Neonatal Ventilation:

New Ventilatory Modes and Assessment of Technology

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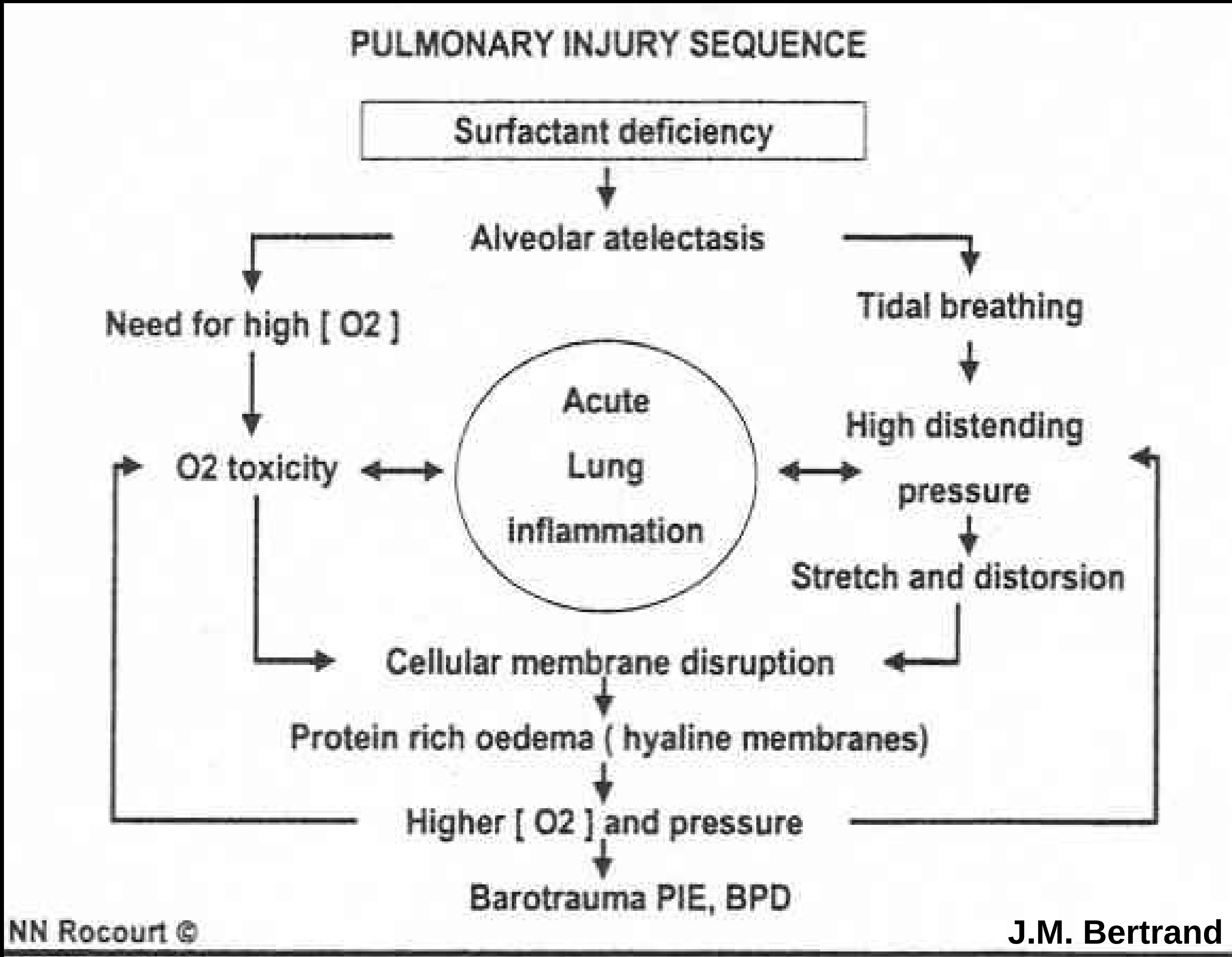
Technology Assessment:

Health Technology Assessment (HTA) defines the systematic analysis of short and longterm consequences of the application of medical technologies with the aim of supporting decisions in policy-making and practice.

Pereth M, Schwartz FW

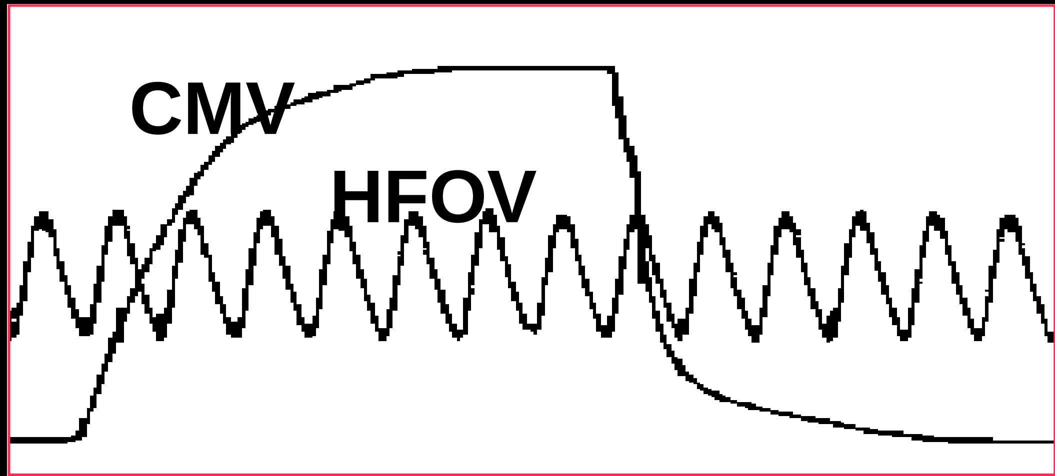
Bundesgesundheitsbl - Gesundheitsforsch – Gesundheitsschutz 2001; 44:857–864

Neonatal Mechanical Ventilation and the Pulmonary Injury Sequence



Technology 1:

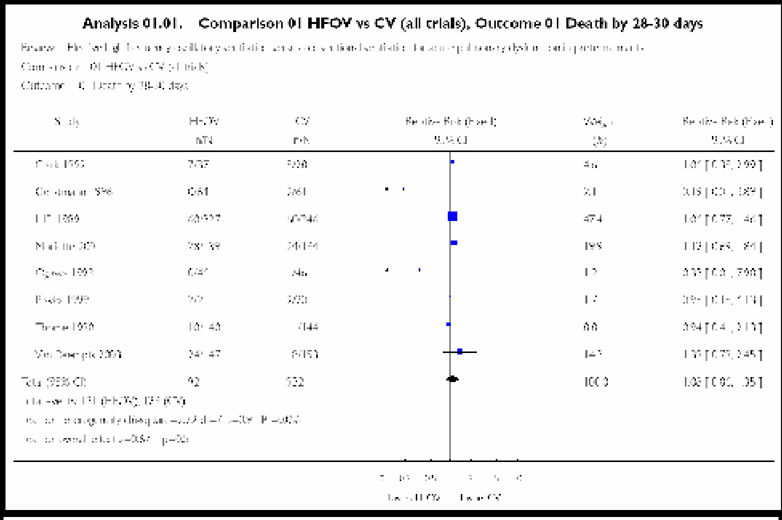
HFOV
1989 - 2003

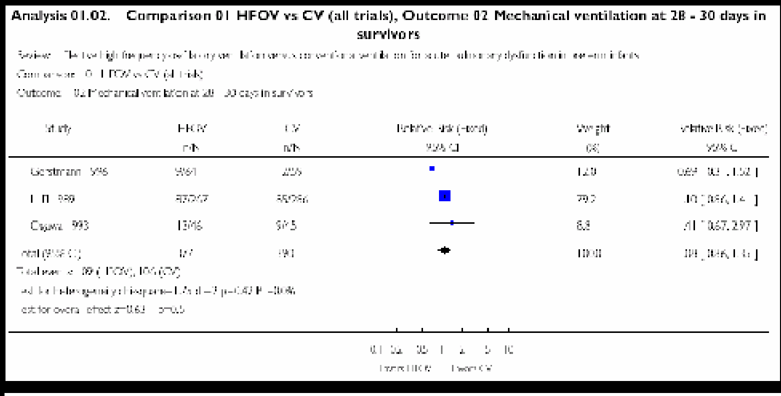


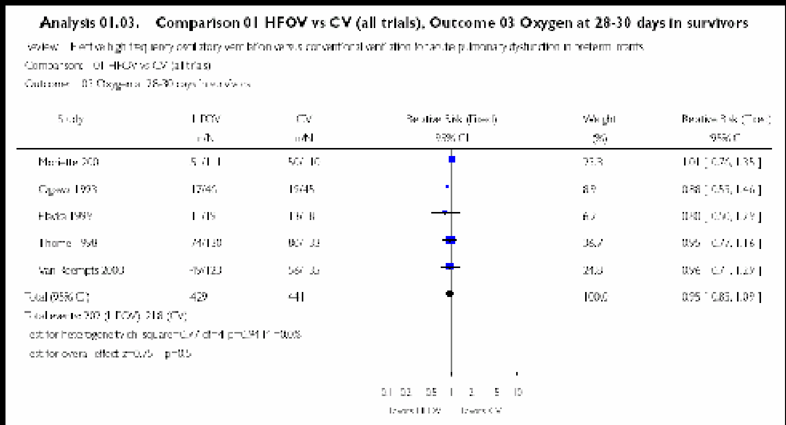
Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants (Review)

Henderson-Smart DJ, Bhuta T, Cools F, Offringa M

THE COCHRANE COLLABORATION®







all trials

Death by 28 – 30 days

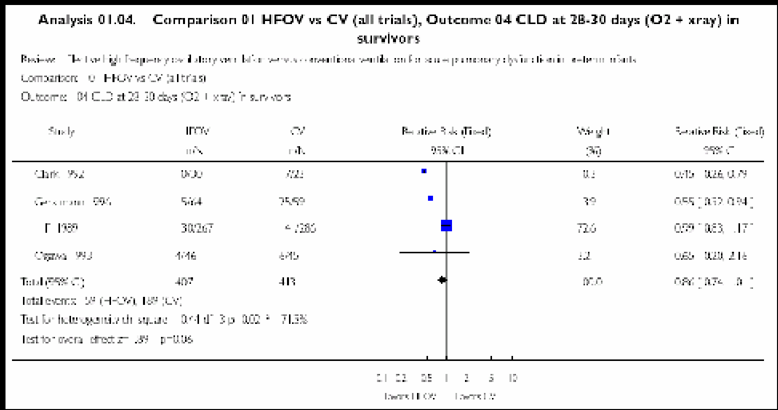
RR (96% CI): 1.08 (0.86, 1.35)

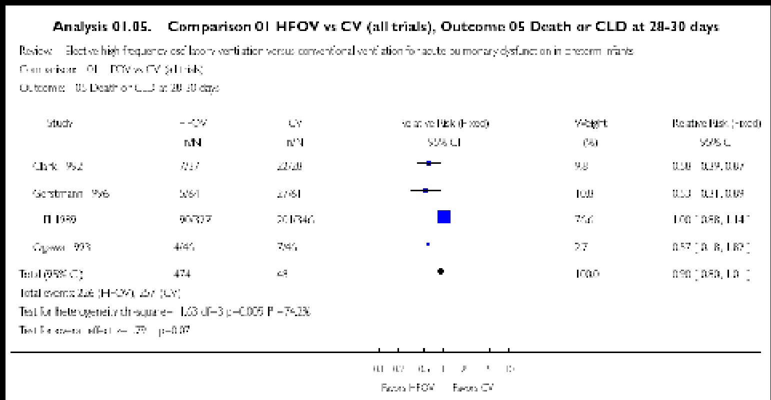
Mech. Ventilation at 28 – 30 days

RR (96% CI): 1.08 (0.86, 1.35)

Oxygen at 28 – 30 days

RR (96% CI): 0.95 (0.83, 1.09)





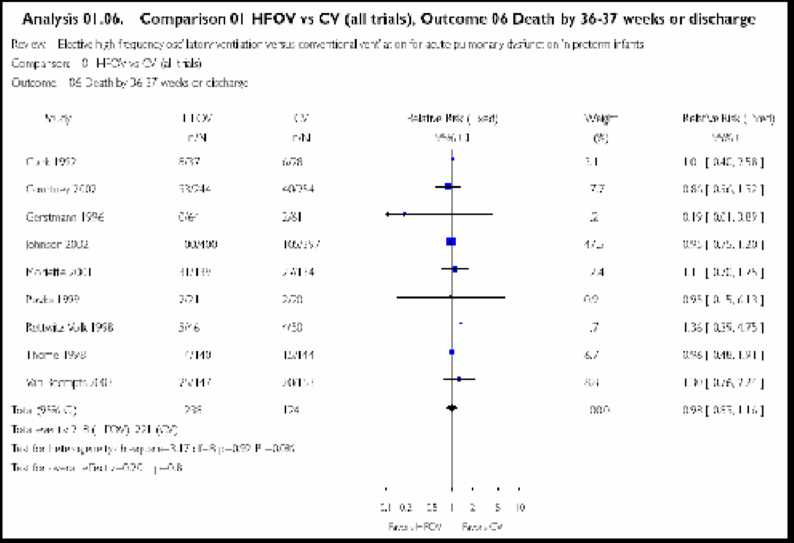
all trials

CLD at 28 – 30 days (O2 + xray)

RR (96% CI): 0.86 (0.74, 1.01)

Death or CLD at 28 – 30 days

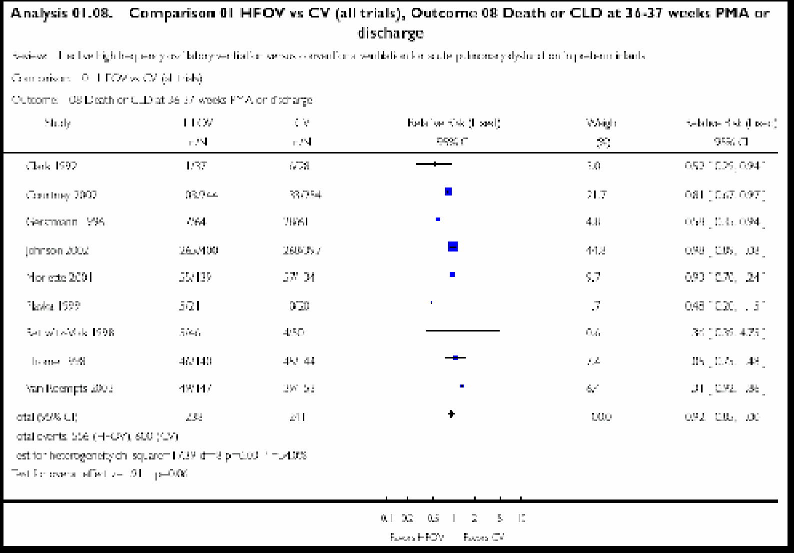
RR (96% CI): 0.90 (0.80, 1.01)



all trials

Death by 36-37 weeks or discharge

RR (96% CI): 0.98 (0.83, 1.16)



Death or CLD at 36-370 weeks

RR (96% CI): 1.08 (0.86, 1.35)

all trials

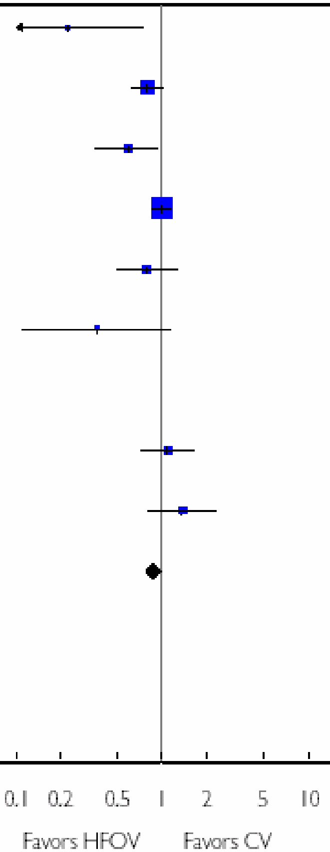
Analysis 01.07. Comparison 01 HFOV vs CV (all trials), Outcome 07 CLD at 36-37 weeks PMA or discharge in survivors

Review: Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants

Comparison: 01 HFOV vs CV (all trials)

Outcome: 07 CLD at 36-37 weeks PMA or discharge in survivors

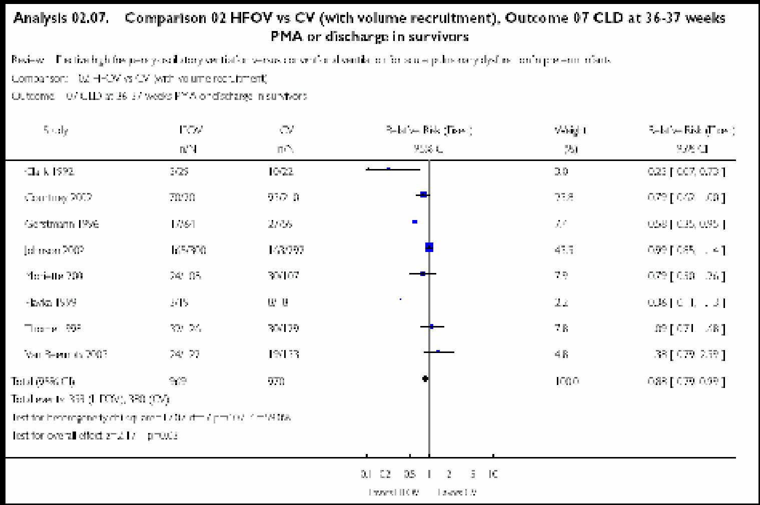
Study	HFOV n/N	CV n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Clark 1992	3/29	10/22		3.0	0.23 [0.07, 0.73]
Courtney 2002	70/201	93/210		23.8	0.79 [0.62, 1.00]
Gerstmann 1996	17/64	27/59		7.4	0.58 [0.35, 0.95]
Johnson 2002	165/300	163/292		43.3	0.99 [0.85, 1.14]
Moriette 2001	24/108	30/107		7.9	0.79 [0.50, 1.26]
Plavka 1999	3/19	8/18		2.2	0.36 [0.11, 1.13]
× Rettwitz-Volk 1998	0/41	0/46		0.0	Not estimable
Thome 1998	32/126	30/129		7.8	1.09 [0.71, 1.68]
Van Reempts 2003	24/122	19/133		4.8	1.38 [0.79, 2.39]
Total (95% CI)	1010	1016		100.0	0.88 [0.79, 0.99]

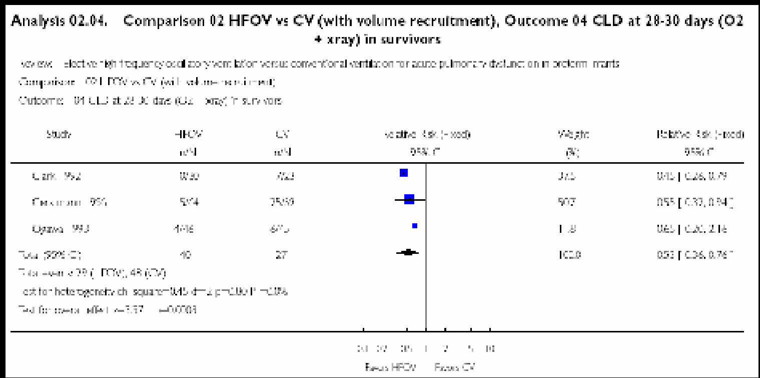


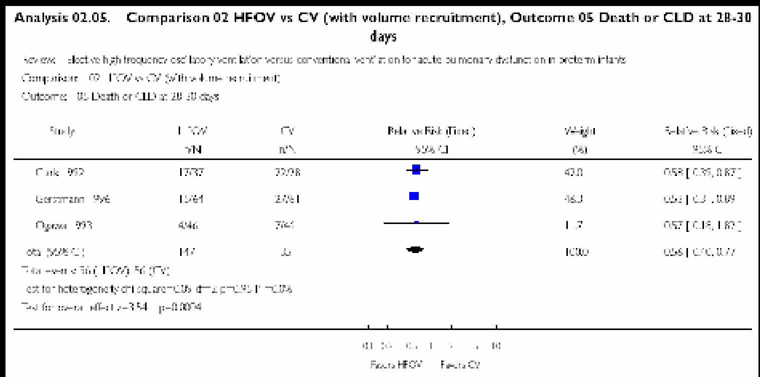
Total events: 338 (HFOV), 380 (CV)

Test for heterogeneity chi-square=17.07 df=7 p=0.02 I² =59.0%

Test for overall effect z=2.17 p=0.03







with volume recruitment

CLD at 36- 37 weeks or discharge

RR (96% CI): 0.88 (0.79, 0.99)

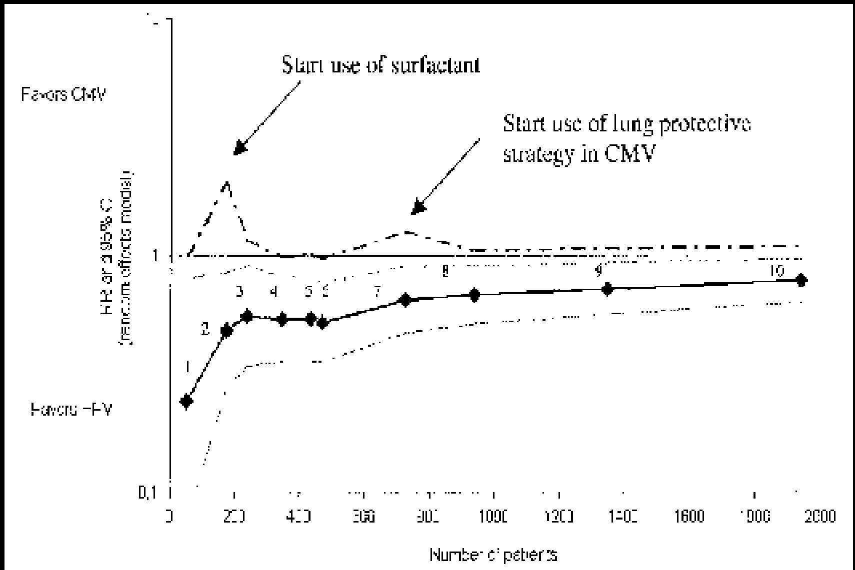
CLD at 28 – 30 days

RR (96% CI): 0.53 (0.36, 0.76)

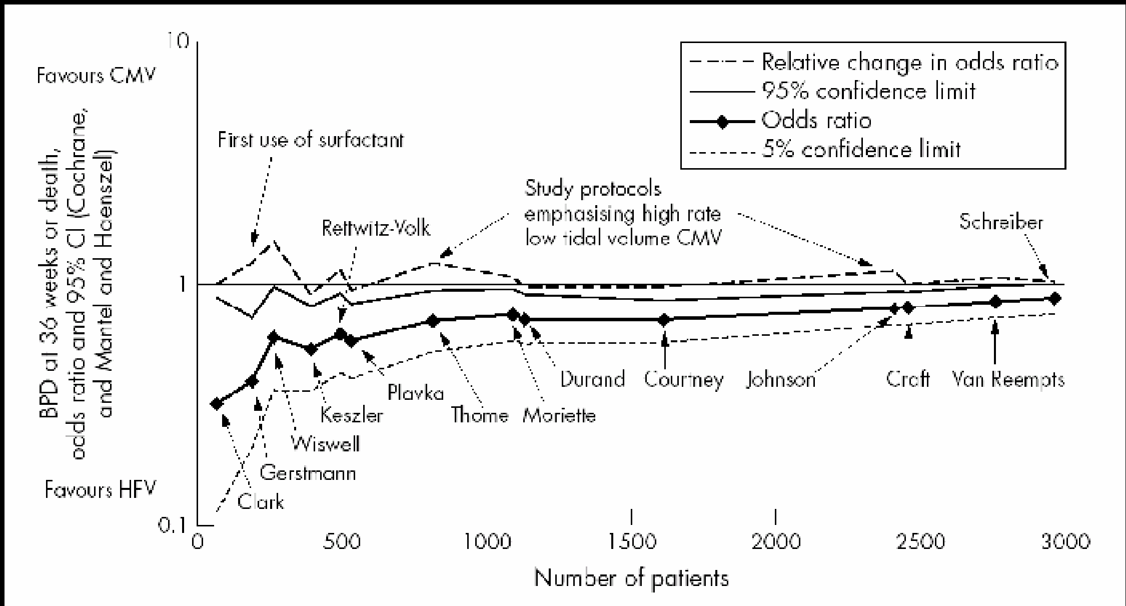
Death or CLD at 28 – 30 days

RR (96% CI): 0.956 (0.40, 0.77)

Cumulative Metaanalysis: HFV vs CMV



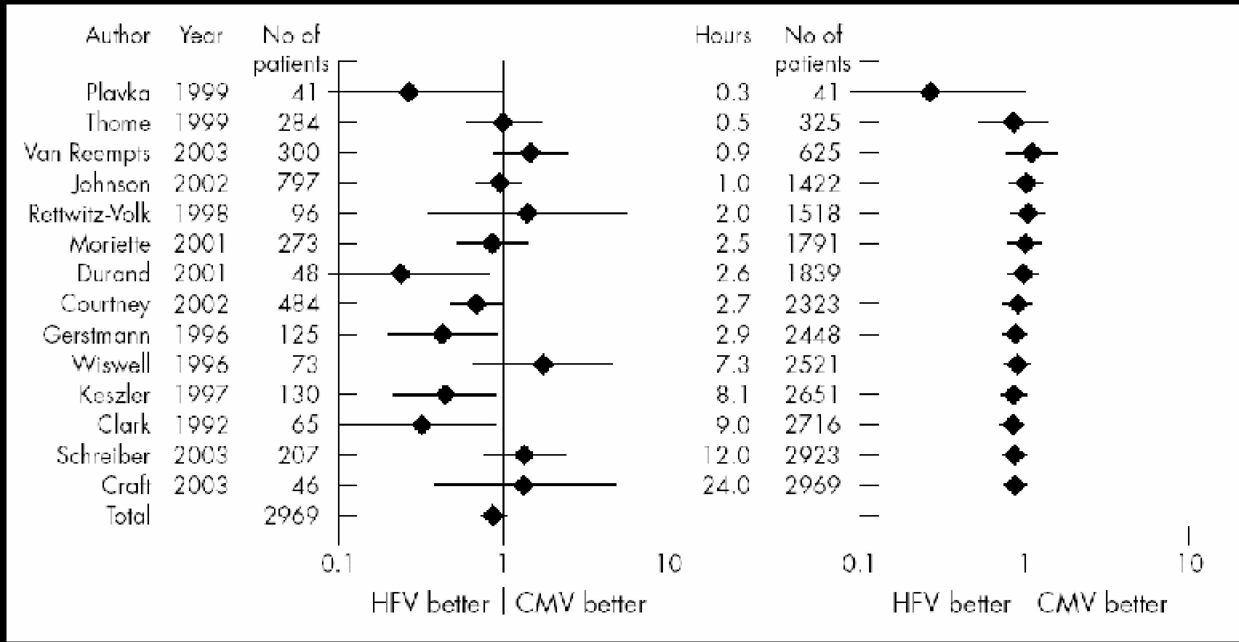
Bollen et al. AJRCCM 2003; 168: 1150–1155



Thome UH
Arch Dis Child Fetal Neonatal Ed
2005;90:F466–F473

Cumulative Metaanalysis: HFV vs CMV

Cumulative
meta-analysis
ordered
by time delay
to randomisation

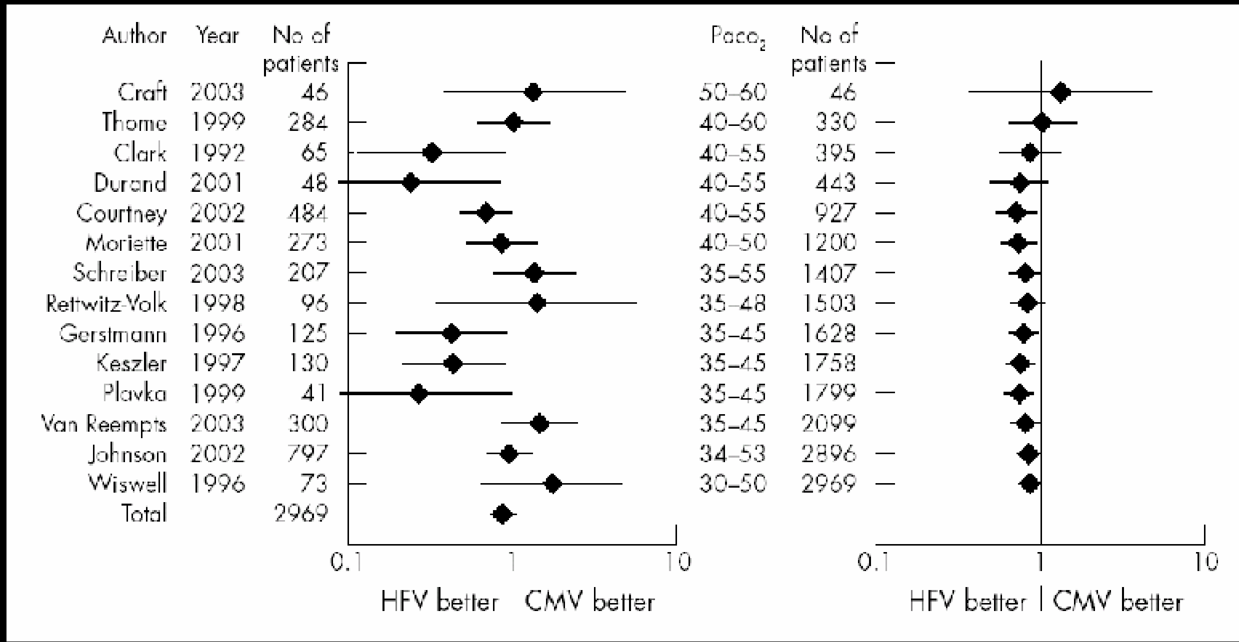


Thome UH Arch Dis Child Fetal Neonatal Ed 2005;90:F466–F473

Covariate: CMV strategy used before randomization ! ?

Cumulative Metaanalysis: HFV vs CMV

Cumulative
meta-analysis
ordered
by pCO2



The authors
conclusions

- Optimising conventional mechanical ventilation strategy appeared to be as effective as high frequency ventilation in improving pulmonary outcome in preterm infants
- Purchasing costly HFV ventilators appears to be unnecessary for most neonatal intensive care units

Thome UH Arch Dis Child Fetal Neonatal Ed 2005;90:F466–F473

Lung-protective ventilation strategies in neonatology: What do we know—What do we need to know?

Anton H. van Kaam, MD, PhD; Peter C. Rimensberger, MD

[Crit Care Med 2007; 35:925–931]

A total of 16 RCTs and 4 systematic reviews comparing HFOV with CMV failed to show consistent differences in mortality and bronchopulmonary dysplasia.

A total of 24 RCTs and 3 systematic reviews comparing various CMV modes and settings and 2 RCTs investigating permissive hypercapnia reported no differences in mortality or bronchopulmonary dysplasia.

No RCT in newborn infants has substantiated so far that avoiding large tidal volumes and low positive end-expiratory pressure during CMV is lung protective in newborn infants.

Based on the experimental evidence, **HFV should be combined with an optimal recruitment strategy** using oxygenation as an indirect marker for lung volume (FiO2 below 30%).

Some trials used a low lung volume strategy

	Methods			Results			
Author	(Y/N)	FiO_2	CXR[b]	HFV	CMV	HFV	CMV
HIFI et al. (4)	N	—	—	9	9	0.43	0.42
Carl							—
Clark							c
Ogaw							).50
Wisw							—
Gerstmann et al. (9)	Y	≤0.30	8–9	11	9	0.28	0.36
Keszler et al. (10)	Y	—	—	11	10	0.50	0.65
Rettwitz et al. (11)	N	—	—	8	8	0.45	0.42
Thom							0.25
Plavk							—
Morie							0.68[d]
Court							0.33
Johns							0.38
Craft							c
Reemp							0.50
Vento et al. (19)	Y	≤0.25	—	13	11	0.29[e]	0.67

Some trials do even not report on the ventilation strategy applied

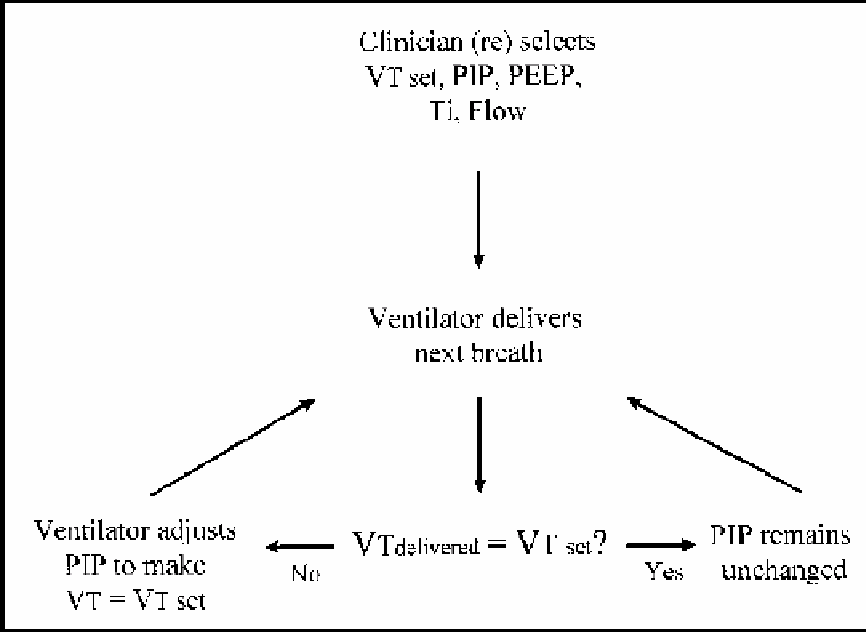
Most trials failed to obtain optimal lung volume -
that was part of the study protocol!

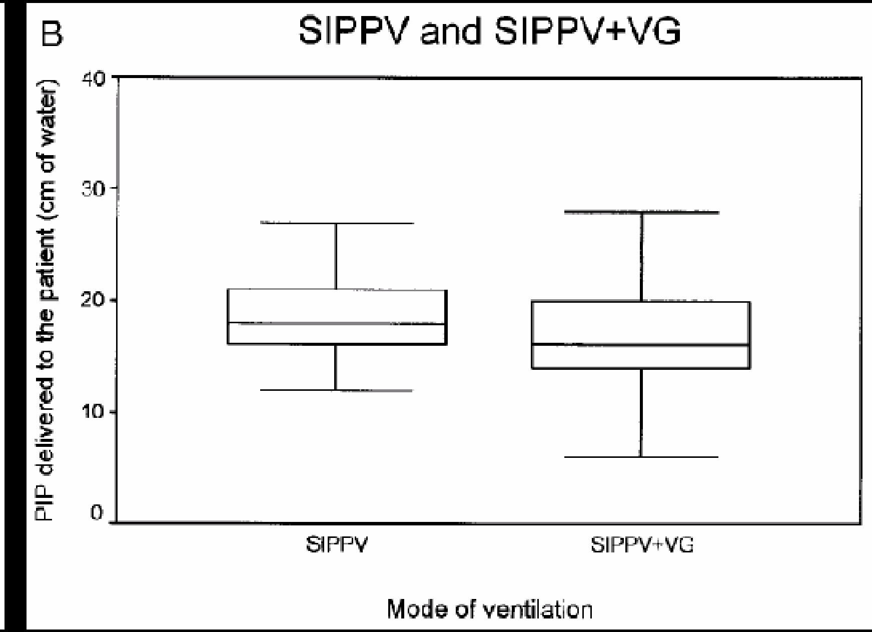
Van Kaam A, Rimensberger PC CCM 2007; 35:925-931

Technology 2

Volume Targeted Ventilation: 2001 - 2007

Concept: deliver the set Vt at the lowest airway pressure possible





Cheema IU ***Pediatrics*** **2001;107:1323–1328**

Technology 2

Volume Targeted Ventilation: 2001 - 2007

	SIMV	SIMV + VG	*P* Value	SIPPV	SIPPV + VG	*P* Value
PIP, mean (standard error) cm of water	17.1 (3.4)	15.0 (7.5)	<.001	18.7 (8.3)	17.1 (9.3)	<.001
Mean airway pressure, mean (standard error) cm of water	6.9 (2.8)	6.5 (3.1)	.005	9.8 (4.6)	9.6 (4.5)	.008
Expired tidal volume, mean (standard error) mL/kg	5.0 (5.6)	4.9 (5.2)	.59	4.8 (3.4)	4.8 (3.2)	.62
Expired minute volume, mean (standard error) mL/min/kg	291 (2.1)	289 (2.1)	.89	331.6 (2.0)	334.5 (2.2)	.72
Fractional inspired oxygen, mean (standard error)	0.31 (0.3)	0.31 (0.3)	.38	40.4 (0.4)	41.0 (0.4)	.56
Transcutaneous partial pressure of carbon dioxide, mean (standard error) kPa	5.9 (2.2)	6.0 (2.2)	.47	6.4 (2.8)	6.4 (2.9)	.86
Transcutaneous partial pressure of oxygen, mean (standard error) kPa	8.6 (8.8)	8.4 (8.7)	.40	7.7 (4.4)	7.6 (4.0)	.30

Cheema IU ***Pediatrics* 2001;107:1323–1328**

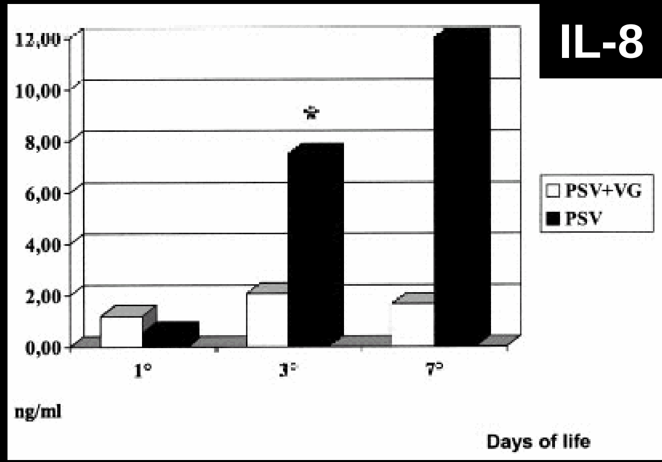
	PSV + VG (n = 30)	PSV (n = 23)
Birth weight (g)	1,125 ± 370	1,197 ± 333
GA (weeks)	28.5 ± 2	29.4 ± 1.6
Antenatal steroids	26 (86%)	20 (86%)
Age at study (hours)	3 ± 2	3 ± 2

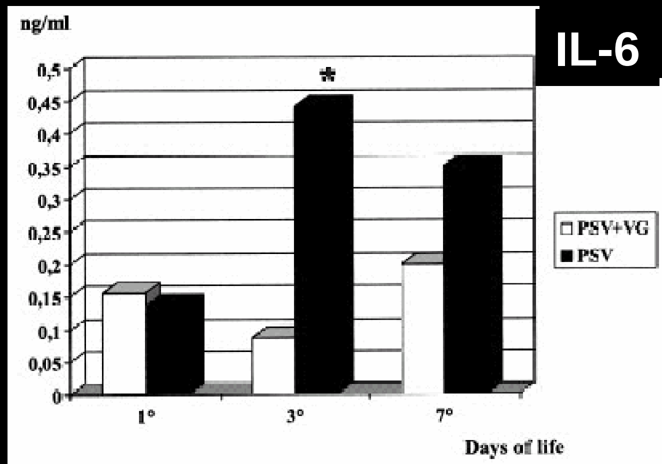
[1] P = ns. SD, standard deviation.

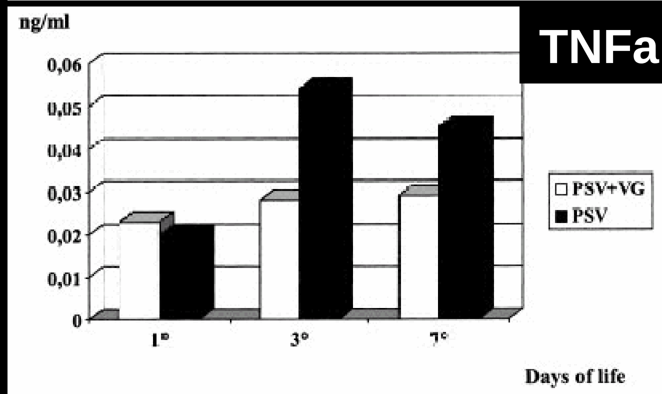
TABLE 3—Outcome[1]

	PSV + VG group (n = 30)	PSV group (n = 23)
Length of ventilation (days; mean ± standard deviation)	8.8 ± 3	12.3 ± 3
Surfactant (doses; median)	1	1
BPD (n)[2]	3 (10%)	4 (17%)
CLD (n)[3]	3 (10%)	4 (17%)
Deaths (n)	5 (16%)	6 (26%)
IVH (≥3) (n)	1 (3%)	2 (8%)
PLV (n)	1 (3%)	2 (8%)
ROP (≥2) (n)	2 (6%)	1 (4%)
PIE (n)	2 (6%)	2 (8%)
PDA closure (n)	22 (73%)	20 (86%)
PNX (n)	0 (0%)	3 (13%)

[1]ROP, retinopathy of the premature; PIE, pulmonary interstitial emphysema; PNX, pneumothorax; PDA, patency of ductus arteriosus; BPD, bronchopulmonary dysplasia. P = ns.
[2]O_2 dependency at 28 days.
[3]O_2 dependency at 36 weeks.







Lista G Pediatr Pulmonol. 2004; 37:510–514

Volume targeted ventilation: A Self Weaning Mode

?

Methods:

PSV group: The weaning strategy consisted of reducing the pressure support level progressively over time, so that the work of breathing was shifted from ventilator to the patient.

PSV-VG group: Weaning was a moreautomatic process once appropriate levels of Vt had been established.

Similar blood gas goals (e.g., pH>7.25; pO2, 50–75 mmHg; pCO2, 40–65 mmHg) were achieved during weaning from mechanical ventilation in both groups.

Infants at less than 30 weeks of gestation with RDS

	HFOV (n = 13)	PSV + VG (n = 12)	*P*
Mechanical ventilation at 7 days	3/13 (23)	2/12 (17)	1.000
O_2-therapy duration (days)	20.3 ± 14.6	22.0 ± 15.9	0.783
NCPAP duration (days)	6.9 ± 4.2	5.2 ± 2.4	0.232
Mechanical ventilation duration (days)	4.1 ± 1.1	4.5 ± 2.2	0.566
Second dose of surfactant	12/13 (92)	12/12 (100)	1.000
Patent ductus arteriosus	11/13 (85)	9/12 (75)	0.644
Pneumothorax	0/13	1/12 (8)	0.480
Bronchopulmonary dysplasia	4/13 (31)	3/12 (25)	1.000
Intraventricular hemorrhage	2/13 (15)	2/12 (17)	1.000
Periventricular leucomalacia	1/13 (8)	1/12 (8)	1.000
Retinopathy of prematurity	2/13 (21)	3/12 (25)	0.644
Necrotizing enterocolitis	0/13	0/12	1.000
Length of stay in intensive care	26.4 ± 11.8	27.3 ± 12.4	0.854
Length of stay in hospital	66.2 ± 19.9	62.8 ± 24.2	0.704
Mortality	2/13 (15)	2/12 (17)	1.000

[1]Mean ± SD or rate (%).

C Dani Pediatr Pulmonol. 2006; 41:242–249

Weaning Criteria:	**FiO2 0.40**
	MAP 6 cmH2O,
	pO2 50 mmHg and pCO2 50 <65 mmHg

Lista G et al. Pediatr Pulmonol 2006; 41:357–363

?

Length of mechanical ventilation as an outcome parameter

Outcome VTV: Death in Hospital

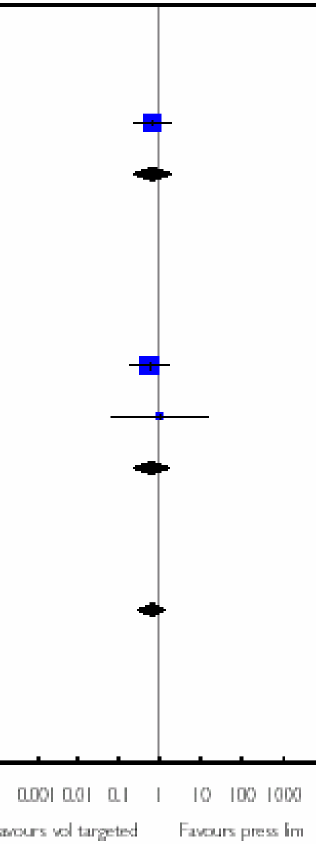
Analysis 01.01. Comparison 01 Volume-targeted vs pressure limited ventilation, Outcome 01 Death in hospital

Review: Volume-targeted versus pressure-limited ventilation in the neonate

Comparison: 01 Volume-targeted vs pressure limited ventilation

Outcome: 01 Death in hospital

Study	Volume targeted n/N	Pressure limited n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Volume guarantee					
× Keszler 2004	0/9	0/9		0.0	Not estimable
Lista 2004	5/30	6/23		44.2	0.64 [0.22, 1.84]
Subtotal (95% CI)	39	32		44.2	0.64 [0.22, 1.84]
Total events: 5 (Volume targeted), 6 (Pressure limited)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					
02 Volume controlled					
Piotrowski 1997	4/27	8/30		49.3	0.56 [0.19, 1.64]
Sinha 1997	1/25	1/25		6.5	1.00 [0.07, 15.12]
Subtotal (95% CI)	52	55		55.8	0.61 [0.22, 1.65]
Total events: 5 (Volume targeted), 9 (Pressure limited)					
Test for heterogeneity chi-square=0.16 df=1 p=0.69 I² =0.0%					
Test for overall effect z=0.98 p=0.3					
Total (95% CI)	91	87		100.0	0.62 [0.30, 1.29]
Total events: 10 (Volume targeted), 15 (Pressure limited)					
Test for heterogeneity chi-square=0.16 df=2 p=0.92 I² =0.0%					
Test for overall effect z=1.28 p=0.2					



The Cochrane Library 2007, Issue 1

Outcome VTV: Duration of mechanical ventilation

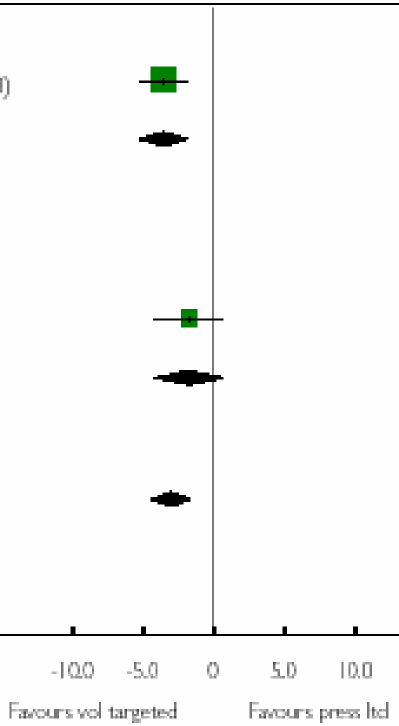
Analysis 01.04. Comparison 01 Volume-targeted vs pressure limited ventilation, Outcome 04 Duration of intermittent positive pressure ventilation (days)

Review: Volume-targeted versus pressure-limited ventilation in the neonate

Comparison: 01 Volume-targeted vs pressure limited ventilation

Outcome: 04 Duration of intermittent positive pressure ventilation (days)

Study	Volume targeted N	Volume targeted Mean(SD)	Pressure limited N	Pressure limited Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Volume guarantee							
Lista 2004	30	8.80 (3.00)	23	12.30 (3.00)		69.0	-3.50 [-5.13, -1.87]
Subtotal (95% CI)	30		23			69.0	-3.50 [-5.13, -1.87]
Test for heterogeneity: not applicable							
Test for overall effect z=4.21 p=0.00003							
02 Volume controlled							
Sinha 1997	25	5.10 (2.72)	25	6.75 (5.58)		31.0	-1.65 [-4.08, 0.78]
Subtotal (95% CI)	25		25			31.0	-1.65 [-4.08, 0.78]
Test for heterogeneity: not applicable							
Test for overall effect z=1.33 p=0.2							
Total (95% CI)	55		48			100.0	-2.93 [-4.28, -1.57]
Test for heterogeneity chi-square=1.53 df=1 p=0.22 I² =34.8%							
Test for overall effect z=4.24 p=0.00002							



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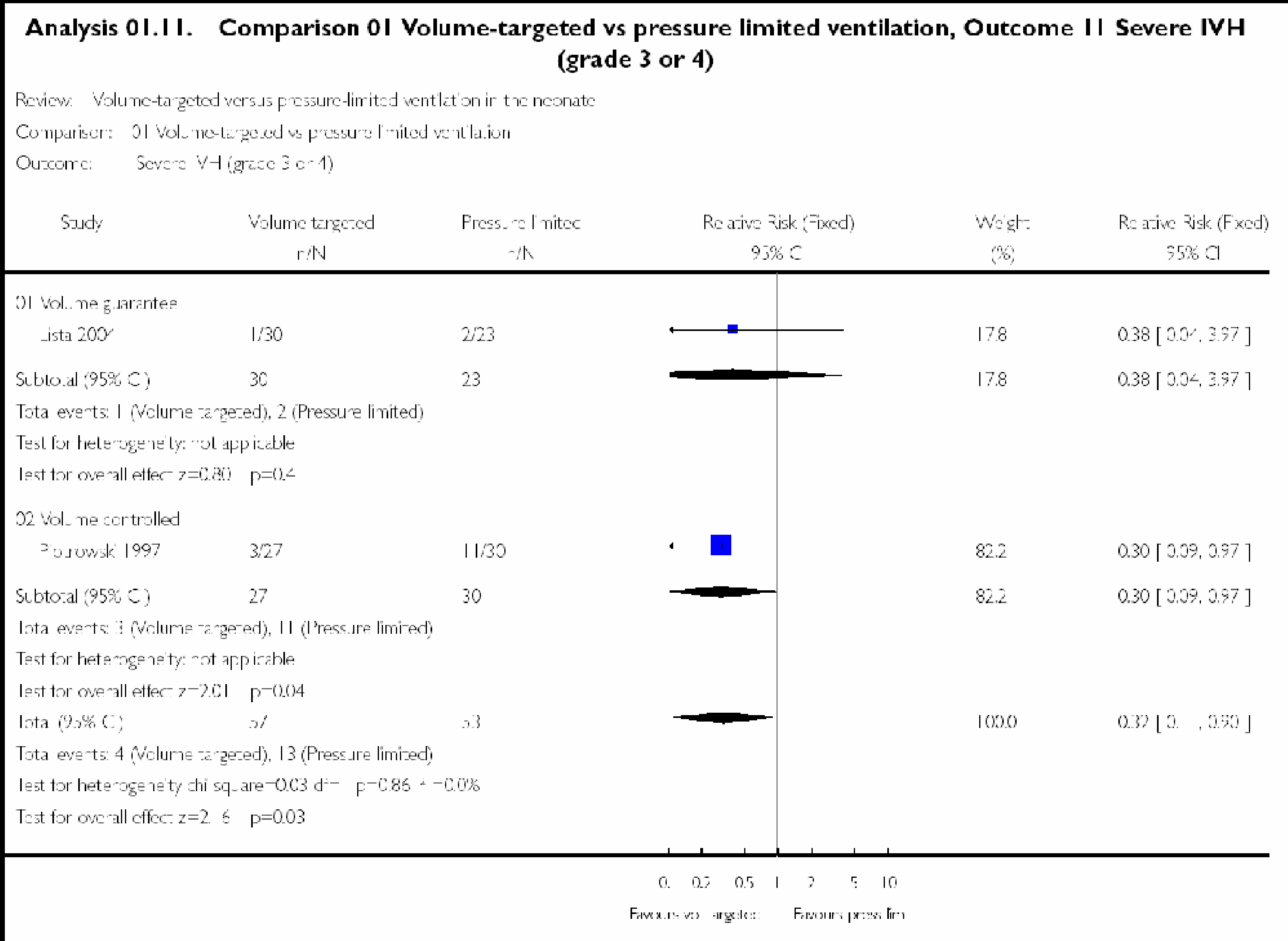
Outcome VTV: Severe IVH (grade 3 – 4)



Analysis 01.11. Comparison 01 Volume-targeted vs pressure limited ventilation, Outcome 11 Severe IVH (grade 3 or 4)

Review: Volume-targeted versus pressure-limited ventilation in the neonate

Comparison: 01 Volume-targeted vs pressure limited ventilation

Outcome: Severe IVH (grade 3 or 4)

Study	Volume targeted n/N	Pressure limited n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Volume guarantee					
Lista 2004	1/30	2/23		17.8	0.38 [0.04, 3.97]
Subtotal (95% CI)	30	23		17.8	0.38 [0.04, 3.97]
Total events: 1 (Volume targeted), 2 (Pressure limited)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.80 p=0.4					
02 Volume controlled					
Piotrowski 1997	3/27	11/30		82.2	0.30 [0.09, 0.97]
Subtotal (95% CI)	27	30		82.2	0.30 [0.09, 0.97]
Total events: 3 (Volume targeted), 11 (Pressure limited)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.01 p=0.04					
Total (95% CI)	57	53		100.0	0.32 [0.[illegible], 0.90]
Total events: 4 (Volume targeted), 13 (Pressure limited)					
Test for heterogeneity chi square=0.03 df=1 p=0.86 I^2 =0.0%					
Test for overall effect z=2.[illegible]6 p=0.03					

0.1 0.2 0.5 1 2 5 10

Favours vol targeted Favours press lim

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Performance of neonatal ventilators in volume targeted ventilation mode

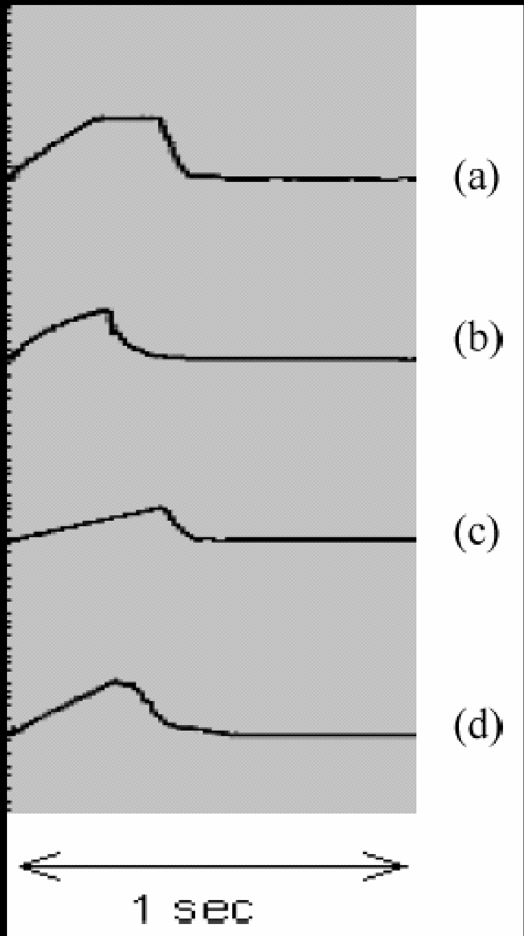
Airway Pressure Waveforms:

Ti of 0.35 sec

Peak inflating pressure of 25 cm H2O

PEEP of 5 cm H2O.

Volume guarantee level 10 mL



(a) Draeger Babylog 8000 (Draeger Medical, Germany),

(b) SLE 5000 infant ventilator (SLE systems, UK),

(c) Stephanie paediatric ventilator (F. Stephan Biomedical, Germany)

(d) V.I.P. Bird Gold (Viasys Healthcare, USA)

Atul Sharma et al *Acta Pædiatrica* 2007; **96**: 176–180

Performance of neonatal ventilators in volume targeted ventilation mode

Settings:

Inflation time of 0.35 sec

Peak inflating pressure of 25 cm H2O

PEEP of 5 cm H2O

Volume guarantee level 10 mL

Lung model:

Crs = 0.4 mL/cm H2O

Rrs = 70 cm/H2O/L/sec

"similar to the compliance and resistance of babies with the respiratory distress syndrome"

Results: Measured volume delivery

All ventilators delivered a lower Vt than preset

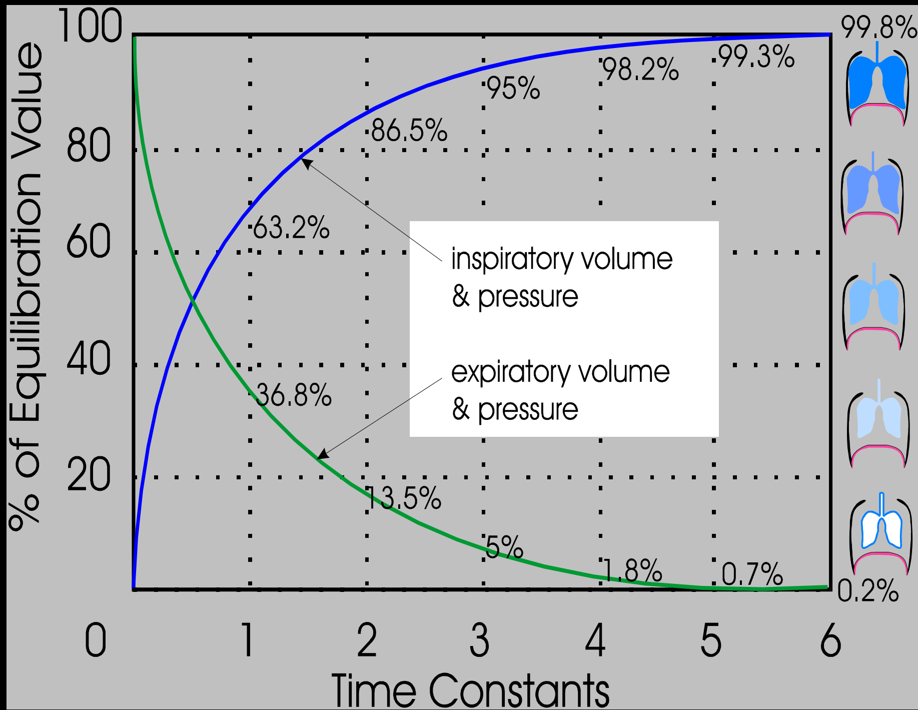
Atul Sharma et al *Acta Pædiatrica* 2007; **96**: 176–180

Time constant: T = Crs x Rrs

Resulting time constant:

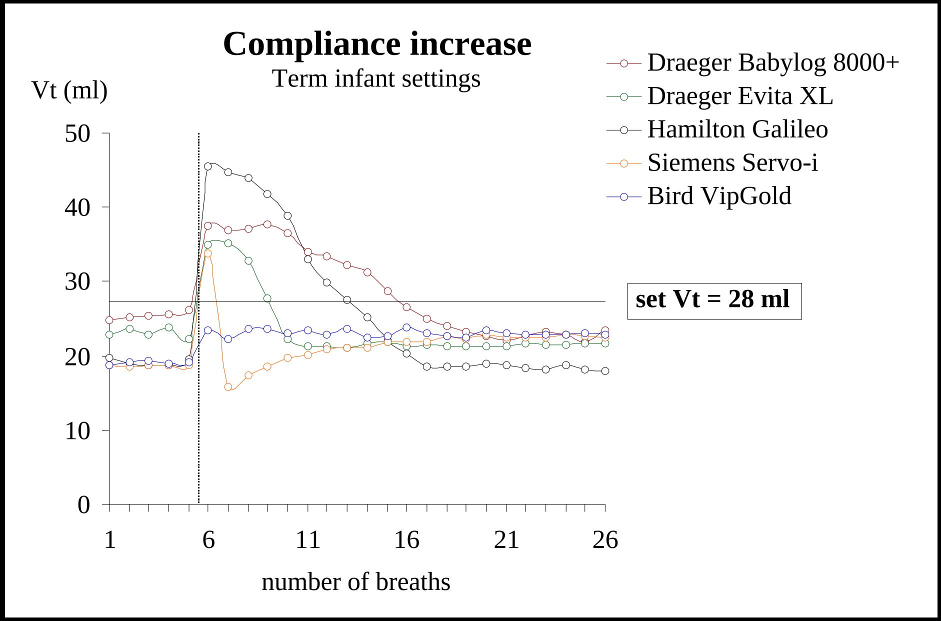
T = 0.4 mL/cm H2O **x** 70 cm/H2O/L/sec = **0.28 sec**

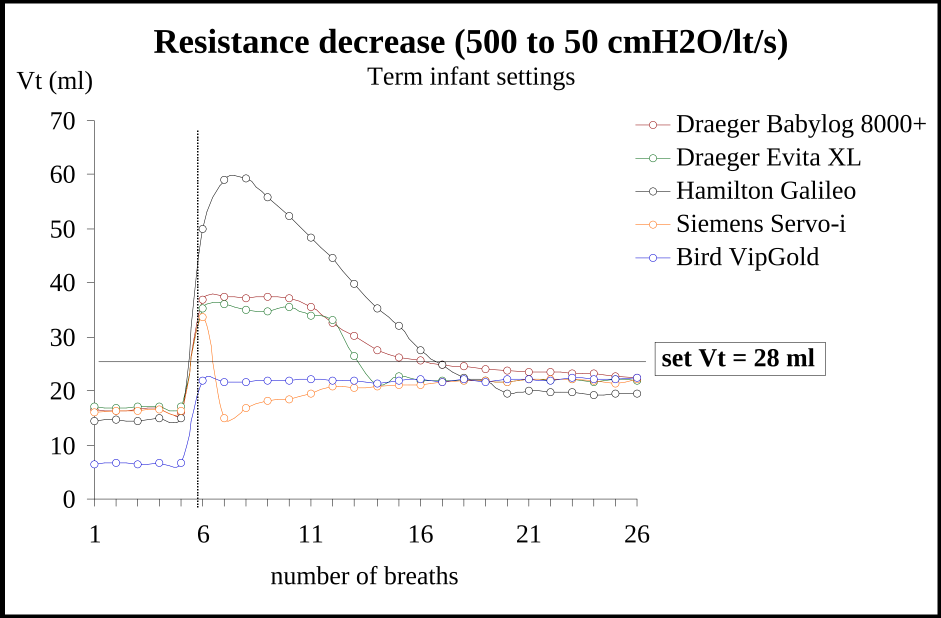
Will pressure equilibrium be reached in the lungs?



3 x T = 3 x (0.4 mL/cm H2O **x** 70 cm/H2O/L/sec) = **0.84 sec**

Is VTV safe?





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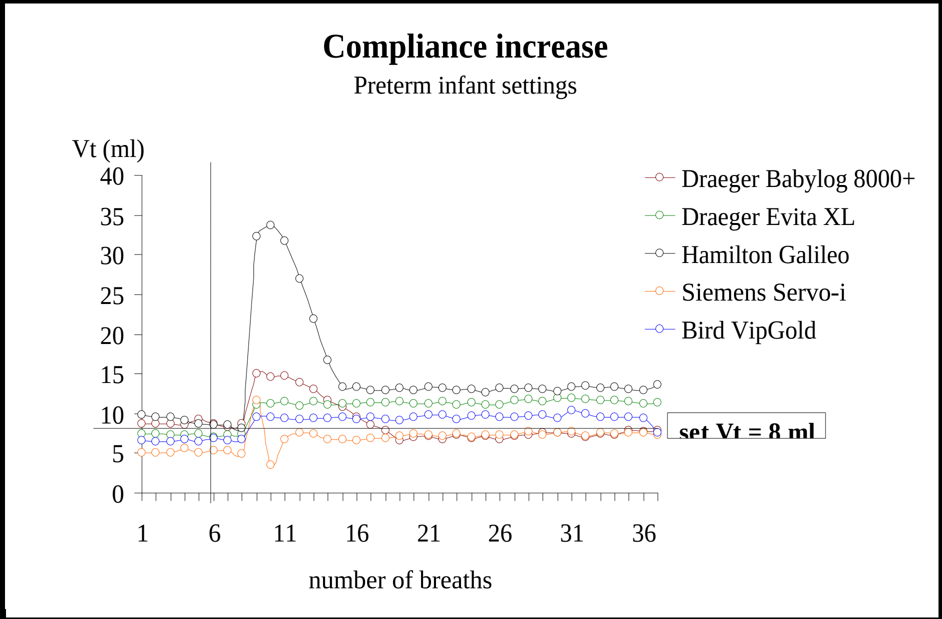
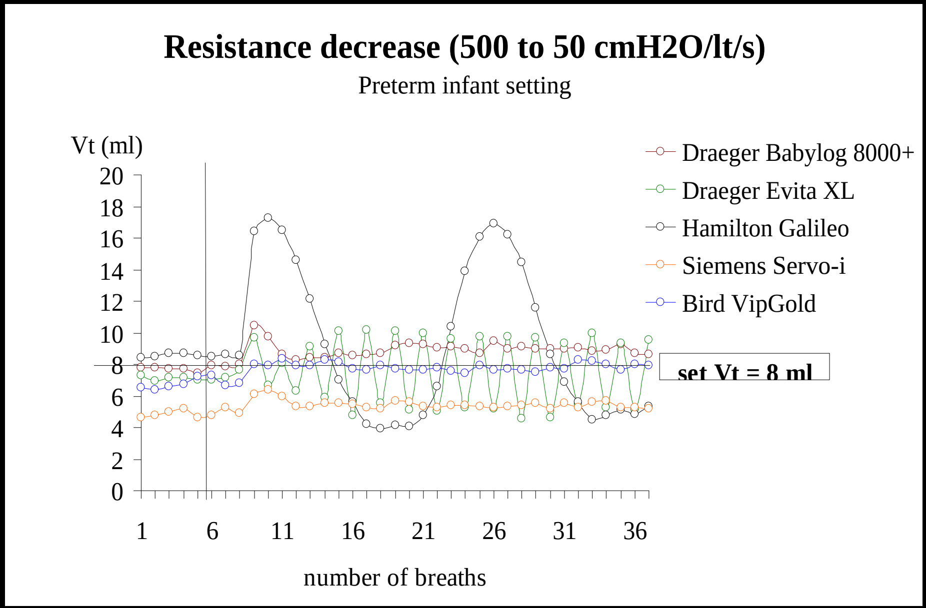
Is VTV safe?





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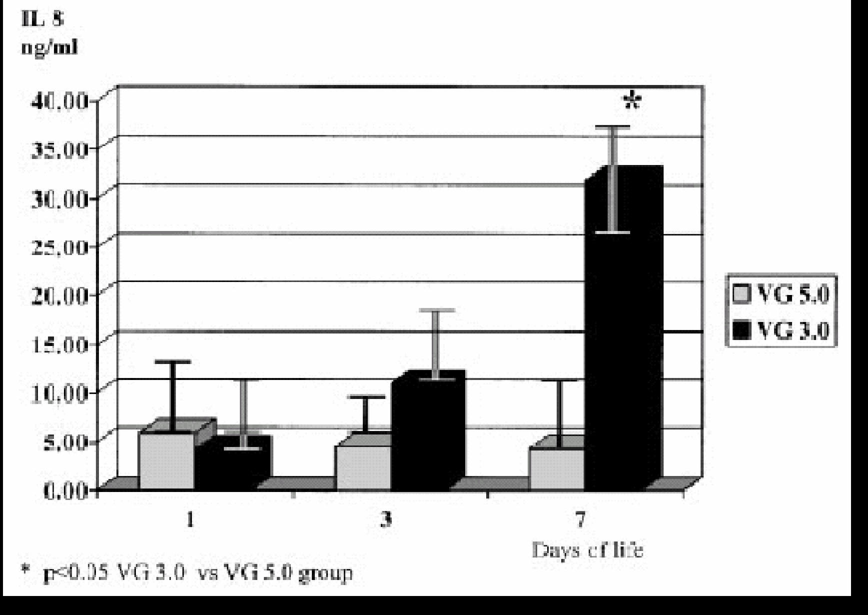
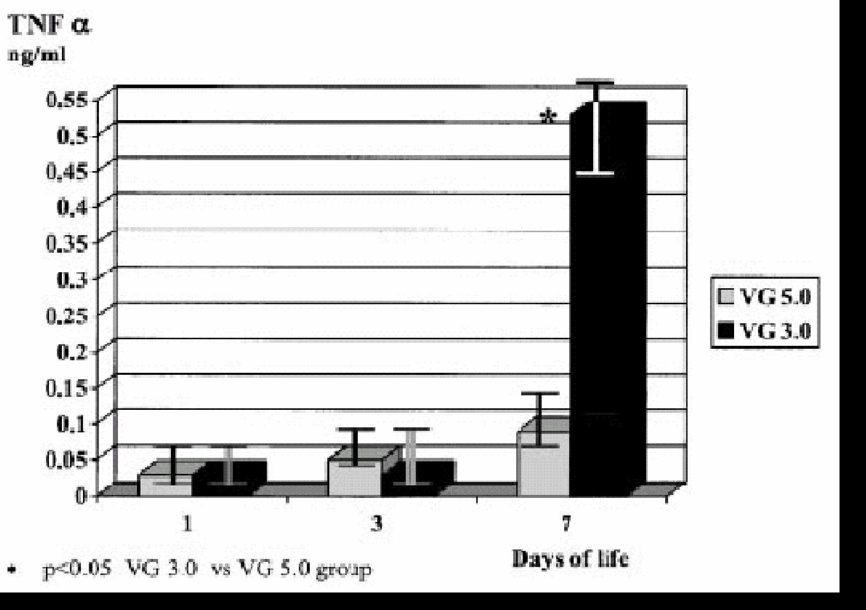
Effects of Ventilation With Different Tidal Volumes

3 ml/kg versus 5 ml/kg

	VG 5.0 (n = 15)	VG 3.0 (n = 15)
Birth weight (g)	1,150 ± 360	1,085 ± 290
Gestational age (weeks)	27 ± 1.2	27 ± 1.6
a/APO$_2$	0.15 ± 0.05	0.15 ± 0.04
Antenatal steroids, complete course (two cycles), n (%)	12 (80%)	12 (80%)

[1] P = ns.





Lista G et al. Pediatr Pulmonol 2006; 41:357–363

Effects of Ventilation With Different Tidal Volumes

3 ml/kg versus 5 ml/kg

TABLE 3—Outcomes of Neonates in Two Groups[1]

	VG 5.0 group (n = 15)	VG 3.0 group (n = 15)
Length of ventilation (days; mean ± SD)	9.2 ± 4	16.8 ± 4*
Surfactant (number of doses; median)	2 ± 1	2 ± 1
BPD (n)	2 (13%)	3 (20%)
Deaths (n)	1 (6.6%)	1 (6.6%)
IVH (>/ = 3) (n)	1 (6.6%)	1 (6.6%)
PLV (n)	1 (6.6%)	1 (6.6%)
ROP (>/ = 2) (n)	0	0
PIE (n)	1 (6%)	1 (6%)
PNX (n)	0	0
PDA closure (n)	11 (73.3%)	10 (66.6%)
Postnatal steroid therapy	2/15 (13%)	3/15 (20%)

[1]In terms of incidence of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), pulmonary interstitial emphysema (PIE), pneumothorax (PNX), and patency of ductus arteriosus (PDA).
*$P = 0.05$.

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Technologie 3:

Maintenance of spotaneous breathing efforts:

Pressure Support
BiPAP
APRV

2005 - ……

	HFOV (n = 13)	PSV + VG (n = 12)	*P*
Mechanical ventilation at 7 days	3/13 (23)	2/12 (17)	1.000
O_2-therapy duration (days)	20.3 ± 14.6	22.0 ± 15.9	0.783
NCPAP duration (days)	6.9 ± 4.2	5.2 ± 2.4	0.232
Mechanical ventilation duration (days)	4.1 ± 1.1	4.5 ± 2.2	0.566
Second dose of surfactant	12/13 (92)	12/12 (100)	1.000
Patent ductus arteriosus	11/13 (85)	9/12 (75)	0.644
Pneumothorax	0/13	1/12 (8)	0.480
Bronchopulmonary dysplasia	4/13 (31)	3/12 (25)	1.000
Intraventricular hemorrhage	2/13 (15)	2/12 (17)	1.000
Periventricular leucomalacia	1/13 (8)	1/12 (8)	1.000
Retinopathy of prematurity	2/13 (21)	3/12 (25)	0.644
Necrotizing enterocolitis	0/13	0/12	1.000
Length of stay in intensive care	26.4 ± 11.8	27.3 ± 12.4	0.854
Length of stay in hospital	66.2 ± 19.9	62.8 ± 24.2	0.704
Mortality	2/13 (15)	2/12 (17)	1.000

[1]Mean ± SD or rate (%).

Dani C Pediatr Pulmonol 2006; 41:242–249

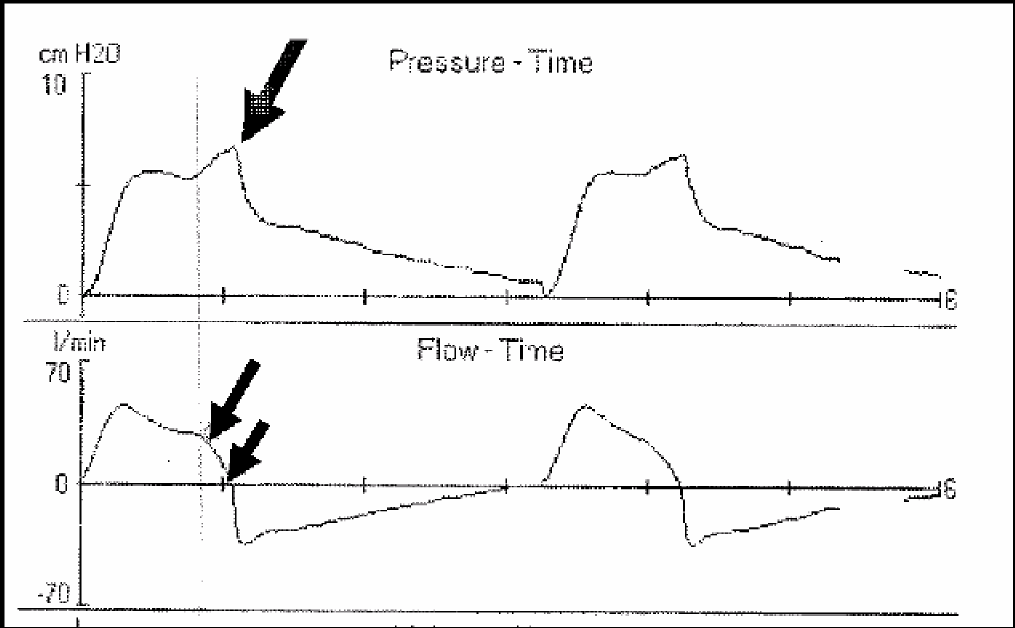
HFOV: The high-volume startegy was used **???**

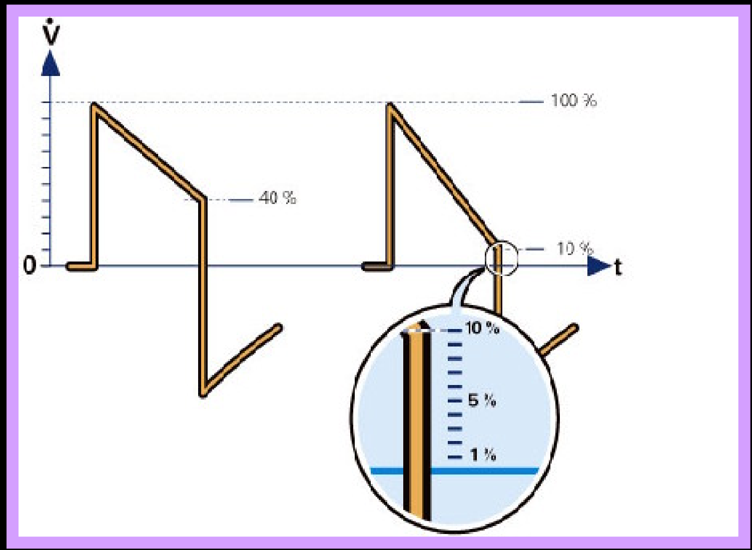
PSV + VG: Vt 5 ml/kg, PEEP of 3 cmH2O

Ventilatory Goal: pH >7.20 , pCO2 <65 mmHg, and pO2 >50 mmHg.

Pressure-Support and flow termination criteria

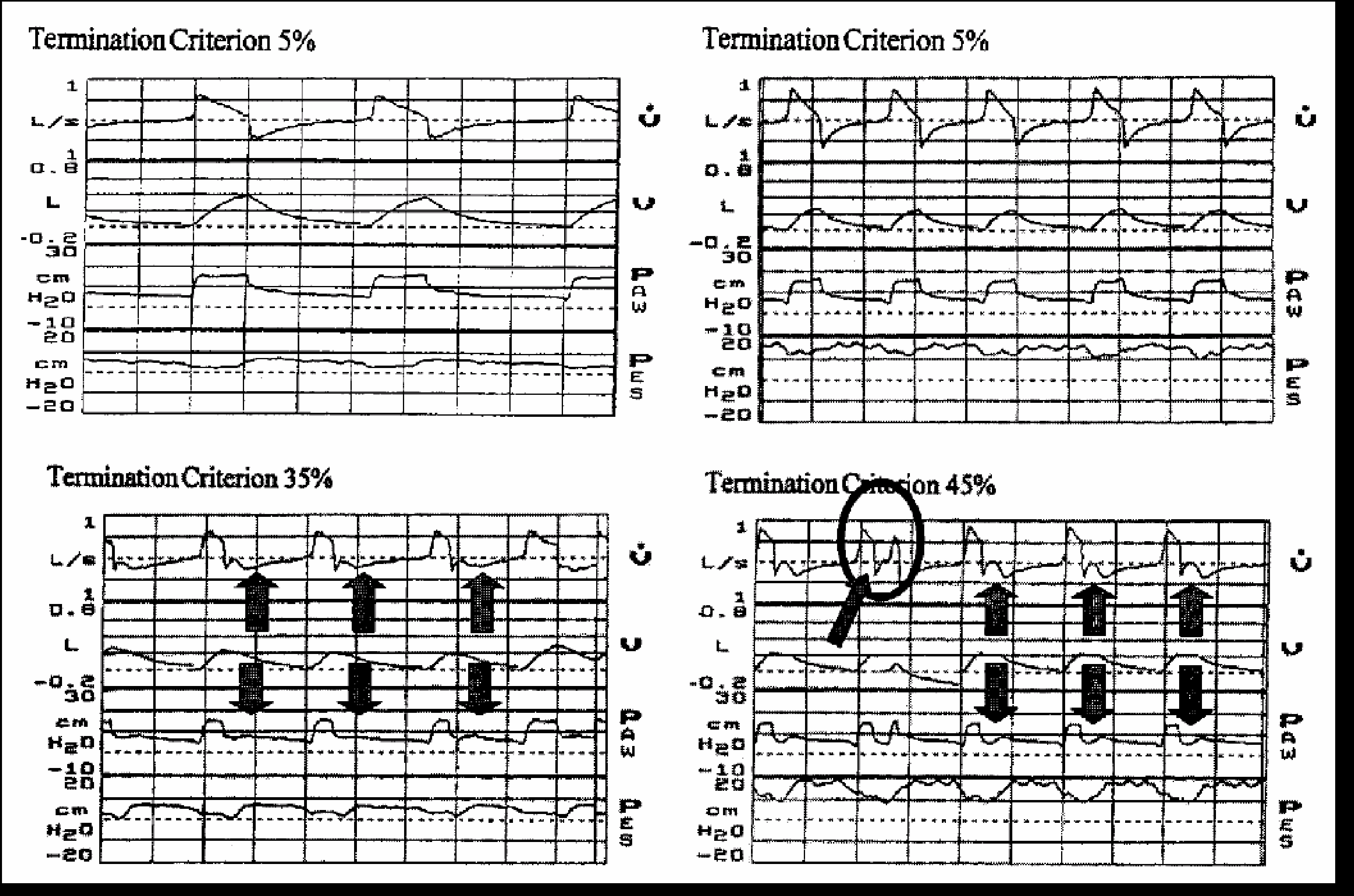
The non synchronized patient during Pressure-Support (inappropriate end-inspiratory flow termination criteria)





Nilsestuen J Respir Care 2005;50:202–232.

Pressure-Support and flow termination criteria



Increase in RR, reduction in VT, increase in WOB

Nilsestuen J
Respir Care 2005

Health technology assessment is only useful when the policy environment is mature enough to handle its results

van Beusekom I, Kahan J.

Annu Meet Int Soc Technol Assess Health Care Int Soc Technol Assess Health Care Meet. 2002; 18: abstract no. 323.

Lung-protective ventilation strategies in neonatology: What do we know—What do we need to know?

Anton H. van Kaam, MD, PhD; Peter C. Rimensberger, MD

Crit Care Med 2007; 35:925–931

Have the study questions be addressed adequately?

Most of the RCTs show weaknesses in the design, which may explain the inconsistent effect of high-frequency ventilation on bronchopulmonary dysplasia.

RCTs on CMV only focused on comparing various modes and settings, leaving the important question whether reducing tidal volume or increasing positive end-expiratory pressure is also lung protective in newborn infants unanswered.