

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Taskforce/Subcommittee: __BLS __ACLS x PEDS __ID __PROAD __x_Other: N
Author's Home Resuscitation Council: __AHA __x_ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	Date Submitted to Subcommittee: 10/1/04; Revised 03Nov04

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity, or new guideline: Revision to current guideline

To create a new guideline encouraging the use of continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP) during neonatal resuscitation in the delivery room, particularly for very premature infants.

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

During the resuscitation of very premature infants the use of CPAP will reduce the baby's oxygen requirements and the need for ventilation. The use of either CPAP or PEEP during the resuscitation of very premature infants at birth will reduce the proportion requiring oxygen when they reach the equivalent of 36 weeks gestation.

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

Search with MESH headings all fields: CPAP AND resuscitation limited to the first 28 days, PEEP AND resuscitation limited to the first 28 days, neonatal resuscitation, delivery unit AND resuscitation.

Cochrane database of systematic reviews.

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE

[<http://www.ncbi.nlm.nih.gov/PubMed/>], and Embase), and hand searches of journals, review articles, and books. Pubmed, Embase, Cochrane database, ECC EndNote library, Review articles

Medline(Pub Med1966 to 2004), Cochrane Systemic reviews, Embase and ECC library,

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

Limited to birth to 28 days. Animal studies were not excluded

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.

Searches narrowed after abstract review to 27 articles

STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	
Level 2	Sandri(04), Han(87), Finer(04),
Level 3	
Level 4	Jacobsen(93), Avery(87), Van Marter(00), Narendran(03), Lindner(99), Aly(04), Millet(97), Gittermann(97),
Level 5	Kamper(93), Kamper(04),
Level 6	Jobe(02), Michna(99), Probyn(04), Thomson(01), Dick(80),

Level 7	Elgalleb(01), Gregory(71), Poets(96), Latini(03), Rhodes(73), Lundstrom(93), Thome(98), Dinger(01), De Klerk(01),
Level 8	

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased OR Adequate under the circumstances	<i>Small or clearly biased population or model</i> OR <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> OR <i>Not defensible in its class, insufficient data or measures</i>

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the

Neutral or Opposing grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

During the resuscitation of very premature infants the use of CPAP will reduce the baby's oxygen requirements and the need for ventilation. The use of either CPAP or PEEP during the resuscitation of very premature infants at birth will reduce the proportion requiring oxygen when they reach the equivalent of 36 weeks gestation.

Quality of Evidence	Excellent							
	Good				Avery(87) Van Marter(00)		Jobe(02) Probyn(04)	
	Fair				Aly(04) Gittermann(97) Jacobsen(93) Lindner(99) De Klerk(01) Millet(97)	Kamper(93) Kamper(04)	Dick(80) Michna(99) Thomson(01)	Elgalleb(01) Gregory(71) Latini(03) Lundstrom(93) Poets(96) Rhodes(73) Thome(98) Dinger(01)
	1	2	3	4	5	6	7	8
Level of Evidence								

A = Return of spontaneous circulation C = Survival to hospital discharge **E = Other endpoint (outcome for all**

B = Survival of event D = Intact neurological survival

citations)

Neutral or Opposing Evidence

During the resuscitation of very premature infants the use of CPAP will reduce the baby's oxygen requirements and the need for ventilation. The use of either CPAP or PEEP during the resuscitation of very premature infants at birth will reduce the proportion requiring oxygen when they reach the equivalent of 36 weeks gestation.

Quality of Evidence	Excellent		Finer(04)						
	Good								
	Fair		Han(87) Sandri(04)		Narendran(03)				
		1	2	3	4	5	6	7	8
		Level of Evidence							

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint (outcome for all citations)
 B = Survival of event D = Intact neurological survival

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
Class I <i>Definitely recommended.</i> Definitive, excellent evidence provides support.	<ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness • Must be used in the intended manner for proper clinical indications. 	<ul style="list-style-type: none"> • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling
Class II: <i>Acceptable and useful</i>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Not yet confirmed definitively 	<ul style="list-style-type: none"> • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power • No evidence of harm
• Class IIa: <i>Acceptable and useful</i> Good evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered treatments of choice 	<ul style="list-style-type: none"> • Generally higher levels of evidence • Results are consistently positive

<ul style="list-style-type: none"> • Class IIb: <i>Acceptable and useful</i> <p>Fair evidence provides support</p>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative treatments 	<ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results
<p>Class III: <i>Not acceptable, not useful, may be harmful</i></p>	<ul style="list-style-type: none"> • Unacceptable • Not useful clinically • May be harmful. 	<ul style="list-style-type: none"> • No positive high level data • Some studies suggest or confirm harm.
<p>Indeterminate</p>	<ul style="list-style-type: none"> • Research just getting started. • Continuing area of research • No recommendations until further research 	<ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling

STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Indicate if this is a **Condition** or **X Intervention**

Final Class of recommendation: **Class I-Definitely Recommended** **Class IIA-Acceptable & Useful; good evidence** **X Class IIB-Acceptable & Useful; fair evidence** **Class III – Not Useful; may be harmful** **Indeterminate-minimal evidence or inconsistent**

REVIEWER’S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

I am Professor/Director of Neonatal Medicine at the Royal Women’s Hospital and Royal Children’s Hospital, Melbourne, Australia. Before that I worked for the University of Cambridge, UK, and Addenbrooke’s Hospital. I have spent most of my professional life in academic neonatology. Initially I worked on the development and testing of artificial surfactant. My recent research interests are neonatal ventilation, CPAP, and resuscitation. I am conducting an NHMRC funded randomized controlled trial comparing CPAP versus intubation in the DR with very premature babies. I am also conducting resuscitation studies with very premature lambs. I do not believe these represent conflicts of interest with developing this guideline

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. “Mismatches” refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

More than 30 years ago Gregory showed that a continuous positive airway pressure (CPAP) improved oxygenation and survival for neonates with severe respiratory difficulties (1). Since then there have been many reports that treatment with CPAP after birth reduces the rate of intubation and improves respiratory function (2-16).

Nasal CPAP is only used to support spontaneously breathing babies. It helps neonatal respiration in several ways as reviewed by Morley (17;18). It increases the mean airway pressure, improves lung expansion,

increases functional residual capacity (FRC) and thereby improves oxygenation; improves ventilation-perfusion mismatch; reduces inspiratory resistance by dilating the airways; and increases the compliance of the respiratory system of stiff lungs with a low FRC by stabilizing the chest wall and counteracting paradoxical movements(19;20). The latter allows a larger tidal volume for a given pressure with a reduction in the work of breathing and improved carbon dioxide elimination. CPAP also slows the respiratory rate and reduces the incidence of apnoea (21). After extubation, nasal CPAP reduces the proportion of infants that need re-intubation (22). There are few reports of any serious or worrying problems from the use of early CPAP.

The few minutes after birth are the time when a premature baby has most difficulty expanding its immature, fluid filled, surfactant deficient, lungs and establishing a functional residual capacity. Despite this, so far, CPAP has not been officially recommended during neonatal resuscitation.

The common practice of intubating and ventilating most very premature infants at birth with a self inflating bag is not based on controlled trials. Small early studies that compared intubation with head box oxygen showed that intubation was life saving (23). However, this was before the time that CPAP was readily available.

Intubation and ventilation is associated with many different problems: Gas is pushed into the lungs rather than sucked in by the infant's own efforts; the endotracheal tube (ETT) bypasses the larynx and if there is no positive end-expiratory pressure (PEEP), intubation is associated with a reduced FRC, an increase in the resistance to gas flow and it adds to the work of breathing. Intubation and positive pressure ventilation is strongly associated with injury to the airways and alveoli, increased risk of lung infection and hypocarbia (24-28). This suggests that intubation and ventilation should only be used if the baby's spontaneous respiratory efforts cannot be supported.

While PEEP is always used during neonatal ventilation there are no current recommendations about the use of PEEP during neonatal resuscitation. PEEP is used to prevent the complete deflation of the lungs of ventilated infants at the end of expiration, and so it is important for establishing and maintaining functional residual capacity (FRC) (20). This is particularly important when the larynx has been by-passed by an endotracheal tube(29). In preterm infants there is a strong association between a low FRC and subsequent lung injury. PEEP conserves surfactant on the alveolar surface (30). In very preterm lambs, the application of PEEP during resuscitation halves the oxygen requirements within ten minutes (31). The response varied according to the level of PEEP, with optimal oxygenation being seen at 8 cm H₂O. The use of PEEP from the initiation of ventilation has been shown to reduce hyaline membrane formation, preserve surfactant function and reduce the expression of inflammatory markers in the lungs of preterm animal models (32).

If PEEP were provided during resuscitation and early ventilation of premature infants this should lead to improved oxygenation and lung volume with less lung injury.

There is a range of devices to assist neonatal ventilation in the delivery room. Some provide no PEEP or CPAP (e.g. a standard self inflating bag); some provide variable PEEP (e.g. flow inflating or anaesthesia bags) and some provide a predetermined and measured PEEP (e.g. the Neopuff Infant Resuscitator or a self inflating bag with a CPAP valve attached). CPAP may be delivered to babies through a face-mask, bi-nasal prongs or a shortened endotracheal tube in one nostril. It can also be given through an ETT in the trachea but this increases the resistance and work of breathing and so is not recommended.

Randomised controlled trials of CPAP at birth

There are two RCTs of CPAP at birth.(33;35) One (33) had four arms: 1) ventilation and surfactant, 2) intubation then surfactant then CPAP, 3) CPAP alone, 4) conventional management. There was no significant difference in the combined outcome of death or need for oxygen at 36 weeks between the groups. This suggests that in these babies treating with CPAP from birth was no worse than intubation and ventilation and reduced the trauma of ventilation. The other(35)enrolled infants less than 28 weeks gestation and randomised them to be treated soon after birth with CPAP or PEEP in one group or neither CPAP nor PEEP in the other group

In the Cochrane review (16), "Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants," the reviewers' comment, "There were no statistically significant differences in any outcomes reported in the single study of 82 very low birth weight infants

(36).” However, in this study all the babies were initially intubated and ventilated and then randomised to CPAP. They concluded, “There is currently insufficient information to make recommendations for clinical practice.”

Animal studies

Probyn et al (31), reported a randomised study of ventilated very premature lambs (125 d gestation) resuscitated with a PEEP of 0, 4, 8, or 12 cm H₂O. This study showed that the AaDO₂ was halved within 5 minutes of birth by the use of 8 cm H₂O PEEP compared with zero PEEP.

Jobe et al (32;37), investigating the lungs of premature lambs (133d gestation) treated with ETT CPAP, conventional ventilation, or no ventilation found that the CPAP treated lambs had a higher lung volume and less neutrophils on the alveolar surface than the ventilated lambs.

Michna et al (30), investigated the effect of different PEEP levels on the clinical responses, and surfactant pools in surfactant treated 126 d gestation preterm lambs. They showed that a PEEP of 4 and 7 cm H₂O improved oxygenation and compliance and the lung volume after 7 hours ventilation was nearly doubled compared with zero PEEP. The surfactant large aggregate pools sizes were three times higher at a PEEP of 4 cm H₂O and four times higher at a PEEP of 7 cm H₂O compared with zero PEEP.

Reference List

- (1) Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N Engl J Med* 1971; 284:1333-1340.
- (2) Aly H, Milner JD, Patel K, El Mohandes AA. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? *Ped* 2004; 114(3):697-702.
- (3) Sandri F, Ancora G, Lanzoni A, Tagliabue P, Colnaghi M, Ventura ML et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. *Arch Dis Child Fetal Neonatal Ed* 2004; 89(5):F394-F398.
- (4) Jacobsen T, Gronvall J, Petersen S, Andersen GE. "Minitouch" treatment of very low birth weight infants. *Acta Paediatr* 1993; 82:934-938.
- (5) Avery ME, Tooley WH, Keller JB. Is chronic lung disease in low birthweight infants preventable? a survey of eight centres. *Ped* 1987; 79:26-30.
- (6) Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? *Ped* 2000; 105(6):1194-1201.
- (7) Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early bubble CPAP and outcomes in ELBW preterm infants. *J Perinatol* 2003; 23(3):195-199.
- (8) Lindner W, VoBbeck S, Hummier H, Pohlandt F. Delivery Room Management of Extremely Low Birth Weight Infants: Spontaneous Breathing or Intubation. *Ped* 1999; 103(5):961-967.
- (9) Millet V, Lacroze V, Bartoli JM, Samperiz S, Leclaire M, Unal D. [Early continuous positive pressure in the labor room]. *Arch Pediatr* 1997; 4(1):15-20.
- (10) Gittermann.M.K., Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. *Eur J Pediatr* 1997; 156:384-388.

- (11) Kamper J, Feilberg JN, Jonsbo F, Pedersen-Bjergaard L, Pryds O. The Danish national study in infants with extremely low gestational age and birthweight (the ETFOL study): respiratory morbidity and outcome. *Acta Paediatr* 2004; 93(2):225-232.
- (12) Poets CF, Sens B. Changes in intubation rates and outcome of very low birth weight infants: a population-based study. *Ped* 1996; 98(1):24-27.
- (13) Latini G, De Felice C, Presta G, Rosati E, Vacca P. Minimal handling and bronchopulmonary dysplasia in extremely low-birth-weight infants. *Eur J Pediatr* 2003; 162(4):227-229.
- (14) De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health* 2001; 37:161-167.
- (15) Rhodes PG, Hall RT. Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome: a controlled study. *Ped* 1973; 52:1-5.
- (16) Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2002;(2):CD002271.
- (17) Morley CJ. Continuous Distending Pressure. *Arch Dis Child Fetal Neonatal Ed* 1999; 81:F152-F156.
- (18) Morley C, Davis P. Continuous positive airway pressure: current controversies. *Curr Opin Pediatr* 2004; 16(2):141-145.
- (19) Dick W, Ahnefeld FW, Lotz P, Milewski P, Schindewolf H, Wyrwoll K. [Aspects of primary PEEP ventilation for immediate treatment of emergency patients (author's transl)]. *Anaesthetist* 1980; 29(8):407-413.
- (20) Thome U, Topfer A, Schaller P, Pohlandt F. The effect of positive endexpiratory pressure, peak inspiratory pressure, and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. *Eur J Pediatr* 1998; 157(10):831-837.
- (21) Miller MJ, Carlo WA, Martin RJ. Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. *J Pediatr* 1985; 106(1):91-94.
- (22) Davis PG, Davies M, Faber B. A randomised controlled trial of two methods of delivery nasal continuous positive airway pressure after extubation to infants weighing less than 1000g: binasal (Hudson) versus single nasal prongs. *Arch Dis Child Fetal Neonatal Ed* 2001; 85:F82-F85.
- (23) Drew J.H. Immediate intubation at birth of the very-low-birth-weight infant. Effect on survival. *American Journal of Disease of Children* 1982; 136:207-210.
- (24) Thomson MA, Yoder BA, Winter VT, Martin H, Catland D, Siler-Khodr TM et al. Treatment of immature baboons for 28 days with early nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2004; 169(9):1054-1062.
- (25) Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol* 2002; 7(5):353-360.
- (26) Bjorklund L, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O et al. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Ped Res* 1997; 42 No 3:348-355.
- (27) Okumura A, Hayakawa F, Kato T, Itomi K, et al. Hypocarbica in preterm infants with periventricular

- leukomalacia: the relation between hypocarbia and mechanical ventilation. *Ped* 2001; 107(3):469-475.
- (28) Giannakopoulou C, Korakaki E, Manoura A, Bikouvarakis S, Papageorgiou M, Gourgiotis D et al. Significance of hypocarbia in the development of periventricular leukomalacia in preterm infants. *Pediatr Int* 2004; 46(3):268-273.
- (29) Harrison VC, Heese HB, Klein M. The significance of grunting in hyaline membrane disease. *Ped* 1968; 41:549.
- (30) Michna J, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. *Am J Respir Crit Care Med* 1999; 160(2):634-639.
- (31) Probyn M, Hooper S, Dargaville P, McCallion N, Crossley K, Harding R et al. Positive End Expiratory Pressure during Resuscitation of Premature Lambs Rapidly Improves Blood Gases without Adversely Affecting Arterial Pressure. *Pediatr Res* 2004; 0: 01.PDR.0000132752.94155.13v1-0.
- (32) Jobe AH, Kramer BW, Moss TJ, Newnham JP, Ikegami M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. *Pediatr Res* 2002; 52(3):387-392.
- (33) Thomson MA, et al. Early nasal CPAP + prophylactic surfactant for neonates at risk of RDS. The IFDAS trial. *Ped Res* 2001;304.
- (34) Thomson MA. Continuous positive airway pressure and surfactant; combined data from animal experiments and clinical trials. *Biol Neonate* 2002; 81 Suppl 1:16-19.
- (35) Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. *Pediatrics* 2004; 114(3):651-657.
- (36) Han VKM, Beverley DW, Clarson C, Sumabat WO, Shaheed WA, Brabyn DG et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. *Early Human Dev* 1987; 15:21-32.
- (37) Naik AS, Kallapur SG, Bachurski CJ, Jobe AH, Michna J, Kramer BW et al. Effects of ventilation with different positive end-expiratory pressures on cytokine expression in the preterm lamb lung. *Am J Respir Crit Care Med* 2001; 164(3):494-498.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Citation List

Citation Marker	Full Citation*
-----------------	----------------

Aly (04)	Aly H, Milner JD, Patel K, El Mohandes AA. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? <i>Ped</i> 2004; 114(3):697-702.
Avery (87)	Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. <i>Ped</i> 1987; 79(1):26-30.
De Klerk (01)	De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. <i>J Paediatr Child Health</i> 2001; 37(2):161-167.
Dick (80)	Dick W, Ahnefeld FW, Lotz P, Milewski P, Schindewolf H, Wyrwoll K. [Aspects of primary PEEP ventilation for immediate treatment of emergency patients (author's transl)]. <i>Anaesthetist</i> 1980; 29(8):407-413.
Dinger (01)	Dinger J, Topfer A, Schaller P, Schwarze R. Effect of positive end expiratory pressure on functional residual capacity and compliance in surfactant-treated preterm infants. <i>J Perinat Med</i> 2001; 29(2):137-143.
Elgellab (01)	Elgellab A, Riou Y, Abbazine A, Truffert P, Matran R, Lequien P et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. <i>Intensive Care Med</i> 2001; 27(11):1782-1787.
Finer (04)	Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. <i>Ped</i> 2004; 114(3):651-657.
Gittermann (97)	Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. <i>Eur J Pediatr</i> 1997; 156(5):384-388.
Gregory (71)	Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. <i>N Engl J Med</i> 1971; 284:1333-1340.
Han (87)	Han VK, Beverley DW, Clarson C, Sumabat WO, Shaheed WA, Brabyn DG et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. <i>Early Hum Dev</i> 1987; 15(1):21-32.
Jacobsen (93)	Jacobsen T, Gronvall J, Petersen S, Andersen GE. "Minitouch" treatment of very low-birth-weight infants. <i>Acta Paediatr</i> 1993; 82(11):934-938.
Jobe (02)	Jobe AH, Kramer BW, Moss TJ, Newnham JP, Ikegami M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. <i>Pediatr Res</i> 2002; 52(3):387-392.
Kamper (93)	Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. <i>Acta Paediatr</i> 1993; 82(2):193-197.
Kamper (04)	Kamper J, Feilberg JN, Jonsbo F, Pedersen-Bjergaard L, Pryds O. The Danish national study in infants with extremely low gestational age and birthweight (the ETFOL study): respiratory morbidity and outcome. <i>Acta Paediatr</i> 2004; 93(2):225-232.
Latini (03)	Latini G, De Felice C, Presta G, Rosati E, Vacca P. Minimal handling and bronchopulmonary dysplasia in extremely low-birth-weight infants. <i>Eur J Pediatr</i> 2003; 162(4):227-229.
Lindner (99)	Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? <i>Ped</i> 1999; 103(5 Pt 1):961-967.
Lundstrom (03)	Lundstrom KE. Early nasal continuous positive airway pressure for preterm neonates: the need for randomized trials. <i>Acta Paediatr</i> 2003; 92(10):1124-1126.
Michna (99)	Michna J, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. <i>Am J Respir Crit Care Med</i> 1999; 160(2):634-639.
Millet (97)	

Narendran (03)	Millet V, Lacroze V, Bartoli JM, Samperiz S, Leclaire M, Unal D. [Early continuous positive pressure in the labor room]. Arch Pediatr 1997; 4(1):15-20.
Poets (96)	Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early bubble CPAP and outcomes in ELBW preterm infants. J Perinatol 2003; 23(3):195-199.
Probyn (04)	Poets CF, Sens B. Changes in intubation rates and outcome of very low birth weight infants: a population-based study. Ped 1996; 98(1):24-27.
Rhodes (73)	Probyn M, Hooper S, Dargaville P, McCallion N, Crossley K, Harding R et al. Positive End Expiratory Pressure during Resuscitation of Premature Lambs Rapidly Improves Blood Gases without Adversely Affecting Arterial Pressure. Pediatr Res 2004; 56(2):198-204
Sandri (04)	Rhodes PG, Hall RT. Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome: a controlled study. Ped 1973; 52:1-5.
Thome (98)	Sandri F, Ancora G, Lanzoni A, Tagliabue P, Colnaghi M, Ventura ML et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. Arch Dis Child Fetal Neonatal Ed 2004; 89(5):F394-F398.
Thomson (01)	Thome U, Topfer A, Schaller P, Pohlandt F. The effect of positive end expiratory pressure, peak inspiratory pressure, and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. Eur J Pediatr 1998; 157(10):831-837.
Thomson (02)	Thomson MA, et al. Early nasal CPAP + prophylactic surfactant for neonates at risk of RDS. The IFDAS trial. Ped Res 2001;304.
Van Marter (00)	Thomson MA. Continuous positive airway pressure and surfactant; combined data from animal experiments and clinical trials. Biol Neonate 2002; 81 Suppl 1:16-19.
	Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. Ped 2000; 105(6):1194-1201.

*Type the citation marker in the first field and then paste the full citation into the second field. You can copy the full citation from EndNote by selecting the citation, then copying the FORMATTED citation using the short cut, Ctrl-K. After you copy the citation, go back to this document and position the cursor in the field, then paste the citation into the document (use Ctrl-V). For each new citation press Tab to move down to start a new field.

1. Aly H, Milner JD, Patel K, El Mohandes AA. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? *Pediatrics* 2004; 114(3):697-702. LOE 4
Abstract: OBJECTIVE: Early use of nasal continuous positive airway pressure (ENCPAP) in extremely low birth weight (ELBW) infants continues to be a source of debate. Centers are applying this management strategy with varying success. Our center has implemented this strategy of care over the past 4 years, and the objective of this study was to evaluate the impact of experience over time with the use of ENCPAP on outcomes of ELBW infants. METHODS: All ELBW infants who were born at our hospital since the institution of the ENCPAP practice (n = 101) were analyzed retrospectively. Patients were divided into 3 terciles according to their birth date. A baseline group of ELBW infants who were born in the 2 years preceding the institution of the ENCPAP practice (group 0; n = 45) were used for comparison. Trends in practices and outcomes over time were analyzed using the 2-sided Cochran-Armitage linear trend test. Statistical significance for these trends were then analyzed again using a multivariate regression model controlling for significant variables. Bivariate analyses comparing individual groups were also conducted. RESULTS: There were no significant trends in mortality rate among the baseline group and the 3 terciles since the institution of the ENCPAP practice (26.7% vs 26.5% vs 11.8% vs 18.2%). ENCPAP management increased in the surviving infants over time (14% vs 19.2% vs 65.52% vs 70.4%), whereas the use of surfactant decreased (51.5% vs 48% vs 13.3% vs 33.3%) and the incidence of bronchopulmonary dysplasia (BPD) decreased (33.3% vs 46.2% vs 25.9% vs 11.1%). The average ventilator days per infant decreased, the rate of sepsis decreased, and the average daily weight gain increased. There were no significant trends in the incidence of intraventricular hemorrhage or necrotizing enterocolitis (NEC). When comparing the cohorts of survivors in the 3 terciles since the institution of ENCPAP system, ELBW infants who were started on ENCPAP but intubated within 1 week (CPAP failure) decreased over time (38.5% vs 13.8% vs 7.4%). There were other trends that did not reach significance, such as increased incidence of necrotizing enterocolitis (NEC). In a multivariate analysis controlling for gestational age, birth weight, and sepsis, the incidence of BPD was significantly lower over time (regression coefficient = -1.002 +/- 0.375). CONCLUSIONS: The frequency of use of ENCPAP in ELBW infants and its success improved in our unit over time. The major positive association in this population was a reduction in BPD rates and an increase in average weight gain. Relation of ENCPAP and NEC should be evaluated further

Level of evidence 4

Evidence-supportive

Quality fair

2. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987; 79(1):26-30. LOE 4
Abstract: Chronic lung disease in prematurely born infants, defined as the need for increased inspired oxygen at 28 days of age, was thought to be more common in some institutions than in others. To test this hypothesis, we surveyed the experience in the intensive care nurseries at Columbia and Vanderbilt Universities, the Universities of Texas at Dallas, Washington at Seattle, and California at San Francisco, the Brigham and Women's Hospital in Boston, Texas Children's Hospital in Houston, and Mt Sinai Hospital in Toronto. The survey included 1,625 infants with birth weights of 700 to 1,500 g. We confirmed the relationship of risk to low birth weight, white race, and male sex. Significant differences in the incidence of chronic lung disease were found between institutions even when birth weight, race, and sex were taken into consideration through a multivariate logistic regression analysis. Columbia had one of the best outcomes for low birth weight infants and the lowest incidence of chronic lung disease

Level of evidence 4

Evidence-supportive

Quality Good

3. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health* 2001; 37(2):161-167. LOE 7
Abstract: OBJECTIVES: To document the effects of changing to a primarily nasal continuous positive airway pressure (CPAP)-based system of respiratory support on respiratory and non-respiratory outcomes in preterm infants. METHODOLOGY: Outcomes in two groups of preterm infants with a birthweight of 1000-1499 g were compared retrospectively over a 5-year period before (period I; n = 57) and after (period II; n = 59) the introduction of a primarily nasal CPAP-based approach to respiratory support, modelled closely on that used at the New York Presbyterian Hospital (Columbia University), formally known as the

Columbia-Presbyterian Medical Center, in New York. RESULTS: From period I to period II, there was a decline in the number of infants ventilated (65 vs 14%, respectively) and receiving surfactant (40 vs 12%, respectively) and in the median days of ventilation (6 vs 2, respectively) and oxygen (4 vs 2, respectively). There were decreases in chronic lung disease (CLD) at 28 days (11 vs 0%, respectively), death or CLD at 28 days (16 vs 3%, respectively), the use of pressor support (34 vs 7%, respectively), the incidence of necrotizing enterocolitis (11 vs 0%, respectively), time to reach full oral feeds (17.3 vs 13.2 days, respectively), discharge weight (2569 vs 2314 g, respectively) and average length of stay (61 vs 52.9 days, respectively). There were no differences in neurosonographic or other morbidity outcomes. CONCLUSIONS: A CPAP-based approach to respiratory support of the preterm infant may decrease the invasiveness and duration of respiratory support and may decrease respiratory and some non-respiratory adverse outcomes without an associated increase in neurosonographic or other morbidity outcomes. Further prospective trials are warranted

Level of evidence 7

Evidence-supportive

Quality Fair

4. Dick W, Ahnefeld FW, Lotz P, Milewski P, Schindewolf H, Wyrwoll K. [Aspects of primary PEEP ventilation for immediate treatment of emergency patients (author's transl)]. *Anaesthesist* 1980; 29(8):407-413. LOE 6 **Abstract:** PEEP ventilation is frequently used in intensive care patients: its particular effects in the immediate treatment of emergency patients are discussed. In animal experiments different studies were performed using manually operated resuscitators combined with a newly designed PEEP valve. The most important results in neonatal pigs show that the post partum compliances and the neonatal PO₂ values were much better after primary PEEP ventilation than after IPPB or 2-phases unfolding inflation. The worst method of respiratory resuscitation is the use of PNPB. In 2 other groups of animals immediate PEEP ventilation was compared to IPPB, after 25 ml of fresh water/kg BW had been instilled into the animals lungs. The PaO₂ and AaDO₂ values of those animals, treated immediately with PEEP were much better than the corresponding values of the ZEEP group animals. But, the PEEP-treated animals showed a significant reduction of the cardiac output. The article deals further with the results of different authors, as far as PEEP and lung edema, PEEP and CPR, PEEP and shock are concerned. In our opinion, the present clinical and experimental results lead to the following conclusions: The immediate PEEP ventilation at the scene is indicated 1. in neonatal resuscitation - 2. in near drowning - 3. in lung edema - 4. in cardiopulmonary resuscitation. PEEP ventilation should however not exceed 10 cm H₂O

Level of evidence 6

Evidence-supportive

Quality Good

5. Dinger J, Topfer A, Schaller P, Schwarze R. Effect of positive end expiratory pressure on functional residual capacity and compliance in surfactant-treated preterm infants. *J Perinat Med* 2001; 29(2):137-143. LOE 7 **Abstract:** Positive end expiratory pressure is routinely used when ventilating preterm infants. Elevation of PEEP increases lung volume, as does surfactant treatment. The purpose of this study was to investigate the effect of various levels of PEEP within the range of 0.2 to 0.4 kPa on lung volume, compliance and gas exchange. We measured functional residual capacity, compliance of the respiratory system and arterial blood gases in 20 infants (median birth weight 1240 g, range 660-1690 g; median gestational age 28 weeks, range 24-32 weeks; postnatal age 3-4 days). The infants were studied at 72 hours after their last dose of natural surfactant. At this time the patients were routinely nursed at 0.3 kPa of PEEP, the PEEP level was lowered to 0.2 kPa or raised to 0.4 kPa in random order. The PEEP level was then changed to the third level 0.4 kPa or 0.2 kPa. Each new setting was maintained for 20 min before FRC, compliance and blood gases were measured. FRC was assessed using SF₆ washout technique. Increasing PEEP from 0.2 to 0.3 to 0.4 kPa resulted in increases in FRC ($p < 0.01$) and oxygenation (ns) in all infants. In 16 infants compliance decreased and paCO₂ increased with elevation of PEEP. Only in 4 infants compliance increased and CO₂ fell. CONCLUSION: In the majority of our infants reduction of PEEP from 0.4 to 0.2 kPa resulted in increases in compliance and CO₂ reduction. Our results might suggest that relatively low levels of PEEP < 0.3 kPa may be appropriate at 72 hours after surfactant replacement. Furthermore, these results underline the importance of PEEP test in clinical practice

Level of evidence 7

Evidence-supportive

Quality Fair

6. Elgellab A, Riou Y, Abbazine A, Truffert P, Matran R, Lequien P et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. *Intensive Care Med* 2001; 27(11):1782-1787. **LOE 7 Abstract:** **OBJECTIVE:** The aim of the study was to assess the influence of nasal continuous positive airway pressure (NCPAP) on breathing pattern in preterm newborns. **DESIGN:** Prospective study. **SETTING:** Neonatal intensive care unit. **PATIENTS:** Ten premature newborn infants on NCPAP (gestational age range from 27 to 32 weeks, mean birth weight 1300+/-460 g) admitted in our neonatal intensive care unit (NICU) for respiratory distress syndrome. **METHODS:** Breathing patterns and changes in lung volumes level were obtained using respiratory inductive plethysmography (RIP), at random CPAP levels (0, 2, 4, 6 and 8 cmH₂O). Raw data were analysed for end-expiratory lung volume level (EELV-level), tidal volume (V_t), respiratory rate, phase angle and labour breathing index (LBI). **RESULTS:** CPAP increased EELV-level by 2.1+/-0.3xV_t from 0 to 8 cmH₂O (p<0.01). V_t increased by 43% from CPAP of 0 cmH₂O to CPAP of 8 cmH₂O (p<0.01). We also found that CPAP lowered the phase angle (from 76+/-21 degrees at CPAP of 0 cmH₂O to 30+/-15 degrees at CPAP of 8 cmH₂O; p<0.01) and LBI (from 1.7+/-0.8 at CPAP of 0 cmH₂O to 1.2+/-0.3 at CPAP of 8 cmH₂O; p<0.05). **CONCLUSION:** NCPAP improves the breathing strategy of premature infants with respiratory failure, as reflected by improved thoraco-abdominal synchrony, increased V_t and reduction of the LBI. This effect is associated with an increase in EELV-level with CPAP level. However, further investigations are necessary to establish the best CPAP level that ensures both safety and efficiency

Level of evidence 7

Evidence-supportive

Quality Fair

7. Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. *Pediatrics* 2004; 114(3):651-657. **LOE 2 Abstract:** **OBJECTIVE:** Although earlier studies have suggested that early continuous airway positive pressure (CPAP) may be beneficial in reducing ventilator dependence and subsequent chronic lung disease in the extremely low birth weight (ELBW) infant, the time of initiation of CPAP has varied, and there are no prospective studies of infants who have received CPAP or positive end-expiratory pressure (PEEP) from initial resuscitation in the delivery room (DR). Current practice for the ELBW infant includes early intubation and the administration of prophylactic surfactant, often in the DR. The feasibility of initiating CPAP in the DR and continuing this therapy without intubation for surfactant has never been determined prospectively in a population of ELBW infants. This study was designed to determine the feasibility of randomizing ELBW infants of <28 weeks' gestation to CPAP/PEEP or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine DR intubation for surfactant administration, initiating CPAP on neonatal intensive care unit (NICU) admission, and assessing compliance with subsequent intubation criteria. **METHODS:** Infants who were of <28 weeks' gestation, who were born in 5 National Institute of Child Health and Human Development Neonatal Research Network NICUs from July 2002 to January 2003, and for whom a decision had been made to provide full treatment after birth were randomized to receive either CPAP/PEEP or not using a neonatal T-piece resuscitator (NeoPuff). Infants would not be intubated for the sole purpose of surfactant administration in the DR. After admission to the NICU, all nonintubated infants were placed on CPAP and were to be intubated for surfactant administration only after meeting specific criteria: a fraction of inspired oxygen of >0.3 with an oxygen saturation by pulse oximeter of <90% and/or an arterial oxygen pressure of <45 mm Hg, an arterial partial pressure of carbon dioxide of >55 mm Hg, or apnea requiring bag and mask ventilation. **RESULTS:** A total of 104 infants were enrolled over a 6-month period: 55 CPAP and 49 control infants. No infant was intubated in the DR for the exclusive purpose of surfactant administration. Forty-seven infants were intubated for resuscitation in the DR: 27 of 55 CPAP infants and 20 of 49 control infants. Only 4 of the 43 infants who had a birth weight of <700 g and 3 of the 37 infants of <25 weeks' gestation were resuscitated successfully without positive pressure ventilation, and no difference was observed between the treatment groups. All infants of 23 weeks' gestation required intubation in the DR, irrespective of treatment group, whereas only 3 (14%) of 21 infants of 27 weeks' required such intubation. For infants who were not intubated in the DR, 36 infants (16 CPAP infants and 20 control infants) were subsequently intubated in the NICU by day 7, in accordance with the protocol. Overall, 80% of studied infants required intubation within the first 7 days of life. The care provided for 52 (95%) of 55 CPAP infants and 43 (88%) of the 49 control infants was in compliance with the study protocol, with an overall compliance of 91%. **CONCLUSIONS:** This study demonstrated that infants could be randomized successfully to a DR intervention of CPAP/PEEP compared with no CPAP/PEEP, with intubation provided only for resuscitation indications, and subsequent intubation for prespecified criteria. Forty-five percent (47 of 104) of infants <28 weeks' gestation required intubation for resuscitation in the DR. CPAP/PEEP in the DR did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life. This experience should be helpful in facilitating the design of subsequent prospective studies of ventilatory support in ELBW infants

Level of evidence 2

Evidence-Neutral to opposing

Quality Excellent

8. Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr* 1997; 156(5):384-388. **LOE 4 Abstract:** Nasal continuous positive airway pressure (CPAP) applied shortly after birth is said to be an effective treatment of respiratory distress in very low birth weight infants (VLBW). We tested the hypothesis that the use of early nasal CPAP (applied as soon as signs of respiratory distress occurred, usually within 15 min after birth) reduces the need for intubation, the duration of intermittent mandatory ventilation and the incidence of bronchopulmonary dysplasia. All liveborn VLBW infants (birth weight < 1500 g) admitted to our tertiary neonatal intensive care unit in 1990 (historical controls) and in 1993 (early nasal CPAP group) entered the study. The intubation rate was significantly lower after introduction of nasal CPAP (30% vs 53%, $P = 0.016$). Median duration of intubation was 4.5 days (interquartile range 3-7 days) before versus 6.0 days (2.8-9 days) after nasal CPAP was introduced ($P = 0.73$). The incidence of bronchopulmonary dysplasia was not reduced significantly (32% vs 30%, $P = 0.94$). Survival until discharge was 89.5%, before versus 92.9% after introduction of nasal CPAP ($P = 0.54$). **CONCLUSION:** Early nasal CPAP is an effective treatment of respiratory distress in VLBW infants, significantly reducing the need for intubation and intermittent mandatory ventilation, without worsening other standard measures of neonatal outcome. We found no significant decrease in the incidence of bronchopulmonary dysplasia

Level of evidence 4

Evidence-supportive to neutral

Quality Fair

9. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N Engl J Med* 1971; 284:1333-1340. **LOE 7 Abstract:** We applied a continuous positive airway pressure to 20 infants (birthweight 930 to 3800g) severely ill with the idiopathic respiratory distress syndrome. They breathed spontaneously. Pressure, up to 12 mm Hg, was delivered through an endotracheal tube to 18 infants and via a pressure chamber round the infant's head to two. Arterial oxygen tension rose in all, permitting us to lower the inspired oxygen an average of 37.5% within 12 hours. Minute ventilation decreased with increased CPAP, but this had little effect on arterial carbon dioxide tension, pH, arterial blood pressure and lung compliance. Sixteen infants survived, including seven of ten weighing less than 1500g at birth.

Level of evidence 7

Evidence-supportive

Quality Fair

10. Han VK, Beverley DW, Clarson C, Sumabat WO, Shaheed WA, Brabyn DG et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. *Early Hum Dev* 1987; 15(1):21-32. **LOE 2 Abstract:** Application of continuous distending pressure at birth (very early CDP) should stabilize the immature airways and reduce the severity of respiratory distress syndrome (RDS) in preterm infants. Eighty-two preterm infants of less than 32 weeks gestation were randomly assigned at birth to early treatment group (TG), in which CDP of 6 cm water pressure was applied at birth by the nasopharyngeal route (NP-CDP), or to control group (CG), in which CDP was applied when indicated for established criteria (pO_2 less than 50 mmHg in FiO_2 greater than 0.5). Characteristics of the infants in the two groups were comparable. No statistically significant difference between the two groups was found in the incidence of RDS. The course of RDS, and oxygen and ventilatory requirements also did not appear to be changed. In blood gas parameters of most of the time frames, no significant difference was found between the two groups when the results were analyzed according to the assigned group. When the results were analyzed separately for the infants who developed RDS, infants in TG appear to have fared worse from the therapy in terms of oxygenation, as indicated by significantly higher FiO_2 (P less than 0.01) and lower a/A (P less than 0.01) values on the third day of the course of RDS, as compared to infants in CG. The incidence of complications was comparable in the two groups. Four infants from TG (9.3%) and one from CG (2.6%) died ($P = NS$). We conclude that VECDP by nasopharyngeal route does not reduce the incidence of RDS and does not appear to improve the outcome and may worsen the severity of RDS when compared to application of CDP for established criteria

Level of evidence 2

Evidence-neutral to opposing

Quality Fair

11. Jacobsen T, Gronvall J, Petersen S, Andersen GE. "Minitouch" treatment of very low-birth-weight infants. *Acta Paediatr* 1993; 82(11):934-938. LOE 4 **Abstract:** In a cohort study with historical controls of non-asphyxiated very low-birth-weight infants (birth weight \leq 1500 g and gestational age $<$ 33 completed weeks), we evaluated the use of a "minitouch" regime for stabilization after birth and treatment of respiratory distress. This combination of early (prophylactic) treatment with nasal continuous positive airway pressure and minimal handling was introduced as a routine in our Department in 1986. We compared infants born in 1987 and in 1985, when ventilator treatment was used initially in all infants with progressing respiratory distress. The frequency of mechanical ventilation was reduced significantly from 76% in 1985 to 35% in 1987 ($p = 0.00001$). This reduction reflected the smaller number of infants who received ventilator treatment for less than one week, whereas the frequency of long-term ventilator treatment remained unchanged. Intracranial haemorrhage grade II-IV was reduced from 49% in 1985 to 25% in 1987 ($p = 0.01$). Mortality rate, average duration of hospitalization, number of infants with pneumothorax, patent ductus arteriosus, need for oxygen at 28 days and number of surviving infants with handicap did not differ significantly between the two study periods. Septicaemia was diagnosed in 16% of the infants in 1987 versus 7% in 1985 ($p = 0.045$). This difference coincided with an increased use of total parenteral nutrition (18% in 1987 versus 3% in 1985, $p = 0.007$). We conclude that the minitouch regime prevents progression of respiratory distress, reduces the need for ventilator treatment and is a safe and convenient alternative to mechanical ventilation in preterm infants with mild respiratory problems.(ABSTRACT TRUNCATED AT 250 WORDS)

12. Jobe AH, Kramer BW, Moss TJ, Newnham JP, Ikegami M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. *Pediatr Res* 2002; 52(3):387-392. LOE 6 **Abstract:** Continuous positive airway pressure (CPAP) is being used clinically to avoid mechanical ventilation of preterm infants as a strategy to minimize lung injury. There is little experimental information about how CPAP might minimize lung injury after preterm birth. We induced preterm labor in antenatal glucocorticoid-treated sheep carrying twins at 133 d gestation with an inhibitor of progesterone synthesis. The lambs delivered spontaneously approximately 2 d later and were randomized to three groups: no ventilation ($n = 4$), conventional mechanical ventilation to a target PCO_2 of 40 mm Hg ($n = 5$), or CPAP using a bubble CPAP device set to deliver 5 cm H₂O pressure ($n = 6$). The CPAP lambs breathed without distress and maintained PCO_2 values of approximately 60 mm Hg. At 2 h of age, the lungs of the CPAP lambs held 74 \pm 4 mL/kg air at 40 cm H₂O pressure, which was more than the 60 \pm 3 mL/kg for the ventilated lambs ($p < 0.05$). Lymphocyte and monocyte numbers in alveolar washes were equivalent in the unventilated, ventilated, and CPAP lambs. However, no neutrophils were found in the unventilated lambs, and the ventilated lambs had 6.6 times more neutrophils in alveolar washes than did the CPAP lambs ($p < 0.05$). The cells in alveolar wash from CPAP lambs contained less hydrogen peroxide than did the cells from ventilated lambs ($p < 0.05$). In this model in preterm lambs CPAP results in lower indicators of acute lung injury than does mechanical ventilation during the first 2 h of life

Level of evidence 6

Evidence-supportive

Quality Good

13. Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. *Acta Paediatr* 1993; 82(2):193-197. LOE 5 **Abstract:** During 1988 and 1989, a regional cohort of 81 infants with birth weights less than 1501 g were treated with oxygen only ($n = 11$), early continuous positive airway pressure (CPAP) ($n = 68$) or mechanical ventilation from birth ($n = 2$). We used an easily applicable lightweight CPAP system with nasal prongs and a gas jet supplemented with ventilator treatment if necessary, but with conservative criteria for ventilator treatment with tolerance of high PCO_2 . A total of 65 infants (80%) survived to discharge, 61 of whom were supported solely with CPAP or oxygen. Nineteen infants (26%) developed periventricular-intraventricular haemorrhage, but only 4 survivors (6%) developed prognostically significant bleedings grade 2-4. No survivors had bronchopulmonary dysplasia. Follow-up at 12-39 months of age revealed definite disabilities in 6 (10%) and suspected disabilities in 2 of 62 long-term survivors. The results suggest that treatment by early CPAP with nasal prongs with tolerance of high PCO_2 may be effective and lenient in most infants more than 25 weeks' gestation

Level of evidence 5

Evidence-supportive

Quality Fair

14. Kamper J, Feilberg JN, Jonsbo F, Pedersen-Bjergaard L, Pryds O. The Danish national study in infants with extremely low gestational age and birthweight (the ETFOL study): respiratory morbidity and outcome. *Acta Paediatr* 2004; 93(2):225-232. LOE 5 **Abstract:** AIM: To describe and analyse neonatal care, short and long-term morbidity with special reference to ventilatory support and chronic lung disease (CLD) in a population-based study. METHODS: During 1994 and 1995 a prospective, nation-wide, multicentre study was conducted, comprising 477 liveborn infants with gestational age (GA) < 28 wk and/or birthweight < 1000 g. Of these, 407 infants received active treatment. The ventilatory treatment was based on the principle of permissive hypercapnia and early nasal continuous positive airway pressure (NCPAP) supplemented with surfactant and ventilator therapy in case of CPAP failure. RESULTS: Among actively treated infants 85% received CPAP and 23% mechanical ventilation from the first day of life. A total of 269 infants (56%) survived to discharge. Of these, 195 had a GA < 28 wk. One-hundred and five survivors with GA < 28 wk survived with NCPAP as sole respiratory support. In surviving infants, periventricular leucomalacia/intraventricular haemorrhage grade 3-4 was found in 10%, retinopathy of prematurity grade > 2 in 4%, and oxygen requirement at 36 and 40 wk of postmenstrual age (CLD) in 16 and 5%, respectively. Three infants either died of CLD (n = 1) or required oxygen therapy beyond 43 wk of postmenstrual age. Logistic regression analysis showed significant associations between oxygen requirement at 40 wk and GA, septicemia, mechanical ventilation, symptomatic patent ductus arteriosus and Clinical Risk Index for Babies score. Only the two last-mentioned factors proved significant in infants with GA < 28 wk. No infant died after discharge and 253 (94%) were followed up at 2 y of corrected age; one or more moderate to severe impairments were found in 66 (26%) of the examined children. CONCLUSION: Ventilatory treatment in extremely premature and extremely low-birthweight infants based on early NCPAP and permissive hypercapnia may result in comparable survival rates and sensorineural outcome; however, the incidence of CLD seems lower than that reported on conventional treatment

Level of evidence 5

Evidence-supportive

Quality Fair

15. Latini G, De Felice C, Presta G, Rosati E, Vacca P. Minimal handling and bronchopulmonary dysplasia in extremely low-birth-weight infants. *Eur J Pediatr* 2003; 162(4):227-229. LOE 7 **Abstract:** Over the last 16 years a minitouch regime, i.e., nasal continuous positive airway pressure (n-CPAP) and/or nasal intermittent positive pressure ventilation (n-IPPV), together with a minimal intubation policy has been routinely used for the treatment of respiratory distress syndrome (RDS) in preterm infants. Only 1.39 (1 out of 72) of the extremely low-birth-weight babies admitted to our Neonatal Intensive Care Unit (NICU) and surviving for at least 36 weeks' postconceptional age developed bronchopulmonary dysplasia at 36 weeks (BPD 36-wk). The BPD-36 wk incidence observed in our population is significantly lower than expected (30%) from the literature (p=0.000002). CONCLUSION: Our experience supports the effectiveness of the minitouch regime as a way to ventilate premature babies, reducing BPD risk
16. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics* 1999; 103(5 Pt 1):961-967. LOE 4 **Abstract:** OBJECTIVE: To study the effect of two different delivery room (DR) policies on the rate of endotracheal intubation and mechanical ventilation (EI/MV) and short term morbidity in extremely low birth weight infants (ELBWI; <1000 g, >=24 weeks). METHODS: Retrospective cohort study of 123 inborn ELBWIs born in 1994 and in 1996. DR policies have changed. Until 1994, ELBWIs were intubated immediately after delivery when presenting the slightest signs of respiratory distress or asphyxia after initial resuscitation using a face mask and a handbag. During 1995, the guidelines for respiratory support were changed. In 1996, continuous (15 to 20 seconds), pressure controlled (20 to 25 cm H₂O) inflation of the lungs using a nasal pharyngeal tube, followed by continuous positive airway pressure (CPAP; 4 to 6 cm H₂O) was applied to all ELBWIs immediately after delivery to establish a functional residual capacity and perhaps to avoid EI/MV. In addition to the changes in respiratory support, the prevention of conductive and evaporative heat loss was improved in 1996. For analysis of morbidity and mortality, infants were matched for gestational age and birth weight. RESULTS: The rate of EI/MV in the DR decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBWIs were never intubated (7% in 1994), but 35% of the ELBWIs needed secondary EI/MV, primarily because of respiratory distress syndrome (RDS). Initial ventilator settings, ventilator days, mortality, and morbidity were not different between ELBWIs with EI/MV in the DR and infants with secondary EI/MV attributable to RDS in the intensive care unit. ELBWIs with no EI/MV that was caused by RDS had a lower morbidity (ie, bronchopulmonary dysplasia, intraventricular hemorrhage >grade 2 and/or periventricular leukomalacia), mortality, and fewer hospital days (mean: 79 vs 105 days). The incidence of gastrointestinal adverse effects like feeding intolerance or necrotizing enterocolitis was not increased in 1996.

PaCO₂ was significantly higher at admission to the neonatal unit in ELBWIs with CPAP in 1996 (54 +/- 15 mm Hg, 7.2 +/- 2.0 kPa) compared with infants with EI/MV in 1994 (38 +/- 11 mm Hg, 5.1 +/- 1.5 kPa). A total of 26% of spontaneously breathing infants had hypercapnia (PaCO₂ >=60 mm Hg [8.0 kPa]), compared with 7% of infants with EI/MV in 1994. Within the first few hours of life, PaCO₂ decreased to 46 (32 to 57) mm Hg (6.1 [4.3 to 7.6] kPa) in never intubated ELBWIs (n = 17), but increased to 70 (57 to 81) mm Hg (9.3 [7.6 to 10.8] kPa) in ELBWIs (n = 14) with RDS and secondary EI/MV (age 5.5 [1 to 44] hours). CONCLUSIONS: In our setting, the individualized intubation strategy in the DR restricted EI/MV to those ELBWIs who ultimately needed it, without increasing morbidity or mortality in infants with secondary EI/MV attributable to RDS. We speculate that an individualized intubation strategy of the ELBWI is superior to immediate intubation of all ELBWIs with slight signs of respiratory distress after birth

Level of evidence 4

Evidence-supportive

Quality Good

17. Lundstrom KE. Early nasal continuous positive airway pressure for preterm neonates: the need for randomized trials. *Acta Paediatr* 2003; 92(10):1124-1126. LOE 7 **Abstract:** The use of early nasal continuous positive airway pressure (nCPAP) as prophylaxis and treatment for respiratory distress syndrome in preterm neonates, with or without prophylactic surfactant, is becoming increasingly popular. However, the justification for this is limited to comparisons between centres and comparisons of historical controls. CONCLUSION: Randomized trials and appropriate evaluation of the nCPAP technique are needed
18. Michna J, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. *Am J Respir Crit Care Med* 1999; 160(2):634-639. LOE 6 **Abstract:** Ventilation style influences lung injury and the amount of large-aggregate biophysically active surfactant in adult lungs. We asked how positive end-expiratory pressures (PEEP) would influence clinical responses and surfactant pools in surfactant-treated preterm lambs ventilated for 7 h with tidal volumes (VT) of 10 ml/kg. The 126-d gestation preterms were delivered and treated with 100 mg/kg recombinant human surfactant protein C (rSP-C) containing surfactant and ventilated with zero, 4, or 7 cm H₂O of PEEP. A comparison group was treated with natural sheep surfactant and ventilated with zero PEEP. Physiologic measurements were similar for lambs treated with rSP-C surfactant and natural surfactant. PEEP 4 and 7 improved oxygenation and compliance relative to either group of lambs ventilated with PEEP zero. The maximal lung volumes measured at 40 cm H₂O pressure after 7 h ventilation for the PEEP 4 and 7 groups were more than double those measured for either PEEP zero group. Alveolar surfactant pools were larger for the PEEP 7 group, and the large-aggregate fraction was increased for the PEEP 4 and 7 groups, resulting in large-aggregate pool sizes that were 3-fold higher for the PEEP 4 and 4-fold higher for the PEEP 7 groups relative to the PEEP zero group treated with rSP-C surfactant. All large-aggregate surfactants lowered minimal surface tensions of a captive bubble to less than 5 mN/m. In preterm surfactant-treated lambs PEEP improved lung function and maintained more of an rSP-C surfactant in the biophysically active form

Level of evidence 6

Evidence-supportive

Quality Good

19. Millet V, Lacroze V, Bartoli JM, Samperiz S, Leclaire M, Unal D. [Early continuous positive pressure in the labor room]. *Arch Pediatr* 1997; 4(1):15-20. LOE 4 **Abstract:** BACKGROUND: Indication for intubation and mechanical ventilation in premature infants may be reduced by initiating continuous positive airway pressure (CPAP) in delivery room. POPULATION AND METHODS: Immediately after birth, respiratory support with CPAP was given to all infants with gestational age less than 32 weeks. In case of apnea or progressing symptoms with hypoxemia or carbonic acidosis, with PCO₂ increasing to more than 60 mmHg, infants were treated with nasotracheal intubation and ventilation. RESULTS: One hundred and fifty one infants, with mean gestational age 29.6 +/- 1.9 weeks and mean birth weight 1,326 +/- 378 g were delivered in the obstetrical department of Marseille. In delivery room, 63% were treated with CPAP, and only 13% with nasotracheal intubation. The need for subsequent mechanical ventilation was reduced to 40% of the population. Surfactant therapy was used in 17% of this cohort. Two infants were given surfactant and extubated. Three of 14 deaths (9.2%) were caused by respiratory disease. CONCLUSIONS: Early CPAP reduces the indication of mechanical ventilation in premature infants. Incidence of pulmonary complications such as pneumothorax or bronchopulmonary dysplasia is low among those infants who require mechanical ventilation later. Early CPAP takes place in a general policy to decrease neonatal morbidity

Level of evidence 4

Evidence-supportive

Quality Fair

20. Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early bubble CPAP and outcomes in ELBW preterm infants. *J Perinatol* 2003; 23(3):195-199. LOE 4 **Abstract:** OBJECTIVE: To test whether the introduction of early bubble continuous positive airway pressure (CPAP) results in improved respiratory outcomes in extremely low birth-weight infants. STUDY DESIGN: Outcomes of all infants between 401 and 1000 g born in a level 3 neonatal intensive care units (NICU) between July 2000 and October 2001 (period 2) were compared using historical controls (period 1). Early bubble (CPAP) was prospectively introduced in the NICU during period 1. Univariate and adjusted comparisons were made across time periods. RESULTS: Delivery room intubations, days on mechanical ventilation and use of postnatal steroids decreased ($p < 0.001$) in period 2, while mean days on CPAP, number of babies on CPAP at 24 hours ($p < 0.001$) and mean weight at 36 weeks corrected gestation also increased ($p < 0.05$) after introduction of early bubble CPAP. CONCLUSIONS: Early bubble CPAP reduced delivery room intubations, days on mechanical ventilation, postnatal steroid use and was associated with increased postnatal weight gain with no increased complications

Level of evidence 4

Evidence-supportive

Quality Fair

21. Poets CF, Sens B. Changes in intubation rates and outcome of very low birth weight infants: a population-based study. *Ped* 1996; 98(1):24-27. LOE 7 **Abstract:** OBJECTIVE. There have been indications of a recent decrease in intubation rates of very low birth weight (VLBW) infants in Germany. We wanted to quantify this decrease and analyze its effect on clinical outcome. METHODS. Population-based data on the treatment and outcome at hospital discharge from a statewide quality assurance program were analyzed for 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 in Lower Saxony, North Germany. RESULTS. The proportion of patients not intubated and mechanically ventilated increased from 7% to 14% in infants less than 1000 g and from 28% to 44% in those greater than or equal to 1000 g ($P < .02$ and $< .01$, respectively). This increase was not associated with any significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leucomalacia, or bronchopulmonary dysplasia (BPD). Instead, there was an increase in the proportion of infants less than 1000 g who survived without BPD (from 38% in 1992 to 48% in 1994; $P < .05$) and a decrease in the proportion of infants greater than or equal to 1000 g in whom BPD developed (from 14% to 9%; $P < .05$). CONCLUSIONS. The data from a statewide quality assurance program show a significant reduction in the aggressiveness of the treatment of VLBW infants, which was not associated with an increased mortality or morbidity. This observational study, however, cannot define whether a more selective approach to the intubation of VLBW infants will ultimately result in a better outcome. A randomized, controlled trial would be required to answer this clinically important question

Level of evidence 7

Evidence-supportive

Quality Fair

22. Probyn M, Hooper S, Dargaville P, McCallion N, Crossley K, Harding R et al. Positive End Expiratory Pressure during Resuscitation of Premature Lambs Rapidly Improves Blood Gases without Adversely Affecting Arterial Pressure. *Pediatr Res* 2004; 56(2):198-204 LOE 6

Abstract: Positive end expiratory pressure (PEEP) is important for neonatal ventilation but is not considered in guidelines for resuscitation. Our aim was to investigate the effects of PEEP on cardiorespiratory parameters during resuscitation of very premature lambs delivered by hysterotomy at ~125 d gestation (term ~147 d). Before delivery, they were intubated and lung fluid was drained. Immediately after delivery, they were ventilated with a Drager Babylog plus ventilator in volume guarantee mode with a tidal volume of 5 mL/kg. Lambs were randomized to receive 0, 4, 8, or 12 cm H₂O of PEEP. They were ventilated for a 15-min resuscitation period followed by 2 h of stabilization at the same PEEP. Tidal volume, peak inspiratory pressure, PEEP, arterial pressure, oxygen saturation, and blood gases were measured regularly, and respiratory system compliance and alveolar/arterial oxygen

differences were calculated. Lambs that received 12 cm H₂O of PEEP died from pneumothoraces; all others survived without pneumothoraces. Oxygenation was significantly improved by 8 and 12 cm H₂O of PEEP compared with 0 and 4 cm H₂O of PEEP. Lambs with 0 PEEP did not oxygenate adequately. The compliance of the respiratory system was significantly higher at 4 and 8 cm H₂O of PEEP than at 0 PEEP. There were no significant differences in partial pressure of carbon dioxide in arterial blood between groups. Arterial pressure was highest with 8 cm H₂O of PEEP, and there was no cardiorespiratory compromise at any level of PEEP. Applying PEEP during resuscitation of very premature infants might be advantageous and merits further investigation

Level of evidence 6

Evidence-supportive

Quality Fair

23. Rhodes PG, Hall RT. Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome: a controlled study. *Ped* 1973; 52:1-5. LOE 7
24. Sandri F, Ancora G, Lanzoni A, Tagliabue P, Colnaghi M, Ventura ML et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. *Arch Dis Child Fetal Neonatal Ed* 2004; 89(5):F394-F398. LOE 2 **Abstract:** BACKGROUND: The role of nasal continuous positive airways pressure (nCPAP) in the management of respiratory distress syndrome in preterm infants is not completely defined. OBJECTIVE: To evaluate the benefits and risks of prophylactic nCPAP in infants of 28-31 weeks gestation. DESIGN: Multicentre randomised controlled clinical trial. SETTING: Seventeen Italian neonatal intensive care units. PATIENTS: A total of 230 newborns of 28-31 weeks gestation, not intubated in the delivery room and without major malformations, were randomly assigned to prophylactic or rescue nCPAP. INTERVENTIONS: Prophylactic nCPAP was started within 30 minutes of birth, irrespective of oxygen requirement and clinical status. Rescue nCPAP was started when Fio₂ requirement was > 0.4, for more than 30 minutes, to maintain transcutaneous oxygen saturation between 93% and 96%. Exogenous surfactant was given when Fio₂ requirement was > 0.4 in nCPAP in the presence of radiological signs of respiratory distress syndrome. MAIN OUTCOME MEASURES: Primary end point: need for exogenous surfactant. Secondary end points: need for mechanical ventilation and incidence of air leaks. RESULTS: Surfactant was needed by 22.6% in the prophylaxis group and 21.7% in the rescue group. Mechanical ventilation was required by 12.2% in both the prophylaxis and rescue group. The incidence of air leaks was 2.6% in both groups. More than 80% of both groups had received prenatal steroids. CONCLUSIONS: In newborns of 28-31 weeks gestation, there is no greater benefit in giving prophylactic nCPAP than in starting nCPAP when the oxygen requirement increases to a Fio₂ > 0.4

Level of evidence 2

Evidence-Neutral

Quality Fair

25. Thome U, Topfer A, Schaller P, Pohlandt F. The effect of positive end expiratory pressure, peak inspiratory pressure, and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. *Eur J Pediatr* 1998; 157(10):831-837. LOE 7 **Abstract:** In mechanical ventilation of preterm infants, positive endexpiratory pressure (PEEP) is widely used to prevent alveolar collapse, maintain functional residual capacity (FRC) and improve oxygenation. Prolongation of inspiratory time (ti) and increase of peak inspiratory pressure (PIP) are also used for this purpose. We investigated the effect of variations of PEEP, PIP and ti on FRC in ten infants with hyaline membrane disease and onset of bronchopulmonary dysplasia (BPD, n = 7), pulmonary hypertension (n = 1), pulmonary hypoplasia (n = 1) or severe BPD (n = 1) (gestational age 24-39 weeks, median 26 weeks; birth weight 590-2960 g, 785 g; chronological age 7 84 days, 19 days; weight 689-4650 g, 1185 g). FRC, measured using the sulphur hexafluoride washout technique, was between 6.2 and 48.3 ml/kg (median 21.5 ml/kg). PEEP was changed stepwise 2-5 times in each patient (median 3) and mean airway pressure (MAP) was modified independently of PEEP by changing PIP 0 2 times (median 1) and ti 0(2 times (median 2). Changes of FRC correlated well with modifications of PEEP in each patient (r = 0.90, range 0.71 0.99). The slope factors of linear correlations had a median value of 2.94 ml/cm H₂O per kg, which was significantly different from zero (P < 0.01) and significantly higher than the slope factors of linear correlations between FRC and MAP after modifications of PIP or ti (P < 0.01). The latter two were statistically not different from zero. The quotients ΔFRC/ΔMAP were significantly higher after adjustments of PEEP than after adjustments of PIP or ti (P < 0.01). The time lag between the change of PEEP and the stabilization of FRC on a new level ranged from 2 to 14 min (median 5). CONCLUSION: FRC is mainly determined by PEEP but not by PIP or ti. Stabilization of FRC after a change of PEEP can last up to 14 min. Its duration is unpredictable and has to be waited for when testing pulmonary function in ventilated preterm infants

Level of evidence 7

Evidence- neutral

Quality Fair

26. Thomson MA, et al. Early nasal CPAP + prophylactic surfactant for neonates at risk of RDS. The IFDAS trial. *Ped Res* 2001;304. LOE 6
27. Thomson MA. Continuous positive airway pressure and surfactant; combined data from animal experiments and clinical trials. *Biol Neonate* 2002; 81 Suppl 1:16-19. LOE 6 **Abstract:** Bronchopulmonary dysplasia (BPD) remains a cause of considerable morbidity for the preterm infant. Ventilation is a primary risk factor. This review discusses the rationale for combining surfactant and nasal continuous positive airway pressure (nCPAP) using evidence from both clinical and animal studies. The early application of nCPAP with or without surfactant is safe and reduces the need for mechanical ventilation. Combining nCPAP with surfactant results in dramatically improved lung structure in a primate model of BPD, but still does not allow for normal alveolarization. BPD is a complex condition resulting from the interaction of many factors. Experimental evaluation of nCPAP in appropriate animal models will allow new strategies for prevention and treatment of BPD to be developed

Level of evidence 6

Evidence- neutral

Quality Fair

28. Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Ped* 2000; 105(6):1194-1201. LOE 4 **Abstract:** OBJECTIVE: To explore the hypothesis that variation in respiratory management among newborn intensive care units (NICUs) explains differences in chronic lung disease (CLD) rates. DESIGN: Case-cohort study. SETTING: NICUs at 1 medical center in New York (Babies' and Children's Hospital [Babies']) and 2 in Boston (Beth Israel Hospital and Brigham and Women's Hospital [Boston]). STUDY POPULATION: Four hundred fifty-two infants born at 500 to 1500 g birth weight between January 1991 and December 1993, who were enrolled in an epidemiologic study of neonatal intracranial white matter disorders. CASE DEFINITION: Supplemental oxygen required at 36 weeks' postmenstrual age. RESULTS: The prevalence rates of CLD differed substantially between the centers: 4% at Babies' and 22% at the 2 Boston hospitals, despite similar mortality rates. Initial respiratory management at Boston was more likely than at Babies' to include mechanical ventilation (75% vs 29%) and surfactant treatment (45% vs 10%). Case and control infants at Babies' were more likely than were those at Boston to have higher partial pressure of carbon dioxide and lower pH values on arterial blood gases. However, measures of oxygenation and ventilator settings among case and control infants were similar at the 2 medical centers in time-oriented logistic regression analyses. In multivariate logistic regression analyses, the initiation of mechanical ventilation was associated with increased risk of CLD: after adjusting for other potential confounding factors, the odds ratios for mechanical ventilation were 13.4 on day of birth, 9.6 on days 1 to 3, and 6.3 on days 4 to 7. Among ventilated infants, CLD risk was elevated for maximum peak inspiratory pressure >25 and maximum fraction of inspired oxygen = 1.0 on the day of birth, lowest peak inspiratory pressure >20 and maximum partial pressure of carbon dioxide >50 on days 1 to 3, and lowest white blood count <8 K on days 4 to 7. Even after adjusting for white blood count <8 K and the 4 respiratory care variables, infants in Boston continued to be at increased risk of CLD, compared with premature infants at Babies' Hospital. CONCLUSION: In multivariate analyses, a number of specific measures of respiratory care practice during the first postnatal week were associated with the risk of a very low birth weight infant developing CLD. However, after adjusting for baseline risk, most of the increased risk of CLD among very low birth weight infants hospitalized at 2 Boston NICUs, compared with those at Babies' Hospital, was explained simply by the initiation of mechanical ventilation

Level of evidence 4

Evidence-supportive

Quality Fair