Optimizing resuscitation of extremely preterm infants

Peter Davis
The Royal Women's Hospital
University of Melbourne

The program

- Cord management
- Supplemental oxygen

Worldwide group - develops Consensus on Science with Treatment Recommendations (CoSTR) - serves as a scientific foundation

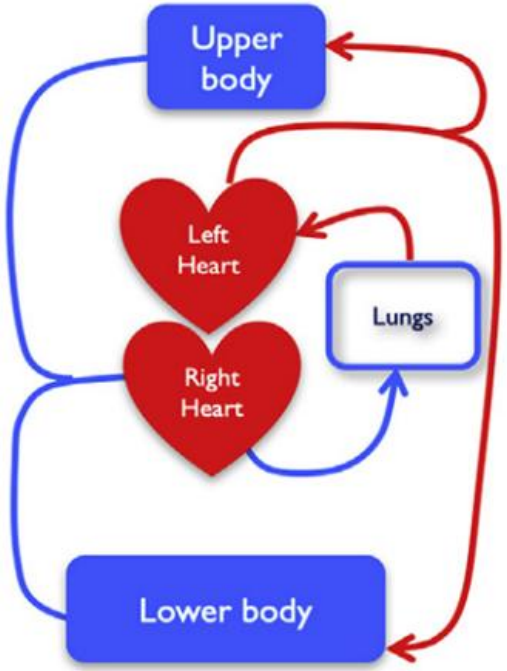
EUROPEAN RESUSCITATION COUNCIL

Develops and publishes its own guidelines, training programs, and policy recommendations based on CoSTR, adapted for European healthcare context

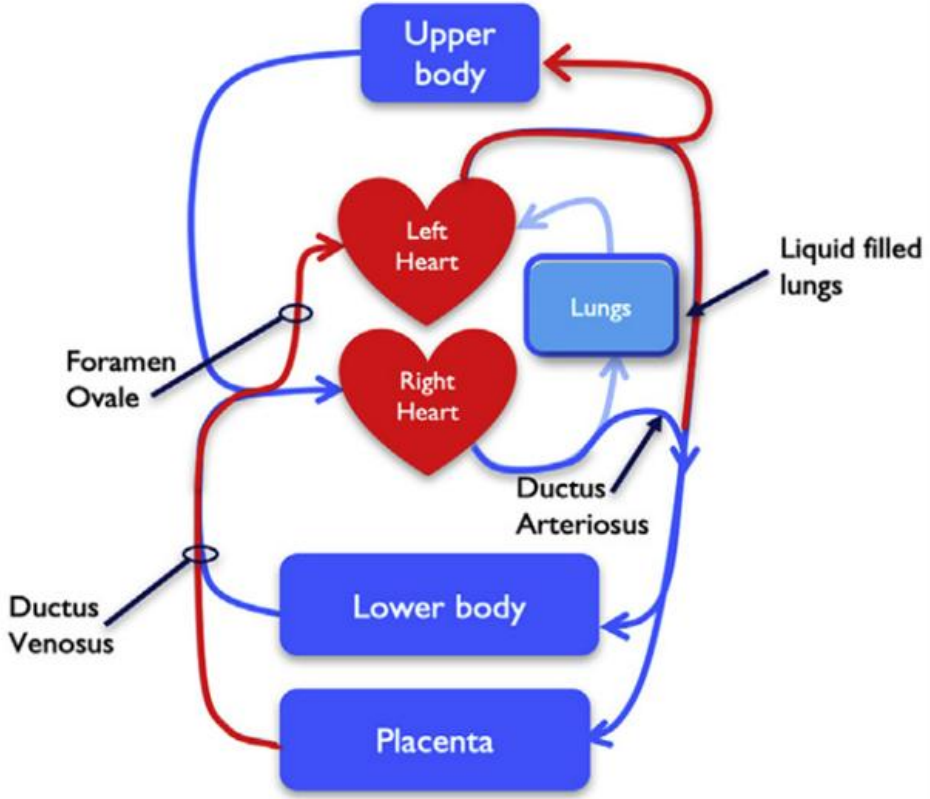
Implement and customize these frameworks for real-world, local application

Cord clamping in preterm infants: The evidence

After birth



Before birth



Background

- Infants born at <34 weeks' gestation are more likely to need resuscitation and stabilization at birth compared with those born late preterm or at term
- Immaturity of multiple organ systems puts at high risk for:
  - mortality
  - intraventricular hemorrhage (IVH)
- Therefore, might require different policies and management than infants born late preterm or term
- Affects 15 million preterm babies around the world annually

INDIVIDUAL PARTICIPANT DATA ON CORD MANAGEMENT AT PRETERM BIRTH (iCOMP)

Pairwise meta-analysis

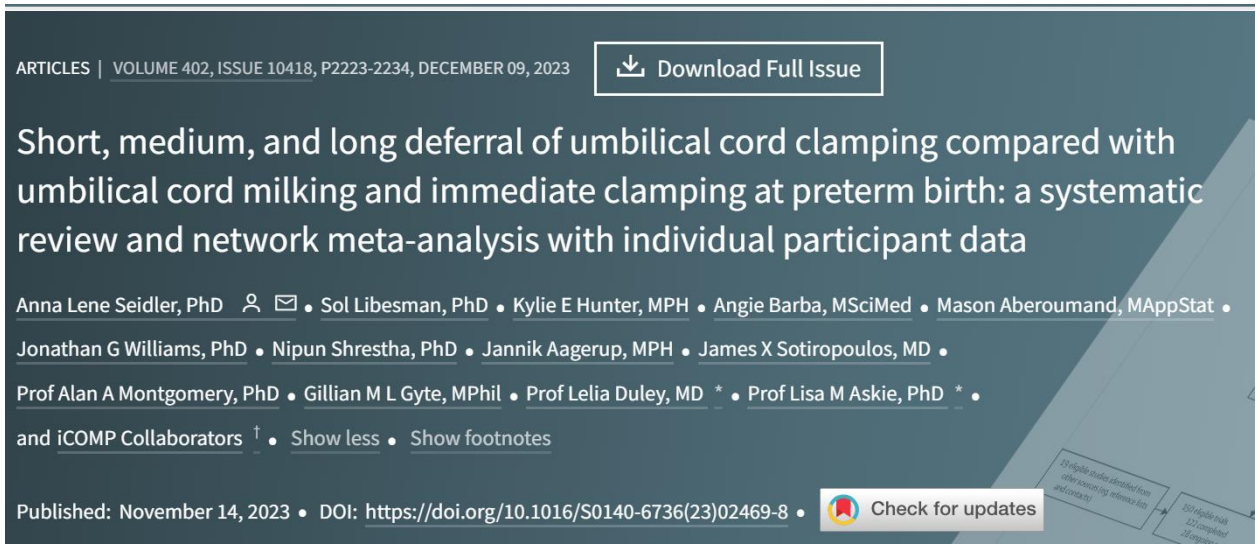
ARTICLES | VOLUME 402, ISSUE 10418, P2209-2222, DECEMBER 09, 2023 Download Full Issue

Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis

Anna Lene Seidler, PhD • Mason Aberoumand, MAppStat • Kylie E Hunter, MPH • Angie Barba, MSciMed • Sol Libesman, PhD • Jonathan G Williams, PhD • Nipun Shrestha, PhD • Jannik Aagerup, MPH • James X Sotiropoulos, MD • Prof Alan A Montgomery, PhD • Prof Gillian M L Gyte, MPhil • Prof Lelia Duley, MD * • Prof Lisa M Askie, PhD * • and iCOMP Collaborators † • Show less • Show footnotes

Published: November 14, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)02468-6 • Check for updates

Network meta-analysis



ARTICLES | VOLUME 402, ISSUE 10418, P2223-2234, DECEMBER 09, 2023 Download Full Issue

Short, medium, and long deferral of umbilical cord clamping compared with umbilical cord milking and immediate clamping at preterm birth: a systematic review and network meta-analysis with individual participant data

Anna Lene Seidler, PhD • Sol Libesman, PhD • Kylie E Hunter, MPH • Angie Barba, MSciMed • Mason Aberoumand, MAppStat • Jonathan G Williams, PhD • Nipun Shrestha, PhD • Jannik Aagerup, MPH • James X Sotiropoulos, MD • Prof Alan A Montgomery, PhD • Gillian M L Gyte, MPhil • Prof Lelia Duley, MD * • Prof Lisa M Askie, PhD * • and iCOMP Collaborators † • Show less • Show footnotes

Published: November 14, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)02469-8 • Check for updates

Lancet, December 2023

Individual patient data (IPD) vs Conventional (aggregate data) meta-analyses

- **Advantages**
  - Greater precision and power
  - More reliable subgroup analyses
  - Standardization of inclusion criteria, outcomes, statistical methods
  - Improved data quality and validation (fraud detection)
  - More sophisticated handling of missing data (multiple imputation)

- **Disadvantages**
  - **Resource intensive (time, $, statistical skills)**
  - Ethical/legal barriers to data sharing
  - Potential selection bias is only a subset of studies provides IPD

Definitions: Timing of cord clamping

- Immediate: as soon as possible or <15 s
- Short deferral: ≥15 s to <45 s
- Medium deferral: ≥45 s to <120 s
- Long deferral: ≥120 s

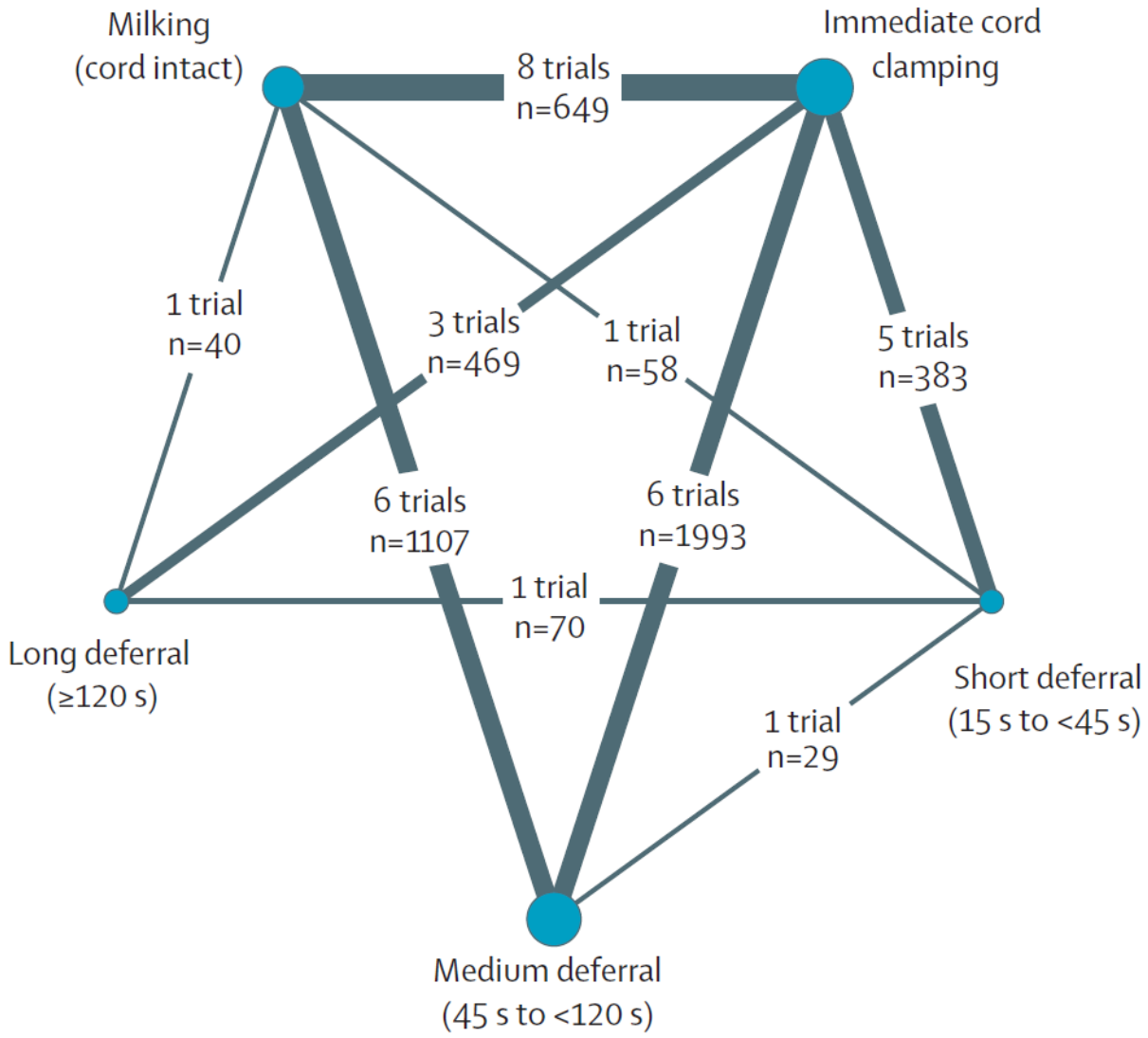
Strengths ($)

- Rigorous search strategy (medical databases, trial registries)
  - RCTs comparing deferred (delayed) cord clamping, cord milking, and immediate cord clamping for births <37 weeks' gestation
- Individual patient data
  - Harmonised outcomes, checked data, risk of bias assessments
- Power: 48 RCTs, 6367 infants

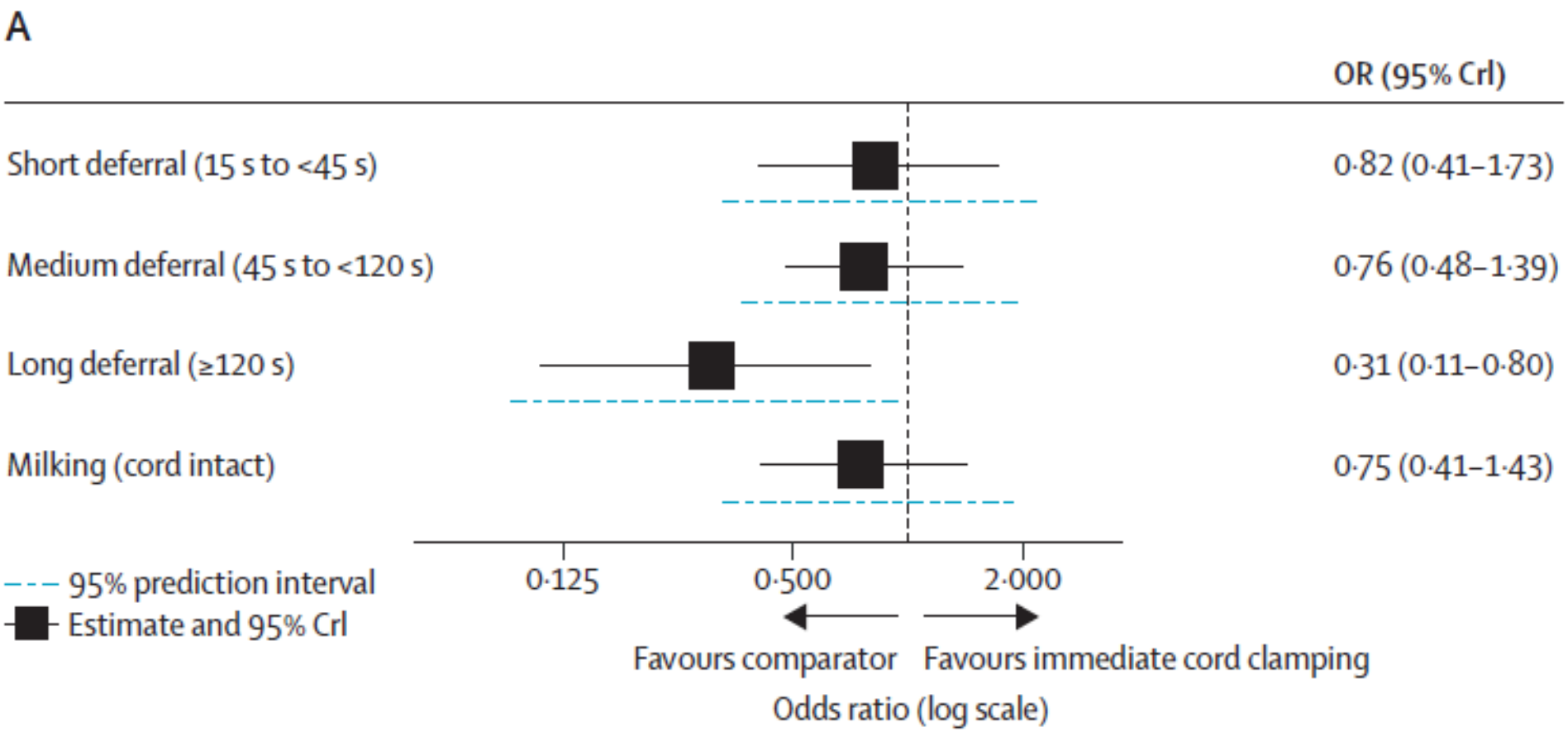
Pairwise meta-analysis: Messages

- Deferred cord clamping reduces mortality compared to immediate cord clamping
  - OR 0·68 (95% CI 0·51–0·91)
  - High certainty evidence
- Consistent results across
  - Subgroups by GA, mode of delivery, era, perinatal mortality rates
- No clear difference between cord milking and DCC/ICC

Network meta-analysis: Death before discharge

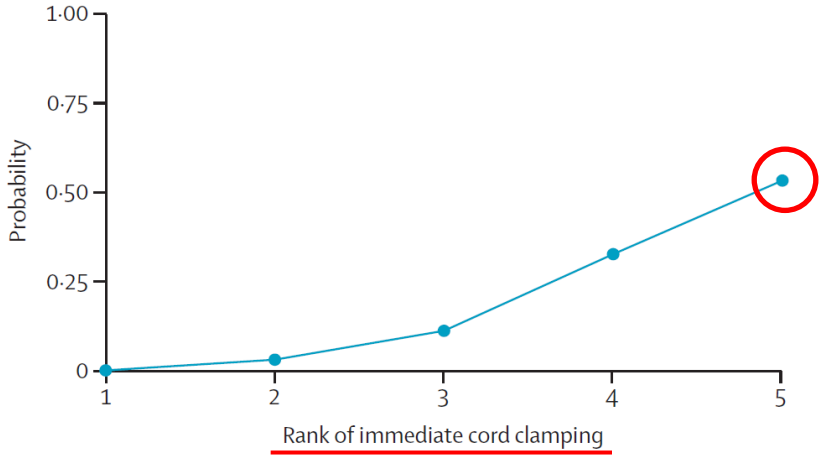


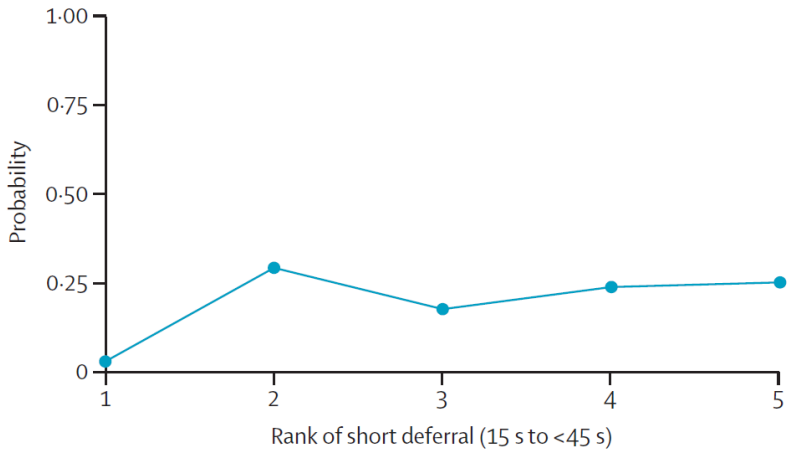
NMA: Mortality (compared with immediate cord clamping)

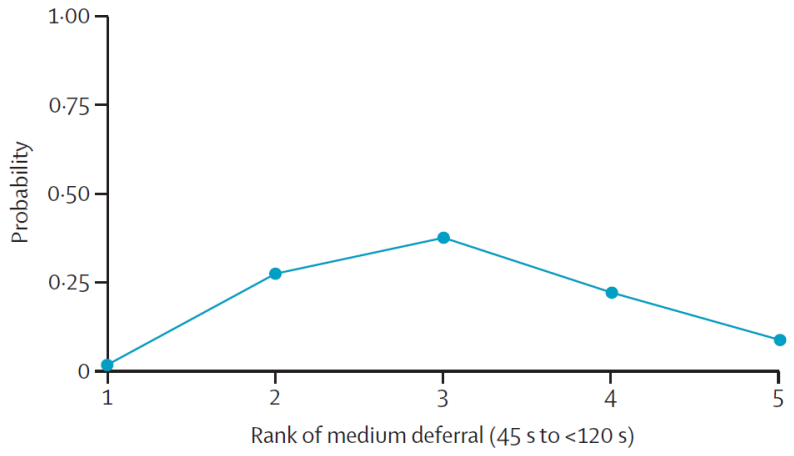


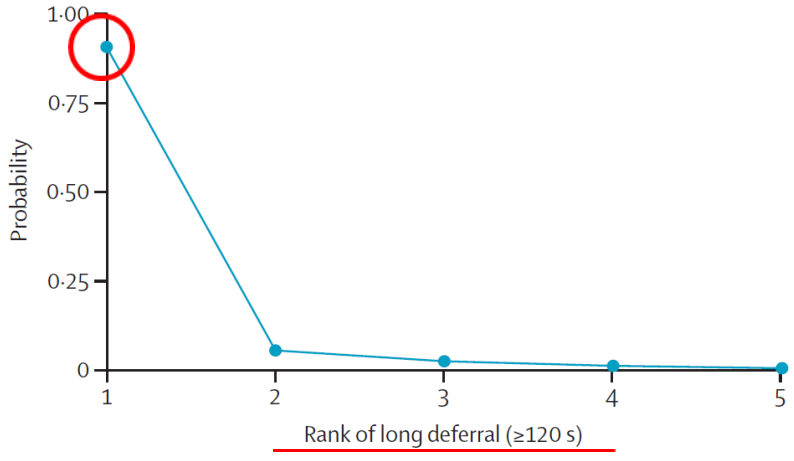
Conclusion

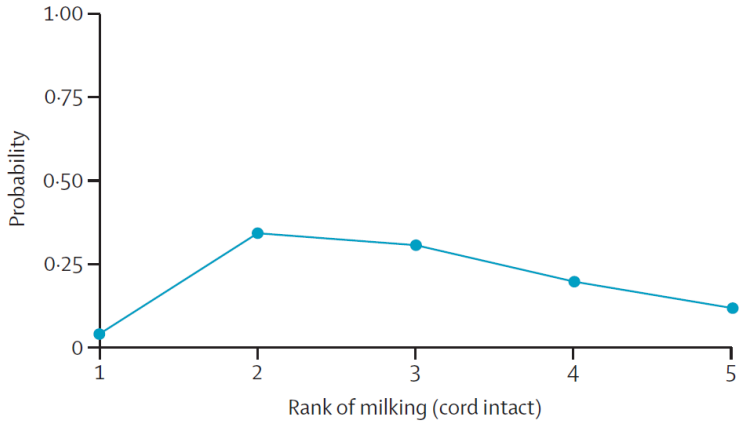
- Long deferral (≥120s) reduced death before discharge the most











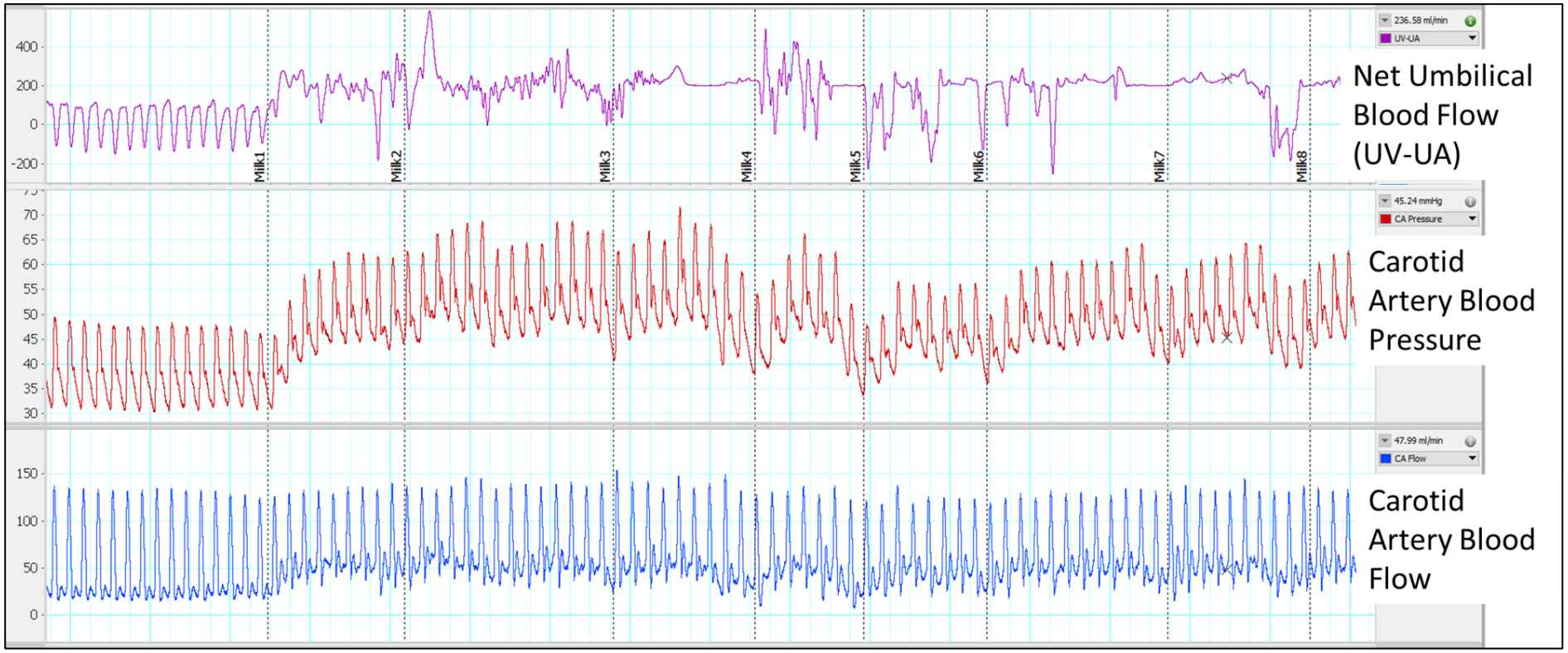
Outcome: ILCOR Recommendations

- In preterm infants born <37 weeks' who are deemed not to require immediate resuscitation at birth, we ***recommend*** deferring clamping of the umbilical cord for at least 60 seconds ***(Strong recommendation, high certainty evidence)***
  - Reduced mortality
  - High quality meta-analysis
  - Consistent across subgroups
  - Other outcomes better
    - Fewer blood transfusions
    - Higher Hb concentrations
  - 120 seconds is *reasonable* but not recommended
    - Appropriate if skilled team, appropriate equipment, enough space and appropriate thermal management

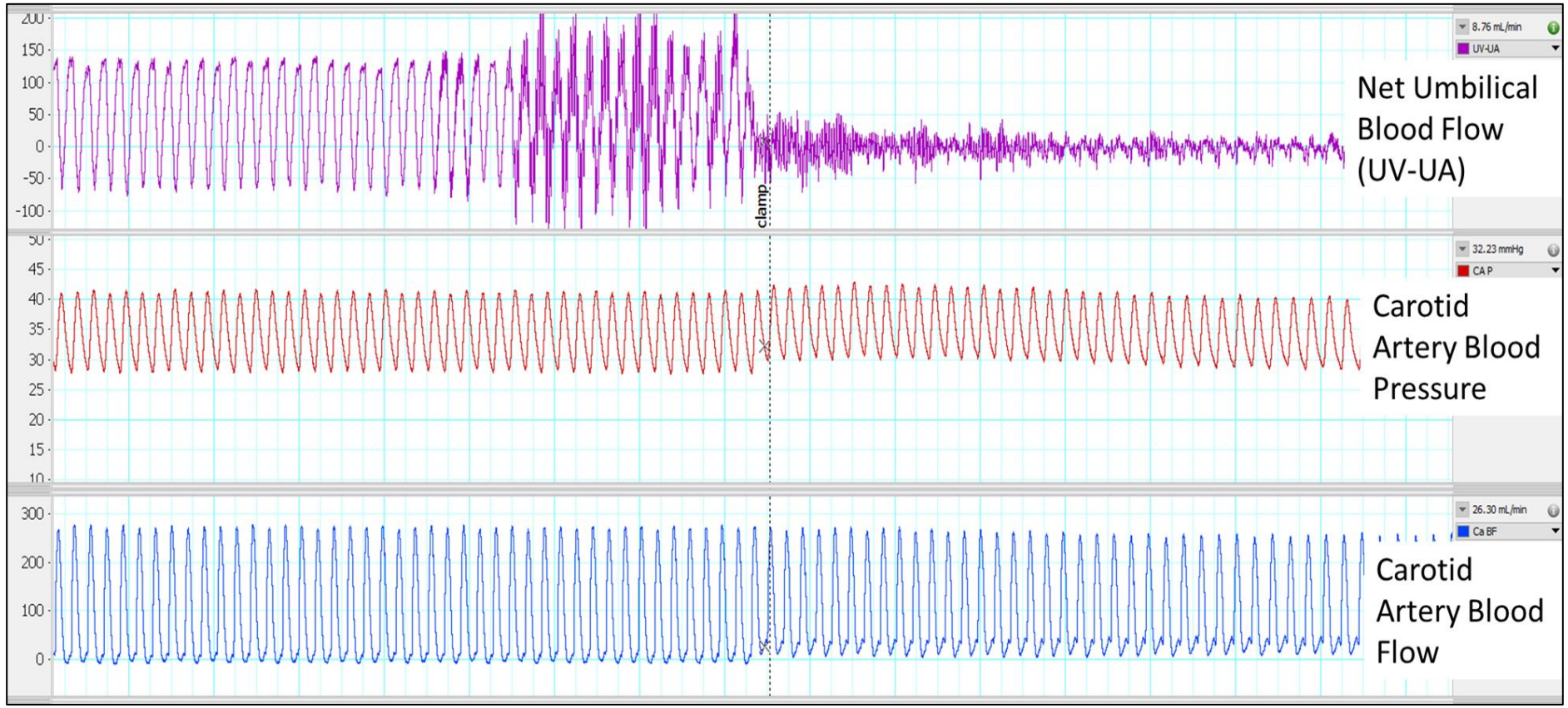
Outcome: ILCOR Recommendations

- We suggest against cord milking for infants born <28 weeks' (weak recommendation; low certainty evidence)
  - Driven by Katheria et al: higher rates of severe IVH in cord milking group

Lamb model of cord milking



Lamb model: Ventilation then cord clamping



Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe IVH Among Preterm Infants

Katheria et al, JAMA 2019

- Death or severe IVH: UCM 28/236 (12%) vs DCC 19/238 (8%) (p=0.16)
- Severe IVH in the lower GA strata: UCM 22% vs DCC 6%, p=0.0019)
- DSMB recommended stopping recruitment after interim analysis
- Conclusion: Centers practicing UCM should consider discontinuing this practice in infants 23-27 weeks gestation

Outcome: ILCOR Recommendations

- Insufficient evidence to make a recommendation on
  - **Infants <37 weeks' requiring resuscitation**
  - Multiple fetuses
  - Congenital anomalies
  - Alloimmunisation
- Individualised decisions based on assessment of neonatal and maternal risk

FIRST GAP: PRETERM INFANTS - RESUSCITATION ON THE CORD

JAMA Network Open

Original Investigation | Pediatrics

Ventilatory Assistance Before Umbilical Cord Clamping in Extremely Preterm Infants

A Randomized Clinical Trial

Karen D. Fairchild, MD; Gina R. Petroni, PhD; Nikole E. Varhegyi, MS; Marya L. Strand, MD; Justin B. Josephsen, MD; Susan Niermeyer, MD; James S. Barry, MD; Jamie B. Warren, MD; Monica Rincon, MD; Jennifer L. Fang, MD; Sumesh P. Thomas, MBBS; Colm P. Travers, MD; Andrea F. Kane, MD; Waldemar A. Carlo, MD; Bobbi J. Byrne, MD; Mark A. Underwood, MD; Francis R. Poulain, MD; Brenda H. Law, MD; Terri E. Gorman, MD; Tina A. Leone, MD; Dorothy I. Bulas, MD; Monica Epelman, MD; Beth M. Kline-Fath, MD; Christian A. Chisholm, MD; John Kattwinkel, MD; for the VentFirst Consortium

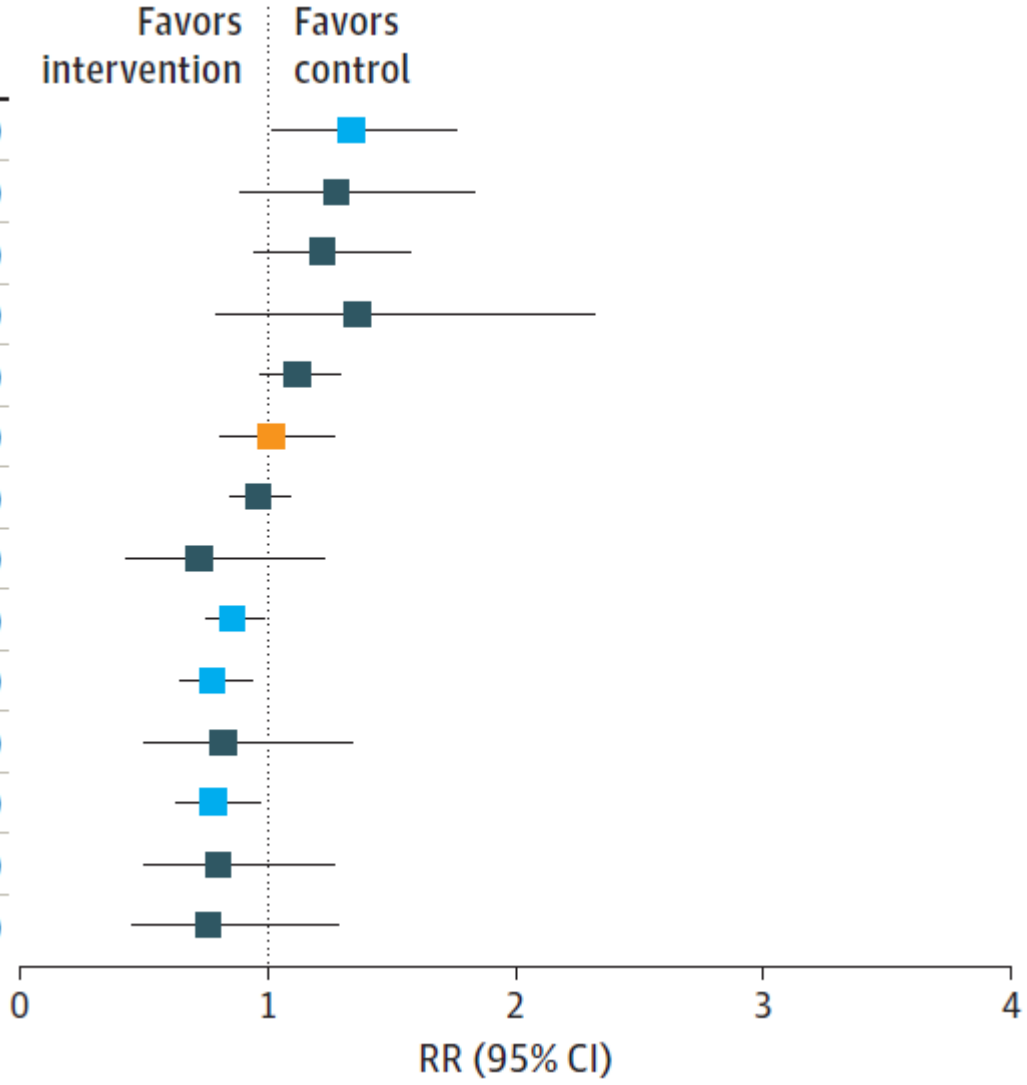
JAMA Network Open. 2024;7(5):e2411140.doi:10.1001/jamanetworkopen.2024.11140

The VentFirst Trial

- Patients: ***548*** infants delivered <29 weeks' at 12 US/Canadian sites
- Intervention:
  - continuous positive airway pressure if breathing well at 30 sec
  - positive-pressure ventilation if not breathing well
  - cord clamping at 120 seconds
- Control:
  - 30 to 60 seconds of delayed cord clamping followed by standard resuscitation (depending on breathing at 30 sec)
- Sample size: ***940*** infants to provide 80% power (2-sided P = .05) to detect an odds ratio of 0.50 for intervention compared with control in the not-breathing-well cohort

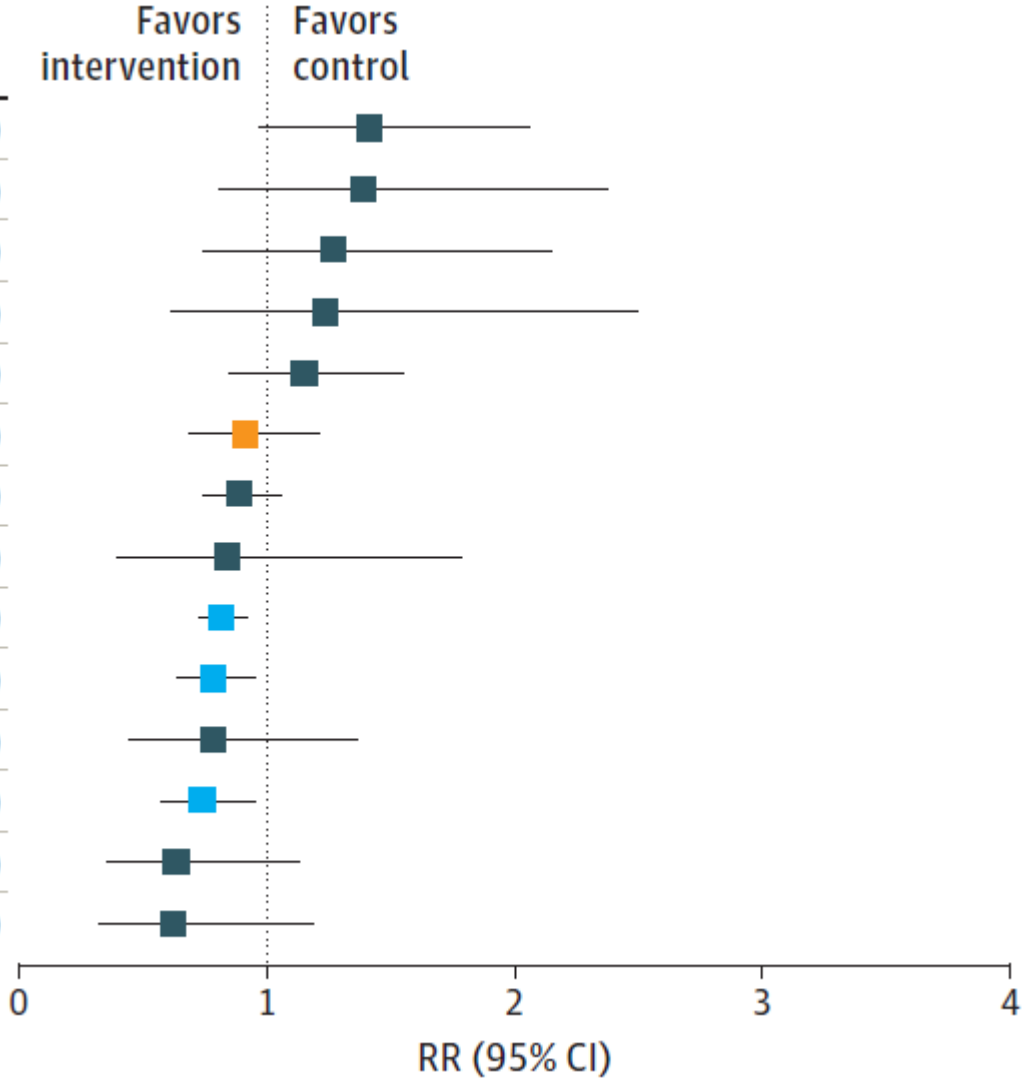
Results: Overall

Source	RR (95% CI)
Temperature <36.5 °C at admission	1.34 (1.02-1.76)
Late-onset sepsis	1.28 (0.89-1.84)
Any mechanical ventilation first 10 d	1.22 (0.94-1.58)
ROP stage ≥3	1.36 (0.80-2.32)
RBC transfusion first 10 d	1.12 (0.97-1.30)
Primary outcome: IVH or death <7 d	1.02 (0.81-1.27)
Bronchopulmonary dysplasia	0.96 (0.85-1.09)
Necrotizing enterocolitis	0.72 (0.43-1.23)
Apgar score <5 at 1 min	0.86 (0.75-0.98)
Intubation in delivery room	0.78 (0.65-0.93)
Death before 36 wk PMA	0.82 (0.50-1.34)
Hematocrit <40% first 24 h	0.78 (0.62-0.97)
Severe brain injury to 36 wk PMA	0.80 (0.50-1.27)
Severe IVH grade 3-4	0.76 (0.45-1.29)



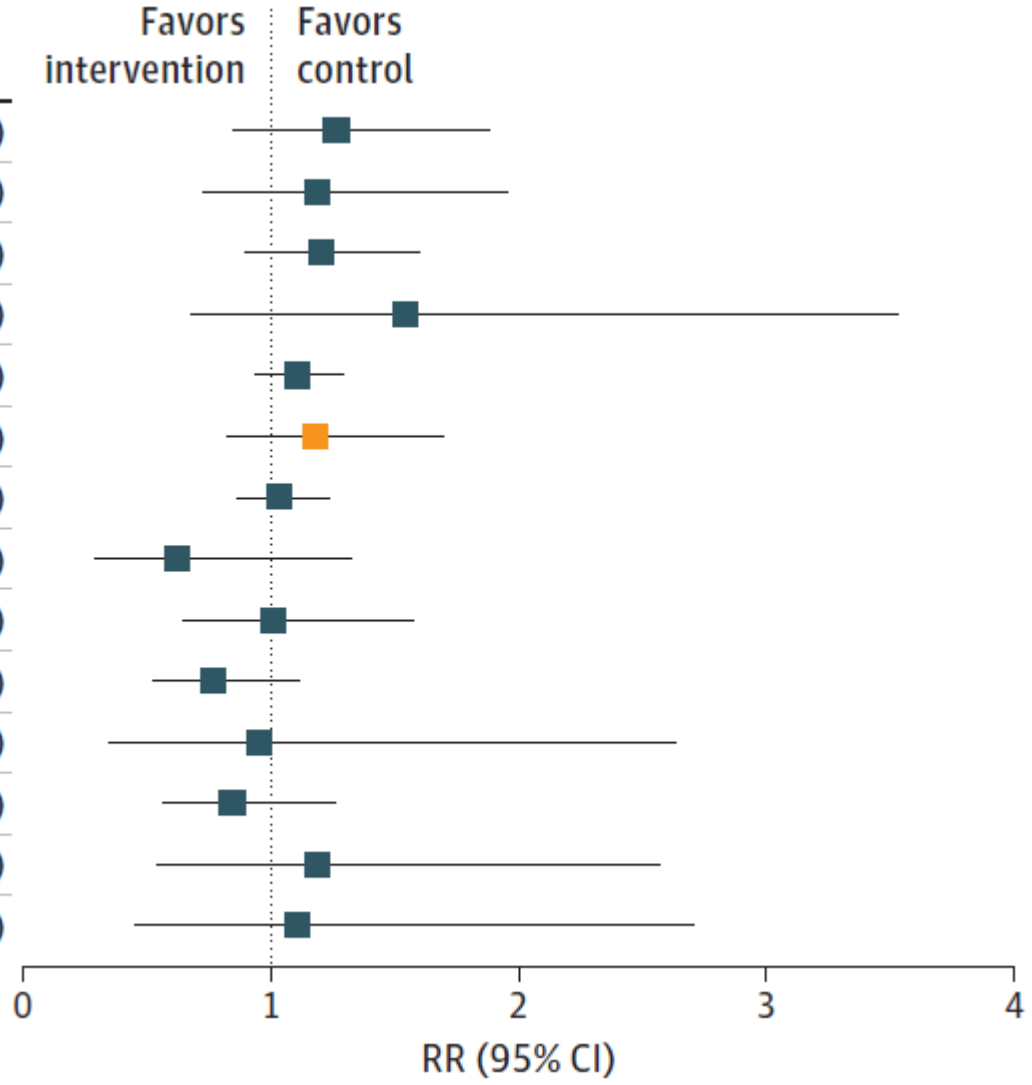
Results: Not breathing well

Source	RR (95% CI)
Temperature <36.5 °C at admission	1.41 (0.97-2.06)
Late-onset sepsis	1.38 (0.81-2.37)
Any mechanical ventilation first 10 d	1.27 (0.75-2.15)
ROP stage ≥3	1.23 (0.61-2.49)
RBC transfusion first 10 d	1.15 (0.85-1.55)
Primary outcome: IVH or death <7 d	0.91 (0.68-1.21)
Bronchopulmonary dysplasia	0.89 (0.74-1.06)
Necrotizing enterocolitis	0.84 (0.40-1.79)
Apgar score <5 at 1 min	0.82 (0.72-0.92)
Intubation in delivery room	0.78 (0.64-0.96)
Death before 36 wk PMA	0.78 (0.45-1.37)
Hematocrit <40% first 24 h	0.74 (0.57-0.96)
Severe brain injury to 36 wk PMA	0.63 (0.35-1.13)
Severe IVH grade 3-4	0.61 (0.32-1.19)



Results: Breathing well

Source	RR (95% CI)
Temperature <36.5 °C at admission	1.26 (0.85-1.89)
Late-onset sepsis	1.19 (0.73-1.95)
Any mechanical ventilation first 10 d	1.20 (0.90-1.61)
ROP stage ≥3	1.54 (0.68-3.53)
RBC transfusion first 10 d	1.11 (0.95-1.30)
Primary outcome: IVH or death <7 d	1.18 (0.82-1.70)
Bronchopulmonary dysplasia	1.04 (0.87-1.24)
Necrotizing enterocolitis	0.63 (0.30-1.33)
Apgar score <5 at 1 min	1.01 (0.65-1.57)
Intubation in delivery room	0.77 (0.53-1.12)
Death before 36 wk PMA	0.95 (0.35-2.63)
Hematocrit <40% first 24 h	0.85 (0.57-1.26)
Severe brain injury to 36 wk PMA	1.19 (0.55-2.57)
Severe IVH grade 3-4	1.11 (0.45-2.71)



CONCLUSIONS AND RELEVANCE: This study did not show that providing assisted ventilation before cord clamping in extremely preterm infants reduces IVH or early death

Physiological versus time based cord clamping in very preterm infants (ABC3): a parallel-group, multicentre, randomised, controlled superiority trial

Ronny Knol,[a,*] Emma Brouwer,[b] Thomas van den Akker,[c,d] Philip L. J. DeKoninck,[e,f] Wes Onland,[g,h] Marijn J. Vermeulen,[a] Willem P. de Boode,[i] Anton H. van Kaam,[g,h] Enrico Lopriore,[b] Irwin K. M. Reiss,[a] G. Jeroen Hutten,[g,h] Sandra A. Prins,[g,h] Estelle E. M. Mulder,[j] Esther J. d'Haens,[j] Christian V. Hulzebos,[k] Helene A. Bouma,[k] Sam J. van Sambeeck,[l] Hendrik J. Niemarkt,[l] Mayke E. van der Putten,[m] Tinta Lebon,[m] Inge A. Zonnenberg,[n] Debbie H. Nuytemans,[g,h] Sten P. Willemsen,[o] Graeme R. Polglase,[f,p] Sylke J. Steggerda,[b] Stuart B. Hooper,[f,q] and Arjan B. te Pas[b]

https://doi.org/10.1016/j.lanepe.2024.101146

The Lancet Regional Health - Europe
2025;48: 101146

ABC3 Trial

- P: Very preterm infants born before 30 weeks of gestation
  - stratified by gestational age (<27+0 and ≥27+0 weeks)
- I: Concord trolley used to perform PBCC, respiratory support commenced CPAP and PPV via facemask, umbilical cord clamped when heart rate >100 bpm and SpO2 >85% using <40% oxygen (3-10 min)
- C: Clamping time-based 30–60 s, depending on clinical condition, then moved to standard resus table
- O: intact survival at NICU discharge, survival without major cerebral injury (IVH ≥ grade 2 or PVL)

Results

	PBBC (n=339)	TBCC (n=330)	Risk difference (adj)	p value
Composite primary outcome (survival without major cerebral injury or NEC)	71%	68%	3.1 ((-11 to 15.8)	0.33
Death	14%	14%	-0.2 (-8.8 to 14.1)	0.96
Major cerebral injury	17%	17%	-0.4 (-6.0 to 10.9)	0.69
Necrotising enterocolitis	7%	9%	-0.6 (-6.0 to 16.1)	0.43

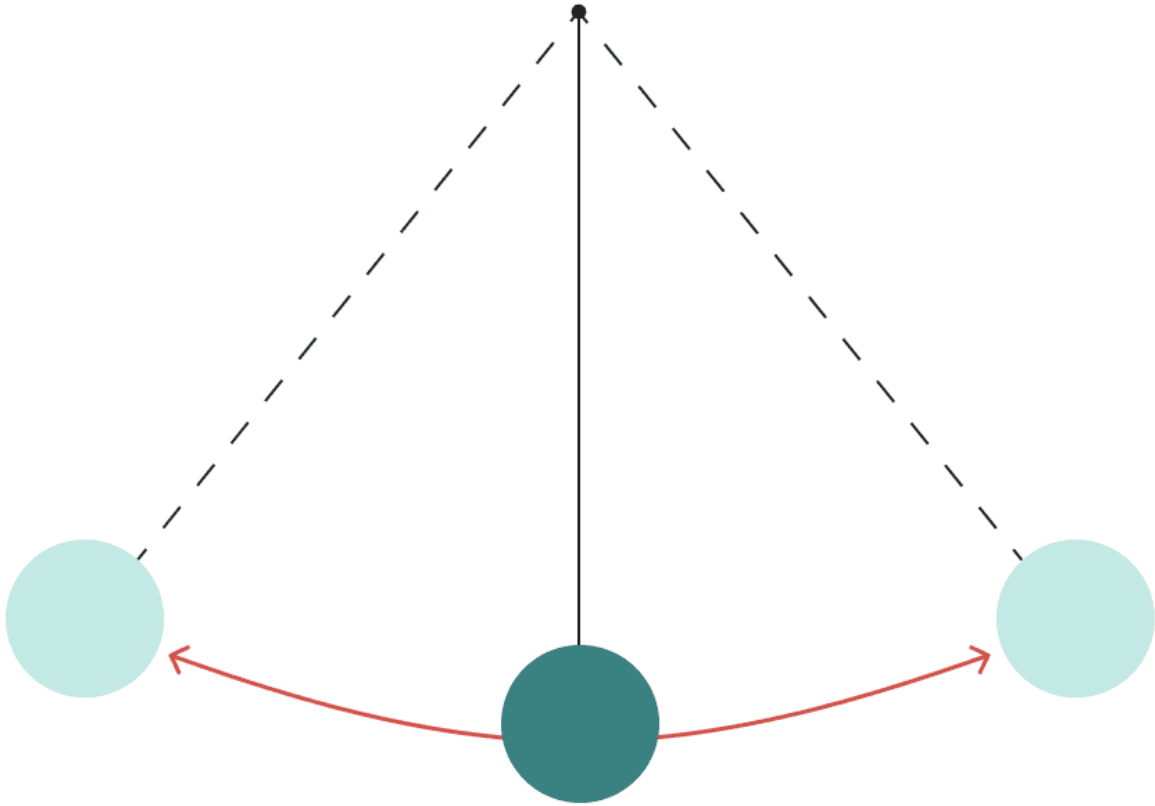
Authors' "hypothesis generating" findings

- A learning effect – results of PBCC seemed to improve with experience
- An effect in male babies
- (Parents happier with PBCC)

My thoughts

- The magnitude of beneficial effect less than hoped for given our understanding of the physiology (we've seen this before)
- These were experts, therefore "safety" may not generalise to all units
  - If you are experienced and happy with PBCC consider keeping doing it
  - If you haven't started, wait for more data

OXYGEN AS THERAPY IN THE DR



Oxygen and Resuscitation: Beyond the Myth

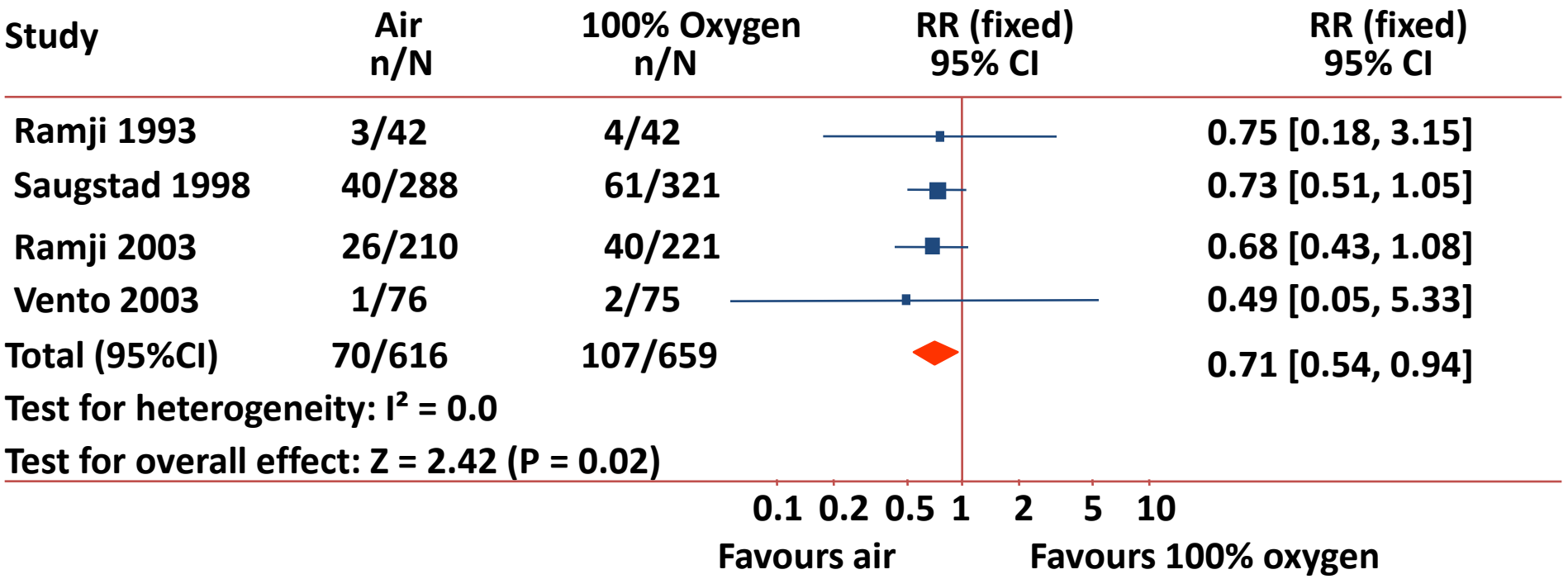
"We started using oxygen for resuscitation because it seemed like a good idea. Now we use it because we always have."

William Lefkowitz, Pediatrics 2002;109;517-519

Air vs oxygen for resuscitation

- Ola Saugstad: showed it is possible to conduct international, multicentred trials of critically ill infants in the delivery room
- Max Vento: showed that these trials can be randomised and blinded

Mortality



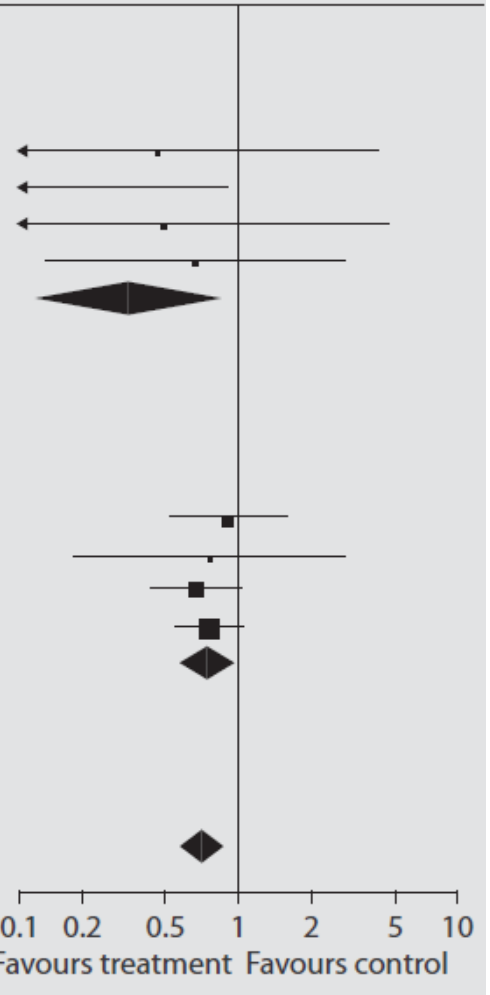
Tan A, Schulze A, O'Donnell CP, Davis PG. Air versus oxygen for resuscitation of infants at birth. Cochrane Database Syst Rev (2004).

Air vs oxygen for resuscitation

- Ola Saugstad: showed it is possible to conduct international, multicentred trials of critically ill infants in the delivery room
- Max Vento: showed that these trials can be randomised and blinded
- Babies (Term) resuscitated with air
  - Commence breathing earlier
  - Have better Apgar scores
  - **Have improved survival rates**

Mortality (Saugstad 2008)

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



Preterm infants: recent history

- 2019: ILCOR (10 RCTs and 4 cohort studies) – no difference between starting with low vs high oxygen
  - We suggest starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks' gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence)
- 2024: NetMotion (Sotiropoulos JAMA Pediatr)
  - High initial FiO_2 (≥0.90) may be associated with reduced mortality in preterm infants born at less than 32 weeks' gestation compared to low initial FiO_2 (low certainty). ***High initial FiO_2*** is possibly associated with ***reduced mortality*** compared to intermediate initial FiO_2 (very low certainty) but more evidence is required.

NetMotion: JAMA Pediatr 2024

JAMA Pediatrics | Original Investigation

Initial Oxygen Concentration for the Resuscitation of Infants Born at Less Than 32 Weeks' Gestation

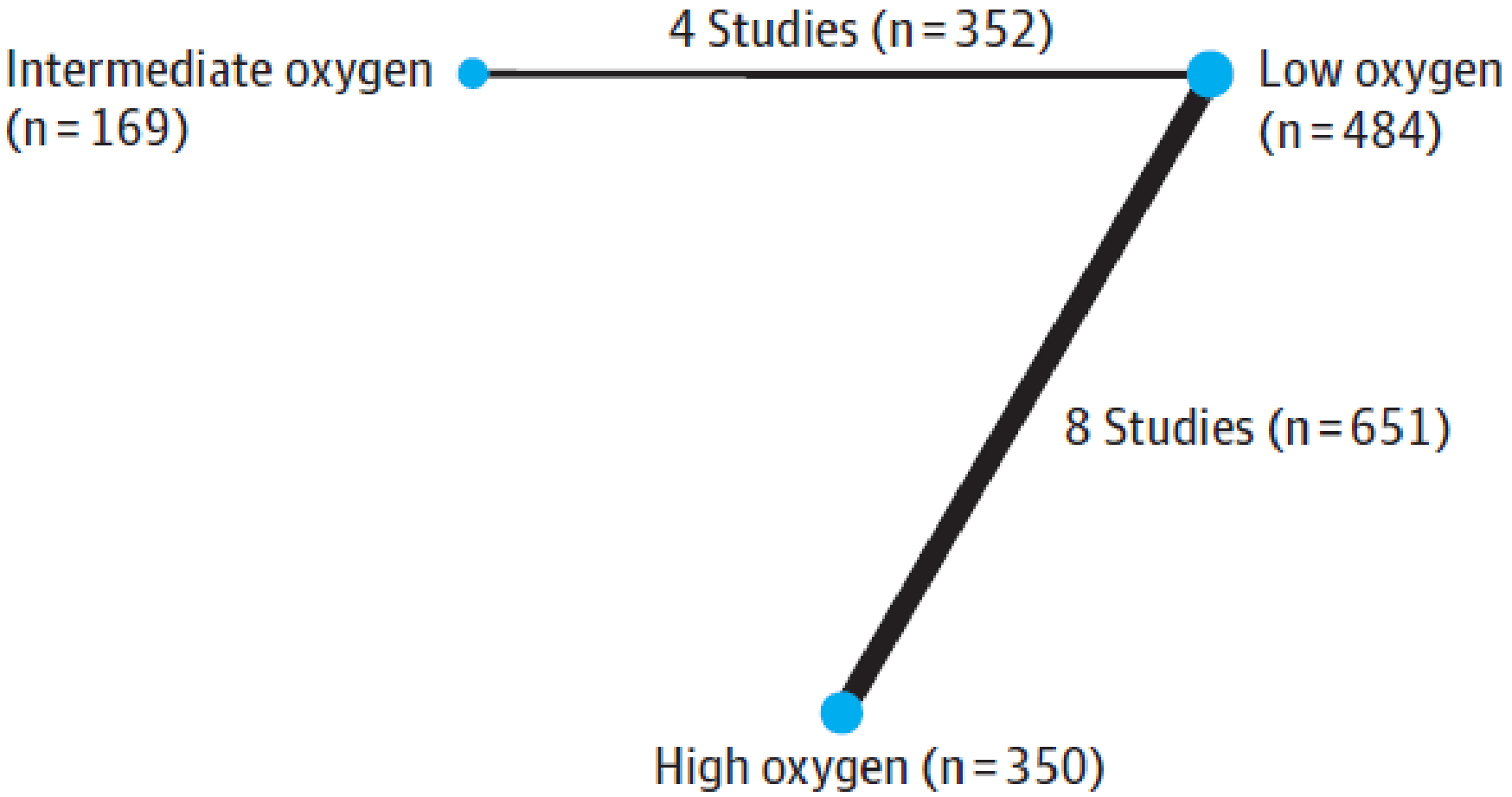
A Systematic Review and Individual Participant Data Network Meta-Analysis

James X. Sotiropoulos, MD; Ju Lee Oei, MD; Georg M. Schmölzer, MD, PhD; Sol Libesman, PhD; Kylie E. Hunter, PhD; Jonathan G. Williams, PhD; Angela C. Webster, PhD; Maximo Vento, MD, PhD; Vishal Kapadia, MD; Yacov Rabi, MD; Janneke Dekker, PhD; Marijn J. Vermeulen, MD, PhD; Venkataseshan Sundaram, MD; Praveen Kumar, MD; Risma K. Kaban, MD, PhD; Rinawati Rohsiswatmo, MD, PhD; Ola D. Saugstad, MD, PhD; Anna Lene Seidler, PhD

NetMotion

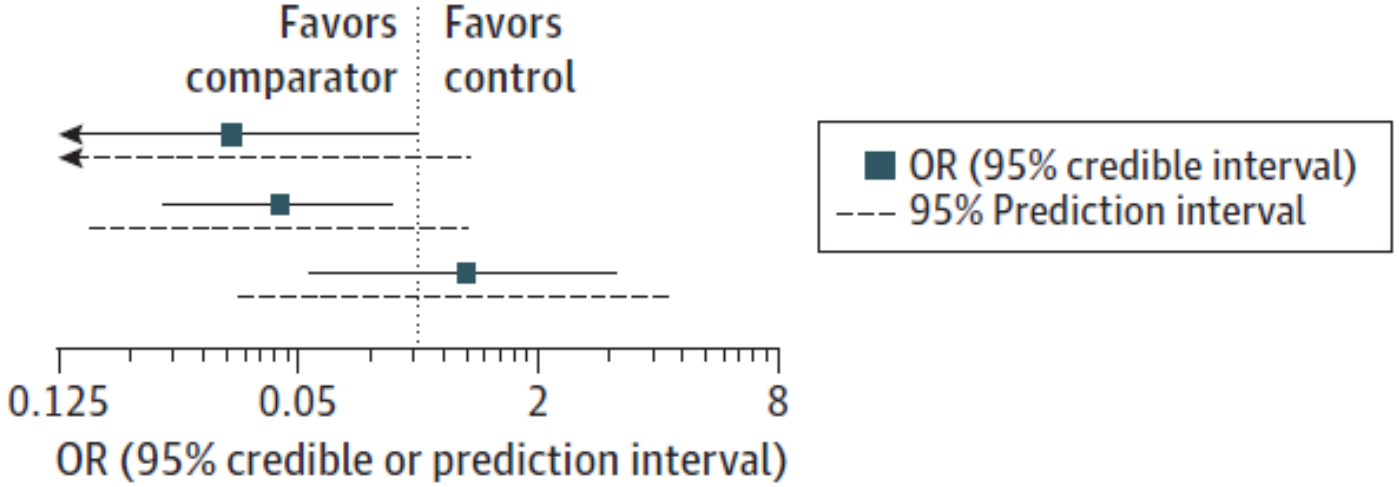
- RCTs enrolling preterm infants born at less than 32 weeks' gestation
- Individual patient data for 1055 infants from 12 of the 13 eligible studies (2005-2019)
- Compared low (≤0.3), intermediate (0.5-0.65), or high (≥0.90) FiO_2

Network diagram



All cause mortality to hospital discharge

Comparator vs control	OR (95% credible interval)
High vs intermediate	0.34 (0.11–0.99)
High vs low	0.45 (0.23–0.86)
Intermediate vs low	1.33 (0.54–3.15)



Outcomes

Outcome	Comparison[a]	OR or MD (95% CrI)[b]	Certainty of evidence[c]	Oxygen, No./total No. (%) or median (IQR)[d]		
				Low	Intermediate	High
Binary outcomes, No./total No. (%)[e]						
Death	High vs intermediate	0.34 (0.11 to 0.99)[f]	⨁◯◯◯	69/483 (14)	26/169 (15)	30/350 (9)
	High vs low	0.45 (0.23 to 0.86)[f]	⨁⨁◯◯			
	Intermediate vs low	1.33 (0.54 to 3.15)	⨁◯◯◯			
	τ^{2g}	0.06	NA			
Severe IVH	High vs intermediate	0.76 (0.05 to 6.17)	⨁◯◯◯	37/469 (8)	13/166 (8)	19/340 (6)
	High vs low	0.56 (0.10 to 1.82)	⨁◯◯◯			
	Intermediate vs low	0.74 (0.12 to 4.25)	⨁◯◯◯			
	τ^{2g}	1.14	NA			
Chronic lung disease	High vs intermediate	1.34 (0.38 to 4.30)	⨁◯◯◯	117/455 (26)	35/155 (23)	108/328 (33)
	High vs low	1.17 (0.55 to 2.52)	⨁◯◯◯			
	Intermediate vs low	0.86 (0.35 to 2.39)	⨁◯◯◯			
	τ^{2g}	0.27	NA			

Conclusions

- High initial FiO_2 (≥0.90) *may* be associated with reduced mortality in preterm infants born at less than 32 weeks' gestation compared to low initial FiO_2(low certainty)
- High initial FiO_2 is *possibly* associated with reduced mortality compared to intermediate initial FiO_2 (very low certainty) but more evidence is required

ILCOR's view!

- NetMotion – overall certainty of evidence was very low
  - Relatively small sample sizes (below optimal information size)
- Among newborn infants <32 weeks' gestation, it is reasonable to begin resuscitation with 30% oxygen or more (weak recommendation, low-certainty evidence)
- (Reluctance to recommend large swings in therapy – 30% to 90%)
- For infants born at 32 to 34+6 weeks' gestation, there is insufficient evidence to make a recommendation

ILCOR's view (Gaps)

- Two trials comparing 30% vs 60% are expected – watch this space
- We need more than just the starting oxygen concentration - comparison of targets and strategies for oxygen saturation levels in the first 10-20 min after birth in preterm infants
- The uncertainty over the optimal initial oxygen concentration means that it is reasonable to study a full range of oxygen concentrations (21-100%) within a research protocol

Targeted Oxygenation in the Respiratory Care of Preterm Infants at Delivery: Torpido 30/60

A Randomized Clinical Trial

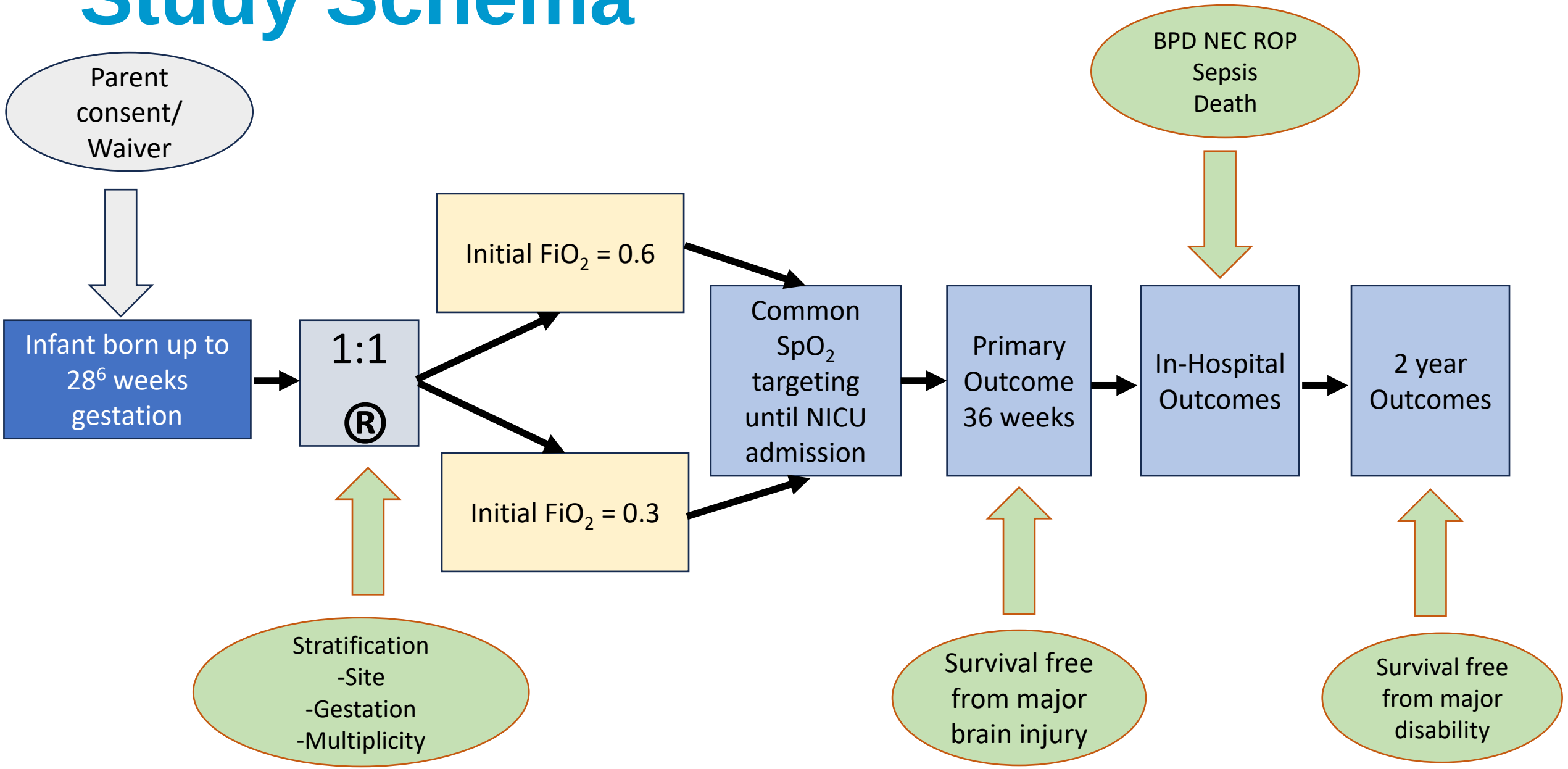
Trial Registration number: ACTRN12618000879268

Design

- Randomised controlled, phase III trial
- Stratified by site, gestation & multiplicity

- **P**atient — Preterm infants from 23+0 to 28+6 weeks gestation
- **I**ntervention — Initial FiO_2 0.6
- **C**ontrol — Initial FiO_2 0.3
- **O**utcome — **Survival free from brain injury at 36 weeks post menstrual age**

Study Schema



Primary Outcome

	FiO_2 0.6 (n=728)	FiO_2 0.3 (n=741)	P-value
Death or brain injury at 36 weeks	330 (47%)	344 (48%)	0.76
Death by 36 weeks	112 (15%)	117 (16%)	0.84

Brain Injury

	FiO_2 0.6 (n=728)	FiO_2 0.3 (n=741)	P-value
Any intraventricular hemorrhage (IVH)	282 (40%)	270 (38%)	0.58
Grade III/IV IVH	70 (10%)	54 (8%)	0.11

Pre-specified Delivery Room Outcomes

	FiO_2 0.6 (n=728)	FiO_2 0.3 (n=741)	P value
Intubated in DR	47%	52%	0.16
At 5 minutes			
$SpO_2 \leq 80\%$	32%	45%	<0.001
Heart rate <100 bpm	9%	14%	0.002
Adrenaline	1%	2%	0.02
Chest compression	2%	5%	0.03

Conclusion

After initiating respiratory support of preterm infants between 23^{+0} to 28^{+6} weeks gestation at birth with either FiO_2 0.3 or 0.6 titrated to meet pre-defined SpO_2 targets:

1. There was no difference in death or brain injury at 36 weeks corrected age, in all infants and in all predefined subgroups
2. Almost all infants did not meet recommended SpO_2 targets
3. Infants given FiO_2 0.6 had higher SpO_2, oxygen use and heart rates until 10 minutes of age and less need for major resuscitation interventions

From the cutting edge: lamb model

Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
0(0) 1–13
© The Author(s) 2024
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0271678X241302738
journals.sagepub.com/home/jcbfm
Sage

Rapid oxygen titration following cardiopulmonary resuscitation mitigates cerebral overperfusion and striatal mitochondrial dysfunction in asphyxiated newborn lambs

Shiraz Badurdeen[1,2,3], Robert Galinsky[1], Calum T Roberts[1,4], Kelly J Crossley[1], Valerie A Zahra[1], Alison Thiel[1], Yen Pham[1], Peter G Davis[3], Stuart B Hooper[1,6], Graeme R Polglase[1,5,*] and Emily J Camm[1,6,*]

- Air vs 100% oxygen (for 5 min) vs rapid wean (100% to ROSC and then weaned to air). All groups titrated FiO_2 to achieve sats 90-95% from 5 min after ROSC
- Rapid wean following ROSC preserved mitochondrial function in deep grey nuclei (striatum)

AND IN TERM BABIES FROM THE ICE TRIAL

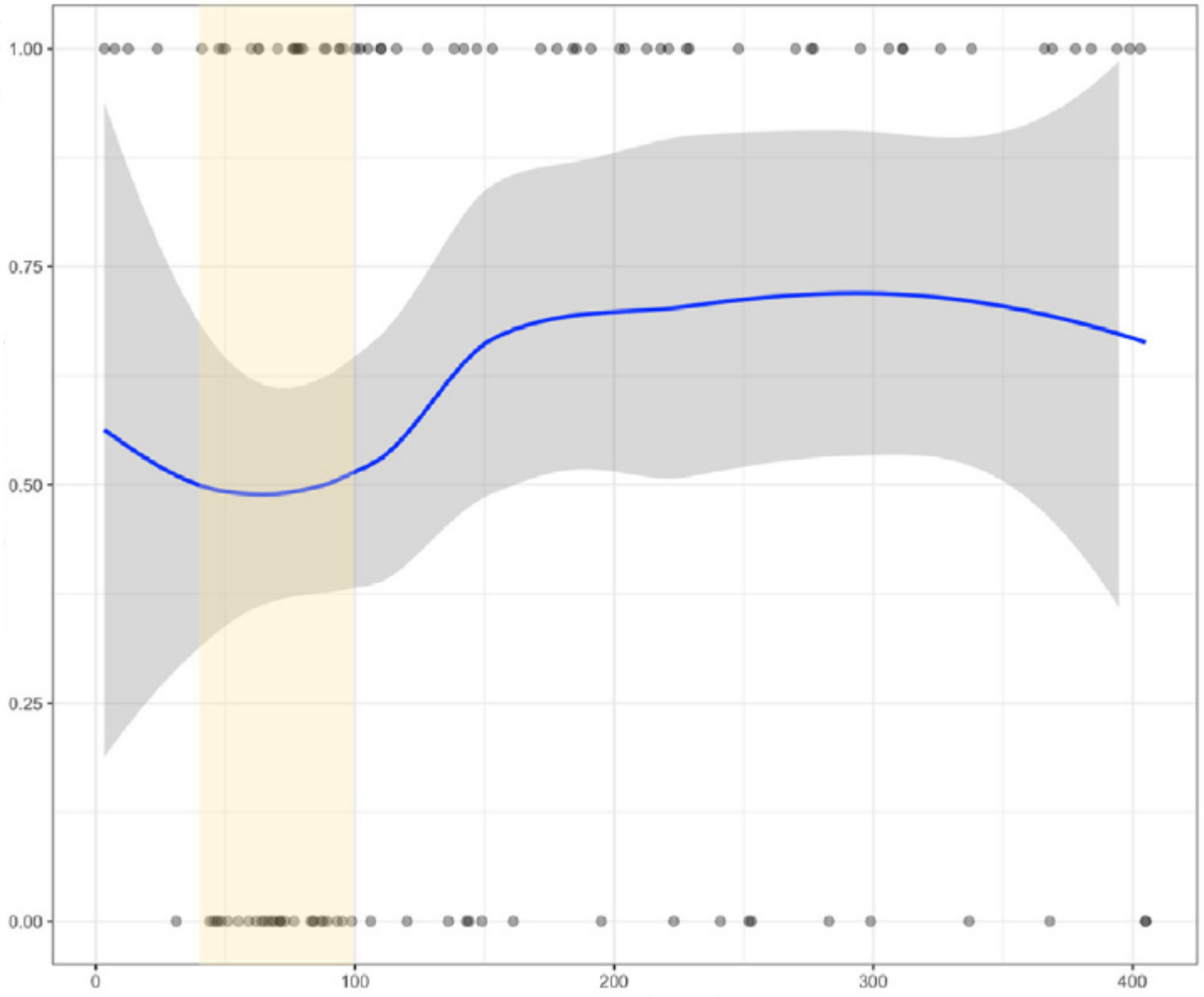
THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Early Hyperoxemia and 2-year Outcomes in Infants with Hypoxic-ischemic Encephalopathy: A Secondary Analysis of the Infant Cooling Evaluation Trial

Shiraz Badurdeen, MPRCPCH, PhD[1,2,3,4], Jeanie L. Y. Cheong, FRACP, PhD[1,4,5,6], Susan Donath, MA[7], Hamish Graham, FRACP, PhD[2,5], Stuart B. Hooper, PhD[8,9], Graeme R. Polglase, PhD[8,9], Sue Jacobs, FRACP, PhD[1,4,6], and Peter G. Davis, FRACP, MD[1,4,6]

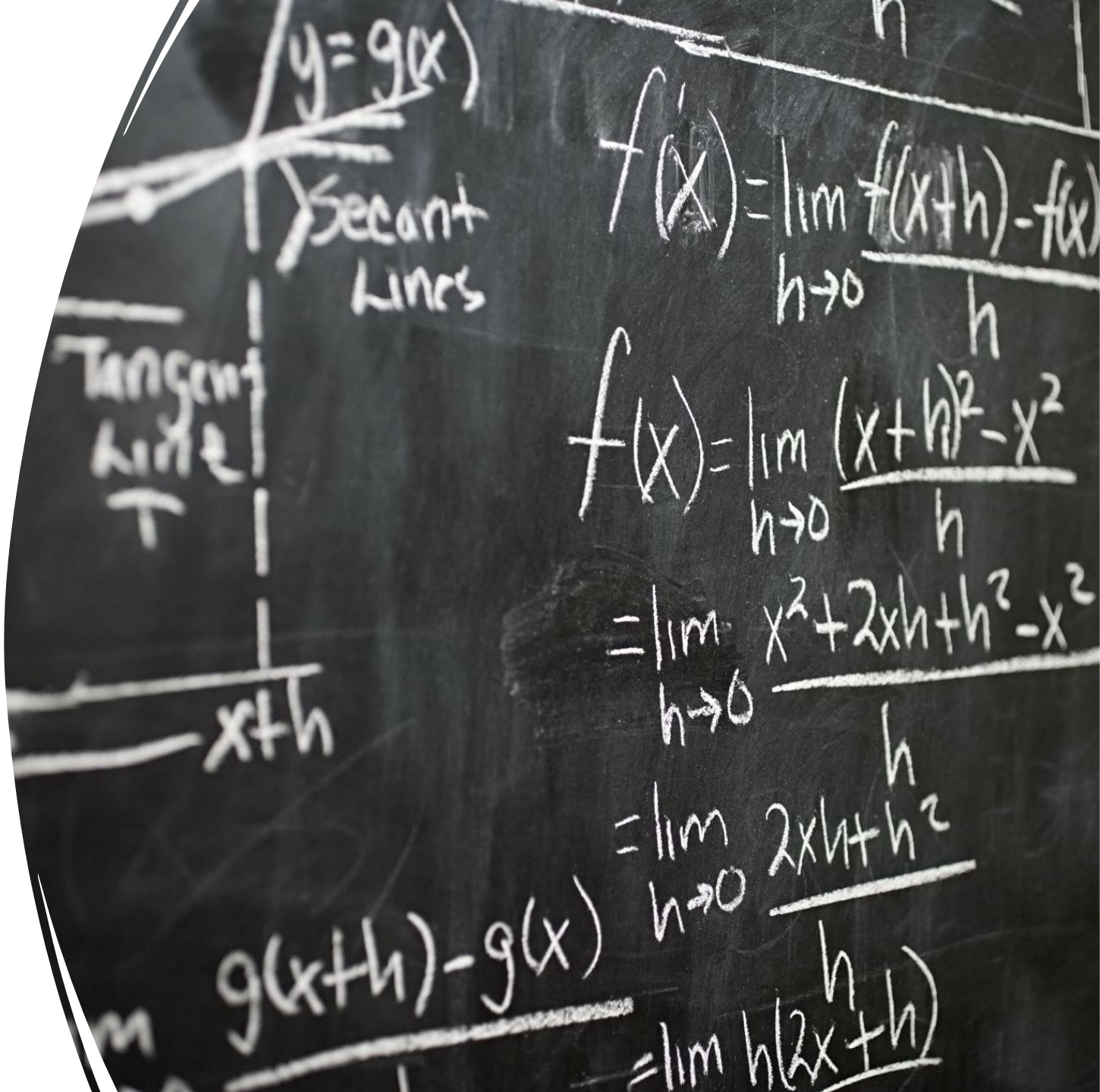
J Pediatr. 2024 Apr;267:113902. doi: 10.1016

Probability of death or disability



Arterial pO_2 (mm Hg)

THIS IS HYPOTHESIS GENERATING!



My guess

- Based on animal data – hypoxia slows transition and exacerbates apnea, particularly in preterm animals
- Perhaps a “pulse” of high oxygen (>80%) followed by a **rapid wean** might be the best strategy

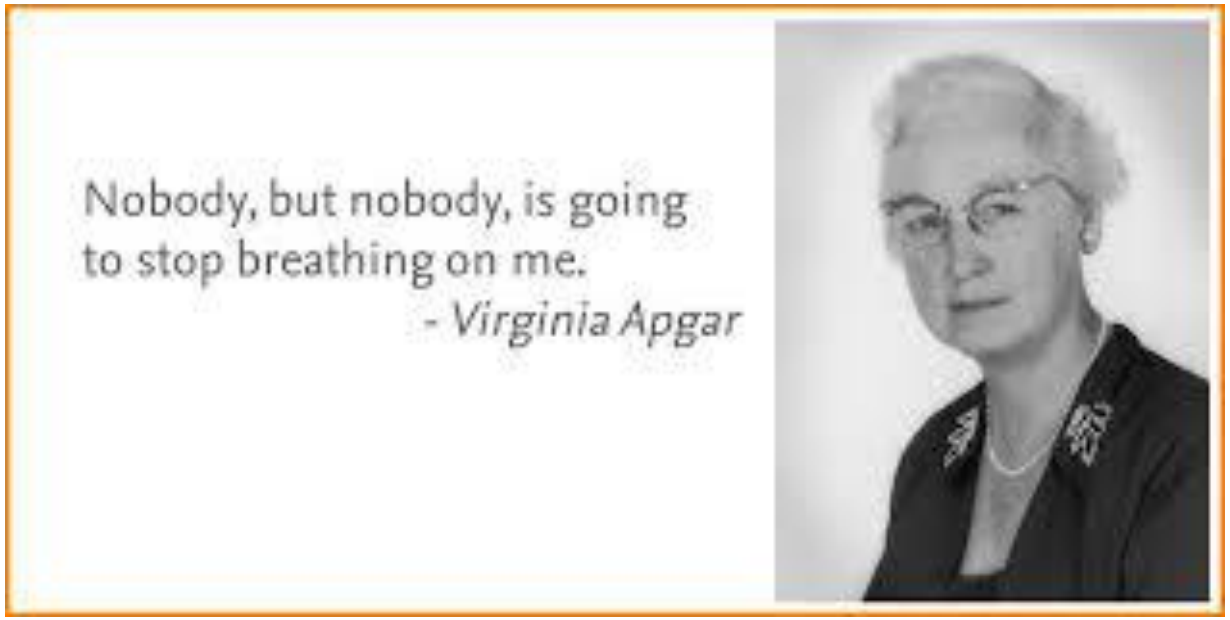
Area Under the Curves

		FiO_2 0.6	FiO_2 0.3	Mean difference (95%CI)	P
SpO_2 %	5 min	221.4 (93.6)	197.0 (85.2)	24.4 (14.9, 33.8)	**<0.001**
	10 min	621.4 (162.8)	583.5 (161.8)	37.9 (21.0, 54.9)	**<0.001**
FiO_2 %	5 min	229.1 (79.0)	186.4 (81.0)	42.7 (34.4, 51.1)	**<0.001**
	10 min	484.1 (183.8)	446.8 (192.7)	37.3 (17.7, 56.9)	**<0.001**
Heart Rate bpm	5 min	417.8 (139.1)	392.4 (145.6)	25.4 (10.4, 40.3)	**<0.001**
	10 min	1090 (256.6)	1050 (285.6)	40.5 (12.1, 68.9)	**0.005**

Predefined Subgroups for Primary Outcome

	Level	FiO_2 0.6	FiO_2 0.3	P
Gestation	<26 weeks	156/238 (66%)	166/252 (67%)	0.85
	≥26 weeks	174/490 (37%)	178/489 (38%)	0.89
Consent waiver	Yes	274/602 (47%)	288/599 (49%)	0.42
	No	56/126 (47%)	56/142 (41%)	0.35
Antenatal steroids	Yes	237/569 (43%)	253/592 (44%)	0.81
	No	10/23 (46%)	10/14 (77%)	0.06
Sex	Female	101/251 (42%)	114/276 (43%)	0.83
	Male	146/341 (44%)	150/331 (46%)	0.61

Some observations about heart rate

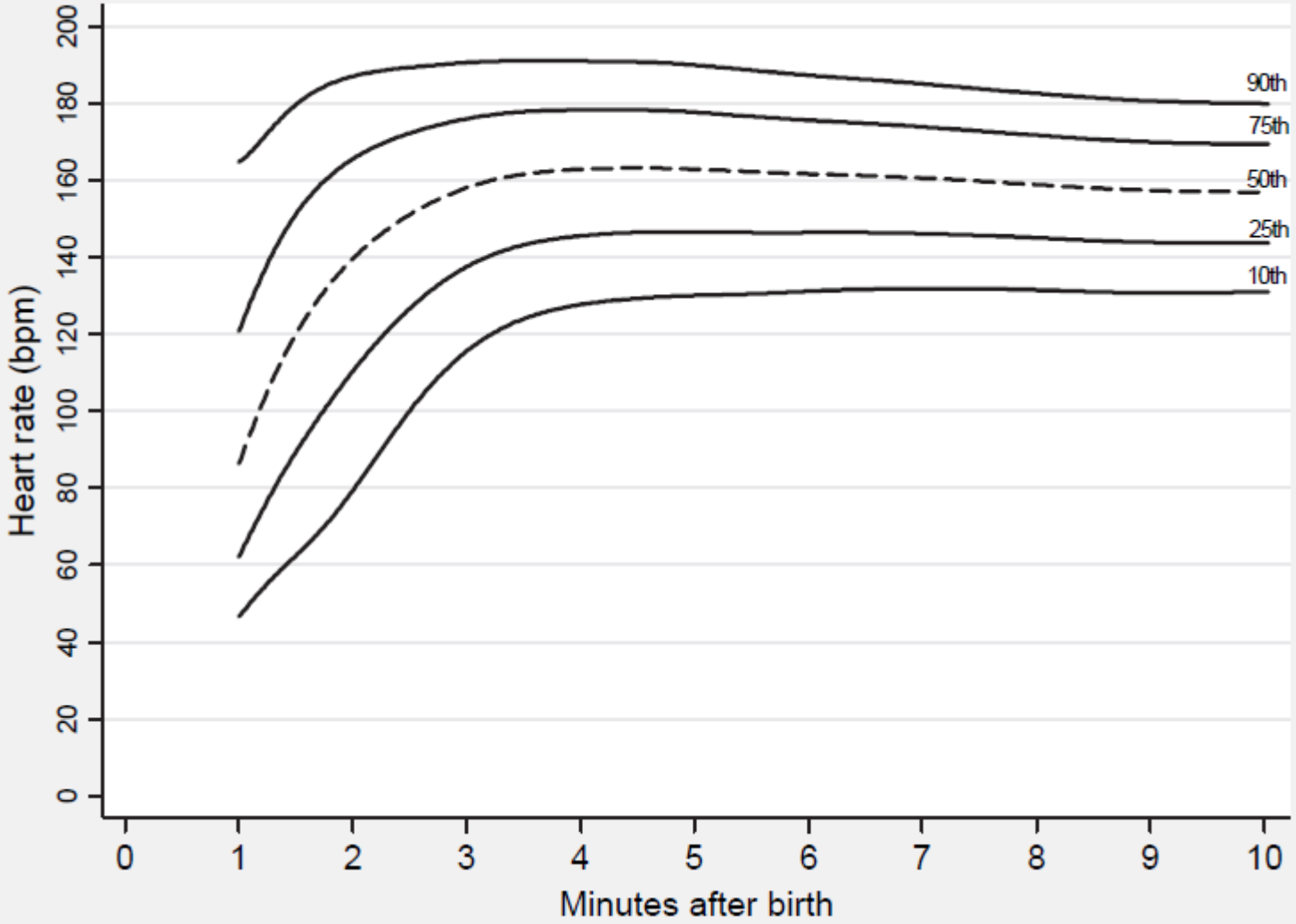


- Heart rate (HR) is the most important, objective clinical indicator of the health of newly born infants

Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg 1953;32:260–7.

Changes in heart rate in the first minutes after birth

JA Dawson,[1,2,3] COF Kamlin,[1,2,3] C Wong,[1] AB te Pas,[4] M Vento,[5] TJ Cole,[6] SM Donath,[3] SB Hooper,[7] PG Davis,[1,2,3] CJ Morley[1,2,3]

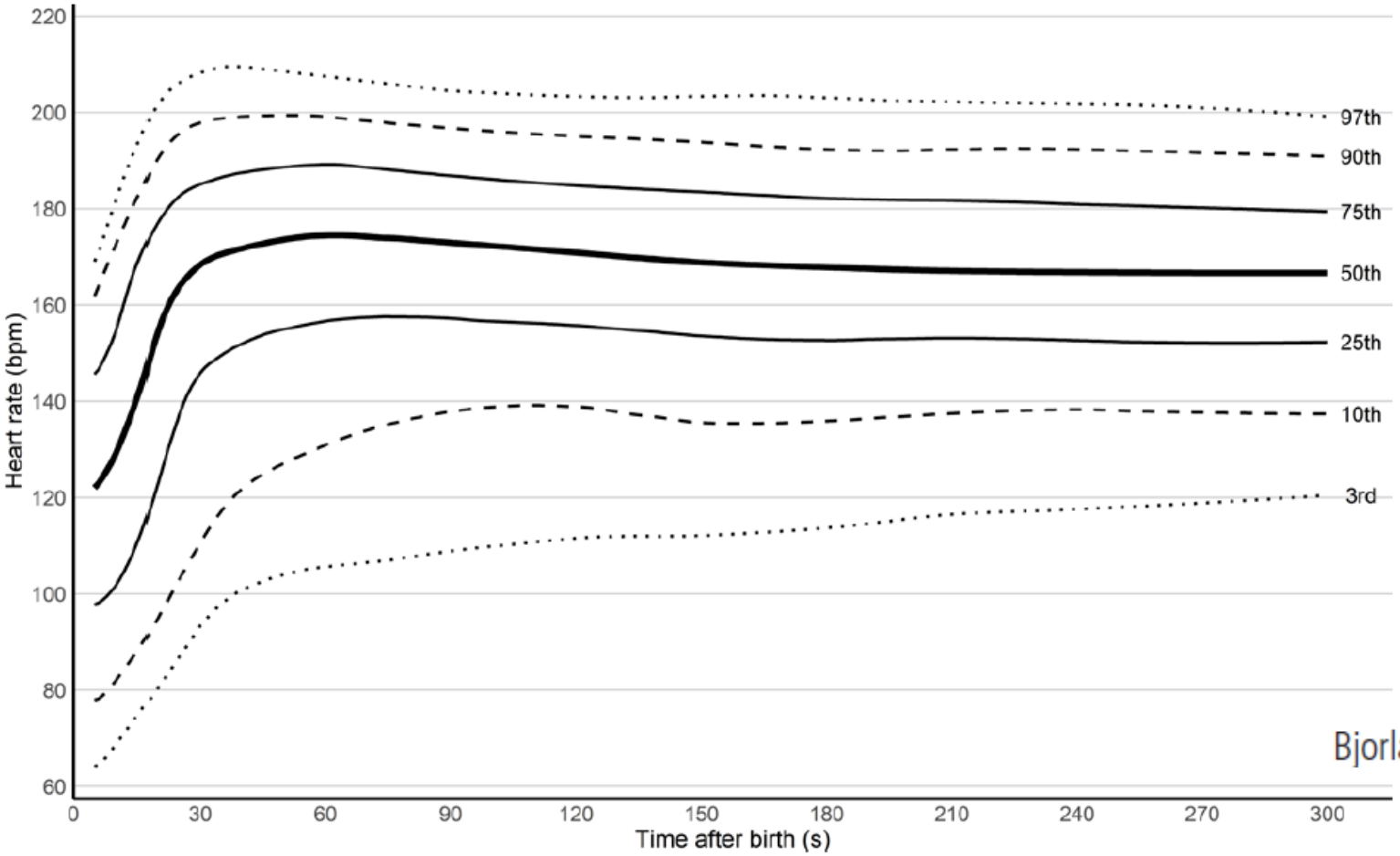


Mostly term babies
Immediate cord clamping
SVD and CS
No interventions
Pulse oximeter HR

Arch Dis Child Fetal Neonatal Ed 2010;**95**:F177–F181.

Changes in heart rate from 5 s to 5 min after birth in vaginally delivered term newborns with delayed cord clamping

Peder Aleksander Bjorland ,[1,2] Hege Langli Ersdal,[3,4] Joar Eilevstjønn,[5] Knut Øymar,[1,2] Peter G Davis ,[6] Siren Irene Rettedal[1]

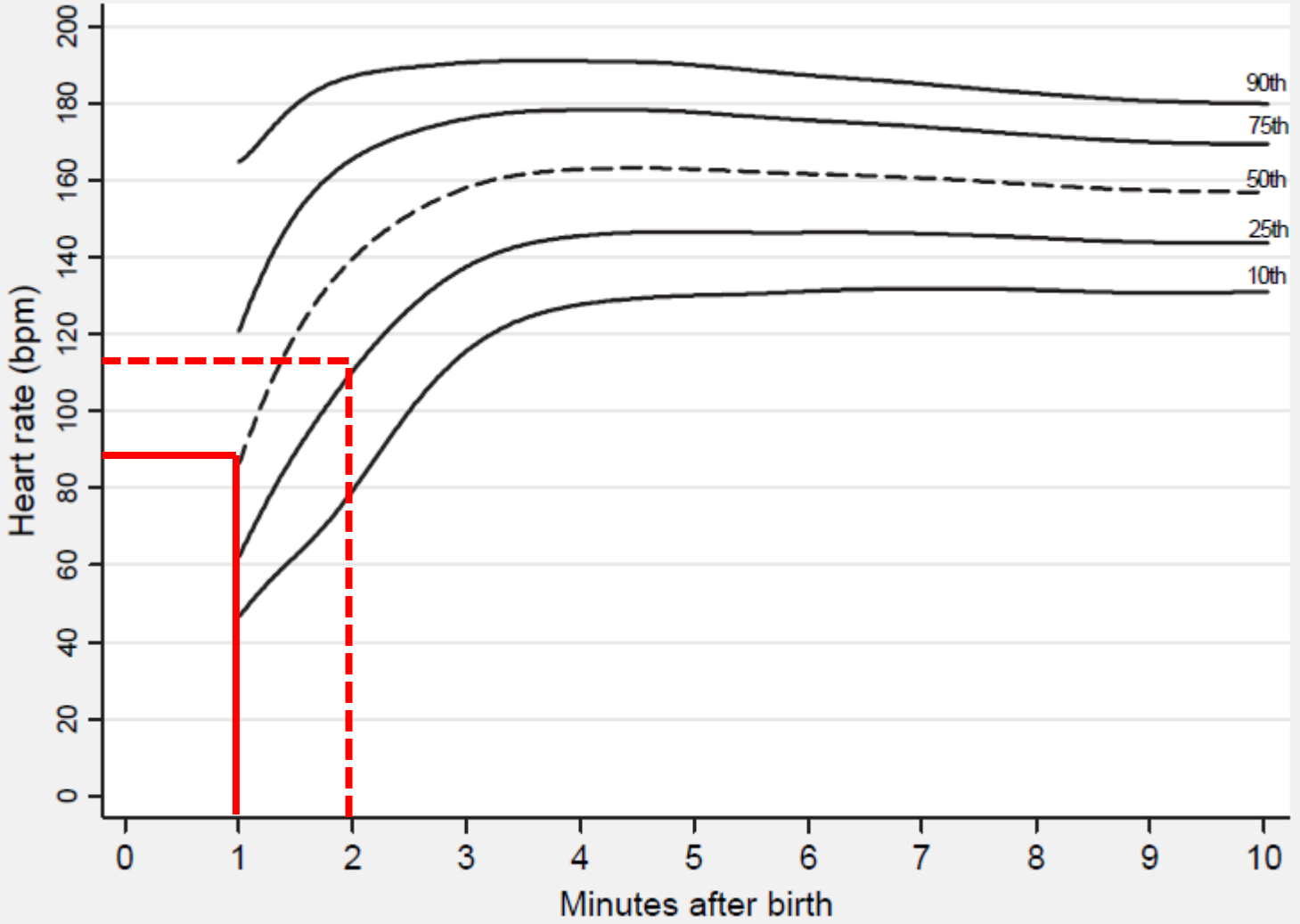


Term infants
Deferred cord clamping
NVD
No interventions
ECG HR

Bjorland PA, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2020;**0**:F1–F5.

Changes in heart rate in the first minutes after birth

JA Dawson,[1,2,3] COF Kamlin,[1,2,3] C Wong,[1] AB te Pas,[4] M Vento,[5] TJ Cole,[6] SM Donath,[3] SB Hooper,[7] PG Davis,[1,2,3] CJ Morley[1,2,3]



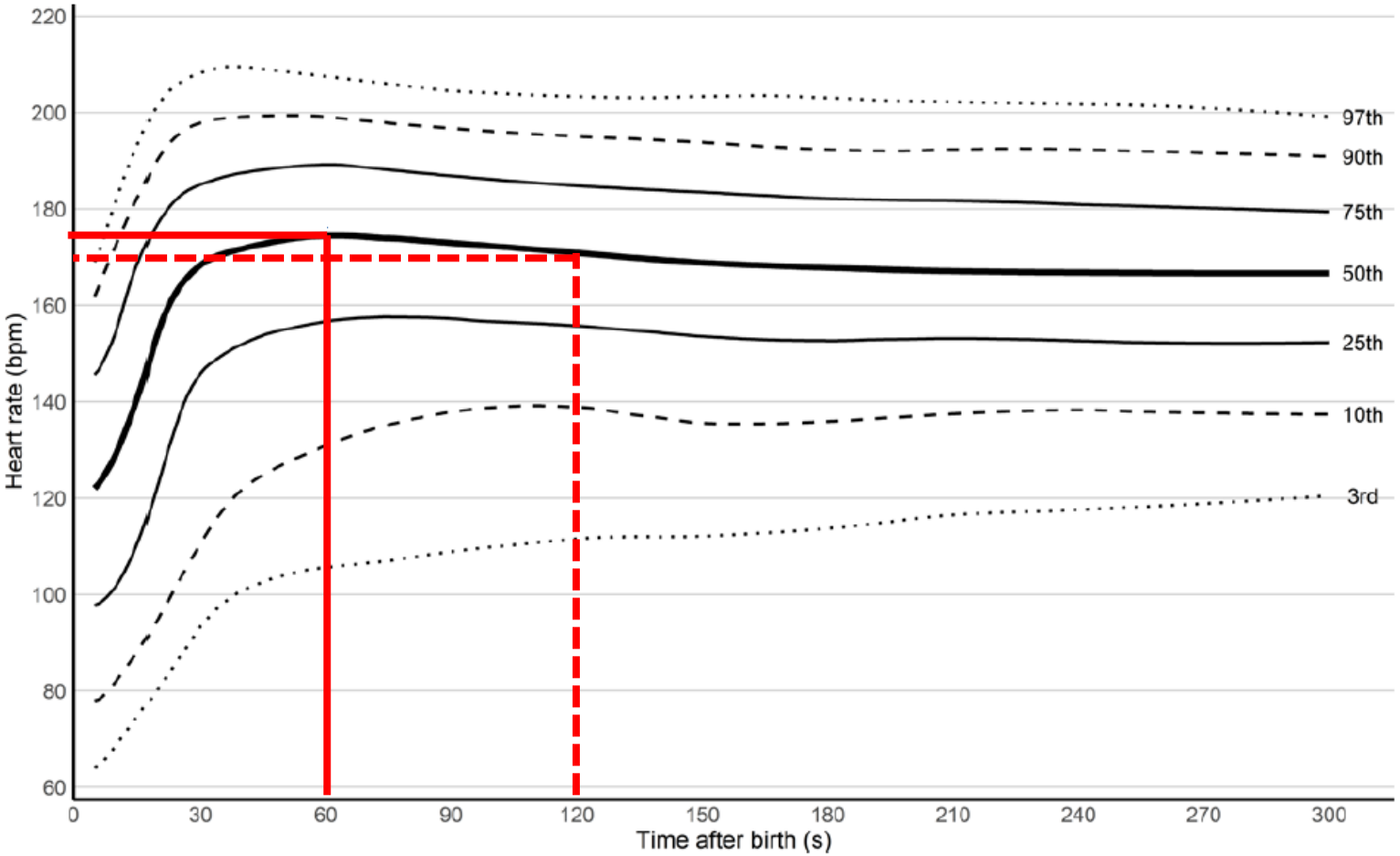
Mostly term babies
Immediate cord clamping
SVD and CS
No interventions
Pulse oximeter HR

What this study adds

- Some healthy infants will have a heart rate less than 100 bpm in the first 2 min after birth.
- Heart rate <100 bpm, in the first 2 min when breathing and tone are normal, and should not be an indicator for immediate ventilation.

Changes in heart rate from 5 s to 5 min after birth in vaginally delivered term newborns with delayed cord clamping

Peder Aleksander Bjorland ,[1,2] Hege Langli Ersdal,[3,4] Joar Eilevstjønn,[5] Knut Øymar,[1,2] Peter G Davis ,[6] Siren Irene Rettedal[1]



Term infants

Deferred cord clamping

NVD

No interventions

ECG HR

What this study adds?

- A heart rate centile chart from 5 s to 5 min after birth in healthy newborns delivered vaginally and with delayed cord clamping.
- The median heart rate increases rapidly and peaks at approximately 1 min after birth, earlier than previously reported.
- Heart rates below 100 beats per minute are uncommon in newborns who do not need intervention and account for less than 5% of newborns at 30 s after birth.

THE PHYSIOLOGY OF TRANSITION

Aerating the lung: The first and most important step

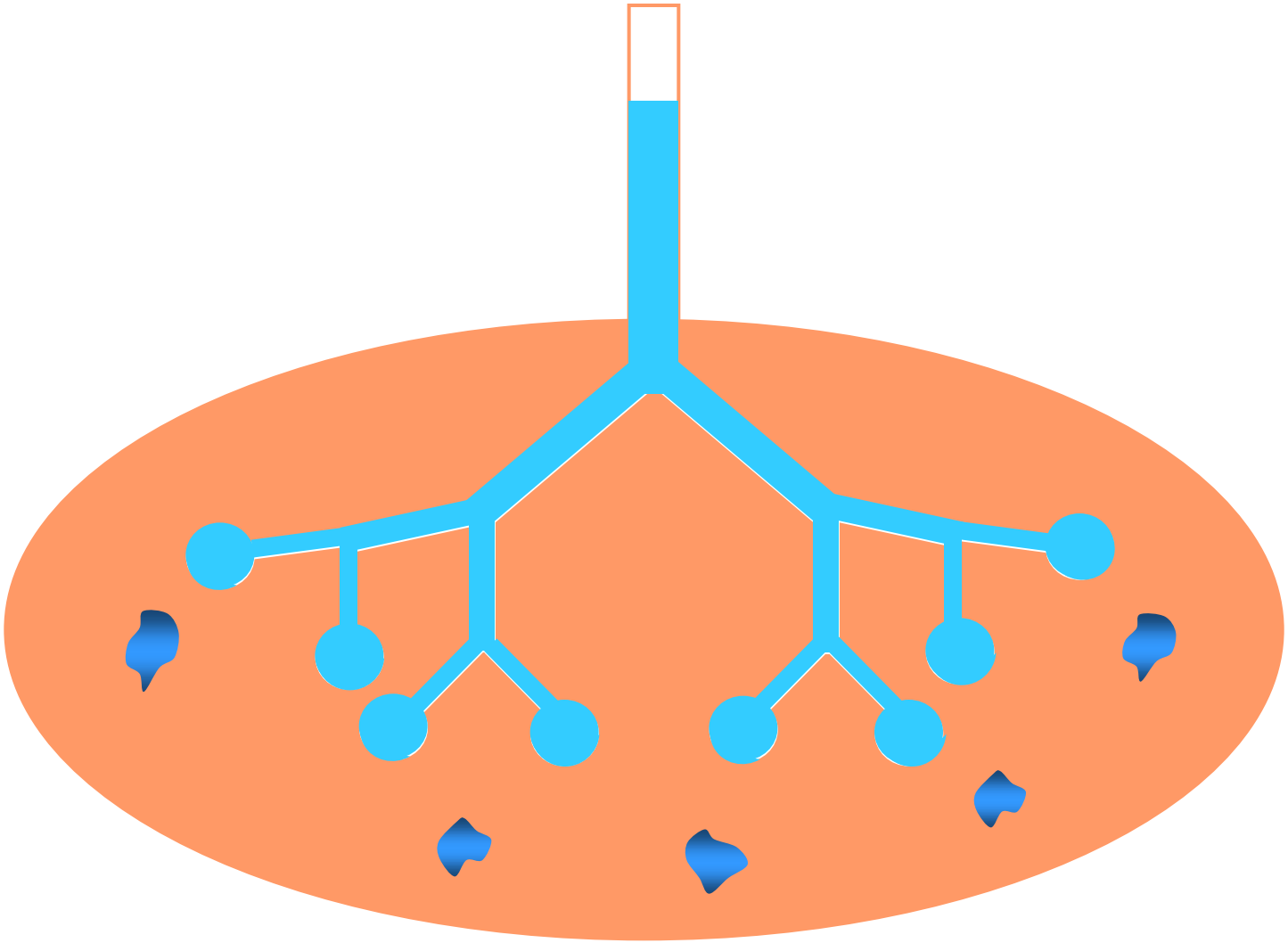
Aerating the lung: Physiology

- Airway liquid clearance
  - Sodium reabsorption and reversal of the osmotic gradient across the epithelium
  - Posture-induced increases in trans-pulmonary pressure
  - Increases in trans-epithelial pressure generated by inspiration

Aerating the lung: Physiology

- Airway liquid clearance
  - Sodium reabsorption and reversal of the osmotic gradient across the epithelium
  - Posture-induced increases in trans-pulmonary pressure
  - **Increases in trans-epithelial pressure generated by inspiration**

Aerating the lung at birth

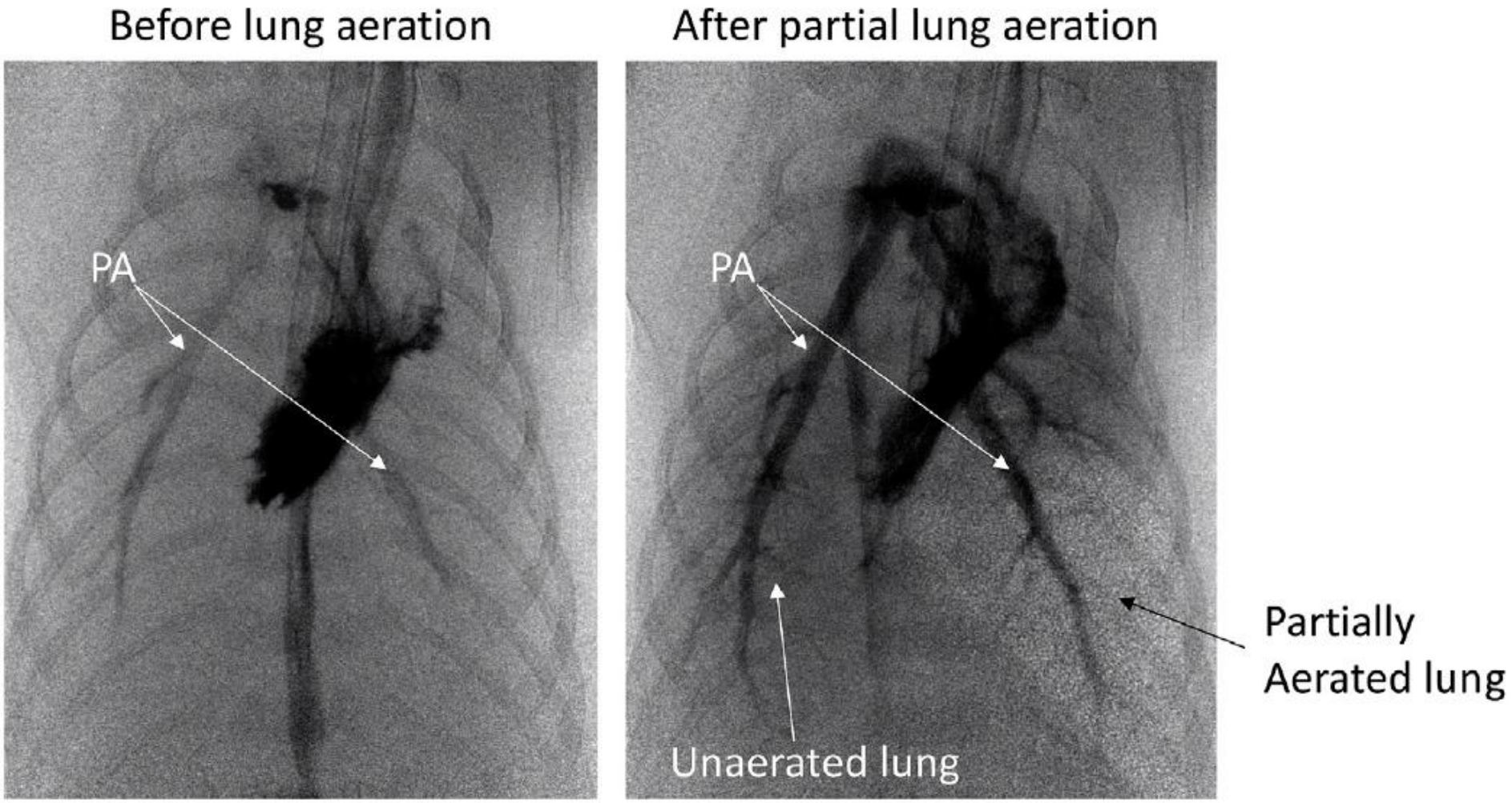


Clinical implications

- Gas exchange only commences once liquid clearance is achieved (crying, expiratory braking helps, implications for PPV?)
- During second phase infants are at risk of fluid re-entering the alveoli (potential role for CPAP)

CHANGES TO CIRCULATION

The important relationship:
Lung aeration and pulmonary circulation



Hooper et al, Seminars in Fetal and Neonatal Medicine 24 (2019)