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Universitair Medisch Centrum Rotterdam

CDH Euro-Consortium

# Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia: A randomized clinical trial (the VICI-trial)

on behalf of the CDH-Euroconsortium


## Irwin Reiss, MD PhD


# Bochdalek Hernia Causing Pulmonary Hypertension

David Dobarro, MD; Benjamin E. Schreiber, MD, MRCP; Jamanda Haddock, MD;
Sri Mandumula, MD; John G. Coghlan, MD, FRCP

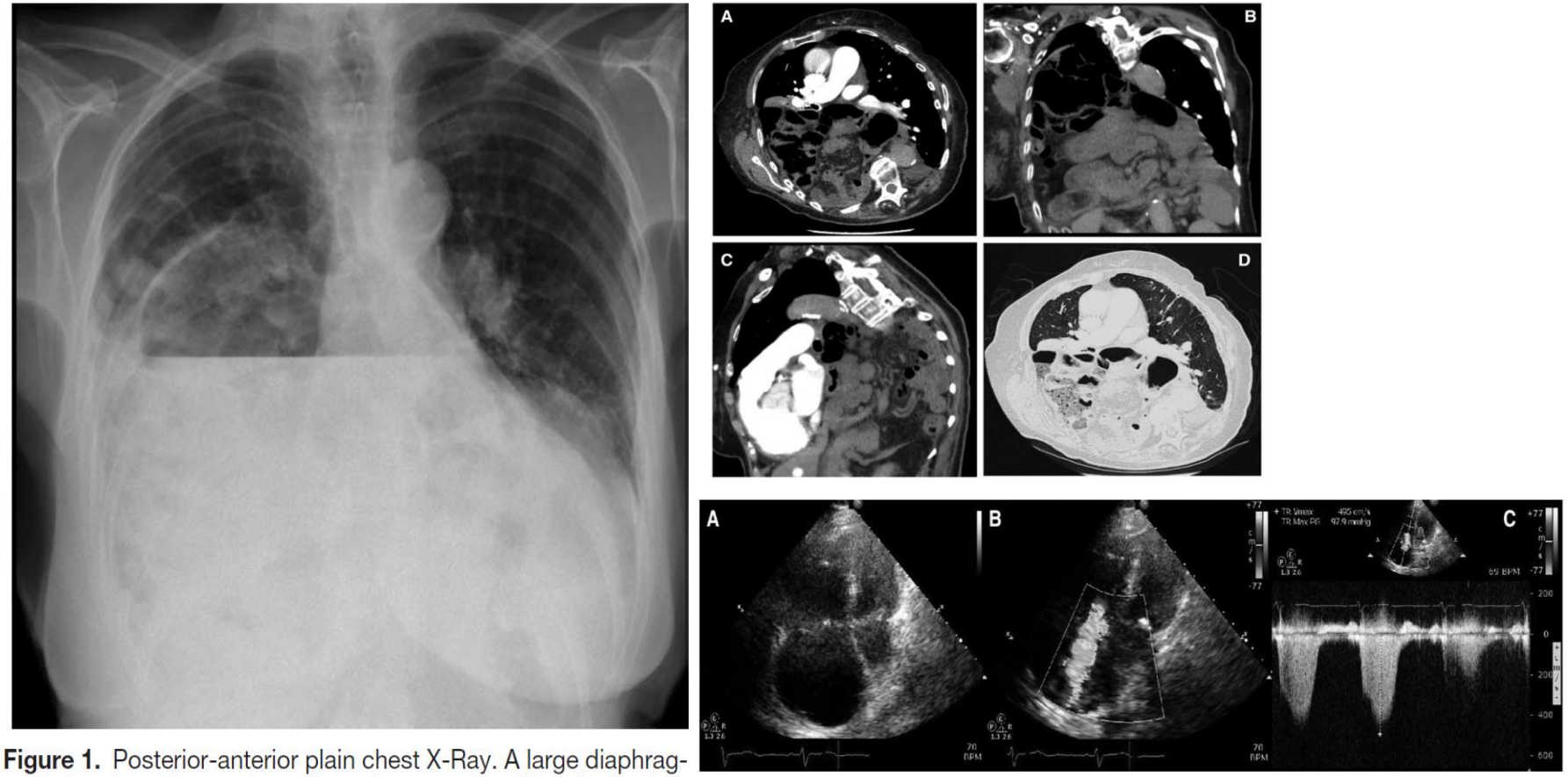


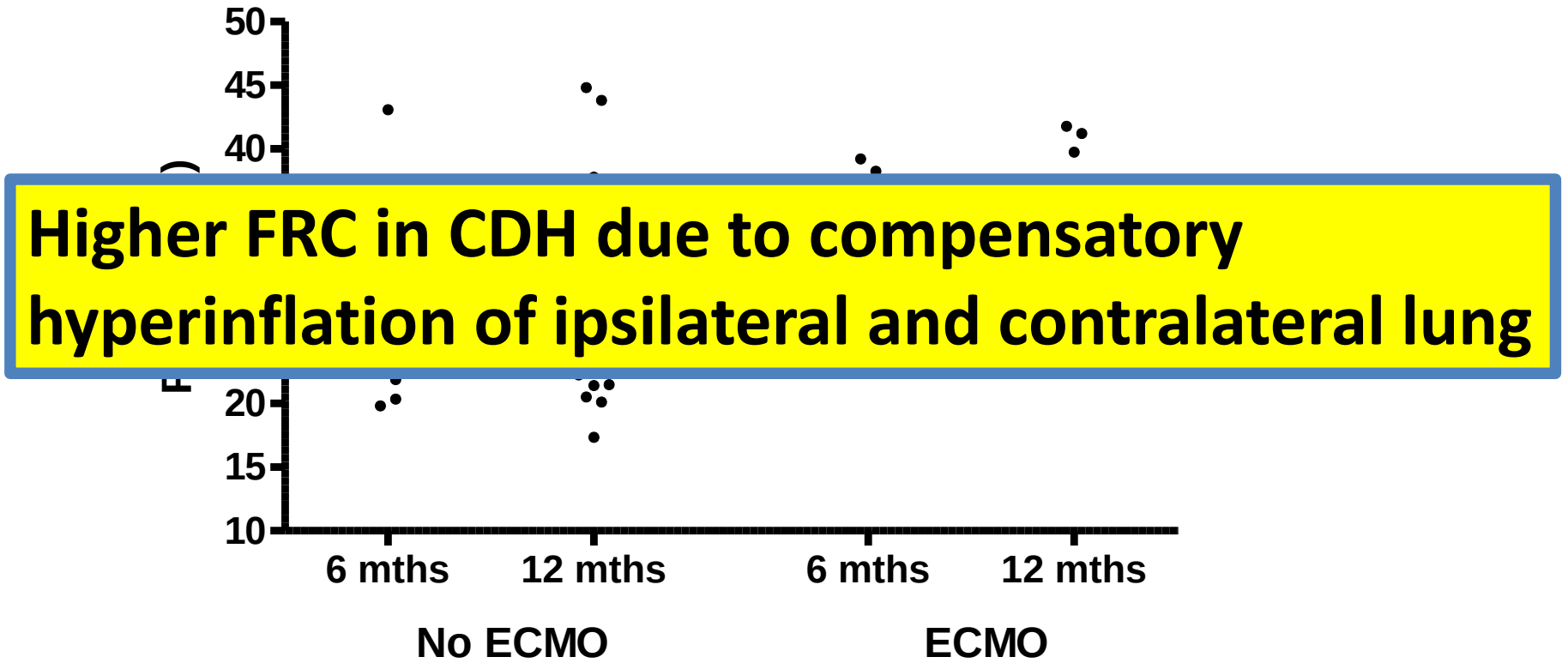

**Figure 1.** Posterior-anterior plain chest X-Ray. A large diaphragmatic hernia with gastric and bowel content is evident in the right and center chest.

Circulation 2013

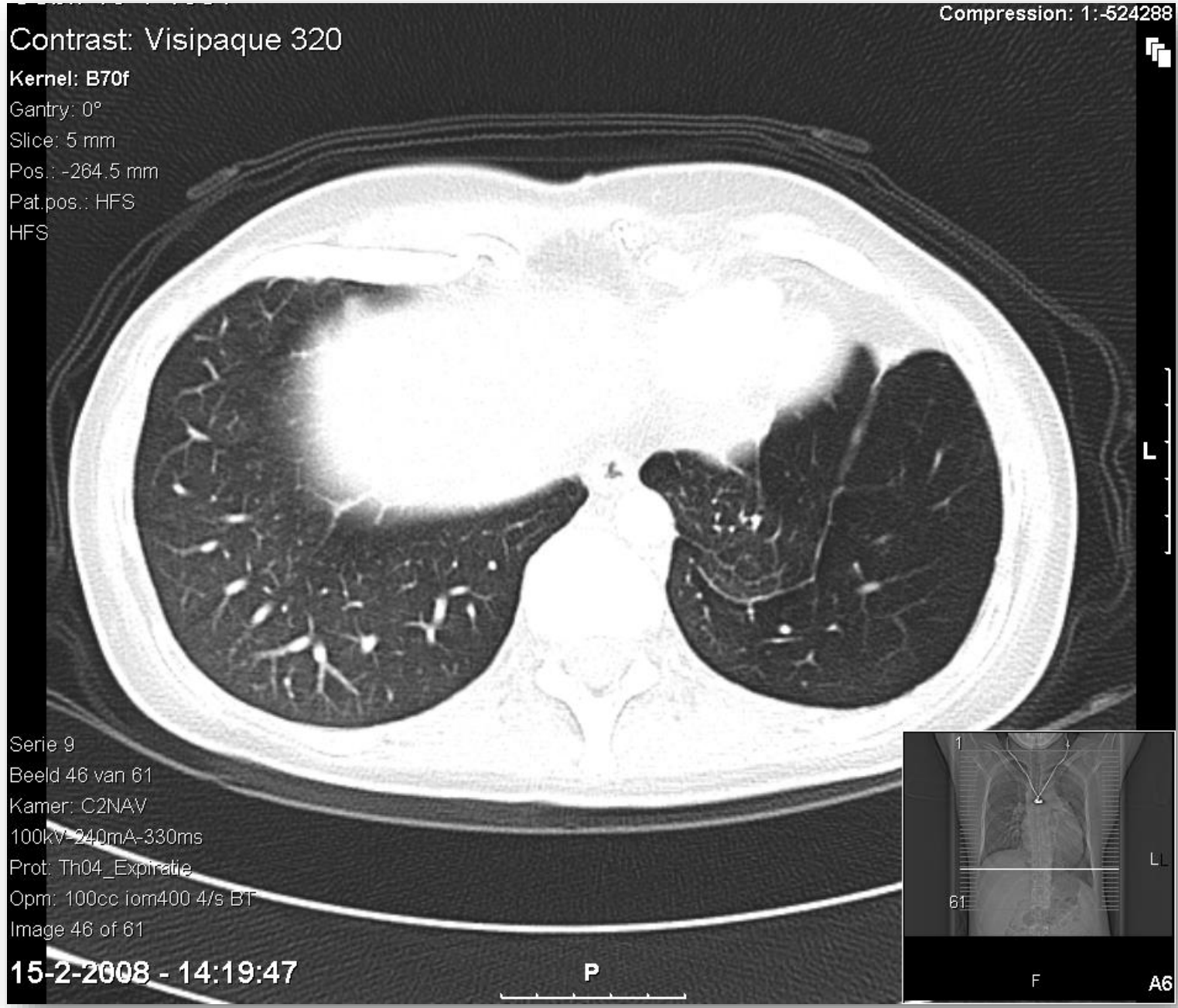
# Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia

Marjolein Spoel, MD*; Lieke van den Hout, MD*; Saskia J. Gischler, MD, PhD; Wim C. J. Hop, PhD; Irwin Reiss, MD, PhD; Dick Tibboel, MD, PhD; Johan C. de Jongste, MD, PhD; Hanneke IJsselstijn, MD, PhD

Spoel et al. Ped Crit Care Med 2011




**Higher FRC in CDH due to compensatory hyperinflation of ipsilateral and contralateral lung**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Kamer: C2NAV
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# Ricardo Rodríguez

## *25 august 1992

# Ventilator-induced lung injury

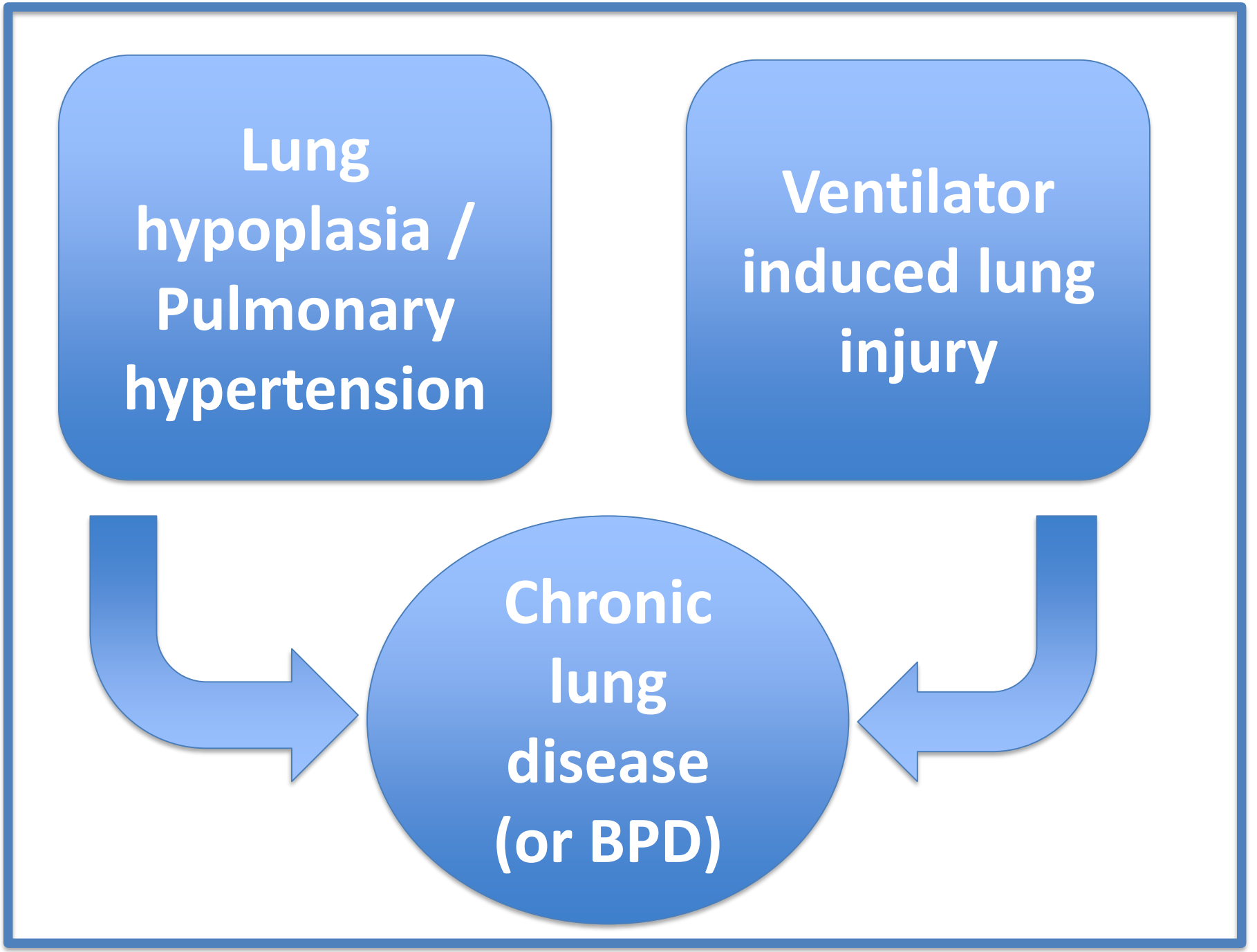
Seminars in Pediatric Surgery (2007) 16, 115-125

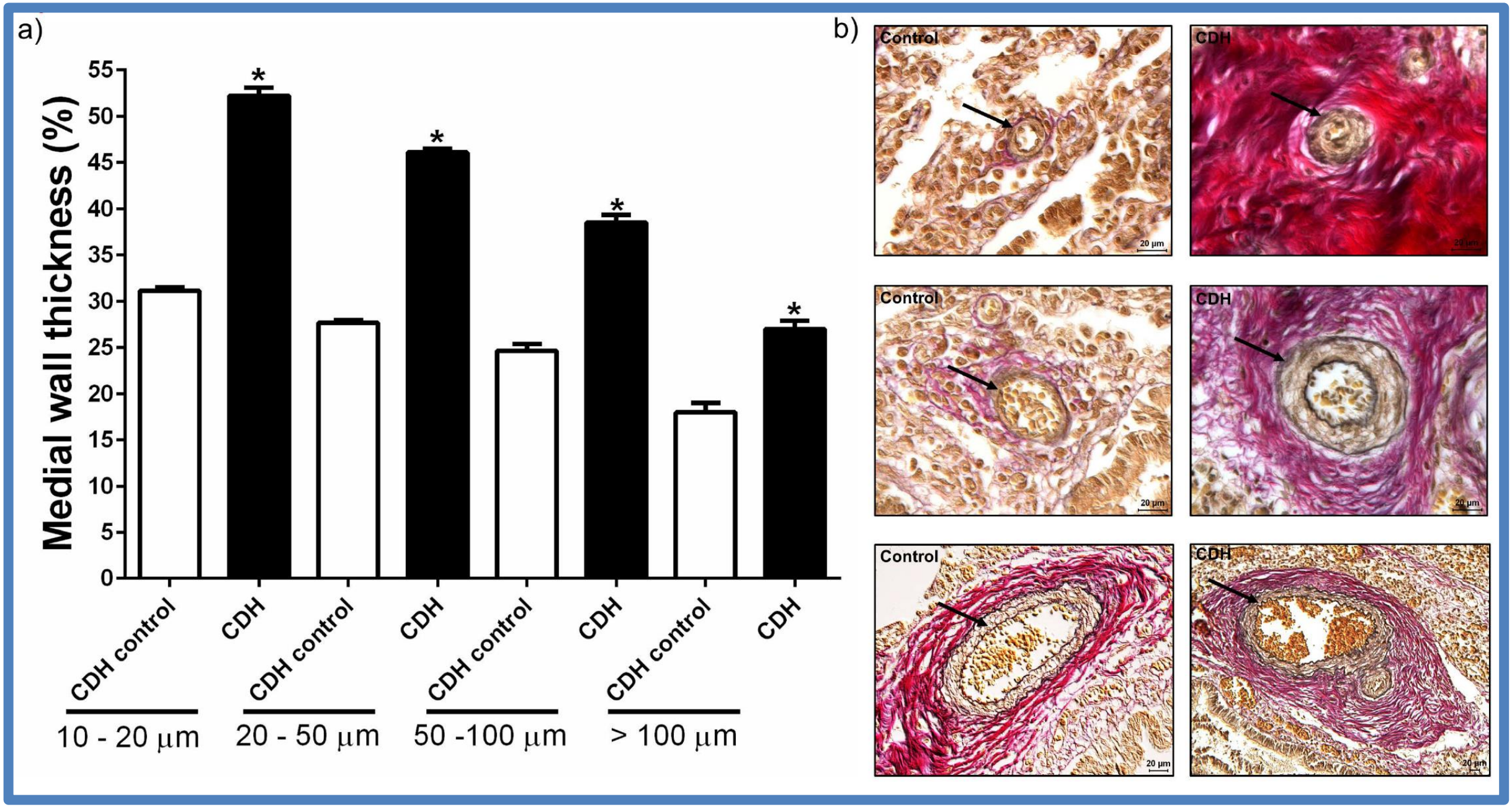

SEMINARS IN
PEDIATRIC
SURGERY

**As much as 25% of mortality is due to potentially preventable complications of care**

**J. Wells Logan, MD,[a] C. Michael Cotten, MD, MHS,[a] Ronald N. Goldberg, MD,[a] Reese H. Clark, MD[b]**

*From the [a]Division of Neonatology, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina; and the*
*[b]Clinical Research and Education, Pediatrix Medical Group, Sunrise, Florida.*

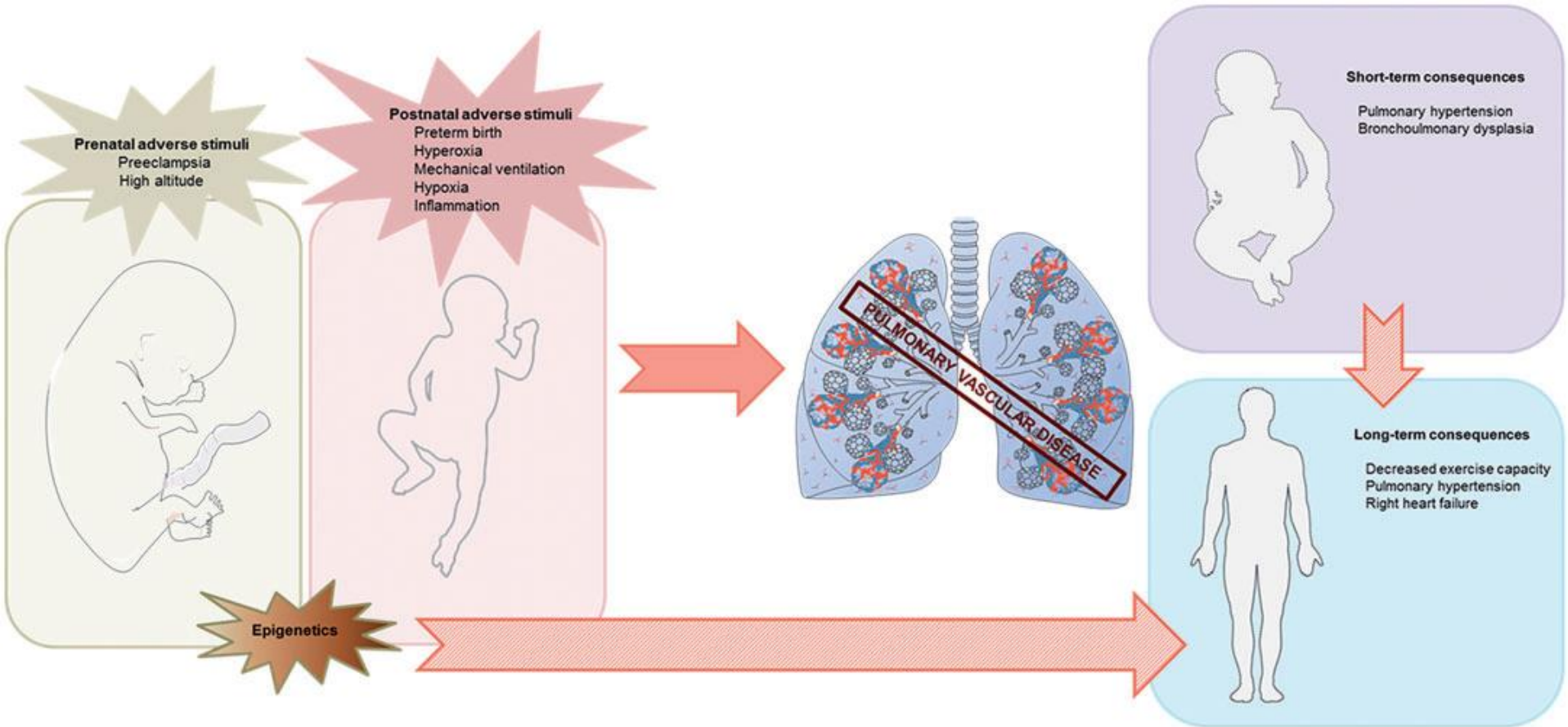

Lung hypoplasia / Pulmonary hypertension
Ventilator induced lung injury
Chronic lung disease (or BPD)

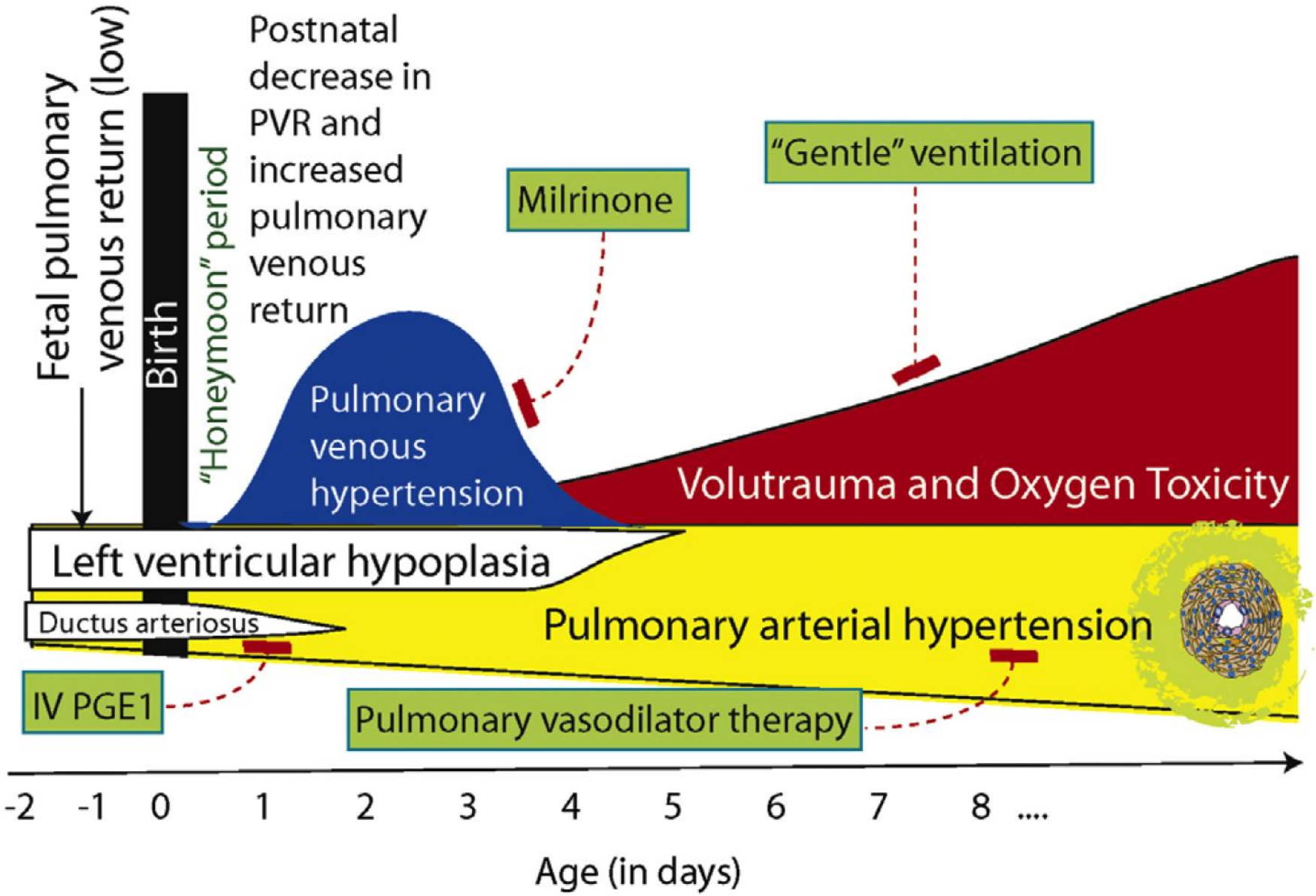

a)
Medial wall thickness (%)
55
50
45
40
35
30
25
20
15
10
5
0
*
*
*
*
CDH control
CDH
CDH control
CDH
CDH control
CDH
CDH control
CDH
10 - 20 μm
20 - 50 μm
50 -100 μm
> 100 μm
b)
Control
CDH
Control
CDH
Control
CDH
20 μm

# Oxidative injury of the pulmonary circulation in the perinatal period: Short- and long-term consequences for the human cardiopulmonary system

Daphne P. de Wijs-Meijler[1,2], Dirk J. Duncker[1], Dick Tibboel[3], Ralph T. Schermuly[4], Norbert Weissmann[4], Daphne Merkus[1] and Irwin K.M. Reiss[2]

Pulm Cir 2017






Nair J et al. Sem Perinat 2014

# Right- versus left-sided congenital diaphragmatic hernia: Postnatal outcome at a specialized tertiary care center*

Thomas Schaible, MD; Thomas Kohl, MD; Konrad Reinshagen, MD; Joachim Brade, PhD; K. Wolfgang Neff, MD; Rüdiger Stressig, MD; Karen A. Büsing, MD

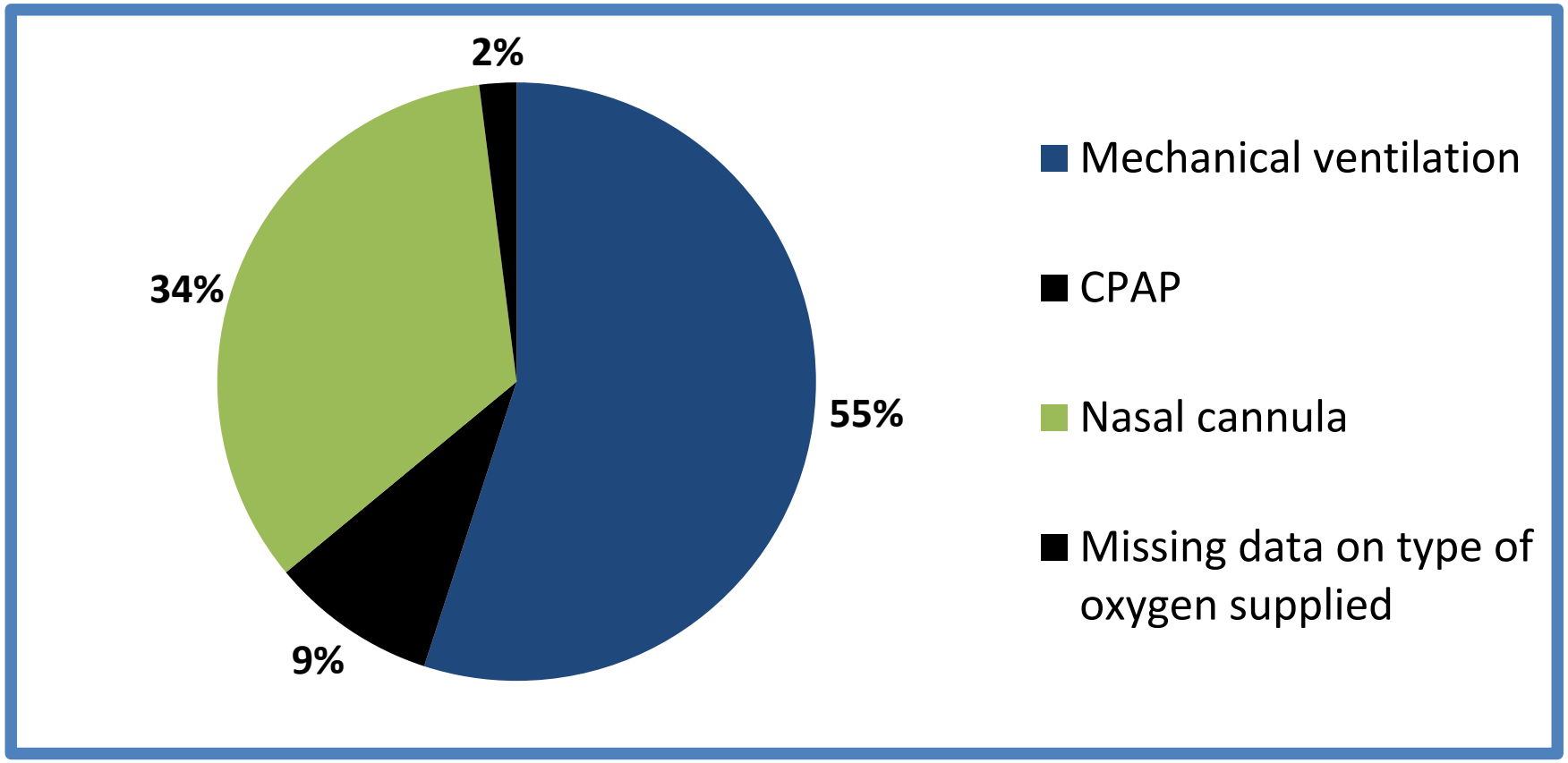
**Pediatr Crit Care Med 2012**

Table 5. Pulmonary outcome in right versus left congenital diaphragmatic hernia, no matched-pair analysis

| Pulmonary Outcome | Right CDH | Left CDH | *p* | Left CDH Liver Up Only | *p* |
|---|---|---|---|---|---|
| Others | | | | | |
| Survival | 77% (37 of 48) | 76% (178 of 233) | .918 | 59% (47 of 79) | .001 |
| Extracorporeal membrane oxygenation therapy | 71% (29 of 41) | 38% (79 of 210) | <.001 | 46% (36 of 79) | .009 |
| Survival with extracorporeal membrane oxygenation therapy | 83% (24 of 29) | 59% (47 of 79) | .002 | 67% (17 of 36) | <.001 |
| Survivors | | | | | |
| Chronic lung disease | 90% (27 of 30) | 45% (72 of 159) | <.001 | 71% (12 of 17) | .089 |
| Chronic lung disease grading | 2.1 | 1.8 | .378 | 1.8 | .846 |

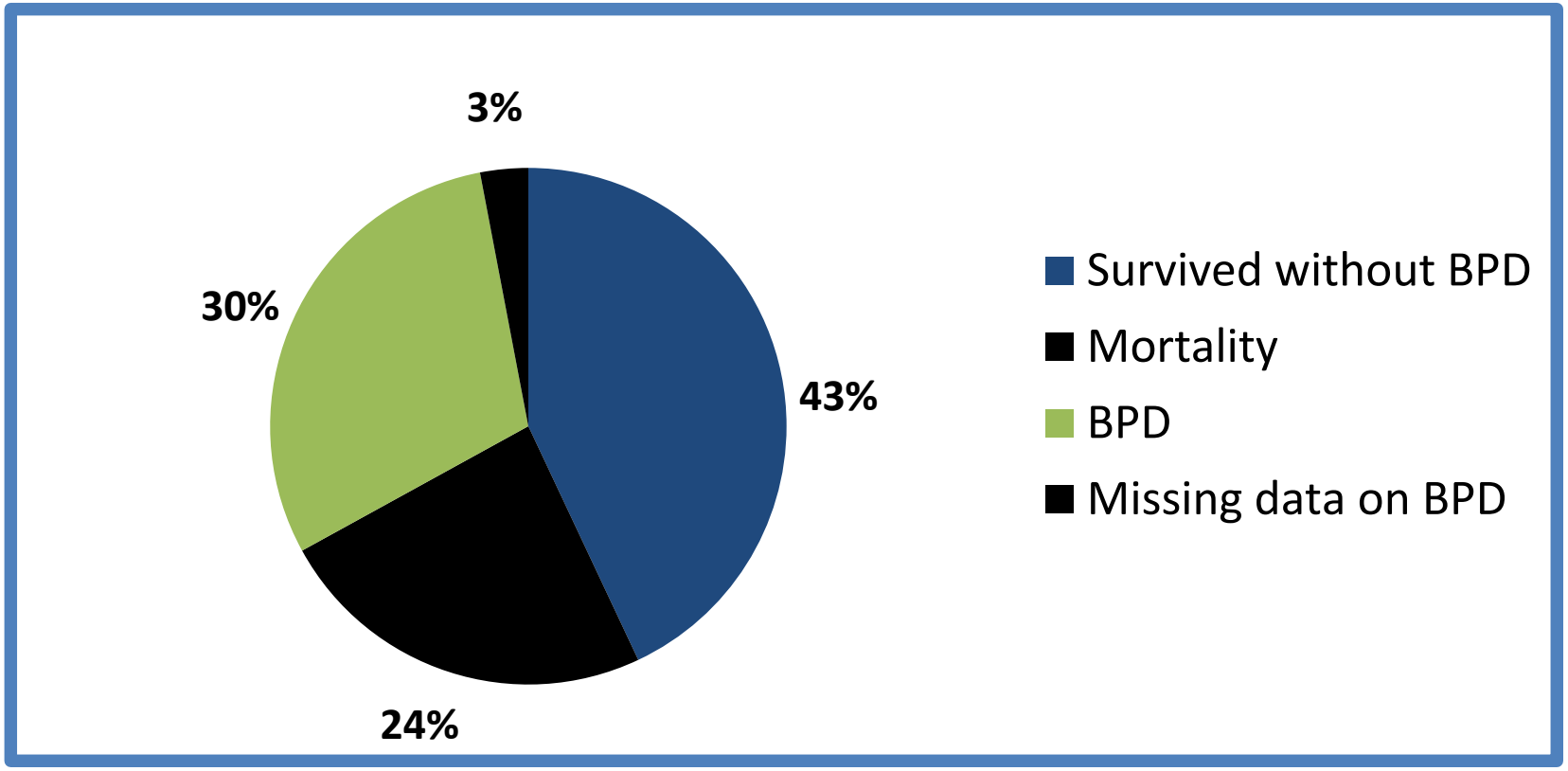
CDH, congenital diaphragmatic hernia.

# Majority of CDH survivors is still on mechanical ventilation @ day 30




Van den Hout et al. (CDH Study Group) Neonatology 2010

# 41% of CDH survivors has BPD @ day 30




Van den Hout et al. (CDH Study Group) Neonatology 2010

# Risk factors for CLD and mortality

**Table 6.** Multivariate logistic regression analysis for BPD (n = 1,293)

| Variable | OR | 95% CI | p value |
|---|---|---|---|
| Gestational age in weeks | 0.87 | 0.82–0.92 | <0.001 |
| Cardiac abnormality | 2.42 | 1.85–3.67 | <0.001 |
| Inborn | 0.70 | 0.52–0.95 | 0.023 |
| Prenatal diagnosis | 4.27 | 3.05–5.80 | <0.001 |
| Right-sided defect | 2.51 | 1.73–3.64 | <0.001 |
| Apgar score at 5 min | 0.66 | 0.61–0.71 | <0.001 |
| HFO as initial ventilation mode | 2.29 | 1.73–3.04 | <0.001 |

Nonsignificant variables in the multivariate analysis: birth in ECMO center (odds ratio 1.81, 95% confidence interval 0.94–3.48; p = 0.074) and having a chromosomal abnormality (odds ratio 1.37, 95% confidence interval 0.57–3.26; p = 0.480). OR = Odds ratio; CI = confidence interval.

Van den Hout et al. (CDH Study Group ) Neonatology 2010

# Risk factors for CLD and mortality

**Table 5.** Multivariate logistic regression analysis of BPD and/or death by day 30 (n = 1,686)

| Variable | OR | 95% CI | p value |
|---|---|---|---|
| Gestational age in weeks | 0.84 | 0.81–0.90 | <0.001 |
| Cardiac abnormality | 2.62 | 1.85–3.72 | <0.001 |
| Chromosomal abnormality | 3.04 | 1.42–6.51 | 0.004 |
| Prenatal diagnosis | 3.90 | 3.00–5.00 | <0.001 |
| Right-sided defect | 2.76 | 1.96–3.89 | <0.001 |
| Apgar score at 5 min | 0.61 | 0.57–0.65 | <0.001 |
| HFO as initial ventilation mode | 2.53 | 1.95–3.27 | <0.001 |

Nonsignificant variables in the multivariate analysis: birth in ECMO center (odds ratio 1.39, 95% confidence interval 0.80–2.44; p = 0.244) and location of birth (odds ratio 1.1, 95% confidence interval 0.83–1.46; p = 0.487). OR = Odds ratio; CI = confidence interval.

Van den Hout et al. (CDH Study Group ) Neonatology 2010

# Risk factors for CLD and mortality

**Table 7.** Multivariate logistic regression analysis for mortality by day 30 (n = 1,749)

| Variable | OR | 95% CI | p value |
|---|---|---|---|
| Gestational age in weeks | 0.87 | 0.83–0.92 | <0.001 |
| Cardiac abnormality | 1.54 | 1.11–2.14 | 0.010 |
| Chromosomal abnormality | 4.49 | 2.63–7.67 | <0.001 |
| Inborn | 1.76 | 1.30–2.38 | <0.001 |
| Prenatal diagnosis | 1.80 | 1.28–2.02 | <0.001 |
| Right-sided defect | 1.88 | 1.35–2.63 | <0.001 |
| Apgar score at 5 min | 0.68 | 0.64–0.73 | <0.001 |
| HFO as initial ventilation mode | 1.85 | 1.42–2.41 | <0.001 |

Nonsignificant variable in the multivariate analysis: birth in ECMO center (odds ratio 0.71, 95% confidence interval 0.37–1.34; p = 0.286). OR = Odds ratio; CI = confidence interval.

Van den Hout et al. (CDH Study Group ) Neonatology 2010

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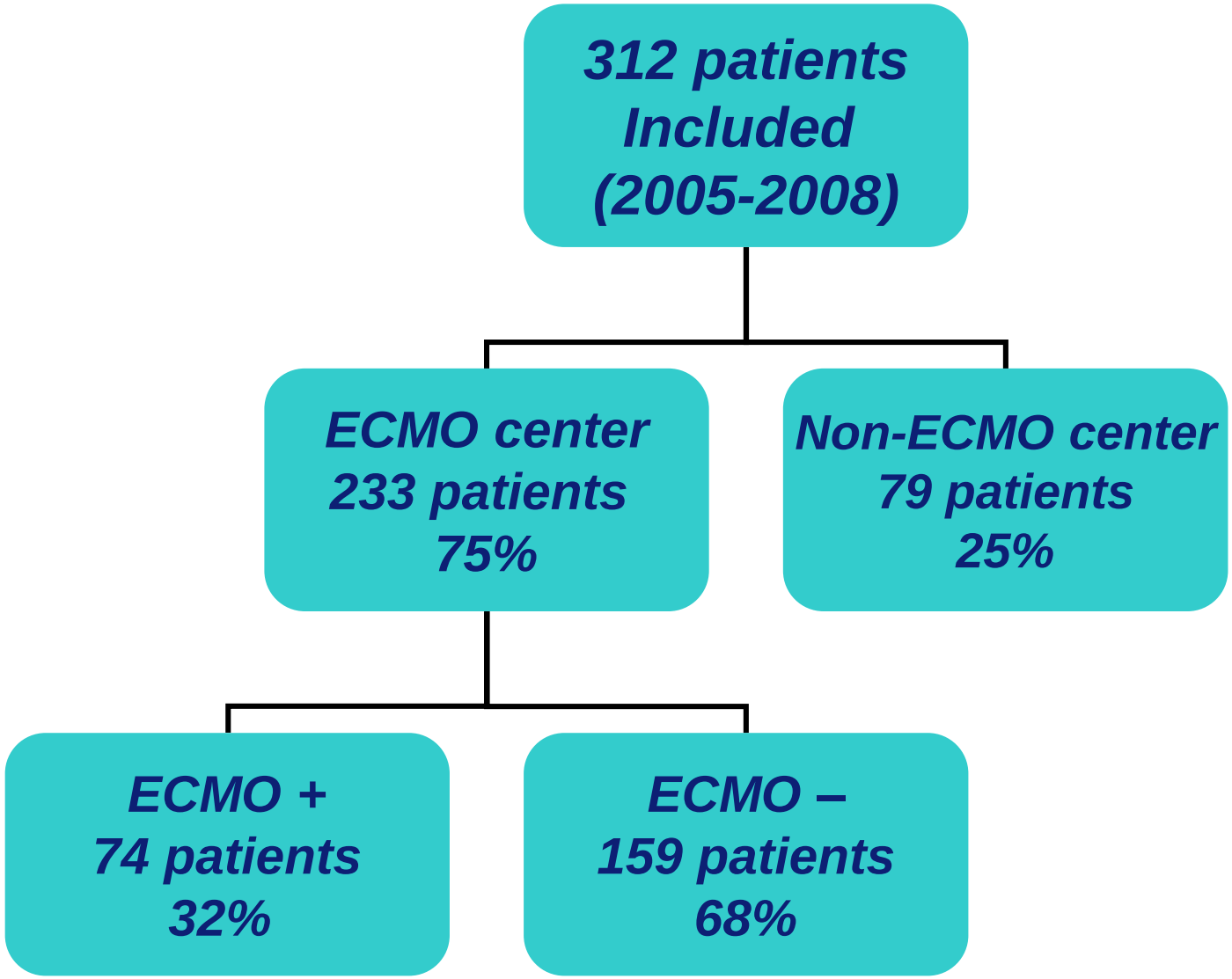

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## Multivariate analysis of baseline characteristics for mortality by day 28

| | Odds Ratio | 95% CI | P-value |
|---|---|---|---|
| **ECMO center** | 0.197 | 0.092 – 0.423 | <0.001 |
| **Birth-weight > 2kg** | 0.163 | 0.038 – 0.694 | 0.014 |
| **Initially HFO** | 5.610 | 2.443 – 12.883 | <0.001 |
| **Liver Up** | 3.609 | 1.626 – 8.009 | 0.002 |

* Not-significant in multivariate analysis were: in/outborn, prenatal diagnosis, birth-method and centervolume.


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Bambino Gesù
CDH Euro-Consortium


# *VENI, VIDI, VICI*

**I came, I saw,**
**I conquered**

**Julius Caesar, 100BC-44BC**

Neonatology

Consensus Statement

Neonatology 2010;98:354–364
DOI: 10.1159/000320622

Received: May 10, 2010
Accepted after revision: August 24, 2010
Published online: October 27, 2010

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

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for the CDH EURO consortium

Neonatology

Consensus Statement

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

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

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# Ventilation modalities in infants with congenital diaphragmatic hernia

Francesco Morini, MD[a,*], Irma Capolupo, MD, PhD[a,1], Willem van Weteringen, MD[b,1], Irwin Reiss, MD, PhD[c]

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[b] Department of Pediatric Surgery, Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam, The Netherlands
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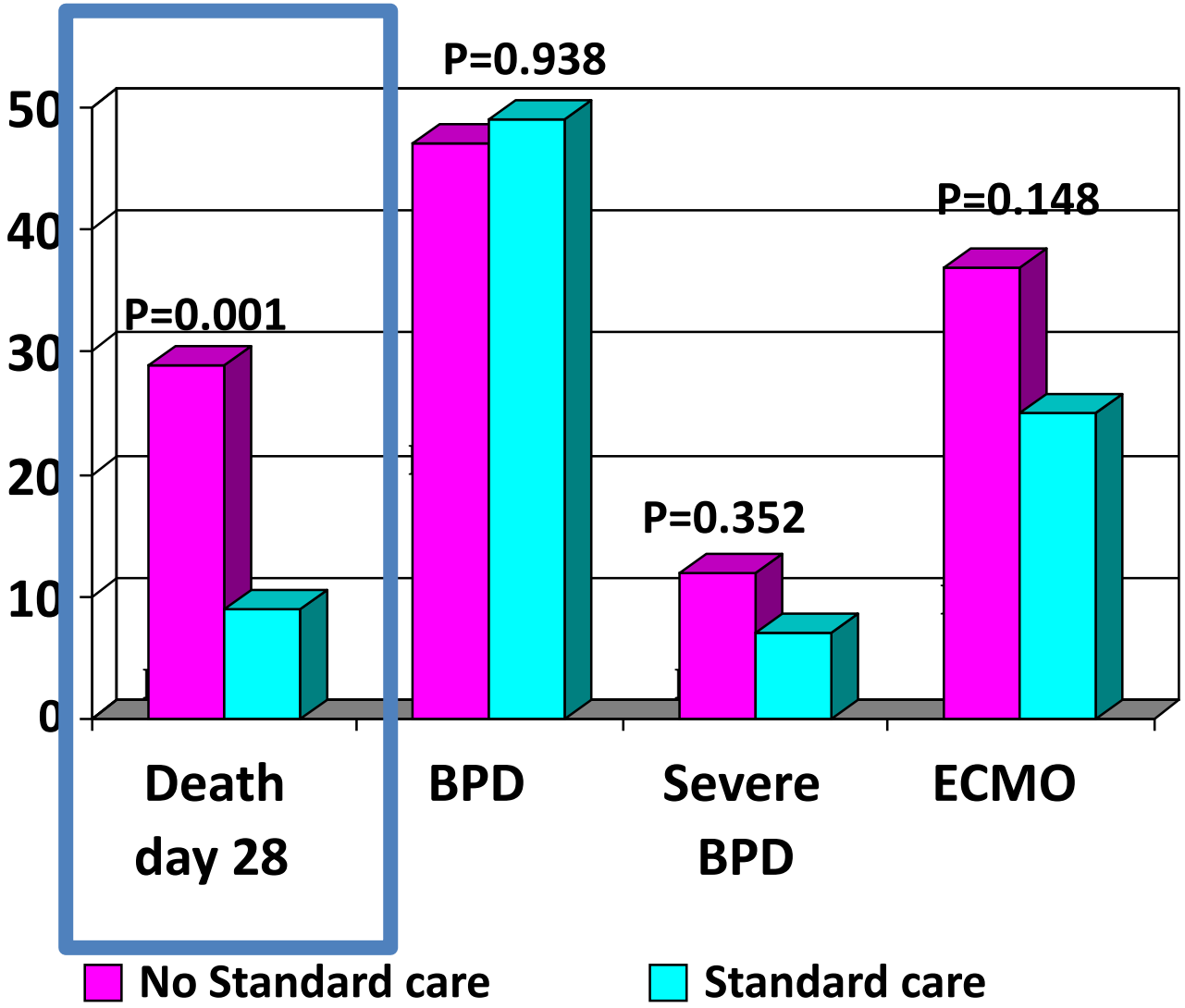
Synopsis of recommendations for ventilation strategies in CDH patients from the CDH Euro Consortium[70,71] and the APSA outcomes and evidence-based practice committee.[72]

| | CDH Euro Consortium | APSA OEBP committee |
|---|---|---|
| Delivery room management | Immediate intubation; no bag/mask ventilation; PIP < 25 cm $H_2O$; goal: preductal $SaO_2$: 80–95%; no muscle paralyzing agents; no surfactant. | – |
| Initial ventilation mode | CMV recommended; rescue HFOV | CMV recommended; HFOV possible |
| Goals | Preductal $SaO_2$: 80–95%; postductal $SaO_2$ > 70%; $pCO_2$: 50–70 mmHg | Preductal $SaO_2$ > 85%; $pCO_2$ < 60 mmHg |
| CMV—ventilatory mode | IMV | IMV |
| CMV—parameters | PIP < 25 cm $H_2O$; PEEP: 3–5 cm $H_2O$; ventilatory rate: 40–60/min | PIP < 25 cm $H_2O$; PEEP: 3–5 cm $H_2O$ |
| HFOV—rescue indication | PIP > 28 cm $H_2O$; preductal $SaO_2$ < 85% or postductal $SaO_2$ < 70% with optimal parameters | PIP > 25 cm $H_2O$ or preductal $SaO_2$ < 85% with optimal parameters |
| HFOV—parameters | MAP: 13–17 cm $H_2O$; frequency 10 Hz; $\Delta P$: 30–50 cm $H_2O$ based on chest rise | MAP: 13–15 cm $H_2O$; $\Delta P$: 30–40 cm $H_2O$ based on chest rise |

Abbreviations: APSA OEBP committee, American Pediatric Surgical Association outcomes and evidence-based practice committee; CDH, congenital diaphragmatic hernia; CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; IMV, intermittent mandatory ventilation; MAP, mean airway pressure;$pCO_2$, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; $SaO_2$, oxygen saturation; $\Delta P$, pressure delta, change in pressure from the highest pressure to the lowest pressure.

# Effect standardized treatment protocol




Van den Hout et al. Fetal Diagn Ther 2011

Netherlands Trial Register (NTR): NTR1310

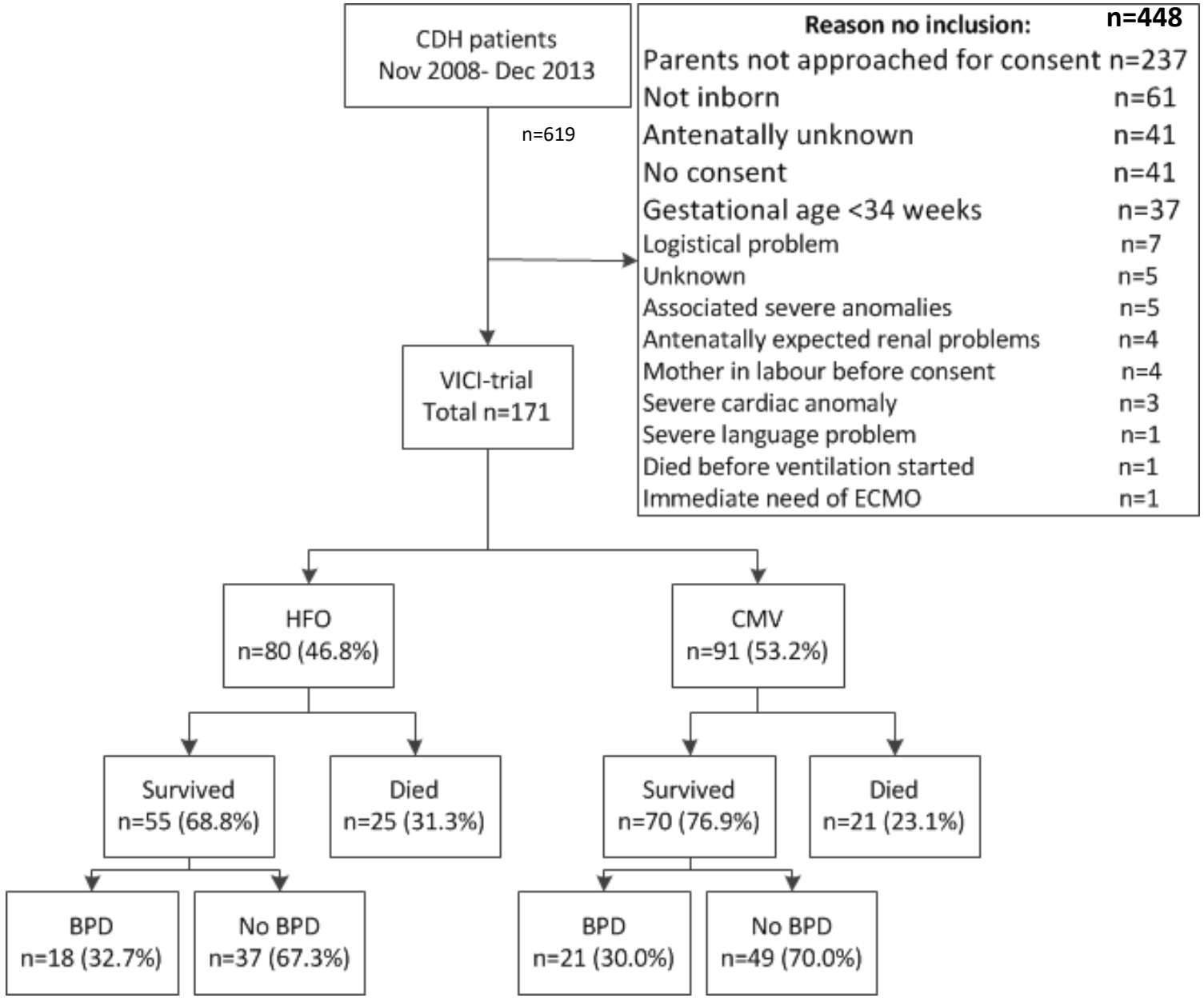
STUDY PROTOCOL Open Access

# The VICI-trial: high frequency oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: an international multicentre randomized controlled trial

BMC Pediatrics 2011, 11:98

**Secondary outcome measures:**

- Length of ventilation
- Severity of BPD
- ECMO need
- Frequency of inhaled NO
- Use of sildenafil
- Use and duration of inotropics
- Number of treatment failures
- Pulmonary hypertension



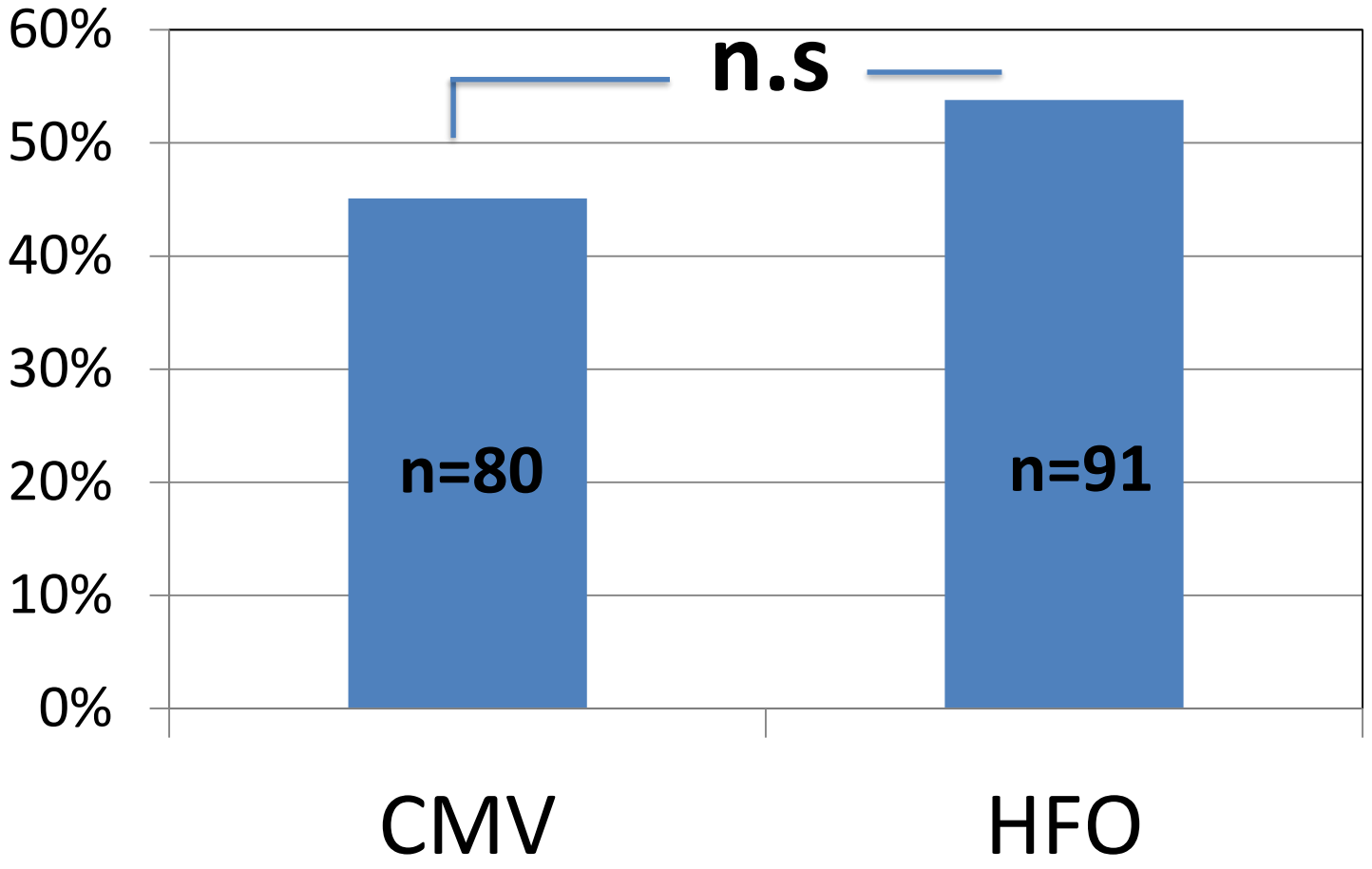

Snoek K et al. Ann Surg 2016

# Patient characteristics

| Variable | HFO (n= 80) | CMV (n= 91) | p-value |
|---|---|---|---|
| **FETO** | 12 (15.0%) | 7 (7.7%) | 0.15 |
| **O/ E LHR** | 47% (15%-141%) | 48.0% (21%- 100%) | 0.46 |
| **Male sex** | 36 (45.0%) | 48 (52.7%) | 0.36 |
| **Birth weight (kg)** | 2.89±0.47 | 2.95±0.46 | 0.38 |
| **Gestational age** | 38 (37.3- 39.0) | 38.1 (37.4- 38.9) | 0.39 |
| **SNAP-II score** | 25 (12.5- 37) | 21 (10- 38.5) | 0.63 |
| **Left side CDH** | 73 (91.3%) | 75 (82.4%) | 0.12 |
| **Liver** | | | 0.76 |
| Intrathoracic | 46 (57.5%) | 55 (60.4%) | |
| Abdominal | 34 (42.5%) | 36 (39.6%) | |
| **Type of repair** | | | 0.73 |
| Primary closure | 27 (34.6%) | 26 (38.2%) | |
| Patch repair | 51 (65.4%) | 42 (61.8%) | |
| **Defect** | | | 0.10 |
| A | 6 (7.5%) | 5 (5.5%) | |
| B | 21 (26.3%) | 28 (30.8%) | |
| C | 28 (35.0%) | 40 (44.0%) | |
| D | 10 (12.5%) | 2 (2.2%) | |
| No repair | 12 (15.0%) | 14 (15.4%) | |
| Unknown | 3 (3.8%) | 2 (2.2%) | |
| **Major cardiac anomaly** | | | 0.42 |
| Aortic hypoplasia | 2 (2,6%) | 0 (0%) | |
| Ductus aneurysm | 1 (1.3%) | 0 (0%) | |
| ASD and VSD | 1 (1.3%) | 0 (0%) | |
| HLHS variant | 0 (0%) | 1 (1.1%) | |
| Aortic stenosis | 0 (0%) | 1 (1.1%) | |
| **Results presented as n (%), mean± SD or median (IQR).** | | | |

Snoek K et al. Ann Surg 2016

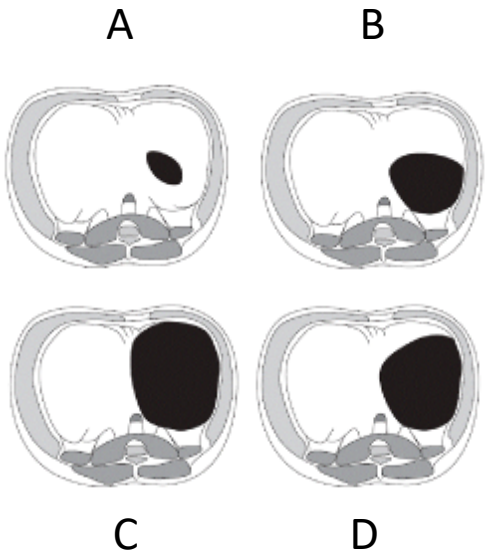
# Oxygen dependency and/or death @ day 28

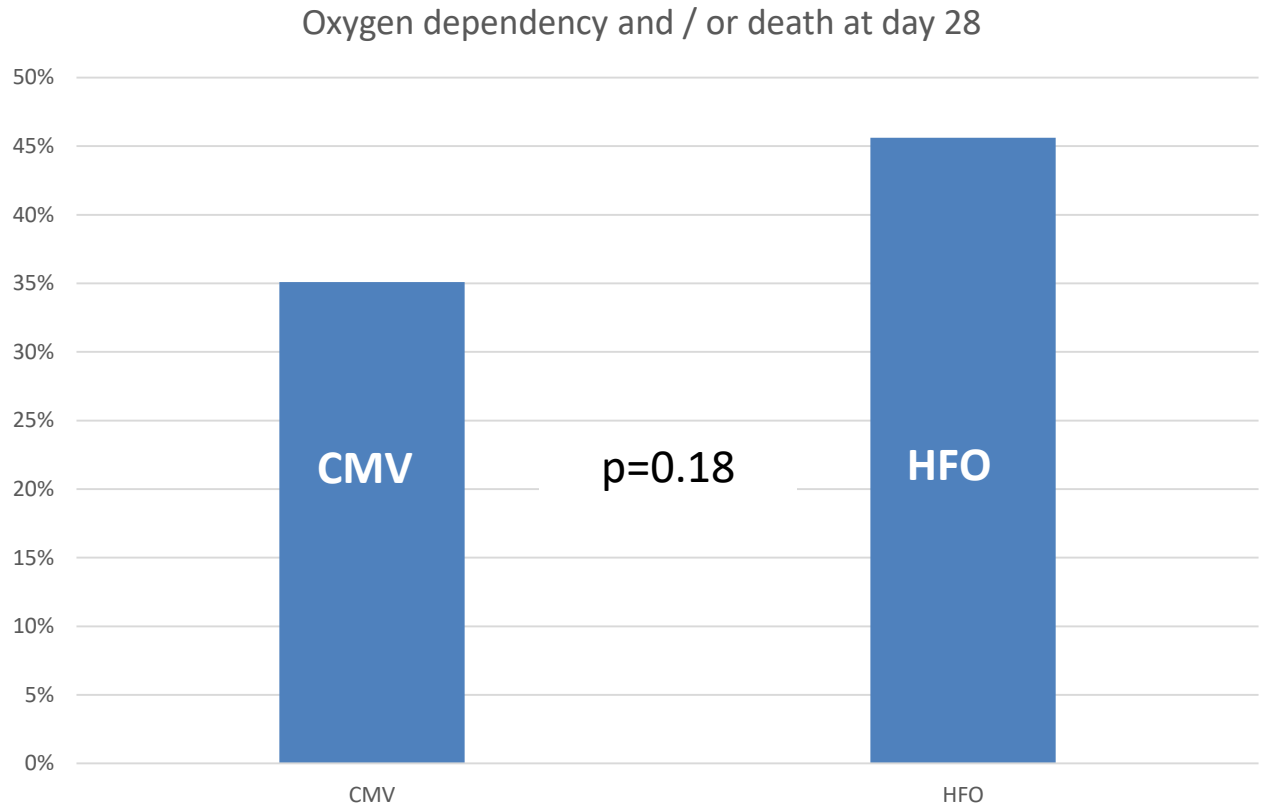



*Corrected for centre, side of defect, liver position

Snoek K et al. Ann Surg 2016

# Primary outcome: operated infants




*Corrected for: centre, side of defect, liver position,

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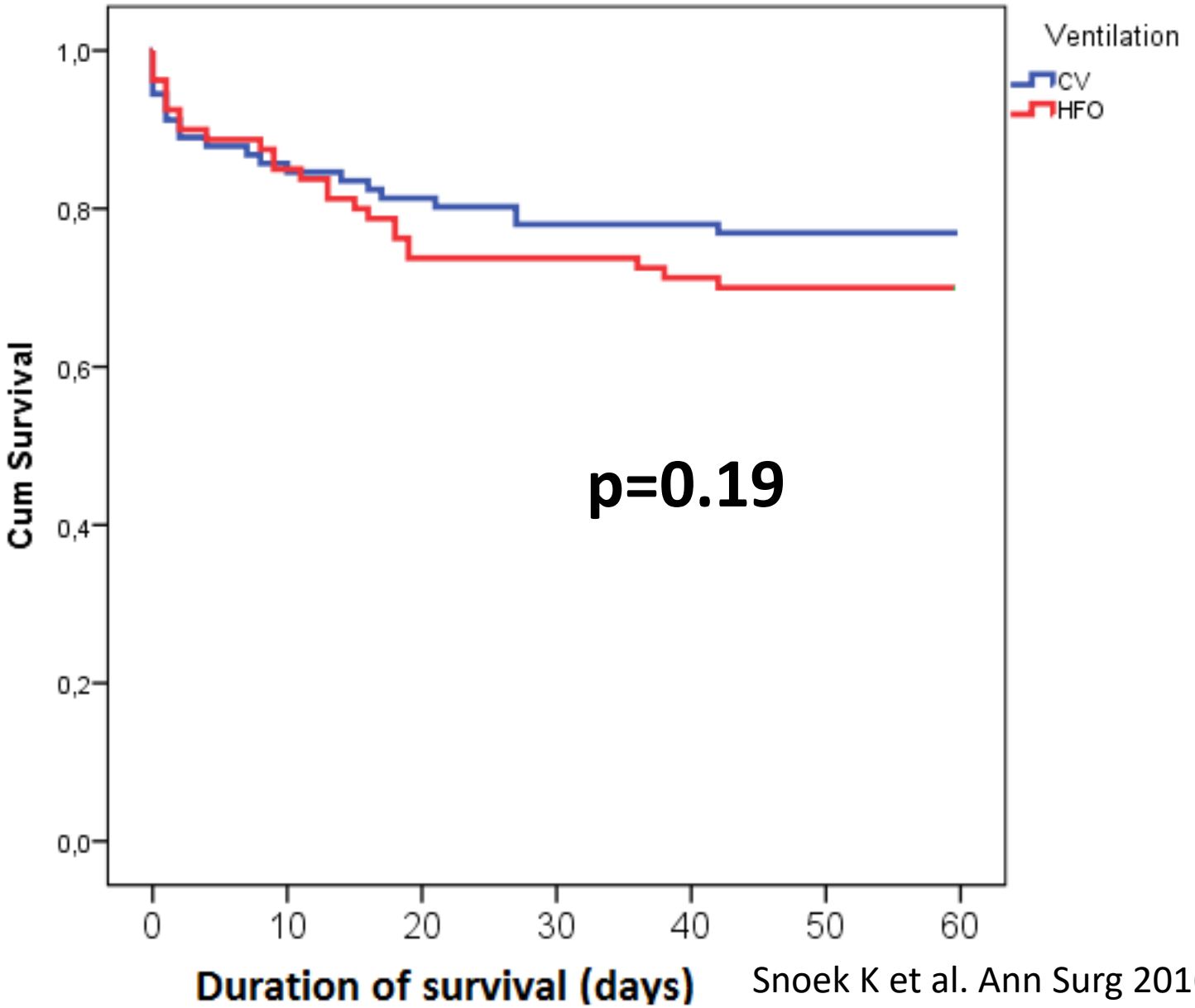
# Kaplan- Meier curve

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# Secondary outcome

| Variable | HFO (n= 80) | CMV (n= 91) | p-value |
|---|---|---|---|
| **Length of ventilation (days)** | **13 (8- 23)** | **10 (6- 18)** | **0.03** |
| **Severity BPD** | | | 0.13 |
| No BPD | 37 (46.3%) | 50 (54.9%) | |
| Mild BPD | 7 (8.8%) | 13 (14.3%) | |
| Moderate BPD | 2 (2.5%) | 1 (1.1%) | |
| Severe BPD | 9 (11.3%) | 6 (6.6%) | |
| Died | 25 (31.3%) | 21 (23,1%) | |
| **ECMO (in ECMO centers only)** | **24 (48.9%)** | **16 (26.2%)** | **0.007** |
| **Inhaled nitric oxide** | **45 (56.2%)** | **39 (42.9%)** | **0.045** |
| **Phosphodiesterase inhibitor 5 (Sildenafil®)** | **25 (31.2%)** | **11 (12.1%)** | **0.004** |
| Inotropics | 73 (91.2%) | 73 (80.2%) | 0.08 |
| **Duration inotropics (days) (in survivors only)** | **8 (4.25- 19)** | **6 (3.25- 11.75)** | **0.02** |
| **Number of total treatment failures** | **37 (46.3%)** | **22 (24.2%)** | **0.03** |
| Pulmonary hypertension | 55 (71.3%) Missing: n=3 | 58 (63.7%) Missing: n=4 | 0.16 |

Results presented as n (%) or median (IQR).

Snoek K et al. Ann Surg 2016

# Conclusion- VICI trial

- No statistical difference in primary outcome (oxygen dependency and / or death @ day 28).

- **Initially ventilated** with CMV:
  - Shorter ventilation
  - Less need of ECMO
  - Less inhaled NO
  - Less need of sildenafil
  - Shorter duration of inotropics
  - Less treatment failures.

**CMV should be considered as the best initial ventilation strategy in prenatal diagnosed patients with CDH**

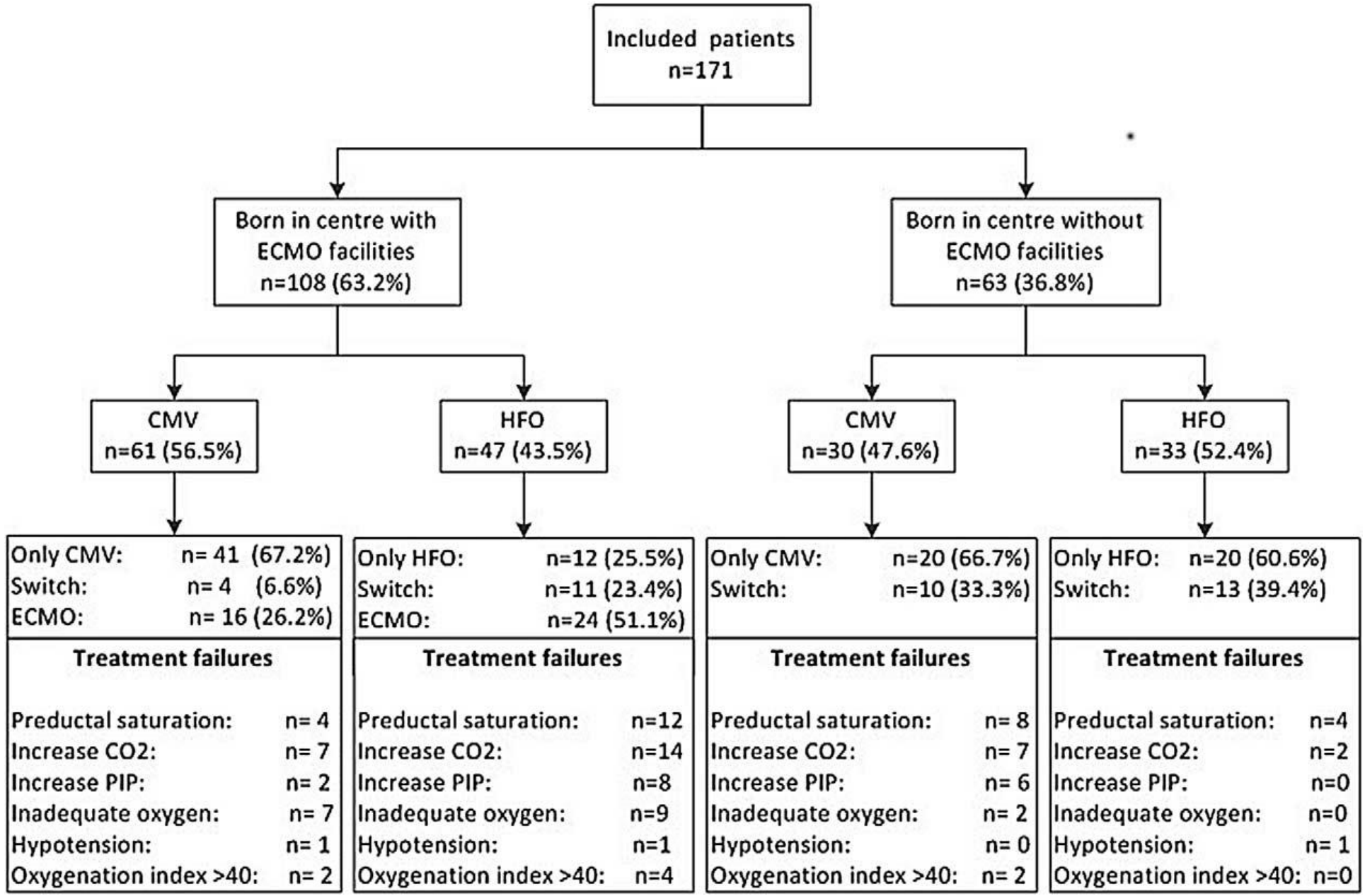
CDH Euro-Consortium

# Acknowledgements

## All participating patients, parents and centers from the CDH Euro-Consortium


Bambino Gesù Hospital, Rome, Italy (I. Capolupo, A. di Pede, P. Bagolan)
Erasmus MC-Sophia, Rotterdam, the Netherlands (D. Tibboel, R. Wijnen, A. Ekking)
Hospital Pediatrico de Coimbra, Coimbra, Portugal (C. Pinto)
Hospital San Joao, Porto, Portugal (M. Gorett Silva)
Hospital de Santa Maria, Lisboa, Portugal (J. Saldanha)
King's College, London, United Kingdom (P. Bhat, V. Murthy, A. Greenough)
UMC Radboud, Nijmegen, the Netherlands (A. van Heijst)
Universitätsklinikum Mannheim, Mannheim, Germany (T. Schaible; L. Wessel)
Universiteitsziekenhuis Gasthuisberg, Leuven, Belgium (K. Allegaert, A. Debeer).

- CDH Study Group (Kevin Lally)



Included patients
n=171
Born in centre with ECMO facilities
n=108 (63.2%)
Born in centre without ECMO facilities
n=63 (36.8%)
CMV
n=61 (56.5%)
HFO
n=47 (43.5%)
CMV
n=30 (47.6%)
HFO
n=33 (52.4%)
Only CMV: n= 41 (67.2%)
Switch: n= 4 (6.6%)
ECMO: n= 16 (26.2%)
Only HFO: n=12 (25.5%)
Switch: n=11 (23.4%)
ECMO: n=24 (51.1%)
Only CMV: n=20 (66.7%)
Switch: n=10 (33.3%)
Only HFO: n=20 (60.6%)
Switch: n=13 (39.4%)
Treatment failures
Preductal saturation: n= 4
Increase CO2: n= 7
Increase PIP: n= 2
Inadequate oxygen: n= 7
Hypotension: n= 1
Oxygenation index >40: n= 2
Treatment failures
Preductal saturation: n=12
Increase CO2: n=14
Increase PIP: n=8
Inadequate oxygen: n=9
Hypotension: n=1
Oxygenation index >40: n=4
Treatment failures
Preductal saturation: n= 8
Increase CO2: n= 7
Increase PIP: n= 6
Inadequate oxygen: n= 2
Hypotension: n= 0
Oxygenation index >40: n= 2
Treatment failures
Preductal saturation: n=4
Increase CO2: n=2
Increase PIP: n=0
Inadequate oxygen: n=0
Hypotension: n= 1
Oxygenation index >40: n=0