WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)
Benjamin Stenson

Clinical question.

In depressed neonates requiring positive pressure ventilation (P) does the administration of longer inspiratory times, higher inflation pressures, use of PEEP (I) as compared to standard management (C) improve outcome (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? yes

State if this is a proposed new topic or revision of existing worksheet: This is a new specific question, although the items included in the question were reviewed as part of a larger worksheet for C2005.

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

25/09/09
1. I searched all the titles in the neonatal Cochrane reviews. 1 review identified.
2. I pulled all studies identified as relevant in the previous C2005 worksheet and all other relevant articles already known to me.
3. I searched Pub med (medline)
a. CPAP and newborn – no other limits 534 hits. All titles reviewed. 3 additional articles selected.
b. PEEP and newborn – no other limits 2424 hits. Limit to abstracts 1518 hits, all titles reviewed 2 additional studies identified.
c. Inspiration time and newborn, limit to records with abstracts 812 hits. No additional studies identified.
d. Sustained inflation and newborn 21 hits. No new studies identified.
e. Inflation pressure and newborn 237 hits. 2 extra studies identified.
f. Resuscitation and newborn, limited to records with abstracts 6054 hits. No additional studies identified.
A further 3 relevant articles were identified by searching for other articles by Morley C.

Searched EMBASE 1980-2008
a. CPAP (keyword and all related terms) 15692 hits, limit to abstracts 11499, limit to infant 144. Titles and abstracts reviewed. 1 additional study identified.
b. PEEP (keyword plus all related terms) 15874 hits, limit to abstracts 11676, limit to infant 148. Titles and abstracts reviewed. Additional 4 studies added.
c. Inspiratory time (keyword, plus lung ventilation or artificial ventilation or tidal volume) 42724 hits, limit to Abstract 32075 hits, limit to infant 710. Titles and abstracts reviewed. No additional papers selected.
d. sustained inflation (all terms) 58 hits. No additional papers selected.
e. Inflation pressure (keyword, or lung injury or lung pressure or lung inflation) 18224 hits. Limit to abstract 14925 hits, limit to infant 71 hits. Titles and abstracts reviewed. No additional studies identified.
f. Resuscitation (all terms) 32860, limit to, abstract 23175, infant 253. Titles and abstracts reviewed. No additional studies identified.

• State inclusion and exclusion criteria

All studies, human or animal that were describing the initial inflation of the lungs after birth with positive pressure and might include clinically relevant outcome data regarding the choice of inflation time or pressure and or the use of positive end-expiratory pressure were considered. Because of variable interpretation of what might constitute positive pressure ventilation, randomised studies describing methods of applying any positive pressure support to the lungs immediately after birth in the delivery room were also considered. Single case reports and review articles were not included.
• Number of articles/sources meeting criteria for further review: 57 – 33 ultimately accepted as relevant to the worksheet and 24 not included after review. 7 new relevant articles published since 2005.
# Summary of evidence

## Evidence Supporting Clinical Question

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When the lungs require to be inflated after birth by positive pressure ventilation because the infant has not breathed spontaneously the most efficient way to do this is controversial. There is still remarkably little high quality evidence to guide practice. This worksheet considers whether the use of longer inspiratory times, higher inflation pressures or positive end expiratory pressure (PEEP) improve outcome.

To evaluate the evidence these measures must be considered separately but in the clinical setting they are seldom administered in isolation. Sometimes defining the contribution of one or other component of a package of measures described in a study is not possible. It is relevant to separate the care of term and preterm newborns to some degree as often the clinical situation and priorities are different. In the case of the apnoeic term infant, the principal concern is asphyxia, the priority is to establish adequate oxygenation rapidly and the likelihood of causing lasting pulmonary injury with the measures chosen is small. In the preterm infant apnoea is less likely to be due to asphyxia. There is consequently less urgency in most cases and there may be lasting pulmonary consequences to overzealous intervention.

**Longer inspiratory times**
No randomised controlled trials or case-control studies of longer versus shorter inspiratory times during neonatal resuscitation in term infants were identified, so there is no level 1 to 3 evidence to guide practice in this group of infants.

In 1981 Vyas et al described a case series of 9 infants in which a prolonged inflation of 5 seconds was used for the first breath only; subsequent breaths had an inflation time of 1 second. In four patients, the peak inspiratory pressure of the first inflation was set at 30 cm H\(_2\)O and maintained for 5 seconds; in five patients, the peak inspiratory pressure of the first inflation was increased to 30 cm H\(_2\)O slowly over 3 to 5 seconds. The infants began forming a functional residual capacity with the first breath. Gas was still entering the lungs at the end of the 5 second inflation. In 1987 Hoskyns et al described a further case series of 22 infants where an initial sustained inflation of 2-5 seconds had been used, followed by subsequent inflations at a shorter inspiratory time. In this study the inflation pressure was varied but again did not exceed 30cmH\(_2\)O. In both of these studies effective aeration of the lungs began with the first breath. The fact that gas was still entering the lungs after 5 seconds at constant inflation pressure indicates that the time constant of the lung during initial aeration is very long and that to achieve similar inflation volumes with a shorter inspiration time would require higher pressures. This was the experience in other case series describing shorter inspiratory times (Hull, Upton) where sometimes pressures of 40cmH\(_2\)O were needed. Once the lung was recruited similar volumes could be exchanged with lower pressures (Upton). With shorter inspiratory times, lung recruitment occurred gradually, with the volumes of gas entering the lung with each breath increasing progressively over 30 to 60 seconds. (Boon, Hull).

These limited data suggest that the use of sustained inflations during resuscitation in term infants may enable effective ventilation to be established slightly more quickly than when shorter inspiratory times are used (LOE 4). This may be important because Palme-Kilander demonstrated in human infants that, as in animal studies, improvement in heart rate during neonatal resuscitation usually occurs within 15 seconds of the onset of effective ventilation and because algorithms for neonatal resuscitations typically incorporate time-based guidance.

Three randomised controlled trials have evaluated the use of sustained inflations during initial lung inflation in newborn preterm infants. Harling et al performed a small trial in which 52 infants <31 weeks gestation were randomised to receive either a 5 second or a 2 second initial inflation by t-piece. Subsequent inflations in both groups were the same. Both groups got PEEP between inflations. There was no difference between groups in...
Apgar scores, or need for intubation. There was no difference in lung inflammation demonstrable during subsequent days. Lindner et al (2005) randomised 61 infants of 25-28+6 weeks of gestation to receive their initial lung aeration by 15 second sustained inflation followed by IPPV or simply by IPPV with short inspiratory time. Both groups received their inflations by nasopharyngeal tube and both received PEEP between inflations. The aim was to stabilise the infants without intubation and there was no statistically significant difference between groups in this outcome. In a larger study Te Pas et al (2007) randomised 227 preterm infants 25-32 weeks gestation to a similar protocol of sustained nasopharyngeal inflation followed by IPPV with PEEP or to conventional mask IPPV without PEEP. Fewer infants randomised to sustained inflation and IPPV with PEEP required intubation and fewer of them developed BPD. With the intervention group differing in 2 important respects (both sustained inflation and provision of PEEP during initial ventilation) from the control group it cannot be concluded that it was the sustained inflation that was the key component of this strategy.

Several animal studies have examined the effects of rapid lung recruitment at birth in immature animals using sustained inflations. Five large or moderate volume sustained inflations generated with high pressure and without intervening PEEP produced histological lung injury and persisting impairment in gas exchange in immature lambs (Bjorklund 1997, Bjorklund 2001). Prior treatment of the lungs with surfactant did not prevent this injury (Ingimarsson). Klopping-Ketelaars et al randomised immature lambs to receive 4 pressure-limited 5 second sustained inflations, with intervening PEEP of 5cmH2O before commencing pressure-controlled ventilation with PEEP. Control lambs were simply commenced on the same pressure-controlled ventilation with PEEP. The sustained inflations with PEEP, before starting regular pressure controlled ventilation at conventional inspiratory time did not improve gas exchange or lung compliance.

Two further studies have been published recently by te Pas et al examining the use of sustained inflations in preterm rabbits delivered at 28 days of gestation. In one study (te Pas 2009), animals were ventilated with an inflation pressure of 35 cmH2O during initial stabilisation and were randomised to receive zero PEEP, 5cmH2O PEEP, zero PEEP but initial 20 second inflation or 5cmH2O PEEP and an initial 20cmH2O inflation. Animals who did not receive PEEP did not establish FRC regardless of the presence or absence of a sustained inflation. The use of a 20second inflation for the first breath established FRC with the first inflation and this was retained in the presence of PEEP. Animals who were ventilated with PEEP but without a sustained inflation took around 16 inflations to establish a similar FRC to that established in a single inflation in the animals exposed to a sustained inflation plus PEEP. In a second study (tePas 2009b), again in 28 day preterm rabbits, the duration of the sustained inflation required to establish FRC was investigated. Animals were ventilated with an inflation pressure of 35 cmH2O and all received 5cmH2O of PEEP throughout. Ventilation commenced with a sustained inflation of 1,5,10, or 20 seconds. FRC was established with the first sustained 20 second inflation. Shorter sustained inflations established less FRC and this then built up further with successive inflations. Animals with a 1 or 5 second first inflation took around 16 subsequent non-sustained inflations to reach FRC comparable with that obtained with the single 20 second sustained inflation. It took an average of 14 seconds of sustained inflation for 90% of the final FRC to be established.

These data are consistent with the limited observations in term human infants and the studies in preterm infants. It is likely that use of a sustained inflation will establish lung inflation a little more rapidly than conventional IPPV in term infants. This is also true in the case of immature lungs but the FRC will not be retained unless PEEP is also applied between breaths. If sustained inflations are not used the lungs will be recruited gradually with successive inflations and this may take around 30 seconds. Whether this more rapid establishment of FRC obtainable with sustained inflations results in important improvements in clinical outcome is unknown. Studies so far in immature human infants given pressure controlled ventilation with PEEP from birth have not demonstrated any convincing or clinically appealing advantage to the use of sustained inflations (LOE 1, Linder 2005). Animal studies suggest that vigorous recruitment of immature lungs with high pressures immediately after delivery may be harmful (LOE5 Bjorklund 1997, 2001). Sustained
inflations at controlled pressure, with intervening PEEP do not appear to be harmful (LOE 1 Lindner 2005, te Pas 2007, LOE 5 te Pas 2009, 2009b) and may allow successful transition to be achieved without intubation more often in preterm infants (LOE 1 te Pas 2007).

Higher pressures

No randomised controlled trials or case-control studies comparing different initial inflation pressures were identified either for term or for preterm infants. Several case series reported inflation pressures that were effective.

Most reports indicate that term infants can usually be resuscitated using an inflation pressure of around 30cmH₂O (Hull, Boon, Vyas, Field, Hoskyns 1987). Sometimes this pressure is not adequate to move the chest initially and higher pressures may be required (Hull, Upton, Palme-Kilander).

Case series in preterm infants have tended to obtain satisfactory responses with lower pressures. Hird et al studied 70 preterm infants 24-36 weeks gestation (median 28). They used an initial inflation pressure of 16cmH₂O and increased it in increments of 2 cmH₂O until satisfactory chest movement was obtained. The median pressure required was 22cmH₂O. Lindner et al (1999) used an initial inflation pressure of 20cmH₂O and increased to 25 if this did not produce a satisfactory response. Hoskyns et al (1987b) used a mean pressure of 27cmH₂O. Menakaya et al used a ventilator or an anaesthetic re-breathing bag to deliver initial lung aeration in 24 preterm infants <27 weeks gestation and did so using a mean inflation pressure of 24cmH₂O.

Hillman et al ventilated preterm lambs with tidal volume 15ml/kg without PEEP for 15 minutes from birth to simulate initial stabilisation in preterm infants. They found that this produced significant lung injury which then worsened during subsequent pressure controlled ventilation with PEEP. Bjorklund et al (1997,2001) found that high pressure, large and moderate volume inflations after birth caused lung injury, reduced lung compliance and gas exchange impairment. Wada et al found that ventilation with large tidal volumes for 30 minutes after birth caused lung injury and reduced lung compliance.

There is no evidence to support the use of inflation pressures higher than those that are necessary to achieve chest expansion. This can usually be achieved in term infants with an inflation pressure or 30cmH₂O (LOE 4) and in preterm infants with pressures of 20-25cmH₂O (LOE 4 Hird, Lindner, Hoskyns 1987b, Menakaya). Occasionally higher pressures are required (LOE 4 Hull, Boon, Vyas, Field, Hoskyns). Ventilation at birth with high pressures or volumes for a few minutes causes lung injury, impaired gas exchange and reduced lung compliance in immature animals (LOE 5 Bjorklund 1997, 2001).

PEEP

Few would dispute the importance of positive end-expiratory pressure during ongoing ventilation in intubated babies or the value of CPAP in non-intubated babies with respiratory distress. Much of the initial IPPV performed in the delivery room is by mask, with no impedance to normal laryngeal function. Intubated IPPV in the delivery room is usually of short duration before the infant is admitted to the neonatal unit. Provision of PEEP in the delivery room requires special equipment. The focus within this worksheet is therefore to review the evidence for PEEP being of demonstrable benefit during initial stabilisation at birth before admission to the neonatal unit rather than to look at the wider use of PEEP.

A Cochrane review published in 2004 found no suitable trials to examine the question whether PEEP during neonatal resuscitation reduces mortality or morbidity (O'Donnell et al). Two small trials have since been published examining the role of PEEP in preterm infants in the delivery room. Te Pas et al used PEEP as part of a combined strategy that included a sustained inflation and nasal IPPV. The control group got no PEEP but because of the package of interventions the role of PEEP cannot be determined. Later studies in preterm animals, discussed below, suggest that the PEEP may have been more important than the sustained inflation (te
Pas 2009, 2009b Siew 2009). Finer et al randomised infants to receive PEEP or not during initial stabilisation of preterm infants <28 weeks gestation. 104 infants were studied in 8 centres. There was no significant difference in the number of infants who required intubation in the delivery room.

At least 11 studies in immature animals have now examined the role of PEEP during initial ventilation after delivery using protocols analogous to the delivery room care of preterm infants. Nilsson et al ventilated preterm rabbits for 10 minutes after birth with or without PEEP with a set tidal volume or set inflation pressure and found that when PEEP was used there was less lung injury and better lung compliance. Probyn et al performed 2 similar studies which showed that animals treated with PEEP had improved lung mechanics and oxygenation during the first 15 minutes after birth. Animals exposed to PEEP of 12cmH$_2$O suffered from pneumothoraces. Crossley et al found that PEEP improved oxygenation during initial stabilisation of preterm animals whether or not antenatal steroids and surfactant had been administered. In contrast, Polglase et al (2008) ventilated immature lambs with volume guarantee with or without PEEP for the first 15 minutes and then continued pressure controlled ventilation with PEEP until 2 hours and were unable to demonstrate consistent beneficial effects of PEEP during initial ventilation on lung injury or gas exchange. In order to deliver the set inflation volumes to fluid filled lungs during their initial aeration high pressures were required and this may be a caution against the use of volume targeted initial stabilisation in preterm infants as Bjorklund et al also found lung injury when high pressures were used to generate the first 5 inflations at volumes of 8ml/kg. Johe et al treated moderately preterm lambs that had received antenatal steroids and were capable of breathing independently with either pressure controlled ventilation with PEEP or with CPAP. Animals treated with CPAP developed less lung injury. Polglase et al (2005, 2009) found that PEEP improved oxygenation during initial lung aeration in preterm lambs but that it also reduced pulmonary blood flow and pulmonary vascular resistance at PEEP levels of 8 and 12 cmH$_2$O. Siew et ventilated preterm rabbits from birth with or without PEEP and documented the establishment of FRC during the first 2 minutes of ventilation. As in the animal studies by te Pas, the provision of PEEP allowed a rapid progressive improvement in FRC with the initial breaths and animals ventilated without PEEP did not establish FRC.

So there is no evidence to determine the value of PEEP during resuscitation of term infants. In preterm infants one small study did not show a benefit from PEEP during initial stabilisation in reducing the number of infants who required intubation in the delivery room (LOE 2 Finer). The use of PEEP during initial stabilisation after birth in immature animals improves oxygenation, lung compliance and FRC and reduces lung injury (LOE5, Nilsson, Probyn, Crossley, te Pas 2009, 2009b, Siew) but high levels of PEEP reduce pulmonary blood flow and carry a risk of pneumothorax (LOE5 Polgalse 2005, 2009, Probyn).

**Acknowledgements:**
Citation List


LOE: 5. Quality: Good. Direction of support: Against (sustained inflations). Outcome: Lung injury (Li), Lung compliance (Crs). Magnitude of effect: Not possible to quantify meaningfully as not a human study. Summary: 5 pairs of 128 day lambs were delivered and, with the umbilical circulation maintained, were prevented from breathing whilst they were intubated and cannulated. By random allocation, one of each pair then received 5 large volume 5-second sustained lung inflations and was then placed on pressure controlled ventilation with PEEP. The sustained inflation were delivered by Laerdal bag with the pop-off occluded. (pressures of 50-70cmH2O were generated). The other lamb was placed directly on pressure controlled ventilation with PEEP. Lung mechanics were measured and then both groups were treated with surfactant at 30 mins. Ventilation continued for 4 hours. Bagged lambs showed minimal response to surfactant and had much lower lung compliance over 4 hours than un-bagged lambs. Bagged lambs had more histological lung injury and poorer lung aeration than controls. This study suggests that when immature lungs are inflated at birth using very large volume inflations (35-40 ml/kg) that are sustained to 5 seconds, significant injury is produced that results in functional impairment over several hours. Because the inflations were both large volume and sustained, it cannot be determined from the protocol whether one or other aspect was most relevant. It must be noted that these inflations required very high pressures to generate them and these pressures would only be produced during human resuscitation in exceptional circumstances.


LOE: 5 Quality: Good. Direction of effect: Against (sustained inflations). Outcome: Lung injury (Li), Lung compliance (Crs). Magnitude of effect: Not possible to quantify meaningfully as not a human study. Summary: Randomised study in ten 127 day lambs. Animals were delivered and, with the umbilical circulation maintained, were prevented from breathing whilst they were intubated and cannulated. By random allocation, they then received either no sustained inflations (4 lambs) or 5 sustained inflations lasting 5-seconds at volumes of 8, 16, or 32 ml/kg (2 lambs each). All lambs were then treated with surfactant and placed on pressure controlled ventilation with PEEP for 4 hours. 8ml/kg inflations required an inflation pressure of 30-40cmH2O. 16ml/kg - 48-58cmH2O and 32ml/kg 60cmH2O. There was a dose response effect of these sustained inflations on lung injury and compliance with both getting worse as the volume of the sustained inflations increased. Sustained Inflations of 8ml/kg at pressures of 30-40cmH2O without PEEP are analogous to what might be achieved in human infants "resuscitated" by bag using sustained inflations and this appears to be deleterious in comparison with starting pressure controlled ventilation with PEEP and not to have any benefits.


LOE: 4 Quality: good. Direction of effect: Positive (increased inflation pressure) Outcome: Tidal volume (Vt). Magnitude of effect: N/A Summary: Study of the response of human infants to resuscitation at birth. 20 (mostly term) infants delivered by GA section who did not breathe for themselves were intubated and got measurements of pressure and volume during their initial lung inflations. A t-piece system was used without
PEEP with an inspiratory time of 1 second. The infants all had an opening pressure that had to be exceeded before any volume entered their lungs. This ranged from 13-30cmH$_2$O and was usually nearer 30. Tidal volume increased over successive breaths during the first 30 seconds. Establishment of FRC was variable. Conclusion: apnoeic term infants ventilated without sustained inflation need pressures of around 30cmH$_2$O and have tidal volumes that gradually increase over 30 seconds.


LOE: 5. Quality Good (for PEEP). Outcome - oxygenation (Ox) Direction of effect positive. Magnitude of effect N/A. Summary: This is a study in 125 day lambs (roughly equivalent in maturity to 26 week gestation infants). The effects of ventilation with PEEP on gas exchange immediately after birth were measured in 4 groups (AN steroids, Curosurf, Both, Neither). The animals were cannulated and intubated before delivery, with the fetal circulation intact so that the protocol could mimic the immediate neonatal period. All animals were then placed on volume guarantee ventilation with PEEP 4 for 5 minutes and then the surfactant treated animals were treated. All animals were investigated at a series of PEEP levels (0,4,8,10 in random order). The role of PEEP during lung initial aeration after birth cannot be evaluated because all animals received it. However this study is relevant to delivery room management because different PEEP levels were investigated from 5 minutes onwards before comparable infants would be transferred to the neonatal unit. All levels of PEEP greater than 0 improved oxygenation in all groups, including those that had received both antenatal steroids and surfactant. The effects of this protocol on lung injury parameters was not assessed.


LOE:2 Quality: Fair. Outcome: tidal volume (vt), inflation pressure (PIP). Direction of effect: positive. magnitude of effect: N/A. Summary: the authors compared 5 different manual ventilation devices in apnoeic C/section delivered mature infants, aiming to produce high pressure sustained inflations with each. Inflations were around 1 second long for all devices. Devices with bigger bags produced higher pressures and these were associated with higher expiratory tidal volumes during the first 5 breaths. The mean birth weight of the subjects was 3240g. An inflation pressure of 30cmH$_2$O produced a mean exhaled tidal volume of 15ml. Lower pressures were associated with lower volumes. If one of the aims of initial lung inflation is to achieve satisfactory tidal ventilation then pressures of 30cmH$_2$O appear to do achieve this more effectively during the first 5 breaths in term infants than lower pressures.


LOE: 1. Quality: good. Outcome: DR intubation (DRint), intubation in the first 7 days (Int7), Apgar score (As). Direction of effect: neutral (for PEEP) magnitude of effect:N/A. Feasibility trial in 8 centres of use of CPAP and or PEEP during initial stabilisation of preterm infants <28 weeks gestation versus no CPAP or PEEP. Aim was to manage infants on CPAP and not intubate them. Infants were stabilised with mask and neopuff and were randomised to get either 0 or 5cmH$_2$O of CPAP and or PEEP if PPV was required. 104 infants studied. There was no statistically significant difference in the number of infants who required PPV, or intubation in the DR , or intubation during the first 7 days. 45% of infants were intubated in the DR and 80% in the first 7 days. Use of CPAP from birth and PEEP if PPV was required did not reduce the number of preterm
infants <28 weeks gestation who required to be intubated in the delivery room. There was no significant difference in 1 or 5 minute Apgar scores. Small sample so inadequate power to resolve small and moderate differences between groups.


LOE:1 Quality: Fair Outcome: lung inflammation (inf), Apgar score (As), intubation (Int). Direction of support: neutral (for sustained inflations). Magnitude of effect: N/A. Summary: 52 infants <31 weeks gestation who needed PPV at birth were randomised to receive either a 5 second or a 2 second inflation for their first breath. All PPV was by t-piece and mask and all infants received PEEP. There was no difference in lung inflammation, intubation rates or Apgar scores between the 2 groups. Small study with very little power. No benefit demonstrated for a single 5 second sustained inflation in preterm infants.


LOE: 5. Quality: good. Outcome: Lung injury (li). Direction of effect: against (high pressures). Magnitude of effect: n/a . Summary: Experiment on 129 day lambs. Evaluated whether lung injury was caused by a 15 minute period of ventilation to VT of 15ml/kg without PEEP beginning with initial aeration. Measured additive effects of subsequent controlled ventilation with PEEP. 15 mins of high VT ventilation without PEEP from birth injured the lung and this injury was then worsened by subsequent controlled ventilation with PEEP. The pressure required to achieve this VT were 50cmH\textsubscript{2}O. Vigorous ventilation of immature lungs at birth without PEEP is rapidly damaging.


LOE: 4. Quality: good: Outcome satisfactory clinical lung inflation and response to resuscitation. Direction of effect: against (higher pressures). Magnitude of effect: N/A. Summary: Preterm babies requiring PPV due to inadequate respiration at birth were intubated and given PPV with PIP of 16cmH\textsubscript{2}O. with ti 2.0 seconds by equivalent of a t-piece. PIP was then increased in increments of 2 cmH\textsubscript{2}O until chest expansion was obtained. 70 infants 24-36 weeks (median 28). Median inflation pressure was 22.8cmH\textsubscript{2}O. No infant required more than 30. Most preterm infants can be resuscitated with an initial inflation pressure less than 30.


LOE: 4. Quality: poor. Outcome: tidal volume. Direction of effect: neutral. Magnitude of effect n/a. Summary: preterm and term infants could be resuscitated with a mean airway pressure of around 27 cmH\textsubscript{2}O as determined by measurements of tidal volume. Relative merits of higher or lower pressures or PEEP or sustained inflations were not assessed.

LOE: 4. Quality: poor: Outcome tidal volume (Vt) Direction of effect positive (for higher pressures) magnitude of effect n/a. Summary: Described mask resuscitation of term infants using a t-piece system. Single sustained (up to 5s) inflation followed by shorter inflations. Pressure varied to provide a range of pressures up to 30cmH\(_2\)O. 22 infants. Pressures of < 25cmH\(_2\)O were not usually successful in achieving adequate expansion with the first 3 breaths. Higher pressures usually were.


LOE 4: Quality poor: Outcome tidal volume VT, direction of effect positive. Magnitude N/A. Summary Endotracheal resuscitation of term infants who were apnoeic after birth using a pump. Tidal volumes increased gradually over the first minute. FRC varied in terms of when it was retained but was particularly related to the onset of spontaneous breathing. Pressure of 30cmH\(_2\)O was adequate to establish tidal ventilation for most infants. Sustained inflations were not used.


LOE 5. Quality good: outcome: lung mechanics, lung injury. Direction of support against (increased pressures and sustained inflations). Magnitude of effect n/a - not human study. Summary: 127 day lambs were ventilated with pressure controlled ventilation with PEEP and treated with surfactant. The lambs were given 5 sustained (5s) inflations of 16ml/kg, without intervening PEP. Either before or after surfactant and at birth or at 10 mins or at 60 mins. Lambs given sustained inflations at birth whether before or after surfactant had worse lung mechanics and more lung injury than those given them later. vigorous sustained inflations without PEEP are injurious at birth in comparison with pressure controlled ventilation with PEEP. Surfactant before the first breath is not protective against the harm of vigorous lung recruitment at birth.


LOE:5. Quality: good. Outcome: lung injury (li). Direction of support (for CPAP) positive. Magnitude of effect: n/a. Summary: 134 day lambs were delivered, intubated and then given bubble CPAP or ventilation with PEEP. Ventilated lungs showed substantially more neutrophil influx. In immature animals capable of breathing spontaneously on CPAP ventilation from birth induced more injury over 2 hours than CPAP from birth.


LOE: 5. Quality: Good. Outcome oxygenation and lung compliance (CRS). Direction of effect neutral. Magnitude of effect n/a Summary: 131 day lambs were randomised to receive 4 sustained inflations (5s) at pressures 35/5 or not and then placed on pressure controlled ventilation with PEEP. There was no difference
between groups in gas exchange or histological lung appearances or static compliance. Sustained inflations with PEEP offered no advantage in preterm lambs over pressure controlled ventilation with PEEP without the sustained inflations.


**LOE 1.** Quality good. Outcome intubation (int) direction of effect neutral (for sustained inflations). Effect size - none. Summary: RCT in 61 infants 25-28+6 weeks gestation. 15 second sustained inflation or IPPV both given nasally. Pressure of each increased 20-25-30 if not effective. Intubation if still not effective. Both groups got PEEP. No significant difference in intubation rates. This is the only RCT of sustained inflations that allows their effect to be separated from other measures and it shows no advantage to them during initial stabilization in comparison with IPPV when both are given via a nasopharyngeal tube with accompanying PEEP.


**LOE 3.** Quality good. Outcome Direction of effect supportive magnitude of effect n/a as not an RCT. Intubation appeared to be reduced. Summary: Study with historical controls. Introduced a policy of aiming to avoid intubation. Instead gave a sustained (15s) nasopharyngeal inflation at 20 cmH₂O and again at 25 if necessary. Then nasal CPAP. Need for intubation in the DR decreased in comparison with historical controls. Most infants could be stabilised with inflation pressure of 20-25. ? success due to nasal IPPV, nasal CPAP or sustained nasal inflation Later trial suggestss that the sustained inflation was not important as nasal IPPPV was just as effective.


**LOE 1 Quality moderate.** Outcome successful stabilization. Outcome inflation pressure. Effect size none. Summary: Small RCT comparing use of a ventilator giving set PIP and PEEP to use of an anaesthetic bag for initial stabilization in preterm infants. The mean inflation pressure required was 24cmH₂O. Volume guarantee was not effective in limiting exhaled tidal volume to the set value and this was not different to the anaesthetic bag.


**LOE 5.** Quality good. Outcome lung compliance (Crs) and lung injury (Li). Direction of effect (of PEEP) positive. Magnitude of effect n/a. Summary: 27 day rabbits were tracheotomised on delivery and were divided into 4 groups ventilated at VT10 or PIP 35 with PEEP 0 or PEEP 5 for a 10 minute period. Inflation pressures required for VT 10 were lower with PEEP. VT was higher for set PIP in PEEP animals. Histological lung injury was reduced in the animals treated with PEEP. Valuable because only 10 minutes ventilation so relevant to initial stabilisation.

LoE 1 quality low. Summary: No suitable trials


LOE 4. Quality moderate. Outcome n/a for this worksheet. Summary: This paper doesn’t inform the subject of this worksheet. Term and preterm infants were mask ventilated at birth using 50% oxygen. Carbon dioxide output, oxygen saturation, heart rate, oesophageal and airway pressure were measured. Heart rate and saturation increases coincided with effective ventilation measured by CO₂ output. This occurred within 15 seconds at a time when oxygen saturation was around 65%. HR rose transiently without effective ventilation in some infants.


LOE 5 Quality good. Outcome pulmonary blood flow. Direction of support negative. Increasing PEEP during initial ventilation after delivery reduced pulmonary blood flow in preterm lambs.


LOE 5. Quality good. Outcomes Lung injury (Li), oxygenation (Ox). Direction of effect neutral for PEEP, negative for increased pressures., size of effect n/a. Summary. 133 day lambs randomized from birth (7 animals per group) to ventilation with different tidal volumes (8 or 15ml/kg) and with or without PEEP for a 15 minute intervention period. All were then ventilated for a further 1 hr 45 mins with vt<10 and PEEP 5. All groups showed similar but minimal histological injury. No consistent effect of PEEP was noted on gas exchange after the 15 minute intervention or injury at the end of the study. The intervention was analogous to initial stabilisation of preterm infants with volume control. The sample size was small.. The degree of immaturity in terms of lung maturation was moderate rather than extreme. The authors speculated that using volume controlled ventilation might have been an issue as it result in high initial pressures in all groups and may not be the best approach to initial aeration.


LOE 5. Quality good. Outcome pbf. Direction of effect negative. PEEP of 8 and 12 decreased pulmonary blood flow in newborn preterm lambs

LOE 5. Quality good. Outcome. Oxygenation (Ox), pntx. Direction of effect for PEEP positive for oxygenation, negative for pneumothorax. Magnitude of effect n/a. Summary: Tracheotomised 125 day lambs were ventilated from birth with volume guarantee set to 5ml/kg and with PEEP 0, 4, 8, or 12. Measurements were made during the first 15 minutes and the subsequent 2 hours. At 15 minutes Compliance of the lungs was better at 4 and 8 than at 0 PEEP. Oxygenation was better at 8 and 12 than at 4. 12 resulted in pneumothoraces. Arterial BP was highest at PEEP 8. At 15 minutes the lowest PIP was at PEEP 4 and the highest PIP was at PEEP 12. Lowest FiO² at 15 minutes was at PEEP 8. Lambs with 0 PEEP were desaturated at 15 minutes compared with the other groups. PCO² was lowest with PEEP 4. Incorporating a PEEP of 4-8cmH₂O during initial stabilisation at birth was associated with improved oxygenation and lung mechanics.


LOE 5. Quality: good. Outcome. Oxygenation (Ox). Direction of effect positive. Magnitude of effect n/a. Summary: 125 day lambs were randomised to different resuscitation protocols during the first 15 minutes after delivery. Laerdal bag no PEEP, low VT (5ml/kg) ventilation with PEEP 8. Higher VT (10ml/kg) ventilation with PEEP. Ventilation was then continued for 2 hours. At the end of 15 minutes stabilisation the VT10 lambs were hypocarbic compared to the bagged lambs and PEEP lambs. Oxygenation was greatly improved with PEEP compared to no PEEP.


Comment. LOE 5. Quality good. Outcome FRC. Direction of effect positive. 28 day rabbits ventilated from birth with or without PEEP. Animals ventilated without PEEP failed to develop FRC whereas n the presence of PEEP FRC developed steadily during the first 2 minutes of ventilation.


Comment. LOE 5 Quality good. Outcome FRC. Direction of support positive. 28 day preterm rabbits were given either pressure controlled ventilation with PEEP or were first given a sustained inflation of 1,5,10 or 20 seconds. FRC was established more rapidly with sustained inflation of 10 or 20 seconds. 90% of lung aeration was achieved in 14 seconds of sustained inflation. Without sustained inflation around 16 inflations of pressure controlled ventilation with PEEP were needed to establish FRC.

LOE 1. Quality good. Outcome intubation, BPD. Direction of effect positive but unsure whether for PEEP or SI. Summary: RCT 227 preterm infants 25 -32 weeks at birth
10 second sustained nasal inflation and delivery room CPAP using neopuff and nasal prong v’s bag and mask if required and CPAP in the nnu if required. Less infants were intubated with sustained nasal inflation and early CPAP and less got BPD. Initial sustained inflation at 20 cm H$_2$O and repeated at 25 if necessary. Bigger success rate in 28 weeks-32 weeks. Difficult to know whether the sustained inflation was necessary or whether it was the early CPAP. Similar protocol to Lindner trial in which sustained inflation was not superior to nasal IPPV.


LOE 4. Quality moderate. Outcome chest movement. Direction of support positive (for increased pressure). Magnitude of effect n/a. Summary: 30 Apnoeic newborn babies were intubated and resuscitated using an anaesthetic bag. Aimed for chest movement and sustained inflation. The median mean pressure pressure was 40cmH$_2$O and TiO.5. The first 3 breaths were studied and 64% delivered tidal volume that was more than twice anatomic dead space. This was more than had been noted by BOON when a blow-off pressure of 30 was employed. Gestation was not helpful in predicting the pressure required to move the chest. Once chest movements were obtained pressures could be lowered and inflation volumes were maintained. i.e higher pressures were required for initial breaths than for subsequent breaths. Sustained inflations were not used.


LOE 4. Quality poor. Outcome inflation volume. Direction of support positive (for long ti). Effect size n/a. Summary: 9 infants 31-43 weeks were resuscitated by T-piece using a prolonged 5 second inflation to 30cmH$_2$O, followed by IPPV at 30-40/min with ti 1 second. All 9 babies formed an FRC at the end of the first inflation. Air was continuing to enter the lungs at the end of 5 seconds.


LOE 5. Quality good. Outcome lung compliance and lung injury. Direction of effect negative in relation to higher volumes, Magnitude of effect n/a. Summary. 129 day Lambs were treated from birth with pressure controlled ventilation with PEEP to VT5/kg, VT 10/kg or VT 20/kg for half an hour. All groups were then treated with surf and ventilated at VT10 for a further 6 hours. Other lambs were treated with surfactant at birth and then got 30 mins of VT 6, 12 or 20 before ongoing standardised ventilation. Compliance was worse over the subsequent 6 hours in VT20 lambs than VT 5 and 10 lambs. There was a stepwise increase in total protein in alveolar wash with increasing tidal volume. this was less with surf at birth than with surf at 30 mins.

Other Studies reviewed but not considered appropriate for the final worksheet

LOE 4. Quality (in terms of helping to answer the Worksheet question) Poor. Direction of support - Not applicable. Summary: This is a study of the use of early nasal CPAP in the delivery room as the primary mode of intervention. However outcomes are for the whole clinical course and the comparison population is benchmark figures from the Vermont Oxford Network. Delivery room CPAP as used by this group is associated with encouraging outcomes but it is not possible to conclude from a study of this methodology what the effect of CPAP, specifically during the initial lung aeration might be on any key outcome.


Level of evidence: 4. Quality: good. Outcome: tidal volume. Direction of effect: Positive (for increased inflation pressures). Magnitude of effect: N/a. Summary. This is the same patient group as in Boon et al's other 1979 paper. So the intervention is the same. The main observation relevant to this worksheet was (as in the other paper) that babies usually demonstrated an opening pressure before gas would enter their lungs. This varied but was usually close to 30cmH2O.


LOE: 4 Quality: N/A Outcome: N/A Direction of effect: N/A magnitude of effect: N/A Summary: This study does not report any data relating to initial lung inflation by positive pressure after birth. Not considered further.


LOE: 1 Quality: N/A Direction of support: N/A outcome: N/A Magnitude of effect: N/A Summary: this is an RCT of CPAP for infants >30 weeks gestation but the intervention did not begin with initial lung aeration after delivery so it was not considered further.


Not a study of initial aeration so not applicable to this worksheet.


LOE 5. Quality good. Outcome lung compliance (Crs) and lung injury (Li). Direction of support: N/A this is not a study of initial aeration after birth. Magnitude of support: N/A Summary: 5 pairs of 127 day preterm
lambs were ventilated for 4 hours using pressure controlled ventilation with PEEP. Surfactant was given at 30 minutes, either preceded by a recruitment maneuver (5 sustained inflations of 20ml/kg for 5 seconds without PEEP) or not. There was no significant difference over time in lung mechanics, gas exchange or histology between groups. The recruitment maneuver was not advantageous but did not harm the lungs when given 20 mins after birth. This study is interesting because a very vigorous recruitment maneuver given at 30 mins of age was not harmful whereas other studies by the group showed considerable harm from a similar maneuver given at birth. The combined with the latter this re-inforces the suggestion that the lung is particularly susceptible to injury from recruitment maneuvers during initial inflation.


LOE: 5. Quality: good. Outcome: not applicable to this worksheet as not readily applied to initial aeration of the lungs at birth. Summary: 10 preterm lambs were treated with surf before the first breath. Static PV loops were drawn during ventilation cycles with or without PEEP. Hysteresis was greater without PEEP than with PEEP. Inspiratory characteristics did not predict expiratory characteristics.


LOE:3. Quality: good. Outcome: BPD. Direction of support (For PEEP from birth) neutral. Magnitude of effect: none. Summary. Before/after study in a single centre comparing the outcomes of ELBW preterm infants managed with a new practice to historical controls. Historical practice was elective intubation for prophylactic surf at birth. New practice was intention to avoid intubation and use of mask CPAP in DR and NCPAP after admission. 75 CPAP era infants and 96 historical controls. Intubation in DR was 95% in controls and 76% in CPAP era. Surfactant use fell a little. There was not a significant reduction in BPD. Underpowered for modest effect sizes. This study does not support avoidance of intubation in ELBW infants or use of CPAP from birth.


I don't yet have this PDF. It appears to be a parallel study to the other paper on SI in the same animals. Sustained inflations were associated with rise in CVP. Not translatable into an useful conclusion for human infants,


LOE 2: Quality good: Outcome n/a. Direction of support N/A. Summary: This is not a study of initial lung inflation at birth because it only applied to infants who breathed for themselves. Nasal CPAP or synchronised nasal IMV by SLE 2000 via nasal prongs after admission to nnu in infants <34w who had not been intubated in the DR. Intubation if FiO2 50%. In this low risk population NIMV reduced the need for ventilation and the risk of bpd. Small sample. NIMV babies were bigger and more mature.

LOE 5: Quality good: outcome: n/a. Direction of support: n/a. Magnitude of effect: n/a. 27 day rabbits were intubated at birth and randomized to surfactant then ventilation without PEEP or to no surfactant and then ventilation with PEEP or to no surfactant and ventilation without PEEP. Lung mechanics and histological lung expansion were best with surfactant and worst without surf or PEEP. With PEEP they were intermediate. It is difficult to tease out a useful message regarding initial aeration of the lungs at birth from this study as the data do not enable this to be separated from the later management. None would dispute that surfactant and PEEP are useful components of ongoing ventilation in immature surfactant deficient lungs.


LOE 4. Quality: poor. Outcome: n/a, direction of support: n/a. Magnitude of effect: n/a. Summary: Observations on physiological parameters during postnatal adaptation in 48 of the infants enrolled in a RCT of sustained nasal inflation versus nasal IPPV at birth who got UAC inserted in the DR. Infants were started with FiO2 of 1 and this was weaned as long as preductal sats were >80. Within a few minutes most were in 40% or less. Many infants had a period of hypercarbia during the first hour and the incidence of IVH was not increased with hypercarbia. Not possible to determine from these data what may be advantageous techniques in initial aeration. Infants allowed to breathe spontaneously on non-invasive support will usually develop a short period of hypercarbia during the hour after birth and this usually resolves.


LOE 4 Quality good. Outcome: successful stabilization. Effect size NA, Summary: Small case series of preterm infants with prolonged oligohydramnios who could not be resuscitated successfully without increased pressures. Illustrates the point that increased pressures are sometimes required to achieve effective stabilisation. Doesn’t help in recommending any particular starting pressure for routine resuscitation.


LOE 5. Quality good. Outcomes: oxygenation, lung compliance and surfactant function. Effect: n/a in relation to the worksheet. Summary: 126 day lambs were intubated and given R-SPC surfactant or natural surfactant before the first breath and then ventilated at 0.4 or 7cmH2O PEEP for 7 hours. Animals treated with surfactant and PEEP had better gas exchange at lower inspiratory pressures and better preserved surfactant function. Not helpful to this worksheet as immediate postnatal strategy cannot be separated. Surfactant and PEEP for immature infants requiring ongoing ventilation are routine.


LOE 3. Quality poor. Outcome tidal volume. Effect size n/a. Direction of support neutral. Summary. Apnoeic term newborns were given mask ventilation with a Laerdal bag with a blow-off valve at 30cmH2O. Ti 0.5 rate 30 to 40. Pressures and volumes were measured. Despite similar inflation pressures, mask ventilation seldom achieved tidal volume greater than dead space in the first 3 breaths whereas this had been the case at similar inflation pressures in previous infants ventilated at birth by endotracheal tube using sustained inflations. The methodology makes it difficult to draw valid conclusions about the best way to inflate the lungs at birth as there were multiple differences in intervention.


LOE 1. Quality good. Outcome n/a. Direction of support n/a. Summary. Preterm infants who did not require immediate intubation at birth but did not establish adequate spontaneous breathing to be considered capable of managing without support were randomized to intubation and IPPV or nasal CPAP. Large study. Did not show a clear advantage to either approach. Trend towards less BPD with CPAP. Important data. No advantage to elective intubation. Does not help work out how initial aeration of the lungs at birth is best performed.


LOE 5. Quality good. Outcomes lung compliance, gas exchange. Effect size n/a. Direction of effect n/a. Summary. Can’t draw conclusions about initial lung inflation strategies from this study. 130-136 day lambs were delivered after antenatal steroids, were intubated at birth and put on bubble CPAP (5 or 8) or mechanical ventilation. 5/21 CPAP 5 lambs failed to remain stable on CPAP. They had the lowest surfactant pool sizes. Lung mechanics were better on CPAP 8 than CPAP 5 or ventilation. About 1/3 of the lambs in both CPAP groups did not survive the 6 hour protocol.


LOE 5. Quality good. Outcome n/a for this worksheet, Effect size n/a. Direction of effect n/a. Summary: 129 day lambs were treated with R-SPC surfactant before the first breath. They were then ventilated with PEEP 0, 4 or 7 for up to 7 hours. Lung mechanics gas exchange and lung injury markers were better with PEEP than without. Some measures favoured PEEP 4>PEEP7. Can’t separate out what is an issue with initial aeration at birth and what is more to do with lack of PEEP over many hours from this protocol.

LOE 5. Quality good. Outcome lung injury, oxygenation. Effect neutral, effect size n/a. Summary: 133 day lambs delivered after a/n steroids were ventilated with pressure controlled ventilation with PEEP or just with ET CPAP. Animals were then treated with a small amount of surfactant (as vehicle for LPS) at 15 mins with or without LPS. They were then continued on vent or CPAP until 3 hours. Oxygenation was not different between groups. CPAP lambs had elevated PCO2. Lung inflammation was worse after LPS. Lambs with RDS did not get less injury on CPAP than on gentle ventilation.


LOE 2. RCT of prophylactic (within 30 minutes of birth) versus rescue CPAP in spontaneously breathing moderately preterm (28-31 weeks) infants. No advantage to prophylactic use. Not applicable to this worksheet.


LOE 4. Not applicable to this worksheet. Nice study of breathing patterns in spontaneously breathing preterms after birth. Measurements were made via a mask which was administering CPAP. Data collection began at around 3 minutes so not a study of initial aeration. Main finding was that infants had a lot of expiratory braking.


Not got this PDF yet but it is describing spontaneous breathing and not IPPV so is not directly applicable to this worksheet.


LOE 3. Quality poor (in relation to this worksheet). Outcome intubation. Effect N/A Magnitude of effect N/A. Summary: Study with historical controls comparing the outcomes of a population of extremely premature infants who were electively intubated at birth with those of a group who were put on CPAP. In the second period any infant who did not breathe was intubated so this study is not a study of methods of initial lung aeration.