



# Sildenafil versus NO

In congenitale hernia diafragmatica

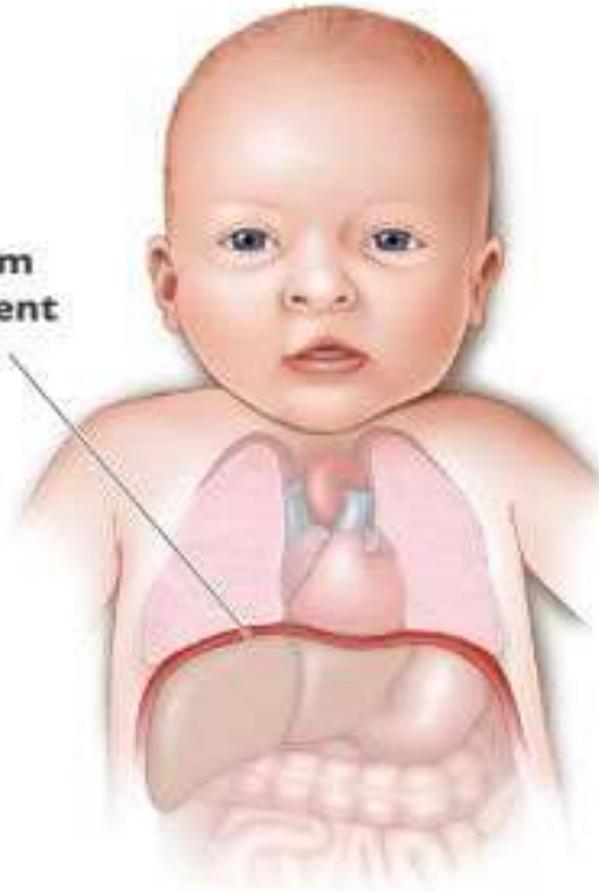
Suzan Cochijs – den Otter  
Hoofd IC Kinderen  
Erasmus MC Sophia  
Rotterdam





# Congenital diaphragmatic hernia

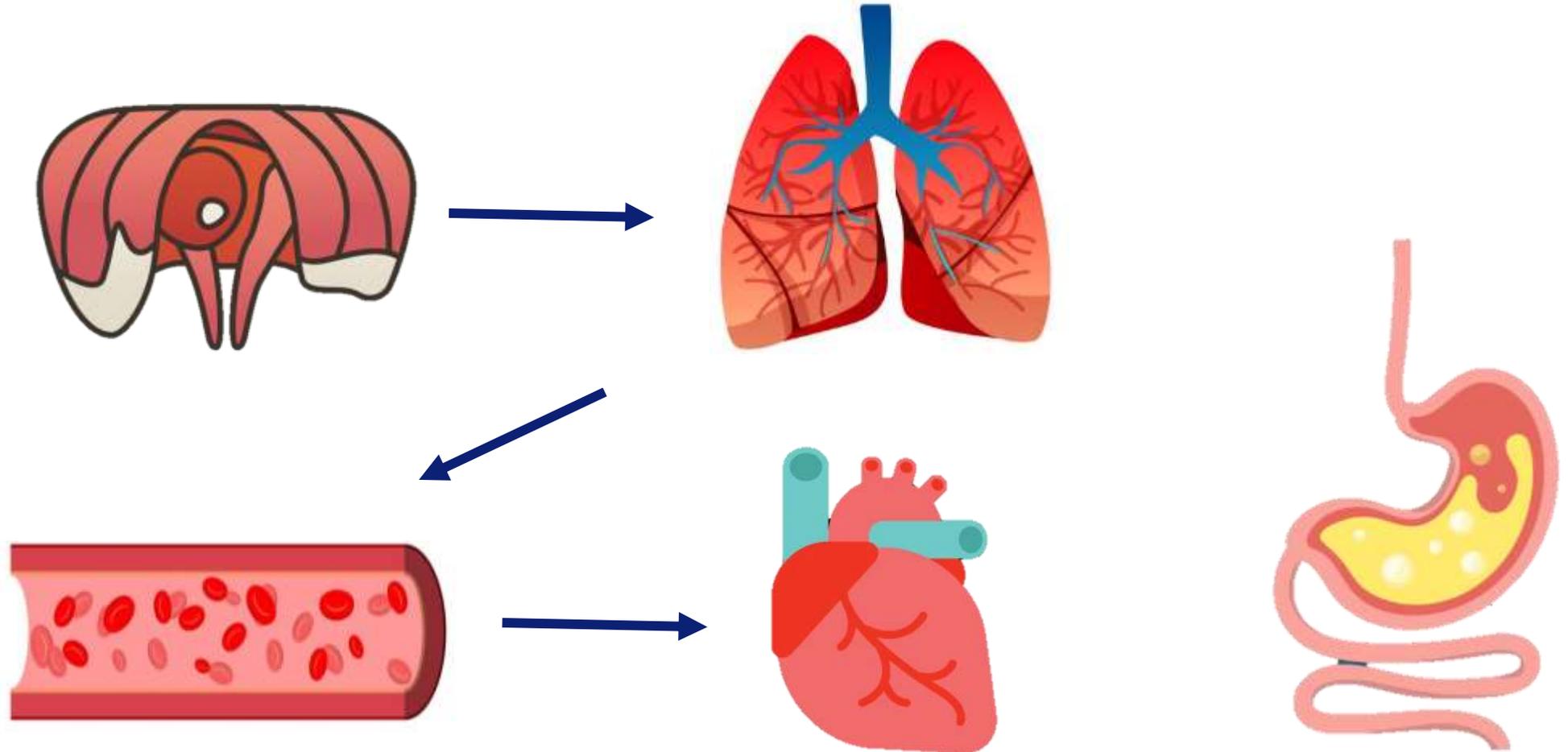
**Normal  
Diaphragm  
Development**



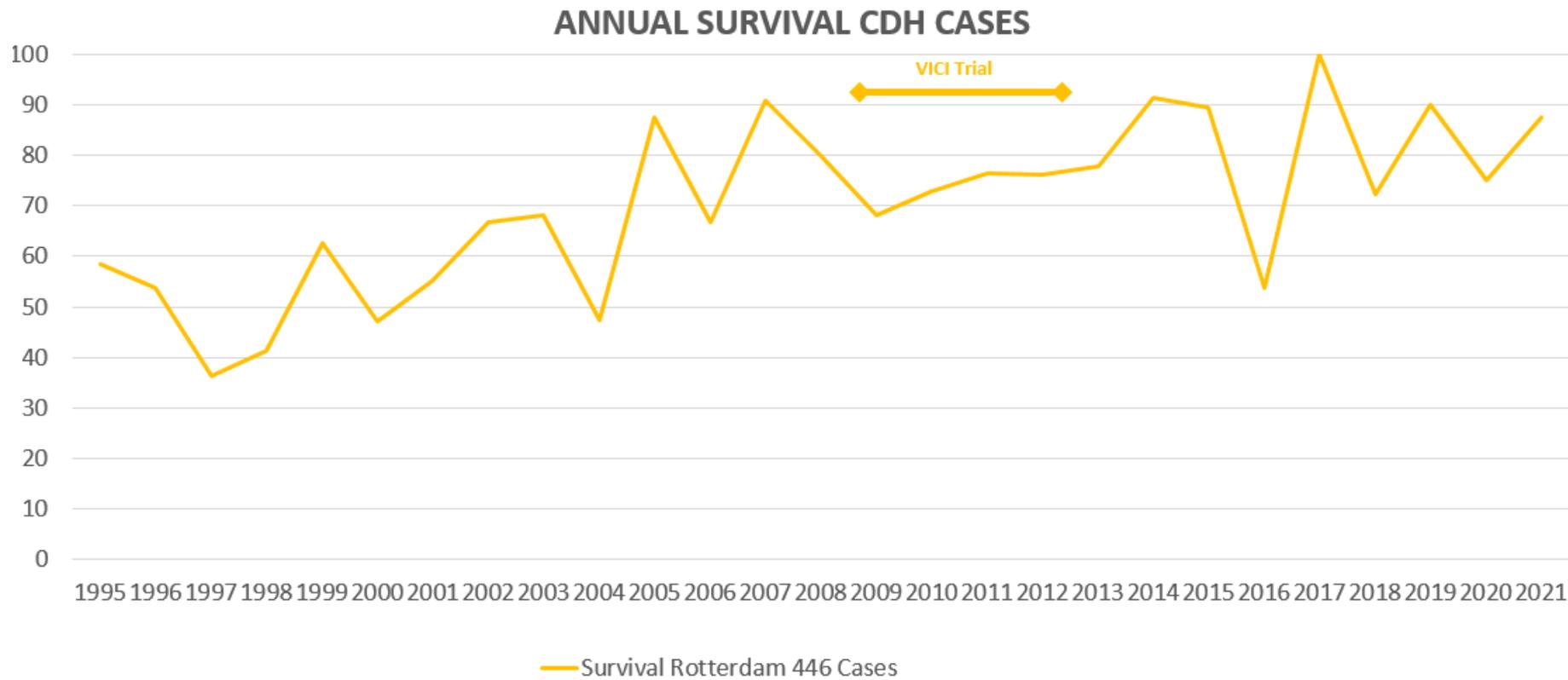
**Congenital  
Diaphragmatic  
Hernia**



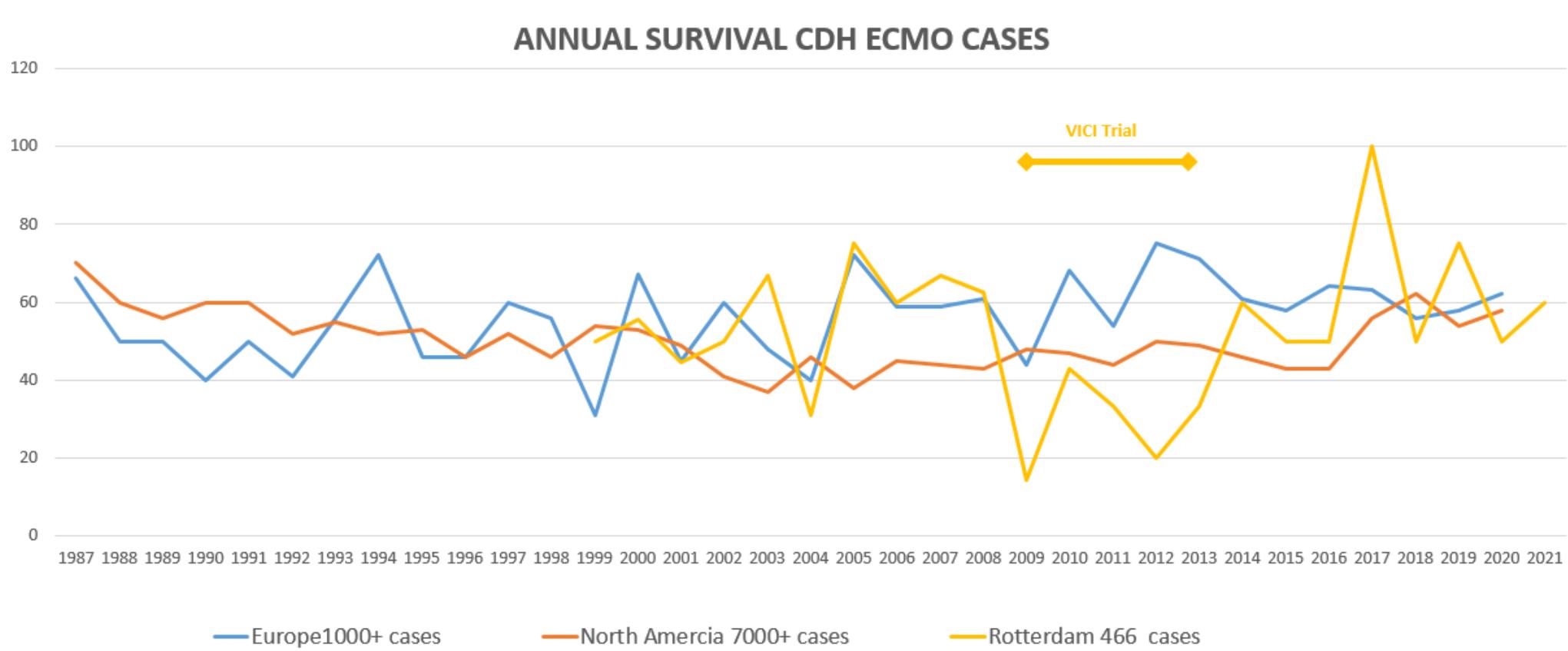
## Congenital diaphragmatic hernia

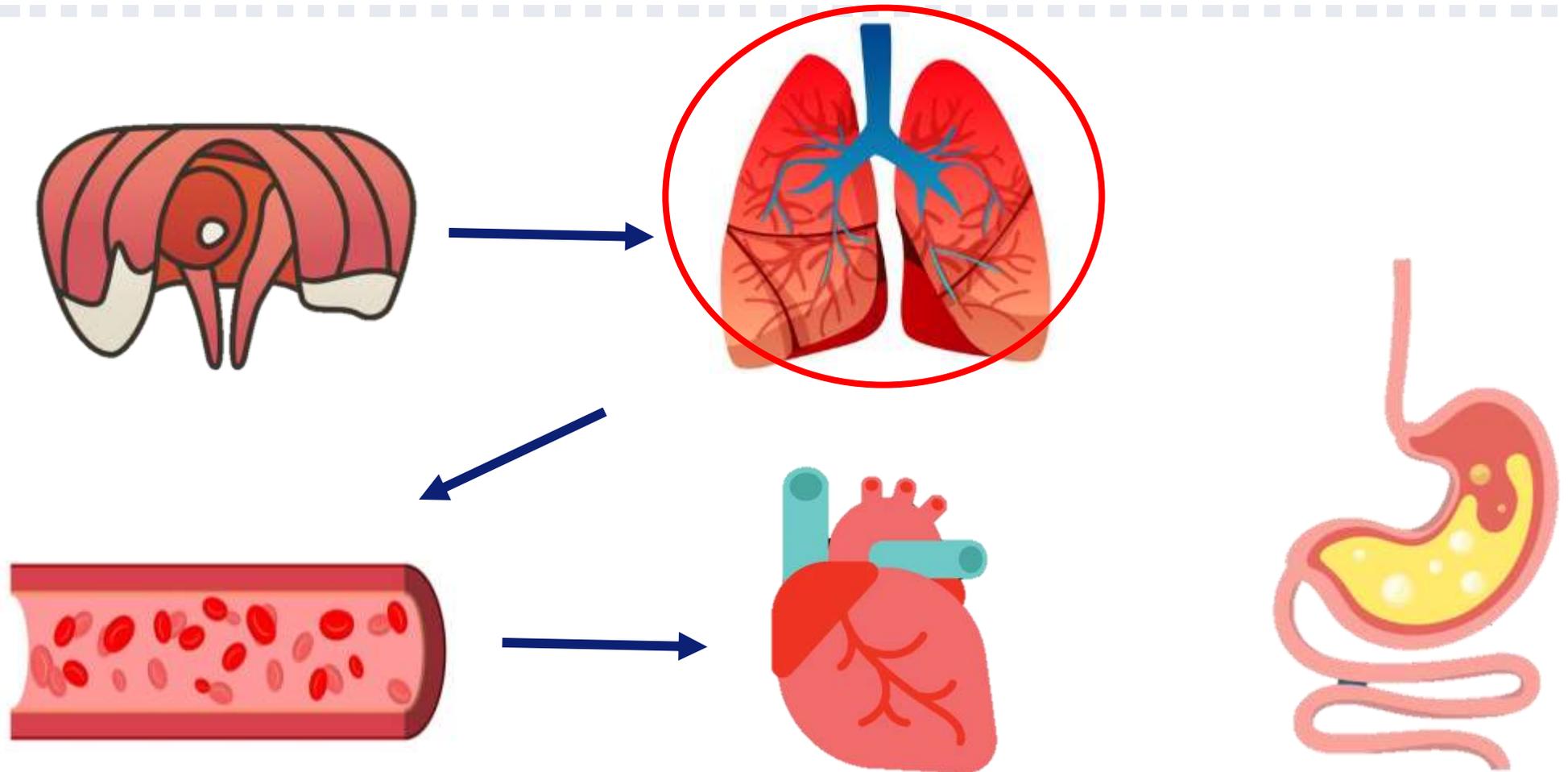


# Congenital diaphragmatic hernia



# Congenital diaphragmatic hernia en ECMO





## Congenital diaphragmatic hernia: longhypoplasie



# Congenital diaphragmatic hernia: longhypoplasie

## Neonatology

### Consensus Statement

Neonatology 2016;110:66–74  
DOI: 10.1159/000444210

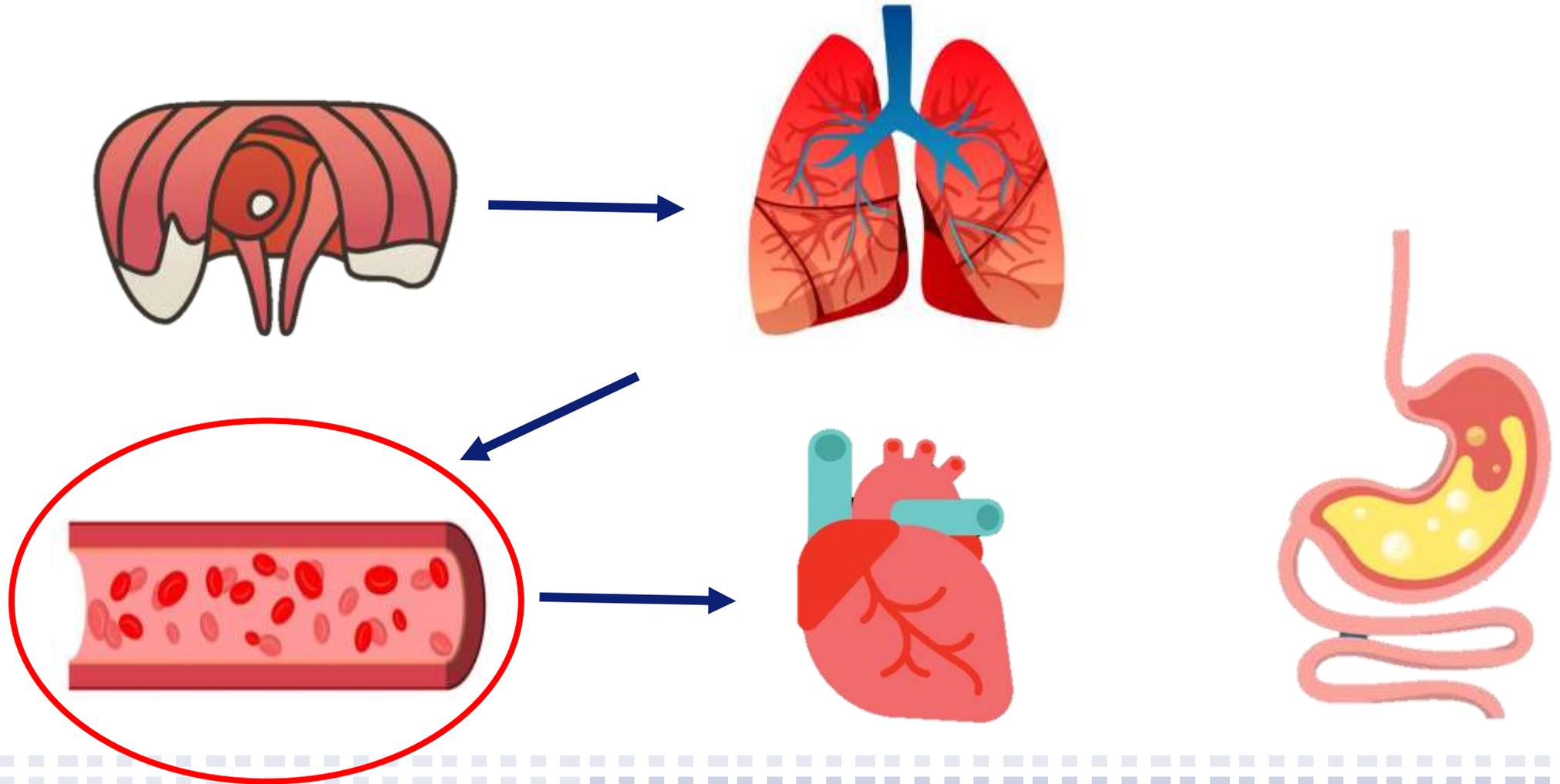
Received: December 3, 2015  
Accepted after revision: January 25, 2016  
Published online: April 15, 2016

## Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus – 2015 Update

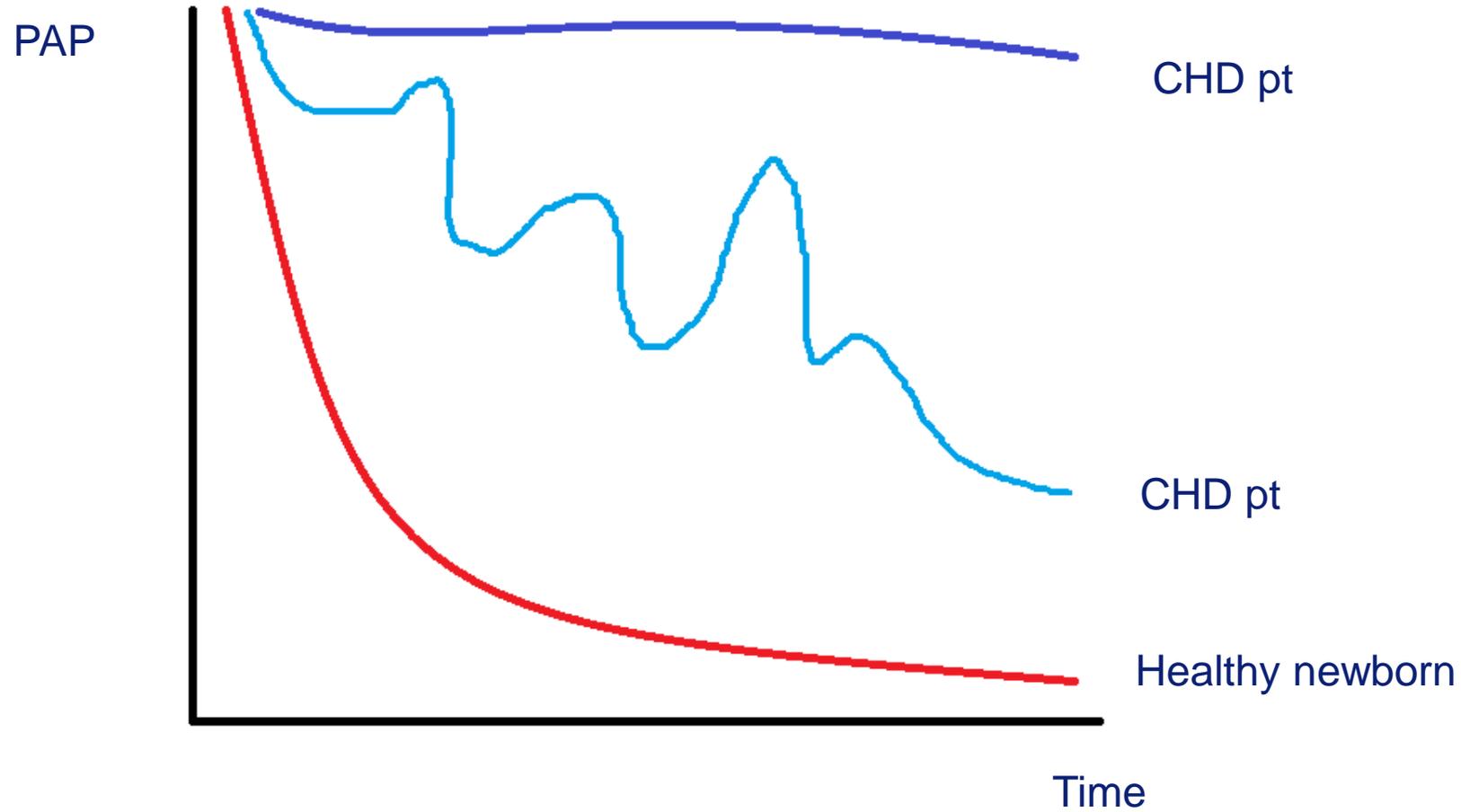
Kitty G. Snoek<sup>a</sup> Irwin K.M. Reiss<sup>a</sup> Anne Greenough<sup>c</sup> Irma Capolupo<sup>e</sup>  
Berndt Urlesberger<sup>f</sup> Lucas Wessel<sup>g</sup> Laurent Storme<sup>h</sup> Jan Deprest<sup>d,i</sup>  
Thomas Schaible<sup>g</sup> Arno van Heijst<sup>b</sup> Dick Tibboel<sup>a</sup> for the CDH EURO Consortium

<sup>a</sup>Erasmus MC – Sophia Children’s Hospital, University Medical Center Rotterdam, Rotterdam, and <sup>b</sup>Radboud University Medical Centre, Nijmegen, The Netherlands; <sup>c</sup>King’s College and <sup>d</sup>University College London Hospitals, London, UK; <sup>e</sup>Bambino Gesù Children’s Hospital, Rome, Italy; <sup>f</sup>Medical University Graz, Graz, Austria; <sup>g</sup>Universitätsklinikum Mannheim, Mannheim, Germany; <sup>h</sup>Hôpital Jeanne de Flandre, Lille, France; <sup>i</sup>University Hospital KU Leuven, Leuven, Belgium

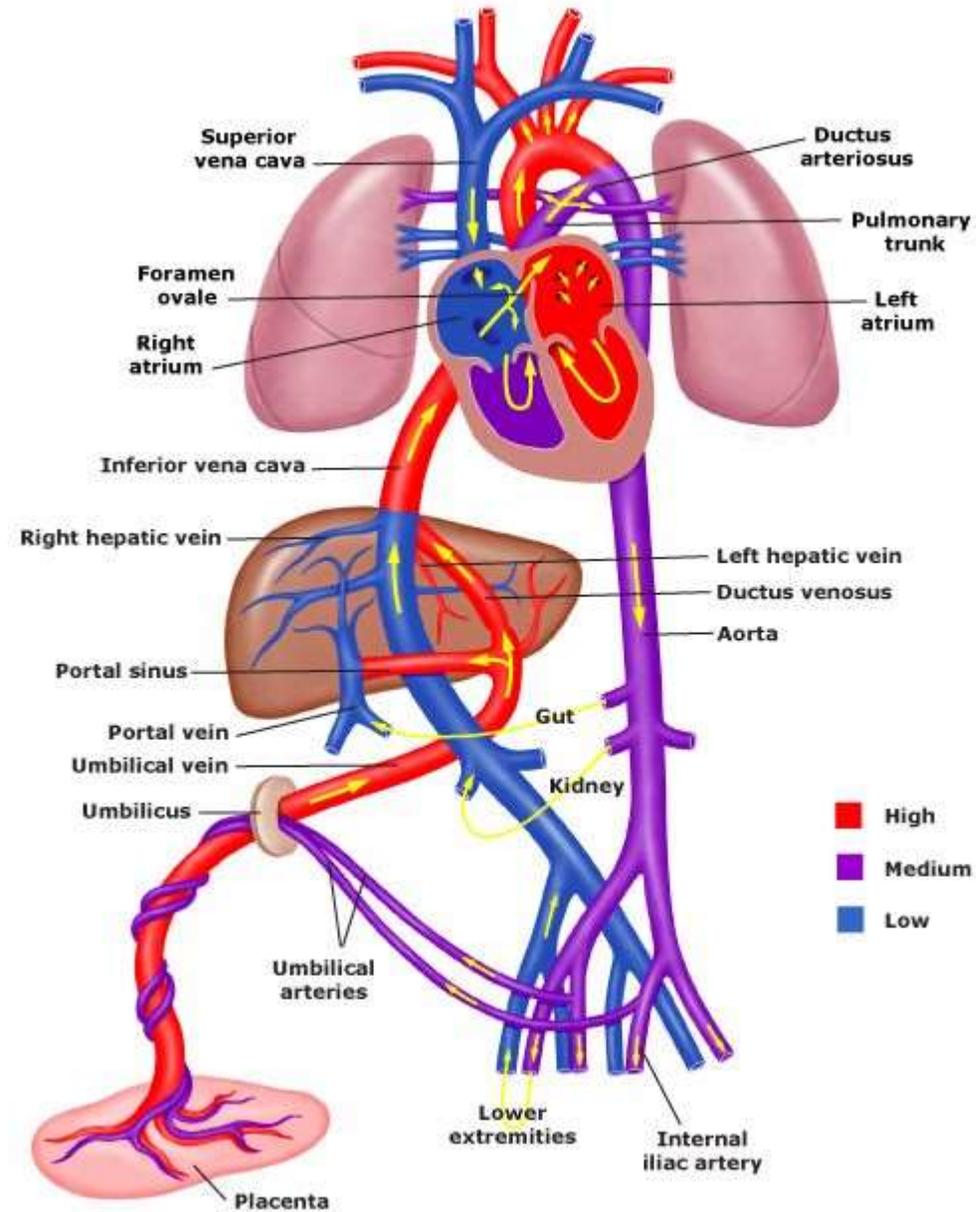
- Gentle ventilatie
  - Lage piek drukken
  - Accepteer lage TV en hoog pCO<sub>2</sub>



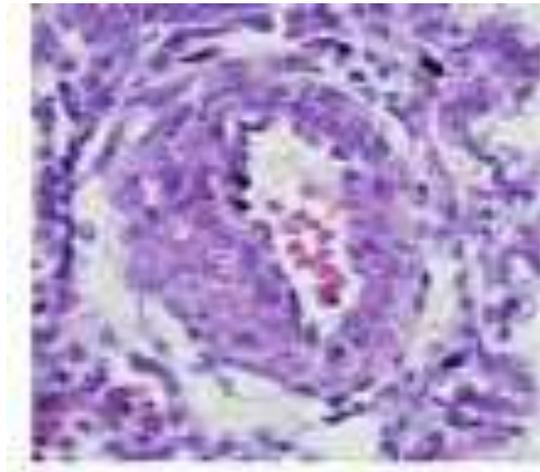
# Congenital diaphragmatic hernia: pulmonale hypertensie



# Fetal circulation



## Congenital diaphragmatic hernia: pulmonale hypertensie

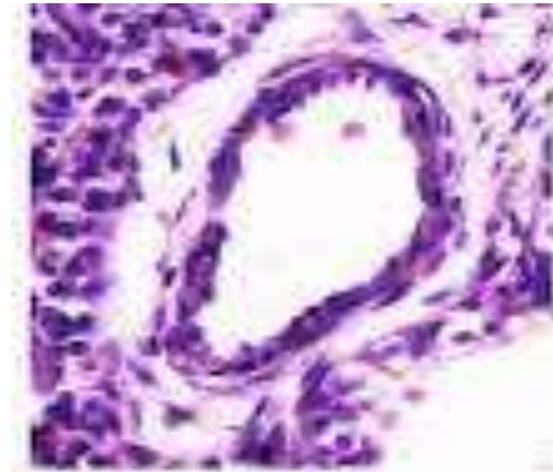


Longbloedvat in CDH

Tijd  
Stress reductie  
Medicatie

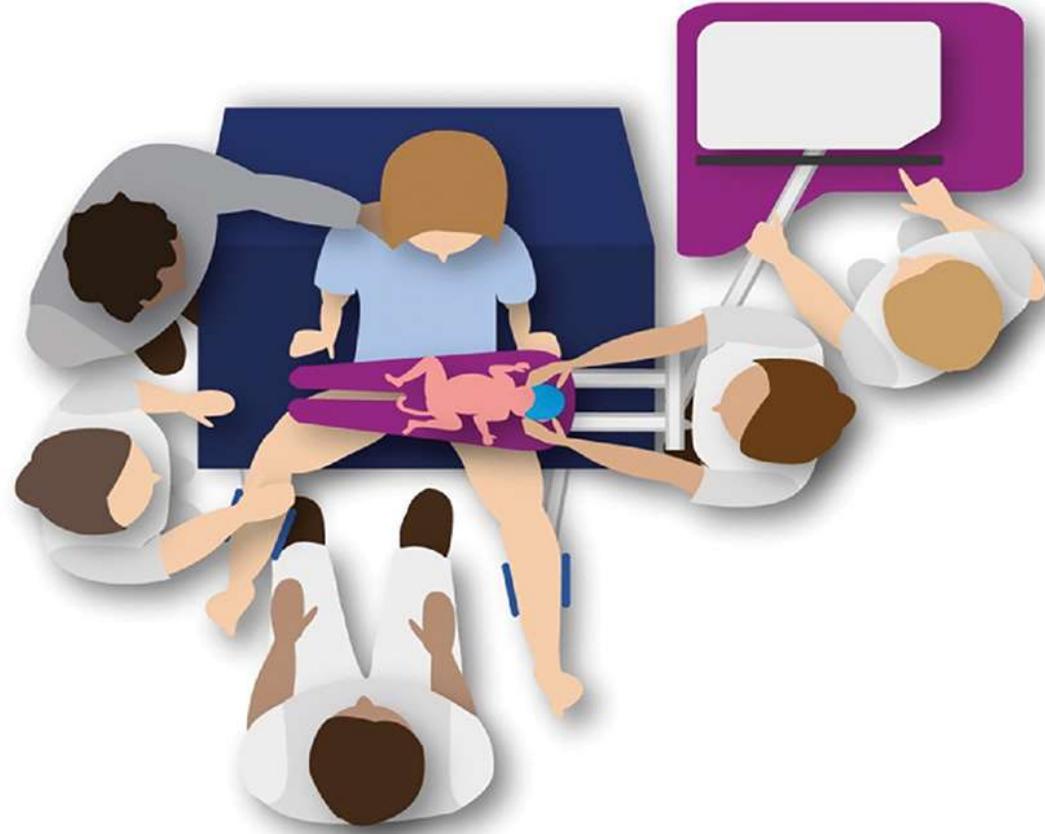


⚡ *Stress*  
⚡ *Infectie*  
*Chirurgie*  
*Acidose*  
*Hypoxie*

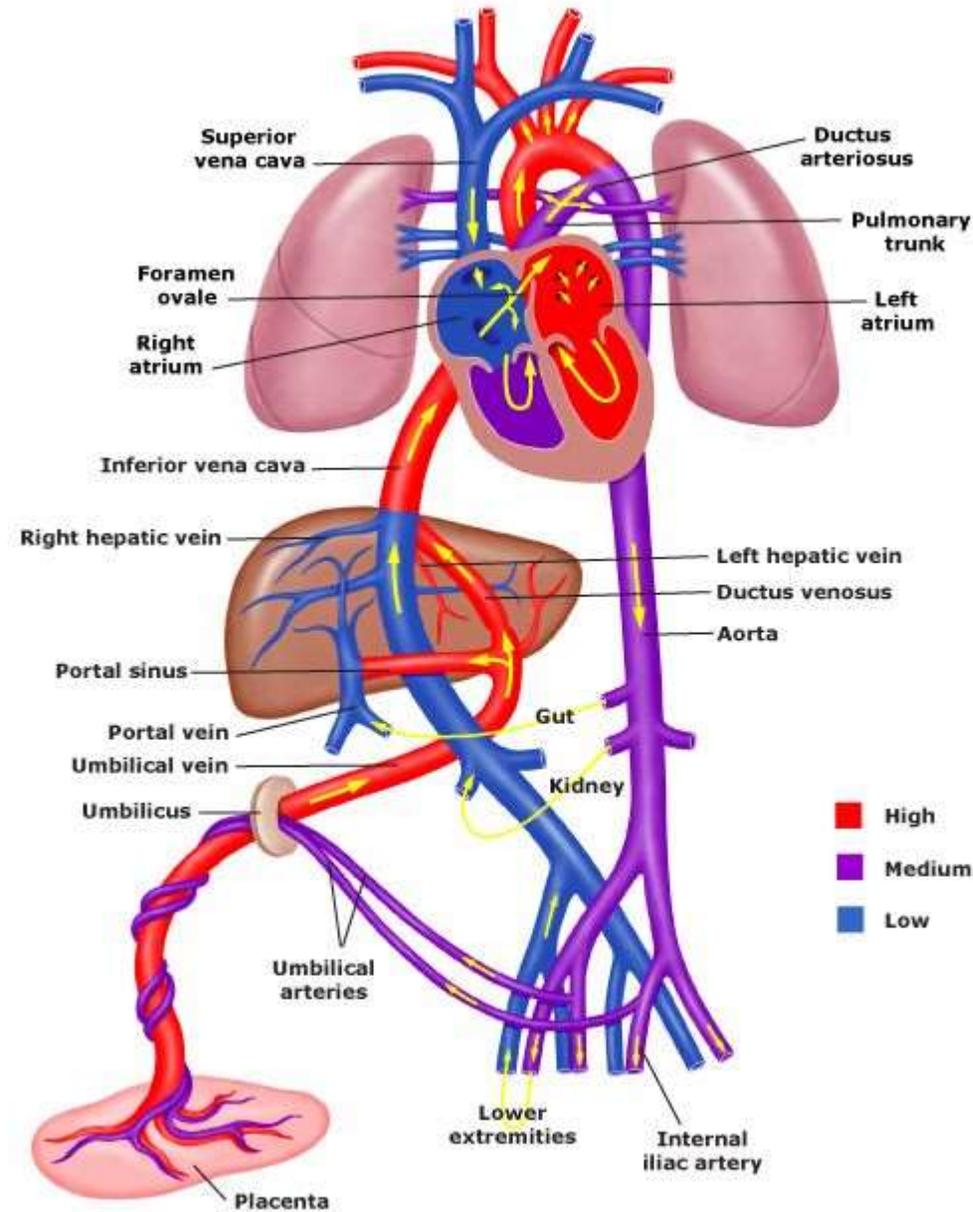


Normaal longbloedvat

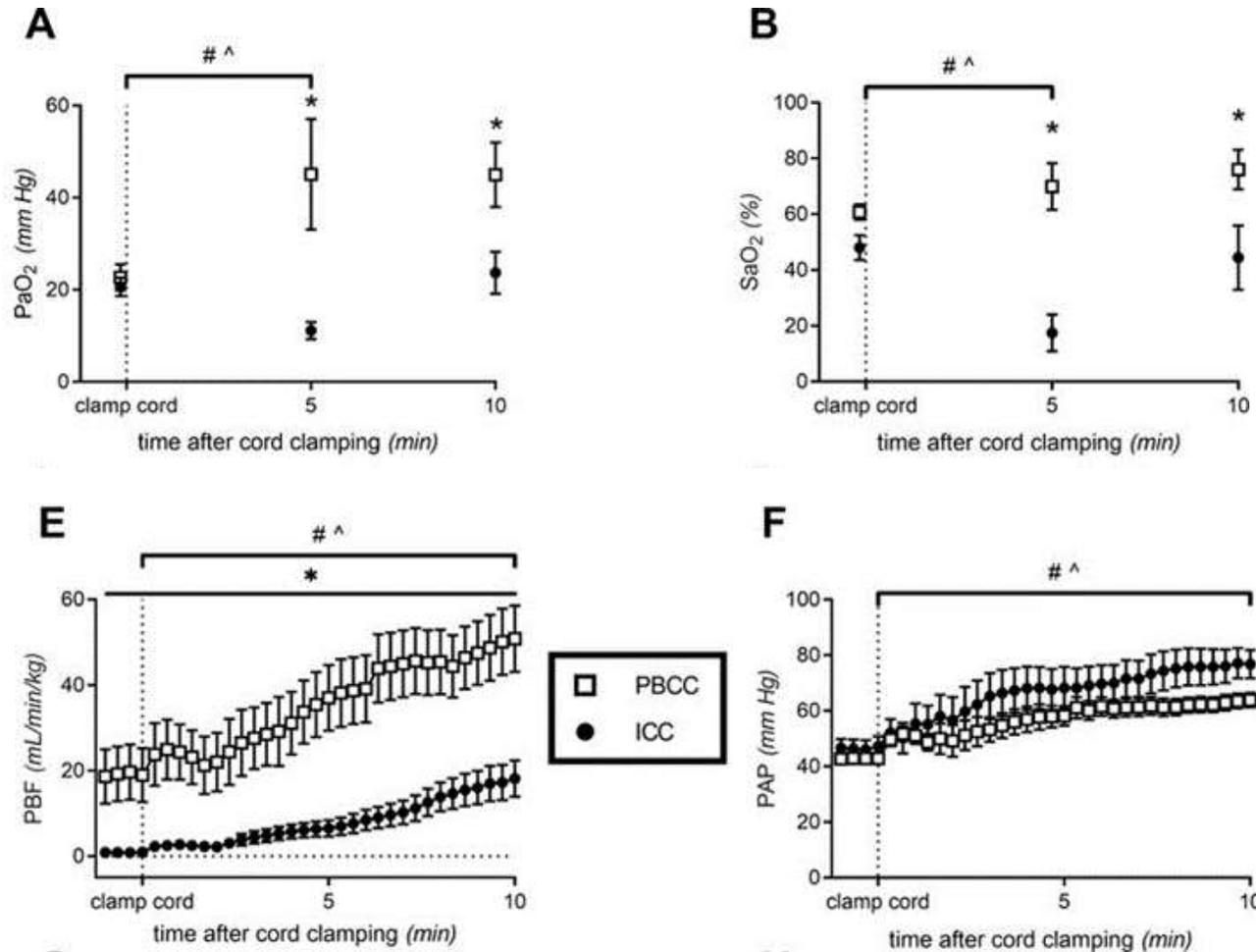
## Congenital diaphragmatic hernia: physiological based cord clamping



# PinC trial



# Physiological based cord clamping in ovine model with CDH



# Routine Intubation in Newborns With Congenital Diaphragmatic Hernia

Suzan C.M. Cochius-den Otter, MD,<sup>a</sup> Emily J.J. Horn-Oudshoorn, MD,<sup>b</sup> Karel Allegaert, MD, PhD,<sup>b,c</sup> Philip L.J. DeKoninck, MD, PhD,<sup>d</sup>  
Nina C.J. Peters, MD,<sup>d</sup> Titia E. Cohen-Overbeek, MD, PhD,<sup>d</sup> Irwin K.M. Reiss, MD, PhD,<sup>b</sup> Dick Tibboel, MD, PhD<sup>a</sup>

Isolated left sided CDH  
o/e LHR  $\geq 50$   
Liver down  
Birth >35 wks

Successfull in 6/15 (40%)

# Congenital diaphragmatic hernia: pulmonale hypertensie in ICU

- Stress reductie
  - Minimal handling
  - Sedatie en pijnstilling
  - Geen chirurgie tot PH afneemt
- Behandeling pulmonale hypertensie
  - Zuurstof
  - iNO / sildenafil / bosentan / iloprost

Neonatology

Consensus Statement

Neonatology 2016;110:66–74  
DOI: 10.1159/000444210

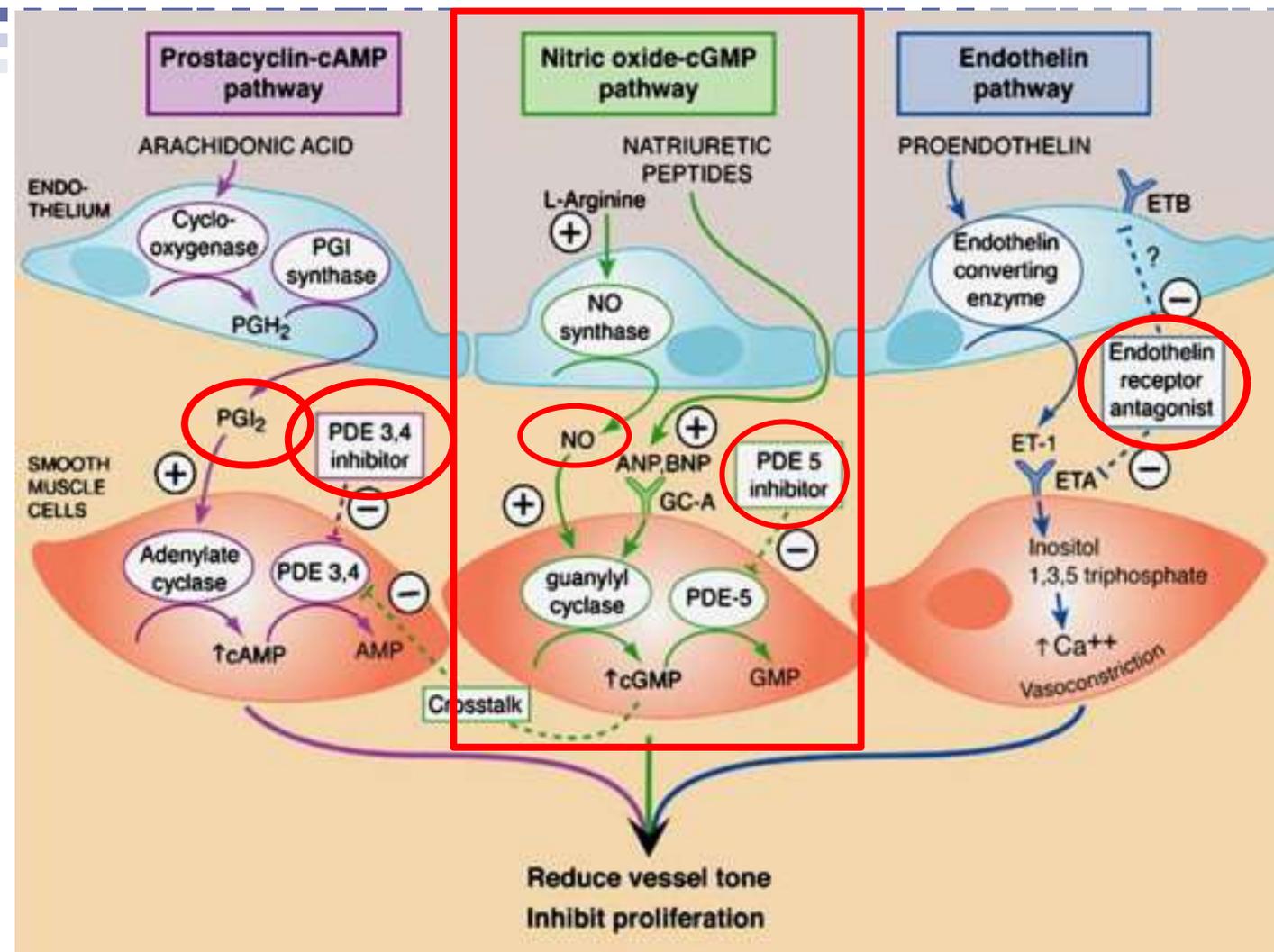
Received: December 3, 2015  
Accepted after revision: January 25, 2016  
Published online: April 15, 2016

## Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus – 2015 Update

Kitty G. Snoek<sup>a</sup> Irwin K.M. Reiss<sup>a</sup> Anne Greenough<sup>c</sup> Irma Capolupo<sup>e</sup>  
Berndt Urlsberger<sup>f</sup> Lucas Wessel<sup>g</sup> Laurent Storme<sup>h</sup> Jan Deprest<sup>d,i</sup>  
Thomas Schaible<sup>g</sup> Arno van Heijst<sup>b</sup> Dick Tibboel<sup>a</sup> for the CDH EURO Consortium

<sup>a</sup>Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, and <sup>b</sup>Radboud University Medical Centre, Nijmegen, The Netherlands; <sup>c</sup>King's College and <sup>d</sup>University College London Hospitals, London, UK; <sup>e</sup>Bambino Gesù Children's Hospital, Rome, Italy; <sup>f</sup>Medical University Graz, Graz, Austria; <sup>g</sup>Universitätsklinikum Mannheim, Mannheim, Germany; <sup>h</sup>Hôpital Jeanne de Flandre, Lille, France; <sup>i</sup>University Hospital KU Leuven, Leuven, Belgium

# Pathways of therapy in PH



---

# The New England Journal of Medicine

---

© Copyright, 1997, by the Massachusetts Medical Society

---

VOLUME 336

FEBRUARY 27, 1997

NUMBER 9



---

**INHALED NITRIC OXIDE IN FULL-TERM AND NEARLY FULL-TERM INFANTS  
WITH HYPOXIC RESPIRATORY FAILURE**

THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP\*

---

**TABLE 3. OUTCOMES OF ADMINISTRATION OF THE STUDY GAS, ACCORDING TO GROUP.\***

OUTCOME	CONTROL GROUP (N= 121)	NITRIC OXIDE GROUP (N= 114)	P VALUE
Death by day 120 or ECMO — no. (%)	77 (63.6)	52 (45.6)	0.006
Death — no. (%)	20 (16.5)	16 (14.0)	0.60
ECMO — no. (%)	66 (54.5)	44 (38.6)	0.014
Change in PaO <sub>2</sub> — mm Hg	9.7±51.7	58.2±85.2	<0.001
Change in oxygenation index	0.8±21.1	-14.1±21.1	<0.001
Change in alveolar-arterial oxygen gradient — mm Hg	-6.7±57.5	-60.0±85.1	<0.001
Outcomes in surviving infants			
Length of hospitalization — days	29.5±22.6	36.4±44.8	0.17
Duration of assisted ventilation — days	11.7±13.0	11.6±7.0	0.97
Air leak after randomization — no. (%)	5 (5.1)	5 (5.2)	0.96
Bronchopulmonary dysplasia — no. (%)†	12 (11.9)	15 (15.3)	0.48

\*Plus-minus values are means ±SD. ECMO denotes extracorporeal membrane oxygenation, and PaO<sub>2</sub> partial pressure of arterial oxygen.

†This condition was considered to be present when there was dependence on oxygen at the age of 28 days accompanied by abnormal results on chest radiography.



ELSEVIER

Journal

journal homepage

Review Articles

## Management of congenital diaphragmatic hernia: from the APSA outcomes and evidence

Pramod S. Puligandla<sup>a</sup>, Julia Grabowski<sup>b</sup>, Matthew R. Williams<sup>c</sup>, Kathleen Graziano<sup>d</sup>, Robert J. Janczewicz<sup>e</sup>, Adam Goldin<sup>f</sup>, Cynthia D.

### 2.4. Recommendations

- Based on **level 2 evidence**, iNO cannot be recommended to routinely treat PHTN in CDH patients (**Grade C recommendation**).
- Based on **level 4 evidence**, there was minimal evidence to support the use of other medical adjuncts to treat PHTN in CDH. There is insufficient evidence to support the use of sildenafil in acute PHTN associated with CDH, but there is potential for its use in chronic PHTN. There is insufficient evidence for the routine use of milrinone, prostacyclin, PGE<sub>1</sub>, and Bosentan to treat PHTN in patients with CDH (**Grade D recommendation**).

JAMA Pediatrics | Original Investigation | Oct 2016

## Evaluation of Variability in Sildenafil and Pulmonary Hypertension Treatment in Children With Congenital Diaphragmatic Hernia

Luke R. Putnam, MD, MS; Kuojen Tsao, MD; Francesco Morini, MD; Kevin P. Lally, MD, MS; Matthew T. Harting, MD, MS; for the Congenital Diaphragmatic Hernia Study Group

**CONCLUSIONS AND RELEVANCE** Inhaled nitric oxide use is common but highly variable among centers, and 36% of patients without PHTN received iNO therapy. Based on data from 70 centers, iNO use in patients with CDH may be associated with increased mortality. Future efforts should be directed toward data-driven standardization of iNO use to ensure cost-effective practices.



Open access

Protocol

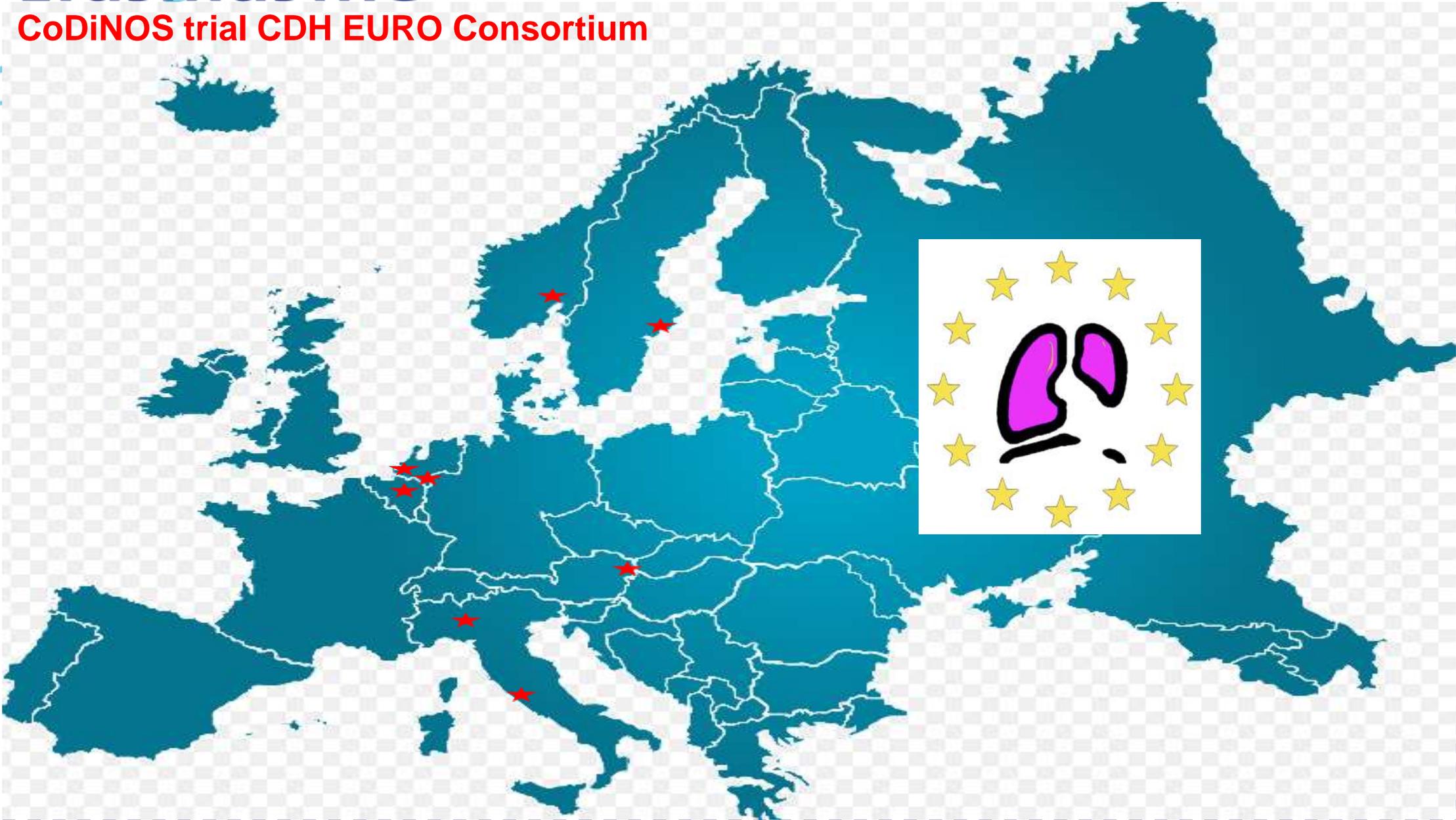
## BMJ Open The CoDiNOS trial protocol: an international randomised controlled trial of intravenous sildenafil versus inhaled nitric oxide for the treatment of pulmonary hypertension in neonates with congenital diaphragmatic hernia

---

Suzan Cochijs-den Otter <sup>1</sup>, Thomas Schaible,<sup>2</sup> Anne Greenough <sup>3</sup>,  
Arno van Heijst,<sup>4</sup> Neil Patel,<sup>5</sup> Karel Allegaert,<sup>6</sup> Joost van Rosmalen,<sup>7</sup> Dick Tibboel,<sup>1</sup>  
on behalf of the CDH EURO Consortium

# Erasmus MC

CoDiNOS trial CDH EURO Consortium



## CoDiNOS trial

**Intervention:** Intravenous sildenafil, loading dose 0,4mg/kg in 3 hours, followed by 1,6mg/kg/day

**Control:** Inhaled NO 20 ppm

**Primary outcome:** Difference in oxygenation index after 12 hours of treatment between CDH patients treated with iNO versus those treated with intravenous sildenafil.





## CoDiNOS trial



## CoDiNOS trial



Wetten en  
goedkeuringen



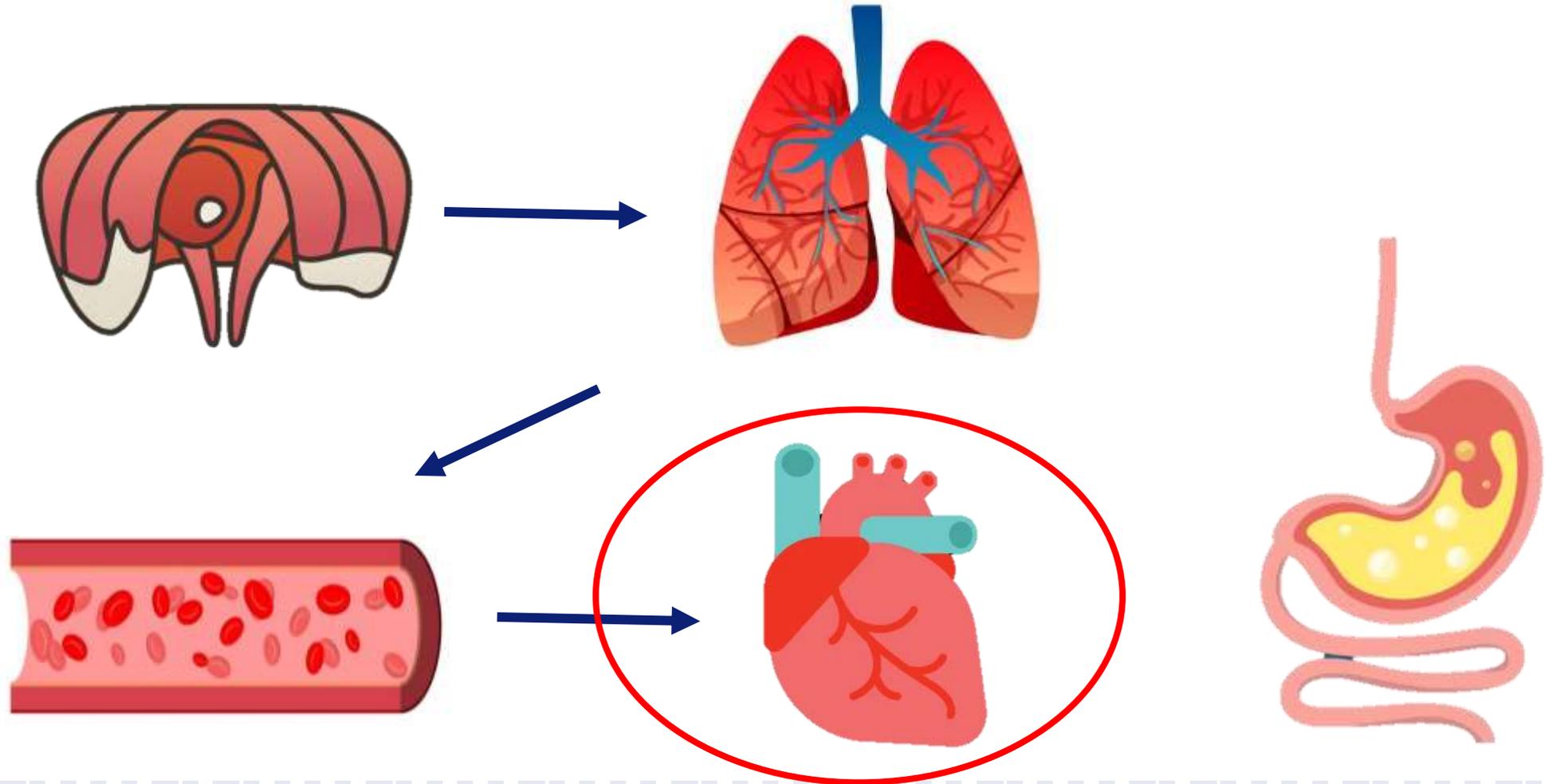
Financiële  
middelen



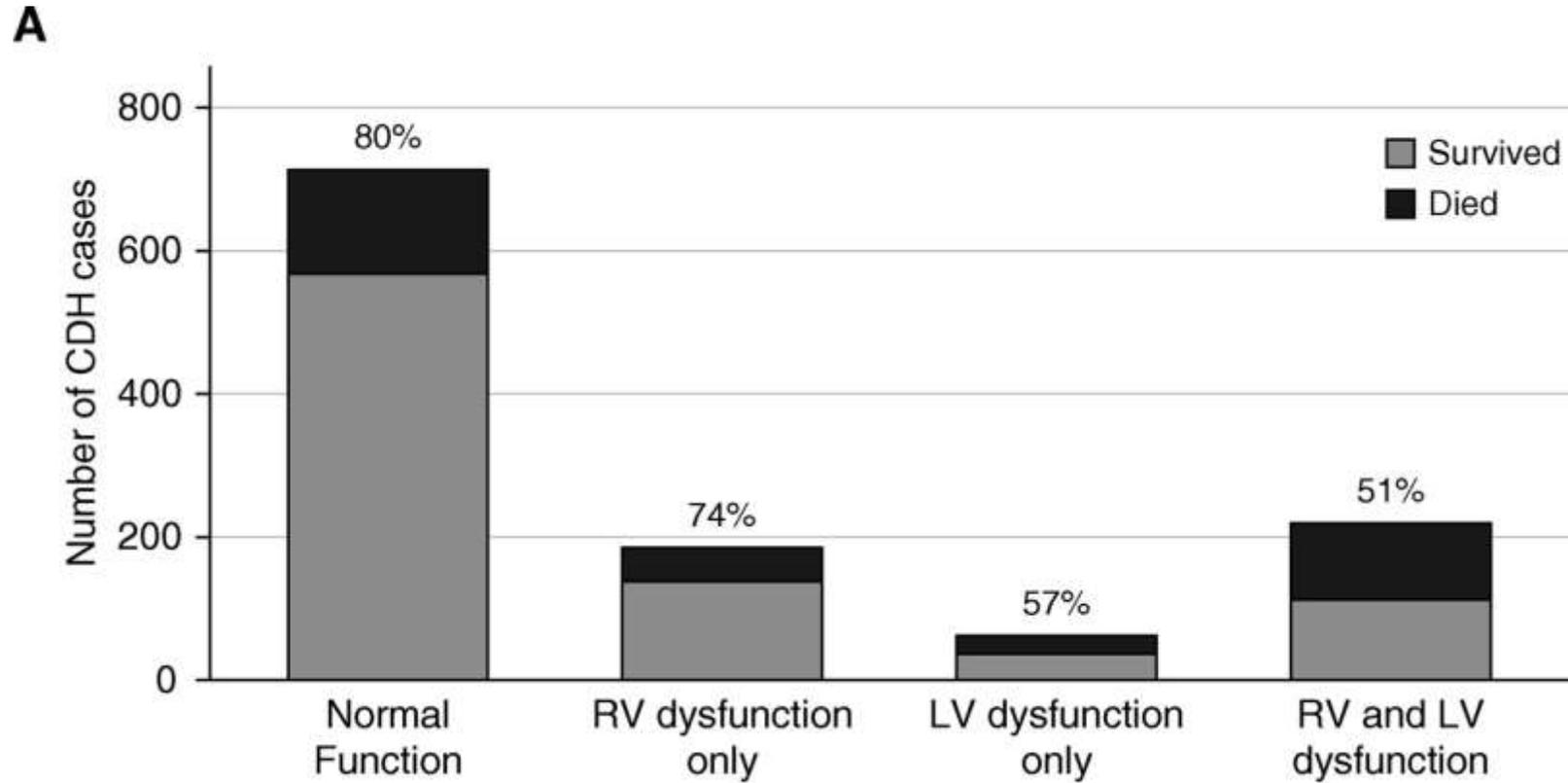
Patienten aantallen



Trial gestopt  
31 pt geïncludeerd  
Resultaten volgen

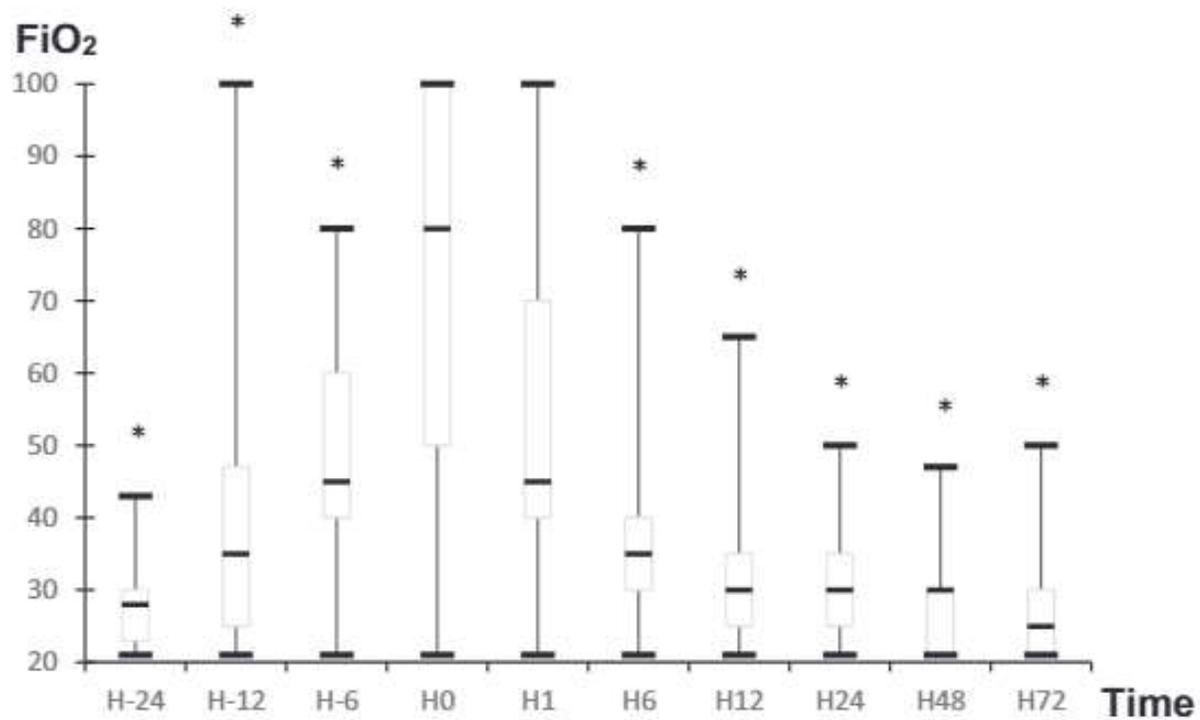


## Congenital diaphragmatic hernia: cardiac dysfunction



## Congenital diaphragmatic hernia and RV failure: prostaglandin E1

K. Le Duc et al. / Journal of Pediatric Surgery 55 (2020) 1872–1878



Life-threatening suprasystemic pulmonary hypertension defined as:

- Increase FiO<sub>2</sub> > 20%
- Circulatory failure
- Bidirectional or exclusive right-to-left shunting across the ductus arteriosus
- No response to inhaled NO

## Congenital diaphragmatic hernia: cardiac dysfunction and milrinone

Lakshminrusimha *et al.* *Maternal Health, Neonatology, and Perinatology*  
(2017) 3:27  
DOI 10.1186/s40748-017-0066-9

Maternal Health, Neonatology,  
and Perinatology

REVIEW

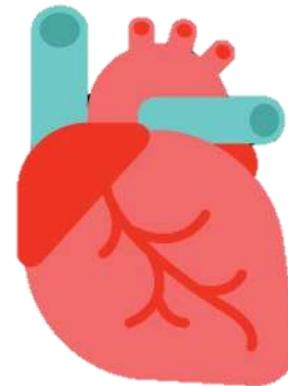
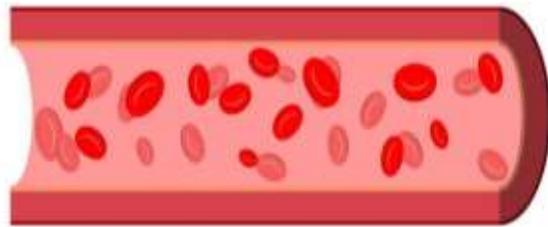
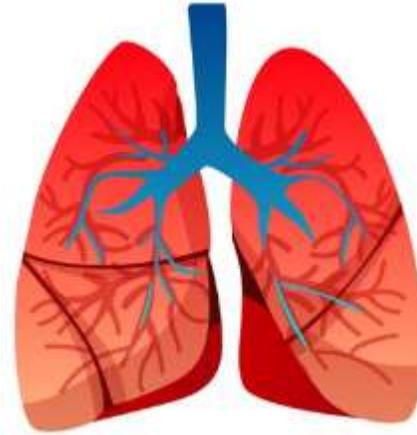
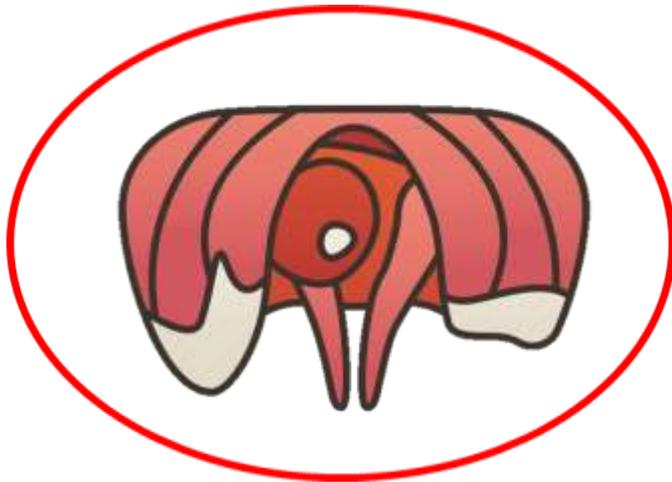
Open Access



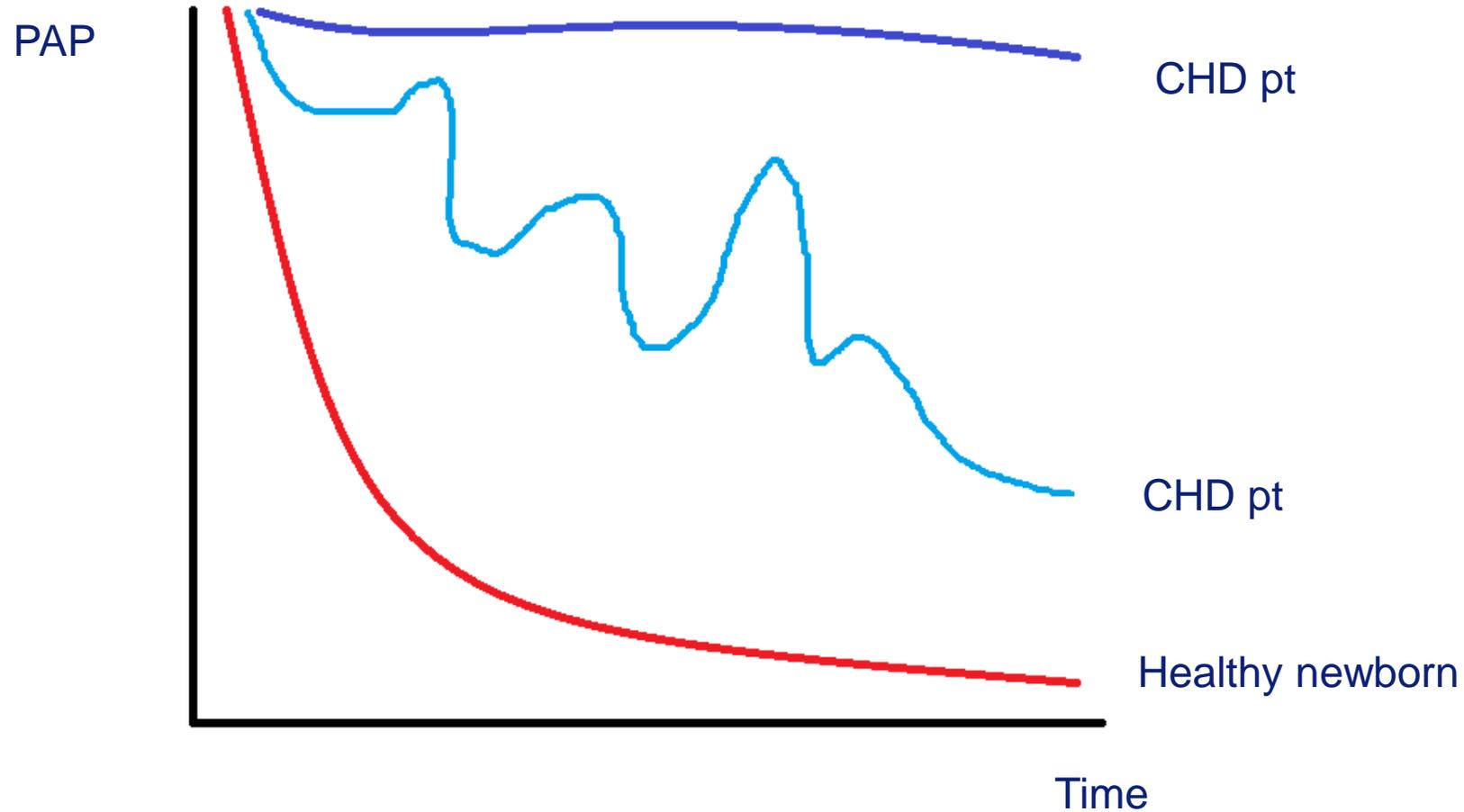
# Milrinone in congenital diaphragmatic hernia – a randomized pilot trial: study protocol, review of literature and survey of current practices

Satyan Lakshminrusimha<sup>1</sup>, Martin Keszler<sup>2</sup>, Haresh Kirpalani<sup>3</sup>, Krisa Van Meurs<sup>4</sup>, Patricia Chess<sup>5</sup>, Namasivayam Ambalavanan<sup>6</sup>, Bradley Yoder<sup>7</sup>, Maria V. Fraga<sup>3</sup>, Holly Hedrick<sup>3</sup>, Kevin P. Lally<sup>8</sup>, Leif Nelin<sup>9</sup>, Michael Cotten<sup>10</sup>, Jonathan Klein<sup>11</sup>, Stephanie Guilford<sup>1\*</sup> , Ashley Williams<sup>1</sup>, Aasma Chaudhary<sup>3</sup>, Marie Gantz<sup>12</sup>, Jenna Gabrio<sup>12</sup>, Dhuly Chowdhury<sup>12</sup>, Kristin Zaterka-Baxter<sup>12</sup>, Abhik Das<sup>12</sup> and Rosemary D. Higgins<sup>13</sup>

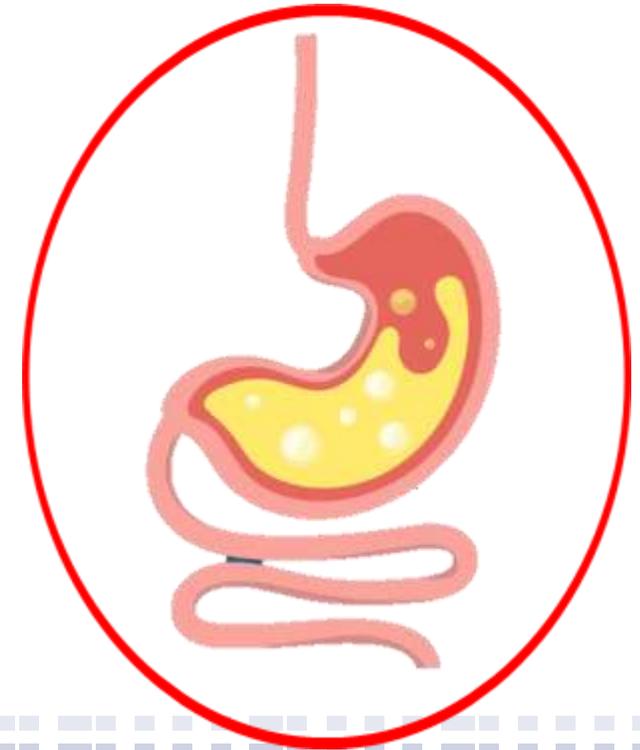
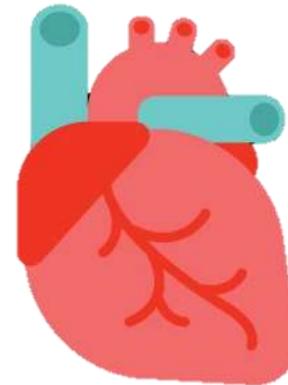
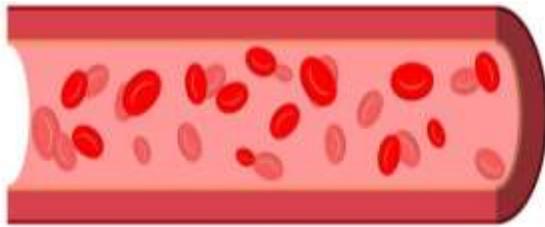
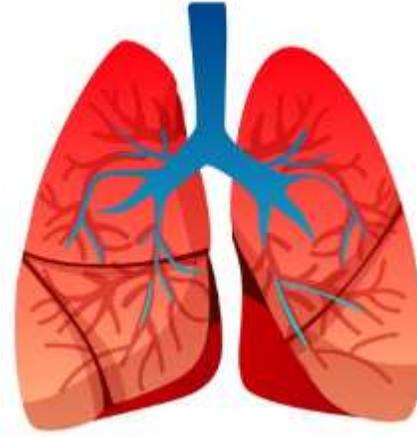
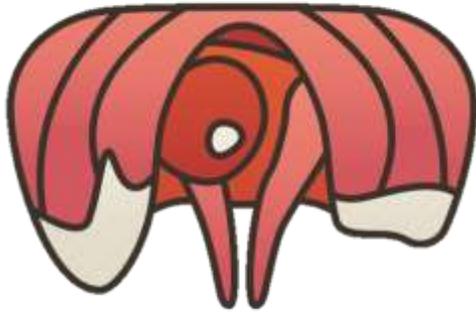
## Congenital diaphragmatic hernia: een multiorgaan ziekte



## Congenital diaphragmatic hernia: pulmonale hypertensie



## Congenital diaphragmatic hernia: een multiorgaan ziekte



In cooperation with:



CDH Euro Consortium



European  
Reference  
Network

for rare or low prevalence  
complex diseases

⚙️ **Network**  
Inherited and Congenital  
Anomalies (ERNICA)

Funded by:

