empowerment
- Influence public policy

Providers

- Improved quality of clinical decision making
- Highlight knowledge gaps and influence research
- Medicolegal protection

Health Systems

- Improve efficiency
- Standardize care
- Guideline compliance is a testament to commitment to excellence

Potential Harms of Clinical Guidelines?

Patients

- Trust
- Patients vs Individuals?
- Threat to shared decision-making
- Reduction of access or coverage for services
- Misuse by advocacy groups

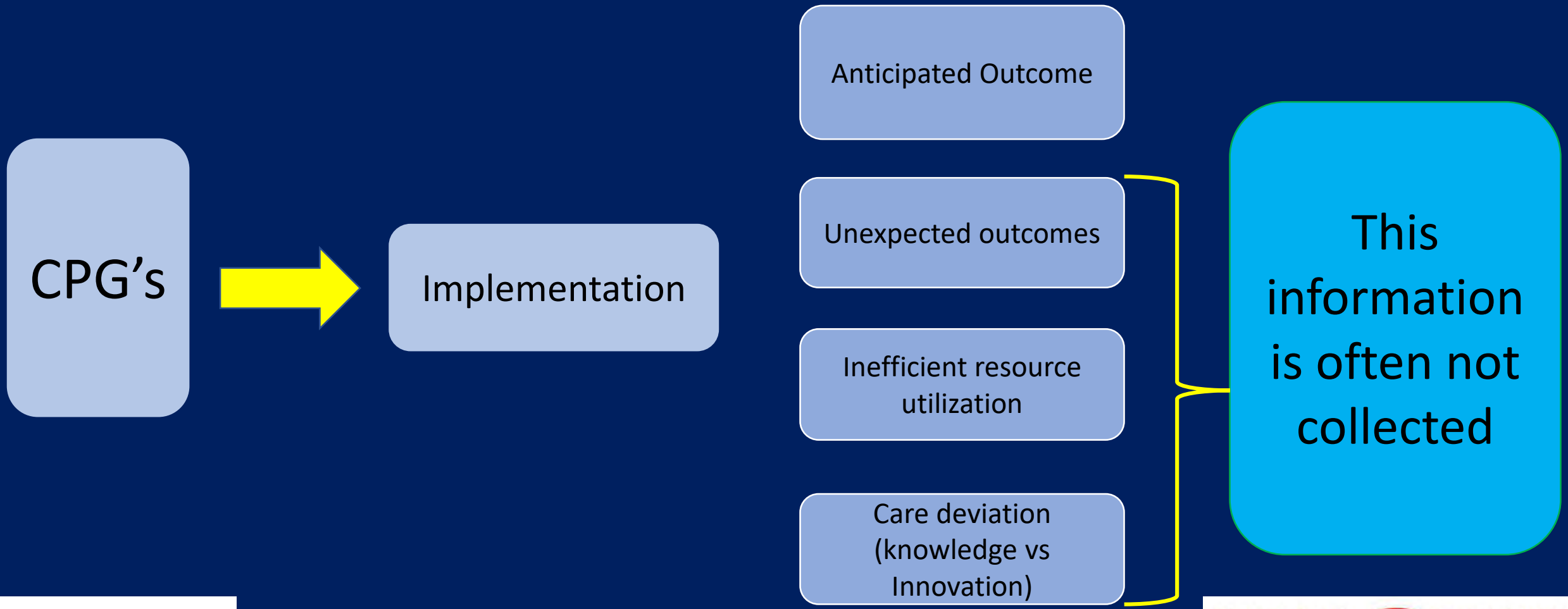
Providers

- Trust
- Poor recommendations are inefficient or wasteful
- Conflicting guidelines?
- Outdated guidelines?
- Discourage ongoing research or innovation?

Health Systems

- Adds cost
- Wastes limited resources

Why are the effects of standardization often less than desired?

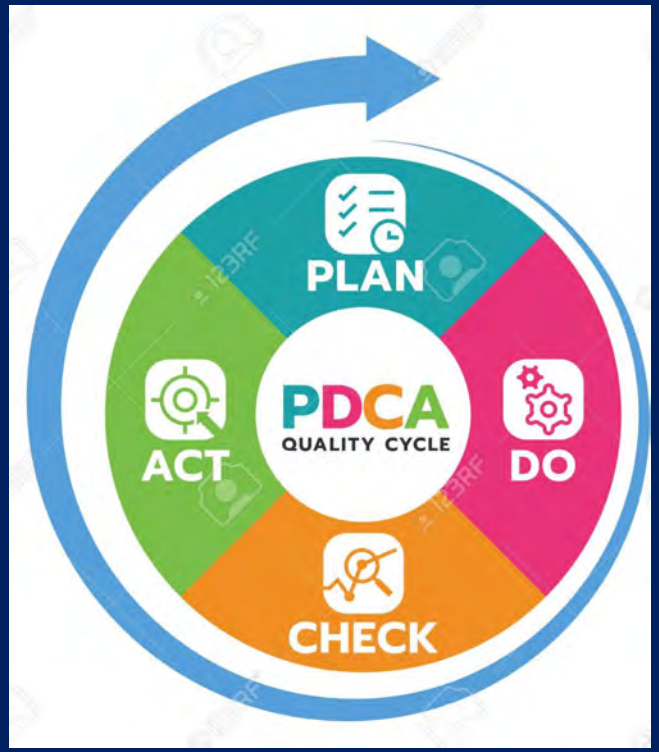


Adapted from J. Sharma, ACS Safety and Quality Conference 2018

Why are the effects of standardization often less than desired?

CPG's

Implementation



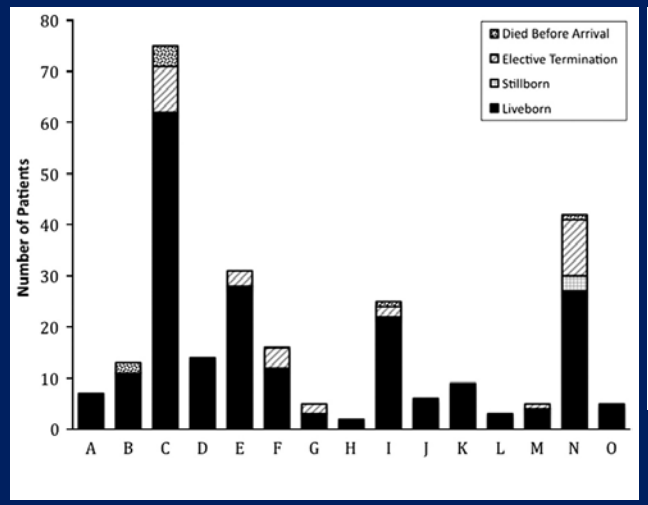
- Anticipated Outcome
- Unexpected outcomes
- Inefficient resource utilization
- Care deviation (knowledge vs Innovation)

Adapted from J. Sharma, ACS Safety and Quality Conference 2018

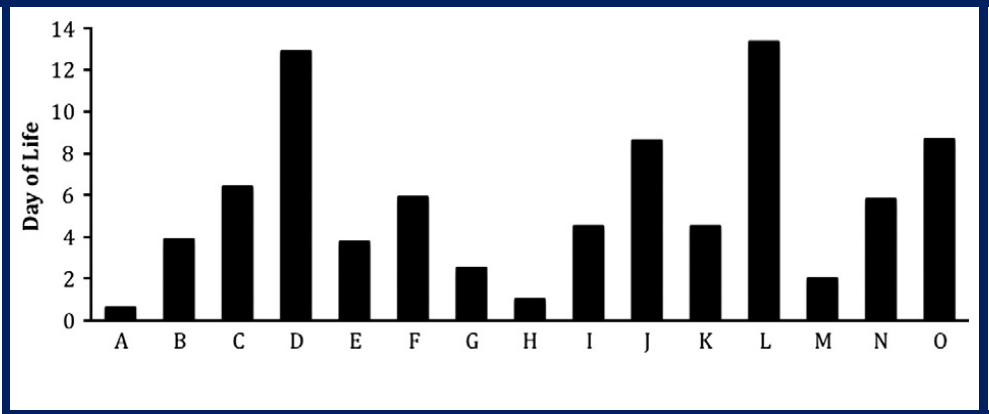
Canadian CDH Collaborative

- The complex interplay of roles between specialists and the lack of evidence informing best practices across the various phases of care leads to
  - **<u>Practice and outcome variation within and between hospitals in Canada</u>**
  - **<u>Inefficiencies in healthcare resource utilization</u>**

Prenatal



Surgery

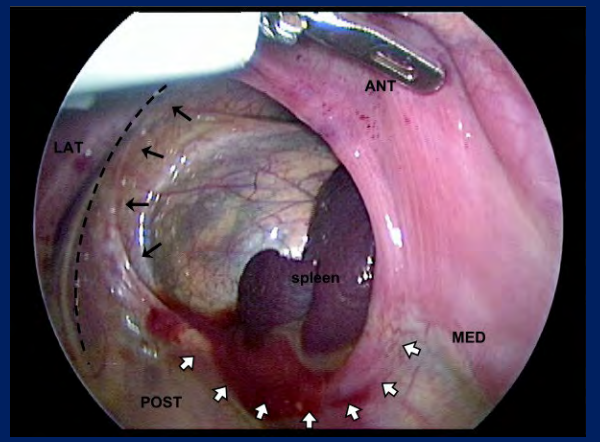


Survival

Baird et al., J Pediatr Surg, 2011

Understanding the Morbidity of CDH…

- Of 100 CDH infants born in Canada with CDH[1]



- 22 will die despite “state of the art” intensive neonatal care
- 55 will have ongoing cardiorespiratory, feeding and/or developmental problems that require specialized follow-up
- 30 will have detectable psychomotor or neurodevelopmental disability by 1 years of age
- 48 will have some form of disability by 3 years of age

[1]CAPSNet Annual Report, 2014 (www.capsnet.org)

CDH

- Improvement in survival has been offset by the substantial disability in survivors
  - Patients and families experience morbidity burdens similar to other chronic diseases

- Multi-system morbidity spans into adulthood
  - Pulmonary
  - Gastrointestinal (feeding, growth)
  - Cardiac
  - Musculoskeletal
  - Neurodevelopmental

Chiu PP, J Pediatr Surg, 2012
Peetshold, Pediatr Surg Int, 2006

CDH

- Financial implications
  - Annual hospitalization costs exceed $10 million[1]
  - Underestimates overall cost burden
    - Direct costs
      - Inpatient care
      - Outpatient care
    - Indirect societal costs
      - Lost caregiver productivity
      - Patient becomes an adult with economically limiting disability

[1]Lam JC et al.,J Pediatr Surg, 2006

Scope and Purpose

- Provide pragmatic guidance on the optimal health care and health surveillance for CDH patients
  - Prenatal diagnosis
  - During birth hospitalization
  - Through childhood/adolescence

Guideline Development Group

- Multi-disciplinary specialist group
  - Maternal-fetal medicine
  - Neonatology
  - Pediatric intensive care
  - Pediatric surgery
  - Pediatric anesthesia
  - Pediatric cardiology
  - Neonatal follow-up
- Views and preferences from
  - Rare Disease Foundation
  - Canadian Family Advisory Board
  - Allied Health Professionals
    - Nursing
    - Respiratory Therapy

Existing Guidelines

- Two groups previously published recommendations relevant to CDH care
  - CDH Euroconsortium (2010[1], 2016[2]) [36 recommendations]
  - ATS/AHA guidelines on the management of pulmonary hypertension (2015[3]) [7 recommendations]

- The CCC steering committee sent a survey to each collaborative member to "accept", "modify", or "reject" these recommendations

[1]Reiss et al., Neonatology, 2010
[2]Snoek et al., Neonatology, 2016
[3]Abman et al., Circulation, 2015

- Accept – recommendation may be adopted without formal discussion
  - >80% agreement amongst participants [6 recommendations]
- Modify – worthy of consideration but not acceptable as written and in need of discussion
- Reject – recommendation is either wrong, out of date or so unimportant as to not require inclusion in the guideline

- Discussions during the consensus meeting would focus on:
  - "Modified" or "Rejected" recommendations from CDH EURO or ATA/AHA
  - Areas of additional prioritization identified by CCC participants

1. What are the preferred methods of antenatal diagnosis, and with what prognostic criteria should antenatal counselling be conducted?
2. What is the current role for fetal intervention for antenatally diagnosed CDH?
3. At what gestation and by what route should CDH infants be delivered?
4. What precautions should be taken for women with CDH pregnancies at risk for premature delivery?

Prenatal

5. When should mechanical ventilation be instituted after an antenatally diagnosed CDH is delivered?
6. What is the role of pharmacologic sedation and paralysis after delivery?
7. What ventilation parameters and blood gas targets should be used to guide cardiopulmonary stabilization?
8. What ventilatory "rescue therapies" should be used when conventional ventilation fails to achieve desired targets?
9. What is the role of surfactant therapy in CDH?
10. What physiologic monitoring, fluid therapy and medications should be used for the optimization of hemodynamic status?
11. When should echocardiography be performed and what functional indices should be trended?
12. What pharmacologic therapies targeting pulmonary hypertension should be used in CDH?
13. What is the therapeutic role of extracorporeal life support (ECLS) in CDH?

Intensive Neonatal Care

14. If ECLS is required, when should surgery be performed?
15. What criteria should be used to determine readiness for surgery?
16. What is the optimal material for patching large diaphragmatic defects not amenable to primary repair?
17. What is the role of minimally invasive surgery (MIS) in CDH treatment?

Surgery

18. What is recommended for treatment of gastroesophageal reflux (GER) associated with CDH?
19. What are the recommendations for long term follow-up?

Surveillance

- Participants were organized into theme-based work groups
  - Tasked with creating visual, summarized evidence reviews to be presented to the consensus group

Prenatal Diagnosis, Risk Stratification, Optimal Delivery	
Dr. Greg Ryan	Dr. Titilayo Oluyomi-Obi
Ventilation Strategies in CDH	
Dr. Shyamala Dakshinamurti	Dr. Doug McMillan
Dr. Brian Kavanagh	Dr. Michael Traynor
Dr. Conor McDonnell	
Management of Pulmonary Hypertension (including ECMO)	
	Dr. Arthur Cogswell
Dr. Therese Perreault	Dr. Bruno Piedbeouf
Dr. Sandesh Shivananda	
Type, Timing and Indications for Surgical Repair in CDH	
Dr. Robert Baird	Dr. Mary Brindle
Dr. Pramod Puligandla	Dr. Erik Skarsgard
Pain Management, Sedation	
Dr. Richard Keijzer	Dr. Thomas Pennaforte
Treatment of GE Reflux	
Dr. Helene Flageole	
Surveillance Protocols for Disability in CDH	
Dr. Anne Synnes	Dr. Michelle Bailey
Dr. Patricia Riley	Dr. Priscilla Chiu

Formulation of Recommendations

- CCC face-to-face meeting was held over 2 days with 17 participants in Banff, AB
  - Experienced guidelines facilitator
  - Record keeper
  - Non-voting observer (USA)
- Facilitator ensured work plan fidelity

Evidence Review Process and Taxonomy

- N
  f
- S

Level A
• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Level B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
Level B-NR (Non-randomized)
• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
Level C-LD (Limited data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Level C-EO (Expert Opinion)
• Consensus of expert opinion based on clinical experience

Evidence Appraisal and Modified Delphi Methods

- Evidence reviews were distributed prior to the face-to-face meeting
- Consensus would be determined using the anonymized audience response tool “Poll Everywhere ™”

Consensus Framework

1) Strongly agree
2) Somewhat agree
3) Neither agree or disagree
4) Somewhat disagree
5) Strongly disagree

★ STRONG AGREEMENT WITH RECOMMENDATION: >80% #1 OR #5

GOOD AGREEMENT WITH RECOMMENDATION: >80% OF #1 + #2 OR #4 + #5 BUT >50% OF THE VOTES AS #1 OR #5

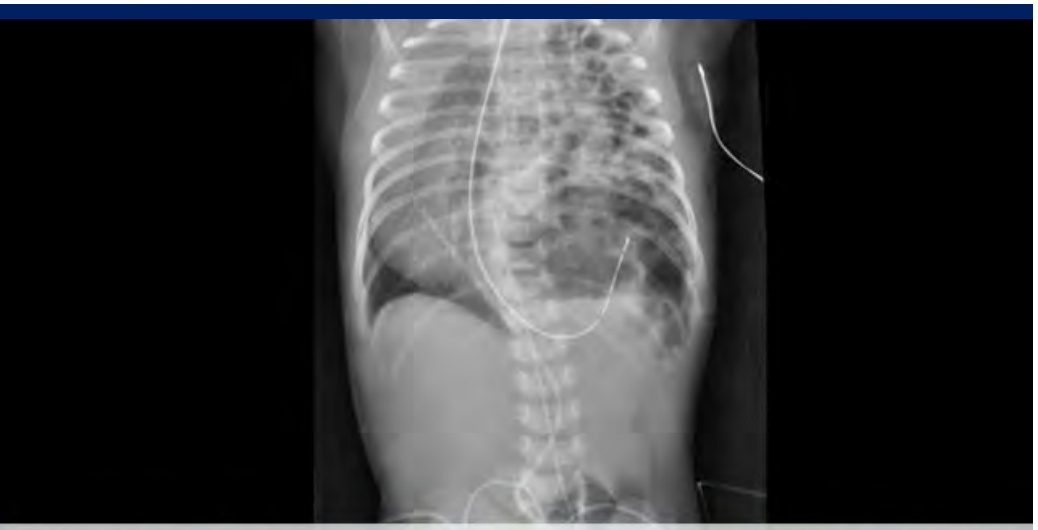
☆ WEAK AGREEMENT WITH RECOMMENDATION: >80% OF #1 + #2 OR #4 + #5 BUT <50% OF THE VOTES AS #1 OR #5

NO CONSENSUS

Preparation of Final Recommendations

- At completion of meeting
  - Compiled, edited and finalized recommendations
  - Work groups prepared evidence summaries, search strategies and PRISMA flow diagrams
  - Summaries and recommendations were prepared into manuscript form
  - “Hot Potato” editing process
  - Format according to AGREE-2 framework

cmaj.ca volume 190, issue 4



Editor's pick: Congenital diaphragmatic hernia guideline

GUIDELINE CPD

Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline

The Canadian Congenital Diaphragmatic Hernia Collaborative*

*The complete list of authors appears at the end of the article.

■ Cite as: *CMAJ* 2018 January 29;190:E103-12. doi: 10.1503/cmaj.170206

CMAJ Podcasts: author interview at https://soundcloud.com/cmajpodcasts/170206-guide

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CMAJ 2018 January 29;190:E103-12. doi: 10.1503/cmaj.170206

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Table 1 (part 1 of 2): Abridged recommendations for diagnosing and managing congenital diaphragmatic hernia

Recommendation	Strength of recommendation*	Level of evidence†
Prenatal diagnosis		
Ultrasound measurement of O/E LHR should be used between 22 and 32 w of gestational age to predict the severity of pulmonary hypoplasia in isolated CDH.	●●●●	B-NR
In left-sided CDH, an O/E LHR < 25% predicts poor outcome. In right-sided CDH, an O/E LHR < 45% may predict poor outcome.	●●●○	B-NR
Fetal magnetic resonance imaging should be used (where available) for the assessment of lung volume and liver herniation in moderate and severe CDH.	●●●●	B-NR
Ventilation		
Newborns with CDH and immediate respiratory distress should be preferentially intubated at birth. Bag-valve-mask ventilation should be avoided.	●●●●	C-EO
Sedation should be provided to all mechanically ventilated newborns with CDH. Deep sedation and neuromuscular blockade should be provided selectively to those with greater ventilation or oxygen requirements.	●●●●	B-NR
A T-piece should be used with the ventilator to avoid a peak inspiratory pressure > 25 cm H_2O.	●●●●	B-NR
An arterial pCO_2 between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH.	●●●●	B-NR
Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not > 95%.	●●●●	B-EO
Gentle, intermittent mandatory ventilation should be the initial ventilation mode for newborns with CDH who require respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used when the peak inspiratory pressure required to control hypercapnia using intermittent mandatory ventilation exceeds 25 cm H_2O.	●●●●	B-NR
Hemodynamic support		
Treatment of poor perfusion (capillary refill > 3 s, lactate > 3 mmol/L, urine output < 1 mL/kg/h) and blood pressure below norms for age should include: • judicious administration of crystalloid, generally not exceeding 20 mL/kg; • inotropic agents such as dopamine or epinephrine; and • hydrocortisone. If poor perfusion continues, assessment of cardiac function (i.e., echocardiogram, central venous saturation) should be performed	●●●●	B-NR
Echocardiography		
Two standardized echocardiograms, one within 48 h of birth and one at 2–3 w of life, are needed to assess pulmonary vascular resistance, as well as left ventricular and right ventricular function. Additional studies may be conducted as clinically indicated.	●●●●	C-LD
Management of pulmonary hypertension		
iNO is indicated for confirmed suprasystemic pulmonary arterial hypertension without left ventricular dysfunction, provided lung recruitment is adequate. In the absence of clinical or echocardiographic response, iNO should be stopped.	●●●○	C-EO
Sildenafil should be considered in patients with refractory pulmonary hypertension (i.e., unresponsive to iNO) or as an adjunct when weaning iNO.	●●●○	B-R
Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension.	●●●●	B-NR
Prostaglandin E_1 can be used to maintain ductus arteriosus patency and reduce right ventricular afterload in patients with pulmonary hypertension with right ventricular failure, or in the presence of a closing ductus.	●●●○	C-LD
Extracorporeal life support		
The possibility of extracorporeal life support should be discussed during prenatal counselling for CDH, and should disclose that available evidence does not suggest a survival benefit to its use.	●●●○	B-R

Table 1 (part 2 of 2): Abridged recommendations for diagnosing and managing congenital diaphragmatic hernia

Recommendation	Strength of recommendation*	Level of evidence†
Surgery		
The following physiologic criteria should be met before surgery: • urine output > 1 mL/kg/h • FiO_2 < 0.5 • preductal oxygen saturation between 85% and 95% • normal mean arterial pressure for gestational age • lactate < 3 mmol/L • estimated pulmonary artery pressures less than systemic pressure. Failure to meet these criteria within 2 w should prompt consideration of either attempted repair or a palliative approach.	●●○○	C-EO
Patch repair: For diaphragmatic defects that are not amenable to primary repair, oversized, tension-free polytetrafluoroethylene/GORE-TEX patches should be used.	●●●●	C-LD
Open repair v. minimally invasive surgery: A minimally invasive surgical approach or technique should not be used in the repair of neonatal CDH because of the high rates of recurrence.	●●●●	B-NR
For patients on extracorporeal life support: Surgery should be avoided until after decannulation. If the patient cannot be weaned off extracorporeal life support, consideration should be given for either surgery or palliation, as appropriate.	●●●●	C-LD
Long-term follow-up		
• We recommend standardized multidisciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk.	●●●●	B-NR
• We recommend identifying the subset of CDH survivors at high risk for long-term morbidity as comprising those infants and children who require extracorporeal life support, who have been repaired with a patch or who required respiratory support at 30 days of life.	●●●●	B-NR

Note: CDH = congenital diaphragmatic hernia, iNO = inhaled nitric oxide, O/E LHR = observed-to-expected lung-head ratio.
*Strength of recommendation: the number of circles represents the level of expert consensus during creation of recommendations (see Box 2).
†Level of evidence: evidence supporting the recommendation (see Box 1).

22 Recommendations covering the 3 phases of CDH care

Implementation

CPG Implementation Barriers

- Utilization of CPG's may be hampered by:
  - Poor acceptance
  - Local implementation barriers
  - Institutional readiness to accept change
- "Organizational readiness to change" (ORCA) is a key overarching principle to assesses the capacity and the collective perception that its members can execute change in an efficacious or successful manner
- If an organization's readiness for change is high
  - More likely to be successful in implementing change
  - More resilient when confronting obstacles

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Standardizing congenital diaphragmatic hernia care in Canada: Implementing national clinical practice guidelines☆

Kathryn LaRusso[a], Robert Baird[b], Richard Keijzer[c], Erik Skarsgard[b], Pramod Puligandla[a,*]

[a] Division of Pediatric General and Thoracic Surgery, The Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada
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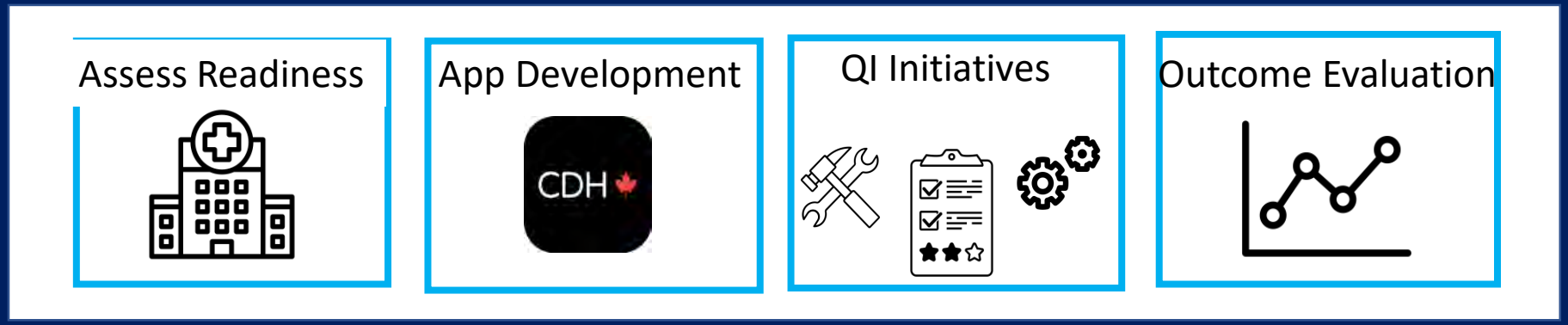
[c] Division of Pediatric Surgery, Health Sciences Centre Children's Hospital, University of Manitoba, Winnepeg, Manitoba, Canada

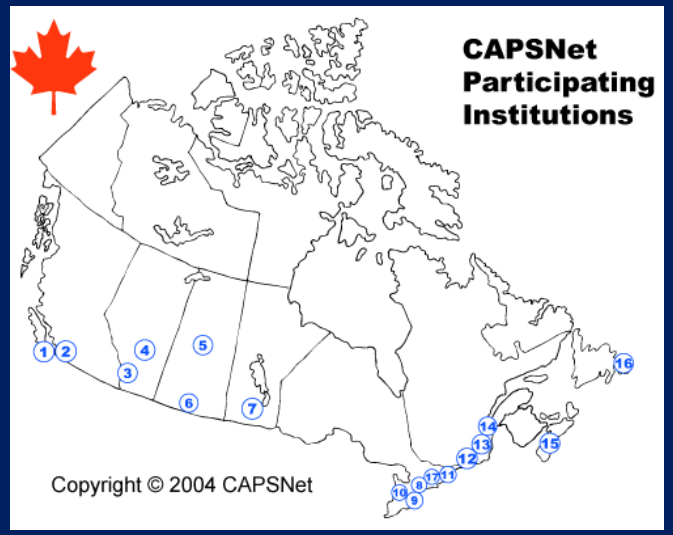
Research Questions

1. Do clinicians across Canada know about CPG?
2. Are they using it?
2. What are the local barriers to using the CPG?
3. How can the CPG be better implemented at the local level?



Methods

- A validated readiness assessment was sent to all 16 CAPSNet site coordinators via SurveyMonkey™
  - 32 questions
  - Forwarded to multidisciplinary CDH stakeholders
- Organizational Readiness to Change Assessment*
  - Stakeholder assessment of evidence strength
  - Quality of the environment slated for change
  - Local facilitation
- Survey valid from 11/2018 - 02/2019
  - 2 email reminders



*Implementation Sci (2009): 4:38

Results

15/16 CAPSNet Sites

- Neonatology (n=27)
- Pediatric Surgery (n=25)
- Respiratory Therapy (n=10)
- Responses from other specialties and health professionals

86 Responses

↓

56 completed entire survey (65%)

↓

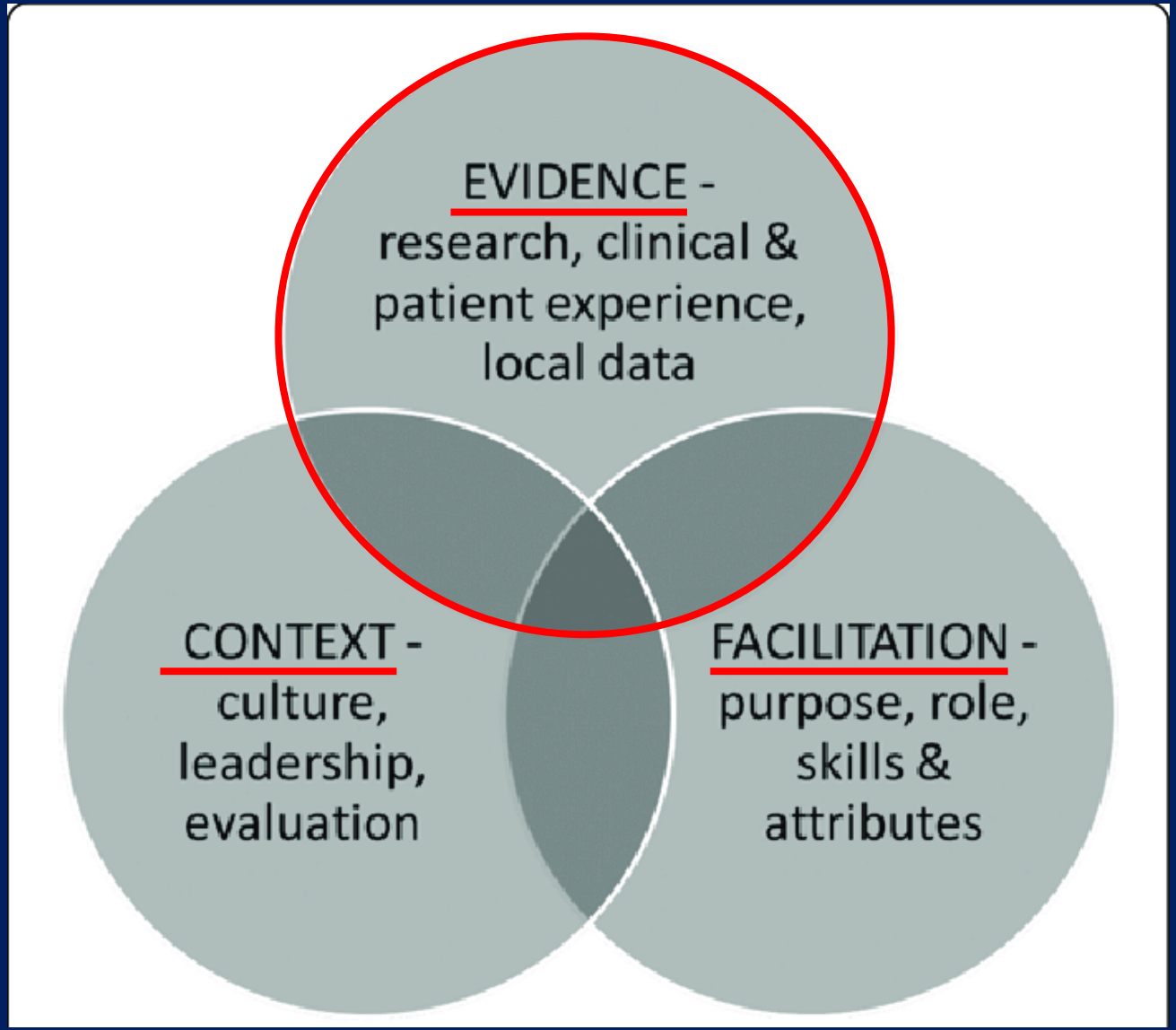
79% aware of CPG

↓

63% using CPG

Promoting Action on Research Implementation in Health Services (PARiHS) Framework

- 70% of respondents felt that the CDH recommendations were informed by the best available evidence



- >75% felt that local clinical leaders would support recommendations

McGill

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

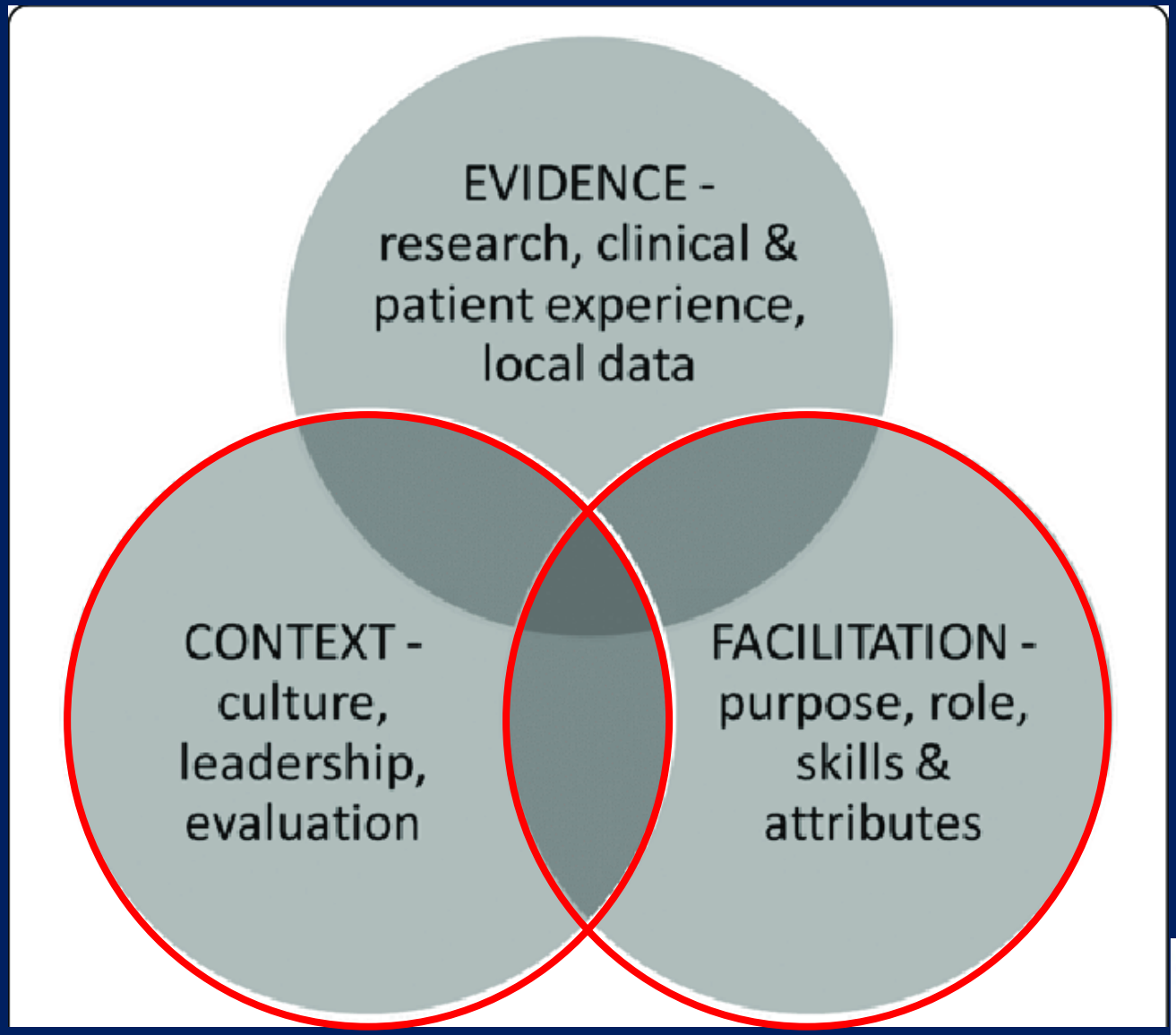
Montreal Children's Hospital
McGill University Health Centre

Can they be implemented?

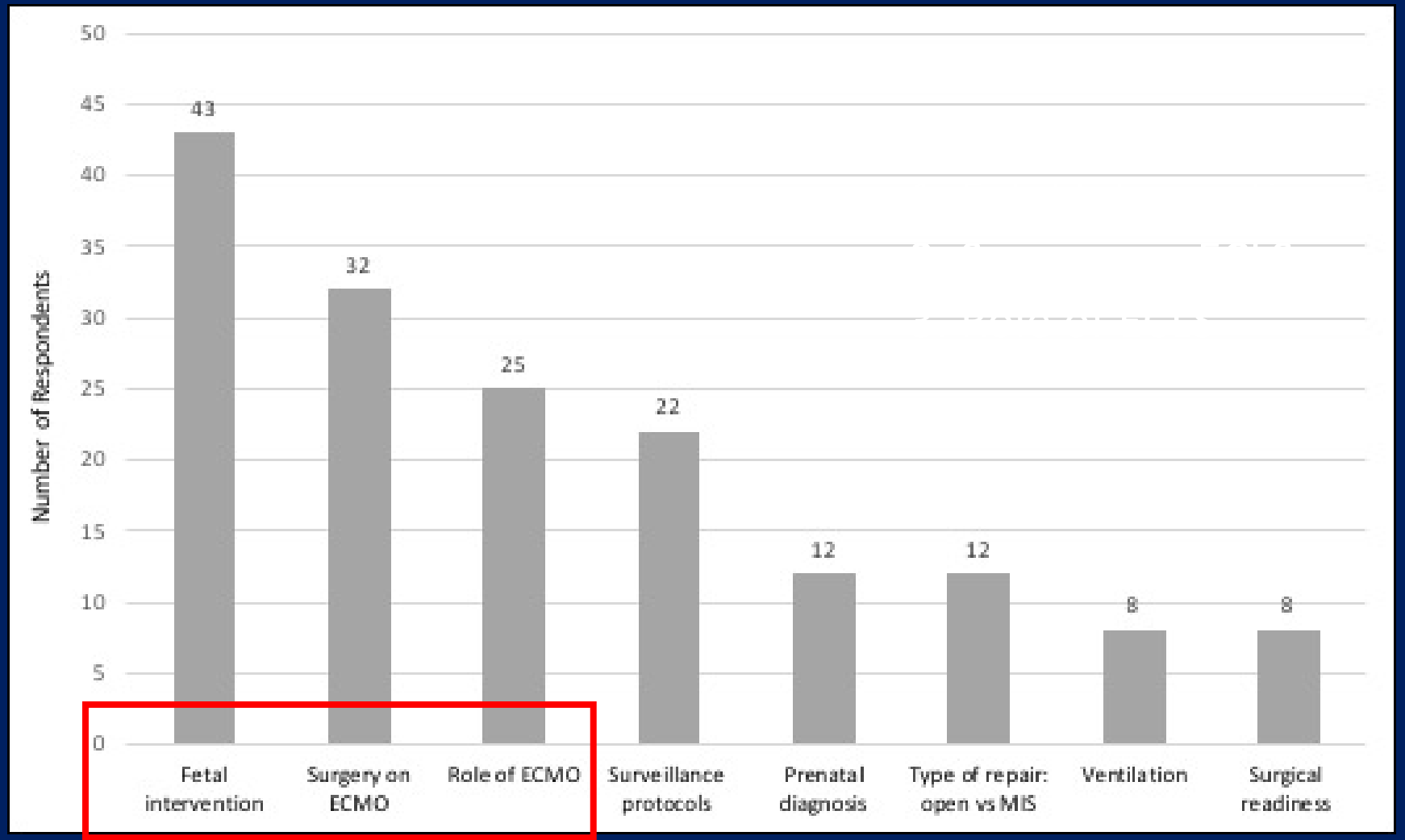
>80% felt they could implement more than three-quarters of the CPG recommendations

Promoting Action on Research Implementation in Health Services (PARiHS) Framework

- 85-90% felt responsibility to improve CDH outcomes and would work collaboratively with clinical leadership and implementation team

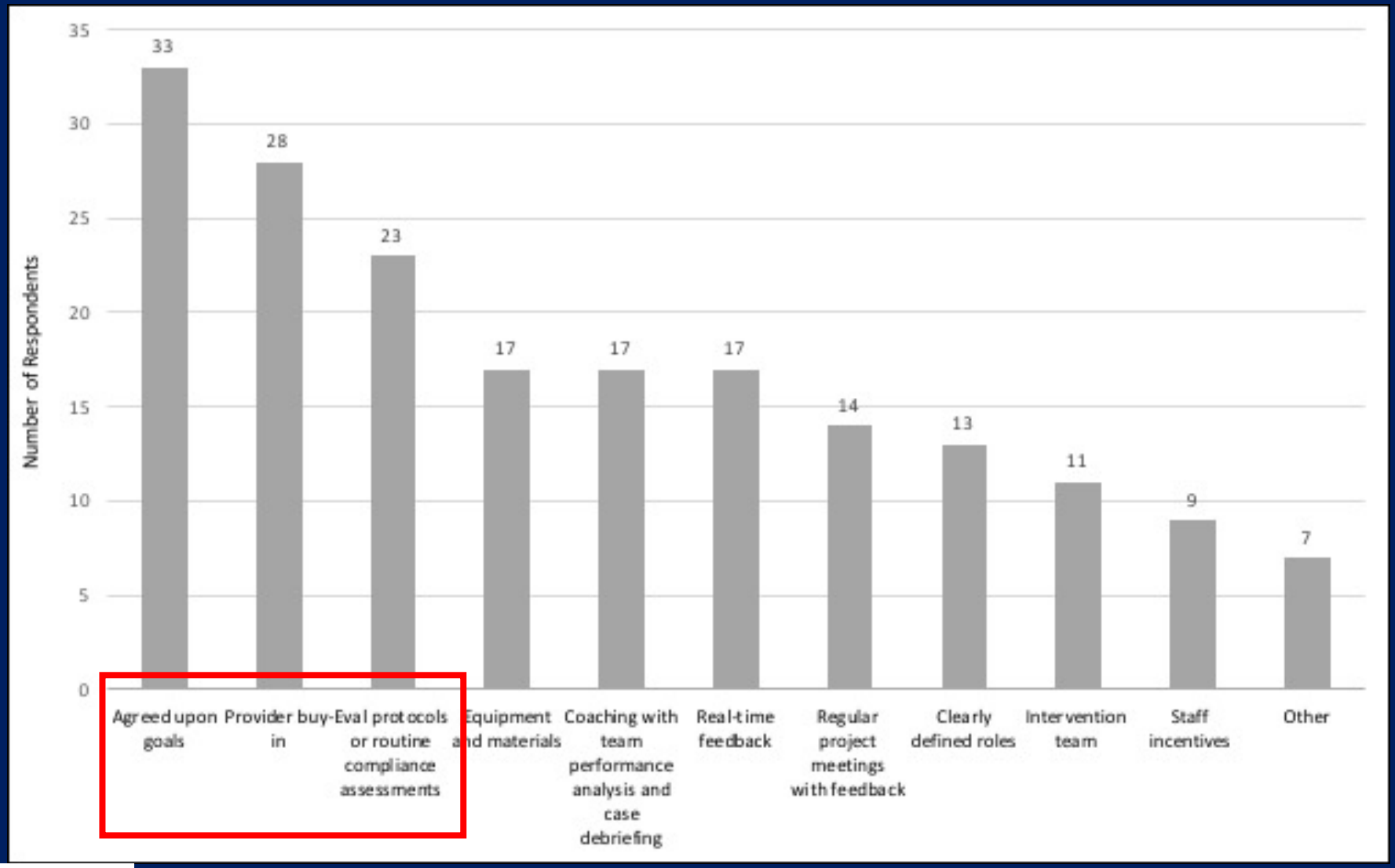


Which recommendations within the CPG would be most difficult to implement?



Fetal Intervention
ECMO
Surgery on ECMO

How can the CPGs be better implemented?



Common team goals
Provider Buy-in
Regular evaluation
Compliance testing

Survey Summary

Majority aware of CPGs

Evidence is strong and broadly utilized in part or whole

Fetal and ECLS are not necessary at all centers

Prenatal and long-term surveillance should be possible with additional resources and network support

Provider buy-in

Multi-D intervention teams

Evaluation

Guideline Updates

New data consistent with current recommendations

- Original report remains unchanged
- Strength of recommendation may be modified

New data is inconsistent with current recommendations

- New evidence does not alter the initial conclusions
- Strength of new evidence will alter current conclusions in original document

Where are we now and how does this affect care delivery CDH?

Clinical Practice Guidelines in CDH?

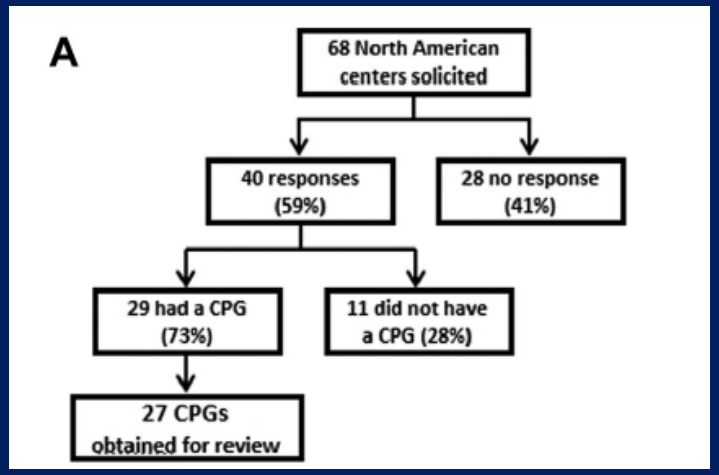


Table 3 – Key components of CDH management with frequency of inclusion in 27 CDH CPGs.

Management component	Number of CPGs (%)	Details
Delivery plan	8 (30)	
Immediate intubation at birth for all CDH patients	19 (70)	Two CPGs recommend intubation only with respiratory distress
Insert Replogle at delivery	24 (89)	
Avoid hand bagging	14 (52)	One CPG recommended bagging pressures <25 cm H_20
Umbilical or right radial arterial line	23 (85)	
Umbilical venous access	20 (74)	1. one CPG recommends femoral line 2. Six recommend early PICC insertion after or concurrent with UVC
Sedation addressed	18 (67)	1. 10 use morphine first-line, 7 fentanyl 2. 12 specify midazolam, 1 lorazepam
Neuromuscular blockade discouraged	19 (70)	10 describe indications for blockade (extremis, procedure, poor ventilation, HFOV)

HFOV = high-frequency oscillatory ventilation; PICC = peripherally inserted central catheter; UVC = umbilical venous catheter.

So where do we go now?

- There is a significant opportunity for standardization of care in CDH
  - CDH Euro-Consortium, Canadian CDH Collaborative
- Process issues
  - Strength of evidence vs expert opinion
  - Pragmatism vs prescription
  - Support innovation
  - Include all stakeholders, including patients, families and advocacy groups
- Applying the best care and evidence to local context

Summary

- ✓There is value in the standardization of care for CDH
  - ✓Removes unwanted variability without stifling innovation
  - ✓Cornerstone for CQI and patient safety
  - ✓Value of pragmatism vs prescription
  - ✓Local context
- ✓Need to update guidelines based on new, emerging evidence
  - ✓Use app to “push” new evidence/recommendations
- ✓Assessment of Implementation barriers is essential for guideline uptake
- ✓Quantify the impact of the CPGs on CDH outcomes

Questions?

THE CANADIAN COLLABORATIVE

CDH

CLINICAL PRACTICE GUIDELINES

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Montreal Children's Hospital
McGill University Health Centre

Congenital Diaphragmatic Hernia
Update on fetal diagnosis

A.Benachi; H.Bouchghoul; J.Saada; V.Fouquet; AG.Cordier

Centre Maladie Rare: Hernie de Coupole Diaphragmatique

Centre Pluridisciplinaire de Diagnostic Prénatal Béclère-Bicêtre Clamart- France

Prevalence and diagnosis

- Epidemiology of CDH using data from high quality, population based registers belonging to EUROCAT
- CDH cases, 1980-2009, 31 registers, 12M births
- 10.4% associated with chromosomal anomalies or genetic syndrome
- 28.2% with major structural anomalies
- Male/female: 1:0.69
- Prevalence
  - 2.3 (95%CI 2.2 to 2.4) per 10 000 births
  - 1.6 (95%CI 1.6 to 1.7) per 10 000 births when isolated

Canada: 3.38/10 000 *(ICBDSR Annu Rep 2014)*

USA: 1.93/10000 (Balayla J et al, J Maternal Fetal Med, 2014)

Utah: 3.17/10 000 *(Shanmugam H et al, Birth Defect Research, 2017)*

McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Prevalence and diagnosis

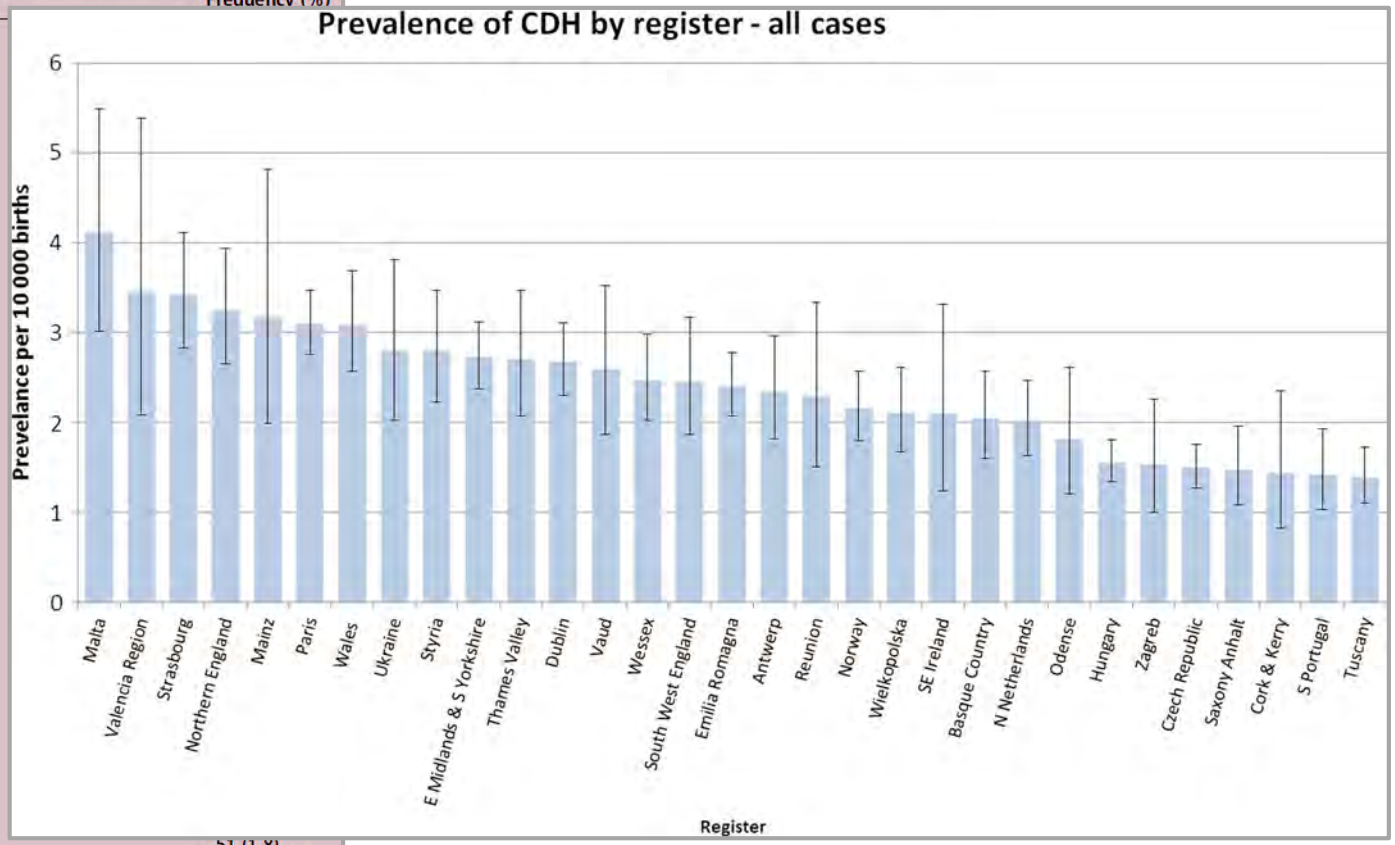
- Increase prevalence over time but not for isolated cases
- Variations among countries
- Mean gestational age at delivery: 39 weeks (IGR 37-40)
- Outcomes overall/isolated
  - Live birth 83.4% /88.7%
  - TOP 13% (4.6% in 1980-84 to 14.4% 2005-09)/8.9% (1.6% to 10.4%)
  - Stillbirth 3.6%/2.4%
- No effect of maternal age

McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Prevalence and diagnosis

Table 1 Commonly associated structural anomalies in singleton cases of congenital diaphragmatic hernia (n=2776)

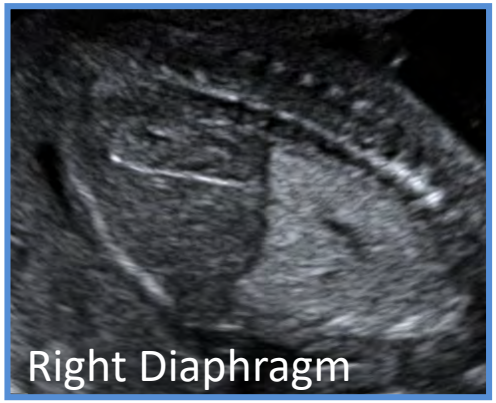
Most common associated anomalies	Frequency (%)
Cardiac anomalies	
Ventricular septal defect	
Atrial septal defect	
Hypoplastic left heart	
Coarctation of aorta	
Urinary	
Congenital hydronephrosis	
Limb	
Limb reduction	
Upper limb reduction	
Lower limb reduction	
Club foot—talipes equinovarus	
Polydactyly	
Syndactyly	
Respiratory (specific groups)	
Nervous system	
Neural tube defects	
Hydrocephalus	
Spina bifida	
Anencephalus and similar	
Oro-facial clefts	
Cleft lip with or without palate	
Cleft palate	
Digestive system (excluding CDH)	
Ano-rectal atresia	
Abdominal wall defects	
Genital	51 (1.8)
Hypospadias	21 (0.8)
Ear, face and neck	43 (1.5)
Eye	18 (0.6)



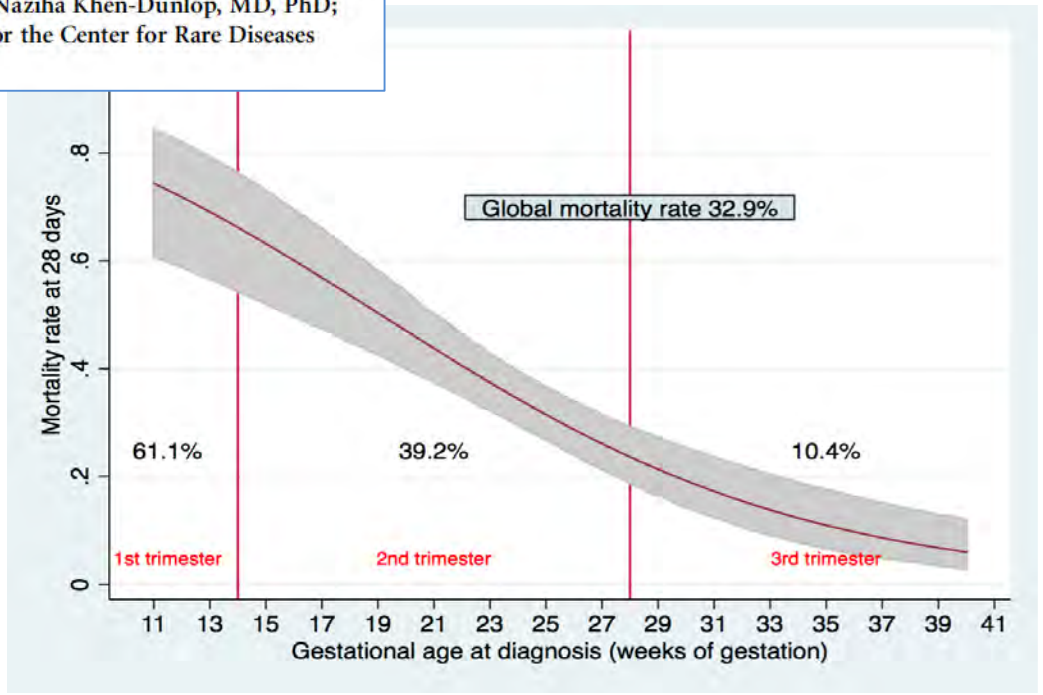
McGivern MR et al. Arch Dis Child Fetal Neonatal Ed, 2015

Congenital diaphragmatic hernia: does gestational age at diagnosis matter when evaluating morbidity and mortality?

Hanane Bouchghoul, MD; Marie-Victoire Senat, MD, PhD; Laurent Storme, MD, PhD; Pascal de Lagausie, MD, PhD; Laetitia Begue, MD; Naziha Khen-Dunlop, MD, PhD; Jean Bouyer, PhD; Alexandra Benachi, MD, PhD; for the Center for Rare Diseases for Congenital Diaphragmatic Hernia



2009-2013: 5% of cases diagnosed at first trimester
Sample size n=377



Mortality rate at 48h and 28 d decreases with GA at diagnosis ($p<0.001$) (adjustment for size of the hernia, thoracic herniation of the liver, GA at birth, LHRo/e, FETO)

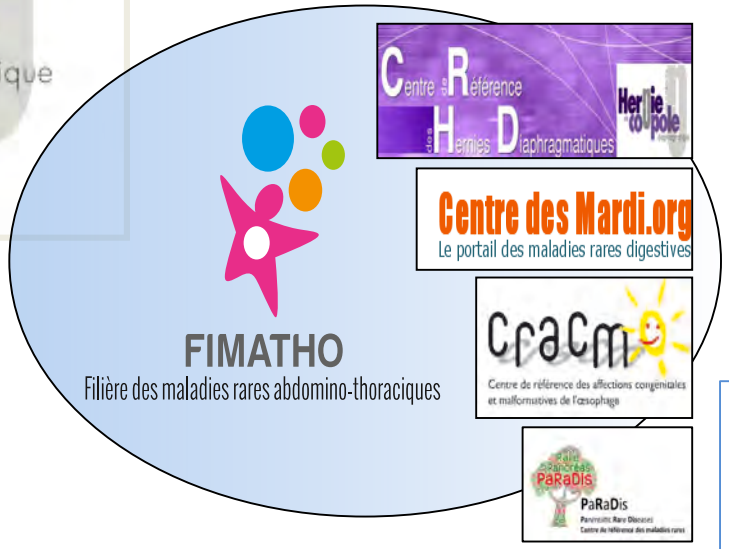
Bouchghoul H et al. Am J Obstet Gynecol, 2015

Hôpitaux universitaires Paris-Sud
Antoine-Béclère

Hernie de coupole diaphragmatique

Centre de Maladie Rare

Hernie de coupole diaphragmatique



European Reference Network

for rare or low prevalence complex diseases

Network
Inherited and Congenital Anomalies (ERNICA)

CDH – Prognostic Evaluation

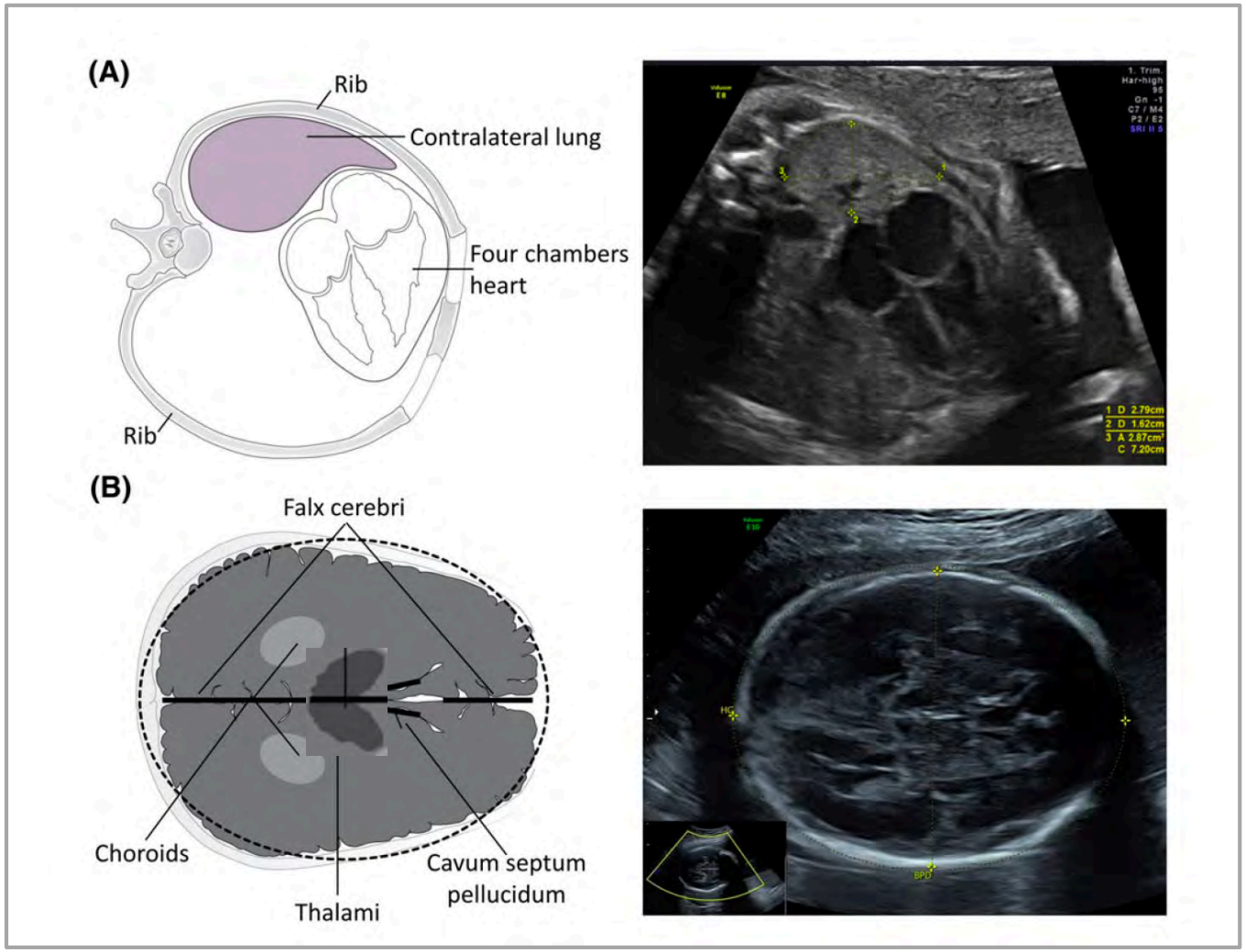
Proposal for standardized prenatal ultrasound assessment of the fetus with congenital diaphragmatic hernia by the European reference network on rare inherited and congenital anomalies (ERNICA)

Francesca Maria Russo[1,2] | Anne-Gael Cordier[3] | Luc De Catte[1,2] | Julien Saada[4] | Alexandra Benachi[3,4] | Jan Deprest[1,2,5] |
on behalf of the Workstream Prenatal Management, ERNICA European reference network

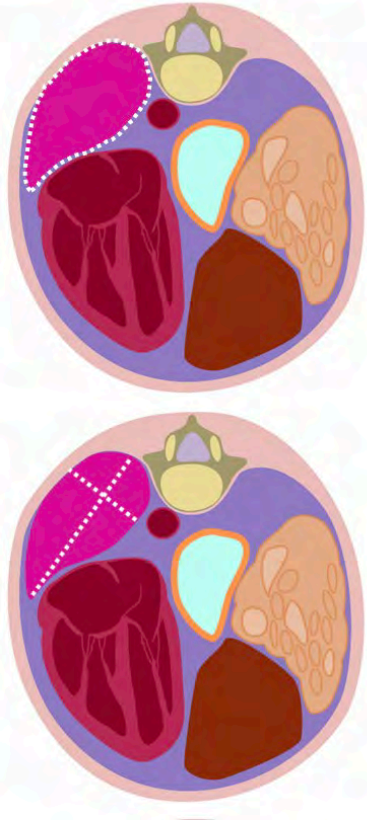
We provide a practical and instructional guide for the standardized assessment of fetuses with isolated left or right congenital diaphragmatic hernia and individualized prediction of neonatal outcome.

Russo FM et al. Prenat Diagn, 2018

Prognostic Evaluation-LHR o/e



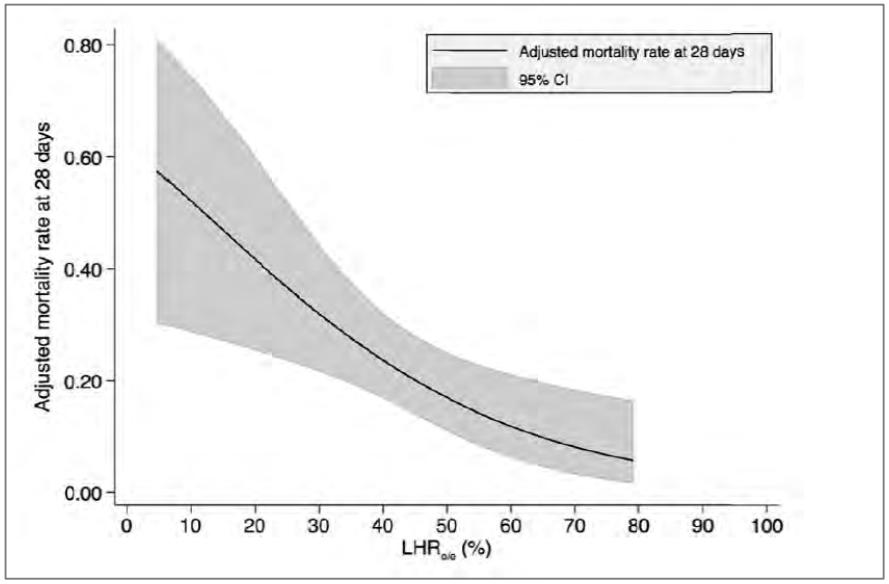
Trace method



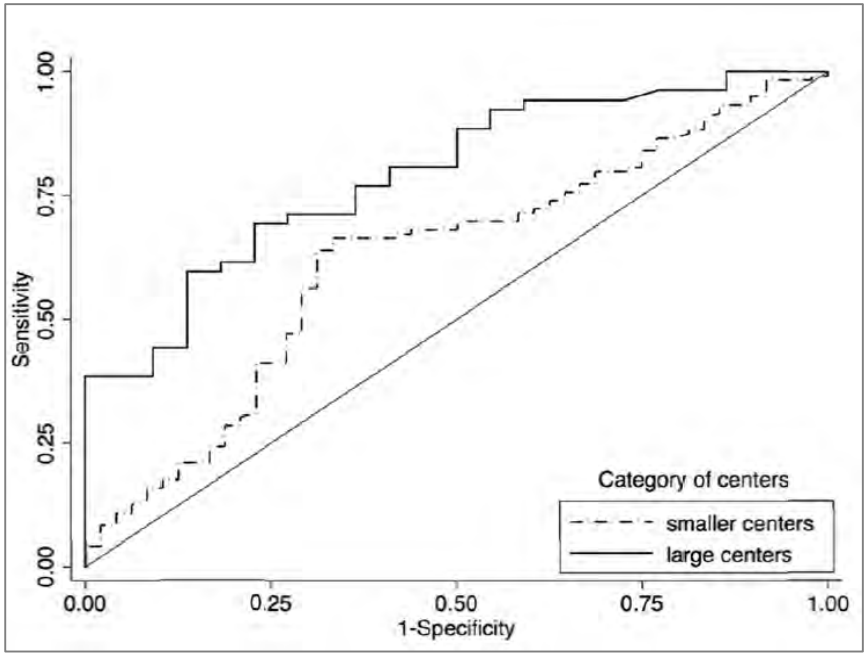
Longest diameters method

Jani J et al, Ultrasound Obstet Gynecol 2012
Russo FM et al, Prenat Diagnosis, 2018

Prognosis of isolated congenital diaphragmatic hernia using lung-to-head circumference ratio: variability across centers in a national perinatal network



Adjusted relationship between 28-days mortality and o/e LHR



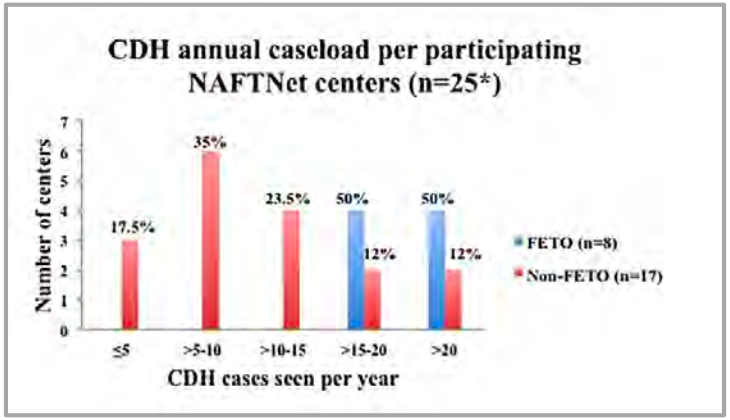
Predictive capacity (AUC) of o/e-LHR for 28 days survival according to category of centers (< ou ≥ 14/year)

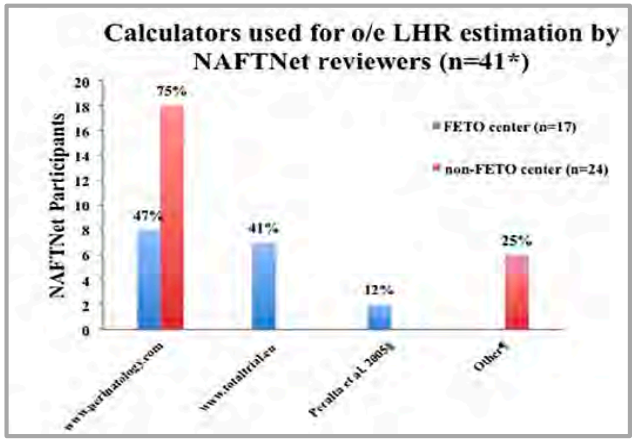
The overall predictive value of o/e-LHR is better when prenatal LHR measurements are performed in centers with the greatest caseload and strong expertise in prenatal assessment of CDH

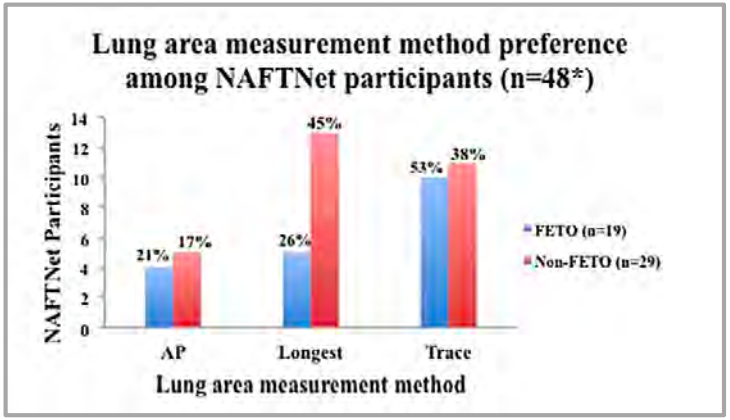
Senat et al. Ultrasound Obstet Gynecol, 2017

Prognostic Evaluation-LHR o/e

Variability in antenatal prognostication of fetal diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)







- Image selection for measurements: Landmarks of a true axial plane and 4-chamber view of the heart
- Formula: *Jani et al. USOG 2012*

Abbasi N et al. Prenat Diagnosis, 2019

Prognostic Evaluation-LHR o/e

Reproducibility of fetal lung-to-head ratio in left diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)

- Comparison of lung area measurement methods on de-identified sonographic clips of left CDH across 26 centers (17 non-FETO and 9 FETO) within the North American Fetal Therapy Network and in comparison with an external European reviewer
- The trace method demonstrated the highest inter-rater agreement with the lowest bias
- Lower expertise in non FETO centers, lower agreement in HC measurements also
- Only for left CDH

Abbasi N et al. Prenat Diagnosis, 2019

Prognostic Evaluation-LHR o/e

The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study

Kitty G. Snoek[1†], Nina C. J. Peters[2*†], Joost van Rosmalen[3], Arno F. J. van Heijst[4], Alex J. Eggink[2], Esther Sikkel[5], René M. Wijnen[1], Hanneke IJsselstijn[1], Titia E. Cohen-Overbeek[2] and Dick Tibboel[1]

- Evaluate predictive value of o/e LHR for survival and chronic lung disease in an era of standardized neonatal management
  - Retrospective cohort, 2 high volume centers in Netherlands
  - 122 isolated cases 2008-2014
- 77.9% survived and 38.9% CLD
  - First measured o/e LHR significantly predict survival and CLD

Snoek KG et al. Prenat Diagn, 2017

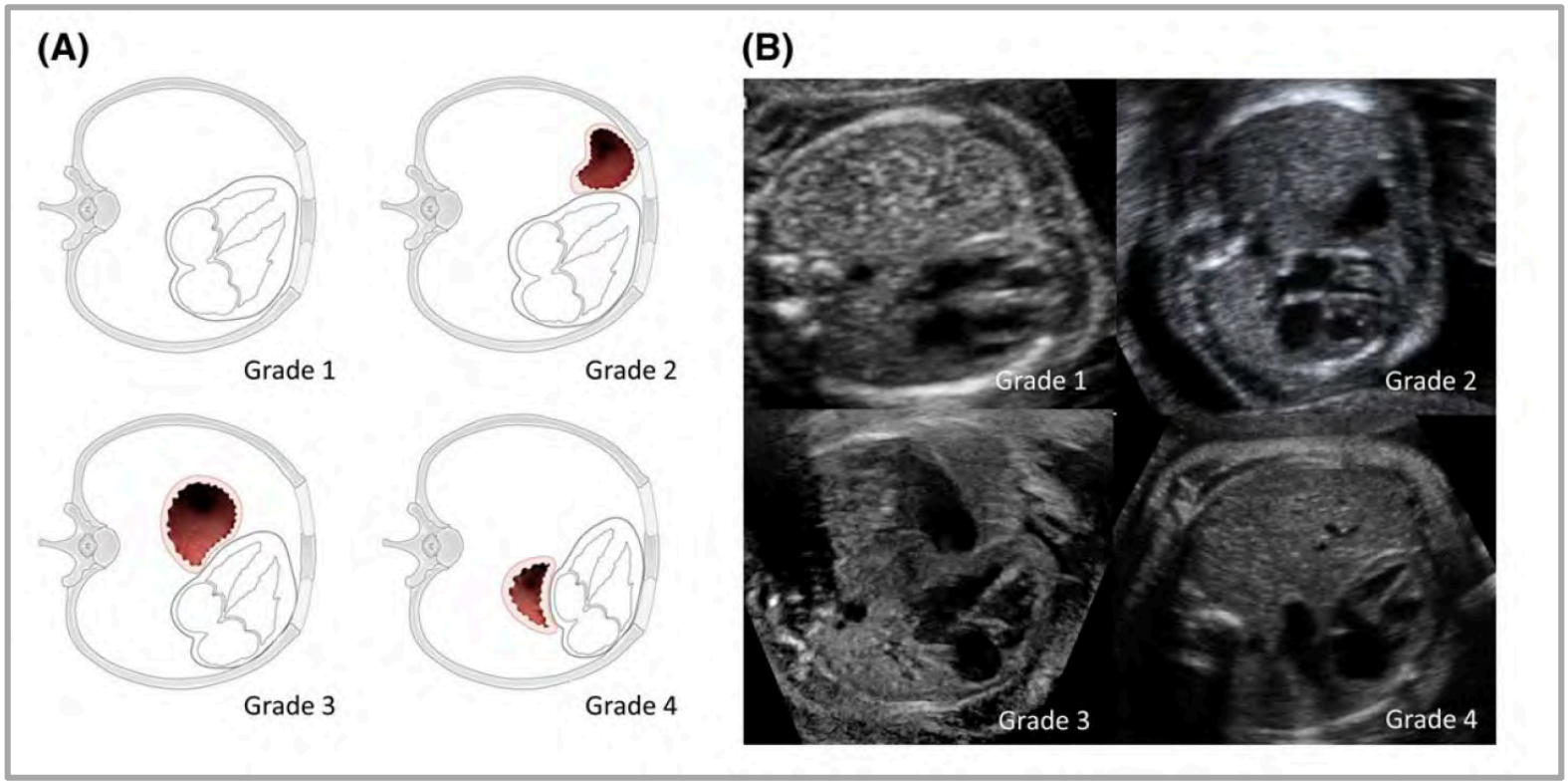
Prognostic Evaluation-LHR o/e

Clinically relevant discordances identified after tertiary reassessment of fetuses with isolated congenital diaphragmatic hernia

N (%)	Assessment referrals 43 (33%)	Fetal surgery referrals 86 (67%)	Entire population over 2-year period 129	P-value
Descriptive statistics (based on assessment at FETO-unit)				
No CDH		2		
Right CDH	5/43 (12%)	13/84 (15%)	18/127 (14%)	ns
Liver up	5/5 (100%)	12/13 (92%)	17/18 (94%)	ns
O/E LHR	32.13%	25.8%	31.4%	ns
Left CDH	38/43 (88%)	71/84 (85%)	109/127 (86%)	ns
Liver up	29/38 (76%)	59/71 (83%)	88/109 (81%)	ns
O/E-LHR	30.9%	23%	24%	ns
% with severe lung hypoplasia[a]	13/38 (34%)	43/71 (61%)	56/109 (51%)	<0.005
Discordance between referring center and FETO-unit				
Absence of DH	0	2/86 (2%)	2 (2%)	
Presence of associated anomalies	6/43 (14%)	8/86 (10%)	14/129 (11%)	ns
Liver discordance	9/18 (50%)	2/29 (7%)	11/47 (23%)	<0.005
Overestimated severity	1/18 (5%)	1/29(3%)	2/47 (4%)	ns
Underestimated severity	8/18 (44%)	1/29(3%)	9/47 (19%)	<0.005
O/E LHR	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns
Overestimated lung size >10%	0/8 (0%)	0/8 (0%)	0/16 (0%)	ns
Underestimated lung size >10%	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns

Done E et al. Prenat Diagn, 2017

Prognostic Evaluation-Liver position



Cordier AG et al. Ultrasound Obstet Gynecol, 2015
Russo FM et al. Prenat Diagn, 2018

Prognostic Evaluation-Liver position

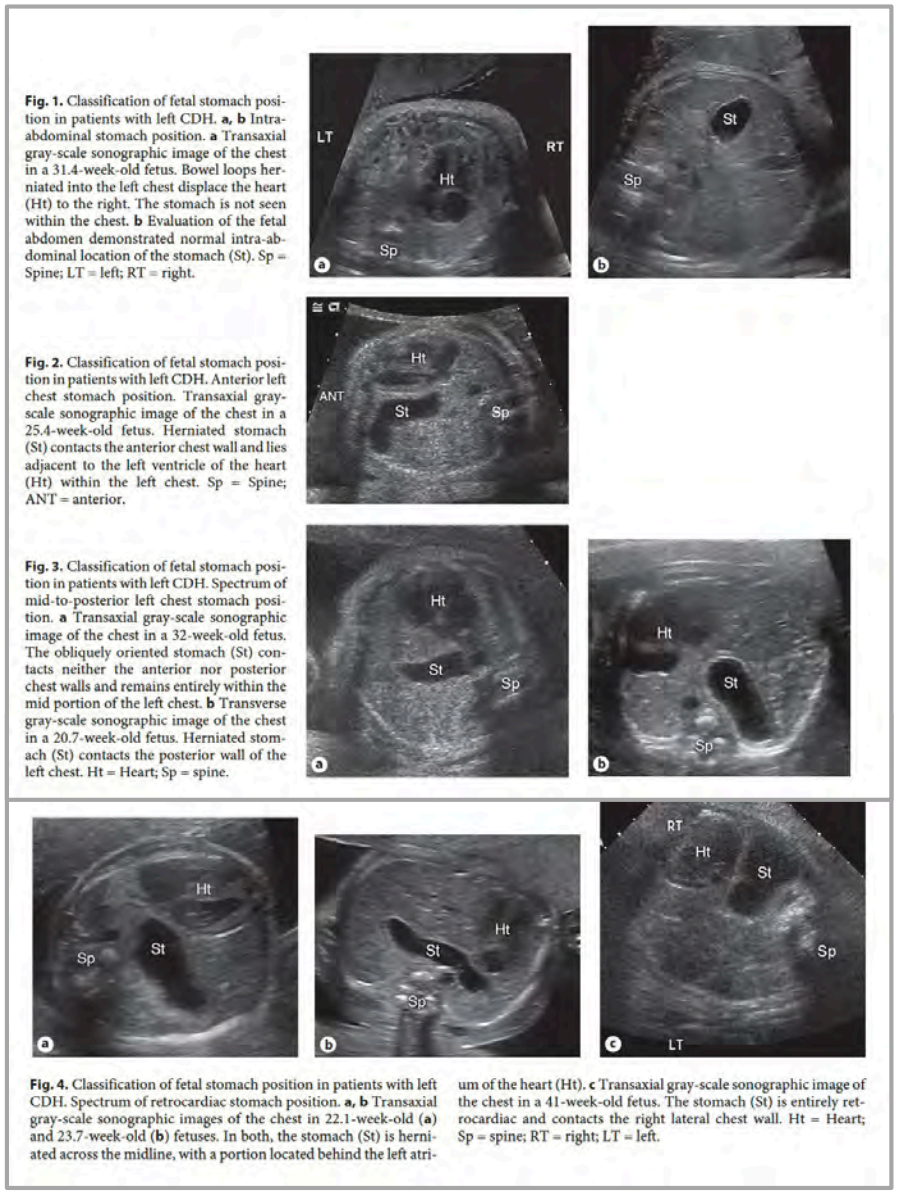


Fig. 1. Classification of fetal stomach position in patients with left CDH. **a, b** Intra-abdominal stomach position. **a** Transaxial gray-scale sonographic image of the chest in a 31.4-week-old fetus. Bowel loops herniated into the left chest displace the heart (Ht) to the right. The stomach is not seen within the chest. **b** Evaluation of the fetal abdomen demonstrated normal intra-abdominal location of the stomach (St). Sp = Spine; LT = left; RT = right.

Fig. 2. Classification of fetal stomach position in patients with left CDH. Anterior left chest stomach position. Transaxial gray-scale sonographic image of the chest in a 25.4-week-old fetus. Herniated stomach (St) contacts the anterior chest wall and lies adjacent to the left ventricle of the heart (Ht) within the left chest. Sp = Spine; ANT = anterior.

Fig. 3. Classification of fetal stomach position in patients with left CDH. Spectrum of mid-to-posterior left chest stomach position. **a** Transaxial gray-scale sonographic image of the chest in a 32-week-old fetus. The obliquely oriented stomach (St) contacts neither the anterior nor posterior chest walls and remains entirely within the mid portion of the left chest. **b** Transverse gray-scale sonographic image of the chest in a 20.7-week-old fetus. Herniated stomach (St) contacts the posterior wall of the left chest. Ht = Heart; Sp = spine.

Fig. 4. Classification of fetal stomach position in patients with left CDH. Spectrum of retrocardiac stomach position. **a, b** Transaxial gray-scale sonographic images of the chest in 22.1-week-old (**a**) and 23.7-week-old (**b**) fetuses. In both, the stomach (St) is herniated across the midline, with a portion located behind the left atrium of the heart (Ht). **c** Transaxial gray-scale sonographic image of the chest in a 41-week-old fetus. The stomach (St) is entirely retrocardiac and contacts the right lateral chest wall. Ht = Heart; Sp = spine; RT = right; LT = left.

- Prognostic factor by itself and not a proxy of liver herniation
- No precise landmarks

Basta AM et al. Fetal Diagn Ther, 2016

Correlation between stomach grading and Gastrointestinal morbidity

- Correlation between defect size and global morbidity

  3665 patients. Overall survival 70.9%

  – 61.7% gastrointestinal morbidity

  – Median age at discharge 38 d :

    ▪ 22 d group A à 89 d group D

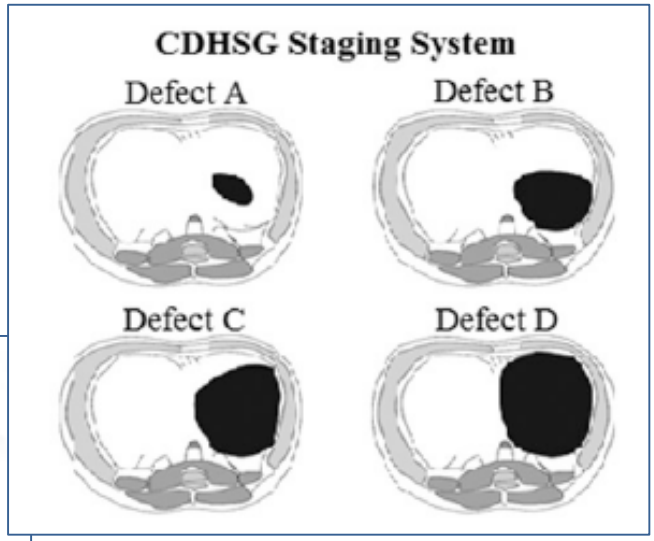


TABLE 3 Morbidity Outcomes at Discharge Based on CDH Defect Size

	All Patients (N = 2183)	No. Missing Data	Defect A (n = 370)	Defect B (n = 979)	Defect C (n = 644)	Defect D (n = 177)	P^a
Any morbidity	1503 (74.6)	167	209 (61.8)	612 (68.4)	514 (85.4)	159 (94.1)	<.001
Pulmonary morbidity	661 (30.4)	6	44 (12.0)	181 (18.5)	312 (48.5)	120 (68.2)	<.001
Supplemental oxygen	417 (19.2)	7	20 (5.5)	95 (9.7)	204 (31.8)	94 (53.4)	<.001
Pulmonary medication	524 (24.0)	0	30 (8.1)	133 (13.6)	246 (38.2)	111 (62.7)	<.001
Neurologic morbidity	447 (21.7)	125	40 (11.7)	137 (15.0)	183 (29.8)	79 (45.7)	<.001
Abnormal neurologic examination	437 (21.2)	125	40 (11.7)	134 (14.6)	177 (28.8)	78 (45.1)	<.001
Neurologic medication	40 (1.8)	0	3 (0.8)	8 (0.8)	18 (2.8)	10 (3.6)	<.001
Gastrointestinal morbidity	1349 (65.2)	114	183 (51.7)	543 (58.8)	474 (77.7)	144 (85.2)	<.001
Supplemental tube feeds	660 (30.5)	22	45 (12.2)	183 (18.9)	309 (48.6)	119 (68.8)	<.001
Gastroesophageal reflux	1227 (58.8)	97	162 (45.6)	496 (53.3)	437 (70.9)	128 (74.4)	<.001
Diagnosed clinically	903 (76.9)	52	144 (90.6)	393 (83.3)	298 (72.7)	62 (50.0)	<.001
Diagnosed radiologically	272 (23.1)		15 (9.4)	80 (16.7)	112 (27.3)	62 (50.0)	<.001
Nuclear scan	33 (12.1)		3 (20.0)	8 (10.0)	12 (10.7)	9 (14.5)	
Upper gastrointestinal series	219 (80.5)	0	10 (66.7)	69 (36.3)	90 (80.4)	48 (77.4)	.564
pH probe	20 (7.4)		2 (13.3)	3 (3.7)	10 (8.9)	5 (8.1)	
Medical therapy	1008 (84.4)		154 (96.3)	450 (92.4)	328 (78.3)	74 (58.7)	
Surgical therapy	184 (15.4)	32	5 (3.1)	35 (7.2)	91 (21.7)	51 (40.5)	<.001
No therapy given	3 (0.2)		1 (0.6)	1 (0.2)	0 (0)	1 (0.8)	
Gastrointestinal medication	353 (16.2)	0	54 (14.6)	145 (14.8)	110 (17.1)	43 (24.3)	.012
Median time on ventilator, d	13 (7–24)	37	7 (4–10)	10 (7–16)	22 (14–34)	30 (22–50)	<.001
Median hospital length of stay, d	38 (23–69)	4	22 (16–32)	31 (22–47)	62 (39–96)	89 (64–132)	<.001

Data are presented as n (%) or median (IQR).

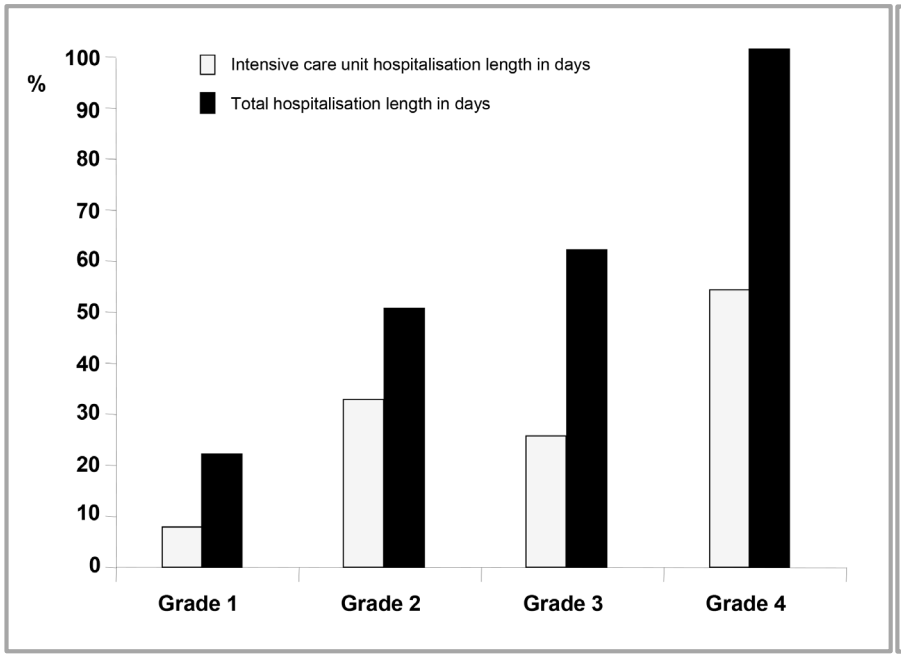
[a] χ^2 or Kruskal–Wallis rank tests comparing these patients with patients without morbidities.

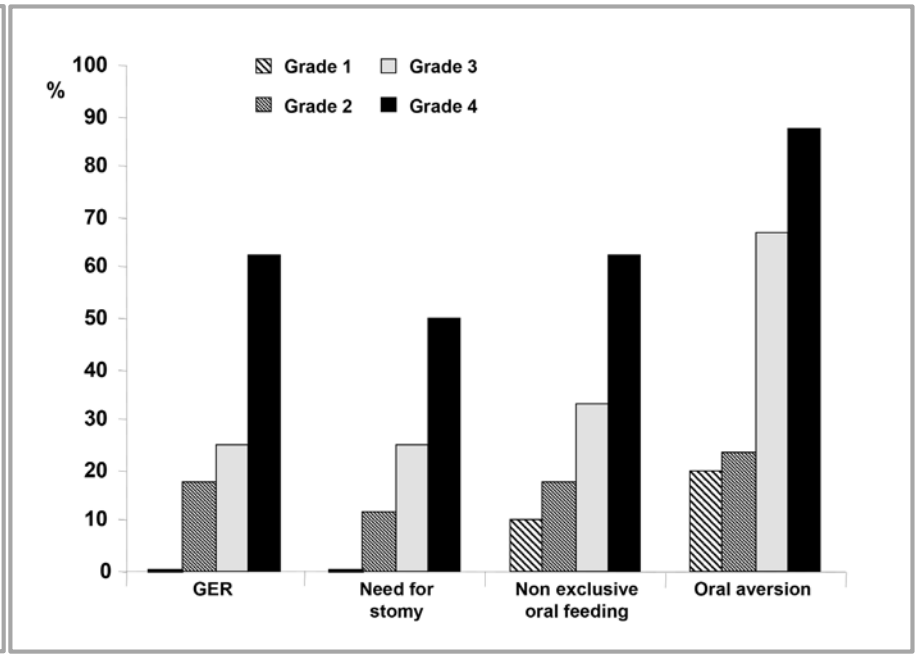
Putnam LR et al. Pediatrics. 2016

Correlation between stomach grading and Gastrointestinal morbidity

Stomach grade (1 à 4)

47 children at 2 years



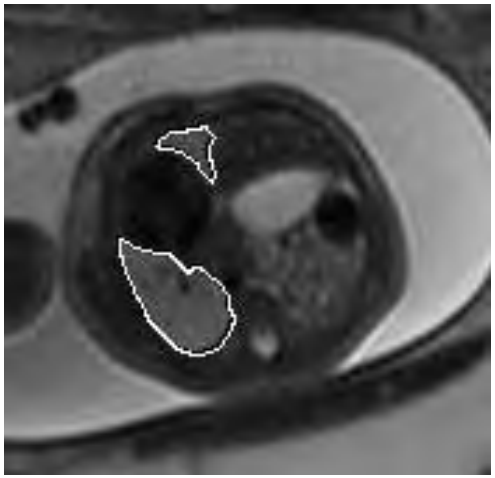


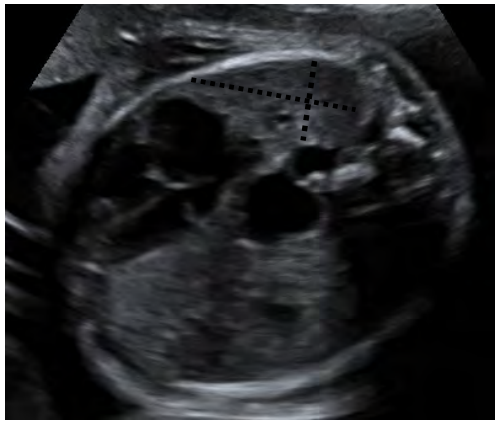
…… Seems to be Independent of FETO

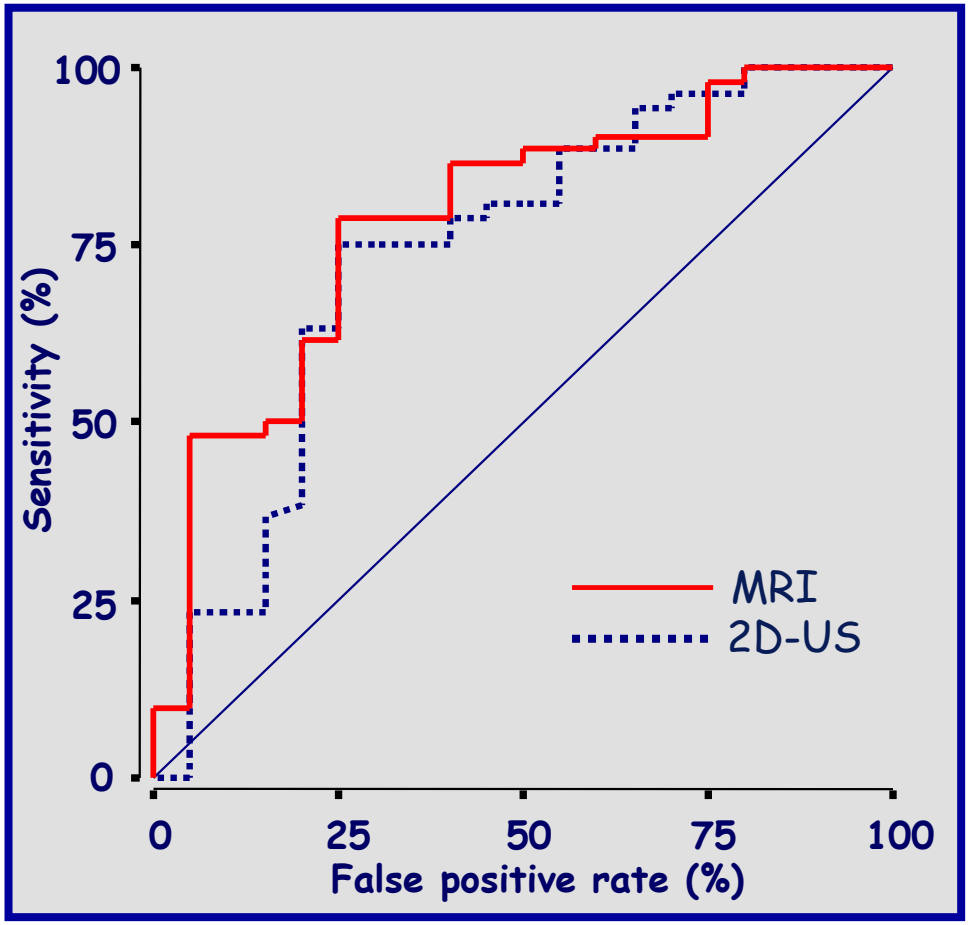
- Same findings at 6 months *Verla MA et a. Fetal Diagn 2019*
- Need for homogenized assessment and follow up of oral disorder and GER

Cordier AG et al, submitted

o/e LHR (2D-US) vs o/e Total lung (MRI)



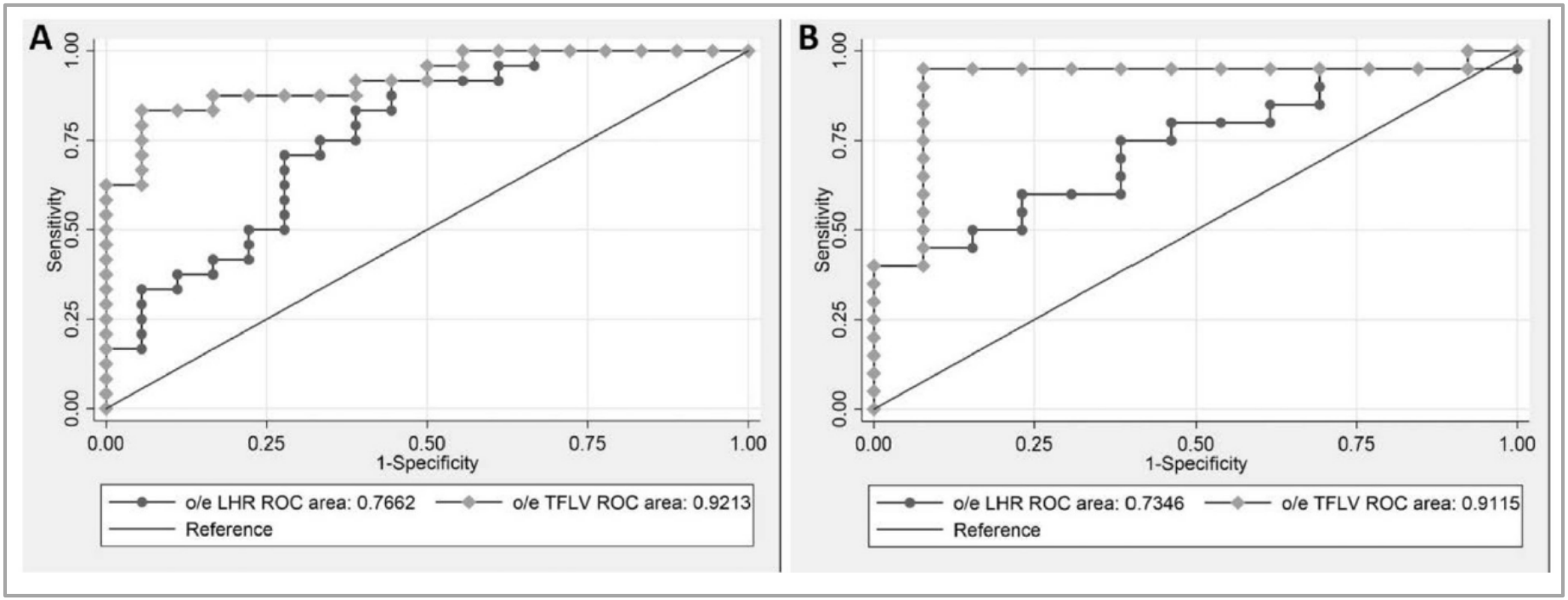




MRI better than 2D LHR in prediction of survival

Jani J et al. Ultrasound Obstet Gynecol, 2008

o/e LHR (2D-US) vs o/e Total lung (MRI)



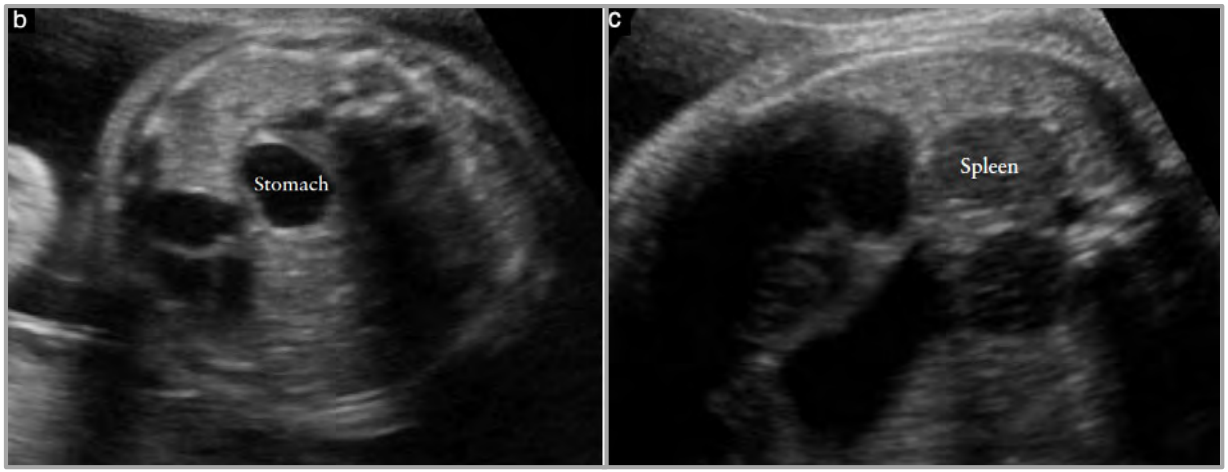
MRI better than 2D LHR in prediction of

- Survival
- Defect size

Kim AG et al. J Ped Surg, 2019

o/e LHR (2D-US) vs o/e Total lung (MRI)

- Reasons for MRI superiority
  - Lung measurement by MRI easier to standardized
  - Both lungs are evaluated
- Reasons for discordance
  - Patient characteristics
  - Fetal position
  - Different timing at measurement and presence of a large stomach or spleen

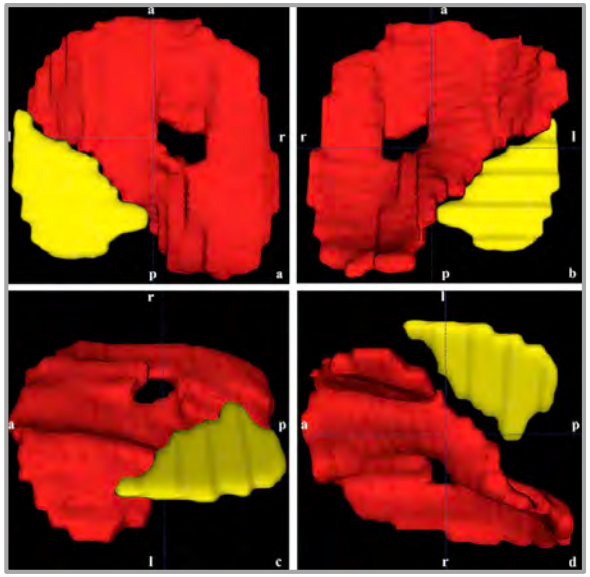


Jani J et al. Ultrasound Obstet Gynecol, 2012

Three-dimensional reconstruction of defects in congenital diaphragmatic hernia: a fetal MRI study

F. PRAYER[1], M. METZELDER[2], W. KROIS[2], P. C. BRUGGER[3], G. M. GRUBER[3], M. WEBER[1], A. SCHARRER[4], A. ROKITANSKY[5], G. LANGS[6], D. PRAYER[1], E. UNGER[7] and G. KASPRIAN[1]

- To assess the clinical feasibility and validity of fetal MRI-based 3D reconstructions to localize, classify, and quantify diaphragmatic defects in congenital diaphragmatic hernia
- Areas of the intact diaphragm and the defect were measured and defect-to-diaphragmatic ratios (DDR) were calculated
- The need for prosthetic patch repair and diaphragm growth dynamics, in cases with repeated in vivo fetal MRI scans, were analyzed based on DDR.



Prayer F et al. Ultrasound Obstet Gynecol, 2019

Prognostic evaluation - R CDH

o/e LHR o/e - Survival

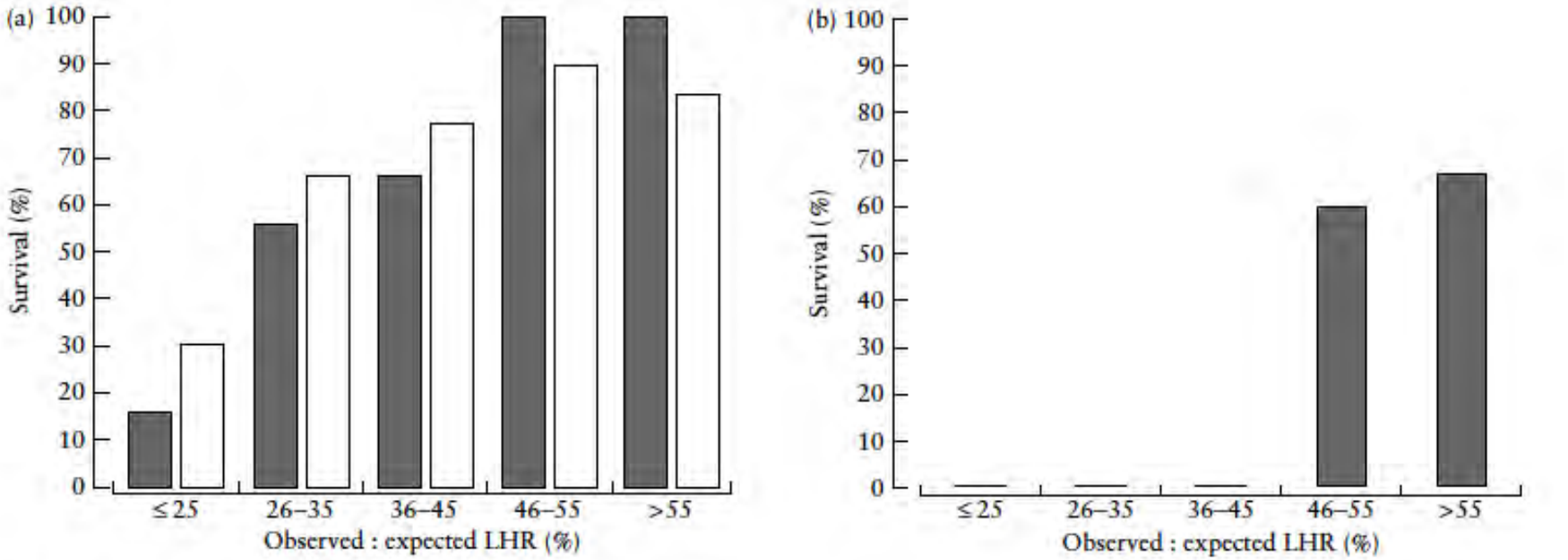


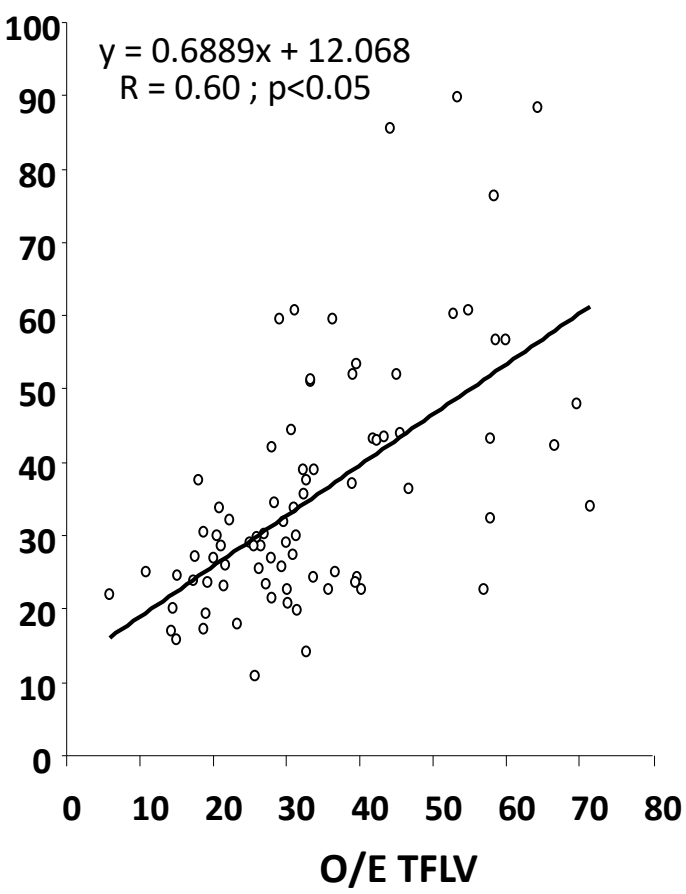
Figure 3 Survival rate according to the fetal observed to expected lung area to head circumference ratio (LHR) in fetuses with isolated left-sided (a) and right-sided (b) diaphragmatic hernia. The filled bars represent fetuses with intrathoracic herniation of the liver and the open bars represent those without herniation.

Jani J et al. Ultrasound Obstet Gynecol, 2007

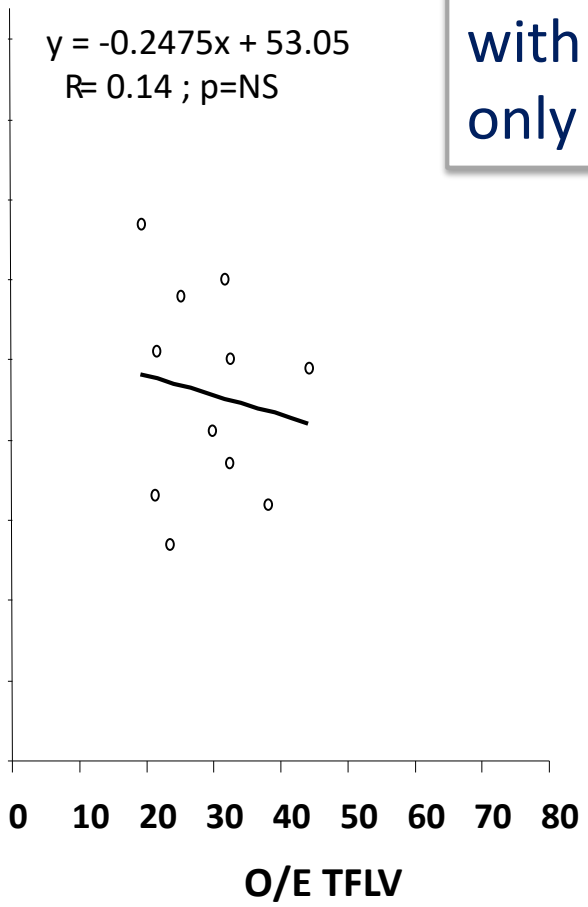
Prognostic evaluation - R CDH

o/e LHR vs o/e TFLV

N= 82 L-CDH



N = 11 R-CDH



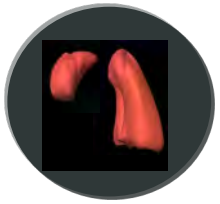
o/e LHR correlates with o/e TFLV at MRI only for left CDH

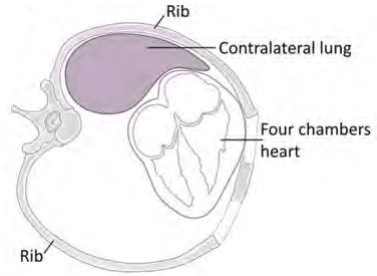
Prognostic evaluation - R CDH

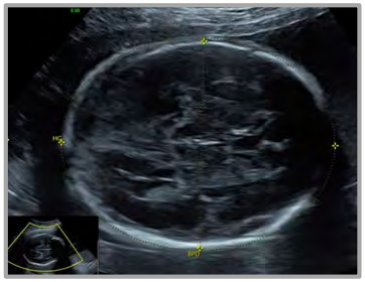
- Controversy over the prognosis due to lack of power and control group in some series
- Identical means of pulmonary volumes for L and R CDH
- Liver amount intra-thoracic is higher in R CDH
- No correlation in R CDH between o/e LHR and
  - Lung volume at pathological examination
  - Lung volume at MRI
  - Therefore, not a good reflection of the total lung volume
- No information on outcome in those studies

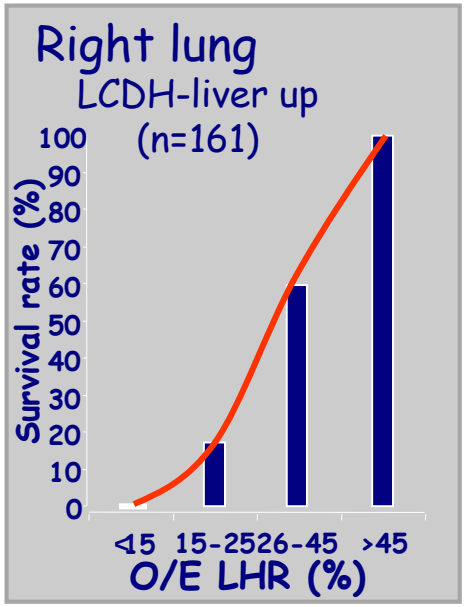
- L and R CDH should not be pooled together in series

Prognostic Evaluation- CDH

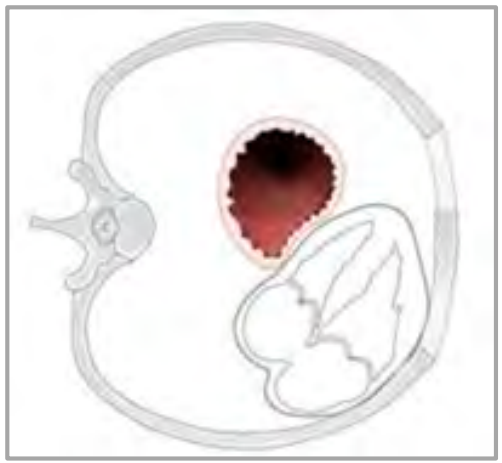








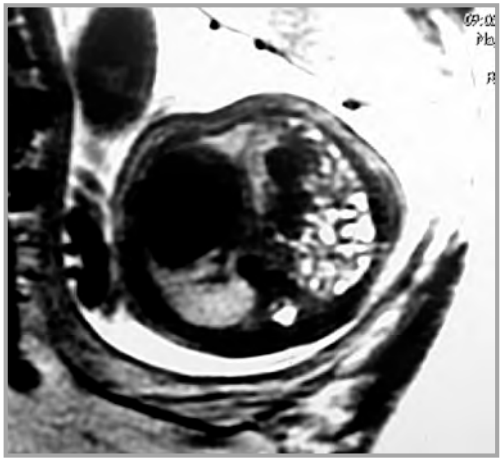
- Detailed scan
- Vascularization
- Heart
- Sac evaluation
- Genetics



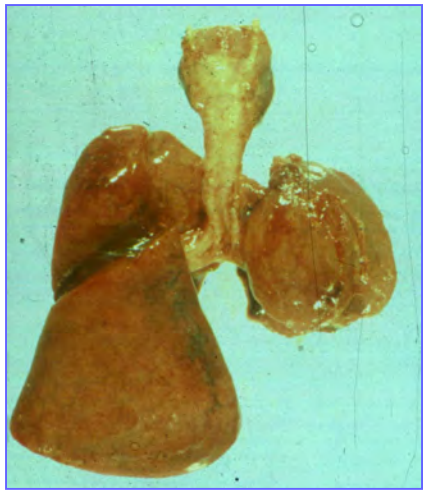
o/e LHR

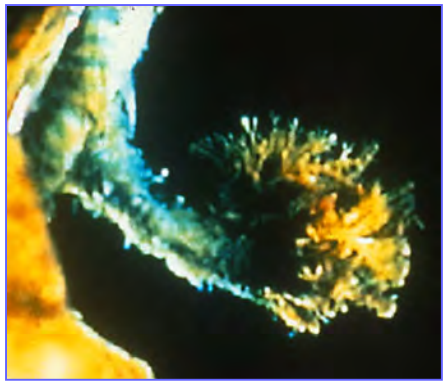
o/e TLV MRI

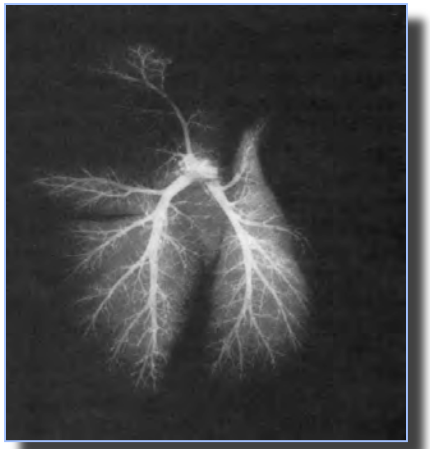
Liver position

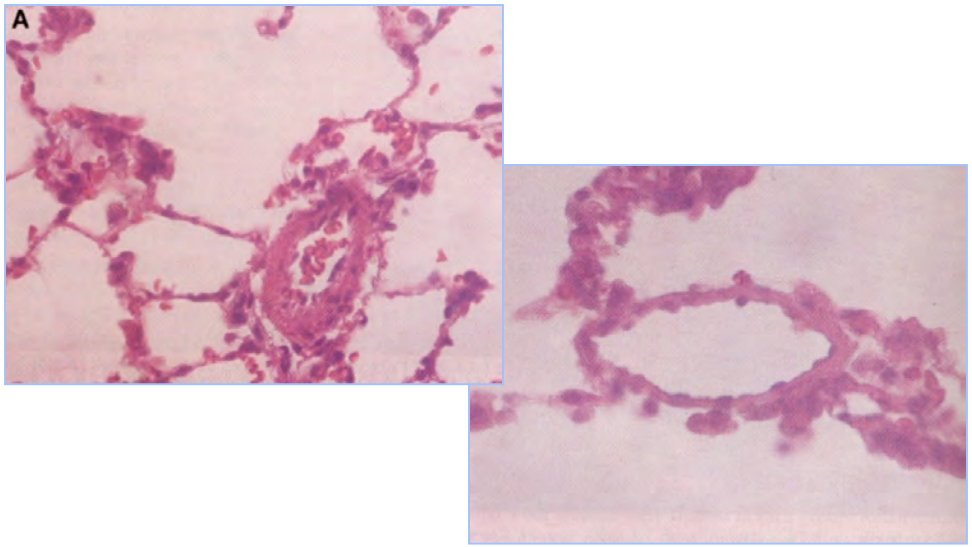


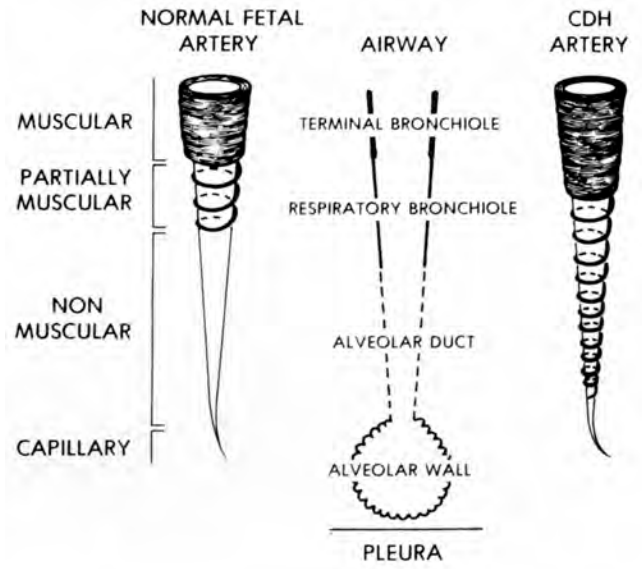
Pulmonary volume does not always correlate with function







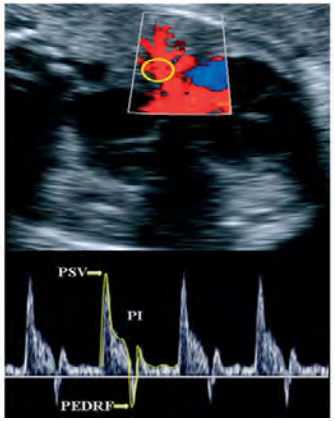




CDH and vascularisation

Aims

- Evaluation of pulmonary hypoplasia
- In addition to the o/e LHR
- Prediction of Pulmonary Hypertension



Techniques

- Pulmonary artery Doppler
  - PI, RI, PSV,PEDRF…
  - Acceleration Time, Ejection Time
- Pulmonary vascularisation index
- Arteries diameter
- Energy Doppler
- 3D Energy Doppler
- Hyperoxygenation

Moreno-Alvarez O et al., 2008
Ruano R et al., 2006

Pulmonary vascularisation Index

- Many papers, lots of measurements and…. not so many conclusive results
- Measurements are sonographer dependent
- Improvement of post-natal care makes prediction of mortality difficult *(Sokol J, 2008)*
- Pulmonary Hypertension linked to intra-parenchymal vascular anomalies
- Functional test

Prenatal heart

- “There is increasing evidence that cardiac dysfunction is a key contributor to CDH pathophysiology”.
- Left Ventricular dysfunction= association of pathological factors in the transition period
  - Reduced pulmonary blood flow and LV preload
  - LV hypoplasia
  - Acute increase in LV afterload at birth
  - Negative effects of systemic hypoxia and acidosis

Patel N et al. Seminars in Perinatol,2019

Prenatal heart

Table 1 – Echocardiographic techniques for assessment of pulmonary artery pressure and cardiac function in congenital diaphragmatic hernia.

Parameter	Technique	Notes and limitations
Pulmonary artery pressure assessment		
Peak Tricuspid Regurgitation Velocity (TR_{max})	Estimates RV peak systolic pressure using modified Bernoulli equation ($RVSP = 4(TR_{max})^2$)	TR_{max} may be absent or difficult to measure accurately.
Patent arterial duct (PDA) flow	Doppler assessment of direction & velocity, estimates PAP relative to systemic BP	Requires patent ductus. Qualitative assessment of PAP.
Interventricular shape and position	Indirect assessment of right ventricular pressure and PAP	Qualitative assessment only.
Acceleration time: right ventricular ejection time ratio (AT:RVET)	Time intervals measured from Doppler of RV outflow.	Correlates with pulmonary vascular resistance. Does not quantify PAP.
Cardiac function assessment		
"Eyeball" of function from 2D loop	Subjective assessment of function from 2D images in long and short axes	Subjective, qualitative, high inter-observer variability
Ejection Fraction (EF)	Percentage of change in LV volume from end- diastole to end-systole	Angle- and load-dependent, inter-observer variability, affected by septal shape and dysfunction.
RV Fractional Area Change (FAC)	Percentage change in RV area between end-diastole and end-systole	Load dependent, high inter-observer variability. Global measure of function.
Tricuspid Annular Systolic Excursion (TAPSE)	Longitudinal displacement of the lateral tricuspid valve annulus during systole	Highly load- and angle-dependence. Assesses systolic function only.
Atrio-ventricular valve (AV) inflow	Doppler analysis of diastolic inflow to ventricles	Diastole only, highly load-dependent.
Right and Left Ventricular Outflow (RVO and LVO)	Estimation of ventricular output, product of stroke volume and valve area	Time-consuming, poor repeatability, affected by shunts
Myocardial Performance Index (MPI)	Global measure derived from time intervals	Highly load-dependent, does not distinguish systolic / diastolic function
Systolic:Diastolic duration (SD:DD)	Time intervals obtained from outflow Doppler.	Heart-rate and load-dependent. Does not distinguish systolic and diastolic function
Tissue Doppler Imaging (TDI) of myocardial velocities	Longitudinal systolic and diastolic velocities measured in basal myocardium of RV, LV and septum.	Quantitative assessment of function. Angle- and load-dependent.
Ventricular strain assessed by Speckle Tracking Echocardiography (STE)	Quantitative assessment of global & regional deformation (strain, strain rate, twist) in multiples planes.	Specific hardware, software, user experience and optimal images. Inter-vendor differences.

Patel N et al. Seminars in Perinatol,2019

Prenatal heart

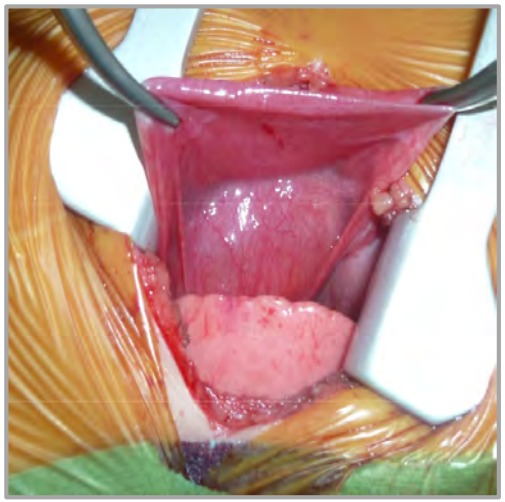
- Ventricular size as an outcome predictor *(Thebaud B et al, Intensive Care Med, 1997)* challenged by Vogel M *(2010)* et al. and Kailin et al. *(2017)* and confirmed by Byrne et al. *(2015)*
- Preferential streaming of the ductus and inferior cava vein towards de right hearth when liver is up *(Stressig R et al, Heart, 2010)*
- Speckle Tracking Echocardiography (STE)
  - Postnatal: Have demonstrated global systolic and diastolic LV dysfunction as well as abnormal synchrony of myocardial regions, associated with reduced left ventricular output *(Massolo AC et al, Neonatology 2019)*
  - Prenatal: No cardiac dysfunction *(DeKoninck P et al, Prenat Diagn, 2014)* *or limited to diastolic dysfunction* *(Cruz-Lemini et al, 2018)*
- Technically challenging (16% of insufficient quality) *(DeKoninck P)*

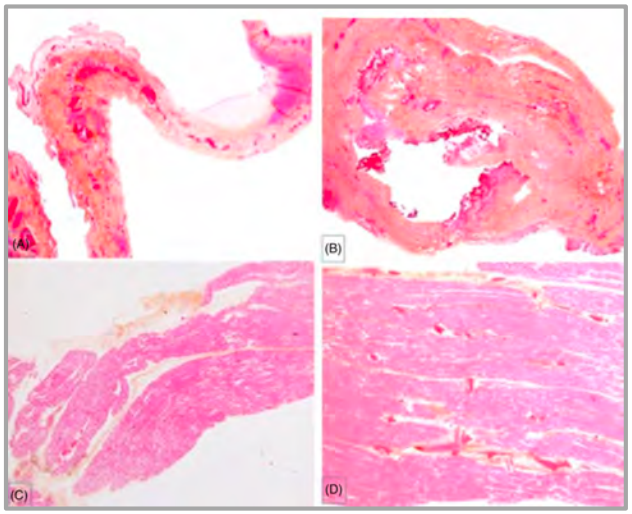
Diaphragmatic Sac

	% sac	Mortality	Oxygen dependency at 28 days	Time on ventimation	New	Comments
Bouchghoul H 2018	23% (17/86)	0/36% (p=0.03)	6/15% (p=0.33)	10.2/16.2d (p=0.32)	Suspected prenatal 33%	- Small series - Sac only
Oliver ER 2019	23% (46/200)	NA	43.9/59.2% (p=0.11)	15.5/23.5d p=0.04	Suspected prenatal 45.7% s /38.6 %(e)	Same incidence of GERD
Levesque M 2019	19.7% (14/71)	0/5.3% (p=1)	7.1/24.6% (p=0.27)	7.62±6.12 /15.9±19.2 (p=0.010)	Less vasoactive medication Less recurrence	- Small series - Exclude 9 surgery> 28d
Heiwegen K 2020	18% (19 s +17 e/200)	0/18% (p=0.03)	45% (s+e)/26% p=0.001	NA	More recurrence for s+e	- Include malformations - separated s+e

Diaphragmatic Sac

- Sac≠eventration
- Factors that may play a role in the observed differences
  - Sample size
  - Old cases included in large series
  - Management protocols (ECMO)
  - Sac + eventration

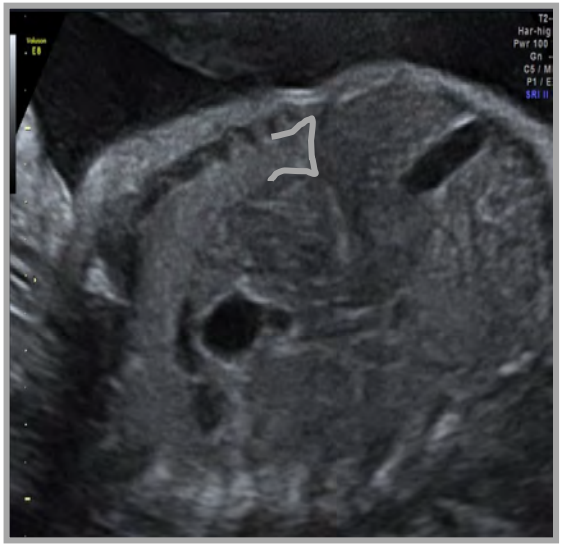


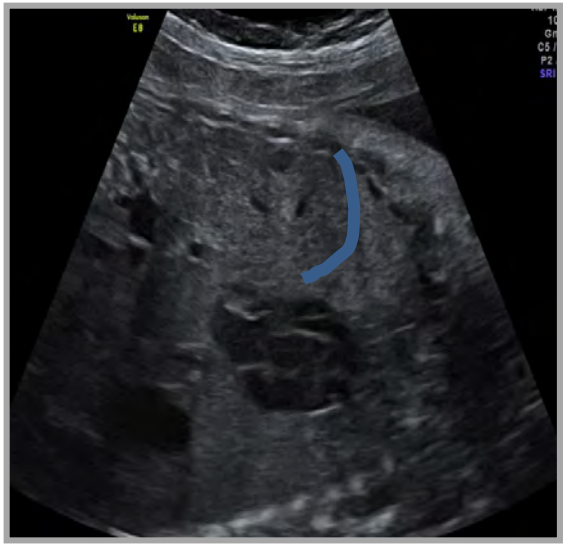


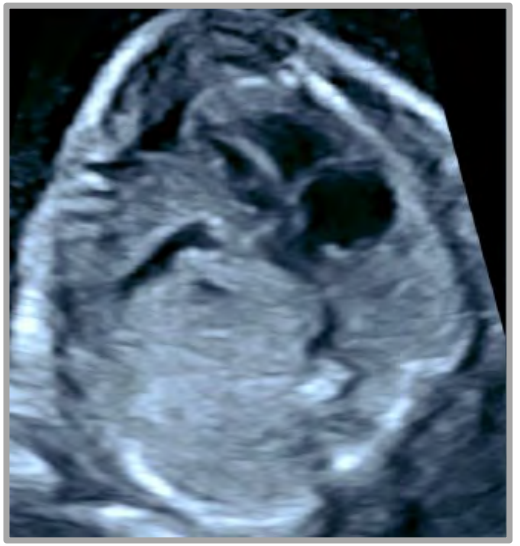
Bouchghoul H et al. Prenat Diagn, 2018

Diaphragmatic Sac

	Sensibility	Specificity	Positive Predictive Value	Negative Predictive Value
Meniscus of lung posterior or apical to the hernia contents	100% [29.2%-100%]	79.7% [68.7%-88.4%]	17.6% [3.8%-43.4%]	100% [93.5%-100%]
Encapsulated appearance of hernia contents	71.4% [41.9%-91.6%]	87.9% [76.7%-95.0%]	58.8% [32.9%-81.6%]	92.7% [82.4%-98.0%]
Presence of pleural fluid outlining a sac or ascites outlining a sac	75.0% [19.4%-99.4%]	79.4% [67.9%-88.3%]	17.6% [3.8%-43.4%]	98.2% [90.3%-100%]







Bouchghoul H et al. Prenat Diagn, 2018
Zamora IJ et al. AJR Am J Roentgenol, 2015

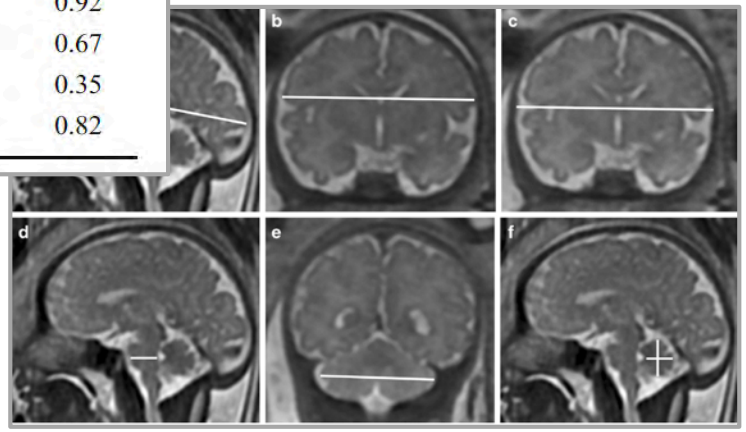
Prenatal brain anomalies ?

- Conditions affecting blood flow and perfusion of the brain such as congenital heart diseases can affect brain growth *(Limperopoulos C et al. Circulation, 2010)*
- Studies in CDH have focused on survivors and showed anomalies such as delayed brain maturation *(Danzer E etal. J Ped Surg, 2012)* or enlarged extraaxial spaces *(Radhakrishnan R et al. AJNR Am J Neuroradiol, 2017)*
- MRI-based brain volumetry in fetuses with CDH *(Prayer F et al, 27th ISUOG, 2017)*

Prenatal brain anomalies ?

Brain morphometry	Gestational age	Survivor z-scores mean ± SD	Non-survivor z-scores mean ± SD	*t*-test *P*-value
Fronto-occipital diameter	<28 weeks	−0.03±1.66	0±1.55	0.95
	≥28 weeks	0.01±1.30	−0.03±1.46	0.93
Brain biparietal diameter	<28 weeks	−0.99±1.69	−0.52±1.48	0.35
	≥28 weeks	−0.67±1.77	−0.20±1.40	0.33
Bone biparietal diameter	<28 weeks	−0.29±1.55	−0.15±1.00	0.73
	≥28 weeks	0.09±1.56	0.02±1.33	0.88
Transverse cerebellar diameter	<28 weeks	0.33±0.97	0.16±0.94	0.55
	>28 weeks	0.01±1.27	−0.15±1.17	0.66
Anteroposterior cerebellar vermis	<28 weeks	−0.61±1.07	−0.78±1.09	0.60
	>28 weeks	−0.73±1.50	−1.91±1.74	0.02*
Craniocaudal cerebellar vermis	<28 weeks	−0.05±0.92	−0.02±1.47	0.92
	≥28 weeks	−0.45±1.71	−0.23±1.69	0.67
Anteroposterior pons	<28 weeks	−0.87±1.44	−1.27±1.31	0.35
	≥28 weeks	−0.81±1.16	−0.89±1.08	0.82

Correlation with o/e TLV



- Enlarged extraaxial spaces (57% > 28 weeks, 60% survivors/53% non survivors, p=0.77)
- Venous sinus distention *(23%/35% > 28 w, p=0.38)*

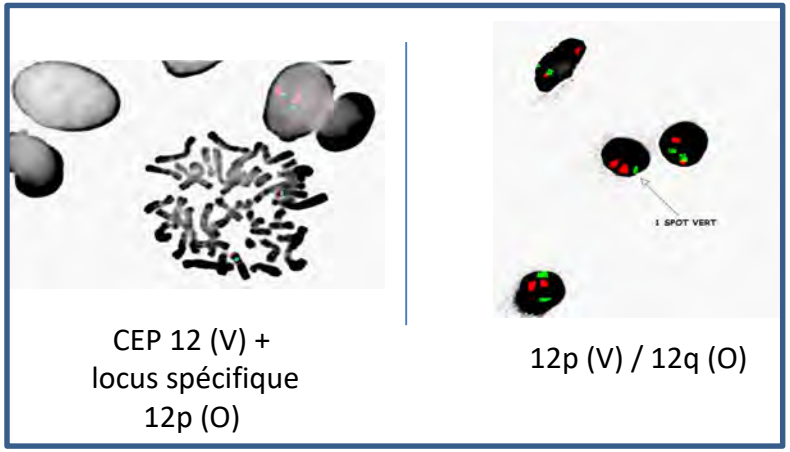
Radhakrishnan R et al. Pediatric Radiology, 2019

Prenatal brain anomalies ?

- Venous hypertension by impaired central venous return of cardiac origin?
- Middle cerebral artery flow velocity lower in CDH/controls
  (Van Mieghem T et al. Ultrasound Obstet Gynecol, 2010)
  - MCA pulsatility index unchanged
  - Cranial biometry and cerebral volume in CDH normal
- Clinical significance?

Genetics and Cytogenetics

- Array-comparative genomic hybridization (a-CGH) *on uncultured cells*
- First trimester diagnosis
  - CVS
  - But if others US anomalies (hydramnios, rhizomelic limb shortening, ventriculomegaly, nuchal fold, maternal age) → amniocentesis
- Pallister Killian syndrome
  - Tissue limited mosaicism for isochromosome 12p
  - Rapid decrease of the supernumerary marker isochromosome during culture



CEP 12 (V) + locus spécifique 12p (O)

12p (V) / 12q (O)

Salzano E et al. Am J Med Genet, 2018 - Frisova V et al, Taiwanese J Obstet Gynecol, 2018
Doray B et al, Prenat Diagn, 2002- Struthers JL et al, Am J Med Genet, 1999

What's next?

- O/E LHR, Liver and TLV at MRI measurements
- Sac and eventration diagnosis
- Need for studies on right CDH
- Intra-parenchymal pulmonary vascularisation evaluation
- Prenatal heart and brain evaluation

Early, Postnatal Pulmonary Hypertension Severity is Predictive of Early Outcomes in Congenital Diaphragmatic Hernia

Abstract 1

Dalya Ferguson, United States - University of Texas McGovern Medical School; Vikas Gupta, United States - University of Texas McGovern Medical School; Pam Lally, United States - University of Texas McGovern Medical School; Matias Luco, Chile - Universidad Catolica de Chile; Kuojen Tsao, United States - University of Texas McGovern Medical School; Kevin Lally, United States - University of Texas McGovern Medical School; Neil Patel, United Kingdom - Royal Hospital for Children; Matthew Harting, United States - University of Texas McGovern Medical School

Purpose

Pulmonary hypertension (PH) is the major, fundamental pathophysiologic consequence associated with congenital diaphragmatic hernia (CDH). Our objective was to evaluate the association between degree of early, postnatal CDH-PH and patient outcomes.

Methods

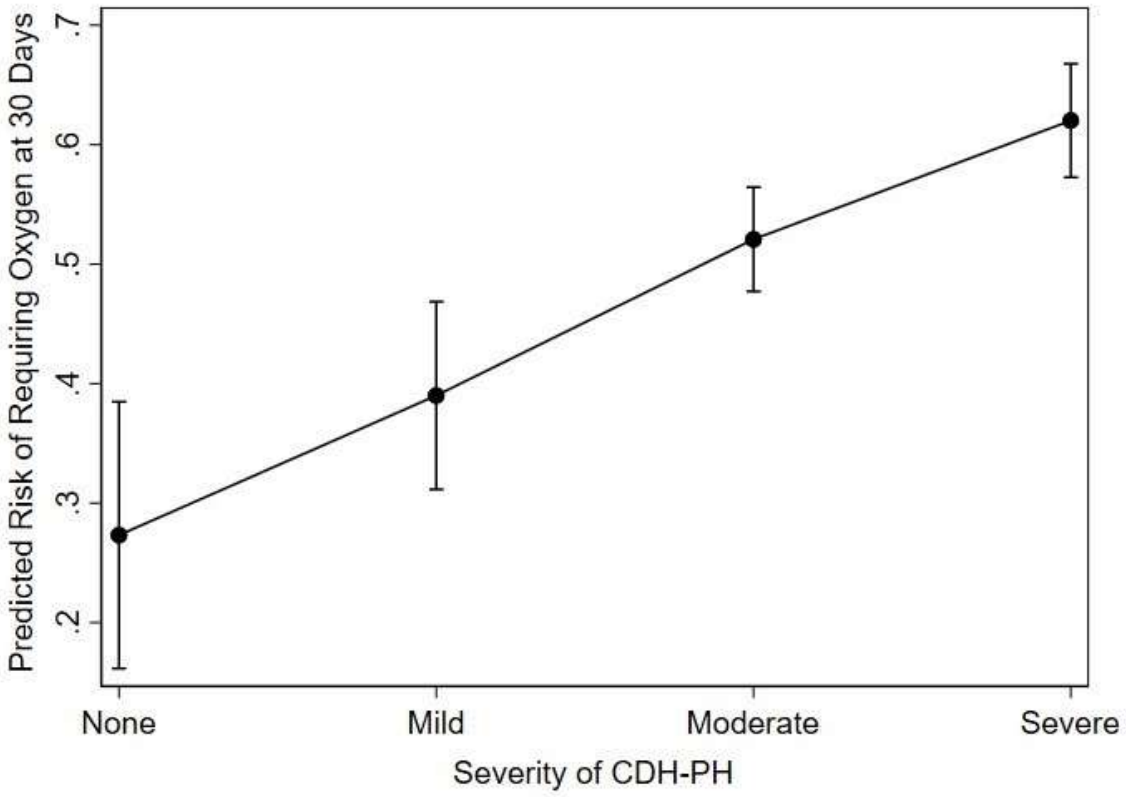
We conducted a retrospective cohort study using multicenter, prospectively collected data from the CDH Study Group (CDHSG) registry (2015-2018). Patients without echocardiograms within the first 48 hours of life were excluded. CDH-PH was categorized into 4 groups based on echocardiographic findings: none, mild (right ventricular systolic pressure detectable but <2/3 systemic), moderate (between 2/3 systemic and systemic), and severe (supra-systemic). Univariate analysis and multivariable Poisson regression were performed.

Results

Of 1,538 patients, CDH-PH was present in 87.2%: mild in 13.3% (n=204), moderate in 42.3% (n=651), and severe in 31.6% (n=486). Survival varied by CDH-PH category: 89.9% in none, 85.3% in mild, 73.6% in moderate, and 62.1% in severe. On univariate analysis, CDH-PH was significantly associated with increased mortality, need for extracorporeal life support (ECLS), oxygen support at 30 days and at discharge/transfer, and length of stay (all p<0.001). After adjusting for known predictors of severity, the incidence rate ratio (IRR) for ECLS in severe CDH-PH was 1.96 (95% CI 1.1-3.6). IRR for oxygen support at 30 days were 1.91 (95% CI 1.3-2.9) and 2.27 (95% CI 1.5-3.5) in patients with moderate and severe CDH-PH, respectively. The adjusted probabilities of requiring oxygen at 30 days are shown (Figure).

Conclusion

Early, postnatal PH is common and independently associated with early morbidity in CDH.



Adult stem cells in newborns with congenital diaphragmatic hernia undergoing ECMO

Abstract 2

Neysan Rafat, Department of Neonatology - University Children's Hospital Mannheim; Christian Patry, Germany - University Children's Hospital Heidelberg; Ursula Sabet, Germany - University Children's Hospital Heidelberg; Thomas Schaible, Germany - Department of Neonatology, University Children's Hospital Mannheim

Abstract:

Purpose: Endothelial progenitor (EPC) and mesenchymal stem cells (MSC) can regenerate damaged endothelium and thereby improve pulmonary endothelial dysfunction. We do not know, how extracorporeal membrane oxygenation (ECMO) might affect EPC- and MSC-mediated regenerative pathways in patients with congenital diaphragmatic hernia (CDH). Therefore, we investigated, if ECMO support impacts EPC and MSC numbers in CDH patients.

Methods:

Peripheral blood mononuclear cells from newborns with ECMO-dependent (n=18) and ECMO-independent CDH (n=12) and from healthy controls (n=12) were isolated. The number of EPC and MSC was identified by flowcytometry. Serum levels of vascular endothelial growth factor (VEGF) and angiopoietin (Ang)-2 were determined.

Results:

EPC and MSC were elevated in newborns with CDH. ECMO-dependent infants had higher EPC subpopulation counts (2,1-7,6-fold) before treatment compared to ECMO-independent infants. In the disease course, EPC and MSC subpopulation counts in ECMO-dependent infants were lower than before ECMO initiation. During ECMO, VEGF serum levels were significantly reduced (by 90,5%) and Ang2 levels significantly increased (by 74,8%). When looking at the prenatal CDH diagnostics, relative lung-to-head ratio (rLHR) and relative lung volume were inversely correlated with numbers of EPC (rLHR: r -0,58, p=0,0044; rel. lung volume: r -0,49, p=0,0217).

Conclusions:

Our data suggest that ECMO might be associated with a rather impaired mobilization of EPC and MSC and with a depression of VEGF serum levels in newborns with CDH.

Impact of time point of ECMO initiation on mortality and morbidity in CDH

Abstract 3

Neysan Rafat, Germany - University Children's Hopital Mannheim, Department of Neonatology; Alba Perez Ortiz, Germany - Department of Neonatology, University Children's Hospital Mannheim; Julia Reinhard, Germany - Department of Neonatology, University Children's Hospital Mannheim; Steffen Hien, Germany - Deparment of Neonatology, University Children's Hospital Mannheim; Kathrin Zahn, Germany - Department of Pediatric Surgery, University Children's Hospital Mannheim; Thomas Schaible, Germany - Department of Neonatology, University Children's Hospital Mannheim

Abstract:

Purpose: The data of the CDH Study Group highlight the trend toward employing ECMO earlier (before CDH repair) as a component of preoperative stabilization. While the inclusion criteria for initiating ECMO have been described in detail, there is no data available on the influence of the time point, when ECMO was initiated, on the morbidity and mortality in CDH patients. We hypothesized that an early initiation of ECMO after birth is associated with a beneficial outcome in severe forms of CDH.

Methods:

In our retrospective analysis, we included all CDH patients undergoing ECMO treated in the period of 2010 - 2018 at our center (n=218). We divided the total population into three groups: 1) ECMO initiation <24 hours after birth, 2) ECMO initiation between 24-120 hours after birth and 3) ECMO initiation >120 hours after birth; and compared the mortality and morbidity between the groups.

Results:

The mortality rate in the first (30%) and third group (38%) was high and in the second group rather low (12%). The morbidity, characterized by chronic lung disease (CLD), did not differ significantly in the three groups, only patients receiving ECMO >120 hours had an increased rate of severe CLD, but the number of patients in this group was very low (n=8).

Conclusions:

Our data, although not randomized, suggest that very early need for ECMO and ECMO initiation >120 hours after birth is associated with increased mortality.

Incidence and impact of prematurity on the clinical course of newborns with CDH

Abstract 4

Neysan Rafat, Germany - University Children's Hopital Mannheim, Department of Neonatology; Alba Perez Ortiz, Germany - Department of Neonatology, University Children's Hospital Mannheim; Julia Reinhard, Germany - Department of Neonatology, University Children's Hospital Mannheim; Steffen Hien, Germany - Deparment of Neonatology, University Children's Hospital Mannheim; Christiane Otto, Germany - Department of Obstetrics and Gynecology, University Medical Center Mannheim; Kathrin Zahn, Germany - Department of Pediatric Surgery, University Children's Hospital Mannheim; Thomas Schaible, Germany - Deparment of Neonatology, University Children's Hospital Mannheim

Abstract:

Purpose: Critical congenital malformations are associated with an increased rate of prematurity and a lower birth weight. For the prognosis of CDH, besides genetic disorders and associated malformations, the fetal lung volume and thereby the degree of lung hypoplasia represent the most important parameter. However, prematurity may also have an impact on the clinical course in CDH. Therefore, we investigated, if prematurity is associated with an increased morbidity and mortality in CDH patients.

Methods:

In our retrospective analysis, we included all CDH patients treated in the period of 2010 - 2018 at our center (n=528), of which 125 (24%) were preterm (GA<37+0). We looked at the cause of prematurity, the use of ECMO and mortality in relation to the gestational age and the employment of FETO.

Results:

Out of the 125 premature newborns with CDH, 26 patients were born before GA 34+0 (5%) with a mortality rate of 50% and one patient receiving ECMO. In the population of CDH patients born between GA 34+0 and 36+6 (n=99) survival rate was 63% and 47 patients received ECMO support (47%). Only 7 out of 36 patients (19%) who underwent FETO were born at term and the mortality rate in the FETO population was 50%, while ECMO support was employed in 70%. In the term-born CDH patients (n=403), survival rate was 85% and ECMO employment 41%.

Conclusions:

Prematurity is associated with an increased mortality in CDH patients. Long-term studies especially investigating the pulmonary outcome are necessary to assess the morbidity of premature CDH patients.

Congenital Diaphragmatic Hernia and associated Omphalocele: A study from the CDHSG Registry

Abstract 5

Carmen Mesas Burgos, Sweden - Karolinska Institutet; Björn Frenckner , Sweden - Karolinska Institutet; Matthew Harting, United States - Children's Memorial Hermann Hospital Houston; Pamela Lally, Sweden - Children's Memorial Hermann Hospital Houston; Kevin Lally, Sweden - Children's Memorial Hermann Hospital Houston

Background:

Congenital Diaphragmatic Hernia (CDH) associated with Omphalocele is a rare condition.

Aim:

The aim of this study was to describe the incidence of this association and postnatal outcomes from a large database for CDH.

Methods:

Data from the multicenter, multinational database on infants with CDH (CDHSG Registry) born from 2007 to 2018 were analyzed.

Results:

5730 patients with a posterolateral CDH were entered into the registry. Omphalocele was present in 36 (0,62%). When comparing CDH with Omphalocele (CDH+O) to CDH without (CDH-), CDH+O were born at younger gestational age, had lower APGAR scores, but received ECMO less often. 53,8 % of the CDH+O had other associated anomalies. Left vs right side or defect size did not differ but CDH+O needed a patch more frequently. CDH+O had surgical repair later, had a higher rate of non-repair (53%) and lower survival (41%). Those who underwent surgical repair had survival of 76%.

Discussion:

CDH associated with Omphalocele is a more severe condition with higher mortality and morbidity.

Table 1	CDH- (n=5694)	Bochdaleck CDH+ Omphalocele (n=36)	p values
	%	%	
Bw (median, IQR)	3.0 (2.6-3.3)	2.5 (2.1-3.0)	<0,0001
ECMO	29,1	13,9	0,03
Prenatal Dx	69,7	63,9	ns
APGAR 1 (median, IQR)	5 (3-7)	3 (1-4)	0,004
APGAR 5 (median, IQR)	7 (5-8)	5 (3-8)	0,001
Chromosomal anomalies	6,6	13,9	0,04
Major cardiac anomalies	8	11,1	ns
Other anomalies	14,1	27,8	0,001
Patch repair	44,8	36,1	ns
Not repair	16,1	52,8	<0,0001
Survival	71,4	41	<0,0001
LOS (median, IQR)	36 (22-68)	102 (42-132)	<0,0001

Clinical exome sequencing data reveals high diagnostic rates and new susceptibility genes for congenital diaphragmatic hernia plus (CDH+)

Abstract 6

Tiana Scott, United States - Brigham Young University; Ian Campbell, United States - Children's Hospital of Philadelphia; Seema Lalani, United States - Baylor College of Medicine; Chad Shaw, United States - Baylor College of Medicine; Jill Rosenfeld, United States - Baylor College of Medicine; Daryl Scott, United States - Baylor College of Medicine

Purpose:

Congenital diaphragmatic hernia (CDH) often occurs in conjunction with other non-hernia-related anomalies (CDH+). Exome sequencing has not been universally adopted as a diagnostic test for individuals with CDH+. Our purpose is to determine the diagnostic efficacy of exome sequencing in CDH+ cases and to identify new CDH susceptibility genes.

Methods:

We reviewed data from a clinical database of approximately 12,000 individuals referred for exome sequencing. We used a machine learning algorithm to evaluate CDH candidate genes identified in this review.

Results:

Exome sequencing identified a molecular diagnosis in 45 out of 82 CDH+ cases for a diagnostic rate of 47%. In individuals with both CDH and cardiovascular malformations, the diagnostic rate was also 47% (21/45). We identified multiple individuals with putatively pathogenic variants in KMT2D (n = 4; Kabuki syndrome 1), EP300 (n = 2; Rubinstein-Taybi syndrome 2), and ALG12 (n =2; congenital disorder of glycosylation 1G). We also identified individuals with putatively pathogenic variants in ANKRD11, BRCA2, FOXC2, FOXP1, MED12, MCPH1, RASA1, SMARCA4 SMARCC4, and TCF12, all of which have been previously associated with a genetic syndrome in humans. A review of the literature, and/or predictions generated using a machine learning algorithm (>80th centile rank among RefSeq genes), provided additional evidence in support of their association with CDH.

Conclusions:

We conclude that exome sequencing can be used to identify a molecular diagnosis in a high percentage of individuals with CDH+. Our data also suggests that pathogenic variants in several known human disease genes may be associated with increased risk for developing CDH.

Maternal vitamin A status and susceptibility to teratogen-induced congenital diaphragmatic hernia

Abstract 7

Robin Clugston, Canada - University of Alberta; Ayanna Rocke, Canada - University of Alberta

Purpose:

The retinoid hypothesis is one of the leading explanations for the development of congenital diaphragmatic hernia (CDH). This hypothesis states that abnormal vitamin A (retinoid) signaling contributes to the development of CDH, and is supported by human and animal studies. It is known that overt vitamin A deficiency causes CDH in rodents, and that pharmacological doses of vitamin A can prevent teratogen-induced CDH. However, the importance of maternal vitamin A status on CDH risk has not been explored. This work tests the hypothesis that maternal vitamin A status affects the susceptibility to teratogen-induced CDH.

Methods:

Experiments were conducted in female BALB/c mice. Maternal vitamin A status was modified using purified diets with different vitamin A content. Timed-pregnant mice were treated with a combination of nitrofen and bisdiamine on day eight of gestation.

Results:

Teratogen administration produced diaphragm defects consistent with Bochdalek CDH (i.e. posterolateral herniation). Experimental manipulation of dietary vitamin A intake produced three groups of mice with a marginal, sufficient and excess vitamin A status, which was confirmed at the metabolic and gene expression level. The incidence of teratogen-induced CDH was highest in mice with a marginal vitamin A status, and lowest in mice consuming excess amounts of vitamin A. The severity or sidedness of CDH was unaffected by maternal vitamin A status.

Conclusion:

In mice, maternal vitamin A status has an impact on the susceptibility to teratogen-induced CDH. A marginal vitamin A status increases the susceptibility to CDH, whereas consuming excess vitamin A is protective.

Prostaglandin E1 in infants with Congenital Diaphragmatic Hernia (CDH) and life-threatening pulmonary hypertension

Abstract 8

Kévin Le Duc, France - Department of Neonatology, Jeanne de Flandre Hospital, University Hospital of Lille; Sébastien Mur, France - Department of Neonatology, Jeanne de Flandre Hospital, University Hospital of Lille; Dyuti Sharma, France - Department of Pediatric Surgery, Jeanne de Flandre Hospital, University Hospital of Lille; Estelle Aubry, France - Department of Pediatric Surgery, Jeanne de Flandre Hospital, University Hospital of Lille; Morgan Recher, France - Paediatric Intensive Care Unit, Jeanne de Flandre Hospital, University Hospital of Lille; Thameur Rakza, France - Department of Neonatology, Jeanne de Flandre Hospital, University Hospital of Lille; Laurent Storme, France - Department of Neonatology, Jeanne de Flandre Hospital, University Hospital of Lille

Purpose:

To report the effects and tolerability of Prostaglandin E1 (PGE1) in newborns with severe CDH and late life-threatening PH.

Methods:

Retrospective study in newborn infants with isolated CDH born between 2009 and 2015. The newborn infants with isolated CDH and life-threatening PH defined by an acute worsening of the cardiorespiratory function, and bidirectional or exclusive right-to-left shunting across the ductus arteriosus (DA) with an acceleration of the blood flow>1.5m.s-1 assessed by Doppler echocardiography. Serial measurements of cardiorespiratory variables have been recorded before and after PGE1.

Results:

18 infants (out of 102 in the cohort) were included in the study (gestational age: 39±2 weeks; birth weight 3.3±0.6Kg). All of these newborn infants were treated with inhaled NO before the initiation of PGE1. The median FiO2, and preductal and post-ductal SpO2 were 80% [50;100], 91% [88;95] and 86% [82;91] respectively before treatment. FiO2 decreased to 35% [30;40] (p = 0.001) at H6. Maximal blood flow velocities in the DA decreased after starting PGE1 from 2.2 m.s-1 [1.5;2.5] to 1 m.s-1 [0.55;1.2] (p<0.001).
5 children (28%) died at a median age of 122 days [56-489]. Survivors had a median length of stay of 64 days [51;80].

Conclusion:

PGE1 treatment is associated with better oxygenation and circulatory function in newborn infants with severe CDH and life-threatening pulmonary hypertension. Our data provide evidence that restrictive ductus arteriosus may result in suprasystemic pulmonary hypertension in CDH infants, and that PGE1 may improve cardiorespiratory failure through reopening of the ductus arteriosus.

Table 1: Change of the cardiorespiratory variables before and after onset of Alprostadil. Alprostadil was started just after H0.

	H-24	H-6	H0	H1	H6	H24
HR (bpm)	155 [133;166]	160 [143;168]	156 [143;169]	153 [143;167]	160 [139;171]	151 [143;166]
MAP (mmHg)	48 [44;59]	49 [43;54]	49 [46;56]	49 [45;55]	50 [47;57]	48 [44;58]
Preductal SpO_2 (%)	94 [92;96]	93 [91;94]	91 [88;95]	93 [88;95]	94 [91;95]	95 [92;97]
Postductal SpO_2 (%)	93 [83;96]	88 [80;93]	86 [82;91]	87 [79;93]	91 [84;93]	92 [86;95]
FiO_2 (%)	28*[23;30]	45*[40;60]	80*[50;100]	45*[40;70]	35*[30;40]	30*[25;35]
Diuresis ($mL.Kg^{-1}.h^{-1}$)	2.9* [2.2;4.9]	2.0* [1.1;3.7]	1.6 [0.9;3.2]	1.6 [1.5;1.8]	2.3* [2.0;3.5]	2.9* [2.0;3.5]
pH	7.29 [7.24;7.33]	7.30* [7.23;7.34]	7.21 [7.16;7.29]	7.28* [7.26;7.30]	7.33* [7.25;7.36]	7.34* [7.26;7.39]
$PaCO_2$ (mmHg)	70 [66;73]	64 [57;72]	66 [61;71]	65 [51;74]	57 [49;65]	62 [55;70]
Lactates (mmol/L)	1.0 [0.7;1.4]	1.2* [0,9;2.2]	2 [1.3; 3]	2.2 [2.1;2.5]	1.5 [1.0;1.8]	1.2 [1.0;1.6]

*Data express as median and IQR, Interquartile Range, * Difference accepted as $p \leq 0.005$. HR, Heart Rates; MAP, Mean Arterial Pressure*

PERIOPERATIVE PROGNOSTIC FACTORS AND SHORT-TERM OUTCOME IN CDH: APPLICATION IN A SINGLE CENTRE POPULATION

Abstract 9

Camilla Pagliara, Italy - Pediatric Surgery Unit, University of Padua (Italy); Alberto Sgro', Italy - Pediatric Surgery Unit, University of Padua (Italy); Francesco Fascetti Leon, Italy - Pediatric Surgery Unit, University of Padua (Italy); Elisa Zambaiti; Italy - Pediatric Surgery Unit, University of Padua (Italy); Giulia Brooks, Italy – Pediatric Surgery Unit, University of Padua (Italy); Piergiorgio Gamba, Italy - Pediatric Surgery Unit, University of Padua (Italy)

Background and Aim of the Study:
Many prognostic factors for CDH patients are described and validated in literature. In our study we analyze which of them actually influence the outcome of CDH patients in our centre.

Material and Methods:
An observational retrospective single-centre study was conducted on patients with posterolateral CDH between 1997 and 2018. The length of stay was used as primary outcome. A univariate and multivariate analysis were performed on neonatal, perioperative and postoperative parameters potentially influencing the primary outcome.

Results:
141 patients with posterolateral CDH were identified with an overall survival of 65,2% (mortality 34.8%). The overall median length of stay until discharge at home was 24 days. The univariate analysis proved that discharge within three weeks was associated with shorter duration of surgery, smaller diaphragmatic defects, reduced need for patch repair and lower incidence of spleen herniated ($p < 0.05$). Multivariate analysis identified that need for patch repair and dopamine maximum dose are independent parameters associated the length of stay.

Conclusions:
Even if the univariate analysis resulted in many factors influencing primary outcome, only two of them were confirmed as independently associated with length of stay in the multivariate analysis: need for patch repair and dopamine maximum dose.

Optimal timing of surgery in infants with neonates with left-sided congenital diaphragmatic hernia diagnosed prenatally

Abstract 10

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Abstract:

Purpose: Compelling evidence demonstrating any incremental survival benefit from timing of surgery has not been obtained yet. The aim of this study was to establish the optimal timing of surgery in neonates with left-sided isolated CDH (L-ICDH) diagnosed prenatally.

Methods:

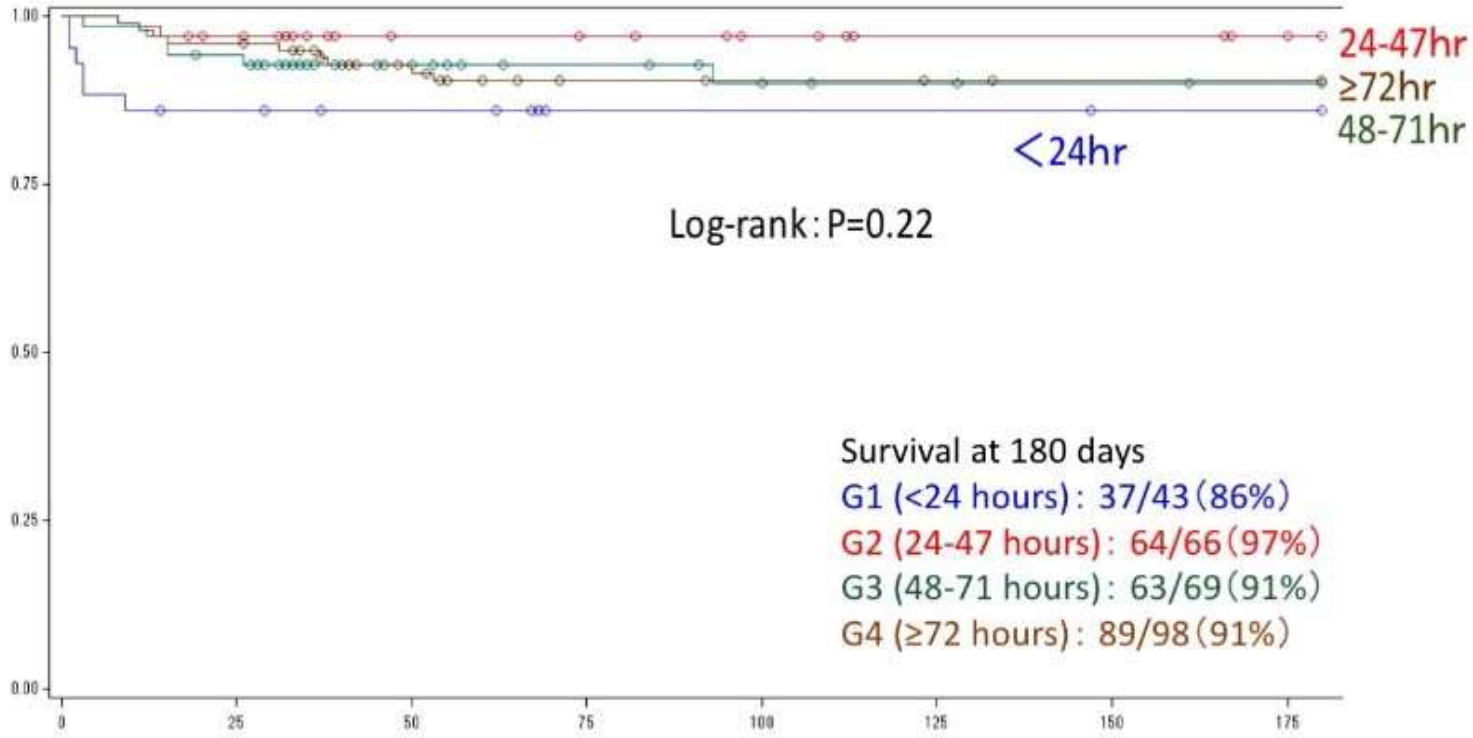
In total, 276 patients with L-ICDH diagnosed prenatally were included. Based on the timing of surgery, the patients were classified into four groups: < 24 hours (G1), 24¬¬–47 hours (G2), 48–71 hours (G3), and ≥ 72 hours (G4). Clinical outcomes were compared among the groups with adjustment for potential confounders, such as disease severity.

Results:

There were no significant differences in demographic data and disease severity among the groups. The survival rate at 180 days was highest in G2 (G1 86%, G2 97%, G3 91%, G4 91%). After adjusting for birth weight, mild congenital malformation, Terui's classification (combination of Apgar score and best oxygenation index), position of the liver and stomach, right-to-left shunt at ductus arteriosus, and observed/expected lung-to-head ratio, multivariate analyses showed that the mortality rate in G2 was significantly lower than in other groups (adjusted OR 0.09; 95% CI 0.01–0.97). Complications during surgery were fewer in G3 than in other groups (adjusted OR 0.11; 95% CI 0.01–0.97). The length of hospitalization was significantly longer in G4 than in other groups (adjusted OR 4.54; 95% CI 1.71–12.05).

Conclusion:

Our data suggested that the optimal timing of surgery in neonates with L-ICDH diagnosed prenatally was 24–71 hours (G2, G3) after birth.



Optimal gestational age at delivery for congenital diaphragmatic hernia

Abstract 11

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Purpose

To evaluate the neonatal morbidity and mortality of neonates with congenital diaphragmatic hernia according to the gestational age at delivery

Methods

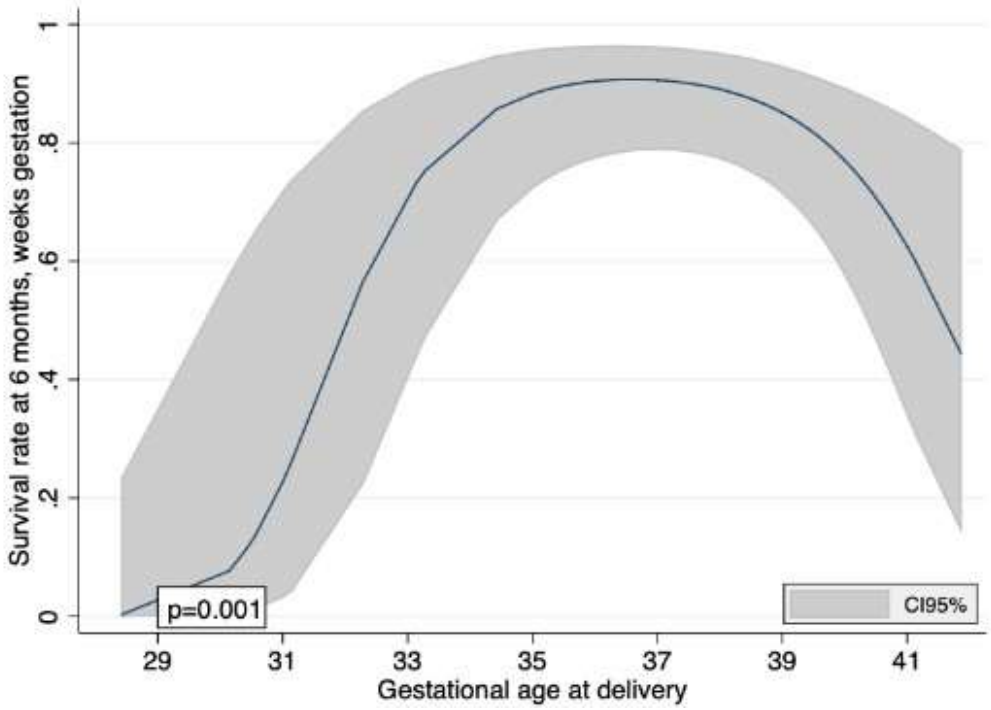
This retrospective study was conducted between January 1, 2010 and December 31, 2018 at the university hospitals of Leuven in Belgium and Antoine Béclère/Bicêtre in France. Fetuses with an isolated left-sided CDH (i.e. no associated malformation, normal karyotype, and CGHarray without genomic imbalance) were included. The exclusion criteria were fetal death in utero, medical termination of pregnancy, and fetuses with a fetal tracheal occlusion during pregnancy.

Results

170 fetuses were included (124 in the French center and 46 in the Belgium center), with a median gestational age at delivery of 38+2 weeks gestation (WG) [37+0 -39+1]. Survival rate at 28 days and 6 months were respectively 71.3% (121/170) and 66.2% (104/157). There was a non-significant trend of less respiratory morbidity for neonates delivered between 37 and 39 WG when compared to neonates delivered after 39 WG. Relation between the survival rate at 28 days and the gestational age at delivery was modelized by a fractional polynomial, with adjustment on intrathoracic liver, o/eLHR and mode of delivery. There was a strong and significant association with an increasing survival rate when increasing gestational age at delivery until 39 WG followed by a decreasing survival rate from 39 WG to the end of pregnancy.

Conclusion

Gestational age at delivery is strongly associated with the survival at 6 months, with an optimal age at delivery of 39WG for fetuses with a left-sided congenital diaphragmatic hernia.



Evaluation of Neurologic Morbidity in Neonates with Congenital Diaphragmatic Hernia Using Plasma Biomarkers of Brain Injury

Abstract 12

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Purpose:

To determine whether neonates with Congenital Diaphragmatic Hernia (CDH) have a temporal elevation in Plasma Markers of Brain Injury (PMBI) during the acute illness period (after birth, through hernia repair and recovery), and whether elevations in PMBI correlate with poor neurologic assessment scores done prior to discharge.

Methods:

Pilot, prospective, observational study of CDH patients in a level IV NICU between 2018 and 2019. Blood samples were collected at: 2 hours of life (2HOL), Before Hernia Repair (BHR), 24 Hours Post-Repair (24HPR), 48 Hours Post-Repair (48HPR) and 5 Days Post-Repair (5DPR). Plasma was tested for GFAP, NRGN, IL-6, 8, 10, VEGF, and BDNF. The Hammersmith Infant Neurologic Examination (HINE) was done prior to discharge. Mixed effects linear models were used to compare biomarker levels at the aforementioned points.

Results:

Five patients were included in the preliminary analysis. Levels for GFAP, NRGN, IL-8, VEGF, and BDNF did not change significantly over time. IL-10 levels decreased over time (p=0.020) and were significantly lower BHR (p=0.008), 24HPR (p=0.030), 48HPR (p=0.009) and 5DPR (p=0.008) vs at 2 HOL. IL-6 levels were higher at 24HPR compared to BHR (p=0.039). Preliminary results for the HINE are shown in Table 1.

Conclusions:

This pilot study provides normative data for PMBI for stable CDH patients not treated with ECMO. Qualitative HINE results were unremarkable for neonates with prolonged hospital stays. We speculate that changes in IL-6 and IL-10 are likely a result of inflammatory responses related to surgery and transition to extra-uterine life, respectively.

Table 1. Hammersmith Infant Neurological Exam Results (HINE)

Patient	Cranial Nerves	Posture	Movements	Tone	Reflex/Reaction	Motor Milestones
1	Normal for age	Normal for age	Normal for age	Normal for age	Normal for age	Normal for age
2	Normal for age	Slightly immature for age	Abnormal, tremulous	Normal - extremities; Abnormal - neck hypotonia (head lag)	Clonus, normal for age	Normal for age
3	Normal for age	Normal for age	Normal for age	Normal - extremities; Abnormal - neck hypotonia (head lag)	Immature, clonus, normal for age	Normal for age
4	Normal for age	Normal for age	Normal for age	Normal for age	Clonus, normal for age	Normal for age
5	Normal for age	Slightly immature for age	Slightly abnormal, decreased movement.	Normal - extremities; Abnormal - neck hypotonia (head lag)	Clonus, normal for age	Normal for age.

Routine intubation in all newborns with congenital diaphragmatic hernia at delivery in the era of advanced prenatal screening: too much too soon?

Abstract 13

Suzan Cochius - den Otter, Netherlands - Erasmus MC; Karel Allegaert, Belgium - Katholieke Universiteit Leuven; Dick Tibboel, Netherlands - Erasmus MC

Purpose:

International consensus guidelines advice routine intubation of CDH neonates after delivery [1-4]. Our local protocol is based on the CDH EURO Consortium guidelines [1]. However, risk of ventilator induced lung injury and the impact on the perinatal transition should not be underestimated. Prenatal diagnostics have increased predictability of postnatal respiratory failure [5, 6]. We hypothesised that for newborns with a low risk of respiratory failure, a spontaneous breathing trial (SBT) is justified.

Methods:

We adjusted our protocol, allowing SBT in patients with O/E LHR >50% and no liver herniation in the absence of other anomalies. We included 17 CDH patients with planned SBT over a 5 year period (December 2014 – July 2019). We used descriptive statistics.

Results:

17 out of 72 (24%) patients born with CDH received a SBT (table 1). This was successful in 9 patients (53%), of which three needed continuous positive air pressure for several minutes after birth. These nine received nasal prongs and a nasogastric tube with continuous suctioning. Subsequently, seven were intubated for surgery, two patients had an eventration and were not operated in the neonatal period. Eight patients needed intubation after birth of which 7 received mild ventilation, they were extubated shortly after surgery. One patient, with an O/E LHR 57% and intra-abdominal liver position, needed respiratory support and developed pulmonary hypertension with need for nitric oxide for 4 days. Survival is 100%.

Conclusion:

In CDH infants with favourable prenatal parameters SBT is feasible, seems safe, and prevents overtreatment with potential adverse side effects.

Table 1 Patient characteristics

N=17	Median / No	%/IQR
Male gender	11	65%
Birth weight (kg)	3.0	2.49 – 3.15
Apgar score 5 minutes	8	7 - 9
Gestational age (in weeks)	38	36.9 – 38.6
O/E LHR (%)	56	52 – 74.9
Liver down	15	88%
Left side defect	16	94%
Non-intubation plan successful	9	53%
Respiratory support in ICU		
- Only for surgery	7	41%
- No intubation	2	12%
- Mild ventilation only	7	41%
- Ventilation and treatment for pulmonary hypertension	1	6%
Surgery		
- Thoracoscopic	6	35%
- Laparotomy	3	18%
- Thoracoscopic converted to laparotomy	6	35%
- No surgery	2	12%

Abbreviations: O/E LHR= observed-to-expected lung-to-head ratio, IQR= interquartile range

Transplacental delivery of nanoparticles for the prenatal treatment of CDH with miR-200b

Abstract 14

Wai Hei Tse, Canada - Children's Hospital Research Institute of Manitoba; Sean Higgins, Canada - University of Manitoba; Daywin Patel, Canada - Children's Hospital Research Institute of Manitoba; Hagar Labouta, Canada - University of Manitoba; Adrian West, Canada - Children's Hospital Research Institute of Manitoba; Richard Keijzer, Canada - Children's Hospital Research Institute of Manitoba

Purpose:

The rescue of abnormal lung development with miR-200b requires a safe delivery method. Nanoparticles surface-modified with human IgG antibodies can encapsulate and selectively deliver miR-200b introduced from the maternal circulation to the fetal lungs. We hypothesize that the maternal transfer of passive immunity can be used for transplacental transport of IgG-modified nanoparticles for the fetal delivery of miR-200b.

Methods:

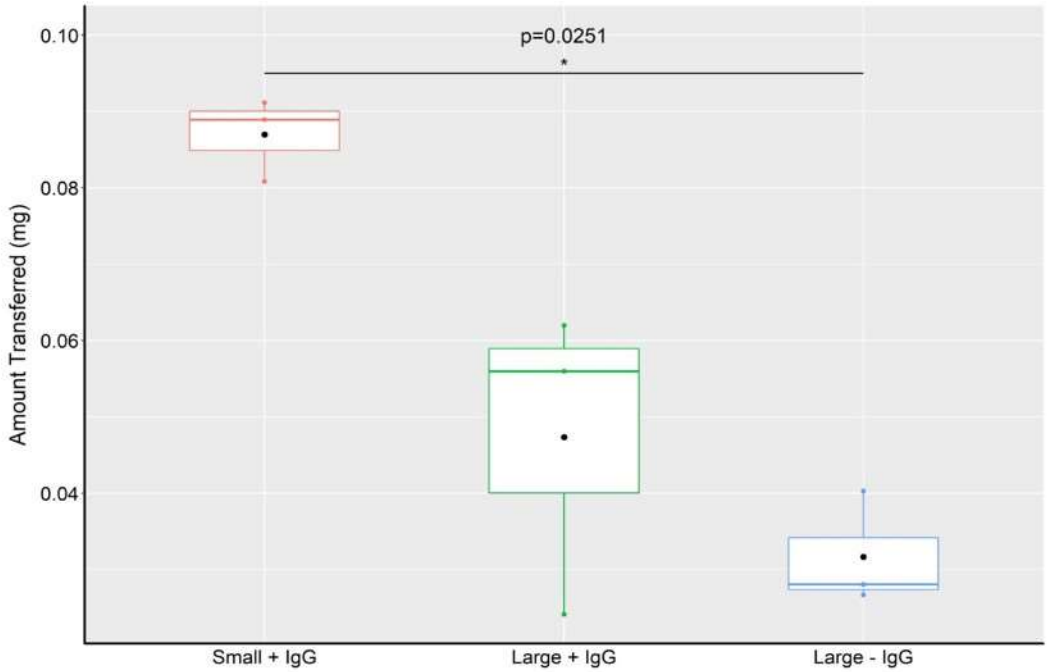
We established an in vitro model of the placenta with human BeWo placental epithelial cells (1X106 cells/cm2) on 3 µm polyester transwell membranes. Barrier function was assessed after 24 hours of exposure to chitosan nanoparticles that were surface-modified covalently with human IgG and fluorescently-tagged with FITC. Barrier function was monitored with transepithelial electrical resistance (TEER) and immunostaining.

Results:

TEER measurements indicated that barrier function was maintained after nanoparticle exposure ($p > 0.05$). This was verified by the immunostaining of intact E-cadherin and zonula occludens-1 junction proteins. Transplacental transport of nanoparticles was determined fluorometrically to be a function of size and presence of IgG. A 2.7 fold increase of IgG-modified nanoparticles (414 nm) was transported across the placental barrier compared to bare nanoparticles (376 nm).

Conclusions:

The transplacental delivery of nanoparticles is a novel prenatal delivery method for miR-200b. TEER measurements indicated that the placental integrity was maintained after exposure to nanoparticles. With immunostaining, the results suggest that nanoparticles pose no adverse effects to the placenta barrier. The increased transport of IgG-modified nanoparticles suggests that maternal transfer of passive immunity is involved. We intend to explore the nanoparticle biodistribution and transplacental efficiency in vivo.



	Small + IgG	Large + IgG	Large - IgG
Size (nm)	414± 27	805 ± 43	375 ± 17
Amount Transferred	16% (0.0870 mg)	8% (0.0473 mg)	6% (0.0317 mg)

Longitudinal follow-up with radiologic imaging is essential to reliably detect recurrence in patients with congenital diaphragmatic hernia

Abstract 15

Katrin Zahn, Germany - UMM Mannheim; Thomas Schaible, Germany - UMM Mannheim; Maike Weis, Germany – Lucas Wessel, Germany

Purpose:

Recurrence is the most important surgical complication after repair of congenital diaphragmatic hernia. Previous studies are difficult to compare, because surgical techniques differ, most are retrospective and do neither offer longitudinal follow-up nor radiologic imaging to all survivors. This is a prospective cohort-study from a single institution with a standardized surgical treatment-algorithm and a structured long-term follow-up to allow a reliant detection of recurrence-rate.

Methods:

Data was collected over 12 years with a minimal follow-up of two years. 508 neonates with congenital diaphragmatic hernia were treated, 410 patients survived, and 90% were followed longitudinally.

Results:

Recurrence after open surgery occured in three patients until discharge, in 28 children thereafter, and in six repeatedly. Overall 38 recurrences were diagnosed – including secondary hiatal hernia. Overall, recurrence-rate after primary repair was 8.8% and 12.7% after repair with a patch ($p=0.53$). Most patients showed no or minimal and unspecific symptoms (97%) and 36/38 recurrences were diagnosed on radiologic screening. 45% of recurrences were diagnosed beyond one year of age. Recurrence was significantly associated with initial defect-size ($p=0.02$). Independent risk-factors for recurrence were a left-sided defect ($p=0.037$), intrathoracic liver-herniation ($p=0.006$), and the need for an abdominal wall patch ($p<0.0001$).

Conclusion:

Only longitudinal follow-up with radiologic imaging of all patients allows a reliant detection of recurrence. Most recurrence-patients only present mild and unspecific symptoms, yet they are at risk of acute incarceration and chronic failure to thrive with their impact on long-term-prognosis.

How to improve long-term outcome after minimal-invasive repair of congenital diaphragmatic hernia – a critical review of all cases in 10 years

Abstract 16

Katrin Zahn, Germany - UMM Mannheim; Thomas Schaible, Germany - UMM Mannheim; Lucas Wessel, Germany - UMM Mannheim

Purpose:
In literature higher recurrence-rates have been reported for minimally invasive surgery (MIS) compared to open surgery (OS) already during the first hospital-stay. Also, higher recurrence-rates have been reported after MIS-patch-implantation and therefore the longterm-efficacy has been questioned. The purpose of this study was to critically review all patients operated within 10 years to draw conclusions how to improve long-term-efficacy.

Methods:
Follow-up-data was collected prospectively with a minimal follow-up of two years.

Results:
Between 2008 and 2017 100 patients were operated by MIS and survival was 100%. 92% were neonates and in 97% thoracoscopy applied. In 75% a primary repair was achieved, in 25% a non-absorbable patch was implanted. There was one in-hospital-recurence. 11 recurrences were observed after primary repair, 2 after implantation of a plane patch, and 1 after implantation of a cone-shaped patch. So far no patient with a ‚sublay'-patch recurred. 3 recurrences were detected after 1 year, with one lethal incarceration.

Conclusion:
Hernial sacs should be resected. It is crucial to reduce tension on the diaphragm and to promote adhesions between prosthetic material and diaphragm to prevent recurrence, because patients do not develop intestinal adhesions. Radiologic imaging and parent-counseling are mandatory in follow-up. With rising experience and meticulous technique recurrence-rates similar to those in open surgery seem to be achievable. Yet longterm follow-up until adulthood has to awaited for final judgement on efficacy.

Does inimal-invasive surgery in neonatal age cause cerebral damage and neurologic deficits?

Abstract 17

Katrin Zahn, Germany - UMM Mannheim; Thomas Schaible, Germany - UMM Mannheim; Lucas Wessel, Germany - UMM Mannheim

Purpose:

Longer operating times and intraoperative metabolic and circulatory changes have risen concerns about the application of minimal-invasive surgery (MIS) in neonates. Especially because neonates present some physiologic peculiarities that make them more vulnerable. There are no studies reporting on neurologic outcome following MIS in neonatal age so far.

Methods:

Data was collected prospectively in our standardized follow-up-program also comprising neurologic testing.

Results:

Between 2008 and 2015 71 neonates with congenital diaphragmatic hernia (CDH) underwent MIS, in 22 it was converted to open-surgery (OS) and in 130 nonECMO-patients OS was performed. There was no difference regarding gestational age or birth-weight. In MIS-patients the incidence of liver-up and patch-repair was significantly lower than compared to OS-patients (liver-up: 6/71 vs. 63/130; $p<0.000001$; patch: 17/71 vs. 102/130; $p<0.000001$). Thoracoscopy was applied with a pressure of 3-5 mm Hg, a flow of 1 l/min and discontinued insufflation. During intraoperative monitoring, pH-values were kept >7.2, $PaCO_2$ < 70 mm Hg and $SatO_2$ >90%. No significant difference between patient-groups could be identified with mean-values within normal age-matched range.

Conclusion:

Longterm-follow-up until adolescence with neurologic testing is essential to detect neurologic deficits after major neonatal surgery. If the vulnerable physiology is taken into account and parameters are kept within near-normal physiologic range, no neurologic deficits could be detected with minimum 4-year follow-up. Yet it has to be awaited, whether these patients show e.g. learning-deficits at older age. Adequate patient-selection and close interdisciplinary exchange between experienced neonatologists, pediatric surgeons and pediatric anaesthesiologists is crucial to apply MIS safely - especially in neonates.

25 Year Demographics from CDH International

Abstract 18

Dawn Ireland, United States - CDH International; Kamal Saleh, Egypt - CDH International; Tracy Meats, United States - CDH International

Purpose:

Our objective was to the assess the amount of medical information retained by parents of children born with Congenital Diaphragmatic Hernia. Our goal is to review the difference in of parent information retention in a 5 year period as last reported to the Study Group in 2015, as well as to look at the overall data of a 25 year population based study.

Methods:

In 2015, we reviewed the answers provided by a survey between 1995 and
2015. Members included 2547 survivors, 1294 non-survivors and 740 expectant or not updated. In 2020, we took another look at the survey that now included 3590 survivors, 1847 non-survivors and 985 expectant or who did not follow up. Parents were asked basic medical questions as well as a 439 question detailed medical and familial history.

Results:

Of the 6422 (3590 survivors, 1847 non-survivors, 985 expectant or not updated) cohorts in our membership, the questionnaire was answered by 4523 families (2509 survivors, 1303 non-survivors, 91 unspecified). Patients / parents were unlikely to answer the entirety of the survey (214 of 4523), despite the vast number wishing to find answers and information about Congenital Diaphragmatic Hernia. They majority of respondents said that they “can’t remember” or “do not know” answers to many of the questions.

Conclusion:

All stakeholders need to work harder to educate and update patient families of medical care and include them on decision making and record keeping so that they are more inclined to feel informed enough to participate in research studies.

Amniotic fluid stem cell exosomes rescue impaired surfactant expression in hypoplastic fetal lungs through an RNA-mediated mechanism

Abstract 19

Lina Antounians, Canada - The Hospital for Sick Children; Benjamin Liu, Canada - The Hospital for Sick Children; Andreea Matei, Canada - The Hospital for Sick Children; Huayun Hou, Canada - The Hospital for Sick Children; Cadia Chan, Canada - The Hospital for Sick Children; Michael Wilson, Canada - The Hospital for Sick Children; Augusto Zani, Canada - The Hospital for Sick Children

Purpose:

Infants with congenital diaphragmatic hernia (CDH) suffer from pulmonary hypoplasia (PH) characterized by impaired lung growth and maturation. We previously demonstrated that exosomes secreted by amniotic fluid stem cells (AFSC-exosomes) improve lung growth in experimental CDH/PH. Exosomes are nanoparticles that are key mediators of paracrine signaling. Herein, we investigated whether AFSC-exosomes: 1. promote lung maturation in fetal rat lungs and 2. contain RNA species that are responsible for their beneficial effects.

Methods:

Exosomes were isolated and characterized from conditioned medium of AFSCs and mesenchymal stem cells (MSCs; control group) using ultracentrifugation.

Lung maturation: Surfactant protein C expression was evaluated on fetal lung explants and organoids (immunofluorescence), in the following groups: A) normal (no nitrofen); B) nitrofen exposure (gavaged to dams at E9.5 to induce CDH/PH); C) nitrofen exposure + AFSC-exosomes; D) nitrofen + MSC-exosomes.

RNA mediators: we used DESeq (FDR<0.01) to differentially analyze RNA from:

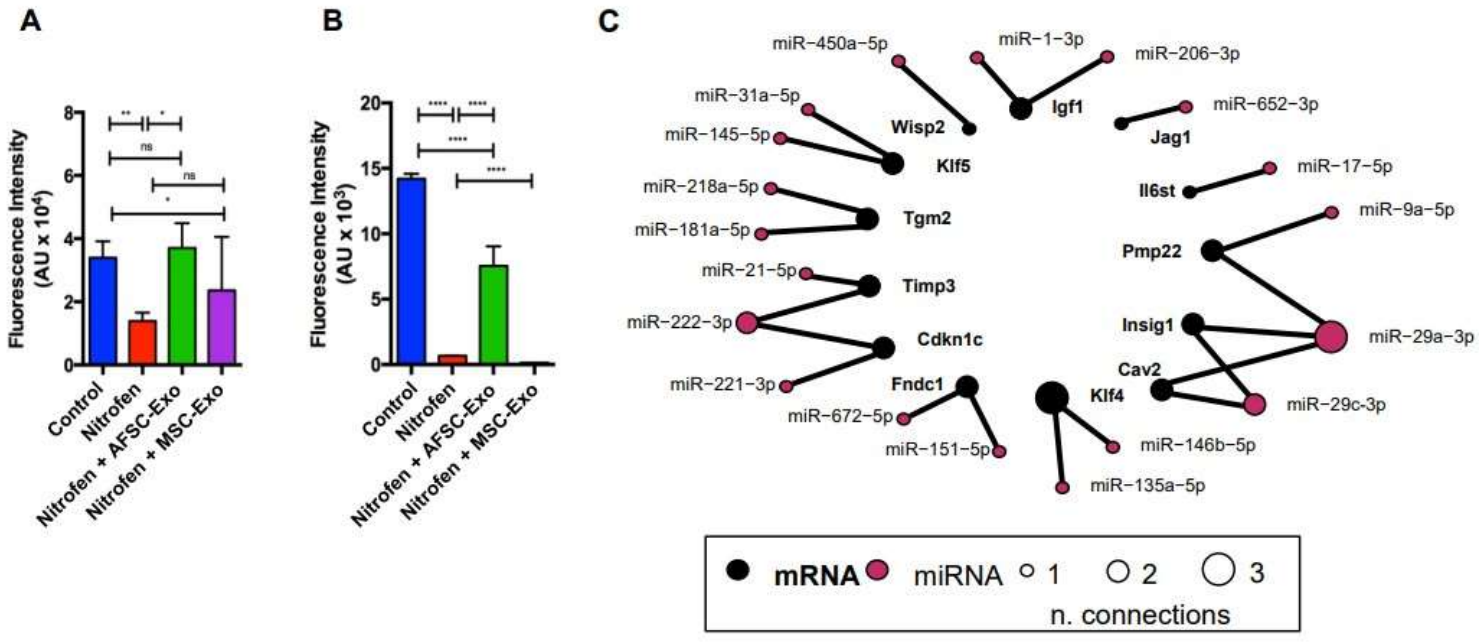
1. ASFC-exosome and MSC-exosome cargo, and 2. lung epithelial cells from groups A-C above.

Results:

In fetal lung explants and organoids, nitrofen exposure decreased SPC levels compared to control, whereas AFSC-exosome but not MSC-exosome administration increased SPC expression back to control levels (Fig.A-B). AFSC-exosomes were enriched for microRNAs that are critical for lung development, i.e. microRNA17~92 that controls lung branching morphogenesis. When we investigated AFSC-exosome microRNA effects on lung epithelium, we found 13 microRNA-mRNA interactions (Fig.C).

Conclusions:

AFSC-exosomes promote fetal lung differentiation and contain key microRNAs that exert beneficial effects on fetal lungs. Further studies are underway to identify critical microRNAs that could be used for clinical application.



Administration of amniotic fluid stem cell exosomes promotes mesenchymal maturation of hypoplastic lungs in fetuses with Congenital Diaphragmatic Hernia

Abstract 20

Louise Montalva, Canada - The Hospital for Sick Children; Rebeca Lopes, Brazil - University of São Paulo; Lina Antounians, Canada - The Hospital for Sick Children; Karina Miura, Brazil - University of São Paulo; Lourenco Sbragia, Brazil - University of São Paulo; Augusto Zani, Canada - The Hospital for Sick Children

Purpose

A critical step for the formation of functional alveoli during fetal lung development includes mesenchymal progenitor differentiation into myofibroblasts and lipofibroblasts, which is disrupted in CDH hypoplastic lungs. We showed that administration of exosomes from amniotic fluid stem cells (AFSC-exosomes) to hypoplastic lungs promotes epithelial maturation. Herein, we tested whether AFSC-exosome administration stimulated pulmonary mesenchymal maturation in an in vivo model of CDH.

Methods

AFSC-exosomes were isolated via ultracentrifugation from AFSC conditioned medium and characterized for size, morphology, and protein markers. Rabbit fetuses were allocated to the following groups (n=9 each): 1.control; 2.CDH, with CDH surgical creation on gestational day (E) 25; 3.CDH+TO, with CDH creation (E25) and tracheal occlusion (E27); 4.CDH+TO+AFSC-exo, with CDH creation (E25), TO, and AFSC-exosome intra-tracheal injection (E27). Lungs were harvested at E31. Mesenchymal maturation was assessed via RT-qPCR by measuring markers of mesenchymal progenitors (PDGFR-A), myofibroblasts (ACTA-2), lipofibroblasts (ADRP), and factors responsible for myofibroblast (PDGF-A, FGF-18) and lipofibroblast (FGF-10) differentiation.

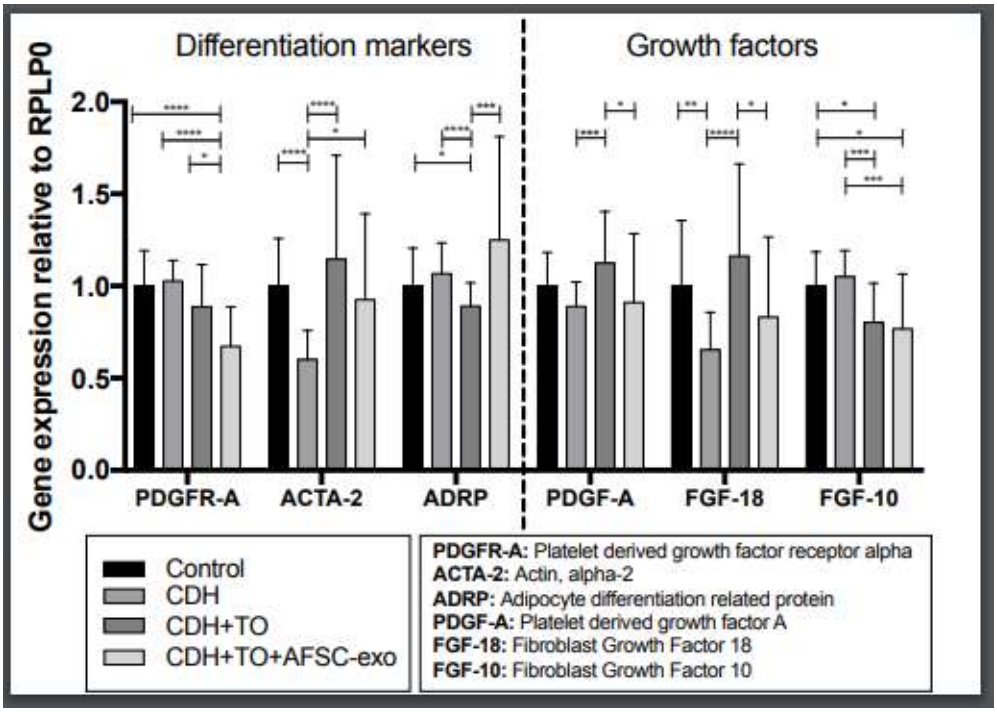
Statistics: One-way ANOVA.

Results

Compared to control, CDH lungs had lower ACTA-2 and unchanged ADRP expression [Figure]. Compared to CDH, TO increased the expression of ACTA-2, PDGF-A, and FGF-18, but decreased ADRP and FGF-10 expression. Conversely, compared to TO, administration of AFSC-exosome rescued ADRP expression to control levels and decreased PDGFR-A, by reducing PDGF-A and FGF-18 expression.

Conclusion

AFSC-exosome administration promotes mesenchymal maturation by stimulating lipofibroblast differentiation, essential for surfactant production and alveolarization. TO alone stimulates only myofibroblast differentiation, with no effect on lipofibroblasts. Exosome administration may confer additional benefits to existing prenatal therapies for hypoplastic CDH lungs.



GMP-grade exosomes derived from clinically compliant human amniotic fluid stem cells regenerate the lung epithelium in a model of pulmonary hypoplasia

Abstract 21

Lina Antounians, Canada - The Hospital for Sick Children; Alyssa Belfiore, Canada - The Hospital for Sick Children; Ornella Pellerito, Canada - The Hospital for Sick Children; Anna David, United Kingdom - University College London; Paolo De Coppi, United Kingdom - University College London; Ketan Patel, United Kingdom - University of Reading; Augusto Zani, Canada - The Hospital for Sick Children

Purpose:

Pulmonary hypoplasia is recognized as the main determinant for poor outcomes in babies with congenital diaphragmatic hernia (CDH). We previously demonstrated that rat amniotic fluid stem cells (rAFSCs) secrete exosomes that promote lung growth in experimental CDH. Herein, we investigated if human AFSC-exosomes (hAFSC-exosomes) obtained from amniocentesis following good manufacturing practices enter lung epithelial cells and have a beneficial effect on an in vitro model of pulmonary hypoplasia.

Methods:

hAFSC-exosome isolation: Conditioned medium (CM) was collected from cKit+ hAFSC harvested during amniocentesis following ethical approval (REB:08/0304). CM was ultracentrifuged to obtain exosomes and exosome-depleted fractions. For vesicle tracking, hAFSC-exosomes were fluorescently labeled with a lipophilic dye, PKH26.

In vitro model: Human alveolar basal epithelial (A549) cells were injured with nitrofen (80µM) for 18h, and treated with hAFSC-exosomes or exosome-depleted CM. Uninjured and untreated cells served as control. Proliferation (EdU) and apoptosis (cytotoxicity) rates were assessed after 24h.

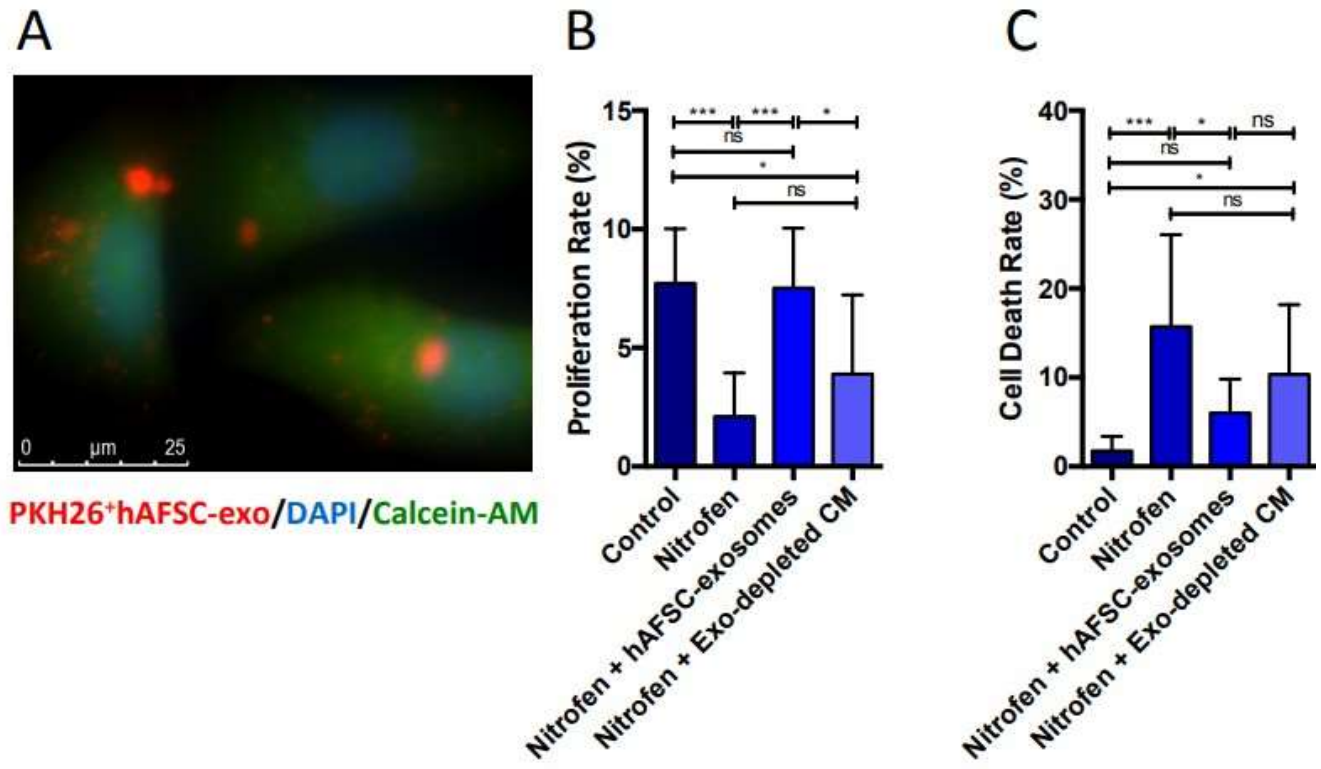
Statistics: One-way ANOVA (Tukey post-test).

Results:

PKH26+ hAFSC-exosomes enter A549 cells (Fig.1 A) and rescue proliferation and apoptosis rates of nitrofen-injured A549s back to control levels (Fig.1 B-C). The exosome-depleted CM fraction does not have the same beneficial effect.

Conclusion:

For the first time, we have shown that AFSC isolated from human amniocentesis secrete exosomes with regenerative potential on lung epithelial cells. Exosomes prepared following clinically compliant and good manufacturing practice protocols could therefore represent a novel therapy for pulmonary hypoplasia secondary to CDH.



Congenital Diaphragmatic Hernia: Prevalence and risk factors across the world

Abstract 22

Monica Paoletti, Canada - The Hospital for Sick Children; Gabriele Raffler, Canada - The Hospital for Sick Children; Maria Sole Gaffi, Canada - The Hospital for Sick Children; Louise Montalva, Canada - The Hospital for Sick Children; Lina Antounians, Canada - The Hospital for Sick Children; Augusto Zani, Canada - The Hospital for Sick Children

Purpose

The aim of the present study was to investigate the prevalence of CDH across the world and to identify the risk factors for CDH by examining the population-based epidemiological studies that have been published in the literature.

Methods

Using a defined strategy, a systematic review of the literature was conducted (Pubmed, Scopus, Cochrane), searching for population-based epidemiological studies reporting the prevalence of CDH per country. Studies that contained overlapping populations or timeframes were excluded. CDH-related risk factors were calculated by meta-analysis using RevMan5.3 and expressed as odds ratio and 95% confidence interval. This study was conducted according to PRISMA guidelines and registered on PROSPERO (CRD42019130519).

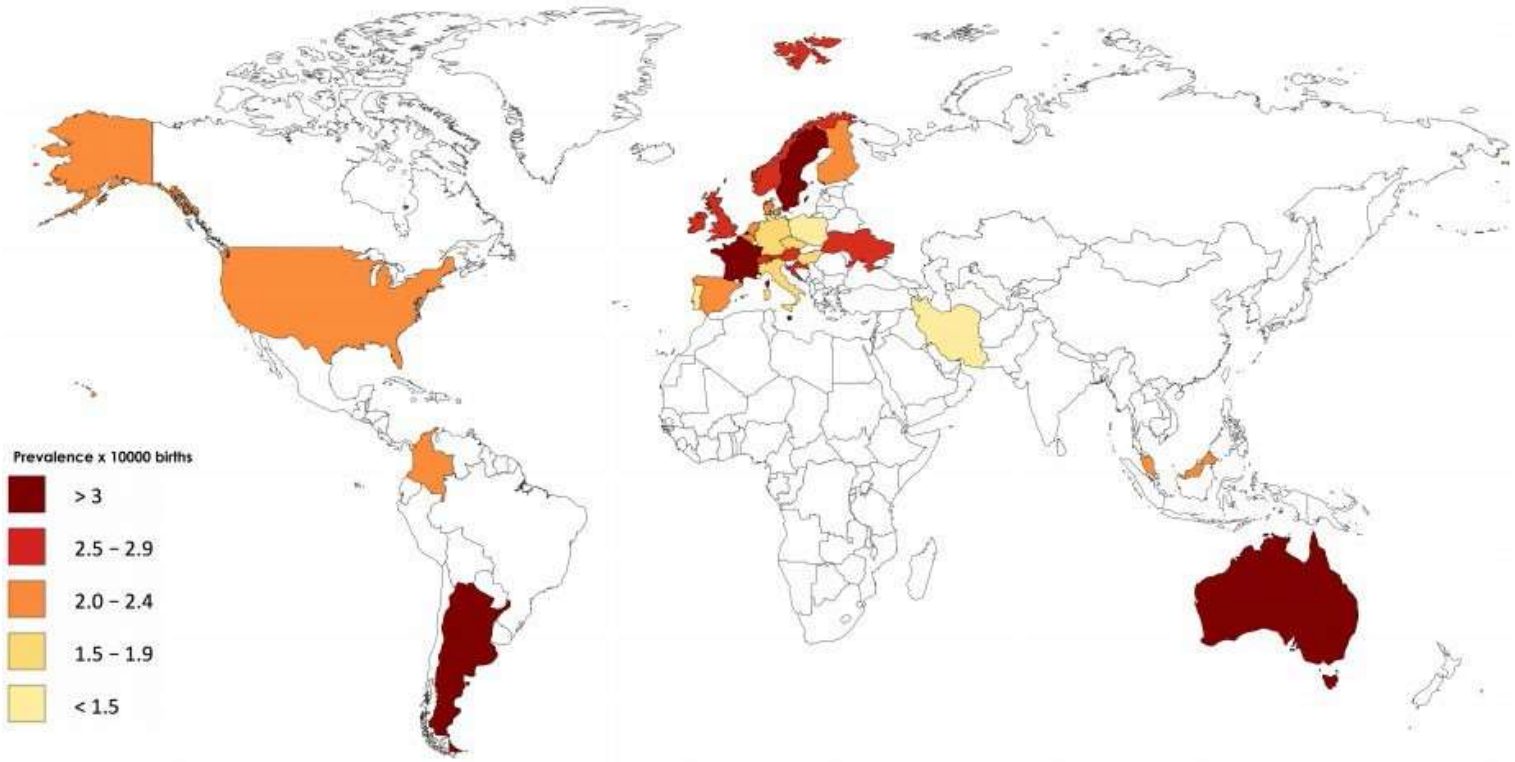
Results

Prevalence: Of 14,080 abstracts screened, 28 full-text articles were included in our analysis. These studies were published between 1967 and 2018 and included 25 countries (Figure). The overall prevalence of CDH was 2.46 (range: 0.08-5.65) in 10,000 births (18,543 CDH babies in 75,430,043 births).

Risk factors associated with CDH were identified from 7 studies: male sex 1.36 (1.21-1.53), p<0.00001, maternal smoking 1.19 (1.09-1.29), p<0.0001, and maternal age >35 years 1.15 (1.04-1.27), p=0.007.

Conclusion

This is the first study investigating the worldwide epidemiology of CDH and revealing a paucity of population-based studies from a relatively small number of countries. The global prevalence of CDH varies within and across geographical world regions. The main risk factors for CDH identified are male sex, maternal smoking, and older maternal age. More epidemiological studies, involving more world regions, are needed to identify possible strategies to prevent CDH.



Weight gain velocity and adequate amount of nutrition for infants of congenital diaphragmatic hernia

Abstract 23

Keita Terui, Japan - Department of Pediatric Surgery, Graduate School of Medicine, Chiba University; Yuko Tazuke, Japan - Department of Pediatric Surgery, Osaka University Graduate School of Medicine; Kouji Nagata, Japan - Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University; Miharu Ito, Japan - Center for Maternal-Neonatal Care, Nagoya University Hospital; Hiroomi Okuyama, Japan - Department of Pediatric Surgery, Osaka University Graduate School of Medicine; Masahiro Hayakawa, Japan - Center for Maternal-Neonatal Care, Nagoya University Hospital; Yasunori Sato, Japan - Department of Preventive Medicine and Public Health, Keio University School of Medicine; Tomoaki Taguchi, Japan - Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University; Noriaki Usui, Japan - Department of Pediatric Surgery, Osaka Women's and Children's Hospital

Purpose:

Growth retardation is problematic in infants with congenital diaphragmatic hernia (CDH). The purposes of this study are 1) to determine when catch-up growth start in infants with CDH, and 2) to assess adequate amount of nutrition during catch-up growth.

Methods:

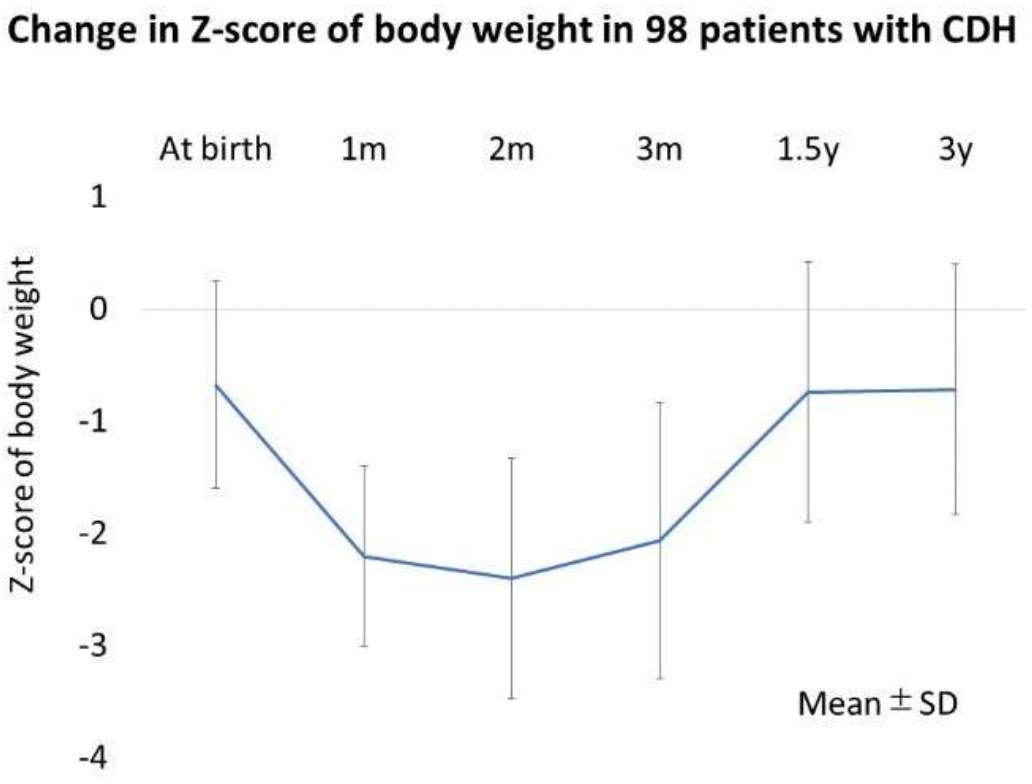
Multicenter retrospective cohort study including neonates with CDH (born 2006–2010; n = 98) who survived to discharge was conducted. Patients with chromosomal abnormality, very low birth weight and severe cardiac anomaly were excluded. Weight gain velocity (WGV) was calculated by using Z-score of body weight of each time point: at birth; 1, 2 and 3 month(s) of age; 1.5 and 3 years of age. The minimum requisite weight gain was defined as WGV ≥0. Total calorie of enteral and parenteral nutrition was assessed in each group.

Results:

Average of WGV was changed from <0 to ≥0 at 2 months of age (WGV between 0 and 1 month, -1.53/month; WGV between 1 and 2 months, -0.20/month; WGV between 2 and 3 moths, +0.34/month; WGV between 3 months and 1.5 years, +1.32/month; WGV between 1.5 and 3 years, +0.03/month) (Figure). Total calorie at 2 months of age was 116±17 Kcal/kg/day when WGV between 1 and 3 month(s) was ≥0; 97±28 Kcal/kg/day when WGV between 1 and 3 month(s) was <0; and they were significantly different (p<0.001).

Conclusion:

Average catch-up growth was observed around 2 months of age. During this period, total calorie more than 120 Kcal/kg/day was needed for the minimum weight gain (WGV between 1 and 3 months ≥0).



Long-term neurologic follow-up of CDH-patients with and without ECMO

Abstract 24

Katrin Zahn, Germany - UMM Mannheim; Thomas Schaible, Germany - UMM Mannheim; Lucas Wessel, Germany - UMM Mannheim

Purpose:

Extracorporeal membrane oxygenation (ECMO) is an invasive method for treatment of neonates with CDH. There is an internationally ongoing discussion about its benefits and the possible risk of long-term neurologic sequelae. The purpose of this study was to prospectively assess neurologic outcome with standardized and validated testing until school-age.

Methods:

Data was collected prospectively in our standardized follow-up-program also comprising neurologic testing.

Results:

Between 2008 and 2017 574 neonates with congenital diaphragmatic hernia (CDH) were treated and 226 received ECMO-therapy for sufficient stabilization (39%). Survival to discharge was 80% and 90% were followed longitudinally. There was no difference regarding gestational age or birth-weight between ECMO- and nonECMO-patients. In ECMO-patients the incidence of right-sided CDH, liver-up in left-sided CDH, patch-repair, larger defect-sizes and necessity for an abdominal wall patch was significantly higher than compared to nonECMO-patients – indicating CDH-severity in our ECMO-cohort. NonECMO-patients showed neurologic development within normal age-matched range, while ECMO-patients demonstrated psychmotorical deficits especially during infancy and catch-up with older age.

Conclusion:

Longterm-follow-up with neurologic testing until school-age in ECMO- and nonECMO-patients revealed differences especially in early infancy – but these may rather be due to disease-severity than to the application of ECMO-therapy itself. Most severely affected children with multiple comorbidities may suffer from persisting neurologic deficits, but the majority of ECMO-patients has a positive neurologic outcome.

"Virtual" long-term outcomes of children with congenital diaphragmatic hernia

Abstract 25

Gabrielle Derraugh, Canada - University of Manitoba; Matthew Levesque, Canada - University of Manitoba; Anna Shawyer, Canada - Departments of Surgery, Division of Pediatric Surgery; Melanie I. Morris, Canada - Departments of Surgery, Division of Pediatric Surgery; Suyin A. Lum Min, Canada - Departments of Surgery, Division of Pediatric Surgery; Richard Keijzer, Canada - Departments of Surgery, Division of Pediatric Surgery

Purpose:

The purpose of this study was to determine if children with congenital diaphragmatic hernia (CDH) have different long-term health, socioeconomic, and educational outcomes compared to controls.

Methods:

We performed a cohort study of CDH children born between 1991-2015. CDH cases were obtained from the Winnipeg Surgical Database of Outcomes and Management (WiSDOM) and a 10:1 date-of-birth matched control population was selected using the Manitoba Centre For Health Policy (MCHP) data repository. Hospital admission frequency, International Classification of Disease (ICD) codes, Socioeconomic Factor Index (SEFI) and grade 3, 7, 8 standardized assessments were used to assess outcomes.

Results:

Ninety CDH children and 898 controls were used. We found that CDH children were admitted to hospital more frequently than controls (OR=2.58, 95% C.I. = 2.17-3.08, $p<0.001$). However, the rate of admissions was found to decrease over time ($r=-0.21$, $p<0.001$). Respiratory admissions (OR=4.95, 95% C.I. = 3.39-7.23, $p<0.001$), gastrointestinal admissions (OR=4.23, 95% C.I. = 2.59-6.92, $p<0.001$) and admissions due to other causes (OR=2.29, 95% C.I. = 1.68-3.11, $p<0.001$) were all found to be significantly different. We also found that the presence of CDH is associated with hearing loss (OR=4.0[1.51 – 9.62], $p = 0.0027$). No difference in SEFI at birth or a change in SEFI over time was found ($p=0.839$). Lastly, we found no difference in performance on the grade assessments between cases and controls ($p=0.678$).

Conclusion:

CDH children have more hospital admissions, higher rates of hearing loss and do not differ in SEFI or grade assessment performance.

High Frequency Jet Ventilation for Rescue from High Frequency Oscillatory Ventilation in Congenital Diaphragmatic Hernia

Abstract 26

Michelle Yang, United States - University of Utah/Primary Children's Hospital; Bradley Yoder, United States - University of Utah/Primary Children's Hospital

Background:

Respiratory support for congenital diaphragmatic hernia (CDH) is key to preoperative management. High frequency ventilation is a lung protective strategy employing high rate, small tidal volume delivery above a baseline distending pressure, with differences between jet (HFJ) and oscillatory modes (HFO). We analyzed HFJ as a rescue mode for CDH neonates failing HFO.

Methods:

We conducted a retrospective review of CDH neonates managed at University of Utah/Primary Children's Hospital from 2009-2018. Infants were changed from HFO to HFJ due to respiratory failure. Within the HFJ group, we analyzed ventilatory and hemodynamic parameters at 2 and 6 hours before and after the switch with paired sample-sign test or paired t-test. We performed sub-group analysis of an HFO "only" to HFJ cohort after matching by oxygenation index (OI).

Results:

We analyzed 82 HFO only and 22 HFJ CDH neonates. The HFJ cohort had clinically more severe disease. When matched by OI (n=32; 16 pairs), survival to discharge without ECMO was higher in the HFJ cohort (50% vs 31%, p=0.28, NNT ~ 5). We identified no time-related differences in oxygenation, ventilation, or mean arterial blood pressure (Table).

Conclusion:

HFJ "rescue" for CDH neonates with hypoxic respiratory failure on HFO was associated with increased survival without ECMO. Early changes in oxygenation and ventilation measures may not immediately reflect improvement. Randomized clinical trials may be of benefit to delineate optimal mode of high frequency ventilation for CDH neonates.

	HFO (IQR) (n=82)	HFJ (IQR) (n=22)
Highest Paw 1st 24 h	12 (11-14)	13 (12-14)
Highest OI 1st 24 h	6 (4-18)	18 (13-30)
	HFO vs HFJ Pre/Post 2h (n=32) Median (IQR)	HFO vs HFJ Pre/Post 6h (n=32) Median (IQR)
FiO_2 (%)	71 (40-71) vs 83 (48-94)	69 (39-92) vs 40 (36-91)
MAP (mmHg)	44 (40-52) vs 50 (42-59)	44 (40-54) vs 46 (43-55)
$PaCO_2$	54 (50-65) vs 54 (48-61)	54 (47-63) vs 47 (40-64)
PaO_2	49 (38-53) vs 58 (39-77)	51 (40-71) vs 60 (47-69)
PF	54 (44-112) vs 55 (43-149)	78 (53-147) vs 149 (64-207)
PF-$PaCO_2$	-5 (-13,64) vs 10 (-14,94)	31 (5,94) vs 91 (21,170)

Table. Comparison of oxygenation, ventilation and hemodynamic measures (all p>0.05). OI: oxygenation index, Paw: mean airway pressure, MAP: mean arterial blood pressure, PF = PaO_2/FiO_2

Cytokeratin Fragment 21-1 is Associated with Mortality and Long-Term Oxygen Therapy in Neonates with Congenital Diaphragmatic Hernia.

Abstract 27

Florian Kipfmueller, Germany - Department of Neonatology and Pediatric Intensive Care, University Children's Hospital Bonn

Background:

The cytokeratin fragment 21-1 (C21-1) is part of the pulmonary cytoskeleton, providing cell stability and cell-to-cell communication. Aim of this study was to investigate the prognostic role of C21-1 in CDH neonates.

Methods:

CDH neonates treated in our department 2014-2018 were eligible for prospective enrollment. C21-1 was measured from arterial blood using electroluminescence immunoassay at the age of 6, 12, 24, and 48 hours. Primary clinical endpoint was death or oxygen dependency at day 28 (BPD).

Results:

90 CDH neonates were enrolled, 40 met the primary endpoint death/BPD (death n=19; BPD n=21). Patients in the death/BPD group had significant lower lung volumes and higher proportion of “liver-up”. C21-1 was significantly higher in the death/BPD group at 6 hours ($p<0.001$), 12 hours ($p=0.005$), 24 hours ($p<0.001$), and 48 hours ($p<0.001$). The following sensitivity and specificity to predict death/BPD were calculated: 6 hours: 80% and 64%, 12 hours: 66.7% and 56%; 24 hours: 77.1% and 66%. CDH neonates with a C21-1 concentration >90. percentile at least at one time met the clinical endpoint in 94.4% while this occurred in 31.9% of patients with C21-1 always <90. percentile. The mortality was 61.1% (>90. percentile) versus 13.9% (<90. percentile), respectively. A significant correlation of C21-1 with the highest oxygenation index and highest peak inspiratory pressure in the first 24 hours was observed.

Conclusion:

High C21-1 levels were associated with increased incidence of death and BPD in CDH newborns and correlated well with the severity of respiratory failure. C21-1 could serve as a prognostic biomarker in high-risk neonates.

Left ventricular parameters from initial ECHO predict survival without ECMO in left-sided congenital diaphragmatic hernia (CDH)

Abstract 28

Kristina Gulliver, United States - University of Utah; Bradley Yoder, United States - University of Utah

Background:

CDH is associated with significant morbidity and mortality, including ECMO. Left ventricular (LV) hypoplasia is reported with CDH and may increase ECMO risk. We assessed LV parameters from the first echocardiogram (ECHO) for prediction of survival without ECMO in CDH.

Methods:

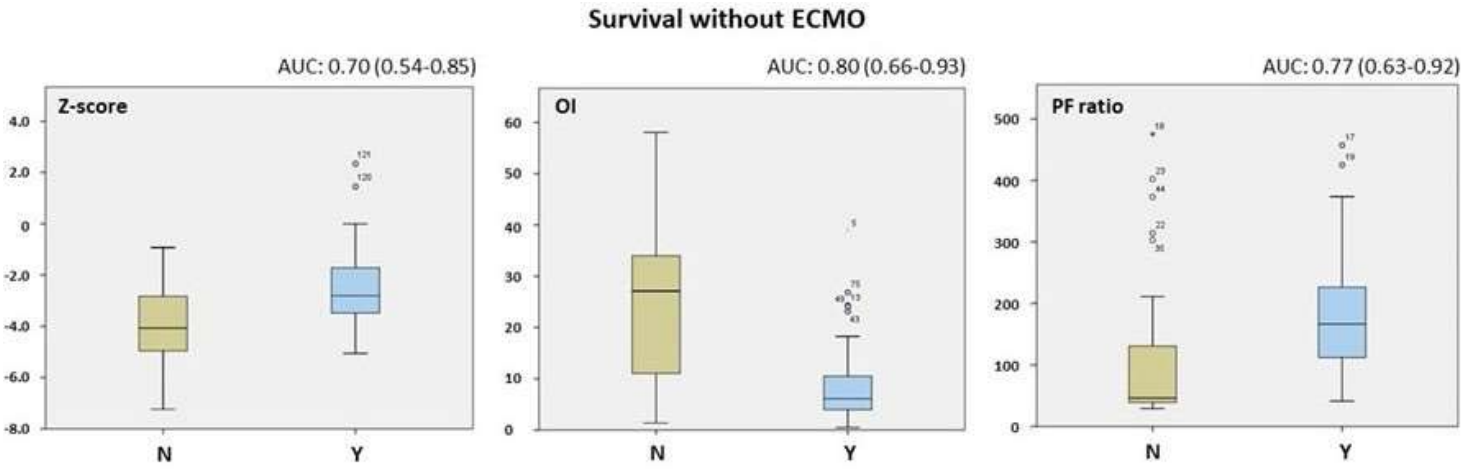
Retrospective review of left-sided CDH managed between 1/2010 and 8/2019. Clinical data and first pre-operative ECHOs were reviewed. LV mass and LVIDd (left ventricular internal diameter end-diastole) z-score were calculated per ECHO software programs. LV diameter index (LVI) was calculated by LVIDd x LVIDs (LVID end-systole).

Results:

ECHO data was available for 87/121 infants. Overall survival was 85%, ECMO 34%, and survival without ECMO 61%. Survivors without ECMO had significantly lower oxygenation index (OI), and higher PF ratio (PaO2/FiO2), and LVIDd z-score than infants who died or needed ECMO. (Figure) We categorized Z-scores as follows: > -2, -2 to -3.99 and < -4. Z-scores < -4 were associated with larger defects, more frequent liver in chest, lower PF, higher OI, higher rates of ECMO, and lower rates of survival or survival without ECMO. AUC to predict survival without ECMO for LVIDd z-score was 0.70 (95% CI 0.54-0.85), as compared to 0.80 for OI and 0.78 for PF ratio.

Conclusion:

We conclude that early, pre-operative ECHO parameters consistent with very small LV are associated with increased risk for ECMO and/or death in left-sided CDH. LVIDd z-score may be a simple ECHO parameter for predicting overall prognosis, but is not better than OI or PF ratio.



Persistent Pulmonary Hypertension in Congenital Diaphragmatic Hernia: Impact on Postnatal Outcome and Antenatal Prediction
Abstract 29

David Basurto, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven, Belgium; Francesca Maria Russo, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven, Belgium; Javiera Fuenzalida, Spain - Fetal i+D Fetal Medicine Research Center; Africa Pertierra, Spain - Department of Neonatology, Sant Joan de Déu University Hospital, Barcelona, Spain; Lennart Van der Veeken, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven, Belgium; Olga Gomez, Spain - Fetal i+D Fetal Medicine Research Center; Jan Deprest, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven, Belgium

Purpose:
To determine: 1)the prevalence of persistent pulmonary hypertension (PPH) and its impact on postnatal outcome in infants with congenital diaphragmatic hernia (CDH); 2)correlation between pre- and postnatal indicators and the presence of (refractory) PPH early in life.

Methods:
Retrospective analysis on prenatally diagnosed isolated, left-CDH cases managed at two centers (UZLeuven/BCNatal) between 2008-2018. The primary outcome was the presence of PPH and refractory PPH on postnatal day 1, 7, 14, 28 and at discharge. PPH was defined as suprasystemic pulmonary arterial pressure on postnatal echocardiography. RPPH was defined as the need of >1 drug for PPH or additional ECMO. Logistic regression was performed to investigate correlations between PPH or RPPH and o/eLHR, liver herniation, gestational age at delivery and survival at discharge.

Results:
Of 179 neonates, 128(71%) survived. The prevalence of PPH decreased from 68%(d1), 45%(d7), 33% (d14), 17% (d28) and 7% at discharge ($\chi 2$ for trend: $p<0.0001$). On d1, but not later, the occurrence of any form of PPH correlated with mortality independently from other parameters. Conversely, all but one neonate without PPH at d1(n=56) survived. The presence of refractory PPH, but not PPH, on d7 and d14 correlated also to mortality independently from other parameters. Moreover, o/eLHR inversely correlated with PPH and refractory PPH from d1 until d14 independently (Table 1).

Conclusions:
The presence and severity of PPH predicts mortality independently from other perinatal variables within the first two weeks of life. A lower o/eLHR is inversely correlated with the chance to develop PPH within two weeks of life.

Persistent pulmonary hypertension			
Predictor	Day 1	Day 7	Day 14
o/e LHR	0.93 (0.90 – 0.97)*	0.95 (0.92 – 0.98)*	0.94 (0.90 – 0.97)*
Liver herniation	1.11 (0.47 – 2.59)	1.09 (0.48 - 2.44)	1.65 (0.68 – 4.00)
GA at delivery	0.93 (0.81 -1.06)	1.07 (0.93 – 1.23)	1.15 (0.98 – 1.36)
Refractory persistent pulmonary hypertension			
o/e LHR	0.90 (0.85 – 0.96)*	0.90 (0.86 – 0.95)*	0.93 (0.89 – 0.98)*
Liver herniation	1.41 (0.41 – 4.84)	1.19 (0.43 – 3.25)	2.32 (0.83 – 6.45)
GA at delivery	1.24 (1.03 – 1.50)*	1.51 (1.22 – 1.87)*	1.26 (1.03 – 1.53)*

Table 1: Logistic regression analysis of predictors of persistent pulmonary hypertension and refractory persistent pulmonary hypertension in LCDH cases. o/e LHR: observed to expected lung to head ratio; GA: gestational age. Data is presented as odds ratio (95% confidence interval).

Prenatal brain development is altered in Congenital Diaphragmatic Hernia on ultrasound

Abstract 30

Lennart Van der Veeken, Belgium - Katholieke Universiteit Leuven; Francesca Russo, Belgium - Katholieke Universiteit Leuven; Ewelina Litwinska, United Kingdom - King's College Hospital, London; David Basurto, Belgium - Katholieke Universiteit Leuven; Luc De Catte, Belgium - Katholieke Universiteit Leuven; Elisenda Eixarch, Spain - Fetal i+D Fetal Medicine Research Center, BCNatal – Barcelona; Kypros Nicolaides, United Kingdom - King's College Hospital, London; Jan Deprest, Belgium - Katholieke Universiteit Leuven

Introduction:

Children born with congenital diaphragmatic hernia (CDH) are at risk for neurodevelopmental problems. It remains unclear if brain development is altered as a consequence of postnatal events and complications or if this occurs prenatally.

Objective:

To describe ultrasound brain biometry and perfusion in a cohort of CDH fetuses.

Study design:

We performed a multicenter retrospective study of CDH cases evaluated in three European referral centers: London (UK), Barcelona (Spain) and Leuven (Belgium). Isolated, left-sided CDH cases that had longitudinal data (at least three measurements within a minimum period of four weeks). Middle Cerebral Artery (MCA) Doppler, Head circumference (HC) and Transcerebellar diameter (TCD) were investigated. Observed-to-expected lung-to-head ratio (o/e LHR) and liver position were included as disease severity markers.

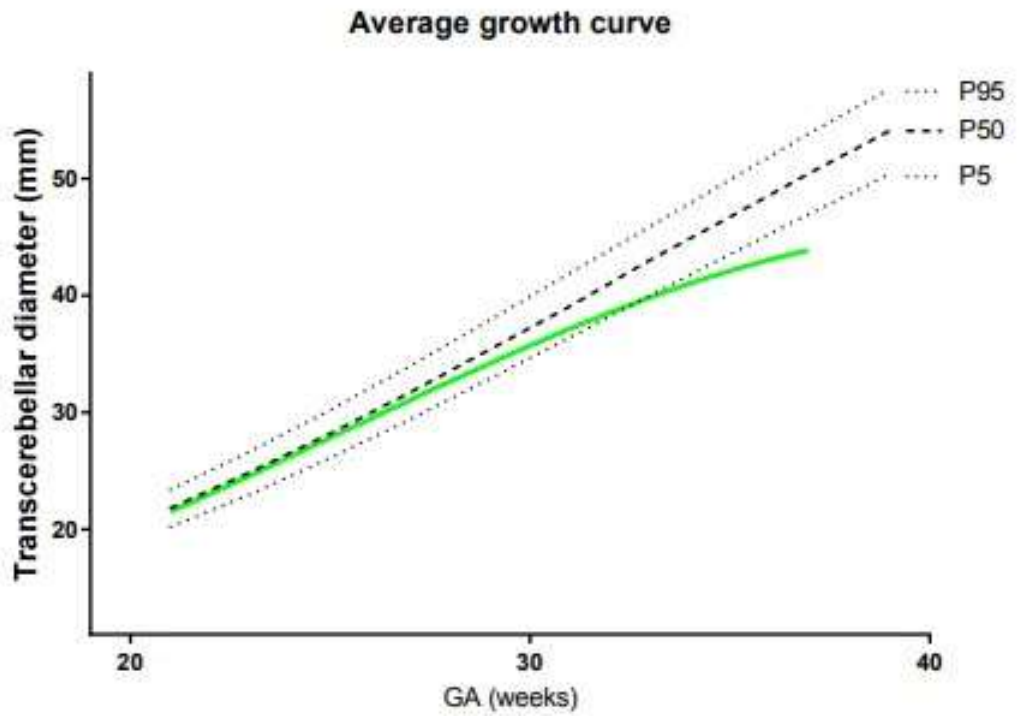
Results:

We included 176 cases. HC Z-score were within normal ranges but different from normal towards the end of pregnancy (p<0,0001). TCD Z-scores were normal at 20 weeks but 55% of measurements was abnormal at the end of pregnancy (p<0.0001), the average growth curve fell below the 5th centile from 32 weeks onwards (R^2= 0.80; p<0.0001). The peak systolic velocity (PSV) of the MCA Doppler was consistently 20% lower than normal (p<0,0001). Liver herniation was correlated to lower PSV values (p=0.002). Fetoscopic endoluminal tracheal occlusion (FETO) did not influence HC, TCD and MCA measurements.

Conclusion:

Fetal brain development seems to be altered in utero in isolated left sided CDH. Fetuses have a different cerebellar growth pattern, falling of normal ranges by 32 weeks gestation, along with a consistently lower PSV of the MCA.

Figure: Average growth curve of the transcerebellar growth curve of CDH patients.



Impact of Objective Echocardiographic Criteria for Timing of Congenital Diaphragmatic Hernia (CDH) Repair

Abstract 31

Timothy Crombleholme, United States - Fetal Care Center Dallas

Abstract:

No clear objective criteria for timing of surgical repair of congenital diaphragmatic hernia (CDH) has yet been defined. We assessed the impact of specific echocardiographic criteria for timing of CDH repair on the incidence of acute postoperative clinical decompensation from pulmonary hypertensive crisis and/or acute respiratory decompensation, with secondary outcomes including patient survival, duration of ventilator support, and length of hospitalization.

Study Design:

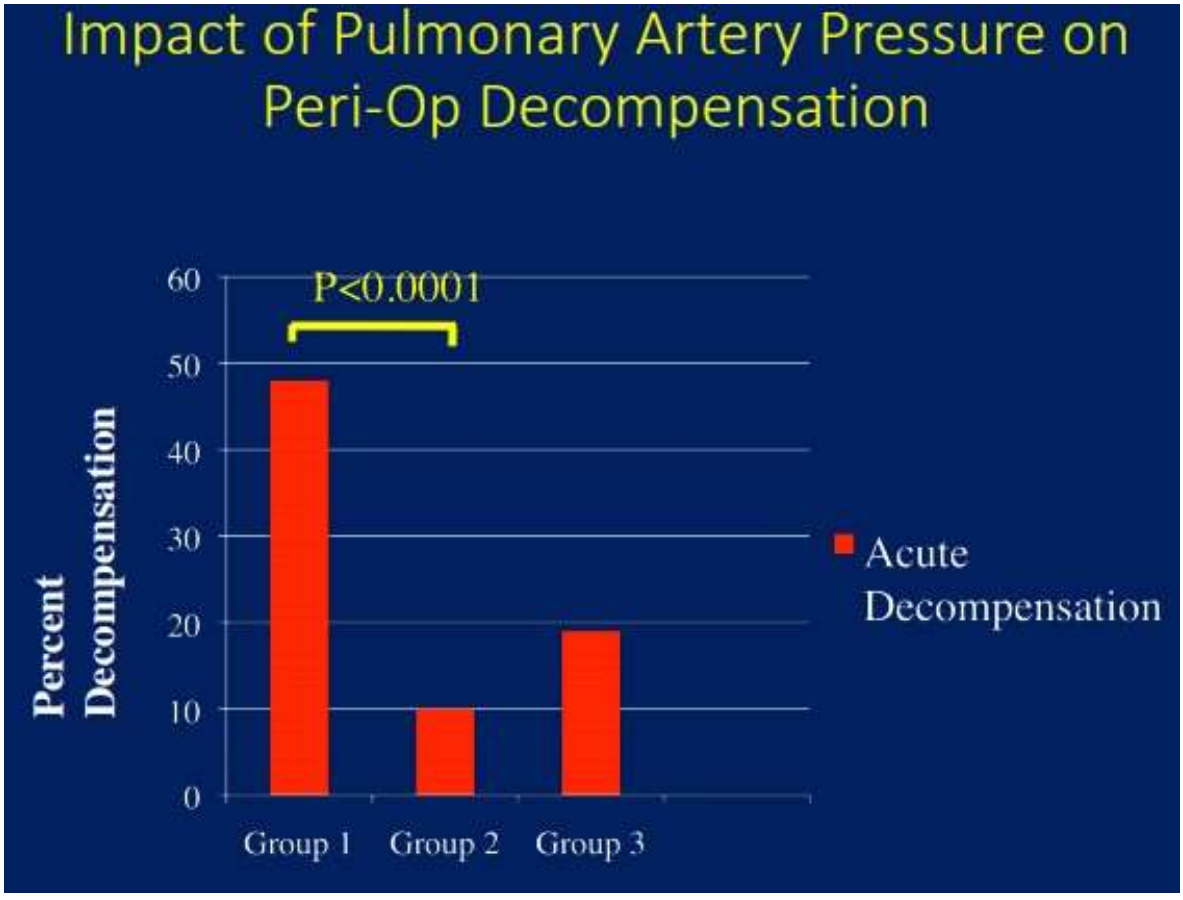
The multidisciplinary CDH management team instituted a protocol in 2012 requiring the specific criterion of echocardiogramestimated pulmonary artery pressure ≤ 80% systemic blood pressure prior to repairing CDH. A retrospective review of 77 neonatal patients with Bochdalek hernias repaired between 2008 and 2015 were reviewed: Group 1 included patients repaired prior to protocol implementation (n=25) and Group 2 included patients repaired after implementation (n=52). Statistical analyses included two-way ANOVA, Student's t-test, Wilcoxon rank sum, Chi-square and Fisher's exact tests.

Results:

The groups had similar baseline characteristics. Postoperative decompensation occurred less often in Group 2 compared to Group 1 (17.31% versus 48%, p=0.01). Adjusted analysis accounting for repair type, liver herniation, and prematurity yielded similar results (15.27% versus 36.6%, p=0.04). Group 2 displayed a trend toward improved survival to 30 days postoperatively, though this did not reach statistical significance (94% versus 80%, p=0.06). Patient survival, duration of ventilator support, and length of hospitalization were not significantly different between groups.

Conclusions:

The implementation of a protocol requiring echocardiogramestimated pulmonary arterial pressure ≤ 80% of systemic pressure prior to CDH repair may reduce the incidence of acute postoperative decompensation.



Prognosis of Neonates with Congenital Diaphragmatic Hernia who are Small for Gestational Age; A Multicenter Study

Abstract 32

Ariela Zenilman, United States - Montefiore Medical Center/Albert Einstein College of Medicine; Rebecca Hernan, United States - Columbia University Irving Medical Center; Weija Fan, United States - Columbia University Irving Medical Center; Julia Wynn, United States - Columbia University Irving Medical Center; Alexey Abramov, United States - Columbia University Irving Medical Center; Christiana Farkouh-Karoleski, United States - Columbia University Irving Medical Center; Gudrun Aspelund, United States - Columbia University Irving Medical Center; Usha Krishnan, United States - Columbia University Irving Medical Center; Julia Khlevner, United States - Columbia University Irving Medical Center; Kenneth Azarow, United States - OHSU Department of Surgery; Dai Chung, United States - Vanderbilt; Timothy Crombleholme, United States - Medical City Children's Hospital; Robert Cusick, United States - Children's Omaha; Melissa Danko, United States - Vanderbilt; Foong Yen Lim, United States - CCHMC; Mahmoud Elfiky, Egypt - Cairo University; David McCulley, United States - Meriter-Unity Point Health in Madison, Wisconsin; George Mychaliska, United States - University of Michigan/ CS Mott Children's Hospital; Douglas Potoka, United States - Children's Hospital of Pittsburgh;David Schindel, United States - University of Texas Southwestern; Samuel Soffer, United States - Northwell Health; Amy Wagner, United States - Medical College of Wisconsin; Brad Warner, United States - Washington University; Wendy Chung, United States - Columbia University Irving Medical Center; Vincent Duron, United States - Columbia University Irving Medical Center

PURPOSE:

Congenital diaphragmatic hernia (CDH) accounts for 8% of all major congenital anomalies. Neonates who are small for gestational age (SGA) generally have a poorer prognosis. We sought to identify risk factors associated with outcomes in neonates with CDH who are SGA in comparison to appropriate for gestational age (AGA).

METHODS:

571 neonates enrolled in Diaphragmatic Hernia Research & Exploration Advancing Molecular Science (DHREAMS) were analyzed. Chi-squared or Fisher's exact tests were used to compare categorical variables and t-tests for continuous variables. Cox model analyzed time to event outcomes and logistic regression analyzed binary outcomes.

RESULTS:

15.6% of our cohort were SGA and were more likely to be female (p=0.005), have left-sided CDH (p=0.026), have additional congenital anomalies (p<0.001), and have genetic syndromes (p<0.001). SGA correlated with higher mortality (p=0.002) and supplemental oxygen at 28 days (p=0.005). 12.4% SGA patients died or did not undergo surgical repair versus 6.4% AGA infants (p=0.049). The risk of mortality among SGA patients was 1.6 times the risk for AGA patients (p=0.03). There was no correlation between SGA and need for ECMO, pulmonary hypertensive medication at discharge, oxygen at discharge, or need for patch repair. After adjusting for the presence of congenital anomalies and genetic syndromes, SGA no longer correlated with poorer outcomes.

CONCLUSION:

Overall, infants with CDH who are SGA have worse survival and poorer lung function than AGA infants. However, this outcome of SGA is due to the association with congenital anomalies and genetic syndromes that contribute heavily to the poorer prognosis.

Likely pathogenic de novo variants in congenital diaphragmatic hernia patients are associated with worse clinical outcomes
Abstract 33

Lu Qiao, United States -Columbia University Irving Medical Center; Julia Wynn, United States - Columbia University Irving Medical Center; Lan Yu, United States - Columbia University Irving Medical Center; Rebecca Hernan, United States - Columbia University Irving Medical Center; Xueya Zhou, United States - Columbia University Irving Medical Center; Vincent Duron, United States - Columbia University Irving Medical Center; Gudrun Aspelund, United States - Columbia University Irving Medical Center; Christiana Farkouh-Karoleski, United States - Columbia University Irving Medical Center; Annette Zygmunt, United States - Columbia University Irving Medical Center; Usha Krishnan, United States - Columbia University Irving Medical Center; Shannon Nees, United States - Columbia University Irving Medical Center; Foong Yen Lim, United States – CCHMC; Timothy Crombleholme, United States - Fetal Care Center Dallas; Robert Cusick, United States - Children's Omaha; Kenneth Azarow, United States - OHSU Department of Surgery; Melissa Danko, United States – Vanderbilt; Dai Chung, United States – Vanderbilt; Brad Warner, United States - Washington University; George Mychaliska, United States - University of Michigan/ CS Mott Children's Hospital; Douglas Potoka, United States - Children's Hospital of Pittsburgh; Amy Wagner, United States - Medical College of Wisconsin; Samuel Soffer, United States - Northwell Health; David Schindel, United States - University of Texas Southwestern; David McCulley, United States - Meriter-Unity Point Health in Madison, Wisconsin; Yufeng Shen, United States - Columbia University Irving Medical Center; Wendy Chung, United States - Columbia University

Purpose:
Congenital diaphragmatic hernia (CDH) is a major congenital anomaly that is associated with significant mortality and long-term morbidity in some individuals. We hypothesize monogenic factors that cause CDH are likely to have pleiotropic effects and be associated with worse clinical outcomes.

Methods:
We enrolled and clinically followed 647 newborns with CDH, 462 trios of which performed sequencing to identify de novo variants. We grouped into cases with and without likely pathogenic (LP) variants and systematically assessed CDH patients for multiple outcomes between the genetic groups.

Results:
Complex cases with additional congenital anomalies had higher mortality than isolated cases (P=3x10-6). Isolated cases with LP variants had similar mortality to complex cases and much higher than isolated cases without LP (P=2x10-2). The trend was similar with pulmonary hypertension at 1 month. Cases with LP variants had an estimated 7-13 points worse across all neurodevelopmental assessments at 2 years than cases without LP, and the difference is consistent in isolated and complex cases.

Conclusion:
We found that the likely pathogenic genetic factors are associated with higher rates of mortality and pulmonary hypertension, and worse neurodevelopment outcomes. Our results have important implications for prognosis and potential intervention and long-term follow up for children with CDH.

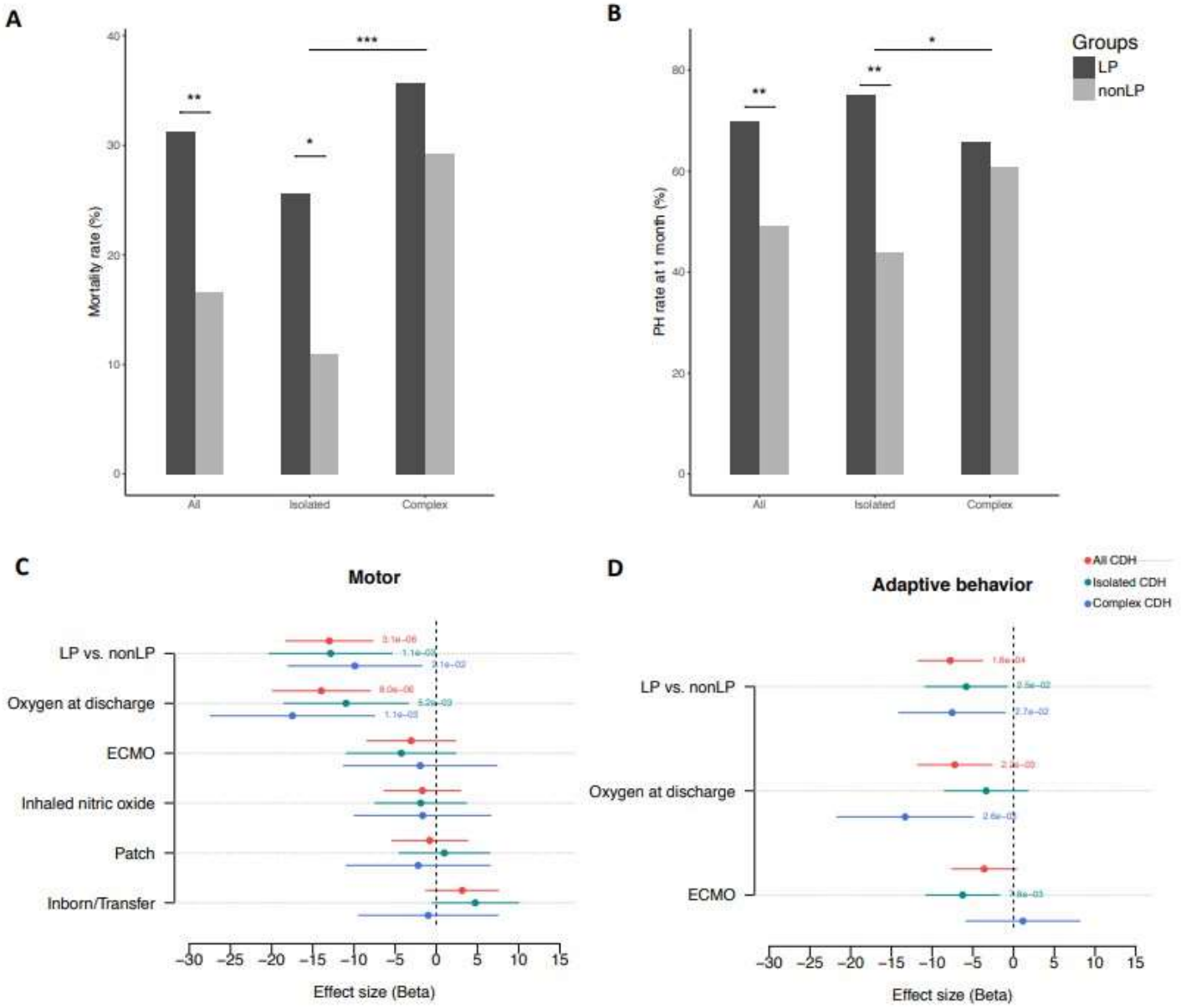


Figure. Association analyses for genetic groups with mortality, pulmonary hypertension and neurodevelopmental outcomes at 2 years. (A) Mortality prior to initial discharge. (B) Pulmonary hypertension at 1 month. Effect size for likely pathogenic variants on (C) motor and (D)adaptive behavior. For (A/B), *P* value are given by Fisher's exact test. ***: *P*<0.001; **: *P*<0.01; *: *P*<0.05. For (C/D), Effect size is the coefficient/beta, which align with outcomes on the y-axis, with the vertical dashed line (v=0) separating positive and negative direction of association. LP: likely pathogenic variants; SES: socioeconomic status; PH: pulmonary hypertension; ECMO: extracorporeal membrane oxygenation.

Contemporary Cost Trends in the Treatment of Congenital Diaphragmatic Hernia (CDH)

Abstract 34

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Purpose:

CDH represents one of the most costly congenital anomalies commonly treated by pediatric surgeons. This study sought to investigate recent trends in spending related to CDH treatment and primary drivers of cost.

Methods:

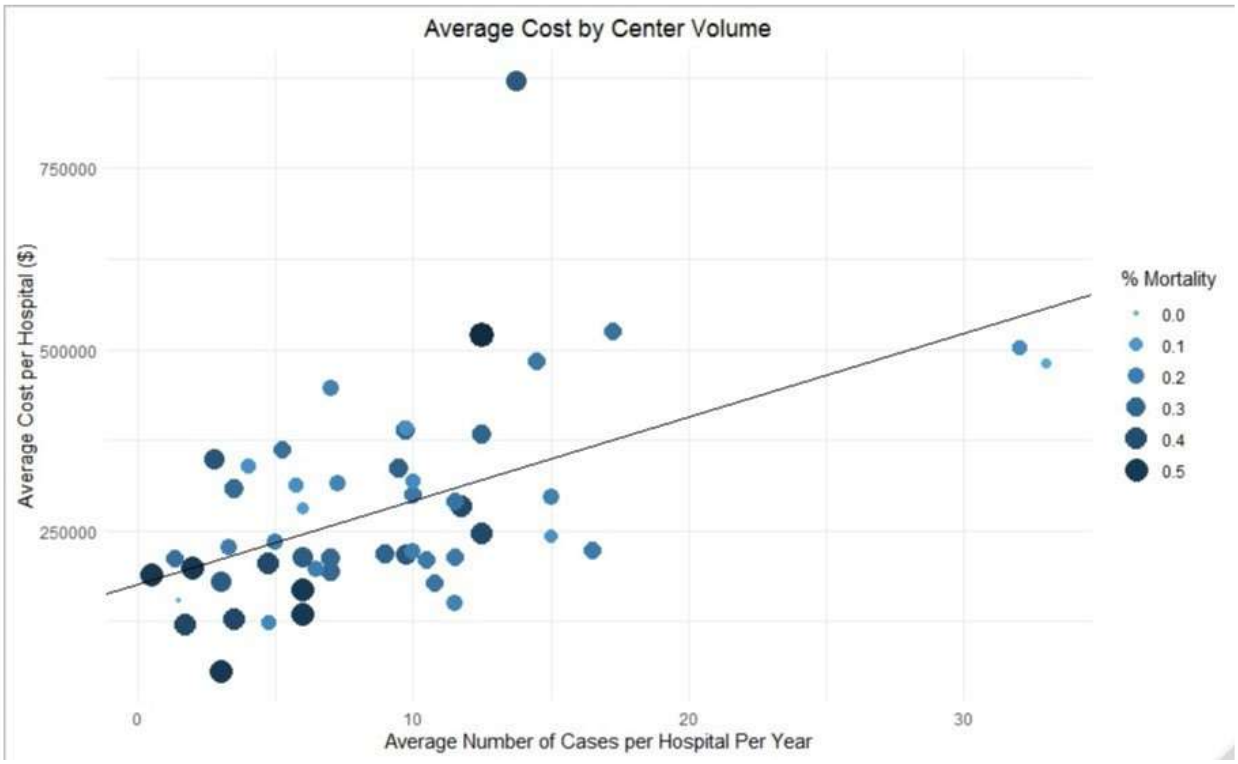
This is a retrospective study of neonatal CDH patients at U.S. hospitals using data from the Pediatric Health Information System (PHIS) database (2015-2018). In addition to patient characteristics, the cost effects of center CDH volume and regional variation were assessed. Student's t-test, Kruskal-Wallis, and Chi-Squared analyses were performed when appropriate; multivariable regression models were used to access factors contributing to overall cost.

Results:

There were 1708 patients from 51 centers included in the study. Overall mortality was 412 (21.2%), 1524 patients (89.2%) underwent operative repair, and 504 (29.5%) were placed on extracorporeal life support (ECLS). The average cost for care for the entire cohort was $337,459. No difference in cost was seen between survivors and non-survivors [$326,889 vs $360,409 (p=0.24)]. On linear regression, there was a statistically significant increase in cost with increasing center volume (p=0.0002), without significant decrease in mortality. On multivariate regression, significant independent drivers of total costs included high vs low volume centers, length of stay, and use of ECLS.

Conclusion:

Overall mortality for CDH in this cohort was 21.2% with an average cost of care of $337,459 and an estimated annual national cost burden of $367,155,392. Cost did not differ between survivors and non-survivors, and while care at higher volume centers was more expensive, there was no corresponding survival advantage.



Mesh matters: patch material in congenital diaphragmatic hernia affects recurrence rate.

Abstract 35

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Purpose:

Although survival for children born with Congenital Diaphragmatic Hernia has increased over the past 20 years, little/no progress has been made to improve prosthetic patch material. Our center has continued to search for a more resilient patch material. Over the past 20 years, we have used Gore- Tex, Alloderm, Surgisis, composite patches, and currently, Ventralight™. This study evaluates expanded polytetrafluoroethylene (Gore-Tex) and macroporous polypropylene coated mesh (Ventralight™) patches, comparing the recurrence rates and risk factors after repair at a single institution.

Methods:

A retrospective review of 89 children with CDH who underwent repair with mesh at Children's Hospital of Illinois from 1997 to 2019 was performed. All children had follow up in multispecialty CDH clinic with surveillance imaging to evaluate for recurrence. A subgroup analysis was performed comparing Gore-Tex versus Ventralight™ repairs. Variables collected included birth data, defect classification, surgical approach and patch material. Outcomes measured included recurrence rate, age, and complications. Statistical analysis utilizing chi-square test was performed between the two groups.

Results:

A total of 35 CDH repairs utilized either Gore-Tex (n=16) or Ventralight™ (n=19) mesh. A chi-square test found that children repaired with Gore- Tex had a significantly higher recurrence rate (50%) compared to when Ventralight™ was used (16%) ($p<0.03$).

Conclusion:

The use of Ventralight™ mesh for repair of CDH with large defects has a significantly lower re-herniation rate at our institution. However, as recurrence rates remain high, we believe routine clinic follow up with surveillance of diaphragmatic integrity is needed to diagnose re-herniation and help prevent related complications.

Prenatal miR-200b Treatment in the Nitrofen Rat Model of Congenital Diaphragmatic Hernia normalizes vascular development
Abstract 36

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Purpose:
Congenital diaphragmatic hernia (CDH) patients experience abnormal lung development which causes vascular remodeling and pulmonary hypertension. Prenatal therapies could improve lung development but are currently limited for these patients. CDH non-survivors have decreased expression of a microRNA called miR-200b compared to survivors. We predict that prenatal miR-200b therapy could prevent vascular remodeling associated with CDH.

Methods:
Following ethical approval, we used the established nitrofen rat model of CDH. Pregnant dams were gavaged with nitrofen on embryonic day 9 and administered either intravenous miR-200b mimic (5mg/kg) or oligo negative control. At embryonic day 21 pups were euthanized and lungs were collected. Lung tissues were formalin fixed, paraffin embedded, and serial sectioned. Verhoeff-van Gieson's staining and immunofluorescence for vascular endothelin growth factor receptor 2 (VEGFR2) were used to characterized changes in the lung vasculature.

Results:
Preliminary morphometric analysis was not significant but showed that prenatal miR-200b treatment decreased mean medial wall thickness (26.93uM, n=2) compared to oligo negative control (30.03uM, n=2) (p=0.261). Immunofluorescence results suggested that VEGFR2 expression was higher in the airways and arteries in miR-200b treated CDH pups compared to oligo negative control CDH pups.

Conclusion:
Our results suggest that prenatal miR-200b administration reduced lung vascular remodeling and increased VEGFR2 expression in the nitrofen rat model. Thus, prenatal miR-200b therapy has the potential to decrease vascular remodeling, which could result in lower morbidity and mortality associated with pulmonary hypertension in CDH patients.

The aryl hydrocarbon receptor (AHR) is involved in the pathogenesis of CDH

Abstract 37

Landon Falk, Canada - Children's Hospital Research Institute of Manitoba; Wai Hei Tse, Canada - Children's Hospital Research Institute of Manitoba; Nolan DeLeon, Canada - Children's Hospital Research Institute of Manitoba; Daywin Patel, Canada - Children's Hospital Research Institute of Manitoba; Richard Keijzer, Canada - Children's Hospital Research Institute of Manitoba

Abstract:

Environmental factors may contribute to 70% of CDH cases. A specific class of environmental chemicals can activate the transcription factor aryl hydrocarbon receptor (AHR) to change gene expression. We hypothesize that activation of AHR by these chemicals is involved in the pathogenesis of CDH.

Ethical approval was obtained prior to experiments (19-010 (AC11436)). We compared the response of AHR to nitrofen to known ligands - benzo[α]pyrene and resveratrol - in the BEAS-2B human epithelial cell line (n=3). AHR activity within a 24 hour exposure period was assessed with immunocytochemistry (ICC/IF). We compared the abundance of AHR in saccular lung sections (n=3) from human CDH patients (Week 39-40) and nitrofen-treated rat pups (E21) to age-matched controls using immunofluorescence.

AHR activation was induced in BEAS-2B cells within six hours of treatment. We observed all ligands to induce the translocation of AHR fluorescence signal from the cytoplasm (inactive) to nucleus (active), suggesting nitrofen activates AHR. After 24 hours of treatment, the AHR signal was strictly cytoplasmic and diminished. CDH patients and rat lung sections have increased AHR abundance in the mesenchyme and airways compared to controls.

We observed nuclear translocation of AHR indicating activation of the receptor. We saw similar changes in AHR abundance in both human CDH and nitrofen rat lungs; suggesting that similar pathological mechanisms are involved. This dysregulated expression of AHR may contribute to abnormal lung development in babies born with CDH. The results suggest that environmental chemicals structurally similar to nitrofen may activate AHR to induce CDH.

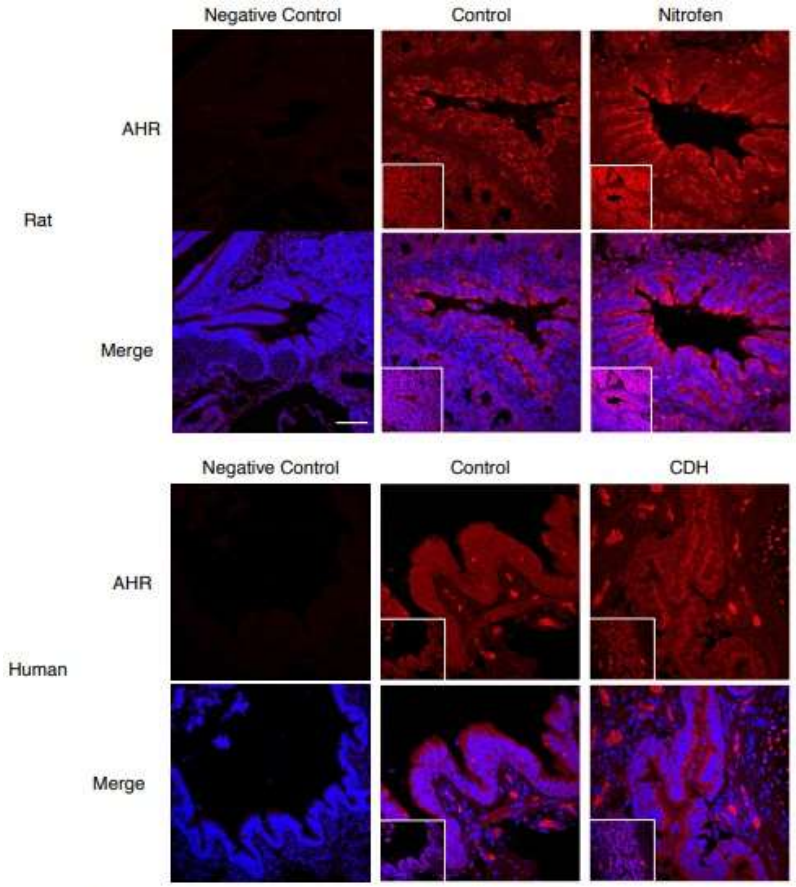

Figure 3. AHR abundance is greater in nitrofen rat-model and CDH. 40x magnification with a 20x magnification inset. A) E21 rat tissue with increased abundance in the nitrofen sample in the cytoplasm. B) Human end-term gestation with greater abundance in the cytoplasm of the CDH sample compared to the control. Scale = 100μm.

Cytokine Profiles In Fetal Tracheal Fluids Can Distinguish Feto CDH Survivors From Non-Survivors

Abstract 38

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Purpose:

There is emerging evidence that immunological processes contribute to the pathogenesis of Congenital Diaphragmatic Hernia (CDH). We found previously that cytokine signalling pathways are enriched in nitrofen-induced hypoplastic lungs. Here, we aimed to analyse cytokine profiles in tracheal fluids from CDH fetuses undergoing fetoscopic endoluminal tracheal occlusion (FETO).

Methods:

Following ethical approval (HS15293) we obtained tracheal fluids from severe CDH cases undergoing FETO at balloon placement. Groups were divided into patients eventually surviving FETO (n=4) and non-survivors (n=4). Cytokines were profiled using a Luminex 42-plex array. Bioinformatic analysis was performed with R Studio. Mann-Whitney U test was used for statistical analysis with significance set at $p<0.05$.

Results:

Cytokine signatures in tracheal aspirates were altered between CDH fetuses that survive FETO and non-survivors. Gestational age was 28.1 (survivors) and 27.9 (non-survivors) weeks and observed-over-expected lung-to-head ratios were 22.5 % and 21.6%, respectively. G-CSF (Fold Change 2.5), IL-2 (FC 2.5), IL-8 (FC 8), IL-9 (FC 1.7) and IL-15 (FC 2.5) were significantly increased in tracheal fluids of survivors. Correlation heat maps showed a stronger correlation of single cytokines among survivors compared to non-survivors. In survivors, EGF, Rantes and IL-1a were negatively correlated with the other cytokines, whereas in non-survivors FGF2 and IL-R1 were negatively correlated with the rest of the profile.

Conclusion:

Cytokine profiles between CDH fetuses that will eventually survive FETO are altered compared to non-survivors. Our results suggest again that immunological processes contribute to the pathobiology of CDH and that a specific cytokine signature is associated with better outcomes.

Abnormal Lung Development In Congenital Diaphragmatic Hernia Might Be Due To An External Viral Stimulus To The Innate Immune System

Abstract 39

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Purpose:

Although evidence suggests that environmental aspects are involved in causing Congenital Diaphragmatic Hernia (CDH), an "external factor" is unknown. Using omics technologies and bioinformatics we aimed to uncover novel biological processes in the pathogenesis of CDH.

Methods:

After ethical approval (19-010 (AC11436)), total proteins were isolated from nitrofen exposed CDH (n=5) and control (n=5) lungs (Embryonic day 21). Label-free 1-D liquid chromatography coupled with mass spectrometry was performed for proteomic profiling. Bioinformatic analysis was performed using R Studio Software. Pathway analysis and protein interaction networks were created with ingenuity pathway analysis and networkanalyst.ca. Immunohistochemistry (IHC) and in-situ Hybridization (ISH) against viral proteins or RNA were performed in human fetal CDH lungs.

Results:

The proteomic profile of hypoplastic nitrofen lungs showed a strong immunological signature with significant upregulation of immune response proteins. Network analysis identified interleukin signalling, cytokine signalling and innate immune response as the most enriched biological processes. CREB-binding protein, Thyrosine-proteine kinase Lyn, Signal transducer and activator of transcription 3 and nuclear factor kappa-light-chain-enhancer of activated B cells were central hubs for protein interactions within our network analysis. Pathways correlated to viral stimuli, especially Epstein Barr Virus (EBV) were significantly enriched in hypoplastic lungs. Using IHC and ISH we could not detect EBV or Human Cytomegalovirus (HCMV) in human fetal CDH lungs yet.

Conclusion:

Nitrofen exposed hypoplastic lungs showed a marked immune response due to an external viral stimulus. Overwhelming immune responses due to viral stimulation in human fetuses or nitrofen in the rat model could potentially explain abnormal lung development in CDH.

Exercise capacity in adolescents born with congenital diaphragmatic hernia

Abstract 40

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Purpose:

Within our prospective multidisciplinary follow-up for children born with foregut anomalies, the pediatric physical therapist evaluates exercise capacity at the age of 5, 8, 12 and 17 years. We previously described decreased exercise capacity in school-aged CDH patients which declined over time. Therefore, we now aimed to evaluate exercise capacity in adolescent CDH survivors.

Methods:

Maximal exercise capacity at the age of 17 years was evaluated with a bicycle ergometer test according to the ten Harkel protocol. Peak workload was our primary outcome variable, defined as the mean highest workload during the last 60s. SD-scores were calculated related to age and height.

Results:

We included 38 participants, 13 (34%) of whom were treated with neonatal ECMO. Sixteen (42%) participated in sports activities. Mean (SD) peak workload was 224.1 (37.9) and 152.7 (24.9) Watt for boys and girls respectively. Mean (SD) SDS peak workload based on reference values related to gender and age was -1.6 (1.4), significantly less than expected ($p < 0.001$). Using reference values related to gender and height this was -0.5 (1.3) p=0.02 (see figure). Mean (SD) SDS height corrected for target height (TH) was -0.5 (1.0), p=0.003. SDS endurance time correlated positively with sports participation (p=0.012, Rho=0.403) and negatively with ECMO treatment (p=0.010, Rho=-0.412).

Conclusion:

Adolescent CDH survivors had lower maximal exercise capacity than expected. Exercise capacity seems to decline further over age, suggesting that adolescents with CDH may experience more difficulties with sports participation than peers. Early guidance regarding physical activities and sports is needed.

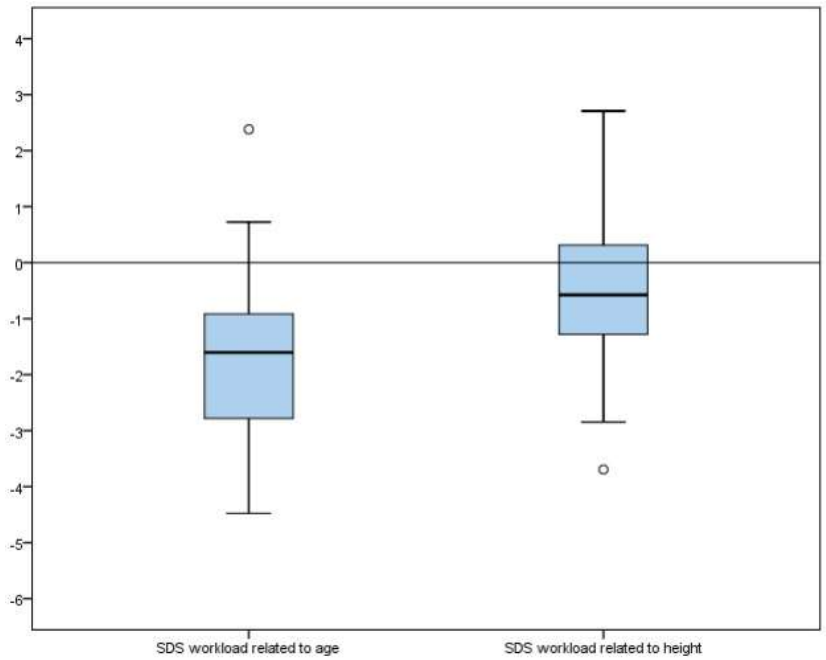

Figure: SDS workload related to age (ten Harkel; left boxplot) and related to height (ten Harkel; right boxplot), bottom and top of the box represent first and third quartiles, the band inside the box represents the median. Whiskers with 1.5 interquartile range.

Improving exercise capacity following neonatal respiratory failure; a randomized controlled trial

Abstract 41

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Purpose:

Children born with anatomical foregut anomalies (including CDH) and/or treated with neonatal ECMO are at risk for long-term respiratory morbidity and reduced exercise capacity. We evaluated whether two different interventions improve exercise capacity in the short- and long-term.

Methods:

In this single-blinded randomized controlled trial, 40 participants (12 children with CDH) were randomly assigned to group A: standardized anaerobic high-intensity interval training near home plus online lifestyle coaching-program for 3 months, B: online lifestyle coaching-program only, or C: standard of care. Inclusion criteria: score ≤ -1 SD on the Bruce-protocol. Exercise capacity was assessed at baseline(T0), after 3 months(T1), and after 12 months(T2). Also actual and perceived motor performance, participation, quality of life, pro-active coping and health status were assessed.

Results:

Exercise capacity improved over time irrespectively of ECMO treatment or diagnosis : mean (SD) SDS endurance time: T0 -1.91 (0.73); T1 -1.35 (0.94); T2 -1.20 (1.03): T0-T1 and T0-T2: both p<0.001 (See figure). No significant differences in maximal endurance time were found between the study-arms at T1 or T2.

Conclusion:

Exercise capacity improved significantly over time, irrespective of the study-arm and diagnosis. This suggests that not only residual morbidity is responsible for reduced exercise capacity. Parental awareness of reduced exercise capacity and their pro-active coping competence rather than specific interventions may have contributed to improvement. Monitoring exercise tolerance and providing counselling on lifestyle factors that improve physical activity should be part of routine care. Recommendations and/or intervention should be offered on an individual basis.

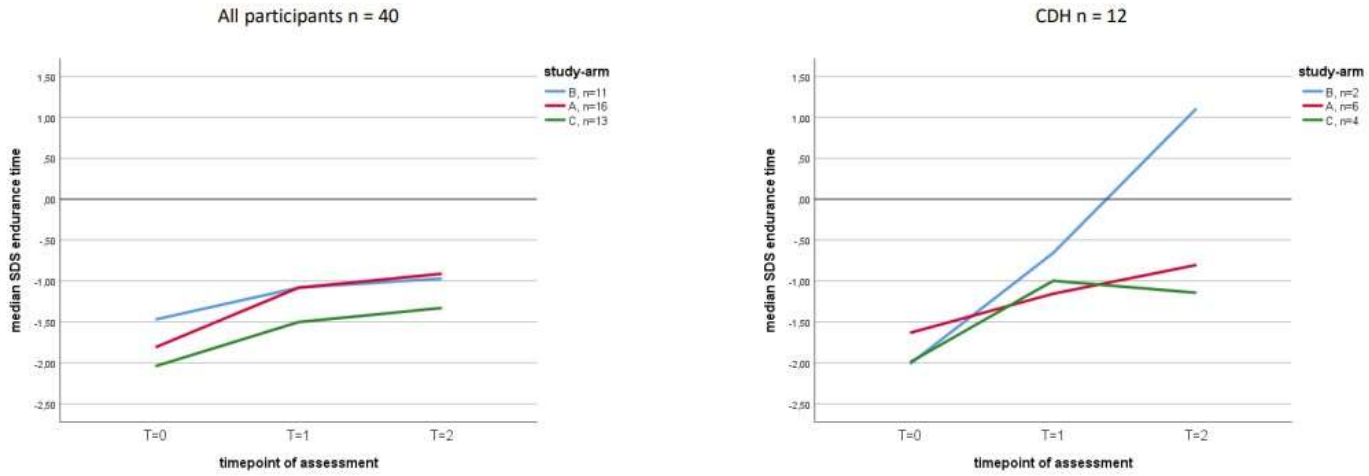

Figure Median SDS endurance time over time of the study arms
Study arm A = standardized training program for the child plus online lifestyle coaching for the child and its family;
study arm B = online lifestyle coaching for the child and its family;
study arm C = standard of care
T0 baseline assessment; T1 assessment after 3 months; T2 assessment after 12 months
SDS = standard deviation score

Abnormal cardiac function at discharge in infants with congenital diaphragmatic hernia

Abstract 42

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Background:
Pulmonary hypertension (PH) and cardiac dysfunction are key pathological findings in congenital diaphragmatic hernia (CDH), however the frequency and timing beyond neonatal discharge are not well understood.

Aims:
To investigate frequency of pulmonary hypertension and cardiac function at discharge in infants with CDH.

Methods:
Retrospective study conducted at the Royal Hospital for Children (RHC), Glasgow, UK and Bambino Gesù Children's Hospital (OPBG), Rome, Italy. Left ventricle (LV) and right ventricle (RV) function were assessed within the first 48 hours of life and at discharge. Cardiac function was evaluated using longitudinal strain measurement and compared to existing normative data. PH was assessed using velocity of tricuspid regurgitation jet (TR), PDA flow, and septal position quantified by end-systolic eccentricity index (EI ES).

Results:
27 cases were included. On initial echo 25 (92%) cases had RV dysfunction and 21 (78%) LV dysfunction. At discharge, RV dysfunction was present in 19 (70%), and LV dysfunction in 12 (44%). At birth TR was present in 19 (70%) patients, PDA flow in all cases (left-to-right in 3 (11%), right-to-left in 1 (4%), and bidirectional in 24 (89%)), mean (SD) EI ES was 1.24 (0.4). At discharge TR was measurable in only 2 (7%) cases, no cases had PDA. Mean (SD) discharge EI ES was 1.07 (0.2).

Conclusions:
- Pulmonary artery pressure assessment at discharge is challenging.
- Persistent RV and LV dysfunction are common.
- Follow-up assessment of cardiac function may be important to monitor disease progression and guide therapy in CDH.

Risk factors for cardiac dysfunction at discharge in congenital diaphragmatic hernia (CDH)

Abstract 43

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Background:

Congenital diaphragmatic hernia (CDH) is associated with pulmonary hypoplasia, pulmonary hypertension (PH), and cardiac dysfunction (CFx). Factors predisposing to ongoing PH and CFx at discharge are not well understood.

Aims:

To identify factors associated with cardiac dysfunction at discharge in infants with CDH.

Methods:

Retrospective study conducted in high-volume centres at Royal Hospital for Children (RHC), Glasgow, UK and Bambino Gesù Children's Hospital, Rome (OPBG), Italy). Left ventricle (LV) and right ventricle (RV) systolic function were measured within the first 48 hours of life and at discharge using longitudinal strain, and compared to existing normative data. Demographics, CDH characteristics, main outcomes (duration of respiratory support, length of stay), and cardiorespiratory therapies were recorded.

Results:

27 cases were identified. At discharge RV dysfunction was present in 19 (70%), and LV dysfunction in 12 (44%), Table 1. iNO use was associated with normal RV function at discharge (p=0.01). Milrinone and adrenaline use, and lower gestational age were associated with normal LV function at discharge (p=0.02; p=0.02; p=0.01 respectively). Day of surgical repair was higher in infants with normal RV and LV function at discharge (p=0.02; p=0.007 respectively). Defect size, duration of respiratory support, and length of stay were not associated with ventricular function at discharge.

Conclusions:

- Persistent cardiac dysfunction at neonatal discharge is common in CDH
- Use of pulmonary vasodilators and cardiotropes are associated with normal function at discharge.
- The relationship between timing of repair and cardiac function at discharge merits further investigation

Table 1: Cardiac function at discharge, relationship to demographics , CDH characteristics, and outcomes

	RV normal function (n=8)	RV dysfunction (n=19)	*P value*	LV normal function (n=15)	LV dysfunction (n=12)	*P value*
Gestational age, weeks median (range)	39 (35-39)	39 (35-40)	P=0.8	39 (35-40)	36,5 (35-39)	**P=0.01**
ECMO, n (%)	0 (0%)	3 (16%)	P=0.15	2 (13%)	1 (8%)	P=0.6
Time to surgery, days (SD)	7.6 (2.8)	4.8 (2.2)	**P=0.02**	6.8 (2.7)	4.1 (1.9)	**P=0.007**
Milrinone, n (%)	7 (87.5%)	11 (58%)	P=0.1	13 (87%)	5 (42%)	**P=0.02**
Dopamine, n (%)	7 (87.5%)	16 (84%)	P=0.8	14 (93%)	9 (75%)	P=0.21
Adrenaline, n (%)	5 (62.5%)	6 (32%)	P=0.1	9 (60%)	2 (17%)	**P=0.02**
Vasopressin, n (%)	0 (0%)	11 (58%)	**P=0.005**	3 (20%)	8 (67%)	**P=0.02**
iNO, n (%)	7 (87.5%)	7 (37%)	**P=0.01**	11 (73%)	3 (25%)	**P=0.01**
Sildenafil, n (%)	3 (37.5%)	10 (53%)	P=0.9	7 (47%)	6 (50%)	P=0.6

Activation of aryl hydrocarbon receptor determined by molecular docking suggests a role in CDH pathogenesis

Abstract 44

Wai Hei Tse; Canada - Children's Hospital Research Institute of Manitoba; Thomas Mahood, Canada - Children's Hospital Research Institute of Manitoba; Landon Falk, Canada - Children's Hospital Research Institute of Manitoba; Richard Keijzer, Canada - Children's Hospital Research Institute of Manitoba

Purpose:

The mechanism of the nitrofen-induced model of CDH is poorly understood. The activation of the xenobiotic transcription factor aryl hydrocarbon receptor (AHR) by chemicals may contribute to the pathogenesis of human and the nitrofen-induced CDH. Nitrofen is a derivative of polybrominated diphenyl ethers (PBDEs), which like the prototypical TCDD, can bind and activate AHR. We hypothesize the activation of AHR by nitrofen is involved in the pathogenesis of CDH.

Methods:

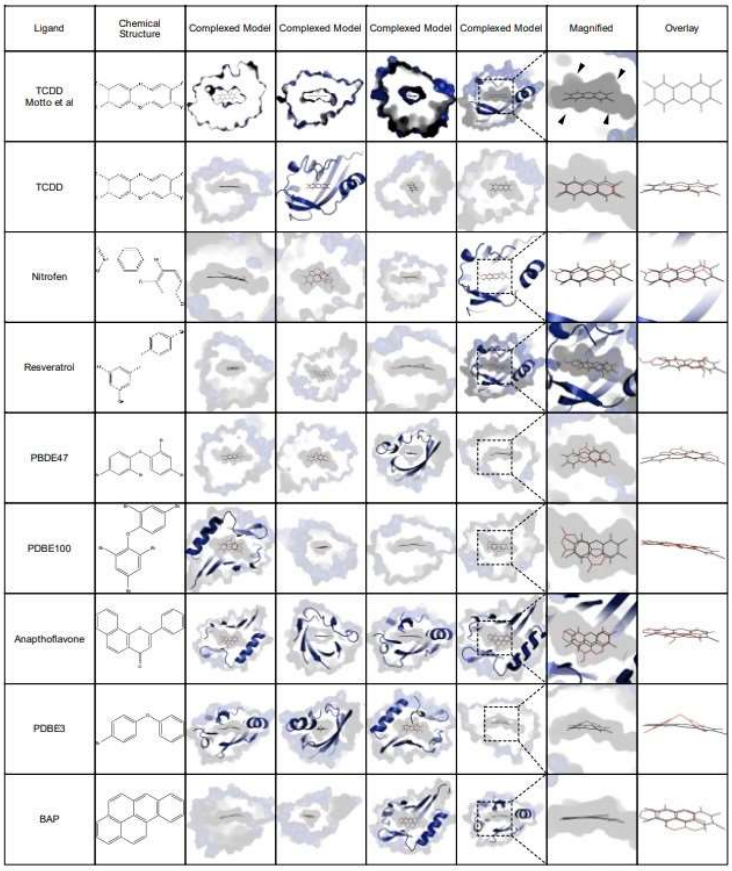
Using an established computational model of AHR, we compared the binding affinities of nitrofen and othe PBDEs and TCDD. Molecular docking was performed using the Autodock Vina package of PyRx. The best model was chosen based upon the lowest Gibbs free energy and docking error rate from 10000 replicate docking models per ligand. The dissociation constant for each model was then calculated.

Results:

Ligand docking revealed the lowest Gibb's free energy for nitrofen and PBDE-47: -8.4 and -8.3 kCal/mol respectively, was comparable to our positive control TCDD (-8.6 kCal/mol). This is supported by the nanomolar range dissociation constants (KD < 780 nM). Additionally, our docking confirmed the ligands were contained in a published docking site for AHR.

Conclusions:

Our molecular docking demonstrates nitrofen is a putative ligand of AHR. Its binding properties determined computationally are similar to known ligands of AHR. Our results suggest that nitrofen-induced AHR activation as a potential mechanism in the nitrofen rat model of CDH. This study introduces a new evidence for a chemically-induced mechanism of action for CDH; one that is conserved in humans.



Using Bosentan to Treat Pulmonary Hypertension in miR-200b Knockout Mice as a Model of Congenital Diaphragmatic Hernia

Abstract 45

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Purpose:

We determined that congenital diaphragmatic hernia (CDH) patients with poor outcomes have decreased levels of a microRNA known as miR-200b, and created a miR-200b null mice. miR-200b null mice have pulmonary hypertension, abnormal lung development, and up regulation of endothelin receptor-A in their lungs similar to that of CDH patients. Our aim is to determine the effectiveness of the drug bosentan, an endothelin receptor antagonist, in miR-200b null mice.

Methods:

Following ethical approval, miR-200b null and wildtype mice were treadmill trained underwent baseline graded maximal exercise tests and echocardiographs at 8 weeks of age. Bosentan was administered via gavage at 100mg/kg of body weight/day for three weeks. Weekly graded maximal exercise tests and end of study echocardiographs were performed to evaluate pulmonary hypertension. After three-week treatment lungs were formalin fixed and paraffin embedded. Embedded lungs were then serial sectioned and Verhoeff-van Gieson stained to evaluate vasculature.

Results:

Preliminary results show that miR-200b null mice have improved VO2 max after bosentan treatment ($p=0.053$, $n=2$) and increased run time to exhaustion. At this time no difference in artery thickness measurements is seen between WT and miR-200b null mice after three week bosentan treatment. We are currently analyzing echocardiographs to determine changes in pulmonary acceleration time.

Conclusions:

These results suggest that Bosentan increases VO2 max and prevents worsening of pulmonary hypertension. In conclusion, determination of the effectiveness of bosentan in the treatment of pulmonary hypertension could lead to better treatment options for patients suffering from pulmonary hypertension in CDH.

The risk factors of pneumothorax associated with isolated congenital diaphragmatic hernia: results of a Japanese multicenter study

Abstract 46

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Purpose:

This study aimed to elucidate the clinical characteristics of neonates with congenital diaphragmatic hernia (CDH) associated with pneumothorax and evaluate the risk factors for the development of pneumothorax.

Methods:

A retrospective cohort study was conducted in the fifteen institutions participating in the Japanese CDH Study Group. A total of 499 neonates with isolated CDH who were born between 2011 and 2018 were analyzed in this study. We compared the clinical characteristics between the CDH patients with and without pneumothorax. Multiple logistic regression analyses were subsequently conducted for the factors that were significant with a p value of less than 0.05 in the univariate analysis and weak correlations with other factors ($r < 0.7$).

Results:

Among the 499 neonates with isolated CDH, 52 (10.4%) developed pneumothorax. Eighteen (35.3%) patients developed pneumothorax before surgery, and 33 (64.7%) patients developed pneumothorax after surgery. The log-rank test showed that the cumulative mortality rate was significantly higher in the patients with pneumothorax than in the patients without pneumothorax. Univariate analysis revealed significant differences between the patients with and without pneumothorax with respect to the best oxygenation index within 24 hours after birth, mean airway pressure (MAP), and diaphragmatic defect size. Multiple logistic regression analysis indicated that higher MAP was associated with increased risks of pneumothorax.

Conclusions:

The mortality rate was significantly higher for isolated CDH patients with pneumothorax than for those without pneumothorax. Higher MAP was a risk factor for developing pneumothorax in CDH patients.

Univariate and Multiple analyses of the risk factors for pneumothorax in the cases with isolated CDH

	Univariate analysis		Multivariate analysis	
Variable	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Best oxygenation index within 24 hours after birth (per 1.0)	1.02 (1.00-1.03)	0.0023*	1.00 (0.97-1.02)	0.8929
Mean airway pressure (per 1.0 cmH_2O)	1.23 (1.10-1.37)	0.0002*	1.19 (1.04-1.38)	0.0091*
Defect size; large (C or D) (ref: small (A or B))	1.95 (1.05-3.61)	0.0330*	1.58(0.80-3.14)	0.1849

CDH, congenital diaphragmatic hernia; OR, odds ratio. * $P < 0.05$.

Nutritional outcome at the age of 16 years of infants included in the Northern France CDH Cohort

Abstract 47

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Purpose:

Congenital diaphragmatic hernia (CDH) is frequently associated with nutritional and growth disorders represented by failure to thrive (FTT), oral aversion (OA), gastro-oesophageal reflux (GER).The aim of this cohort study was to investigate the long-term nutritional and gastrointestinal outcome of survival children with CDH included in the Northern France CDH cohort.

Method:

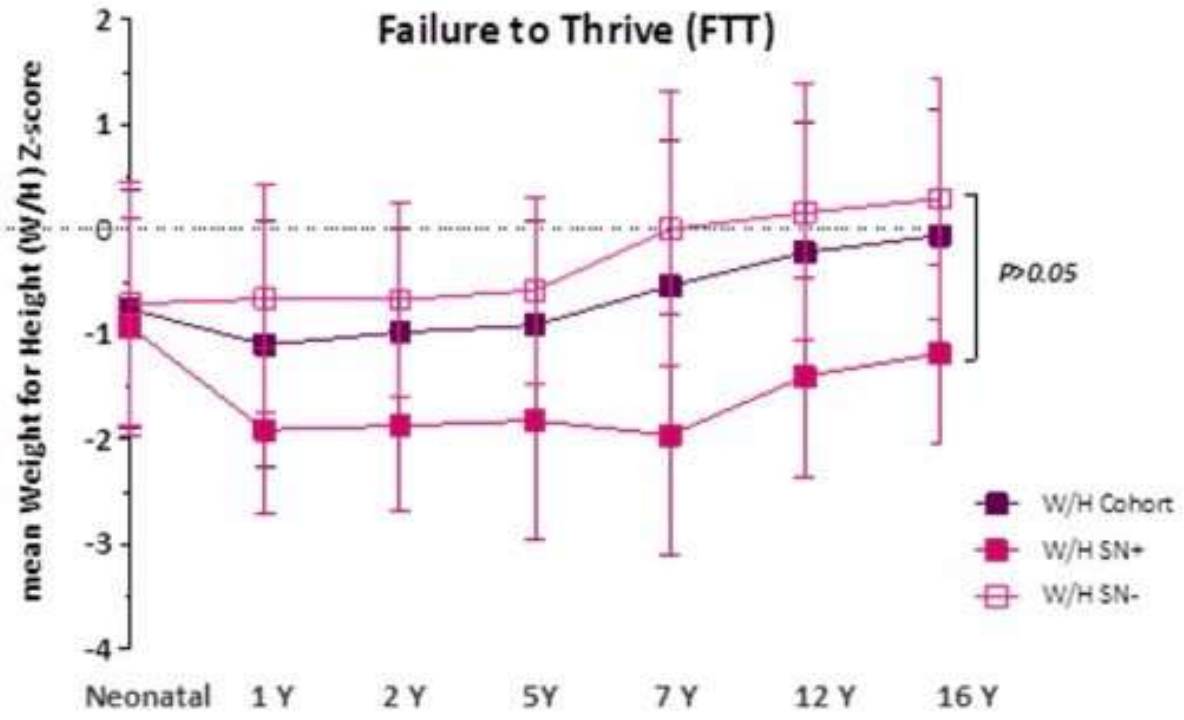
Age at oral feeding autonomy, evolution of weight (W), height (H) and W/H Z-scores, prevalence of OA and GER were prospectively collected in the 58 patients. The population were divided according the need or not of nutritional support (NS) at 1 month-old to compare the nutritional course of NS+ to NS- groups.

Results:

47 of the 1 month-old infants were free from oral support (NS- group). 11 infants required NS+ beyond 1 month. Z scores <-2 rates (FTT) were significantly higher in SN+ Vs. SN- groups (p<.05). In both NS- and NS+ groups, Z-score improved with time till age of 16 years. Incidence of OA and GER was statistically greater in NS+ group at neonatal period, but both disorders improved significantly with time related to early diagnosis and management. At 16 years-old, 5 infants have still symptomatic GER. Diaphragmatic patch, ECMO and herniated liver were the only independent risk factor for prolonged requirement of NS and FTT.

Conclusion:

Despite the high incidence of nutritional disorders during the early life, both growth and gastro-intestinal disorders improve with time. These results may help the healthcare professionals to provide information which may support the parents of infants with congenital diaphragmatic hernia and failure to thrive.



Does Left Ventricular Dysfunction Contribute to elevated pulmonary vascular resistance in CDH?

Abstract 48

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Background:

Elevated pulmonary vascular resistance (PVR) is a key finding in Congenital Diaphragmatic Hernia (CDH), considered to be due to abnormal pulmonary vascular structure. However, left ventricular (LV) dysfunction, leading to elevated pulmonary venous pressure, may also contribute to elevated PVR. This may have important therapeutic implications, including contra-indication to pulmonary vasodilators.

Aim:

This study investigated whether early LV dysfunction is associated with elevated PVR in CDH.

Methods:

Echocardiographic assessment was performed in CDH cases in the first 2 days of life in 2 tertiary NICUs in Glasgow & Rome between 2016-18. PVR was assessed using corrected pulmonary artery acceleration time (PAATi). RV and LV function were assessed using tricuspid annular plane excursion (TAPSE), Tissue Doppler velocities in systole (S') and diastole (E') and longitudinal strain (LS), by speckle tracking echocardiography.

Results:

Data was collected in 34 cases. Cardiac function and PVR measures are listed in Table 1.

Using cut-off values from normative data, 24 cases (70%) had RV systolic dysfunction, 14 (41%) had LV systolic dysfunction. LV GS and RV GS were correlated (r2 0.22, P 0.007). PAATi did not correlate with any measures of LV function in the first 48 hours of life, Table 1.

Conclusions:

o Early LV and RV dysfunction are common in CDH
o Correlation of RV and LV function indicates ventricular interdependence.
o There was no evidence of a relationship between LV function and PVR.
o The role of LV dysfunction as a contributor to increased PVR remains unclear.

Table 1: Cardiac function and PVR in CDH cases, and correlation of function with PVR

Cardiac function and PVR parameters (n=34)		Correlation with PVR (PAATi).
Parameter	**Mean (SD)**	**r^2, P value**
PAATi	0.29 (0.1)	-
TAPSE (mm)	5.7 (1.1)	0.064, 0.148
RVO (mls/kg/min)	331(160.)	0.063, 0.174
RV GS (%)	-12.05 (4.5)	0.014, 0.522
RVs' (cm/s)	4.3 (1.8)	0.001, 0.858
LV GS (%)	-15.7 (5.4)	0.058, 0.169
LV s' (cm/s)	3.69 (1.3)	0.014, 0.507

Abbreviations: PAATi, corrected pulmonary artery acceleration time; TAPSE, tricuspid annular plane excursion; RVO, right ventricular output; GS, global longitudinal strain; s', systolic myocardial velocity.

Foetoscopic endotracheal occlusion (FETO) for severe congenital diaphragmatic hernia vs expectant management

Abstract 49

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OBJECTIVE:

The aim of this study was to compare the survival rates of foetuses with severe left sided congenital diaphragmatic hernia (CDH) managed with FETO versus expectant management.

METHODS:

This was a multicenter retrospective study, comparing the survival rates of foetuses with severe isolated left sided CDH with intrathoracic position of the liver expectantly managed in Mannheim, Germany (n=81) to foetuses managed with FETO in Paris, France or Brussels, Belgium (n=35). The o/e TFLV were centralised and measured by a single team of two operators, which was blinded of the pre- and postnatal data.

RESULTS:

The postnatal overall survival rate of the expectant managed foetuses was with 57% higher compared to the survival rate of the foetuses managed with FETO (40%), while 56% of the neonates in Mannheim were treated with ECMO in contrast to the neonates in Paris or Brussels, where nobody had an ECMO. Splitting the population up in 3 MRI stratified severity groups (1. o/e TFLV <15%, 2. o/e TFLV 15-25%, 3. o/e TFLV 26-35%), the difference of the survival rate was even more clear in favour of the expectant managed group (1.: 48,3% vs 0%, 2.: 56,3% vs 40%, 3.: 70% vs 45,5%).

CONCLUSION:

Survival rates in expectantly managed severe left-sided congenital diaphragmatic hernia born in Mannheim are higher compared to CDH fetuses with the same severity that underwent FETO in Paris or Brussels. Whether this higher survival rate in Mannheim is achieved on the expense of higher morbidity due to ECMO needs further investigation.

Hepatopulmonary Fusion: A Rare Variant of Congenital Diaphragmatic Hernia

Abstract 50

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Background:
Hepatopulmonary fusion (HPF), a rare anomaly associated with right congenital diaphragmatic hernia (CDH), is characterized by a fibrovascular fusion between herniated liver and lung parenchyma. We aimed to clarify patient characteristics, management strategies, and outcomes in HPF.

Methods:
Data on infants with HPF were obtained from the Congenital Diaphragmatic Hernia Registry (CDHR). Patient characteristics, management, and outcomes were compared with the results of a literature review.

Results:
Ten cases of HPF were identified in the CDHR. Five patients survived. The median estimated gestational age was 38 weeks (range 36-40). Median birth weight was 2.7 kg (range 2.0-3.8 kg), but non-survivors had a lower median birth weight (2.3 kg vs. 3.5 kg). All patients had at least 1 congenital anomaly in addition to CDH. Operative approach varied, but most surgeons performed only partial separation of the liver and lung (n=6). The 2 patients who underwent complete separation both ultimately died, 1 due to significant postoperative complications and 1 due to severe pulmonary hypertension with multiple vascular anomalies.

Conclusion:
Partial separation of liver and lung appears to be the wisest surgical approach in HPF, as complete separation has resulted in catastrophic complications due to frequent underlying vascular anomalies.

Levosimendan is associated with improvement of cardiac dysfunction and pulmonary hypertension in infants with congenital diaphragmatic hernia

Abstract 51

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Purpose:

Infants with congenital diaphragmatic hernia (CDH) frequently suffer from cardiac dysfunction (CD) and pulmonary arterial hypertension (PAH) during the postnatal course. With the use of the inodilator levosimendan a promising approach is available in situations with catecholamine-refractory low-cardiac-output failure and severe PAH.

Methods:

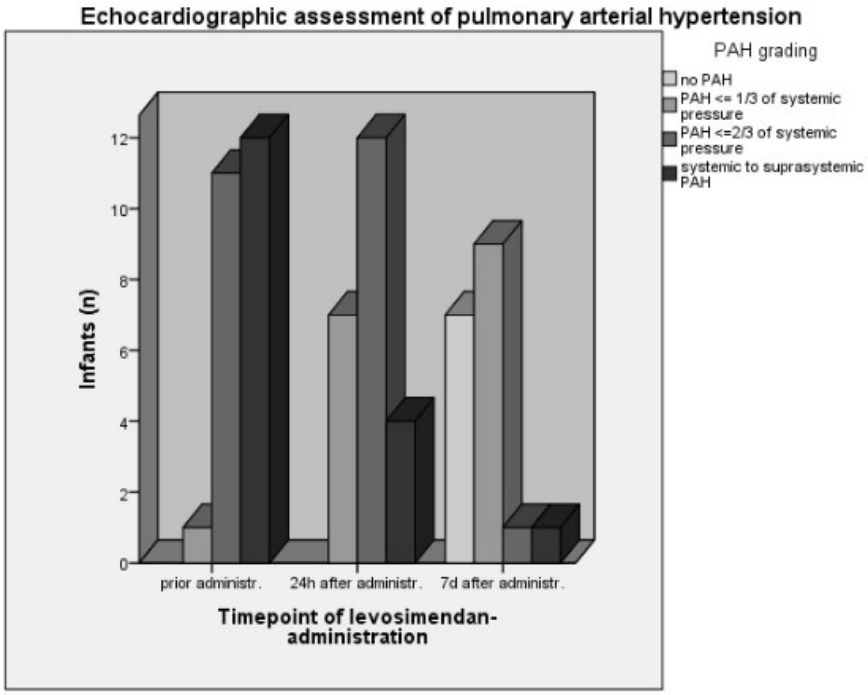
Data off all infants with CDH born between January 2017 and December 2018 were analysed. Inclusion criteria: infants with CDH + levosimendan-therapy. All infants with a mayor cardiac defect were excluded. Laboratory parameters, the vasoactive-inotropic score and oxygenation index, as well as echocardiographic studies were integrated in the analysis.

Results:

26 infants with CDH were treated with levosimendan. In 88% the CDH was left-sided. The o/e lung-to-head ratio was 36% (median). 60% of the infants were supported with ECMO and overall mortality was 38% (9/26). Levosimendan-administration was started in median at day 2 and 38% received a bolus infusion (12.5µg/kg over 10 minutes). The oxygenation index and the vasoactive-inotropic score improved significant after administration (p=0.035 resp. p=0.022). Echocardiographic PAH severity and right ventricular CD improved significant 24h and 7d after levosimendan-administration (p=0.014/ p=0.000 resp. p=0.011/ p=0.000). Similar, the left ventricular CD decreased from 39% (baseline) to 11% after 7d (p=0.044).

Conclusion:

This is the first study analyzing the pharmacological effect of levosimendan in a cohort of infants with CDH. Levosimendan is associated with an improvement in PAH and CD in these infants. Our study adds information on a new promising vasoactive drug in situations of limited conventional therapy strategies.



Increased soluble ST2 concentration in neonates with congenital diaphragmatic hernia and pulmonary hypertension hernia with and without ECMO support.

Abstract 52

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Background and aim:

Pulmonary hypertension (PH) is the most important determiner of mortality in neonates with congenital diaphragmatic hernia (CDH). PH can be assessed by echocardiography but knowledge on potential biomarkers is scarce. Soluble ST2 (sST2) is released by cardiomyocytes experiencing increased workload and has been extensively investigated in the adult population. Aim of our study was to investigate the expression of sST2 in CDH newborns receiving ECMO support compared to patients without ECMO.

Methods:

30 CDH newborns were prospectively enrolled. sST2 concentration was measured from EDTA-Plasma at the age of 0, 6, 12, 24, 48 hours and 7-10 days of life and was compared in CDH newborns with and without ECMO support.

Results:

11/30 patients were allocated to the ECMO group and 19/30 to the non-ECMO group. Patients in the ECMO group were affected more severely (lung-to-head ratio and liver-up). At birth sST2 were similar between groups (p=0.668). At 6, 12, 24, 48 hours and at 7-10 days sST2 concentration was significantly higher in the ECMO group (Table 1). At 6 hours the optimal cutoff to predict ECMO was 48.0 ng/ml (AUC 0.742; p = 0.035) with a sensitivity of 80%, and a specificity of 78.9% (Positive predictive value: 66.7%, Negative predictive value: 88.2%). sST2 correlated significantly with PH severity at 6h (r=0.597, p=0.001), 12h (r=0.616, p<0.001) and 24h (r=0.720, p<0.001).

Conclusion:

sST2 expression differed significantly in CDH newborns according to disease severity and might be a potential parameter to assess risk for ECMO in this population.

	CDH/ECMO n = 11	CDH/Non-ECMO n = 19	p-value
Umbilical cord blood	8.9 (5.3 - 13.3)	9.1 (6.5 - 14.4)	0.956
6 h post partum	55.8 (46.2 - 68.2)	33.0 (25.2 - 46.4)	**0.035**
12 h pp	170.3 (88.2 - 478.6)	51.1 (35.6 - 133.1)	**0.025**
24 h pp	423.7 (281.7 - 602.1)	51.1 (24.8 - 100.5)	**<0.001**
48 h pp	198.5 (91.1 - 400.0)	35.1 (20.3 - 62.4)	**<0.001**
7-10 d pp	117.1 (80.7 - 249.5)	25.4 (18.4 - 31.6)	**0.001**

The Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative Smartphone App: A Guideline Uptake and Care Standardization Strategy

Abstract 53

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Purpose:

Coinciding with the publication of the Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative's clinical practice guidelines, we developed a mobile app to increase guideline utilization and promote knowledge translation.

Methods:

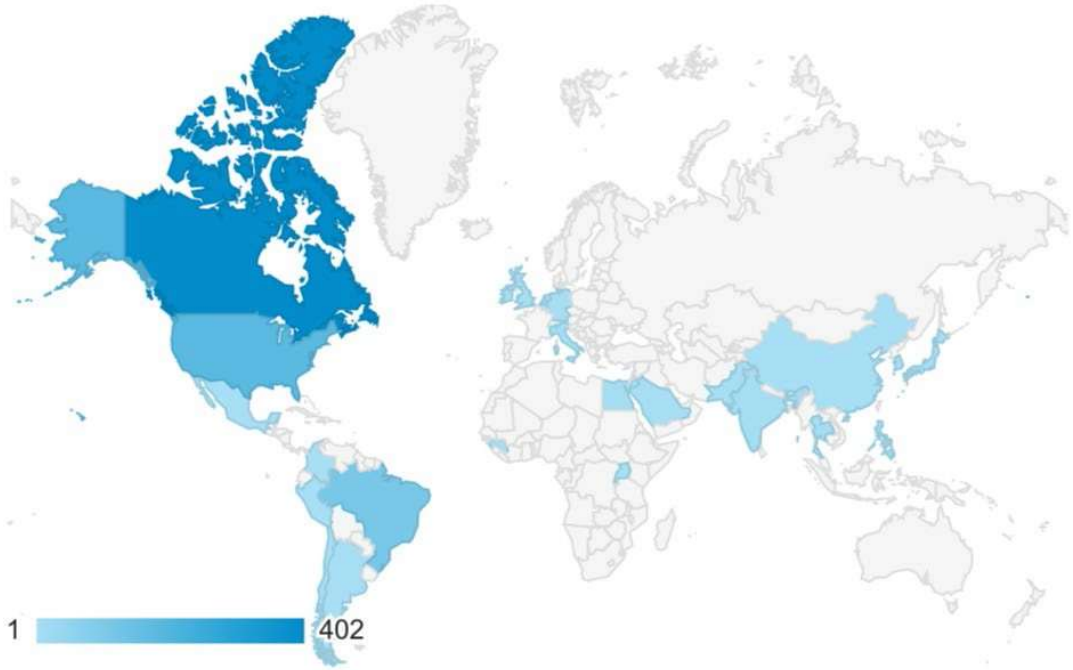
This mobile app was created as part of a guideline implementation strategy (REB2019-4753). Organized into sections corresponding to CDH care phases (prenatal, perinatal/postnatal, long-term surveillance), it contains 22 recommendations supported by evidence summaries, PubMed links, levels of evidence and expert consensus. Download statistics were collected from 2018-09-18 to 2019-08-29. Data regarding user numbers/location, most visited sections, and individual session details were analyzed.

Results:

After two iOS and a recent Android platform release, the app has 737 users predominantly from Canada (54%), USA (24%), and Brazil (15%)(Figure 1). The android release increased app visibility, particularly in Brazil, which had the largest number of new users. Of 1235 sessions, the average session duration and screens viewed/session were 5:44 min and 10.2, respectively. Postnatal ventilation was the most frequently visited subsection after prenatal diagnosis/risk stratification. Measurement of observed-to-expected lung head ratio was the most visited individual recommendation. The guideline compliance checklist was the most frequently accessed resource. Forty percent of users revisited the app within 30 days of initial access.

Conclusion:

This mobile app directly connects users to CDH practice guidelines. The high percentage of Brazilian users suggests worldwide guideline need and relevance. App translation into additional languages, open-access journal publication and professional society and parental support/research network endorsement should facilitate continued app utilization and uptake, leading to high-quality CDH care delivery to infants globally.



Presence of a hernia sac does not impact lung perfusion in CDH

Abstract 54

Akila Ramaraj, United States - Seattle Children's Hospital; Guy Jensen, United States - United States Navy; Rebecca Stark, United States - Seattle Children's Hospital

PURPOSE:

There are variable long-term pulmonary outcomes of children with congenital diaphragmatic hernia (CDH). Diagnostic modalities evaluating pulmonary function can be limited by patient compliance. Pulmonary perfusion scintigraphy is a diagnostic tool to evaluate lung development in younger children. Presence of a hernia sac is known to correlate with less severe disease but little has been reported on any correlation with lung size and function. The purpose of this study was to evaluate the relationship between presence of a hernia sac, pulmonary perfusion and CDH defect size.

METHODS:

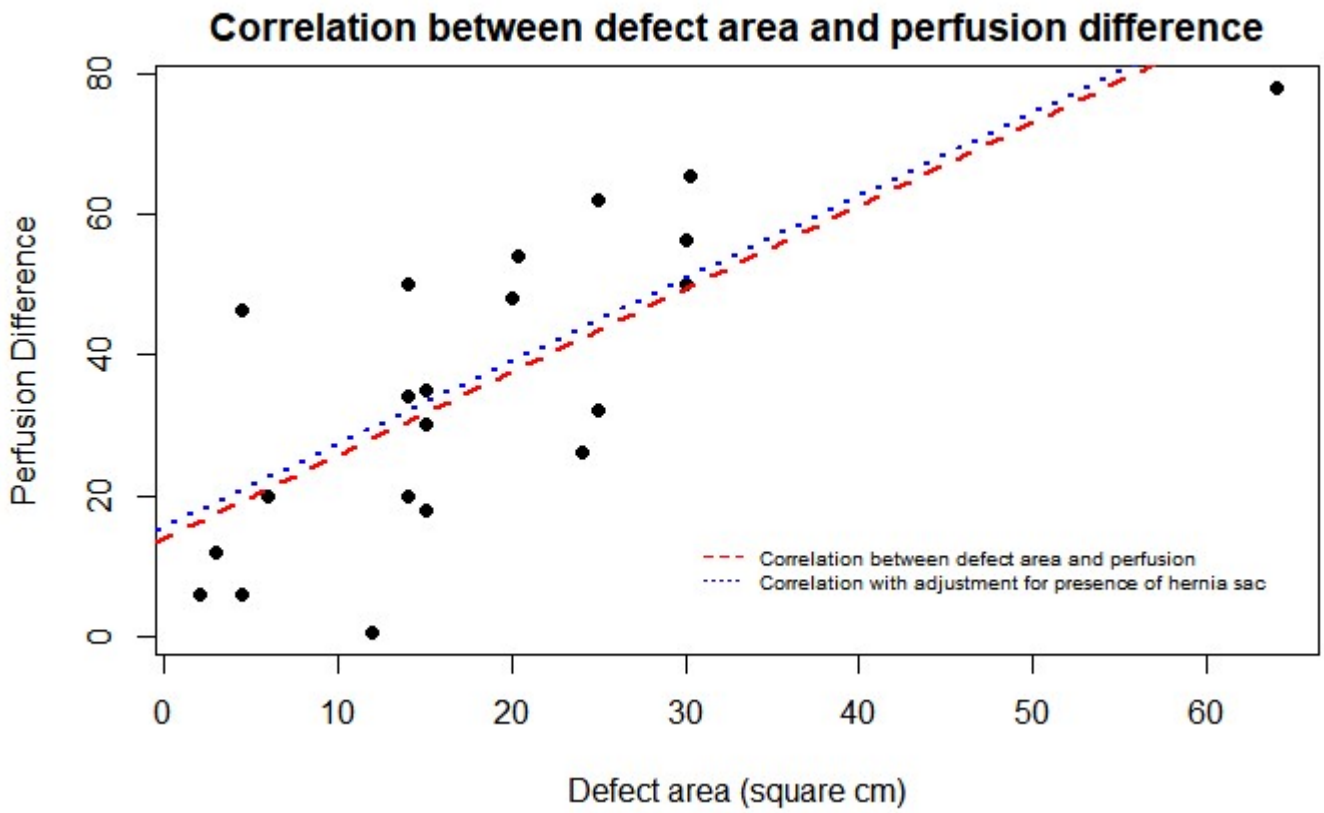
Records of all children treated for CDH at our institution from January 2009 to December 2018 were reviewed. A subset of these children underwent lung perfusion scintigraphy. We hypothesized that the presence of a hernia sac would affect future perfusion studies. We assessed this with two linear regression models.

RESULTS:

One hundred thirty-three children were treated for CDH over 10 years. Twenty-nine children (22%) underwent pulmonary scintigraphy, 9 of whom (31%) had a hernia sac. There was no correlation between hernia sac presence and improved perfusion ($R2 = 0.005$, $p = 0.7$). There was a correlation between area of the defect (cm2), and perfusion difference between the two lungs ($R2 = 0.56$, $p < 0.05$). When adjusting for presence of the hernia sac, the fit of the model was unchanged. ($R2 = 0.57$, $p < 0.05$).

CONCLUSIONS:

As expected, there is a correlation between CDH defect size and lung perfusion. However, presence of a hernia sac did not impact lung function as determined by perfusion scintigraphy.



Perioperative cerebral autoregulation in congenital diaphragmatic hernia neonates.

Abstract 56

Sophie Costerus, Netherlands - Erasmus Medical Centre Rotterdam; Dries Hendrikx, Belgium - Katholieke Universiteit Leuven; Gunnar Naulaers, Belgium - University Hospital Leuven; Sabine van Huffel, Belgium - Katholieke Universiteit Leuven; John Vlot, Netherlands - Erasmus Medical Centre Rotterdam; Rene Wijnen, Netherlands - Erasmus Medical Centre Rotterdam; Dick Tibboel, Netherlands - Erasmus Medical Centre Rotterdam; Jurgen de Graaff, Netherlands - Erasmus Medical Centre Rotterdam

Introduction:

The capability of the brain to maintain consistent perfusion during changes in blood pressure is known as cerebral autoregulation (CAR). Perioperative management might influence the cerebral autoregulation negatively. We hypothesize that perioperative cerebral blood flow fluctuations determine impaired long-term neurodevelopment in CDH infants. The aim of this study is to create a mathematical approach for cerebral autoregulation to measure perioperative cerebral blood flow.

Method:

All CDH neonates had continuous invasive arterial blood pressure measurements and NIRS for cerebral oxygenation (StO2) measurements. Cerebral autoregulation was defined by analyzing the interaction between mean arterial blood pressure (MABP) and StO2. Adequate CAR corresponds with independent changes in MABP and StO2, resulting in low signal coupling. If the values are positive (0 to 1), MABP changes are causing changes in StO2 and if the values are negative (-1 to 0) StO2 changes are causing changes in MABP.

Results:

19 CDH neonates; 9 with liver-down, 5 with liver-up without ECMO and 5 with liver-up with ECMO (also ECMO during surgery) were analyzed. Median gestational age 38.1 weeks (IQR 37.2-38.5), age at surgery 4 days (IQR 2.5-5.5). The model shows that CAR is disturbed most pre- and intraoperative in CDH patients with liver-up and improves after the surgical procedure. CDH patients without a herniated liver had the best-preserved cerebral autoregulation during the whole study period (figure 1).

Conclusion:

Our pilot data of the model suggests changes in cerebral blood flow occur over time with the biggest changes in the liver-up group.

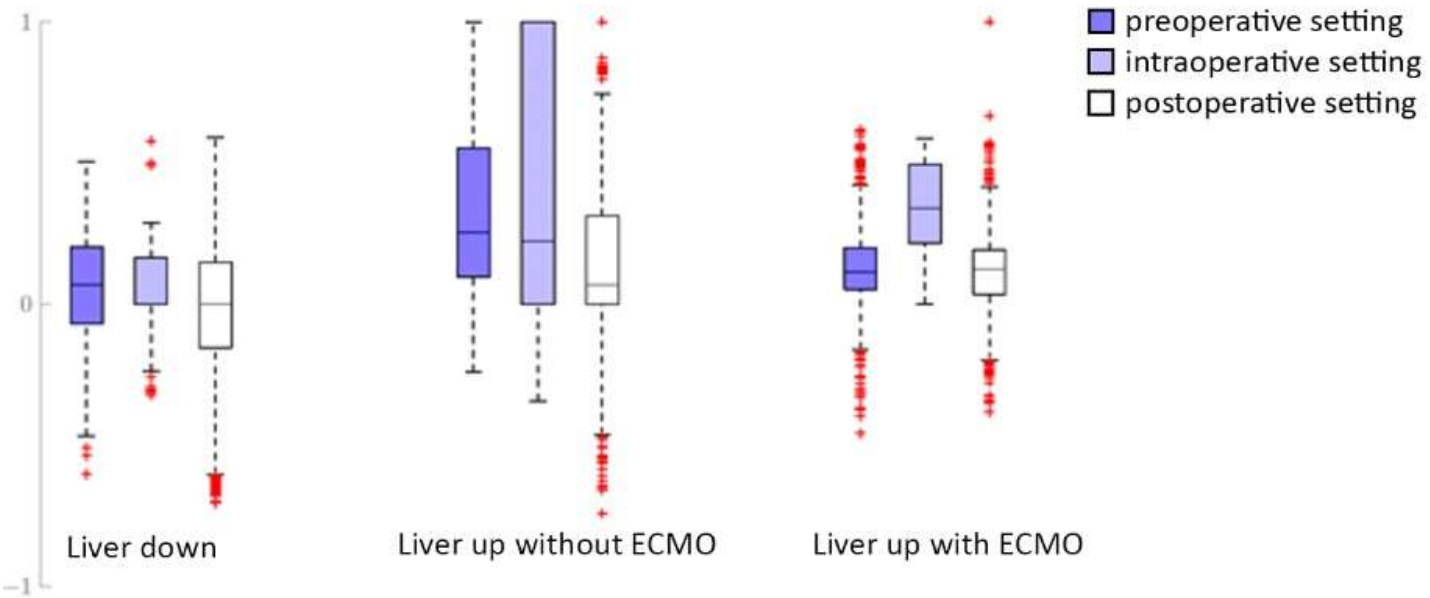


Figure 1. Perioperative cerebral autoregulation.

Neurocardiovascular coupling during surgical repair of congenital diaphragmatic hernia.

Abstract 57

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Introduction:

Dynamic coordinated interactions of organ systems are essential to maintain homeostasis (neurocardiovascular coupling). An important parameter is neural activity because it is one of the primary controllers of cerebral blood flow. With the use of graph models is it possible to learn more about physiology and also to detect altered or disrupted organ communications. The aim of this study is to create insight in the perioperative pathophysiology of CDH neonates.

Method:

Neonates operated for CDH were additionally monitored with NIRS for cerebral oxygenation (StO2) and 4-signal aEEG for cerebral activity. The graph model combines this with heart rate, mean arterial blood pressure and oxygen saturation to analyze the interactions between the parameters so that neurocardiovascular coupling could be determined. Values ranging from 0-1, in which 0 is no interaction and 1 is full interaction.

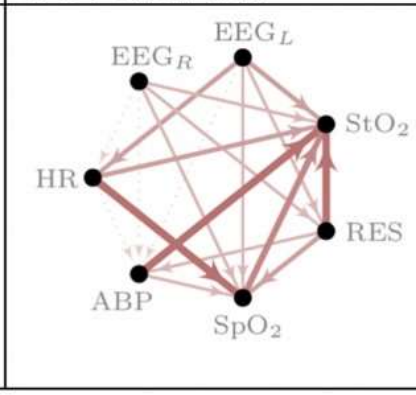
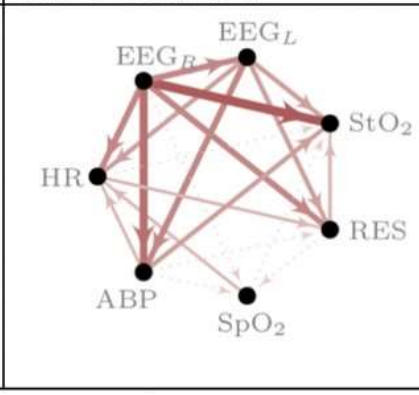
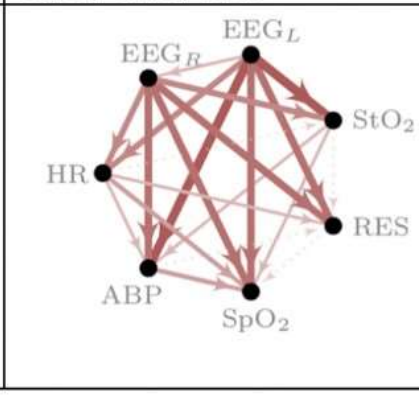
Results:

19 CDH neonates; 9 with liver-down, 5 with liver-up without ECMO and 5 with liver-up with ECMO were analyzed. Median gestational age 38.1 weeks (IQR 37.1-38.5) and age at surgery 4 days (IQR 2.5-5.5). The model shows that changes in neural activity affect all parameters (table 1). The highest signal interactions were found in the liver down group, which also remained during the whole study period. The liver up group with or without ECMO had the biggest decrease in signal interaction during the intraoperative period.

Conclusion:

This is the first step in creating a model for neurocardiovascular coupling. The model suggests that cerebral activity is important to maintain coordinated interactions between the organ systems.

Table 1. Perioperative neurocardiovascular coupling in the 3 different groups

	Preoperative	Intraoperative	Postoperative
	Liver down / up / ECMO	Liver down / up / ECMO	Liver down / up / ECMO
HR	0.49 / 0.55 / 0.41	0.33 / 0.01 / 0.00	0.47 / 0.42 / 0.46
MABP	0.42 / 0.42 / 0.39	0.30 / 0.30 / 0.26	0.43 / 0.34 / 0.36
SpO2	0.32 / 0.31 / 0.31	0.29 / 0.11 / 0.56	0.32 / 0.31 / 0.26
StO2	0.47 / 0.43 / 0.42	0.49 / 0.39 / 0.47	0.43 / 0.40 / 0.45
Graph model			

Prediction of survival in right sided congenital diaphragmatic hernia in the FETO era

Abstract 58

Francesca Russo, Belgium - Katholieke Universiteit Leuven; Anne-Gaelle Cordier, France - Hôpital Béclère; Laura Salazar, Spain - Barcelona Center for Materno-Fetal Medicine; Ewelina Litwinska, United Kingdom - King's College London; David Basurto, Belgium - Katholieke Universiteit Leuven; Olga Gomez, Spain - Barcelona Center for Materno-Fetal Medicine; Eduard Gratacos, Spain - Barcelona Center for Materno-Fetal Medicine; Kypros Nicolaides, United Kingdom - King's College London; Alexandra Benachi, France - Hôpital Béclère; Jan Deprest, Belgium - Katholieke Universiteit Leuven

Purpose:

To provide an update on the outcomes of prenatally diagnosed right-sided CDH (RCDH).

Methods:

Multicenter analysis of prospectively collected data from patients with isolated RCDH managed according to a standardized protocol. Perinatal variables were lung size assessed with ultrasound (observed-to-expected lung-to-head ratio, o/eLHR) and MRI (observed-to-expected total-lung-volume o/eTLV), fetal endoscopic tracheal occlusion (FETO), occurrence of polyhydramnios, pleural or pericardial effusion, preterm rupture of membranes and gestational age at delivery. Outcomes were survival until discharge and morbidity parameters.

Results:

Two-hundred-one infants with RCDH were included. Eighty-six cases were managed expectantly. In this group, the overall survival rate was 40%. Lung size (o/eLHR and o/eTLV) was the only predictor of survival. None of the expectantly managed fetuses with an o/eLHR below 30% survived at discharge. The pooled survival rate in the severe group (o/eLHR <45%) was 15%. This was significantly lower than in the cases with o/eLHR above 45% (52%, p=0.001). One-hundred-twenty cases with o/eLHR<45% underwent FETO. Survival at discharge in this group was significantly higher as compared to the severe cases managed expectantly (41%, p=0.003). FETO was also performed in 8 cases with o/eLHR>45%, with a survival rate of 50%. Gestational age at birth was the only predictor of survival in cases treated in utero (OR 1.24 (1.04-1.49), p=0.01). Morbidity outcomes are displayed in the Table.

Conclusion:

Antenatal measurement of lung size predicts survival in RCDH, and an o/eLHR below 45% corresponds to an estimated survival rate under 20%. In this group, FETO is associated with a significant increase in survival.

Table: Neonatal morbidity

Expectantly managed fetuses				
	Severe N=27	**Mild N=58**	**OR (95% CI)**	**P value**
Patch at surgery	71%	45%	3.00 (0.47-18.93)	0.39
Treatment for pulmonary hypertension	77%	78%	0.95 (0.17-5.23)	1
NICU days in survivors	71 (47-120)	22 (14-51)	--	**0.02**
Oxygen at discharge in survivors	11%	0%	--	0.36
Fetuses with severe pulmonary hypoplasia				
	FETO N=120	**Expectant N=27**	**OR (95% CI)**	**P value**
Patch at surgery	90%	71%	7.00 (0.80-61.46)	0.11
Treatment for pulmonary hypertension	88%	77%	2.10 (0.29-14.98)	0.63
NICU days in survivors	42 (31-69)	71 (47-120)	--	0.14
Oxygen at discharge in survivors	60%	11%	12 (1.05-136.79)	**0.05**

The Morbidity of CDH Uncovered by Multidisciplinary Clinic Follow-up

Abstract 59

Kiloran Metcalfe, United Kingdom - Royal Hospital for Children, Glasgow; Morag Liddell, United Kingdom - Royal Hospital for Children, Glasgow; Gregor Walker, United Kingdom - Royal Hospital for Children, Glasgow; Jonathan Coutts, United Kingdom - Royal Hospital for Children, Glasgow; Kerry Kasem, United Kingdom - Princess Royal Maternity Hospital, Glasgow; Judith Simpson, United Kingdom - Royal Hospital for Children, Glasgow; Neil Patel, United Kingdom - Royal Hospital for Children, Glasgow; Carl Davis, United Kingdom - Royal Hospital for Children, Glasgow

Purpose

Patients with CDH are managed in our institution using a protocol including lung-protection, targeted pulmonary antihypertensive therapy and ECLS. Since 2002, surviving patients are offered follow-up at a multidisciplinary clinic, attended by paediatric surgery, neonatology, respiratory, dietetics, developmental physiotherapy and speech and language therapy. We collected data to establish long term outcomes and facilitate parental counselling.

Methods

Retrospective review of casenotes and electronic patient records for CDH patients followed in the clinic from 1998-2019, including formal developmental assessments. Older patients have undergone pulmonary function tests (PFTs) and cardiopulmonary exercise testing (CPET).

Results

241 children were admitted within the time period (60% inborn, 35% outborn national, 5% international referrals). 58 patients (24%) died prior to discharge. 166 were followed up locally for mean 6 years (range 1- 17 years). 7 patients (4%) died after hospital discharge. Table 1 summarises long term complications and ongoing issues, by repair type and ECLS support. Few patients undergoing primary repair have significant respiratory or pulmonary hypertensive sequelae. Nutritional, musculoskeletal and developmental consequences occur more commonly. Patients with patch repairs and those treated with ECLS have increased morbidity, particularly in the first 2 years.

41 patients have undergone PFTs, with an obstructive pattern found in 16. CPET has been performed in 13 patients with 5 having ventilatory limitation.

Conclusion

These data provide information on long term outcomes which we hope will give parents a realistic understanding of late complications and morbidity throughout childhood. Structured multidisciplinary follow-up is recommended for patients surviving CDH.

Table 1: Complications/morbidity summarised by repair type and need for ECLS

	Primary Repair (n=102)	Patch Repair (N=63)	ECLS (n=22)
Oxygen at discharge	7 (7%)	18 (29%)	11 (50%)
Bronchodilators prescribed	26 (26%)	13 (21%)	3 (14%)
Laparotomy (excluding recurrence)	12 (12%)	11 (17%)	6 (27%)
CDH Recurrence	9 (9%) Mean age 0.6 yr	21 (33%) Mean age 1.7yr	9 (41%) Mean age 1.6yr
GORD requiring medication	41 (40%)	50 (79%)	19 (90%)
Fundoplication performed	10 (10%) Mean age 3.4yr	15 (24%) Mean age 0.8yr	9 (41%) Mean age 1.2
Supplementary feeds after discharge	26 (26%)	37 (59%)	18 (82%)
Pectus/Scoliosis	28 (28%)	30 (48%)	12 (55%)
Developmental delay	16 (16%)	17 (27%)	8 (36%)

Benchmarking against the CDH Study Group (CDHSG) Database – the first 10 years

Abstract 60

Mark Davis, United Kingdom - Royal Hospital for Children, Glasgow; Gregor Walker, United Kingdom - Royal Hospital for Children, Glasgow; Neil Patel, United Kingdom - Royal Hospital for Children, Glasgow, UK; Jonathan Coutts, United Kingdom - Royal Hospital for Children, Glasgow, Morag Liddell, United Kingdom - Royal Hospital for Children, Glasgow; Carl Davis, United Kingdom - Royal Hospital for Children, Glasgow, UK

Purpose

Comparing results between centres managing CDH is notoriously difficult, as highlighted by the seminal 1997 "Tale of two Cities" papers comparing Toronto and Boston outcomes. The CDHSG database has collected defect size data since 2007. The introduction of a staging system for CDH in 2013 to facilitate standardised reporting offers the opportunity to benchmark a local centre against the database.

Methods

The local Neonatal Surgical ICU has "high volume" status (i.e. ≥10 cases/year). A data request was made to CDHSG for the period 2007-2016. Factors known to influence outcome, the use of ECMO and overall survival were studied. The CDHSG Staging System was used to compare results in a standardised fashion. Categorical variables were analysed using Fisher's Exact Test.

Results

Local cases (n=103) were compared with the CDHSG database (n=4625). Demographics were very similar in both groups (median weight 3.0 vs 2.99 kg; median gestational age 38 weeks for both). Table 1 shows the main comparisons. Prenatal diagnosis rates were similar, but local patients had a higher major anomaly rate and more were born in other centres. Despite this, local survival and ECMO use were comparable with the CDHSG in all groups. No repair (NR) rate was lower than CDHSG.

Conclusion

The international CDHSG database offers a unique opportunity for individual units to benchmark against a comprehensive international database, specifically for factors known to influence outcome. We encourage other units to contribute to the database to facilitate this practice.

*Table 1 Comparison of 10 years of local patients against the Congenital Diaphragmatic Hernia Study Group (CDHSG) database. Variables were analysed using Fisher's Exact Test. ** indicates significance of <0.05*

Parameter	Local (n=103)	CDHSG (n=4625)	*P* value
Prenatal diagnosis	69.9%	68.6%	0.99
Inborn	35%	49.5%	<0.01**
Major Anomaly	15.5%	8.1%	0.01**
No Repair rate	11.7%	16.8%	0.21
ECMO use	29.1%	29.4%	0.96
Stage 1	5.9%	4.9%	0.48
Stage 4&5	54.5%	59.0%	0.67
Survival	73.8%	69.6%	0.42
Stage 1	100%	99.4%	1.00
Stage 4&5	59.0%	56.8%	1.00

Dose the sac correlate to the better prognosis of congenital diaphragmatic hernia with hernia sac?

Abstract 61

Takuya Kondo, Japan - Department of Pediatric Surgery, Faculty of Medical Sciences, Kyushu University and Japanese CDH Study Group; Koji Nagata, Japan - Japanese CDH Study Group; Keita Terui, Japan - Japanese CDH Study Group; Masahiro Hayakawa, Japan - Japanese CDH Study Group; Shoichiro Amari, Japan - Japanese CDH Study Group; Kouji Masumoto, Japan - Japanese CDH Study Group; Tadahharu Okazaki, Japan - Japanese CDH Study Group; Noboru Inamura, Japan - Japanese CDH Study Group; Naoto Urushihara, Japan - Japanese CDH Study Group; Katsuaki Toyoshima, Japan - Japanese CDH Study Group; Keiichi Uchida, Japan - Japanese CDH Study Group; Taizo Furukawa, Japan - Japanese CDH Study Group; Manabu Okawada, Japan - Japanese CDH Study Group; Akiko Yokoi, Japan - Japanese CDH Study Group; Hiroomi Okuyama, Japan - Japanese CDH Study Group; Tomoaki Taguchi, Japan - Department of Pediatric Surgery, Faculty of Medical Sciences, Kyushu University and Japanese CDH Study Group

Purpose:

Congenital diaphragmatic hernia (CDH) with sac seems to have better clinical outcome. In this study, we investigated the relationship between hernia sac and prognosis.

Methods:

The retrospective cohort study was conducted based on the Japanese CDH study group (JCDHSG) database between 2011 and 2017. Among 531 CDH neonates, 459 cases were included. Seventy two cases were excluded due to the missing data. Patients were divided into two groups: 65 cases (14.2%) were with sac (Sac group: SG) and 394 cases (85.8%) were without sac (Non-sac group: NSG). Primary outcome was the survival rate. Secondary outcome were inhaled nitric oxide (iNO) use, ventilation periods and duration of hospitalization. P-value <0.05 was defined as the statistical significance.

Results:

There was no difference in characteristics for each group except for laterality, and the ratio of right CDH was higher in SG (SG: 18.5% vs NSG: 5.1%, p <0.001). There was no significant difference in the survival rate at 90 days between two groups (SG: 96.8% vs NSG: 90.5%, p=0.142). And there was also no significant difference in the intubation periods (10 days vs 14days, p=0.153). However, SG had less iNO usage rate (53.8% vs. 75.4%, p <0.001), ECMO usage rate (0% vs. 7.6%, p =0.014), and the duration of hospitalization (37 days vs 51 days, p = 0.017).

Conclusion:

Although there was no significant difference in prognosis in this cohort, CDH neonates with sac have the less use of advanced treatment and the shorter hospitalization.

Safety and efficacy of the “Smart” Tracheal Occlusion™ balloon for congenital diaphragmatic hernia: in-vitro and in-vivo study

Abstract 62

David Basurto, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Nicolas SananÈs, France - INSERM 1121 'Biomaterials and Bioengineering', Strasbourg University; Maternal Fetal Medicine, Strasbourg University; Francesca Maria Russo, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Dyuti Sharma, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Enrico Corno, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Ignacio Valenzuela, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Lennart Van Der Veeken, Belgium - Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven; Erik Verbeken, Belgium - Department of Pathology, University Hospitals Leuven, Belgium.; Jan Deprest, Belgium - Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, KU Leuven

Purpose:

To investigate the reversibility, local side effects and occlusiveness of the “Smart-TO” (Strasbourg University-BSMTI, France) in a simulated in utero environment and in the fetal lamb model.

Methods:

Tracheal occlusion(TO) was performed in a high-fidelity simulator. Thereafter the mannequin was placed inside a water-filled balloon mimicking the uterus and held in different positions. Following exposure to the magnetic field generated by a 1.5 T MRI machine, deflation was assessed. Occlusiveness, tracheal side effects and reversibility were tested in fetal lambs. TO was performed on gestational day 95(GD) with the standard Goldbal2 (n=5) or Smart-TO balloon (5). On GD116 balloon presence was assessed by tracheoscopy. Deflation was performed by puncture (Goldbal2) or by MR-exposure (Smart-TO). Following euthanasia, the lung-to-body-weight-ratio(LBWR), lung morphometry, tracheal circumference and histologic tracheal changes were measured. Six unoccluded lambs served as controls.

Results:

Balloon deflation occurred in 100% of when standing (N=48) and when laying on a stretcher (N=8). When sitting in a wheelchair, three balloons failed to deflate (37.5%) on first exposure, one eventually did neither after third exposure (12.5%). In vivo, all Smart-TO balloons deflated successfully. The LBWR was above the normal and comparable for both balloon types. There were no differences in lung morphometry, tracheal circumference and tracheal histology showed minimal changes for both balloons.

Conclusions:

Smart-TO balloon deflation can be achieved irrespective of the fetal position when standing or laying on a stretcher. Sitting on a wheelchair may affect deflation. In healthy lambs the Smart-TO seems to minimal local effects on the trachea and increases lung weight.

Antenatal sildenafil for congenital diaphragmatic hernia: development of a pharmacokinetic model to predict human fetal exposure

Abstract 63

Francesca Russo, Belgium - Katholieke Universiteit Leuven; Eef Hoeben, Belgium - BioNotus; Kristel Van Calsteren, Belgium - Katholieke Universiteit Leuven; Sailesh Kumar, Australia - Mater Mothers' Hospital, Brisbane; Jessica Turner, Australia - Mater Mothers' Hospital, Brisbane; Pieter Annaert, Belgium - Katholieke Universiteit Leuven; Jan Deprest, Belgium - Katholieke Universiteit Leuven

Purpose:

Transplacental sildenafil has been studied in animal models for congenital diaphragmatic hernia with encouraging results. The aim of this study was to predict fetal exposure to maternally administered sildenafil in humans.

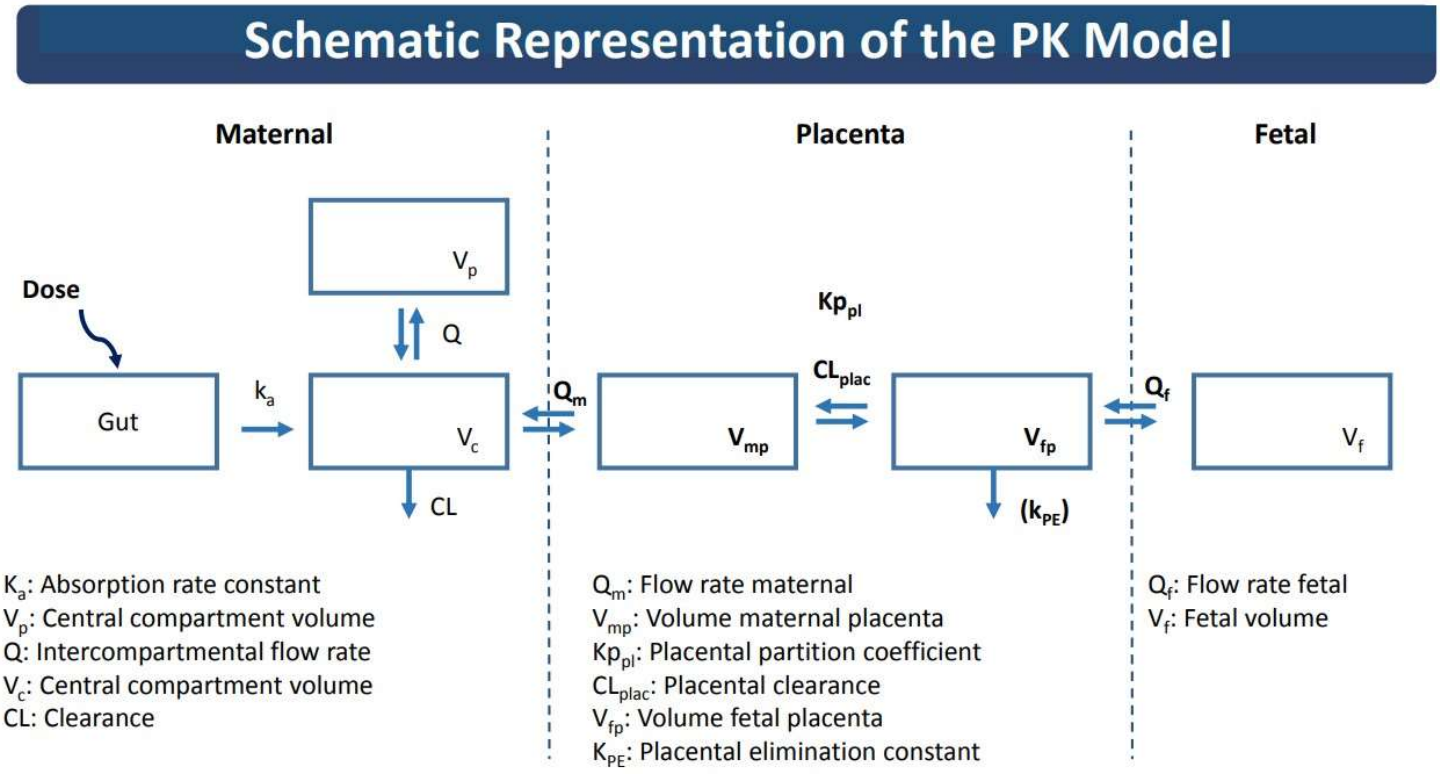
Methods: Population pharmacokinetic (PK) modeling was first performed for male healthy volunteers based on data available in the literature using NONMEM software. Transplacental transfer of sildenafil was measured ex-vivo using the placenta perfusion model and then incorporated in the PK model. Fetal and maternal simulated PK profiles were generated and compared with concentrations measured in maternal plasma and cord blood of patients from an ongoing study on perinatal sildenafil (RIDSTRESS study).

Results:

Twenty-one PK profiles for oral sildenafil at four different doses in male healthy volunteers were derived from the literature. A 2-compartment disposition model best fitted the data. Sildenafil crossed the human placenta ex-vivo, at a rate independent from the initial maternal concentration. A 4-compartment transport model was then used to estimate the transplacental transfer parameters, which were implemented together with the physiological changes occurring during pregnancy. Finally, the fetal compartment was added (Figure). Simulated PK profiles for the pregnant woman and the fetus were generated and compared with observed sildenafil concentrations in maternal and fetal plasma. The goodness-of-fit plots suggestested adequate prediction both in the mother and in the fetus.

Conclusion:

This PK modeling approach enables a basic prediction of fetal PK prior to drug administration to the mother. This will be a useful tool to integrate clinical studies and to help elucidate appropriate dosing information.



Long-term feeding issues impact on the daily life of congenital diaphragmatic hernia survivors: first patient-led survey of CDH UK

Abstract 64

Beverley Power, United Kingdom - CDH UK, Norfolk, United Kingdom; Soichi Shibuya, United Kingdom - Great Ormond Street Institute of Child Health, University College London; Brenda Lane, United Kingdom - CDH UK, Norfolk, United Kingdom; Simon Eaton, United Kingdom - Great Ormond Street Institute of Child Health, University College London; Paolo De Coppi, United Kingdom - Great Ormond Street Institute of Child Health, University College London

Background:
Patients surviving congenital diaphragmatic hernia (CDH) have high morbidity of postoperative long-term sequala. A patient-led survey of CDH survivors highlighting the feeding problems and their impact on the daily life was undertaken by CDH UK, a registered charity governed by volunteer.

Methods:
Answers from CDH survivors were collected through an online questionnaire (SurveyMonkey®). The questionnaire contained 17 questions about their feeding problems, daily life, and support they were receiving for it.

Main Results:
The results consisted of 102 complete response and 151 partial response. Overall, 116 (76.8%) reported they were suffering from any type of feeding issue. Most importantly, 91/102 (89.2%) of the responders reported that feeding problems impacted on their daily life. Gastric acid reflux (GER) and growth retardation were the commonest symptoms experienced by 97 (91.5%) and 72 (62.2%) responders, respectively. Even though majority of responders (78; 76.4%) answered that the whole experience associated with the disease has been very or extremely stressful, only a few responders (18; 17.0%) have received any written information on feeding or details of patient/parent support.

Conclusions:
This is the first patient-led survey focusing on feeding problems in the daily life of CDH survivors. CDH survivors frequently have various issues with feeding, which may not be adequately supported or discussed clinically. It is desirable to assist CDH patients to reliable resources of long-term support and multidisciplinary treatment clinics may play an important role to accomplish it.

The effect of mechanical compression in Ex vivo model of congenital diaphragmatic hernia

Abstract 65

Soichi Shibuya, United Kingdom - Great Ormond Street Institute of Child Health, University College London; Federica Michielin, United Kingdom - Great Ormond Street Institute of Child Health, University College London; Marko Nikolic, United Kingdom - Lungs for Living Research Centre, UCL Respiratory, University College London, London, United Kingdom; Nicola Elvassore, United Kingdom - Great Ormond Street Institute of Child Health, University College London; Paolo De Coppi, United Kingdom - Great Ormond Street Institute of Child Health, University College London

Aim of the Study:

Congenital diaphragmatic hernia (CDH) is still associated to high mortality and significant morbidity. Animal models of CDH are limited and thus ex vivo modelling of the disease will help to find therapeutic targets. In particular, it would be relevant to mimic mechanical compression produced by herniated abdominal viscera. The aim of this research is to develope a novel ex vivo model based on a three-dimensional (3D) printing technique to replicate the impaired lung development in CDH.

Methods:

Embryonic lungs were harvested from E12.5 mice and embedded in a newly defined hydrogel in an air-liquid interphase (ALI) culture condition. On the following day (equivalent to E13.5), a 3D structure surrounding the outer surface of the left lobe was built by polymerization of chemically modified Polyethylene-glycol (PEG) solution, which was added to Matrigel in advance and selectively cross-linked through a two-photon laser.

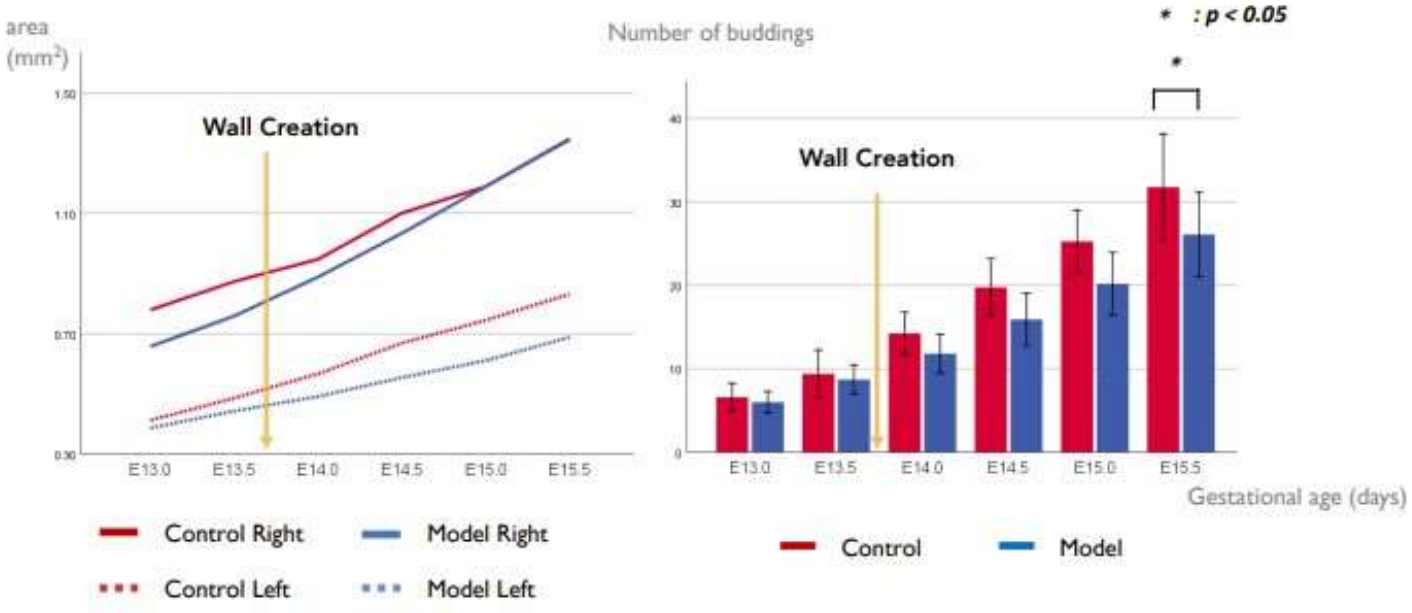
Main Results:

Embryonic lungs could be cultured in ex vivo ALI condition. 3D structure mimicked the physical constraint which is observed in CDH and demonstrated lung hypoplasia characterised by decreased and delayed branching. Lobe size and number of epithelial branching of the affected lungs were significantly diminished after 4 days in culture. In the compressed lung, the mesenchyme appears more prominent than in control lungs.

Conclusions:

Ex vivo models of CDH represent an innovative way to investigate the impact of mechanical compression on the lung development and have the potential to uncovering the molecular pathways implicated in the pulmonary hypoplasia of human CDH.

Fig.1 Area analysis and number of buddings



Evaluation of a new balloon for fetal endoscopic tracheal occlusion in the non-human primate model.
Abstract 66

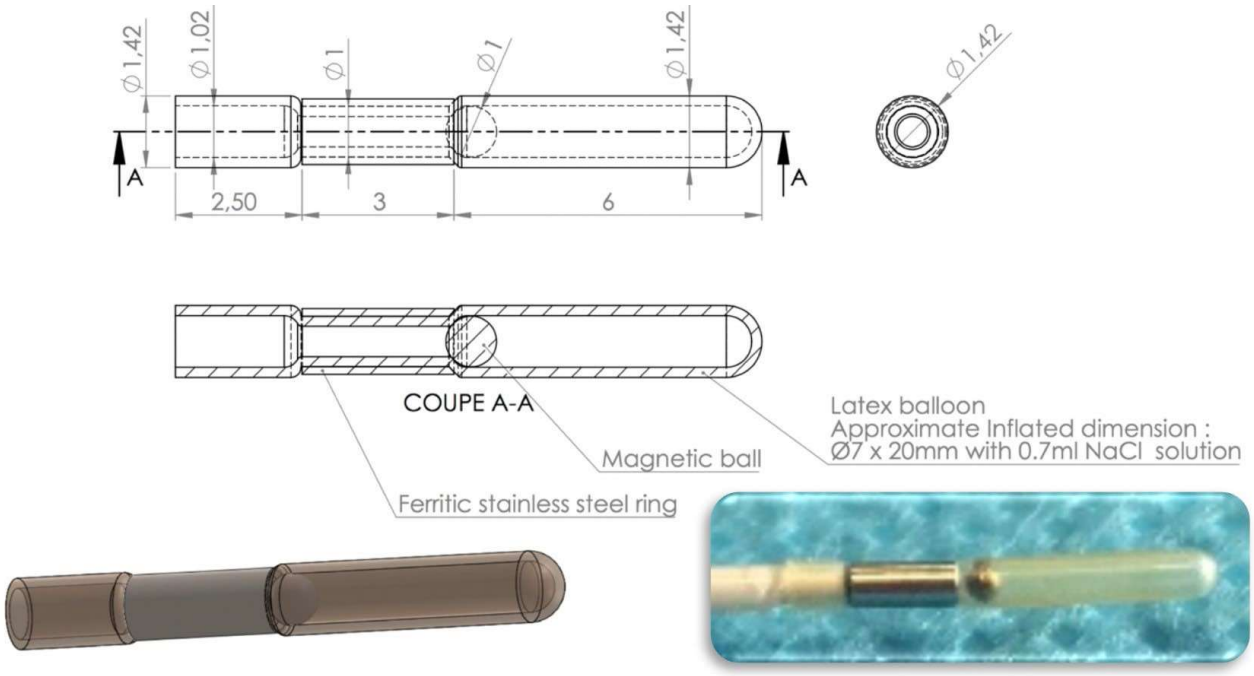
Nicolas Sananes, France - Strasbourg University Hospital; Pierrick Regnard, France - SILABE – ADUEIS Platform; Christian Debry, France - Strasbourg University Hospital; Romain Favre, France - Strasbourg University Hospital

Purpose:
Fetal Endoscopic Tracheal Occlusion may improve survival in severe cases of congenital diaphragmatic hernia. One of the major concerns about tracheal occlusion is the need for balloon removal. We developed a new balloon called “Smart-TO”, which allows non-invasive and easy unplugging, thanks to a magnetic valve actuated by the magnetic fringe field of an MRI scanner. The objective of this feasibility study was to evaluate the operation of this new balloon in a non-human primate model.

Methods:
Four pregnant rhesus monkeys underwent fetal endoscopic tracheal occlusion using the “Smart-TO” balloon. The pregnant monkeys were simply carried around the perimeter of a an MRI scanner a few days later. Study outcomes were feasibility of fetal tracheal occlusion using the “Smart-TO” balloon, persistence of the balloon in the fetal trachea, and deflation of the balloon when subjected to the magnetic fringe field of an MRI.

Results:
At the time of the unplug procedure, in all cases the balloon was still in a correct position and its shape did not change based on their ultrasound appearance. After bringing the pregnant monkeys into the fringe field of the MRI scanner, the balloon deflated in all cases.

Conclusion:
The balloon we developed allows non-invasive, easily triggered, and externally controlled reversal occlusion, based on the non-human primate model. Further tests evaluating occlusiveness and potential adverse effects have also been performed. First-in-man study is planned.



Pharmacokinetics and pharmacodynamics of sildenafil in fetal lambs on extracorporeal support.

Abstract 67

Felix De Bie, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Francesca Russo, Belgium - Department of Development and Regeneration, KU Leuven; James Moon, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Barbara Coons, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Janaina Senra, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Camilla Omann, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Eef Hoeben, Belgium - Department of Development and Regeneration, KU Leuven; Pieter Annaert, Belgium - Department of Development and Regeneration, KU Leuven; Marcus Davey, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Alan Flake, United States - Center of Fetal Research, Children's Hospital of Philadelphia; Jan Deprest, Belgium - Department of Development and Regeneration, KU Leuven

Purpose:

To assess the pharmacokinetic profile of sildenafil in the EXTra-uterine Environment for Neonatal Development (EXTEND) model, to define the pharmacodynamic dose-effect relationship on the fetal pulmonary vasculature and to evaluate short-term hemodynamic fetal tolerance to the drug.

Methods:

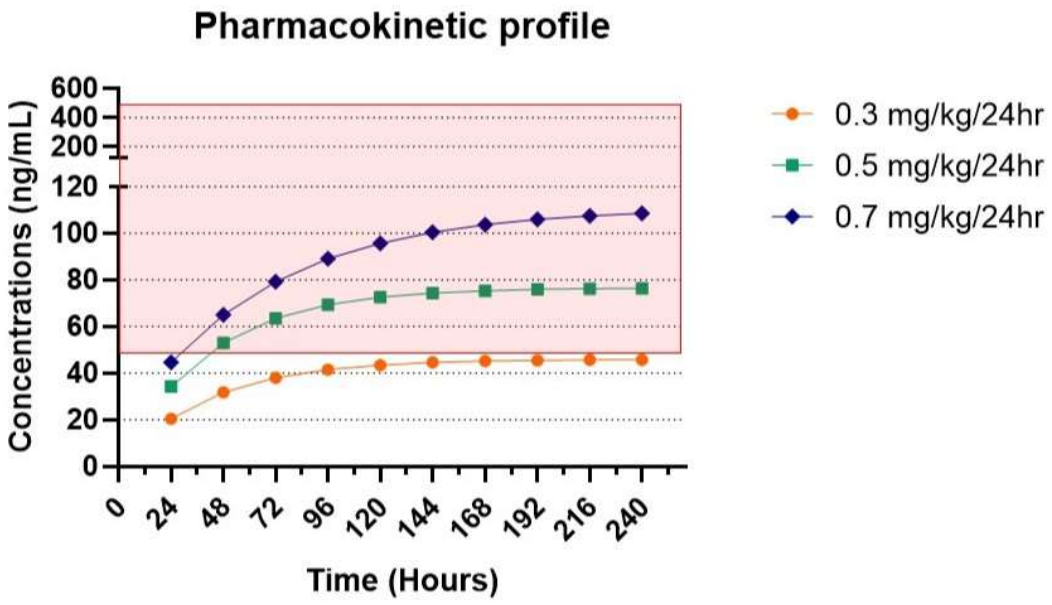
Healthy fetal lambs (GA110-140; term 145) on EXTEND were exposed to different doses of continuous intravenous (IV) sildenafil (0.3 – 0.5 – 0.7 mg/kg/24hr) for a period of one to seven days. A wash-out period of two to six days was scheduled before another dose was tested in the same animal. Blood sampling and Doppler ultrasound were performed at fixed timepoints. Primary outcomes were sildenafil pharmacokinetic profiles generated using NONMEM modeling and changes in the Doppler waveform of the right pulmonary artery (RPA). Secondary outcomes were proxies for hemodynamic fetal tolerance (blood gas and EXTEND circuit parameters).

Results:

A total of nine administrations were tested in six lambs. Sildenafil concentrations reached plateau after six days, with only the 0.5 and 0.7 doses reaching therapeutic concentrations. In 67% (n=6/9) of cases, sildenafil administration was associated with an increase in the acceleration/ejection time of the RPA >15%. Parameters changed 30-60 minutes after starting sildenafil administration and returned to baseline within four hours. The effects were not dose-dependent. No toxicity was observed.

Conclusion:

In 67%, administration of sildenafil caused a non-dose-dependent pulmonary vasodilation in fetal lambs on extracorporeal support. A daily 0.5 mg/kg IV dose of sildenafil allows to achieve therapeutic concentrations and can safely be administered to fetal lambs on EXTEND.



Pharmacokinetic profile obtained through NONMEM modelling. The red quadrangle represents the therapeutic range of sildenafil (47 – 500ng/mL).

Pulmonary complications in Children survivors of Congenital Diaphragmatic Hernia

Abstract 69

Hina Emanuel, United States - Department of Pediatrics, The University of Texas Health Science Center; Harting Mathew, United States - Department of Pediatric Surgery, University of Texas Health Science Center; Ashley Harmon, United States - Department of Pediatric Surgery, University of Texas Health Science Center; Kevin Lally, United States - Department of Pediatric Surgery, University of Texas Health Science Center; James Stark, United States - Department of Pediatrics, The University of Texas Health Science Center; Cindy Jon, United States - Department of Pediatrics, The University of Texas Health Science Center; Katrina Mcbeth, United States - Department of Pediatrics, The University of Texas Health Science Center; Aravind Yadav, United States - Department of Pediatrics, The University of Texas Health Science Center; Carlos Flores, United States - Department of Pediatrics, The University of Texas Health Science Center; Tomika Harris, United States - Department of Pediatrics, The University of Texas Health Science Center; Ricardo Mosquera, United States - Department of Pediatrics, The University of Texas Health Science Center

Background:

Children surviving congenital diaphragmatic hernia (CDH) develop pulmonary complications including asthma; however definitive pathophysiology of asthma remains undefined. Prevalence of asthma in general pediatric population is 8.4%. We hypothesized that pulmonary complications and asthma is prevalent in CDH patient population with possible ciliary dysfunction and ultrastructural abnormalities.

Methods:

A retrospective analysis of 140 patients from CDH birth registry at the University of Texas (UT) at Houston was performed. Nasal ciliary biopsy will be performed in patients with asthma at CDH comprehensive care clinic at UT

Results:

Among cohort of 140 CDH patients {(males; 64%, females; 36%), (CDH A; 22%, CDH B; 35% CDH C; 22%, CDH D;18%),(mean age;4 years, +/- 4 SD)} survival rate was 89% (n=125/140) Average ventilation days was 23. Prevalence of asthma was 37% {(n=46/125), (male; 74%, female; 26%), (CDH A; 26%, CDH B; 28%, CDH C; 52%, CDH D; 57%)} among CDH survivors. 15% (n=19/125) had atopy; out of which 10% had asthma. 9% (n=11/125; CDH B; 64%, CDH C; 36%) of patients had V/Q scan with split perfusion <30% in 45% (CDH B 40%, CDH C 60%). 80% (n=4/5) of patient with perfusion ratio < 30% had asthma (RR 4.8, P = 0.09). 60% {(n=84/140), (CDH A; 23%, CDH B; 51%, CDH C;83%, CDH D; 92%0} of patients had pulmonary hypertension. 22% {(n=31/140), CDH A; 3%, CDH B; 8%, CDH C; 26%, CDH D; 68%)} required ECMO.

Conclusion:

Pulmonary complications are greater in larger defects with asthma being more prevalent in CDH survivors than general population.

Extracorporeal life support is associated with improved survival for newborns with severe congenital diaphragmatic hernia

Abstract 70

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Background:

Extracorporeal life support (ECLS) is commonly used for congenital diaphragmatic hernia (CDH), despite a lack of high-level evidence of effectiveness. The purpose of this study was to determine the actual survival benefit seen with ECLS for these infants.

Methods:

ECLS-eligible patients from the CDH Study Group registry (2007-2019) were used to study the primary outcome measure of survival to discharge. Propensity scoring (PS) was used to match infants who did and did not receive ECLS. Three separate survival comparisons were made between different PS matched groups: (1) the total cohort; (2) a high-risk cohort, defined as those patients with a lowest achievable pCO2≥60 mmHg during the first day of life; and (3) patients with echocardiographic data (pulmonary hypertension, ventricular dysfunction). Center effects analyses measured the influence of CDH volume and ECLS rates on survival.

Results:

Of 5020 ECLS-eligible patients, there were 1677 patients for comparison (1) after PS matching; overall survival was lower with ECLS (54% versus 77%, OR 2.93, 95% CI 2.4-3.6). However, for comparison (2), there was a nearly threefold survival advantage with ECLS (41% versus 14%, OR 0.23, 95% CI 0.11-0.47, N=207). For comparison (3), there was 2.3 times higher survival for high-risk patients in the ECLS group (47% versus 20%, OR 0.29, 95% CI 0.1-0.79, N=80). The ECLS survival advantage was primarily at high-volume centers in high-risk patients (Figure 1).

Conclusions:

ECLS is associated with improved survival among high-risk CDH patients, but this advantage is heavily influenced by center CDH volume and ECLS experience.

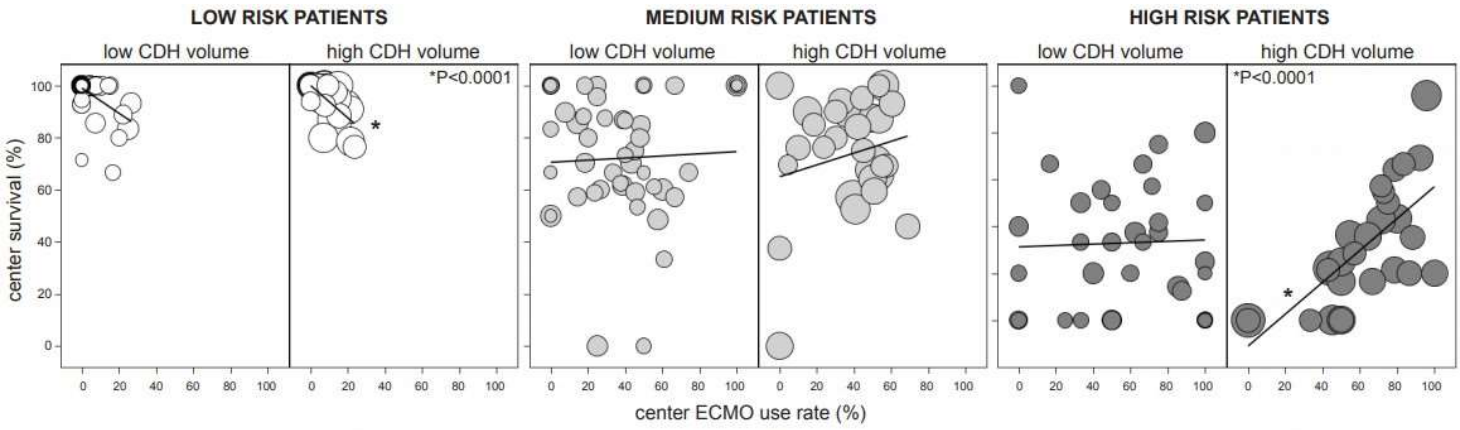

Figure 1. Bubble plots comparing low CDH volume to high CDH volume centers (average of <10 versus 10 or more cases per year, total of 96 centers), plotting % center overall survival against % center ECLS use rate for low (N=1155), medium (N=1949), and high (N=440) risk ECLS-eligible patients (birth weight>1.8kg, gestational age at birth>31 weeks, and no major cardiac or chromosomal anomalies). Lines and P values represent linear regression weighted to average annual center CDH volume.

In vitro cell compression model of congenital diaphragmatic hernia inhibits pulmonary angiogenesis and cell proliferation.

Abstract 74

Kathleen Marulanda, United States - The University of North Carolina at Chapel Hill; Maria Gambarian, United States - The University of North Carolina at Chapel Hill; Sean McLean, United States - The University of North Carolina at Chapel Hill

Purpose:

Pulmonary hypertension in congenital diaphragmatic hernia (CDH) may lead to cardiopulmonary collapse shortly after birth. Reduced vessel formation in hypoplastic lungs is a known component of CDH-induced pulmonary hypertension, but the mechanism remains unclear. We hypothesize that external compression contributes to poor angiogenesis. To evaluate the effect of compression upon pulmonary vascular development, an in vitro cell culture model replicates the external mechanical compression experienced by the developing lungs in CDH.

Methods:

Human pulmonary artery endothelial cells (HPAEC) were cultured and compressed with 15 atmospheres of pressure applied over an agarose cushion for 24 hours. Compressed HPAECs were cultured in conditioned media. The Matrigel angiogenesis assay was performed to quantify the number of branch points and tubes formed as an indicator of angiogenesis. Absorbance was measured with XTT proliferation assay to assess cellular proliferation. Both experiments were performed in triplicate and repeated on three separate occasions.

Results:

Compressed HPAECs generated less branch points (M=244.4, SD=42.9) than controls (M=318.4, SD=37.3); $t(29.4)=5.21$, $p<0.0001$. Decreased tube formation was found in compressed HPAECs (M=31.3, SD=6.4) compared to control HPAECs (M=38.7, SD=9.7); $t(26.0)=2.56$, $p=0.012$. In two of the XTT proliferation assays, absorbance was decreased in compressed HPAECs (M=0.67, SD=0.03) versus controls (M=0.77, SD=0.04); $t(12)=4.99$, $p=0.0003$.

Conclusion:

Our in vitro cell compression model demonstrates that sustained mechanical compression inhibits angiogenesis and cellular proliferation in HPAECs. This supports in vivo results, which show decreased pulmonary vascular arborization in infants with CDH-associated pulmonary hypertension. Additional studies are needed to identify the specific genetic and molecular pathways impacted by mechanical compression.

Figure 1. Matrigel angiogenesis assay of mechanically compressed human pulmonary artery endothelial cells (a) versus control human pulmonary artery endothelial cells (b).

Therapy at 30 days of life predicts lung function at 6-12 months in infants with Congenital Diaphragmatic Hernia (CDH)

Abstract 75

Etze Chotzoglou, United States - Children's Hospital of Philadelphia; Holly Hedrick, United States - Children's Hospital of Philadelphia; Lisa Herkert, United States - Children's Hospital of Philadelphia; Natalie Rintoul, United States - Children's Hospital of Philadelphia; Howard Panitch, United States - Children's Hospital of Philadelphia

Introduction:

Pulmonary support at 30 days postnatal age was found to be the strongest predictor of inpatient mortality and morbidity among CDH infants, and with greater pulmonary morbidity at 1 and 5 years. We previously demonstrated that CDH infants have lower forced expiratory flows and higher fractional lung volumes than healthy infants. It is not known, however, if there is a relationship between the degree of lung hypoplasia as reflected in infant pulmonary function test (iPFT) measurements and need for therapy at 30 days.

Methods:

Medical records of 123 infants with CDH who underwent iPFT at our institution between July 2004 and June 2018 were retrospectively reviewed. Spirometry by the raised volume rapid thoracic compression technique and lung volumes by body plethysmography were offered as part of a standard protocol. Infants were divided into groups based on their need for any type of respiratory assistance (supplemental oxygen, high flow therapy, mechanical ventilation, ECMO), diuretics, or pulmonary hypertension therapy (PHT) at 30 days and compared with non-therapy receivers.

Results:

Median age of first iPFT was 6.6 (IQR=5.3-11.7) months. Those required invasive pulmonary support at 30 days had a higher functional residual capacity (FRC)%predicted (p=0.002), a higher ratio of residual volume to total lung capacity (RV/TLC)%predicted (p<0.001), a lower forced expiratory volume at 0.5 sec (FEV0.5) (p=0.01), than those who did not require any support.

Conclusions:

Infants requiring any pulmonary support, diuretics and/or pulmonary hypertension therapy at 30 postnatal days have lower lung compliance and higher fractional lung volumes, suggesting a greater degree of lung hypoplasia.

iPFT Results	*FRC (%predicted)*	*RV (%predicted)*	*RV/TLC (%predicted)*	*$FEV_{0.5}$ (%)*
Pulmonary support on day of life 30 (n=121)				
Room Air (n=63) (52.1%)	*106±36*	*99±47*	*100±33*	*94±22*
Non-invasive (n=20) (16.5%)	*119±27*	*120±43*	*116±27*	*90±17*
Invasive (n=38) (31.4%)	*127±33*	*128±42*	*129±24*	*81±18*
p-value	*0.002*	*0.001*	*<0.001*	*0.01*
PHT treatment on day of life 30** (n=119)				
Requiring (n=38) (32%)	*132±30*	*138±39*	*132±24*	*84±17*
Not requiring (n=81) (68%)	*106±34*	*99±45*	*102±31*	*92±21*
p-value	*<0.001*	*<0.001*	*<0.001*	*0.05*
Diuretics treatment on day of life 30 (n=120)				
Requiring (n=58) (48%)	*124±34*	*129±45*	*127±28*	*85±18*
Not requiring (n=62) (52%)	*106±34*	*95±42*	*98±29*	*94±21*
p-value	*0.005*	*<0.001*	*<0.001*	*0.01*

Infant's First Blood Gas Predicts Required Therapies at 30 Days of Life in Infants with Congenital Diaphragmatic Hernia

Abstract 76

Etze Chotzoglou, United States - Children's Hospital of Philadelphia; Howard Panitch, United States - Children's Hospital of Philadelphia; Matthew Goldshore, United States - Children's Hospital of Philadelphia; Natalie Rintoul, United States - Children's Hospital of Philadelphia; Herkert Lisa, United States - Children's Hospital of Philadelphia; Holly Hedrick, United States - Children's Hospital of Philadelphia

Purpose:

Risk stratification tools are necessary to identify infants at risk for morbidity and mortality resulting from congenital diaphragmatic hernia(CDH). The pulmonary support at 30 days was found to be a strong predictor of inpatient mortality and morbidity and associated with higher pulmonary associated morbidity at 1 and 5 years. We hypothesized that the initial arterial blood gas (iABG) might be used as an early risk stratification tool.

Methods:

414 subjects with CDH were born between January 2004 and August 2019 at Children's Hospital of Philadelphia (CHOP), and enrolled in the Pulmonary Hypoplasia Program at CHOP. We retrospectively reviewed the hospital records for 199 surviving infants (median gestational age (GA) 38.4 (IQR=37.6-39), 40.2% female) with CDH that had iABG within 60 minutes of life. Infants were divided into groups based on their need for noninvasive (supplemental oxygen, high flow therapy, noninvasive mechanical ventilation) or invasive (mechanical ventilation, ECMO) respiratory assistance, diuretic use, and pulmonary hypertension (PH) therapy (inhaled and/or systemic drugs) at 30 days and compared with non-therapy receivers by iABG results.

Results:

Mean time of the iABG was 40.4±10.1 minutes. Those requiring any pulmonary support, diuretic or PH therapy at 30 days had a lower pH ($p<0.01$), and a higher PCO2 ($p<0.001$) than those who did not require any support.

Conclusions:

Infants with lower arterial pH and higher PCO2 at birth, required more pulmonary support, diuretic or PH therapies at 30 days. Our study suggests iABG results might be used as additional risk stratification measurement for evaluation of infants with CDH.

Arterial Blood Gas within 60 Minutes of Life	*pH*	*CO_2*	*PaO_2/FiO_2*	*HCO_3*	*Base Excess*
Pulmonary support on day of life 30 (n=199)					
Room air (n=60)	*7.2 (7.1-7.2)*	*60.4±19.34*	*96 (70-164)*	*22.8 (20.6-24)*	*-7 (-9—5)*
Non-invasive (n=44)	*7.1 (6.9-7.2)*	*78.4±19.82*	*69.5 (52-88)*	*23.6 (21.3-24.9)*	*-9(-11—6)*
Invasive (n=95)	*6.9 (7-7.1)*	*87.3±24.03*	*53 (40-81)*	*23.3 (21.8-24.9)*	*-9(-11—7)*
p-value	***<0.001***	***<0.001***	***<0.001***	***0.12***	***0.001***
PH treatment on day of life 30 (n=199)					
(+) (n=104)	*7 (6.9-7.1)*	*88.03±21.98*	*53.3 (40-78.3)*	*23.5 (21.8-25)*	*-9 (-12—7)*
(-) (n=95)	*7.2 (7.1-7.2)*	*65.4±21.78*	*88 (62-138)*	*23 (20.6-24.4)*	*-7 (-10—5)*
p-value	***<0.001***	***<0.001***	***<0.001***	***0.04***	***<0.001***
Diuretics treatment on day of life 30 (n=199)					
(+) (n=68)	*7.1 (6.9-7.1)*	*85.5±26.45*	*61 (40-88)*	*23.3 (21.8-24.9)*	*-9 (-11—6)*
(-) (n=131)	*7.1 (7-7.2)*	*72.9±22.51*	*76.3 (50-106)*	*23 (20.8-24.6)*	*-8 (-10—5)*
p-value	***0.003***	***0.001***	***0.003***	***0.13***	***0.08***
Infants died before 30 days of life (n=30)	*6.9 (6.8-7)*	*105.4±23.5*	*45.5 (38.5-52.5)*	*22.1 (19.3-24)*	*-12 (-18—7)*

Right Sided Congenital Diaphragmatic Hernia: The Role Of Prenatal Predictors And Perinatal Characteristics On Early Outcomes. A Fourteen-Year Prospective Study.

Abstract 77

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Aim:

Right sided (R) congenital diaphragmatic hernia (CDH) have been associated with poorer outcomes. Nonetheless, the role of prenatal predictors and perinatal characteristics of R-CDH patients on early outcomes have not been extensively investigated. Aim of the present study was to critically evaluate several pre and perinatal risk factors in predicting mortality in R-CDH.

Methods:

A prospective study on all CDH infants treated in a tertiary care Center was performed. Patients were categorised based on side of the hernia, and possible risk factors were analysed.

Results:

During the study period, 228 HR-CDH were treated. CDH left 191 (84) and CDH right 34 (15); O/E LHR; median, (IQR) 46.3 (35.3-59.5) vs 41.3 (35.5-54) p 0.5; Prenatal diagnosis, n° (%) 184 (96) vs 32 (94) p 0.7 Fetal tracheal occlusion, n° (%) 6 (3) vs 1 (3) p 1; Survival, n° (%) 134 (70)vs 15 (44) p 0.005 ;Associated malformation, n° (%) 30 (16) vs 12 (35) p 0.01; Cardiac Anomaly, n° (%) 17 (9) vs 8 (24) p 0.03; Pulmonary Hypertension, n° (%) 91 (48) vs 21 (62)p 0.14; Liver up, n° (%) 66 (35) vs 30 (88) p 0.0001; Difect type C/D, n° (%) 69 (36) vs 21 (62) p 0.007

Conclusion:

Although mortality rate was significantly higher in R-CDH infants, prenatal predictors of CDH severity were similar between R-CDH and left (L) CDH patients. In our large cohort of patients R-CDH present higher rate of associated malformations and cardiac anomaly, in comparison to L-CDH, and larger diaphragmatic defects

Surgical Complications In Congenital Diaphragmatic Hernia Survivors: Long-Term Follow-Up.

Abstract 78

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Aim:

CDH increasing survival has uncovered an increased rate of co-morbidity in late survivors. Aim of the present study is to evaluate abdominal and small bowel complications rate as well as hernia recurrence on respect of well-kwnone reported risk factors.

Methods:

A lungitudinal prospective study was performed including all high risk CDH survivors treated at our Institution. Data were collected with specific attention to adverse surgical outcomes: small bowel volvulus/obstructions and hernia recurrence.

Results:

During the study period, 127 CDH survivors (70% survival rate) were follow-up. Median age at follow-up was 4.6. Volvulus/ obstruction + tot 15 vs Volvulus/ obstruction - tot 107. Risk factors; Patch repair (%) 3 (20) vs 27 (25) p1; Intestinal Malrotation (%) 10 (67) vs 38 (36) p 0.03; Hernia Sac (%) 0 vs 26 (24)p 0.04; Liver up (%) 3 (20) vs 34 (32)p 0.5; Left CDH (%) 15 (100) vs 93 (87) p 0.2; Recurrence (%) 1 (7) vs 3 (3) p 0.4. Hernia recurrence + tot 4 vs Hernia recurrence - tot 118. Risk factors; Patch repair (%) 2 (50) vs 28 (24) p 0.3; Intestinal Malrotation (%) 1 (25) vs 47 (40) p 1; Hernia Sac (%) 0 vs 26 (22) p 0,6; Liver up (%) 0 vs 37 (31) p 0.3; Left CDH (%) 4 (100) vs 104 (88) p 1

Conclusions:

late intestinal complications correlate with the presence of intestinal malrotation, while hernial sac protect to develop abdominal complications. Recurrences do not correlate with the risk factors considered.

Comparison of two early predictors of mortality for congenital diaphragmatic hernia.

Abstract 79

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Introduction:

Congenital diaphragmatic hernia (CDH) management, as well as the outcomes, vary widely among centers. Having an early and reliable mortality prediction score is very useful to perform stratified comparisons of the results and enhance the development of benchmarking strategies that could improve results from one center to another.

Objective:

To validate and compare two early mortality scores in our CDH population.

Methods:

Results reported to the CDH Study Group by two centers between the years 2013-2018 were analyzed retrospectively. The ECMO-free mortality and survival prediction capacity of the scores proposed by Schultz and Brindle were evaluated by area under the curve (AUC) analysis.

Results:

The reports of 345 patients were evaluated. The mortality and ECMO rate in our population was 27% and 30% respectively. The AUC to predict survival was 0.83 (0.774-0.886) and 0.70 (0.638-0.762); similarly, to predict ECMO-free survival the AUC was 0.80 (0.746-0.854) and 0.735 (0.681-0.788) for Schultz and Brindle scores respectively (Fig.1).

Conclusion: We have validated two efficient mortality prediction scores in our population. The Schultz score is a significantly better early predictor of mortality in our population.

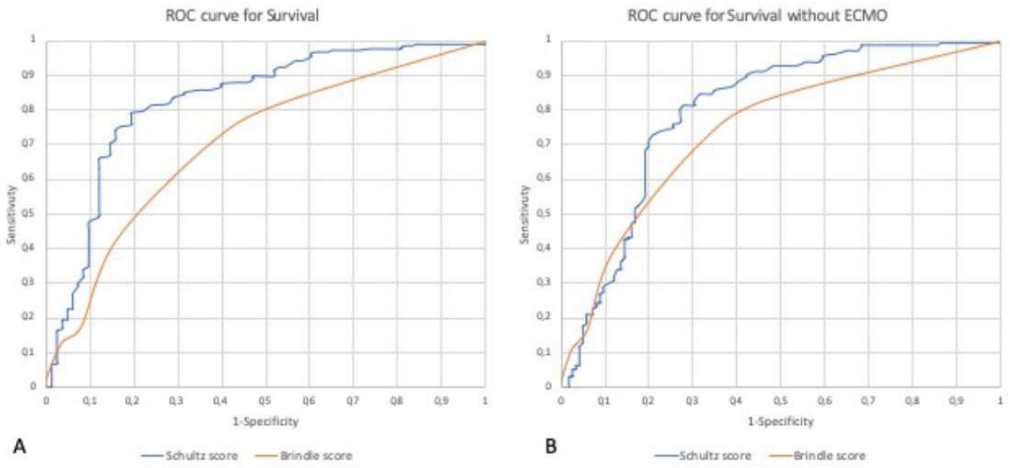

Fig 1: Receiver operating characteristic (ROC) curve for each predictive score. A: Predicting Survival. B:Predicting survival without Extracorporeal membrane oxygenation (ECMO)

Emergency presentation and hospital re-admission for CDH patients within one year of discharge

Abstract 80

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Purpose:

Congenital diaphragmatic hernia (CDH) survivors have significant morbidity. Data regarding their post-discharge course are lacking. Our objective was to characterize emergency department (ED) presentation and hospital re-admission within one year of discharge. We hypothesized that frequency of ED visits would be associated with high-risk disease in CDH.

Methods:

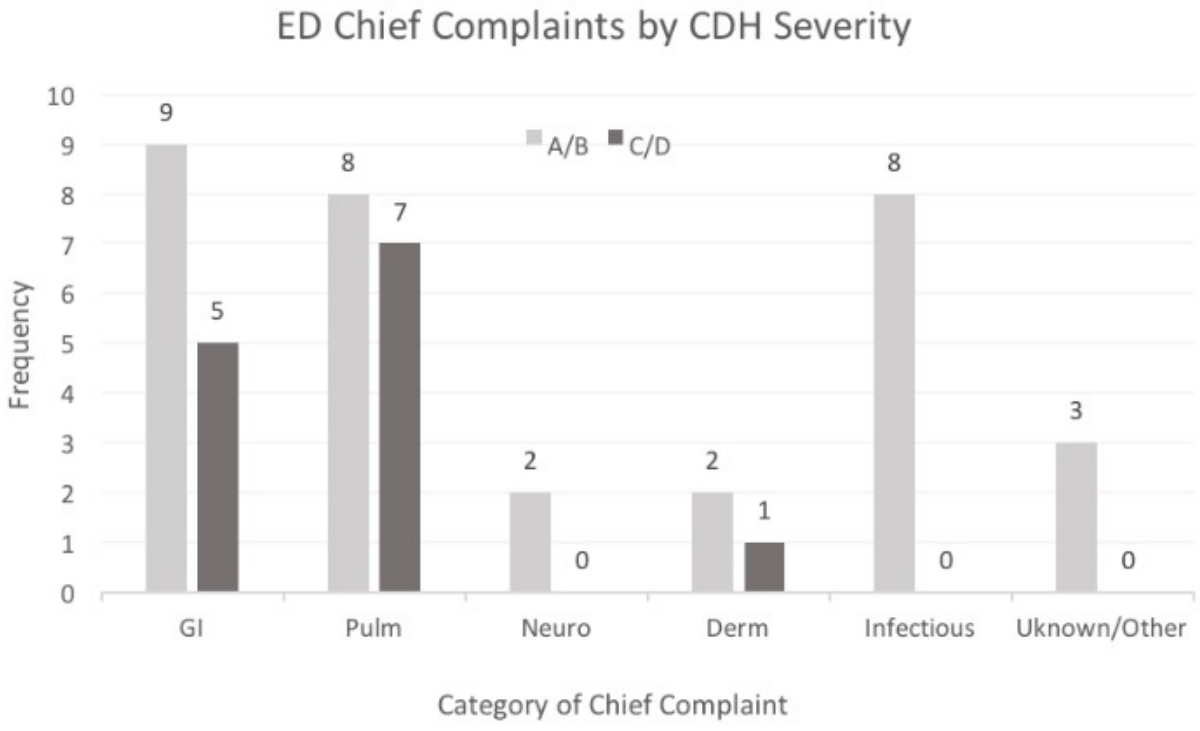
Patients from our CDH long-term follow-up clinic were included. Data were collected from patients' charts and conversation with families. Data collected included demographics, disease characteristics, and re-admission information. Statistics were done using Microsoft Excel and Stata/IC 16.0.

Results:

There were 55 patients with CDH at CMHH from 2015 to 2018, and 39 (71%) survived to discharge. Of the survivors, 32 (84%) followed-up at least once in our clinic, of whom, 28 (88%) were actively followed. Follow-up data was available for 27 patients. A total of 20 (74%) patients had at least one ED visit within one year of discharge (range 0-5, median=1), and 13 (48%) patients had a least one hospital re-admission (range 0-5). Of 45 total ED visits, 15 (33%) had pulmonary chief-complaints, 14 (31%) GI-related, and 15 (36%) were other categories such as neurologic or infectious complaints (Figure). There was no significant difference in number of visits between low and high-risk patients (Size A/B vs. C/D) (p=0.77).

Conclusion:

Minimal data exist to drive care for CDH survivors after discharge. In our review, the ED presentation rate was 73% within one year of discharge. The number of visits did not vary by CDHSG risk group. These data will help counsel families about post-discharge planning.



Morphometric Mri To Evaluate Cortical Thickness In Neonates With Congenital Diaphragmatic Hernia

Abstract 81

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Introduction:

In patients with congenital diaphragmatic hernia (CDH), neurodevelopmental impairment may represent a concerning sequela. Morphometric MRI techniques allow to investigate cortical parameters like cortical thickness (CT) and gyrification index (GI) usually implicated in several neurodevelopmental disorders. The purpose of this study is to elaborate a novel morphometric algorithm to evaluate CT and GI in neonates with CDH.

Materials & Methods:

We acquired 3D T2-w Turbo Spin Echo sequences on a 3T scanner (Siemens, Erlangen, Germany). 15 CDH (mean age = 40 d) and 13 age-matched controls were included in the study. Data were post-processed through a dedicated algorithm. CT was computed as the vertex-wise difference between the inner and the outer surface, while GI was measured as the amount of cortex buried within the sulcal folds, compared with the visible cortex in circular regions of interest. Statistical analyses were performed with Permutation Analysis of Linear Models (PALM) FSL package, using 1000 permutations for each test.

Results:

CT was 2.11 ± 0.31 mm in CDH patients and 2.16 ± 0.34 mm in controls; GI was 2.8 ± 0.38 in CDH patients and 2.83 ± 0.42 in controls. In CDH patients, CT was significantly reduced in parietal, occipital and medial temporal lobe of right hemisphere as compared to controls ($p < 0.01$). No differences were found for GI.

Conclusion:

Patients with CDH have reduced CT in parietal, occipital and medial temporal lobe of right hemisphere. Further studies are needed to define if these changes correlate with neurodevelopmental outcome in CDH patients.

The effect of tracheal occlusion on lung development pathways and vascular morphology in a rabbit model of congenital diaphragmatic hernia

Abstract 82

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Purpose

Congenital diaphragmatic hernia (CDH) results in lung hypoplasia and pulmonary hypertension. Although tracheal occlusion (TO) reverses pulmonary hypoplasia, the transcriptional mechanisms have not been fully elucidated. The aim of this study was to study the effects of TO in a rabbit CDH model on anatomic, morphologic, and molecular markers of fetal lung development.

Methods

Time-dated pregnant does underwent surgery on day 23 to create fetal diaphragmatic defects. Half the CDH fetuses underwent TO on day 28 and lung collection occurred on day 31 (term=32 days). Lung-body weight ratio (LBWR), mean terminal bronchiole density (MTBD), expression of mRNA and microRNA, and immunohistochemistry for Ki67 and smooth-muscle actin (SMA) were determined.

Results

Nineteen does produced 222 fetuses. Fifteen CDH, 15 TO and 15 controls survived. LBWR was significantly lower in CDH while TO was similar to controls ($p=0.003$). MTBD was significantly higher in CDH fetuses and restored to control levels in TO ($p<0.001$). Following TO, expression of miR-33 ($p=0.03$) and mKi67 ($p=0.01$) were increased and Lgl1 was decreased ($p=0.03$). Compared to controls, arterial wall thickness was increased in TO ($p=0.013$) and medial wall thickness was increased in CDH and TO fetuses ($p<0.001$). Immunohistochemistry revealed increased expression of ki-67 in CDH and TO compared to controls ($p<0.001$).

Conclusions

TO reversed pulmonary hypoplasia through increased LBWR and decreased MTBD. Increased cellular proliferation, as shown by increased ki-67, is observed following TO and may underly key changes observed in miRNA and mRNA expression. Vascular changes documented in CDH were unchanged following tracheal occlusion.

Longitudinal Analysis of Pulmonary Function in Survivors of Congenital Diaphragmatic Hernia

Abstract 83

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Background:

There is limited information on the natural history of lung function in survivors of congenital diaphragmatic hernia (CDH). In this study, we analyzed the longitudinal trends of pulmonary function test (PFT) in CDH patients followed in our multidisciplinary clinic.

Methods:

This is a retrospective cohort study of CDH patients born between 1991 and 2013. A linear mixed effects model was fitted to estimate the trends of percent predicted forced expiratory volume in one second (FEV1pp), percent predicted forced vital capacity (FVCpp), and FEV1/FVC over time.

Results:

Of 268 CDH patients that survived to discharge, 119 had at least one PFT study. FEV1pp (P<0.001), FVCpp (P=0.017), and FEV1/FVC (P=0.001) declined with age. Compared to defect size A/B, those with defect size C/D had lower FEV1pp by an average of 11.5% (95% CI: 2.9% – 20.1%; P=0.010). A history of oxygen utilization at initial hospital discharge also correlated with decreased FEV1pp by an average of 8.0% (95% CI: 1.2% – 15.0%; P=0.023).

Conclusion:

In a select cohort of CDH survivors, average pulmonary function declines with age relative to expected population normative values. Those with severe CDH represent a population at risk for worsening PFT measurements, who may benefit from recognition and monitoring for complications.

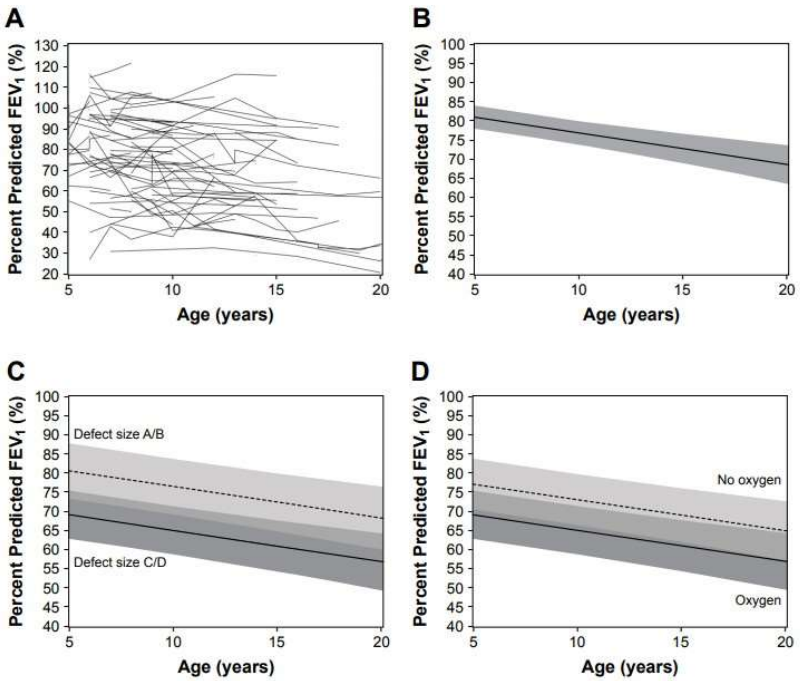

Figure 1. Trends of Percent Predicted Forced Expiratory Volume in 1 Second (FEV_1pp) over Time among Congenital Diaphragmatic Hernia (CDH) Survivors

Individual trends of FEV_1pp are displayed with Spaghetti plots (A). A linear mixed effects model was used to model the average trend of FEV_1pp of the entire cohort over time (B). Next, the average trends of FEV_1pp were stratified based on indicators of CDH severity, i.e. defect size (C) and oxygen requirement at discharge from the index hospitalization (D). Displayed are the regression lines and their associated 95% confidence interval (CI) bands.

Elevated proBNP levels are associated with disease severity, cardiac dysfunction, and mortality in CDH

Abstract 84

Vikas Gupta, United States - McGovern Medical School at UTHealth; Neil Patel, United Kingdom - Royal Hospital for Children Glasgow, Department of Neonatology; Pamela Lally, United States - McGovern Medical School at UTHealth; Kevin Lally, United States - McGovern Medical School at UTHealth; Matthew Harting, Matthew.T.Harting@uth.tmc.edu United States McGovern Medical School at UTHealth

Background:

Cardiac dysfunction is emerging as a key culprit in the morbidity and mortality of congenital diaphragmatic hernia (CDH). N-terminal pro b-type natriuretic peptide (pBNP), a hormone released secondary to ventricular stretch, is used as a prognosticator in heart failure and cardiomyopathy. We hypothesized that pBNP levels would be associated with cardiac dysfunction and high-risk disease in CDH.

Methods:

Patients in the CDH Study Group (CDHSG) from 2015-2019 with at least one pBNP value were included. Mean pBNP was used for patients with multiple values. Cardiac function was determined using echocardiograms from the first 72 hours of life. Statistical analyses were performed using Stata/IC16.

Results:

A total of 2,337 patients were identified, and 212 (9%) had at least one pBNP value, ranging from 2.5 to 142,207.5pg/mL. Of patients who had a pBNP measurement, 3 (1.5%) had CDHSG stage A defects, 58 (29.6%) B, 111 (56.6%) C, and 24 (12.2%) D. Patients with high-risk defects (Stage C/D) had higher pBNP compared with low-risk defects (Size A/B) (14281vs.5025, p=0.007). pBNP was significantly elevated in patients who died (median 14100, IQR 4377–22900 vs 4911, IQR 1883–9810) (p<0.001). Patients with cardiac dysfunction had higher pBNP than patients with normal cardiac function (8379vs.4778, p=0.005), but no pBNP value was highly sensitive and specific for cardiac dysfunction (AOC=0.61) (Figure).

Conclusion:

Among CDH patients, elevated pBNP was associated with high-risk defects, cardiac dysfunction, and mortality. Although additional study is needed to optimize measurement timing and frequency, pBNP shows promise as a prognosticator and biomarker in CDH-associated cardiac dysfunction.

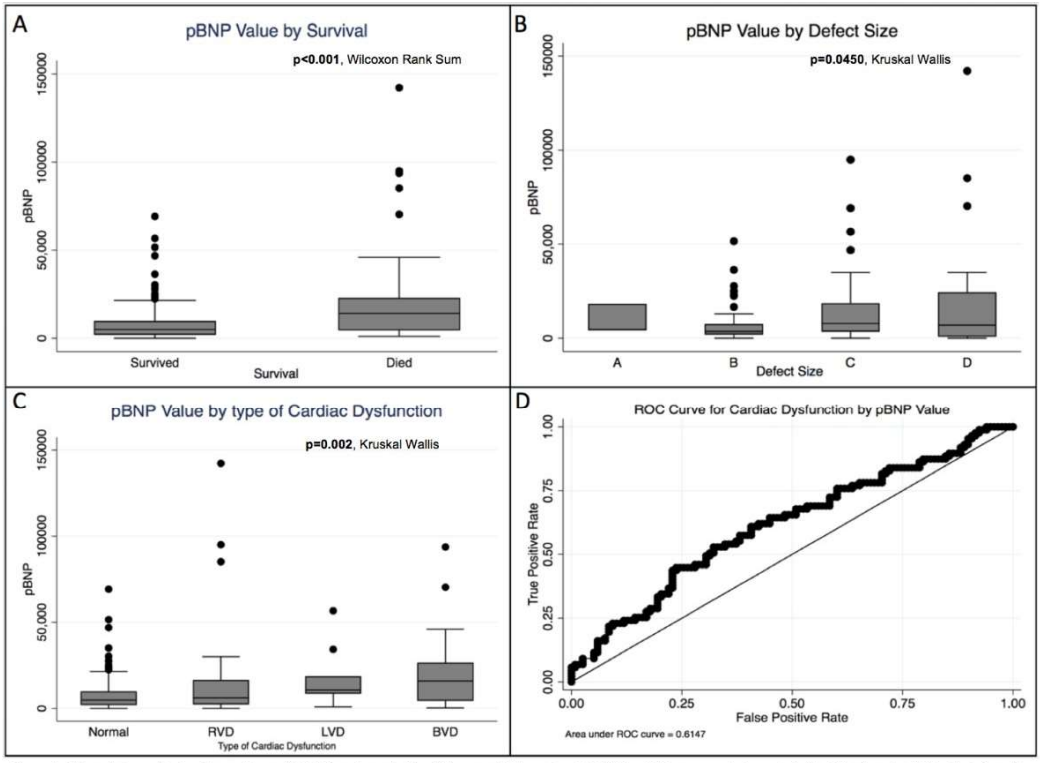

Figure 1: All boxplots are displayed as medians with IQR (grey boxes) with whiskers containing values ± 1.5*IQR; pBNPs are recorded as pg/mL A) pBNP values for CDH patients based on survival B) pBNP values for CDH patients based on CDHSG staging system C) pBNP values for CDH patients with cardiac dysfunction RVD = right ventricular dysfunction only, LVD = Left ventricular dysfunction only, BVD = Biventricular dysfunction D) ROC Curve for likelihood of cardiac dysfunction based on pBNP value

Perinatal hypoxia in congenital diaphragmatic hernia pulmonary parenchyma

Abstract 85

Vikas Gupta, United States - McGovern Medical School at UTHealth; Siqin Zhaorigetu, United States - McGovern Medical School at UTHealth; Di Jin, United States - McGovern Medical School at UTHealth; Nathan Berg, United States - McGovern Medical School at UTHealth; Holger Eltzschig, United States - McGovern Medical School at UTHealth; Kevin Lally, United States - McGovern Medical School at UTHealth; Matthew Harting, United States - McGovern Medical School at UTHealth

Purpose:

Congenital diaphragmatic hernia (CDH) is associated with hypoxia. Our objective was to characterize the degree of hypoxia and hypoxia-inducible factor (HIF) expression in nitrofen model CDH pups at birth.

Methods:

The standard rodent nitrofen model was used. Immediately following birth, Hypoxyprobe, a pimonidazole-HCl based hypoxia marker, was administered intraperitoneally to all pups. Control pups were maintained in an environment of normoxia (room air) or hypoxia (4% O2). CDH pups were maintained on room air. Left lungs were collected at 1 hour of life. The extent of parenchymal hypoxia was assessed by immunofluorescence staining. The relative expression of HIF-1α and HIF-2α were measured by western blotting. Comparative statistics were performed using GraphPad Prism.

Results:

CDH lung tissue showed more hypoxia at birth than both control groups. There was a 5x increase in Hypoxyprobe detection in 4% hypoxemic pups than in control pups ($p<0.01$); CDH pups had 20x more Hypoxyprobe expression than controls ($p<0.01$) (FIGURE). The relative expression of HIF-1α was 4-fold higher in CDH pups than controls ($p=0.005$). HIF-2α expression was also increased, with 2x greater expression in CDH lungs ($p=0.0012$).

Conclusions:

CDH pulmonary parenchyma shows profoundly increased levels of hypoxia compared to control lungs and lungs of pups exposed to 4% O2. Moreover, relative to controls, the expression of HIF-1α and HIF-2α were increased in CDH lung tissue, suggesting HIF stabilization. These data reveal significant early postnatal hypoxia-related alterations in pulmonary development and cell signaling in CDH.

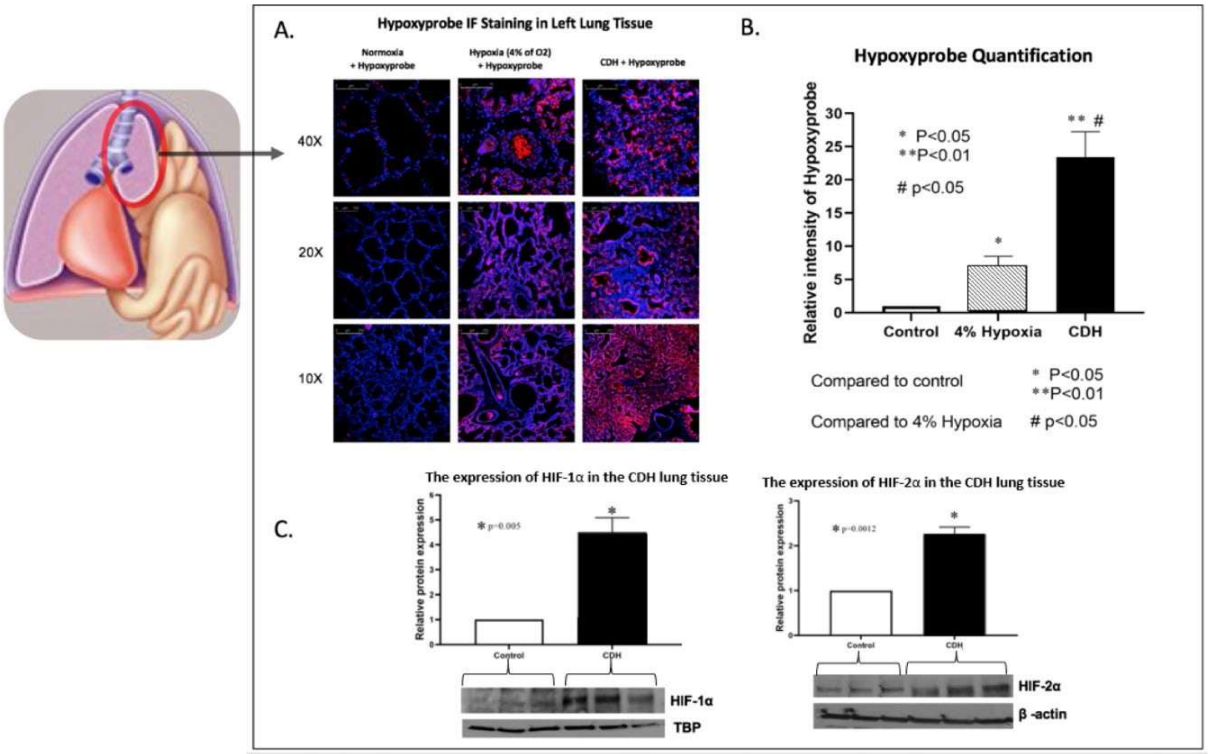

Figure 1: A) Magnified immunofluorescence staining of Hypoxyprobe in left lung tissue of control pups in room air, control pups in 4% O_2, and CDH pups in room air B) Bar graph showing significant differences in Hypoxyprobe intensity between groups C) Bar graphs and western blot images showing relative expressions of HIF-1α and HIF-2α in CDH versus control left lung tissue

Longitudinal Analysis of Ventilation Perfusion Mismatch in Congenital Diaphragmatic Hernia Survivors

Abstract 86

Duy Dao, United States - Harvard University; Lystra Hayden, United States - Harvard University; Terry Buchmiller, United States - Harvard University; Virginia Kharasch, United States - Franciscan Children's Hospital; Ali Kamran, United States - Harvard University; Charles Smithers, United States - Johns Hopkins All Children's Hospital; Samuel Rice-Townsend, United States - Harvard University; Jill Zalieckas, United States - Harvard University; Ronald Becker, United States - Harvard University; Donna Morash, United States - Harvard University; Mollie Studley, United States - Harvard University; Jay Wilson, United States - McGovern Medical School at UTHealth and Children's Memorial Hermann Hospital; Catherine Sheils, United States - Harvard University

Objective:

For survivors of congenital diaphragmatic hernia (CDH), it is important to understand the natural history of their pulmonary function. We performed a longitudinal analysis of pulmonary ventilation (V), perfusion (Q), and V/Q mismatch in CDH survivors followed at our institution.

Study Design:

This is a retrospective cohort study of CDH survivors born during 1991-2016. A generalized linear model (GLM) was fitted to assess the longitudinal trends of V, Q, and V/Q. The association between V/Q ratio and body mass index (BMI) percentile as well as functional status was also assessed with a GLM model.

Results:

During the study period, 212 patients had at least one V/Q study. The average ipsilateral V/Q of the cohort increased over time ($P<0.01$), an effect driven by progressive reduction in relative perfusion ($P=0.012$). A higher V/Q ratio was correlated with lower BMI percentile ($P<0.001$) and higher probability of poor functional status (NYHA class III or IV) ($P=0.045$).

Conclusion:

In this cohort of CDH survivors with more severe disease characteristics, V/Q mismatch worsens over time, primarily due to progressive perfusion deficit of the ipsilateral side. V/Q scans may be useful in identifying CDH patients who are at risk for poor growth and functional status.

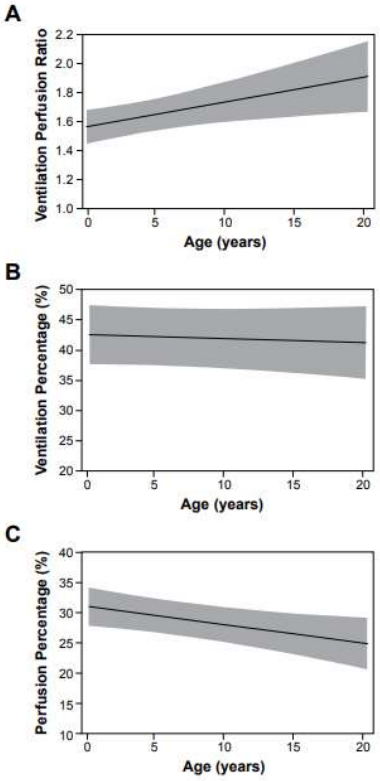

Figure 1. Trends of ventilation/perfusion (V/Q) mismatch.

Longitudinal estimate of the average ipsilateral V/Q ratio (panel A), ventilation (V) percentage (panel B), and perfusion (Q) percentage (panel C) over time was performed with a generalized linear model (GLM). Displayed are the regression lines and 95% confidence bands.

Congenital diaphragmatic hernia in southern South America: stratified outcomes in two high volume, ECMO centers.
Abstract 87

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Introduction:
Neonatal care has improved the survival of Congenital Diaphragmatic Hernia (CDH) patients. This assertion is predominantly supported by data available from European or North American centers. Since 2013, two ECMO centers from different countries of southern South America (SSA) report their results to the Congenital Diaphragmatic Hernia Study Group (CDHSG).

Objectives:
To describe and evaluate the mortality of CDH patients in SSA centers, stratified by an early mortality risk score.

Methods:
All the data filled-in prospectively between 2013 and 2018, from two SSA centers, were analyzed retrospectively. Demographic characteristics of our series were compared, with those reported by the CDHSG. Mortality was reported, according to the early mortality risk stratification proposed by Brindle et al.

Results:
A total of 345 patients were included. Overall survival at discharge was 73%, with a global ECMO rate of 30%. Eighty-four percent of our patients were repaired and 47% of these required a patch. When comparing the main variables of our population, with those reported by the CDH SG, there were only significant differences in the prenatal diagnosis rate (CDH SG:70%; SSA:77%) and the incidence of C/D defects (CDHSG: 38%; SSA: 49%). After applying the Brindle score, the survival rates for low, medium and high-risk groups were of 88%, 73%, and 52% respectively.

Conclusion:
The CDH population in SSA is similar to the CDHSG reporting centers. Our results support the risk stratification suggested by Brindle. The implementation of ECMO programs in our region has centralized and professionalized the management of CDH patients, with good survival outcomes.

	Southern South America Centers (n=345)	CDH SG (n=5671)	P-score
Prenatal Diagnosis	265 (77)	3957 (70)	<0,001
Inborn	183 (53)	2980 (53)	NS
Male	197 (57)	3308 (58)	NS
Mortality	93 (27)	1647 (29)	NS
Right Sided	50 (15)	917 (16)	NS
Repaired	290 (84)	4726 (83)	NS
CD Defect	143 (49)	1579 (38)	<0,05
Patch in repaired	134 (47)	1949 (45%)	NS
ECMO	104 (30)	1646 (30)	NS
Birth weight, mean	3022	2940	
EGA, mean	37,6	37,5	

Table 1. Demographic characterstics from SSA centers and CDHSG reporting centers.

Early Left Ventricular Dysfunction and Severe Pulmonary Hypertension Predict Adverse Outcomes in "Low-Risk" Congenital Diaphragmatic Hernia

Abstract 88

Duy Dao, United States - Harvard University; Neil Patel, United Kingdom - Royal Hospital for Children, Glasgow; Matthew Harting, United States - McGovern Medical School at UTHealth and Children's Memorial Hermann Hospital; Kevin Lally, United States - McGovern Medical School at UTHealth and Children's Memorial Hermann Hospital; Pamela Lally, United States - McGovern Medical School at UTHealth and Children's Memorial Hermann Hospital; Terry Buchmiller, United States - Harvard University

Background:

Given significant focus on improving survival for "high-risk" congenital diaphragmatic hernia (CDH), there is the potential to overlook the need to identify risk factors for suboptimal outcomes in "low-risk" cases, or CDH study group (CDHSG) defect size A and B. Since pulmonary hypoplasia is less severe and structural cardiac defects are uncommon in this population, we hypothesized that early cardiac dysfunction or pulmonary hypertension would be predictors of adverse outcomes in "low-risk" CDH.

Methods:

This study included CDHSG registry patients born between January 2015-December 2018. Infants with CDHSG defect size A and B without structural cardiac and chromosomal anomalies were included. Primary risk factors included left ventricular dysfunction (LVD), right ventricular dysfunction (RVD), and severe pulmonary hypertension (PH) diagnosed on the first post-natal echocardiogram. The primary outcome was composite adverse events, defined as death, use of extracorporeal membrane oxygenation (ECMO), oxygen requirement on day 30 of life, or hospitalization ≥ 8 weeks. Multivariable adjustment was performed with regression, propensity score, and inverse probability weighting.

Results:

778 patients were studied with an overall survival of 97.0%. LVD, RVD, and severe PH were present in 10.8%, 20.5%, and 57.5% of the study population. The primary adverse outcomes occurred in 21.3%. On unadjusted analysis, all 3 risk factors were highly associated with composite adverse outcomes. On all 3 methods of multivariable adjustment, only LVD and severe PH remained significant predictors of adverse outcomes.

Conclusion:

Left ventricular dysfunction and severe pulmonary hypertension diagnosed on early post-natal echocardiograms are independent predictors of adverse outcomes among "low-risk" CDH infants.

Table 1. Determination of the Effect of Each Exposure on Outcomes with Three Different Statistical Methods. The adjusted effect of left ventricular dysfunction (LVD), right ventricular dysfunction (RVD), and severe pulmonary hypertension (PH) on both primary and secondary outcomes was determined with three different statistical approaches: multivariable logistic regression, propensity score, and inverse probability weight. Shown are odds ratios (OR), their 95% confidence interval, and *P* values. ECMO: extracorporeal membrane oxygenation.

Exposure	Unadjusted Analysis			Multivariable Regression			Propensity Score			Inverse Probability Weight		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
LVD												
Composite Outcome	5.06	(3.05, 8.38)	< 0.001	2.31	(1.18, 4.52)	0.01	2.29	(1.22, 4.33)	0.01	2.26	(1.08, 4.74)	0.03
Death	3.60	(1.23, 10.54)	0.03	--	--	--	0.80	(0.19, 3.44)	0.77	0.61	(0.15, 2.40)	0.48
ECMO Utilization	5.06	(3.05, 8.38)	< 0.001	--	--	--	2.67	(1.26, 5.65)	0.01	2.74	(1.15, 6.52)	0.02
RVD												
Composite Outcome	3.68	(2.44, 5.54)	< 0.001	1.68	(0.97, 2.90)	0.06	1.68	(0.99, 2.84)	0.05	1.32	(0.78, 2.24)	0.31
Death	3.65	(1.45, 9.17)	0.007	--	--	--	2.98	(0.80, 11.10)	0.10	2.50	(0.77, 8.13)	0.13
ECMO Utilization	3.68	(2.44, 5.54)	< 0.001	--	--	--	1.89	(0.94, 3.80)	0.08	1.59	(0.79, 3.19)	0.19
Severe PH												
Composite Outcome	6.03	(3.69, 9.84)	< 0.001	4.68	(2.58, 8.48)	< 0.001	4.39	(2.42, 7.97)	< 0.001	3.92	(1.95, 7.87)	< 0.001
Death	12.24	(1.61, 92.85)	0.002	--	--	--	5.18	(0.62, 43.05)	0.13	9.08	(1.16, 70.83)	0.04
ECMO Utilization	6.03	(3.69, 9.84)	< 0.001	--	--	--	5.41	(1.86, 15.75)	0.002	4.86	(1.25, 18.90)	0.02

Centrifugal Pumps Are the Strongest Predictor of Hemolysis During ECLS for CDH

Abstract 90

Yigit Guner, United States - CHOC/UC Irvine; Matthew Harting, United States - UT Houston; Tim Jancelewicz, United States - Le Bonheur Children's Hospital, University of Tennessee Health Science Center

Purpose:

Neonates requiring ECLS for CDH have longer runs compared to neonates with other forms of respiratory failure. Hemolysis is a complication that can be seen during ECLS and can lead to renal failure and potentially to worse outcomes. Purpose of this study was first to identify if hemolysis is a risk factor for mortality and second identify risk factors for the development of hemolysis.

Methods:

The Extracorporeal Life Support Organization (ELSO) database was used to identify infants with CDH (2000-2015). The outcomes were mortality and hemolysis (plasma free hemoglobin >50). We used descriptive statistics and nested multivariable logistic regression models to test the study questions.

Results:

There were 4576 infants with an overall mortality of 52.5%. Rate of hemolysis was 10.5%. Incidence of hemolysis did not change during the study period. Mortality rate in the group of infants with hemolysis was 67% compared to 50.8% non-hemolysis group ($p<0.005$). After adjusting for duration of ECMO and markers for initial severity of illness, hemolysis was still a risk factor for mortality (OR 1.52 95% CI 1.2-1.94). The fully adjusted model of risk factors for development of hemolysis are shown in Table. The use of centrifugal pumps had the greatest effect on odds of hemolysis and additional factors included small arterial or venovenus cannulas, and high pump flow at 24h.

Conclusion:

Development of hemolysis is a risk factor for mortality in infants with CDH requiring ECLS. Clinical management of identified risk factors for the development of hemolysis may decrease its incidence, and potentially improve outcomes.

Logistic regression

Hemolysis	OR	[95% Conf	Interval]	Sig
Centrifugal pump	7.962	6.218	10.195	***
Birthweight	1.087	0.873	1.354	
HFOV	1.653	1.220	2.239	***
pH	1.038	0.518	2.081	
Dobutamine	0.696	0.437	1.108	
Norepinephrine	0.300	0.142	0.634	***
Arterial Cannula≤8F	0.738	0.565	0.963	**
VV Cannula ≤12F	0.973	0.656	1.443	
Pump Flow at 24h	0.067	0.017	0.262	***
Cardiac complications	1.783	1.363	2.332	***
Metabolic complications	2.351	1.824	3.029	***
Renal complications	2.222	1.738	2.841	***
Days of ECMO	1.029	1.014	1.044	***

*** $p<0.01$, ** $p<0.05$, * $p<0.1$

Completing the physiological approach to Congenitak Diaphragmatic Hernia

Abstract 94

Stephen Keeley, Australia - Women's and Children's Hospital

Abstract:

In 2002 Wung and colleagues published an influential case series in support of a now widely accepted hypothesis- attempting to achieve normal levels of alveolar ventilation in hypoplastic lungs is likely to be harmful. As a consequence restrictive application of ventilatory strategies, in effect deliberate hypoventiation,is almost universally applied.

We believe the same insight should be applied to circulatory management. Namely- that accompanying deliberate hypoventilation the pulmonsy circulation should be protected from exposure to the entire cardiac output until able to accept the flow required without excessive right heart strain.

Prostaglandin E1 (PGE1) use has been reported by a number of authors primarily as a rescue intervention in the face of the consequences of right heart failure. We now routinely use PGE1 to ensure ductal patency thereby limiting the exposure of the vulnerable pulmonary vasculature to the entire cardiac output. Pulmonary blood flow is thus determined by the relative circulatory resistances and is more likely to be proportional to the achievable ventilation. A more balanced relationship of ventilation to perfusion results. This can be assessed by pre-ductal saturations and endtidal CO2 measurement in the first instance. As pulmonary resistance improves with time pulmonary blood flow will increase accordingly. We report survival of 87% over a 16 year period using this approach.

Novel Decision Aids and Technology in Neonatal Resuscitation

Abstract 95

Natalie Rintoul, United States - Children's Hospital of Philadelphia; Holly Hedrick, United States - Children's Hospital of Philadelphia; Anne Ades, United States - Children's Hospital of Philadelphia

A Division of Neonatology, Department of Pediatrics, University of Pennsylvania Perelman School of Medicine and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania Department of Surgery and the Center for Fetal Diagnosis and Treatment, University of Pennsylvania Perelman School of Medicine and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Introduction:

Delivery room management can affect the outcomes of newborns. A paucity of literature exists dedicated to neonates with birth defects with regard to specific needs during resuscitation after delivery.

Objectives:

1. Discuss a new model of standardized critical knowledge in the delivery room
2. Discuss practice variability in neonatal resuscitations

Methods:

Literature review, national institutional survey and early experience with the Critical Knowledge prototype will be presented.

Results:

The neonatal resuscitations using this novel technology were more streamlined with less variability.

Conclusions:

Practice variation matters. Given that there is no clear evidence on the best practices, the care of infants with congenital anomalies in the delivery room is extremely variable between and within institutions and subject to "local practice style". We believe that consistent use of protocolized care will allow for analysis of the effects of specific medical therapies for this fragile set of infants with unique perinatal transitions.

Multiple breath washout measurement in patients with CDH at school age compared to Chest CT score and spirometry.

Abstract 97

Proesmans M, Vermeulen F, Boon M, Debeer A.

Purpose:

To present preliminary data on MBW-LCI results and correlation with other outcome measures (chest CT score, spirometry, exercise testing) in school age CDH patients.

Methods:

Prospective, clinical follow-up program of CDH survivors at the University Hospital Leuven. At school age (7-10 years), following tests are performed: nitrogen MBW measurement using an Exhalyzer D (EcoMedics, Duernten, Switzerland; Spiroware V.3.2 software), spirometry according to ATS/ERS guidelines, six minute walk test (Takken 2010) and shuttle run. An unenhanced low dose lung CT scan (Somatom Sensation 64, Siemens Medical Solutions, Ertangen, Germany) was performed at one year and at school age. CT images were anonymized to allow blinded scoring based on the revised Aukland score for chronic lung disease of prematurity (CLD).

Results:

Biometry, lung function data and exercise testing are represented in the table.

LCI was abnormal in 13/18 children. LCI correlates significantly with FEV1% (r= - 0.688, p=0.002) , FVC% (r= -0.469, p= 0.05) and CT score at age 1 ((Pearson r= 0.477, p=0.042). All patients with abnormal FEV1% (n=10) also had an abnormal LCI. Of the 8 patients with a normal FEV1%, 5 had an abnormal LCI. The 6 min walk test % did not correlate with lung function parameters. A significant correlation was found between the shuttle run level and the FEV1% (r=0.651, p=0.001) but not with the LCI.

Conclusion

In this small cohort, MBW-LCI is abnormal in the majority of patients and seems more sensitive to detect lung disease compared to FEV1%. Data needs to be confirmed in a larger patient group.

	valid n	median	min	max	P25	P75
age at visit (y)	22	8,3	7,1	9,6	7,8	8,7
height Z score	22	-0,55	-2,7	3,1	-1,38	0,3
weight Z score	22	-0,85	-3,8	1,8	-2,28	-0,5
BMI Z score	21	-0,9	-4,19	2,5	-2,35	-0,35
CT score age 1	21	15,7	3,7	32	9,1	24
LCI	22	8,1	6,6	13,4	7,3	9,1
FEV1% post SABA	18	77,5	46	127	70,5	90,5
FVC%	18	77	45	115	70,6	90,3
shuttle run level	18	1,75	1	6,5	1	2,75
6 min walk test % predicted	20	94,5	80	124	86,3	99,8

PHYSIOLOGICAL-BASED CORD CLAMPING FOR INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA: PinC TRIAL STUDY PROTOCOL

Abstract 98

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*Presenting author

Purpose:

This clinical trial aims to investigate whether implementation of physiological-based cord clamping (PBCC), i.e. lung aeration prior to cord clamping, reduces the occurrence of PPHN in infants with CDH.

Methods:

We will perform a multicentre, non-blinded, randomised controlled trial in neonates with isolated CDH. Patients will be randomised between immediate cord clamping (ICC) and PBCC, stratified by predicted lung size (antenatal ultrasound) and treatment centre. Inclusion criteria are isolated left-sided CDH and gestational age (GA) at delivery >35 weeks, in the absence of associated structural or genetic abnormalities diagnosed before birth. For performing PBCC a new purpose-designed resuscitation module, the Concord (Concord Neonatal B.V., Leiden, the Netherlands (Fig 1), will be used. After cord clamping further postnatal management will be according to consensus-based guidelines.

Results:

The primary outcome is PPHN diagnosed 12-24hrs after birth and assessed by transthoracic echocardiography. We consider a reduction of the occurrence of PPHN by one third as clinically significant. To detect such a difference and based on a background incidence of 69.7% (CDH registry, 2007-2014, 3367 patients), sample size was calculated of at least 130 infants (65 in each group) (power 80%, α=0.05). Secondary outcomes include neonatal (survival at discharge, ECMO use, number of ventilator days, NICU days) as well as maternal outcomes, specifically the occurrence of postpartum haemorrhage (estimated blood loss >1000mL).

Conclusion:

PBCC integrated in resuscitation/stabilisation of infants with CDH has the potential to improve outcomes and could lead to a significant change of practice in postnatal management of this challenging disease. *Figure 1: Concord table*

Reproducibility of fetal lung-to-head ratio in left diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)

ABSTRACT 99

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ABSTRACT

OBJECTIVE:
To determine the antenatal sonographic lung area measurement method in left congenital diaphragmatic hernia (CDH) with the highest inter-rater agreement amongst North American Fetal Therapy Network (NAFTNet) centers within and outside the fetoscopic tracheal occlusion (FETO) consortium and in comparison to a European "expert" reviewer (ER).

METHODS:
Nineteen members from 9 FETO consortium centers and 29 reviewers from 17 non-FETO centers reviewed ultrasound clips of the chest from 13 fetuses with isolated left CDH and were asked to select a static plane for lung area measurement using antero-posterior (AP), longest and trace methods. Inter-rater agreement in lung area measurements was determined using intra-class correlation coefficient (ICC). Bland-Altman analysis was used to evaluate mean difference (bias) between NAFTNet reviewers and ER.

RESULTS:
Among FETO centers, agreement was highest using trace (ICC 0.94; 95% CI 0.83, 0.98), followed by longest (ICC 0.89; 95% CI 0.75, 0.97) and lowest for A-P (ICC 0.83; 95% CI 0.67, 0.94). Similar trends were noted in non-FETO centers. When compared to ER, bias was lowest for trace: 14 ± 38 mm^2 and 19 ± 36 mm^2 for FETO and non-FETO centers respectively.

CONCLUSION:
Trace method demonstrated the highest inter-rater agreement and lowest bias across NAFTNet.

Inter-rater agreement for sonographic stomach position classification in fetal diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet)

ABSTRACT 100

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ABSTRACT

Objective:

To evaluate inter-rater agreement for sonographic classification of stomach position in fetal left congenital diaphragmatic hernia CDH among: (i) fetal medicine specialists from the North American Fetal Therapy Network (NAFTNet) centres within and outside the Fetal Endoscopic Tracheal Occlusion (FETO) consortium and in comparison to an expert external reviewer (ER1); and (iii) two expert ERs (ER1 and ER2).

Methods:

Forty-eight physicians from 26 NAFTNet centers and 2 ERs were asked to assess 13 sonographic clips to locate stomach position in fetal thorax views from fetuses with isolated left CDH. They were asked to classify it as intra-abdominal, anterior left chest, mid to posterior left chest or retrocardiac. Responses of each NAFTNet participant was matched with response of ER1. Agreement for stomach position was also calculated using kappa statistics between ER1 and ER2.

Results:

Median accuracy for stomach position assessment was 69 % (39-85%; n=19) and 54% (23-92%; n=29) for FETO and non-FETO NAFTNet participants respectively and varied significantly within the latter group. Most errors in stomach position were related to a discrepancy of one position between NAFTNet participants and ER1. ERs were in agreement for stomach position in 5/13 cases (38.5%) and inter-rater agreement was highest for anterior chest position, $p = 0.01$) with no agreement for remaining positions.

Conclusion:

Inter-rater agreement for stomach position assessment as a marker for liver herniation in CDH was found to be poor for NAFTNet participants and between ERs. Future initiatives should be directed toward refinement of the stomach position classification system and training prior to implementation.

Variability in antenatal prognostication of diaphragmatic hernia across the North American Fetal Therapy Network
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ABSTRACT

OBJECTIVE

To evaluate variability in antenatal sonographic prognostication of congenital diaphragmatic hernia (CDH) within the North American Fetal Therapy Network (NAFTNet).

METHODS

NAFTNet centres were invited to complete a questionnaire and participate in videoconference calls, during which participants were observed while measuring lung area using the anteroposterior (AP), longest and trace method. Each centre identified 1-2 experienced fetal medicine or medical imaging specialists locally. Practices were compared among NAFTNet centres within and without the fetal endoscopic tracheal occlusion (FETO) consortium.

RESULTS

Nineteen participants from 9 FETO centres and 30 participants from 17 non-FETO centers completed the survey and 31 participants were observed. All centres measured observed-to-expected lung-to-head ratio (o/e LHR) or LHR for CDH prognostication. Image selection criteria for lung area measurement was consistent, including an axial section of the chest with clear lung borders and a 4-chamber cardiac view. Lung area measurement methods varied across NAFTNet, with most centers using longest (4/9 FETO vs. 13/29 non-FETO) or trace (3/9 FETO vs. 11/29 non-FETO). Centres differed in expected reference ranges for o/e LHR determination and whether the lowest, highest or average o/e LHR was used.

CONCLUSION

Variability in antenatal sonographic prognostication of CDH was identified across NAFTNet, indicating a need for consensus-based standardization.


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specialists
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