Sustained Inflations

NEONATUS 2015

Poznan, Sept 24-25, 2015

Topics

- Introduction
- Experimental studies
- Clinical physiological studies
- Clinical studies on sustained inflations
- Potential risks
- Open questions
- Summary

Introduction

- Immediately after birth residual lung fluid
  - needs to be cleared
  - some fluid needs to be replaced by air
- The first breaths play an important role to achieve a gas-filled Functional Residual Capacity
  (Te Pas et al. J Pediatr 2008;152:607; Hooper et al. NeoReviews 2010;11:e474)
- Fraction of neonates with an Apgar Score ≤3 (Population based data from Sweden, born 1985)
  (Palme-Kilander. Acta Paediatr 1982;81:739)
  - approx. 1% (n=869/97648) of babies ≥2500g
  - 21% (147/707) of babies <1500g
- 80% of ELBWI breathe after birth
  (O'Donnell et al. J Pediatr 2010;156:846)

Introduction

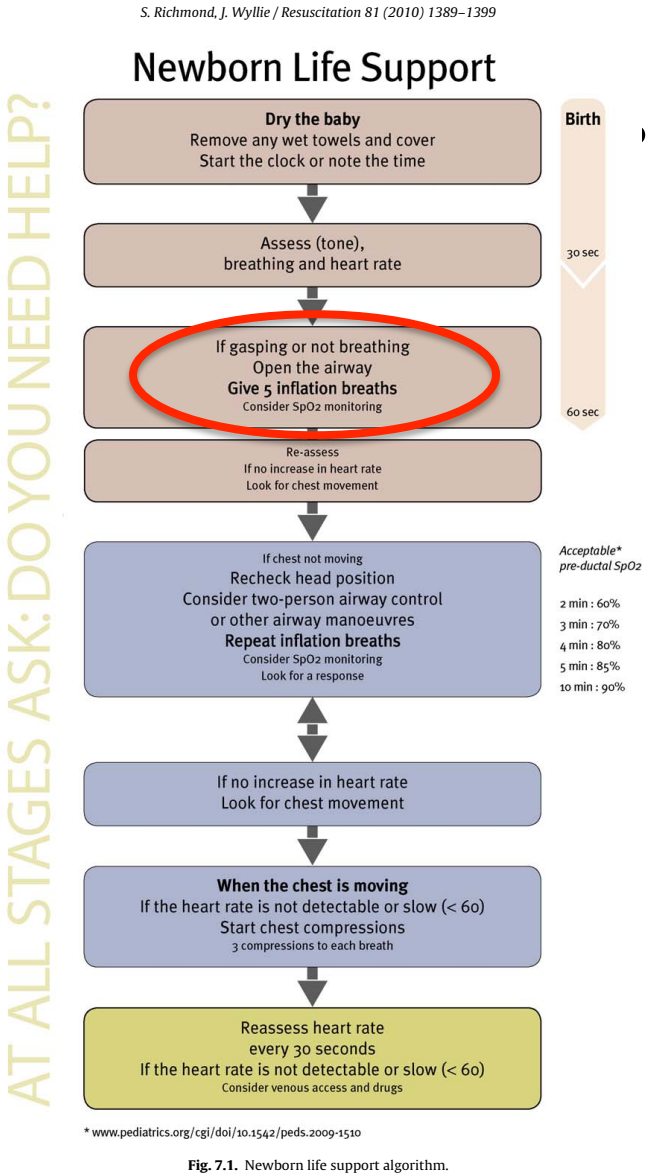

Fig. 7.1. Newborn life support algorithm.

European Resuscitation Council Guidelines for Resuscitation

2010: Section 7. Resuscitation of babies at birth (Richmand & Willie. Resuscitation 2010;81:1389)

– Breathing

- "For the first five inflation breaths maintain the initial inflation pressure for 2–3 s. This will help lung expansion."

➜ Concept of prolonged inspiratory time is mentioned in NLS (Europe), but not in NRP (US)

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Experimental Studies

Lung gas volume

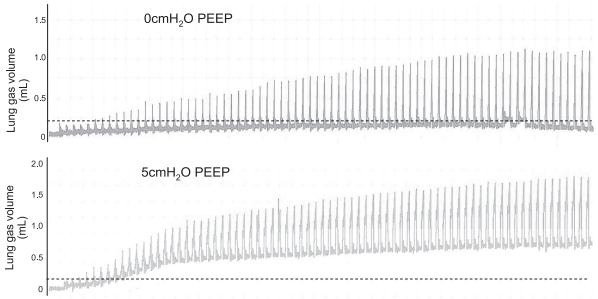


Fig. 3. Lung gas volumes, measured using plethysmography, in preterm rabbit pups ventilated from birth with either 0PEEP (*top*) or 5PEEP (*bottom*). The dotted line represents the calculated anatomic dead space volume. Note that pups ventilated with 5PEEP rapidly established a FRC, whereas pups ventilated in the absence of PEEP (0PEEP) did not develop a FRC.

- PEEP (5 cmH_2O) enhanced the development of a functional residual capacity in preterm rabbits after birth (Siew et al. J Appl Physiol 2009;106:1487)

PEEP + SI

PEEP, no SI

no PEEP, no SI

no PEEP, +SI

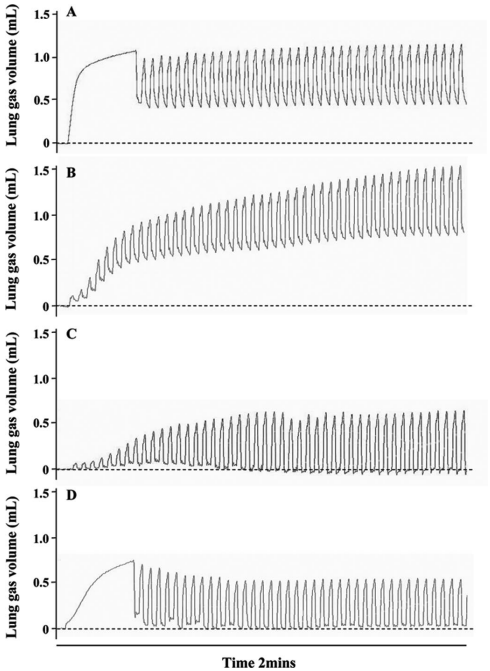
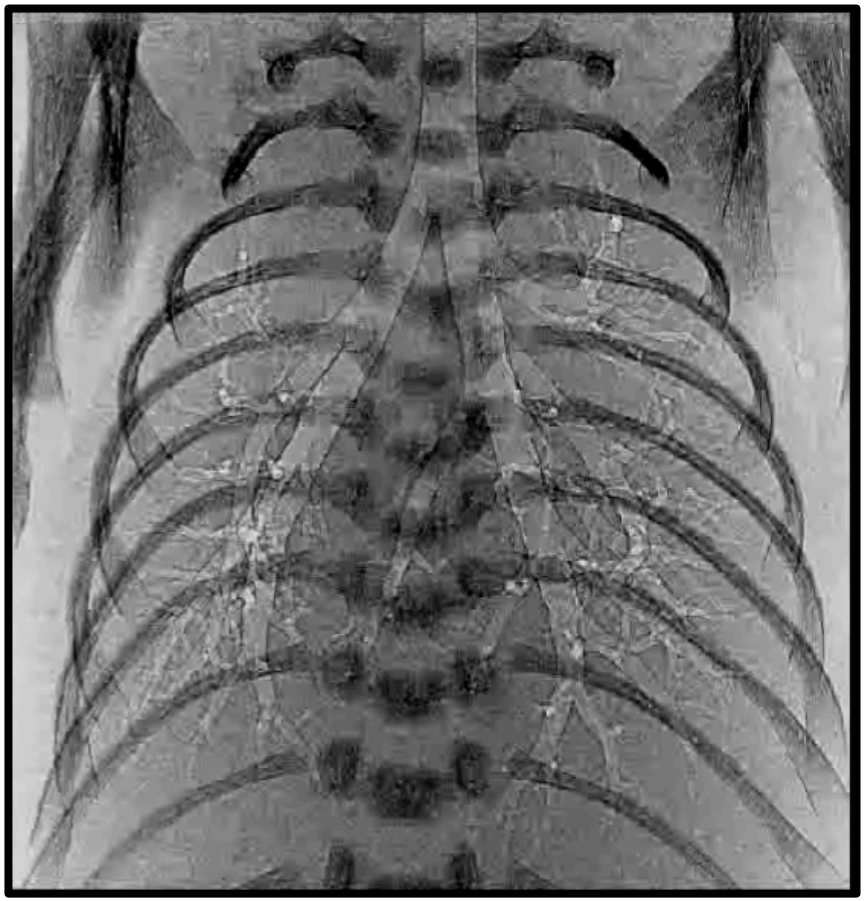


Figure 1. Representative examples of recordings from each group. Change in lung gas volume from birth in anesthetized ventilated preterm rabbit pups using plethysmography. With PEEP (*A* and *B*), an end-expiratory gas volume (FRC) was rapidly formed whereas in the absence of PEEP a significant FRC was not formed (*C* and *D*).

- Rabbit pubs after birth
  (Te Pas et al. Pediatr Res 2009;65:537)
  - Effects of PEEP (5 cmH_2O) and SI (35 cmH_2O; 20s) were additive
  - In ventilated preterm rabbits at birth, combining SI and PEEP improved FRC formation and uniformity of lung aeration,
  - but PEEP had the greatest influence

Lung Recruitment Using Sustained Inflations
Phase-Contrast X-Ray

Hooper et al. NeoReviews 2010;11:e474 (incl. Videos)



IPPV + PEEP

SI 20 s, IPPV/PEEP thereafter

Effect of Sustained Inflation Length on Establishing Functional Residual Capacity at Birth in Ventilated Premature Rabbits

Te Pas et al. Pediatr Res 2009;66:295

- Rabbit pubs
- SI 1,5,10,20s duration, PIP 35 cmH_2O
- Gas volumes: plethysmography
- Aeration: Phase-contrast X-ray

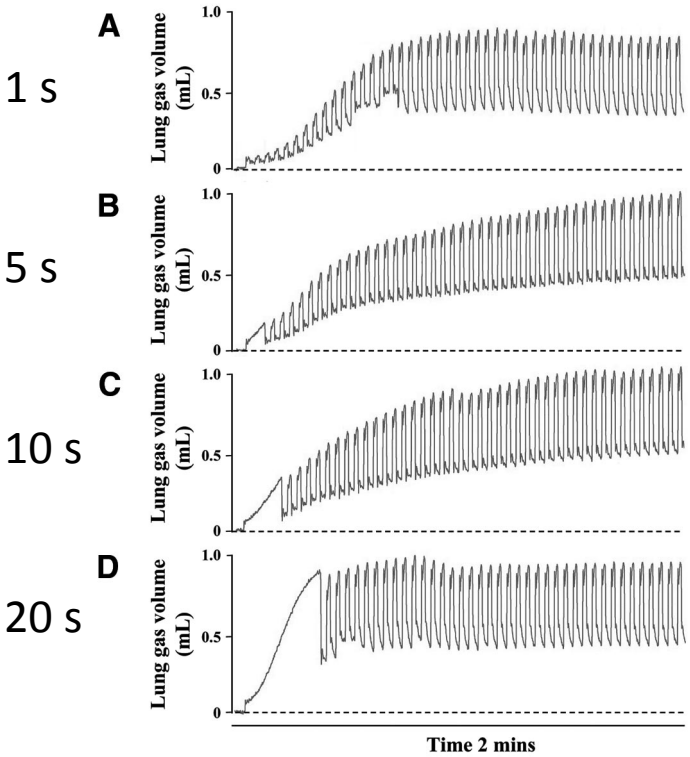


Figure 1. Plethysmograph recordings of lung gas volumes from newborn rabbit pups delivered preterm and ventilated from birth. The four recordings show the following: (*A*) The first inflation was not sustained (no SI; *i.e.* 1 s in duration); (*B*) first inflation held for 5 s; (*C*) first inflation held for 10 s; and (*D*) first inflation held for 20 s. Pups were then ventilated initially with a PEEP of 5 cm H_2O and PIP of 35 cm H_2O, which was later changed to achieve a tidal volume of ~10 mL/kg.

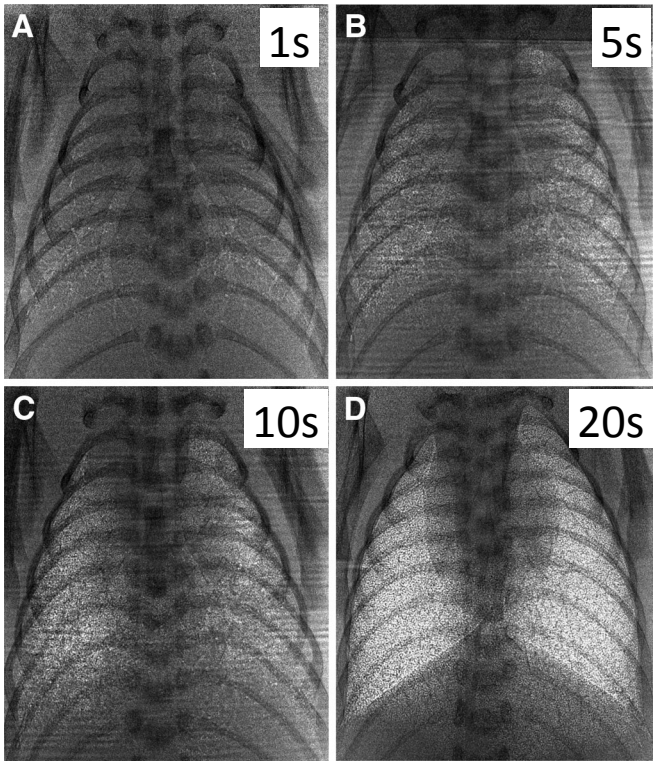


Figure 2. Phase contrast x-ray images acquired at the end of the first inflation after birth in ventilated preterm newborn rabbit pups. The first inflation was either not sustained (No SI; *i.e.* 1 s in duration) (*A*) or sustained for 5 (*B*), 10 (*C*), or 20 (*D*) s.

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Physiological Responses of the Newborn Infant to Resuscitation

Boon et al. Arch Dis Child 1979;54:492

- Paw, Pes and Vt recorded during the <u>first 3 breaths</u>
- Asphyxia, n=20; born by cesarean section
- PIP 30 cmH_2O; Ti 1.0s, Rate 30-40‘

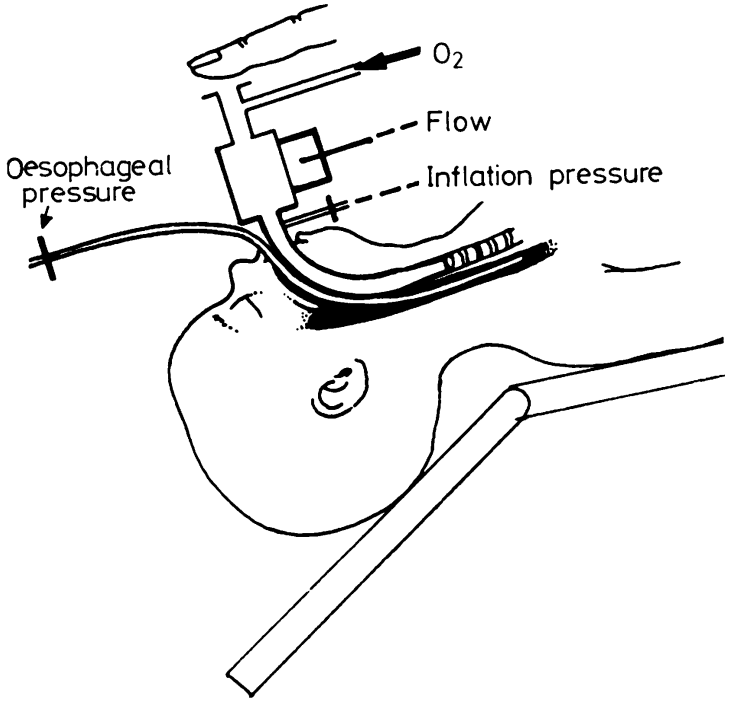


Fig. 1 *Diagrammatic representation of modified T-piece.*

Physiological Responses of the Newborn Infant to Resuscitation

Boon et al. Arch Dis Child 1979;54:492

- No active change in Pe (some passive transmission)
- 17/60 events

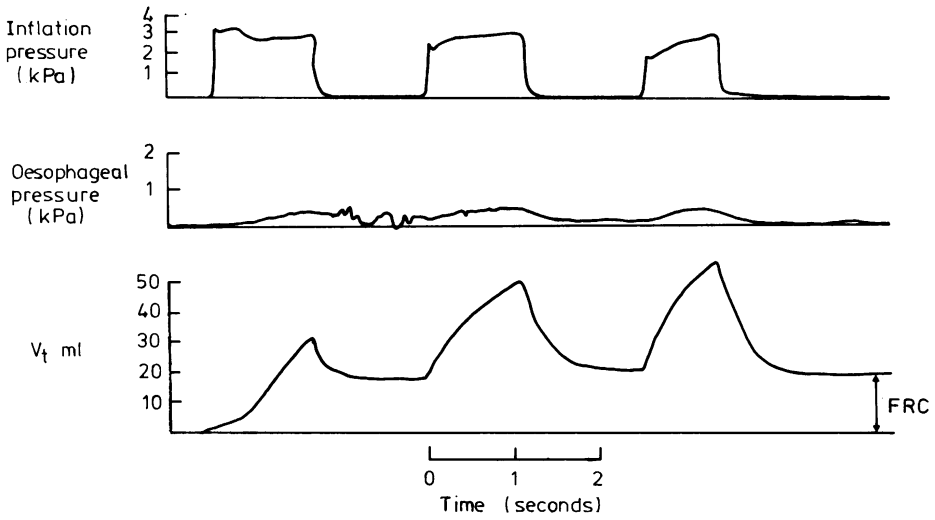


Fig. 6 (*Case 10*). *'Longitudinal trace' showing small passively transmitted changes in oesophageal pressure with each inflation.*

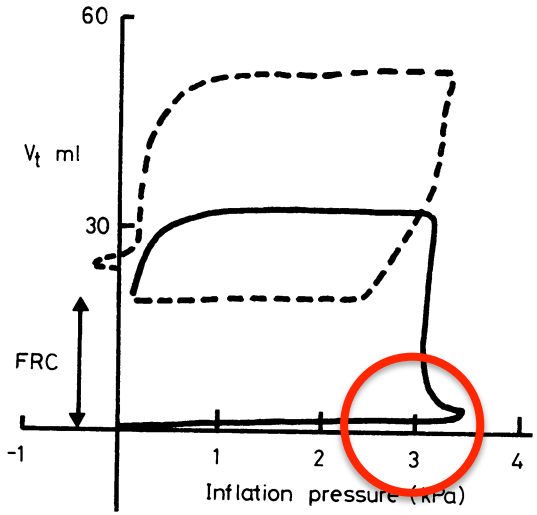
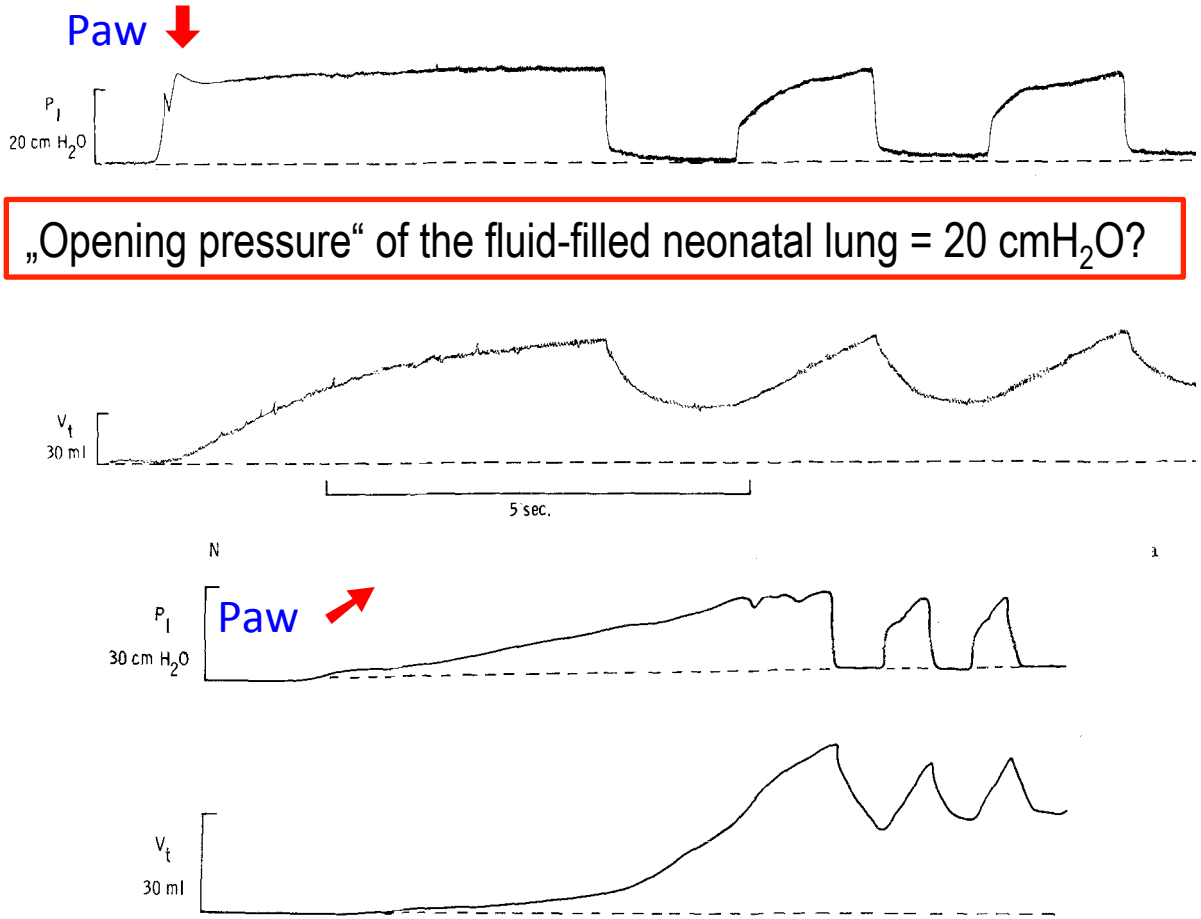


Fig. 7 (*Case 10*). *X–Y plot of the same baby as in Fig. 5. Again, there was an opening pressure in excess of 3 kPa.*

„Opening pressure" of the fluid-filled neonatal lung: 20-30 cmH_2O?

Physiologic Responses to Prolonged and Slow-Rise Inflation in the Resuscitation of the Asphyxiated Newborn Infant

Vyas et al. J Pediatr 1981;99:635



„Opening pressure“ of the fluid-filled neonatal lung = 20 cmH_2O?

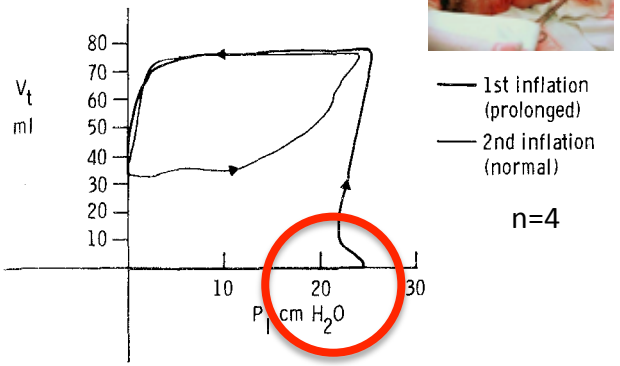


Fig. 3. Pressure/volume loop obtained on a baby using an initial square wave inflation. An opening pressure of 24 cm H_2O was noted.

„Opening pressure“ was much lower (5 cmH_2O)
➜ „Opening pressure“ is caused by rapid rise in Paw in the presence of the slowly responding viscous fluid-filled airways

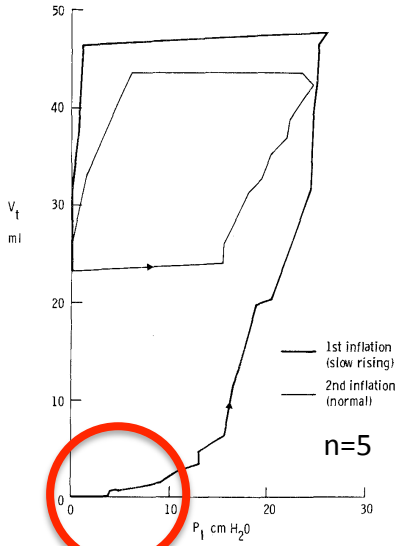


Fig. 4. Pressure/volume loop of a baby resuscitated using an initial slow-rise inflation. Air had started to enter the lungs by the time a positive pressure of 5 cm H_2O had reached.

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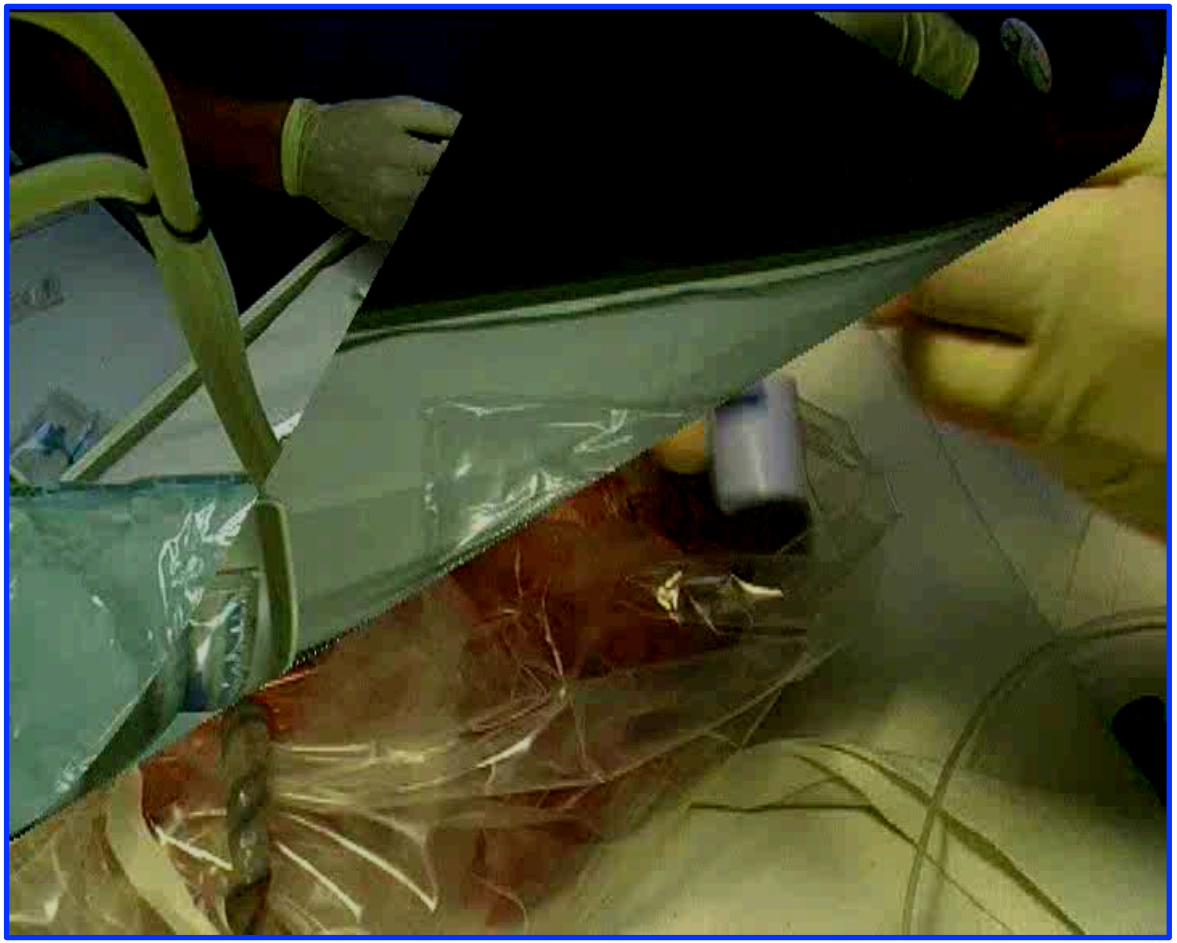
Delivery Room Management of ELBWI: Spontaneous Breathing or Intubation?

Lindner et al. Pediatrics 1999;103:961



Delivery Room Management of ELBWI: Spontaneous Breathing or Intubation?

Lindner et al. Pediatrics 1999;103:961

- Retrospective Analysis ELBWI 1994 vs. 1996
  - **1994:** Bag and mask, intubation + mech. Ventilation
  - **1996: SI 20 cmH_2O - 15s** via nasopharyngeal tube (mouth and other nostril closed) + CPAP 4-6 cmH_2O
    2nd SI with 25 cmH_2O - 15s, if HR <100' or if cyanosis persists
    - N-IMV (PIP 20-25 cmH_2O, 60') optional until sufficient respiratory effort
    - Intub./mech. Ventilation in L&D: if HR remained <100', or SpO_2 <80%
    - Intub./mech. Ventilation NICU: SpO_2 <80%/FiO_2 >0.60, $PaCO_2$ >70 mmHg, severe apnea

	1994 *(n=56)*	1996 *(n=67)*	p
GA (wks)	26.5 ± 1.8	26.9 ± 2.0	n.s.
BW (g)	773 ± 146	739 ± 156	n.s.
Prenatal Steroids	32 (57%)	49 (73%)	0.052
Apgar (5')	7.8 ± 2.1	7.9 ± 1.4	n.s.
Int./mech.Vent (L&D)	47 (84%)	27 (40%)	<0.001
Never intubated	4 (7%)	17 (25%)	<0.01

	1994 *(n=56)*	1996 *(n=67)*	p
Mortality, n(%)	15 (27%)	15 (22%)	n.s.
Air Leak, n(%)	13 (23%)	9 (13%)	n.s.
BPD, n(%)	13 (32%)	6 (12%)	<0.05
IVH grade 3-4, n(%)	21 (38%)	11 (16%)	<0.01
Hospital days	102±27	91±36	<0.05

Does Sustained Lung Inflation at Birth Improve Outcome of Preterm Infants at Risk for RDS?

Lista et al. Neonatology 2011;99:45

Table 2. Outcomes of the SLI and control groups (mean ± SD, or number (%) values)

	SLI group (n = 89)	Control group (n = 119)	p
INSURE	14 (16)	3 (3)	0.001
Mechanical ventilation	45 (51)	90 (76)	<0.0001
duration, days	5 ± 11	11 ± 19	0.008
Exclusive NCPAP	44 (49)	29 (24)	<0.0001
Surfactant	40 (45)	73 (61)	0.027
O_2 therapy	89 (100)	119 (100)	N/A
duration, days	21 ± 27	31 ± 31	0.016
Postnatal steroids	9 (10)	30 (25)	0.010
Pneumothorax	8 (9)	10 (8)	0.920
PDA	24 (27)	29 (24)	0.791
BPD	6 (7)	25 (25)	0.004
Grade 3–4 IVH	1 (1)	5 (4)	0.372
PVL	4 (4)	11 (9)	0.299
ROP more than grade 3	10 (11)	7 (6)	0.255
NEC	4 (4)	0	0.068
Stay in hospital, days	54 ± 29	55 ± 32	0.817
Mortality	8 (9)	17 (14)	0.359

- Cohort-Study: SLI: 2007-2009 vs. historic controls 2004-2006
- GA <32 wks
  - SLI (28.1±2.2 wks; ANS complete 87%; CRIB score 3.6±4.0)
  - Control (28.1±2.0 wks; ANS complete 83%; CRIB score 4.4±4.1)
- T-Piece, PEEP 5 cmH_2O; nIMV allowed
- SLI 25 cmH_2O for 15s; repeated if breathing judged insufficient or HR <100/min or SpO_2 ≤80%
- Primary endpoint: need for mech. Ventilation during first week

- Criteria for Intubation + mech. Vent.:
  - pH<7.20
  - PaO_2 <50 mmHg with FiO_2 >0.50
  - $PaCO_2$ >65 mmHg
  - Frequent episodes of apnea requiring repeated stimulation or bag- and mask ventilation despite CPAP = 5 cmH_2O

Does Sustained Lung Inflation at Resuscitation Reduce Lung Injury in the Preterm Infant?

Harling et al. Arch Dis Child Fetal Neonatal Ed 2005;90:F406

- RCT, GA <31 wks
- Intervention:
  - Sustained inflations (5s) vs. conventional inflation (2s) for the first breath
  - Followed by "standard care"
- PIP 25-30 cmH_2O (discretion of the neonatologist), PEEP 3-4 cmH_2O, FiO_2 0.5 and 1.0 (factorial design)
- Prim. Outcome: evidence for pulmonary Inflammation (cytokines IL 6, 1β, 10 and TNFα in BAL @ 12h in intubated infants only)
- Sample size 2 x 20 ventilated infants (Pilot-Trial)
  - Studied: n=52; intubated in L&D: n=42; intubated in the NICU shortly after birth: n=4

Table 2 Cytokine concentrations in the babies resuscitated with conventional lung inflation compared with those resuscitated with sustained lung inflation

	CLI	SLI	p Value
IL6	790 (104–19708) (n=21)	1156 (42–15192) (n=18)	0.69
IL1β	38 (5–2590) (n=20)	43 (0–663) (n=19)	0.86
IL10	652 (78–1993) (n=21)	608 (0–1242) (n=19)	0.67
TNFα	25 (0–1838) (n=19)	21 (0–143) (n=15)	0.50

Values are median (range) expressed as pg/ml bronchoalveolar lavage fluid.
CLI, Conventional lung inflation (two seconds); SLI, sustained lung inflation (five seconds); IL, interleukin; TNFα, tumour necrosis factor α.

Does Sustained Lung Inflation at Resuscitation Reduce Lung Injury in the Preterm Infant?

Harling et al. Arch Dis Child Fetal Neonatal Ed 2005;90:F406

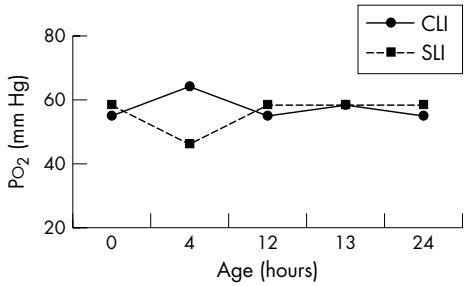


Figure 1 Median partial pressure of oxygen over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

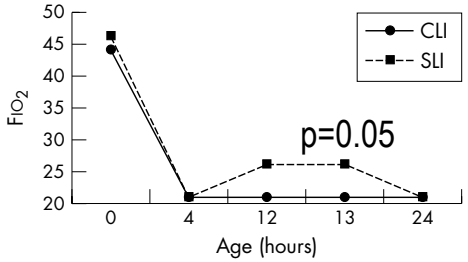


Figure 6 Median fraction of inspired oxygen (F_{IO_2}) over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

Table 3 Long term clinical outcomes in babies resuscitated with conventional lung inflation or sustained lung inflation

Outcome	CLI (n = 26)	SLI (n = 26)	p Value
Died	3	6	0.27
Death from respiratory cause	1	2	0.55
Death or BPD at 36 weeks	13	12	0.78
Respiratory death or BPD at 36 weeks	11	8	0.51
BPD (oxygen therapy after 28 days)	15	11	0.37
BPD (oxygen therapy after 36 weeks)	10	6	0.36
Home in oxygen	5	4	0.54
Patent ductus arteriosus (treated)	1	5	0.08
Necrotising enterocolitis	0	2	0.20
Retinopathy of prematurity (treated/blind)	0	0	
Pneumothorax	1	2	0.55
Abnormal cranial ultrasound	1	4	0.15
Positive blood culture	7	9	0.54

CLI, Conventional lung inflation (two seconds); SLI, sustained lung inflation (five seconds); BPD, bronchopulmonary dysplasia

Sustained Pressure-Controlled Inflation or Intermittent Mandatory Ventilation in Preterm Infants in the Delivery Room? A RCT on Initial Respiratory Support via Nasopharyngeal Tube.

Lindner et al. Acta Paediatr 2005;94:303

- RCT, GA 25+0 – 28+6 wks, need for resp. support (apnea, cyanosis, retractions or HR <100')
- 10/1999- 2/2002
- Sustained inflations vs. N-IMV (nasopharyngeal tube); initial FiO_2=1.0

	Sustained Inflations (SI)	N-IMV
	SI 20 cmH_2O - 15s + CPAP 4-6 cmH_2O	PIP/PEEP 20/4-6 cmH_2O, Ti=0.5s, 60'
Pink color or SpO_2 >80% with FiO_2 <0.60, HR >100'	NCPAP 4-6 cmH_2O*	NCPAP 4-6 cmH_2O*
HR 80-100', or cyanosis or SpO_2 60-80%, or FiO_2 >0.60 to achieve SpO_2 >80%	2nd SI 25 cmH_2O – 15s	PIP/PEEP 25-30/4-6 cmH_2O, Ti=0.3s, 60'
No improvement	3rd SI 30 cmH_2O – 15s	PIP/PEEP 25-30/4-6 cmH_2O, Ti=0.3s, 60'
SpO_2 < 60% or HR <80' or no improvement	Intubation, mech. Ventilation	Intubation, mech. Ventilation

* N-IMV optional with PIP/PEEP 20-30 cmH_2O (according to chest excursions), 60', Ti 0.3s, if apneic

Sustained Pressure-Controlled Inflation or Intermittent mandatory Ventilation in Preterm Infants in the Delivery Room? A RCT on Initial Respiratory Support via Nasopharyngeal Tube.

Lindner et al. Acta Paediatr 2005;94:303

- Criteria for intubation/mech. Ventilation NICU
  - SpO_2 <80%/FiO_2 >0.60 or $PaCO_2$ >70 mmHg or severe apnea
- Prim. Endpoint: treatment failure (Intubation + mech. Ventilation) <48h
  - Failure in the delivery room: cross-over at discretion of the neonatologist
- Closed early because of poor recruitment (61/110 patients)

Failure: SI: 19/31 (61%) vs. N-IMV: 21/30 (70%) n.s.

Table IV. Morbidity data at discharge.

	Sustained Inflation		Nasal IMV	
	All infants (n = 31)	Infants without N-IMV[b] (n = 25)	All infants (n = 30)	Infants without N-SPCI[c] (n = 19)
Survival	28 (90)	22 (88)	30 (100)	19 (100)
Intraventricular haemorrhage, grade 1–2	4 (13)	1 (4)	9 (30)	4 (21)
Intraventricular haemorrhage, grade 3–4	3 (10)	2 (8)	2 (6)	2 (11)
Periventricular leukomalazia	2 (6)	1 (4)	4 (13)	3 (16)
Air leak	3 (10)	1 (4)	4 (13)	1 (5)
Days on ventilator[a]	5 (0–77)	10 (0–40)	7 (0–70)	8 (0–56)
CLD[a]	4/28 (14)	3/22 (14)	6 (20)	3 (16)
FiO_2 >0.21 at discharge	2/28 (7)	2/22 (9)	4 (13)	2 (11)
Retinopathy of prematurity >grade II[a]	5/28 (18)	2/22 (9)	5 (17)	3 (16)
Photocoagulation[a]	2/28 (7)	1/22 (4)	1 (3)	0
Patent ductus arteriosus	13 (42)	12 (48)	7 (23)	5 (26)

[a] Surviving infants.
[b] N-IMV was given after successful N-SPCI for apnoea (n = 3) and in infants with treatment failure until intubation was done (n = 3).
[c] N-SPCI was given in 11 infants with treatment failure after N-IMV in the delivery room. Data are median (minimum—maximum) or n (%). Differences between groups were not significantly different.

A Randomized Controlled Trial of Delivery-Room Respiratory Management in Very Preterm Infants

Te Pas et al. Pediatrics 2007;120:322

- RCT, EFURCI (Early Functional Residual Capacity Intervention) vs. conventional IPPV, GA: 25-32 wks, n=217, 2005-2006
- After suctioning (time 30s), no breathing or signs of poor air entry (retractions, nasal flaring): 3 interventions!
- Initial FiO_2: 1.0, adjusted according to SpO_2
- Prim. Outcome: Rate of intubation/mech. Ventilation <72h
- Criteria for Intubation/mech. Ventilation: SpO_2 <88% or PaO_2 ≤50 mmHg with FiO_2 ≥0.40, or $PaCO_2$ >60 mmHg with pH <7.20, or >4 apnea episodes/h, or >2 episodes requiring bagging/h; Caffeine/Theophylline

Interventions	EFURCI	Conventional IPPV
1. Immediately after suctioning	- 20 cmH_2O, 10s, T-Piece, nasopharyngeal tube (ID 2.5-4.0), mouth + nostril closed - Repeated with 25 cmH_2O @ time 55-65s if breathing insufficient, or HR<100‘, or cyanotic	Self-infl. Bag + mask for 30s, PIP 30-40 cmH_2O, thereafter 20 cmH_2O if necessary
2. Thereafter	Nasal IMV: PIP 20-25 cmH_2O, IMV 60‘	no nasal IMV
3. PEEP/CPAP	5-6 cmH_2O	no PEEP or CPAP in L&D

A Randomized Controlled Trial of Delivery-Room Respiratory Management in Very Preterm Infants

Te Pas et al. Pediatrics 2007;120:322

	EFURCI	Conventional	
Intubation within 72h of age	38/104 (37%)	52/103 (51%)	P=0.04, OR 0.57 (95%CI 0.32-0.98)

TABLE 2 **Secondary Outcomes**

Secondary Outcomes	EFURCI ($N = 104$)	Conventional ($N = 103$)	Univariate Analysis, *P*	OR (95% CI)
Intubation delivery room, *n* (%)	18 (17)	37 (36)	.002	0.37 (0.20–0.70)
Total period of mechanical ventilation of intubated infants <72 h of age, median (IQR), d [*n*]	2.5 (1–8.3)[38]	4.5 (2–11.5)[52]	.2	
Total period of NCPAP of total group, median (IQR), d	2 (0.3–8)	2 (0–11)	.038	
Surfactant doses, mean (SD)	0.4 (0.8)	0.6 (1.0)	.3	
Surfactant >1 dose, *n* (%)	10/103 (10)	22/104 (21)	.02	0.39 (0.18–0.88)
Mortality, *n* (%)	2 (2)	4 (4)	.4	
BPD_{total}, *n* (%)[a]	22 (22[a])	34 (34[a])	.05	
$BPD_{moderate\text{-}severe}$, *n* (%)[a]	9 (9[a])	19 (19[a])	.04	0.41 (0.18–0.96)
PDA needing treatment, *n* (%)	21 (20)	16 (16)	.4	
NEC at least stage 2, *n* (%)	0 (0)	1 (1)	.5	
ROP above grade 3, *n* (%)	0 (0)	1 (1)	.5	
IVH grade 3 + 4, *n* (%)	7 (7)	3 (3)	.3	
Cystic PVL, *n* (%)				

PDA indicates patent ductus arteriosus; NEC, necrotizing e

[a] Percentage of survivors.

Power to detect a significant difference in the rate of IVH °3,4: 0,148

No difference in blood gases upon arrival to the NICU

No difference in PTX: 1/104 (1%) EFURCI vs. 7/103 (7%) Conventional

Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial

- SI (25 cmH_2O, 15‘‘) 1-2x vs. CPAP (5 cmH_2O)
- 25+0 – 28+6 wks GA, n=291, 9/2011-1/2013
- Prim. Outcome: mech. ventilation within 72 h

TABLE 1 Baseline Clinical Characteristics of the Infants and Their Mothers

Characteristic	Control Group (n = 143)	SLI Group (n = 148)
Mothers		
Antenatal steroids	125 (87)	134 (91)
Cesarean delivery	116 (81)	120 (81)
Placental abruption	15 (10)	21 (14)
Hypertension disorders	42 (29)	35 (24)
pPROM	39 (27)	39 (26)
Chorioamnionitis	14 (10)	19 (13)
Other complications	43 (30)	48 (32)
Infants		
Gestational age, mean ± SD, wk	26.8 ± 1.2	26.8 ± 1.1
25–26	55 (38)	52 (35)
27–28	88 (62)	96 (65)
Birth weight, mean ± SD, g	894 ± 247	893 ± 241
Male sex	65 (45)	86 (58)
Birth weight <10th percentile for gestational age	31 (22)	32 (22)
Singleton birth	98 (69)	101 (68)

Unless otherwise indicated, data are n (%). pPROM, prolonged premature rupture of membranes.

Lista et al. Pediatrics 2015;135:e457

Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial

TABLE 2 Primary and Secondary Outcomes

Outcome	Control Group (n = 143)	SLI Group (n = 148)	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)[a]
Primary outcome, n (%)					
MV within the first 72 h of life	93 (65)	79 (53)	0.62 (0.38–0.99)	.04	0.57 (0.33–0.96)
Secondary outcomes, n (%)					
MV within the first 3 h of life	73 (51)	66 (45)	0.77 (0.49–1.22)	.27	0.72 (0.43–1.22)
BiPAP	47 (33)	63 (43)	1.51 (0.94–2.44)	.09	1.51 (0.93–2.43)
Nasal IMV	36 (25)	39 (26)	1.06 (0.63–1.80)	.85	1.07 (0.63–1.81)
Surfactant	110 (77)	109 (74)	0.84 (0.49–1.43)	.52	0.88 (0.50–1.56)
SIMV/SIPPV/PSV	90 (63)	86 (58)	0.82 (0.51–1.31)	.43	0.84 (0.51–1.39)
HFV	31 (22)	32 (22)	1.00 (0.57–1.74)	.99	1.03 (0.58–1.83)
Any mechanical ventilation	98 (69)	88 (59)	0.67 (0.42–1.10)	.11	0.68 (0.41–1.13)
BPD[b,c]	50 (35)	57 (39)	1.17 (0.80–1.71)[d]	.42	1.14 (0.78–1.69)[d]
Death[c]	12 (8)	17 (11)	1.37 (0.66–2.88)[d]	.40	1.39 (0.66–2.93)[d]

BiPAP, bilevel positive airway pressure; HFV, high-frequency ventilation; PSV, pressure support ventilation; SIMV, synchronized intermittent MV; SIPPV, synchronized intermittent positive pressure ventilation.

[a] Adjusted for center and gestational age.

[b] Defined by the use of supplemental oxygen at a postmenstrual age of 36 weeks.

[c] Proportions are estimates of cumulative incidence of events in the presence of competing risks.

[d] Unadjusted hazard ratio (95% confidence interval).

Lista et al. Pediatrics 2015;135:e457

Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial

TABLE 4 Comparison of Other Collected Data

Outcome	Control Group (n = 143)	SLI Group (n = 148)	Unadjusted Odds Ratio (95% CI)	P
RDS	134 (94)	133 (90)	0.60 (0.25–1.41)	.23
Pneumothorax	2 (1)	9 (6)	4.57 (0.97–21.50)	.06
Interstitial emphysema	2 (1)	7 (5)	3.50 (0.72–17.10)	.09
Pharmacologic treatment of PDA	70 (49)	88 (59)	1.53 (0.96–2.43)	.07
Surgical closure of PDA	8 (6)	5 (3)	0.59 (0.19–1.85)	.36
IVH	28 (20)	37 (25)	1.37 (0.79–2.39)	.27
Grade ≥3	8 (6)	12 (8)	1.49 (0.59–3.76)	.39
PVL	5 (4)	1 (1)	0.19 (0.02–1.63)	.08
NEC	4 (3)	7 (5)	1.73 (0.49–6.03)	.38
ROP[a]	58 (41)	60 (41)	0.99 (0.63–1.60)	.99
Grade ≥3	12 (8)	14 (9)	1.14 (0.51–2.56)	.75
Sepsis	44 (31)	54 (36)	1.29 (0.79–2.11)	.30

Data are presented as n (%). IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a] Proportions are estimates of cumulative incidence of events in the presence of competing risks.

Lista et al. Pediatrics 2015;135:e457

Sustained Inflation vs. Positive Pressure Ventilation at Birth: a Systematic Review and Meta-analysis

Mechanical Ventilation <72h

- 4 RCT

Study or Subgroup	SI Events	SI Total	IPPV Events	IPPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Harling 2005	22	26	24	26	33.7%	0.92 [0.75, 1.12]
Lindner 2005	19	31	21	30	9.9%	0.88 [0.61, 1.26]
Lista 2014	88	148	97	143	43.3%	0.88 [0.74, 1.04]
te Pas 2007	38	104	52	103	13.1%	0.72 [0.53, 0.99]
Total (95% CI)		**309**		**302**	**100.0%**	**0.87 [0.77, 0.97]**
Total events	167		194			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.86$, df = 3 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.42 (P = 0.02)

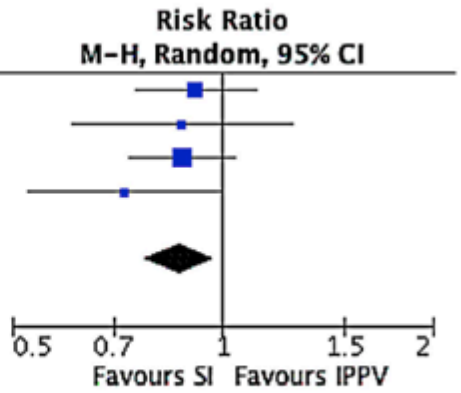


Figure 3 Outcome of mechanical ventilation <72 h after birth. IPPV, intermittent positive pressure ventilation; SI, sustained inflation.

Sustained Inflation vs. Positive Pressure Ventilation at Birth: a Systematic Review and Meta-analysis

BPD

Death

Death or BPD

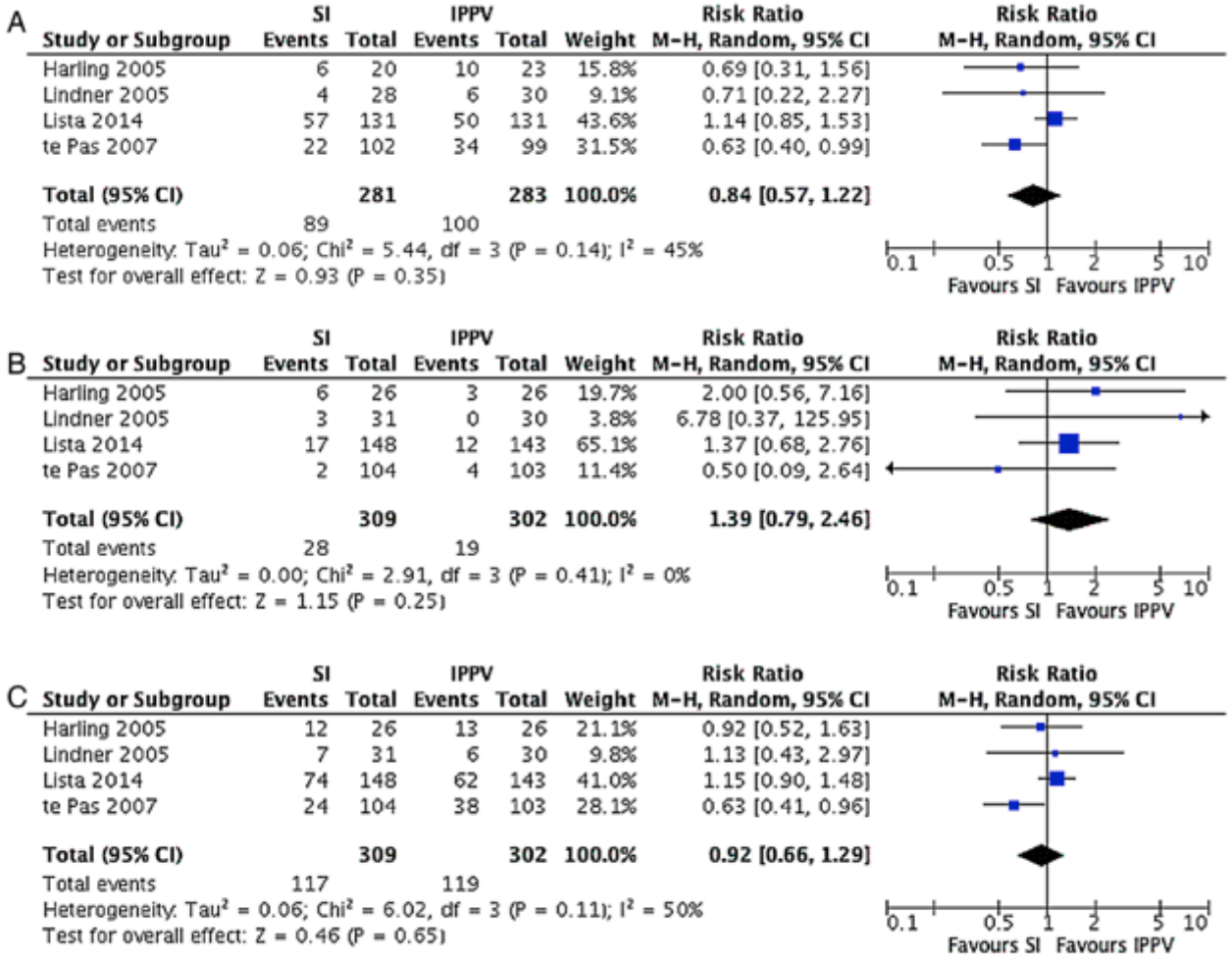


Figure 2 (A) Outcome of bronchopulmonary dysplasia (BPD) at corrected 36 weeks' gestational age. (B) Outcome of death. (C) Composite outcome of death or BPD at corrected 36 weeks' gestational age. IPPV, intermittent positive pressure ventilation; SI, sustained inflation.

Schmölzer et al. Arch Dis Child Fetal Neonatal Ed. 2015;100:F361

Sustained Inflation vs. Positive Pressure Ventilation at Birth: a Systematic Review and Meta-analysis

PDA

Study or Subgroup	SI Events	SI Total	IPPV Events	IPPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Harling 2005	5	26	1	26	0.9%	5.00 [0.63, 39.91]
Lindner 2005	13	31	7	30	6.3%	1.80 [0.83, 3.88]
Lista 2014	88	148	70	143	82.0%	1.21 [0.98, 1.50]
te Pas 2007	21	104	16	103	10.8%	1.30 [0.72, 2.35]
Total (95% CI)		**309**		**302**	**100.0%**	**1.27 [1.05, 1.54]**
Total events	127		94			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.74$, df = 3 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 2.42 (P = 0.02)

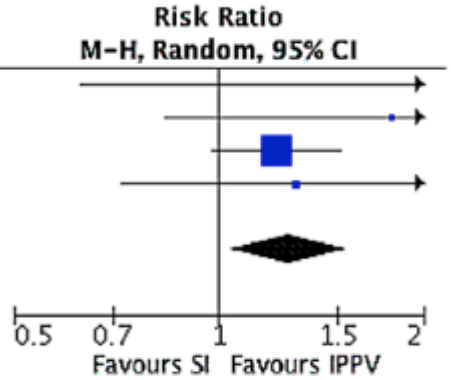


Figure 4 Outcome of patent ductus arteriosus. IPPV, intermittent positive pressure ventilation; SI, sustained inflation.

IVH

Study or Subgroup	SI Events	SI Total	PPV Events	PPV Total	Weight	Risk Ratio M-H, Random, 95% CI
Harling 2005	1	26	1	26	5.7%	1.00 [0.07, 15.15]
Lista 2014	12	148	8	143	56.2%	1.45 [0.61, 3.44]
Lindner 2005	3	31	2	30	14.2%	1.45 [0.26, 8.09]
te Pas 2007	7	104	3	103	23.9%	2.31 [0.61, 8.69]
Total (95% CI)		**309**		**302**	**100.0%**	**1.59 [0.83, 3.03]**
Total events	23		14			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, df = 3 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 1.40 (P = 0.16)

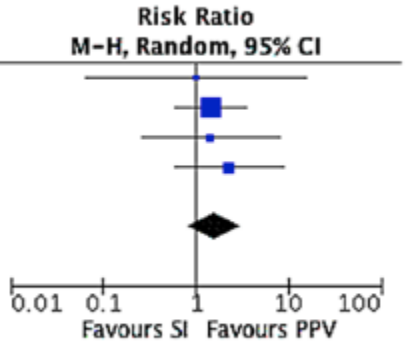


Figure 5 Outcome of intraventricular haemorrhage. IPPV, intermittent positive pressure ventilation; SI, sustained inflation (see online supplement).

Schmölzer et al. Arch Dis Child Fetal Neonatal Ed. 2015;100:F361

Sustained Inflation vs. Positive Pressure Ventilation at Birth: a Systematic Review and Meta-analysis

BPD, <29 wks GA

Death, <29 wks GA

Death or BPD <29 wks GA

IVH, < 29 wks GA

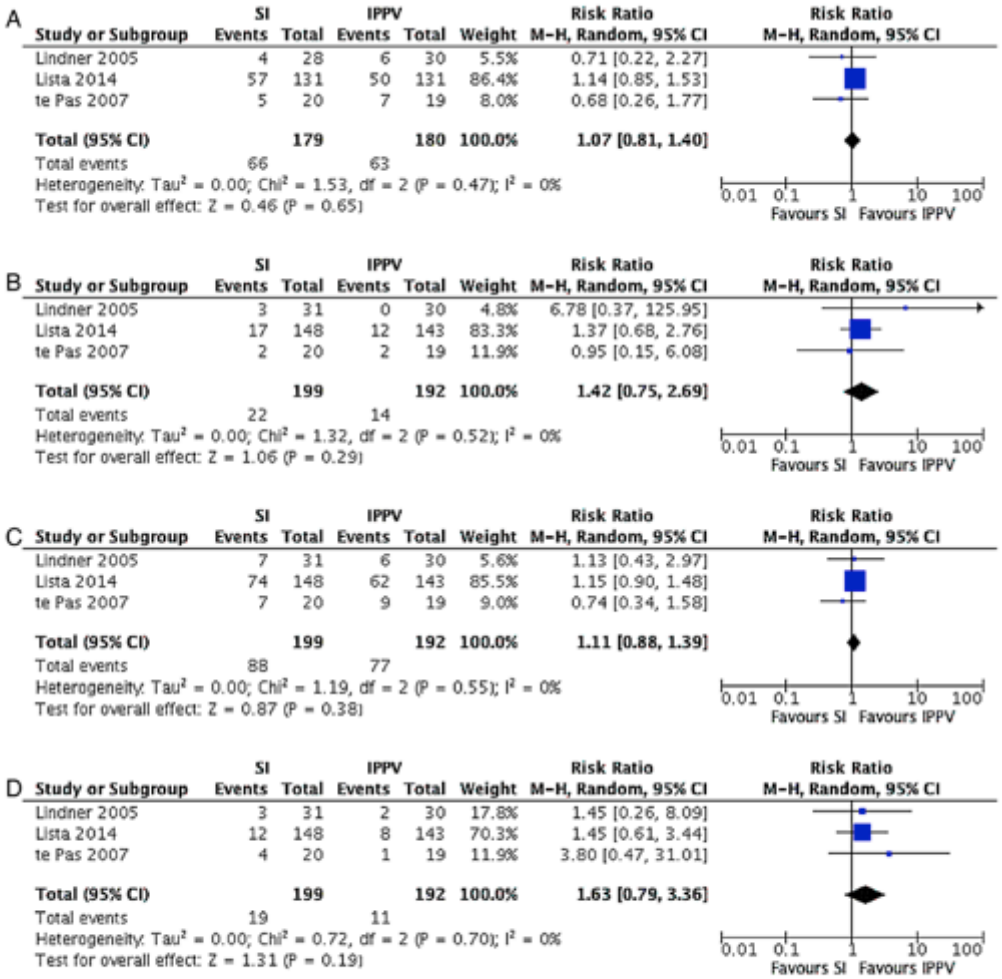


Figure 6 Outcomes in <29 week infants (subgroup analysis; pooled estimates from the three studies providing these data): bronchopulmona dysplasia (BPD) at corrected 36 weeks' gestational age (A), death (B), death/BPD at corrected 36 weeks' gestational age (C) and intraventricul haemorrhage (D). IPPV, intermittent positive pressure ventilation; SI, sustained inflation (see online supplement).

Schmölzer et al. Arch Dis Child Fetal Neonatal Ed. 2015;100:F361

Topics

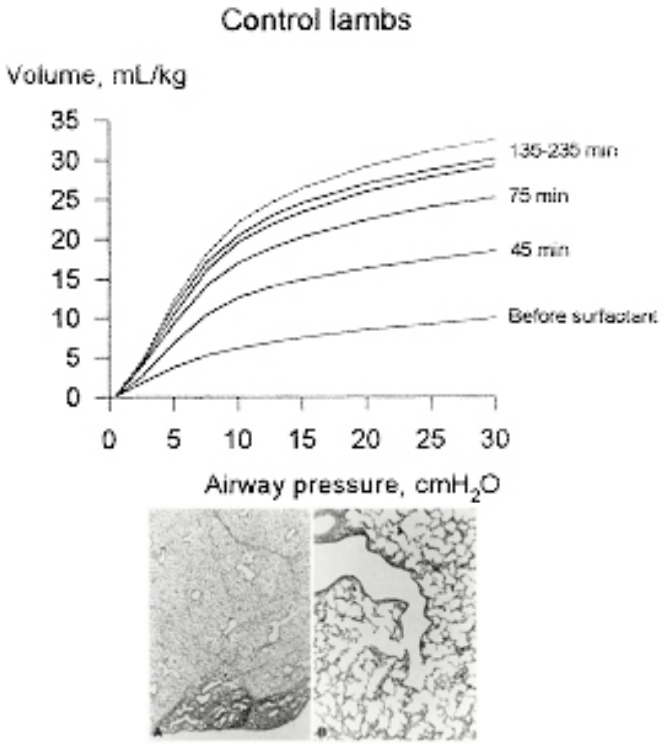
- Introduction
- Experimental studies
- Clinical physiological studies
- Clinical studies on sustained inflations
- Potential risks
- Open questions
- Summary

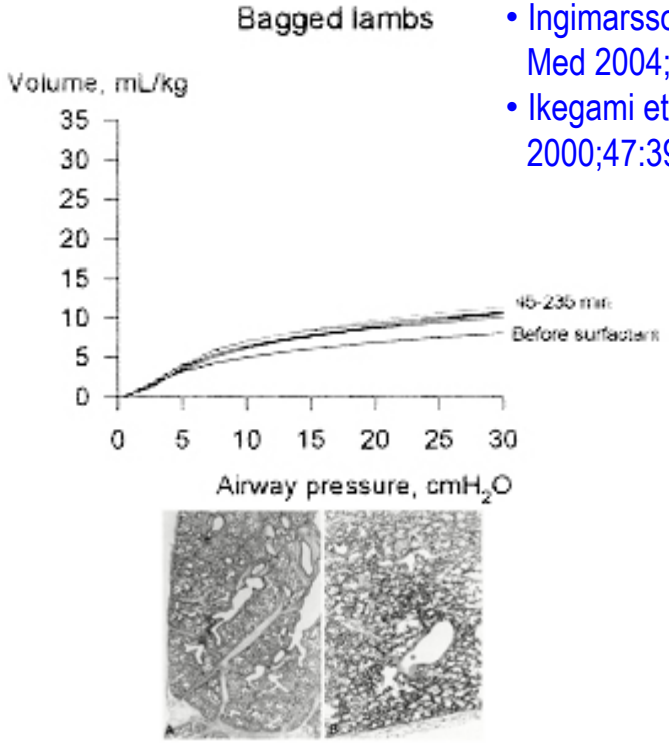
Risk for Overdistension?

Manual Ventilation with a Few Large Breaths at Birth Compromises the Therapeutic Effect of Subsequent Surfactant Replacement in Immature Lambs
(Björklund et al. Pediatr Res 1997:42, 348)

- Preterm lambs (n=10), after drainage of 20 ml lung fluid randomized into 2 groups:
  - 6 inflations 35-40 ml/kg **for 5s** (Bagged lambs), 200 mg/kg surfactant after 30 min
  - Surfactant before mechanical ventilation
- PPV 29/4 cmH_2O, IMV 50', supported for 4h
- Gas exchange was better in the control group

Similar data from:
- Björklund et al. Acta Anaesthesiol Scand 2001;45:986
- Ingimarsson et al. Intensive Care Med 2004;30:1446
- Ikegami et al. Pediatr Res 2000;47:398





Risk Indicators for Air Leaks in Preterm Infants Exposed to Restrictive Use of Endotracheal Intubation

- Retrospective Analysis, GA <29 wks, inborn 2005-2009, Univ. of Ulm, 270/297 (91%) of all infants survived to discharge
  - GA 26+0 (22+4 to 28+6) wks; BW 790 (265 – 1660)g
  - CPAP 5 cmH_2O via nasal tube
  - S.I. if no vigorous respiratory effort: 20, 25 and 30 cmH_2O for 15 s followed by nasal IMV
- 63/297 (21.2%) patients developed air leaks
  - 32 (10.8%) pneumothorax
  - 44 (14.8%) pulmonary interstitial emphysema
  - 1 (0.3%) pneumopericardium

Table 1. Demographic characteristics of infants with and without air leaks

	With air leaks (n = 63)	Without air leaks (n = 234)	p
BW, g	740 (470–1,410)	808 (265–1,660)	0.218
GA, weeks	25+3 (23+1 to 28+5)	26+2 (22+3 to 28+6)	0.007
Male, n	36 (57.1%)	125 (53.4%)	0.598
Small for gestational age, n	5 (7.9%)	30 (12.8%)	0.286
Multiple gestation, n	24 (38.1%)	58 (24.8%)	0.036

Univariate analysis: values presented are medians (min–max) unless otherwise indicated.

Hummler et al. Neonatology 2015;108:1

Risk Indicators for Air Leaks in Preterm Infants Exposed to Restrictive Use of Endotracheal Intubation

Variables of Delivery Room Care

Table 3. Variables of delivery room care in infants with and without air leaks

	With air leaks (n = 63)	Without air leaks (n = 234)	p
Apgar (5 min)	8 (2–10)	9 (1–10)	0.003
Apgar (10 min)	9 (5–10)	9 (3–10)	0.015
Cardiac compressions	9 (14.3 %)	11 (4.7%)	0.007
Epinephrine	16/62 (25.8%)	17 (7.3%)	0.001
Use of sustained inflations	58/63 (92.1%)	218/234 (93.2%)	0.763
Sustained inflations (×2)	20/58 (34.5%)	105/218 (48.2%)	0.061
Sustained inflations (×3)	31/58 (53.4%)	79/218 (36.2%)	0.024
Sustained inflation (25 cm H_2O)	51/58 (87.9%)	178/218 (81.7%)	0.450
Sustained inflation (30 cm H_2O)	32/58 (55.2%)	80/218 (36.7%)	0.014
Endotracheal intubation	36 (57.1%)	82 (35.0%)	0.003

Univariate analysis: values presented are medians (min–max) unless otherwise indicated.

Hummler et al. Neonatology 2015;108:1

Risk Indicators for Air Leaks in Preterm Infants Exposed to Restrictive Use of Endotracheal Intubation

Multivariate Analyisis

Table 6. Risk indicators for air leaks

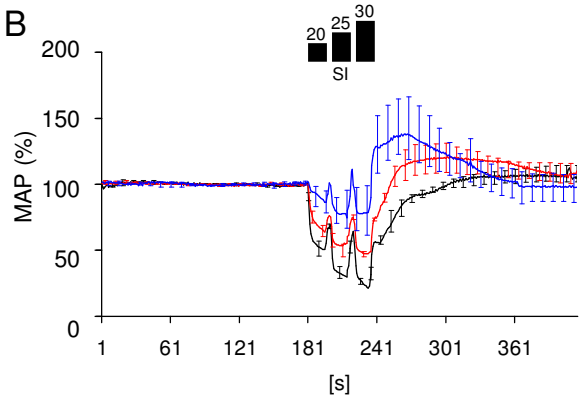
	OR	95% CI	p
Prenatal steroids	0.41	0.20–0.85	0.02
GA (per week)	0.87	0.70–1.06	0.17
Epinephrine use in delivery room	3.56	1.55–8.15	0.003
Surfactant use	12.03	3.39–42.72	0.001
Intubation in delivery room	0.66	0.31–1.38	0.27
Sustained inflation (30 cm H_2O)	1.53	0.79–2.97	0.21

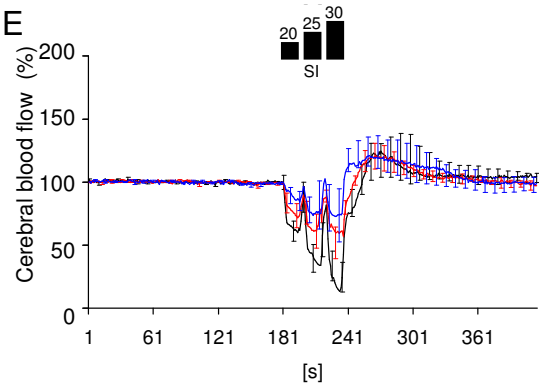
Multivariate logistic regression analysis.

Hummler et al. Neonatology 2015;108:1

Other Safety Issues

- Sustained inflations in rabbits with surfactant deficiency may impair blood pressure and cerebral blood flow (Fuchs et al. Minerva Anesthesiol 2013;79:733)





- Sustained inflations as recruitment procedures in patients with ARDS …
  - may worsen oxygenation (Musch et al. Anesthesiology 2004;100:323)
  - may decrease blood pressure and left ventricular ejection fraction (Park et al. Journal Intensive Care Med 2009;24:376)
  - risk for acute air leaks low (Guerin et al. Annals of Intensive Care 2011;1:9)

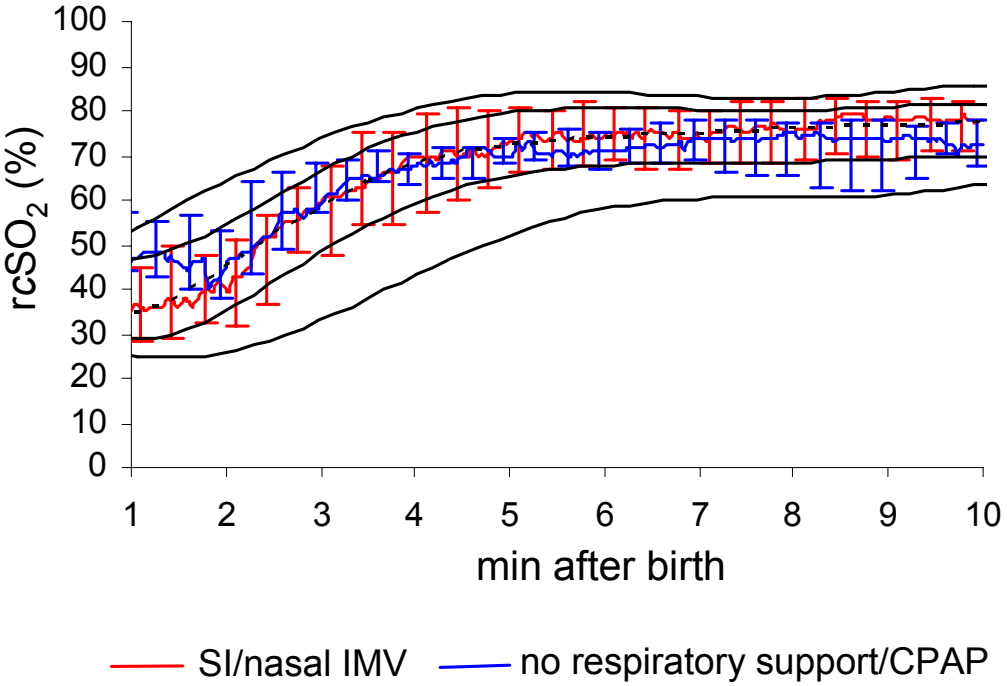
Brain Oxygenation Monitoring during Neonatal Resuscitation of Very Low Birth Weight Infants

Fuchs et al. J Perinatol 2012;32:356

Table 1 Characteristics of infants

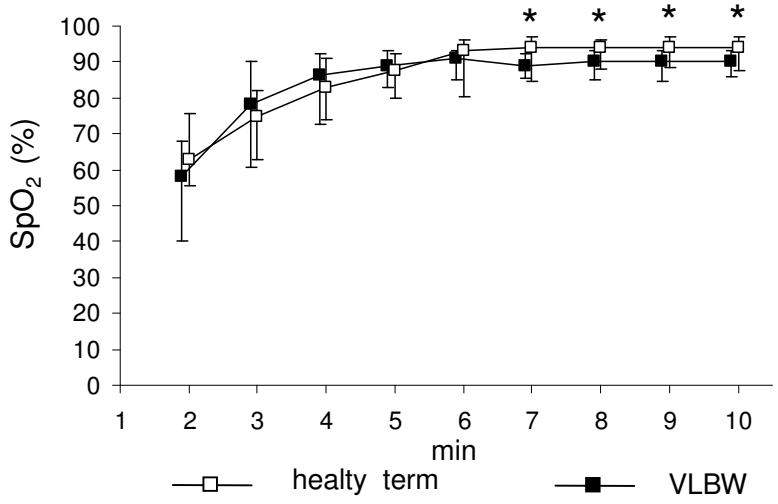
	All study infants (n = 51)	*Infants without respiratory support or with nCPAP only (n = 10)*
Gestational age (weeks)[a]	27.8 (2,6)	29.1 (2.7)
Birth weight (g)[a]	913.3 (298)	1119 (226)
Male	25 (49%)	5 (50%)
Intrauterine growth restriction	15 (29%)	1 (10%)
Premature rupture of membranes (>24 h)	9 (18%)	2 (20%)
Full course of steroids	39 (76%)	7 (70%)
Cesarean section	47 (92%)	8 (80%)
Apgar score at 1 min[b]	6 (4–6)	8 (7–9)
Apgar score at 5 min[b]	9 (8–9)	10 (9–10)
Apgar score at 10 min[b]	10 (9–10)	10 (10–10)
Cord pH[a]	7.31 (0.11)	7.37 (0.05)
Number of sustained lung inflations[b]	2 (1–2)	—
Intubation in delivery room	7 (14%)	—

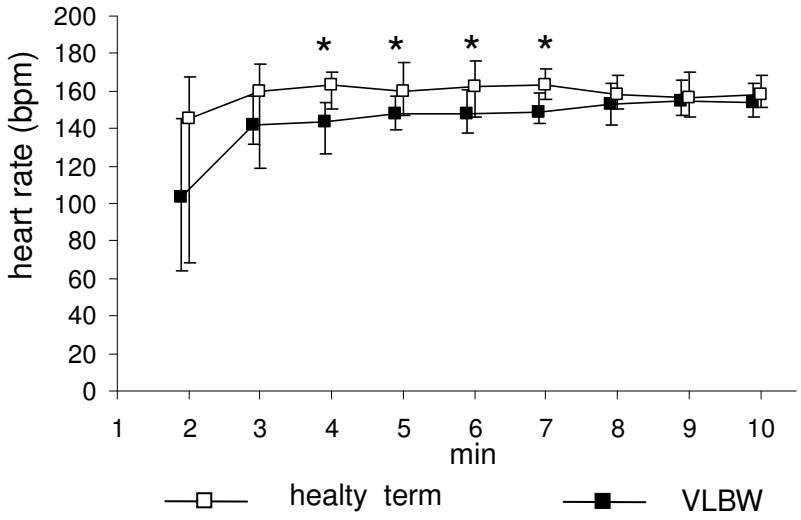
Abbreviation: nCPAP, nasal continuous positive airway pressure
[a]Mean (s.d.).
[b]Median (interquartile range).

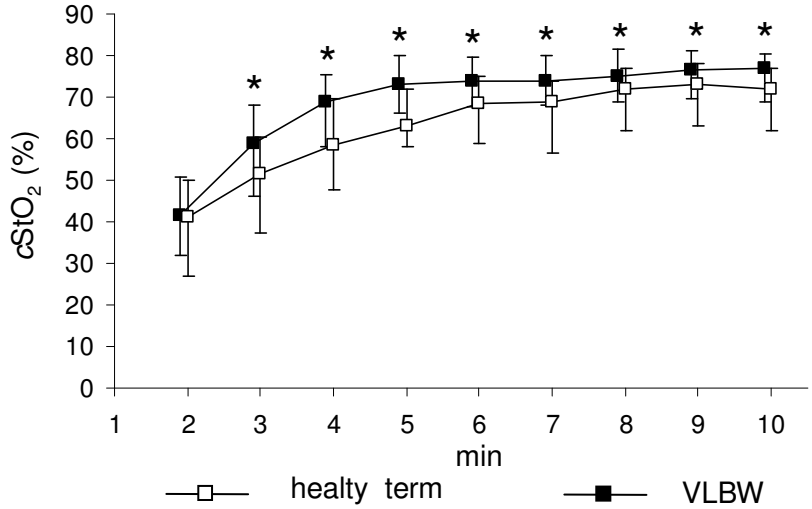


Brain Oxygenation during Transition of Healthy Term Newborns as Compared to VLBWI

Almaazmi et al. Neonatology 2013;103:246







- Cohort-Study:
  - Healthy term newborns after delivery
  - No oxygen, no respir. Support
    - Spont. Vag. Delivery: n=20
    - Cesarean section: n=22
    - Vacuum-assisted: n=4
- Compared to the VLBWI-cohort (n=51)
  - Sustained inflations (n=41)
  - No respiratory support (n=10)
- VLBWI had a similar SpO_2 early on, a lower heart rate but a higher $cStO_2$

Topics

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- Open questions
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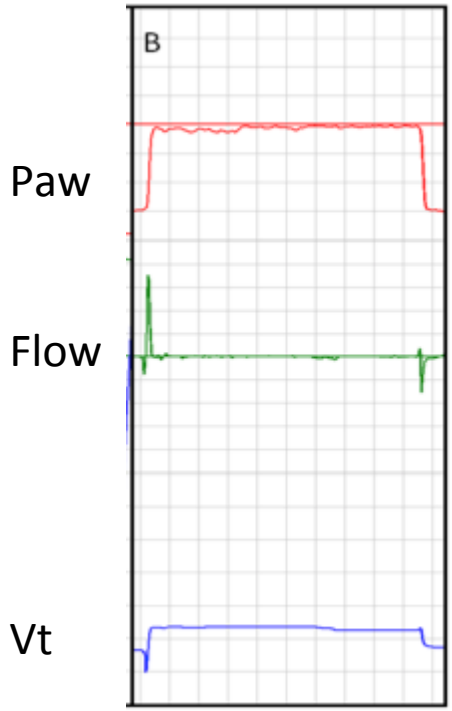
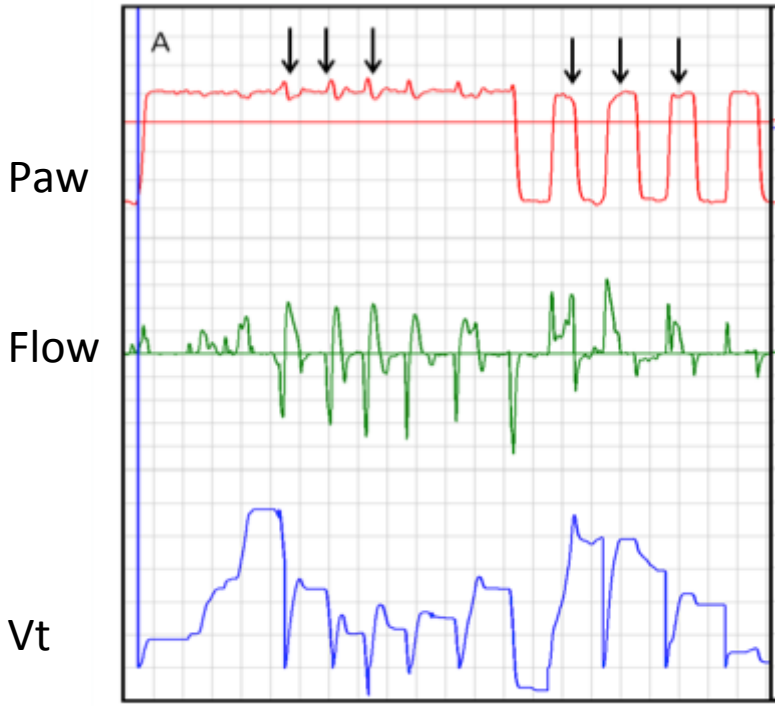
Effect of a S.I. in Preterm Infants at Birth

n=50, with no leak



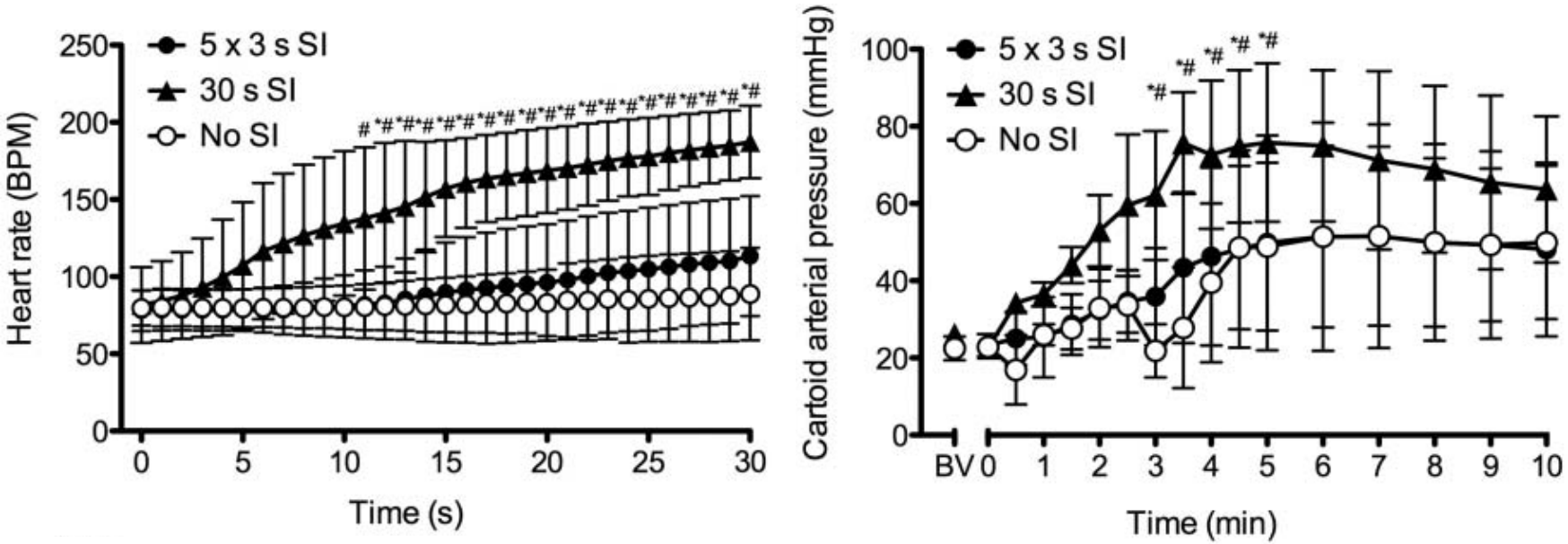


- 14/50 no breathing
  - Vti 0,9 (0,4-2,7) ml/kg
  - Vte 0,6(0,1-2,0) ml/kg
  - FRC gain: 0,0 (-0,5-0,6) ml/kg
- 36/50 breathing
  - Vti 2,9 (0,9-9,2) ml/kg
  - Vte 3,8 (1,0-5,9) ml/kg
  - FRC gain 7,1 (1,7-15,9) ml/kg

van Vonderen et al. J Pediatr 2014; 165:903

Effect of Sustained Inflation Duration – Resuscitation of Near-Term Asphyxiated Lambs

- Asphyxiated (induced by delayed ventilation until BP 25%BL), n=18 3 groups:
  - 0.5s; 60 breaths/min
  - 5 x 3s S.I.
  - 1 x 30s S.I.



Cardiopulmonary Resuscitation with Chest Compressions During Sustained Inflations

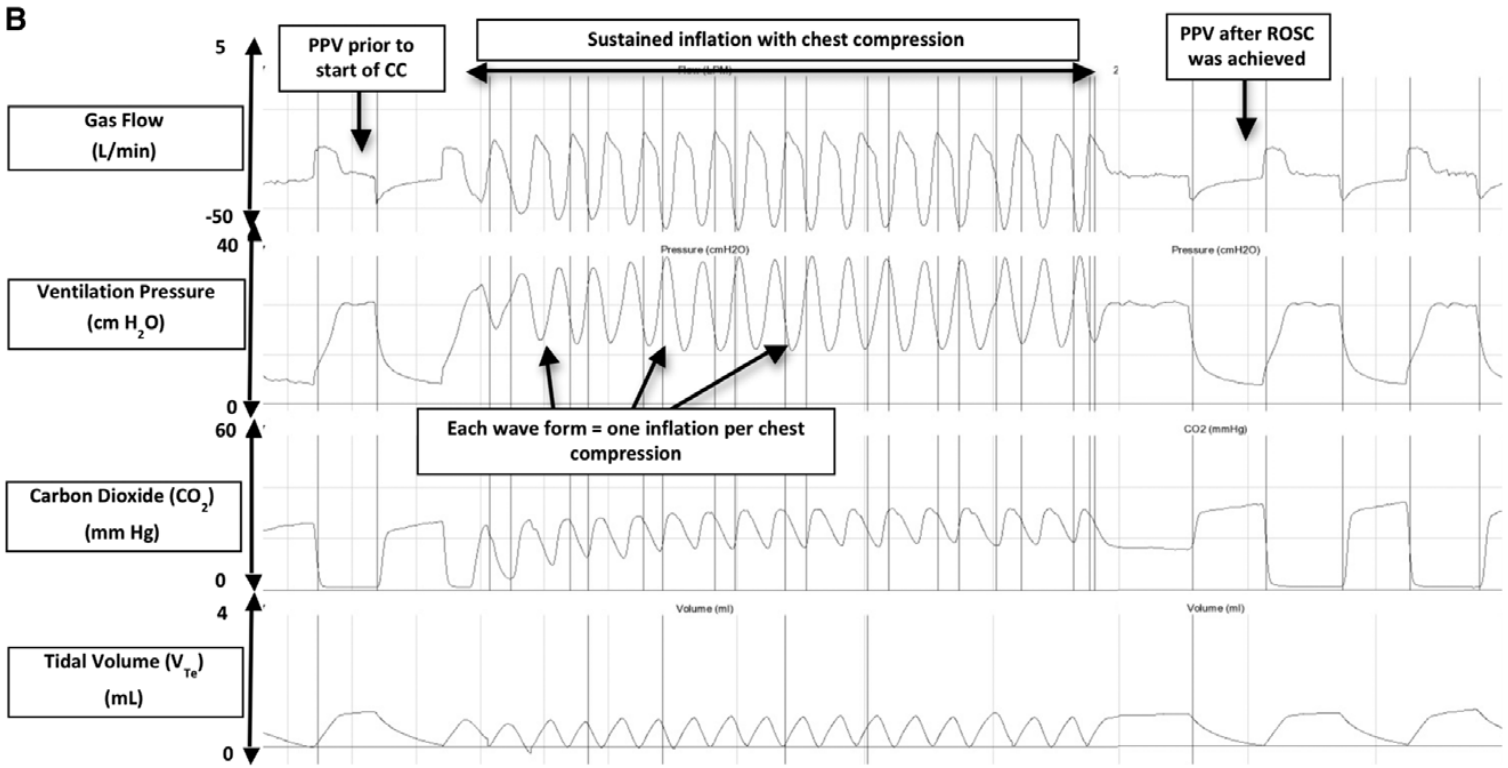


Figure 2. Respiratory waveforms during CPR in the 3:1 (**A**) and SI groups (**B**; gas flow (LPM=L/min), airway pressure, ECO_2, and tidal volume). CPR indicates cardiopulmonary resuscitation; ECO_2, exhaled CO_2; and SI, sustained inflation.

- Asphyxiated newborn piglets, n= 16
  standard resuscitiation 3:1 vs. 120/min with S.I. 30 cmH_2O for 30s
- **ROSC: 32±10s (S.I.) vs. 205±113s (standard group)**

Schmölzer et al. Circulation 2013;128:2503

Sustained Aeration of Infant Lungs (SAIL) trial: Study Protocol for a Randomized Controlled Trial

- The Sustained Aeration of Infant Lungs (SAIL) Study (NIH Grant Number 1-U01-HD072906-01A1; PI: H. Kirpalani)
  - –23-26 wks, n= 600 infants of 23-26 weeks GA
  - –14 sites in US, Canada, Italy, The Netherlands, Australia, Germany
  - –Intervention
    - SI 20/25 cmH_2O, standard PEEP/CPAP of 5-7 cm H_2O in the DR
    - Primary Outcome: death or BPD
    - neurodevelopmental outcome at 18 - 24 mo. of corr. age

Open Questions

- Are S.I. really better than CPAP or conventional respiratory support for babies?
- Which is the right pressure/time for S.I.?
- How important is own respiratory effort?
- Stepwise increase of CPAP spontaneous breathing better than S.I.?
- What is the role of S.I. during cardiac compressions?

Summary

- Experimental and (limited) clinical evidence suggests that sustained inflations may facilitate transition of preterm infants after birth to avoid mechanical ventilation
- Based on current evidence the general use of sustained inflations cannot be recommended
- Large RCTs with important long-term endpoints are needed to prove efficacy and safety
- If sustained inflations for respiratory support immediately after birth are considered, the pressure used should probably be limited to a certain threshold (>25 cmH_2O ?)

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Peter Davis
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