

## ORIGINAL ARTICLE

## Does sustained lung inflation at resuscitation reduce lung injury in the preterm infant?

A E Harling, M W Beresford, G S Vince, M Bates, C W Yoxall



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See end of article for authors' affiliations

Correspondence to: Miss Harling, Neonatal Intensive Care Unit, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, UK; Elizabeth.Harling@lwh-tr.nwest.nhs.uk

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**Background:** Bronchopulmonary dysplasia (BPD) is a common outcome of preterm birth. Experimental animal work has shown that initial ventilation strategies injure the immature lung and may lead to BPD. Studies with asphyxiated babies have shown that, if tidal ventilation at birth is preceded by sustained lung inflation, larger inflation volumes can be achieved, which is thought to lead to clearance of lung fluid and formation of the functional residual capacity (FRC).

**Objective:** To see if sustained lung inflation at initial resuscitation of preterm babies would facilitate the removal of lung fluid, establish the FRC, and allow an even distribution of alveolar opening, permitting less aggressive ventilation, leading to a reduction in pulmonary inflammation and subsequent BPD.

**Method:** The outcomes of 52 babies of less than 31 weeks gestation, resuscitated at birth using either a sustained lung inflation of five seconds or a conventional lung inflation of two seconds for the first assisted breath of resuscitation, were examined. Evidence of pulmonary inflammation was determined by quantification of interleukins 6, 10, and 1 $\beta$  and tumour necrosis factor  $\alpha$  in bronchoalveolar lavage fluid by enzyme linked immunosorbent assay.

**Results:** There were no significant differences in any of the cytokines. Death occurred in 3/26 babies in the conventional group and 6/26 babies in the sustained lung inflation group. Survival without BPD occurred in 13/26 and 14/26 respectively.

**Conclusion:** The use of sustained lung inflation at resuscitation did not reduce lung injury, as measured by inflammatory markers.

Northway *et al*<sup>1</sup> first described bronchopulmonary dysplasia (BPD) in 1967 in babies of about 34 weeks gestation who had been mechanically ventilated for respiratory distress syndrome, and later described barotrauma as one of the principle factors in the pathogenesis of BPD.<sup>2</sup> Mechanical ventilation in the form of positive pressure ventilation has remained the mainstay of treatment for respiratory distress syndrome in newborn babies. In recent years a number of new ventilation strategies have been introduced,<sup>3</sup> but the problem of BPD has not been resolved. Some authors have described a rise in the incidence of BPD in very low birthweight babies, but others have described a gradual decline. This is in spite of the increasing use of antenatal steroids and exogenous surfactant therapies, and it is probable that these treatments have increased the number of very preterm babies who survive to develop BPD.<sup>4-6</sup> It is these babies of low birth weight, low gestation, and requiring prolonged mechanical ventilation who are more likely to develop BPD.<sup>7-13</sup>

Early work by Karlberg *et al*<sup>14</sup> described the first breaths of life in normal full term babies to be characterised by prolonged expiratory phases, associated with high positive intrathoracic pressure, interspersed with brief inspiratory components. They postulated that the phase of high positive pressure may facilitate the distribution of air within the lungs and assist in the formation of the functional residual capacity (FRC).

Vyas *et al*<sup>15</sup> studied the effects of sustained lung inflation (SLI) during the resuscitation of asphyxiated babies and showed that a large increase in the tidal volume and the FRC could be achieved using this method. They suggested that the intervention may influence the clearance of lung fluid and allow a more even distribution of air throughout the lungs, thus facilitating the formation of the FRC.

Current recommendations for resuscitation of babies at birth are that initial inflation of the lung should be two to three seconds in duration.<sup>16 17</sup>

The aim of this study was to investigate whether lung injury in the very premature baby could be ameliorated by using SLI at the start of resuscitation at birth. This was with a view to establishing a more homogeneous and effective FRC that would permit the use of less aggressive tidal ventilation.

## METHODS

The study was a randomised controlled trial with factorial design. The interventions compared were SLI of five seconds duration compared with conventional lung inflation (CLI) of two seconds duration for the first assisted breath of resuscitation at birth and is reported here. The second intervention investigated was the use of 100% oxygen compared with 50% oxygen for resuscitation at birth.

The primary outcome measure was evidence of pulmonary inflammation as determined by concentrations of the cytokines interleukin (IL)6, IL1 $\beta$ , IL10 and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) in bronchoalveolar lavage (BAL) fluid obtained at 12 hours of age. BAL fluid was also obtained immediately after intubation at birth from which we elicited baseline cytokine concentrations.

Secondary outcome measures included: the severity of initial lung disease, as determined by blood gas analyses and oxygen and ventilator requirements over the first 24 hours of postnatal life; death; BPD (oxygen requirement at 36 weeks postmenstrual age); major cranial ultrasound abnormality (post-haemorrhagic ventricular dilatation requiring treatment,

**Abbreviations:** BAL, bronchoalveolar lavage; BPD, bronchopulmonary dysplasia; CLI, conventional lung inflation; FRC, functional residual capacity; IL, interleukin; SLI, sustained lung inflation; TNF $\alpha$ , tumour necrosis factor  $\alpha$

**Table 1** Basic and clinical details of babies receiving conventional or sustained lung inflation, and cytokine concentrations at 0 hours in both inflation groups

	CLI (n = 26)	SLI (n = 26)
Birth weight (g)	1095 (560–1562)	885 (518–1460)
Gestation (weeks)	28 (23–31)	27 (23–30)
Sex (F/M)	12/14	12/14
Apgar at 1 min	5 (2–10)	6 (1–10)
Apgar at 5 min	8.5 (2–10)	8 (3–10)
PROM (h)	1 (0–1221)	0 (0–277)
Cord pH	7.33 (7–7.4)	7.31 (6.95–7.44)
Delivery mode (C/V)	12/14	10/16
IL6 at 0 h (pg/ml)	537 (0–19208) (n = 18)	1768 (16–29205) (n = 16)
IL1β at 0 h (pg/ml)	43 (0–2950) (n = 18)	29 (0–1972) (n = 16)
IL10 at 0 h (pg/ml)	514 (111–2330) (n = 18)	533 (10–1753) (n = 16)
TNFα at 0 h (pg/ml)	44 (8–662) (n = 17)	63 (13–449) (n = 16)

Data are expressed as median (range) or number.  
 CLI, Conventional lung inflation (two seconds); SLI, sustained lung inflation (five seconds); C/V, caesarean/vaginal; PROM, premature rupture of membranes; IL, interleukin; TNFα, tumour necrosis factor α.

parenchymal haemorrhage, or cystic periventricular leucomalacia); necrotising enterocolitis (pneumoperitoneum or pneumatosis on abdominal radiograph or confirmed at laparotomy or postmortem examination); retinopathy of prematurity leading to treatment in accordance with national guidelines<sup>18</sup> or blindness; a patent ductus arteriosus requiring treatment; systemic infection proven by positive blood culture; pneumothorax requiring chest drain insertion.

**Subjects**

Babies of less than 31 completed weeks gestation and without life threatening malformations were recruited into the study; babies who did not require resuscitation at birth were excluded.

**Resuscitation**

Resuscitation was performed if the baby was making little or no respiratory effort and was bradycardic despite having a clear airway. Babies were intubated if they did not sustain adequate respiration after face mask ventilation, did not respond to face mask ventilation, or required long term ventilation because of prematurity.

Resuscitation was conducted on a Vickers Resuscitaire Radiant Warmer Pneumatic System (Air-Shields; Hill-Rom, Leicester, UK) which delivered ventilation via a diaphragm controlled adjustable pressure relief valve. The blow off valve on the resuscitaire was initially set at 25–30 cm H<sub>2</sub>O and

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

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

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

adjusted at the discretion of the attending clinician. A positive end expiratory pressure of 3–4 cm H<sub>2</sub>O was used in all babies.

The lung inflation manoeuvre was delivered for the first assisted breath of resuscitation and preceded normal tidal ventilation. It was delivered through a T piece with blow off valve using either a Laerdal face mask or endotracheal tube and was sustained for five or two seconds timed on the resuscitation clock. Resuscitation then proceeded as normal; once cardiorespiratory stability was achieved, the first dose of surfactant was given. On the neonatal unit, all the babies were ventilated with conventional intermittent positive pressure ventilation using the SLE 2000 time cycled pressure limited ventilator (Specialist Laboratory Equipment, Croydon, Surrey, UK).

**BAL fluid**

The first BAL fluid sample was collected immediately after intubation and stabilisation at birth and before the first dose of exogenous surfactant (0 hours) using a safe, standard technique.<sup>19, 20</sup> The second was collected at 12 hours before the second dose of surfactant was given.

**Cytokine quantification**

An enzyme linked immunosorbent assay (R&D Systems Europe Ltd, Abingdon, Oxon, UK) was used to determine the concentrations of the cytokines in the supernatant. The cytokine concentrations are expressed as pg/ml BAL fluid in line with the current recommendations of the ERS task force.<sup>21</sup>

**Statistical analysis**

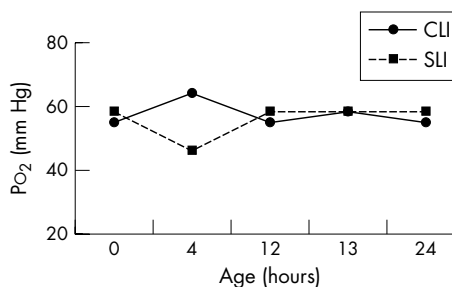
No previously published data were available from which to generate a sample size calculation. We planned to use any differences observed between the groups of this pilot study to calculate a sample size for a later definitive study. To show a difference of one standard deviation in any of the continuous variables, we planned to randomise 20 ventilated babies into each group. The Mann-Whitney U test was used for the continuous data, and the χ<sup>2</sup> test for categorical data. Two tailed tests were used for all statistical comparisons, and p ≤ 0.05 was considered significant. Statistical analyses were performed using SPSS for Windows 10.0.7. (SPSS, Chicago, Illinois, USA).

**Ethical considerations**

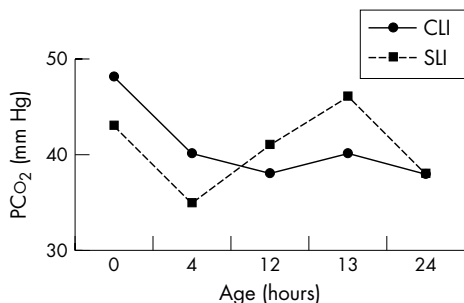
Informed parental consent was obtained in the antenatal period, and the study had the approval of the local paediatric research ethics committee.

**Randomisation**

Block randomisation using sealed envelopes was used. Although consent was obtained earlier, randomisation did not take place until delivery of the baby was imminent.



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



**Figure 2** Median partial pressure of carbon dioxide over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

**RESULTS**

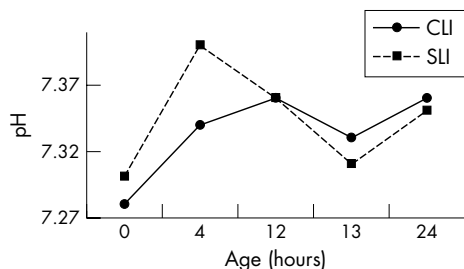
Sixty three babies were recruited in the antenatal period and were then randomised into the inflation group at delivery. Of the 63 randomised babies, 11 did not require any resuscitation and were therefore not recruited into the study. Fifty two required some resuscitation and received the intervention via either the face mask or endotracheal tube. Forty two babies were intubated at birth, and four were intubated shortly after birth on the neonatal unit. BAL fluid samples were only collected from ventilated babies. To measure the primary outcome of BAL fluid inflammatory markers at 12 hours, randomisation continued until there were sufficient babies intubated. Clinical outcomes for all resuscitated babies are reported, including those in whom BAL was not performed. Thirty four samples collected at 0 hours and 40 collected at 12 hours were suitable for analysis. The volume of BAL fluid collected did not permit analysis of all four cytokines at each time point in every baby.

The babies in the SLI group were slightly more premature and had lower median birth weights than the CLI group (27 v 28 weeks gestation and 885 v 1095 g; table 1), otherwise the groups were well matched.

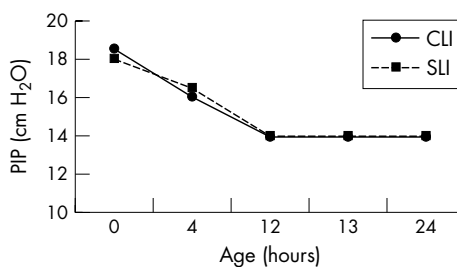
**Cytokine concentrations**

The interassay coefficient of variation and intra-assay coefficient of repeatability<sup>22</sup> for each cytokine were as follows: IL6, 5.98% and 24.11%; IL1 $\beta$ , 1.76% and 19.80%; IL10 16.32% and 33.49%; TNF $\alpha$  5.93% and 42%.

All four cytokines studied were present in the BAL fluid from immediately after birth and at 12 hours of postnatal life, although not all babies had detectable concentrations of each cytokine at each time point. The distribution of cytokine concentrations between each group did not show any significant difference at 12 hours of age (table 2).



**Figure 3** Median pH over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

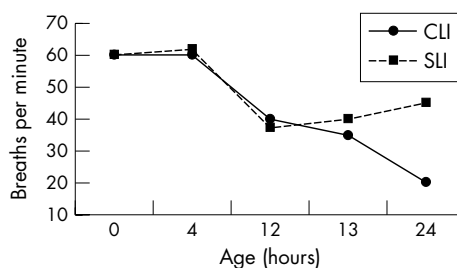


**Figure 4** Median peak inspiratory pressure (PIP) over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

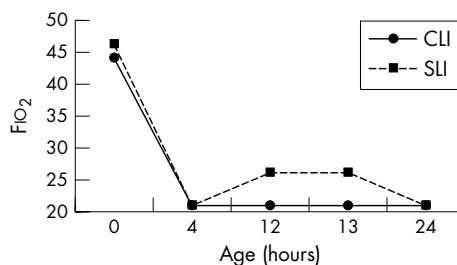
**Ventilator requirements**

The number of babies requiring ventilation during the first 24 hours was evenly distributed between the two groups, 24 and 22 in the two and five second group respectively. The ventilator requirements of the intubated babies and blood gas analyses and fraction of inspired oxygen (FIO<sub>2</sub>) for the whole cohort were similar for the first 4 hours of life. By 13 hours the ventilation in the SLI group began to increase, and we observed higher requirements for the FIO<sub>2</sub> at 13 hours (0.26 in the SLI group v 0.21 in the CLI group; p = 0.05) and the ventilator breaths per minute at 24 hours (50 in the SLI group v 20.5 in the CLI group; p = 0.006). This was reflected in the significantly higher Pco<sub>2</sub> at 13 hours (46.39 in the SLI group v 39.7 in the CLI group; p = 0.04). Figures 1–6 show the blood gas analysis and ventilation requirements (median) for the first 24 hours.

Multiple linear regression analysis using treatment group as a predictive variable between the covariate groups revealed that only the difference in Pco<sub>2</sub> was independently related to the treatment group (p = 0.02), and that the difference in the FIO<sub>2</sub> was also related to gestational age (treatment group, p = 0.01; gestation, p < 0.01), as was the respiratory rate (treatment group, p < 0.01; gestation, p = 0.03).



**Figure 5** Median breaths per minute over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).



**Figure 6** Median fraction of inspired oxygen (FIO<sub>2</sub>) over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SLI; five seconds).

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

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

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

### Clinical outcomes

Although the SLI group was slightly more premature and had a lower median birth weight, there was no significant difference between the two groups in any of the long term clinical outcomes (table 3).

### DISCUSSION

Research involving animal models has shown that the lung sustains mechanical damage when large tidal volume ventilation is used. The damage occurs in pulmonary capillary endothelium and the alveolar and airway epithelium, allowing fluid, protein, and blood to leak into the airspaces and lung interstitium. This begins a sequence of altered lung mechanics that promotes lung inflammation.<sup>23–27</sup>

In an effort to minimise the need for aggressive ventilation and subsequent lung injury after resuscitation at birth, we reproduced the sustained lung inflation described by Vyas *et al.*<sup>15</sup> However, we were unable to show any detectable differences in lung injury between the inflation groups when assessed by BAL fluid cytokine concentrations (table 2).

There was a slight difference between our study groups in the ventilatory requirements during the first 24 hours. The SLI group required more respiratory support than the CLI group, but this appeared to be a consequence of the lower gestation and lower birth weight of the SLI group, rather than a treatment effect. These early differences did not translate into any difference in long term outcomes (table 3).

The observations made by Vyas *et al* were in more mature babies, with lungs rich in surfactant, rather than premature babies predisposed to the development of BPD. The injury that is described usually occurs at a time when premature lung development is in the canalicular or saccular phase. This means that, for the most premature babies, the lungs will only consist of terminal bronchioles, prospective respiratory bronchioles, and a few branched buds that will eventually develop into saccules. We have not been able to show a benefit of SLI during resuscitation of preterm babies in this study. This may be because developmentally the lung structure was immature and deficient in surfactant, and consequently the lungs were unable to respond to the inflation manoeuvre. We are unable to completely exclude a small benefit based on this study, however, as, with an incidence of death or BPD of 50% in our study population, a study of this size would only be able to detect a difference in death or BPD rate of 34% with a power of 80% and significance of 5%.

### What is already known on this topic

- Low birthweight, low gestation preterm infants who require prolonged mechanical ventilation are more likely to develop BPD
- Studies of the effect of a sustained lung inflation at birth suggest that it may assist in fluid clearance and the formation of the FRC, facilitating a more homogeneous distribution of air through the lungs

### What this study adds

- The use of a sustained lung inflation for the first assisted breath of resuscitation of the preterm baby did not prove to be of any benefit to this population

### CONCLUSION

SLI at birth did not prove to be of any benefit to the very premature baby with respect to minimising the injury sustained by the lungs through mechanical ventilation.

### RECOMMENDATIONS

We recommend that current resuscitation guidelines on initial lung inflation<sup>16–17</sup> continue to be followed, and that we strive to find other means to reduce mechanical lung injury in our very premature population.

### Authors' affiliations

A E Harling, M W Beresford, C W Yoxall, NICU, Liverpool Women's Hospital, Liverpool L8 7SS, UK

G S Vince, M Bates, Immunology Department, University of Liverpool, Liverpool L69 3GA, UK

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