ORIGINAL ARTICLE

Cardiorespiratory effects of changes in end expiratory pressure in ventilated newborns

Koert A de Waal, Nick Evans, David A Osborn, Martin Kluckow

Arch Dis Child Fetal Neonatal Ed 2007;**92**:F444–F448. doi: 10.1136/adc.2006.103929

See end of article for authors' affiliations

Correspondence to: Koert A d e Waal, Academic Medical Centre, Department of Neonatology, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; k.a.dewaal@amc.nl

Accepted 19 April 2007
Published Online First 25 April 2007

Background: Positive pressure ventilation in premature infants can improve oxygenation but may diminish cerebral blood flow and cardiac output. Low superior vena cava (SVC) flow increases risk of intraventricular haemorrhage, and higher mean airway pressure is associated with low SVC flow. Whether this is a direct effect of positive pressure ventilation or a reflection of severity of lung disease is not known. This study aimed to determine if positive end expiratory pressure (PEEP) in ventilated newborns could be increased without clinically relevant cardiorespiratory changes.

Method: Ventilated newborns were studied before and 10 min after increasing PEEP (5 cm H_2O to 8 cmH_2O) and again when PEEP returned to baseline. Echocardiographic and respiratory function measurements were collected during the intervention.

Results: In 50 infants, increased PEEP was associated with a non-significant difference in mean SVC flow of −5 ml/kg/min (95% CI −12 to 3 ml/kg/min) but a significant reduction in right ventricular output of 17 ml/kg/min (95% CI 5 to 28 ml/kg/min). The increase in lung compliance was non-significant (median difference 0.02 ml/cmH_2O/kg) and the decrease in lung resistance (18 cmH_2O/l/s; 95% CI 10 to 26 cm H_2O/l/s) was significant. Changes (%) in lung compliance and SVC flow, when corrected for $PaCO_2$, were positively associated (regression coefficient 0.4%; 95% CI 0.2% to 0.6%).

Conclusion: A short-term increase in PEEP does not lead to significant changes in systemic blood flow, although 36% of infants in the present study had clinically important changes in flow (±25%). The intervention can improve dynamic lung function, especially airway resistance. Improvements in compliance tend to be associated with improvements in blood flow.

Low systemic blood flow is common in babies born before 30 weeks and is associated with considerable morbidity. Therefore an understanding of the factors that might affect blood flow in this population is essential.[1 2] Previous studies have shown that higher mean airway pressure is a determinant of low superior vena cava (SVC) flow.[3] Whether this is a direct effect of positive pressure ventilation on reducing systemic venous return, as suggested by animal studies, or a reflection of severity of lung disease, is not known.[4 5]

Positive end expiratory pressure (PEEP) is used to increase end expiratory lung volume to improve arterial oxygen content, decrease the alveolar to arterial oxygen difference, and decrease shunt fraction by preventing alveolar collapse.[6 7] Most neonatal intensive care units use a static level of PEEP, varying between 3 cm H_2O and 8 cm H_2O. The haemodynamic safety of different PEEP levels in a clinical setting has not been investigated yet. Theoretically there is potential for higher PEEP, as by opening up the lungs, it may reduce pulmonary vascular resistance and increase pulmonary and systemic blood flow. Our goal was to study whether end expiratory pressure in ventilated newborns could be increased from 5 cm H_2O to 8 cm H_2O without causing clinically relevant cardiorespiratory changes.

METHODS

All newborn infants admitted to RPA Newborn Care between April 2005 and March 2006, who required assisted ventilation in the first 3 days, were eligible. We excluded infants if they had a major congenital malformation, severe perinatal asphyxia defined as a Sarnat score greater than 2 at any point, or severe hypoxia with fractional inspired oxygen (FiO_2) more than 80%. Infants with peak inspiratory pressure below 12 cm H_2O with a FiO_2 of 21% were also excluded as increasing PEEP in these infants might compromise tidal volume. We obtained informed consent from the parents of eligible infants, and the study was approved by the local ethics committee.

Infants received surfactant as soon as possible after birth on the basis of a surfactant function test (click test) performed on an early tracheal aspirate.[8] Ventilator strategies included adjusting the peak inspiratory pressure to achieve an expiratory tidal volume of 4 ml/kg with the rate adjusted to achieve an arterial carbon dioxide pressure ($PaCO_2$) of 40–55 mm Hg, and FiO_2 adjusted to maintain preductal oxygen saturation between 88% and 95%. At our institution, PEEP is maintained at 5 cm H_2O in all infants. Morphine is used selectively to sedate babies considered to be uncomfortable on the ventilator. Circulatory support interventions were not changed during the period of the study.

Doppler echocardiographic measurements were done by using an Aspen ultrasound machine (Siemens Medical, Germany) with a 7 MHz vector array transducer incorporating colour flow and pulsed wave Doppler. SVC flow, Doppler measurement of right ventricular output (RVO), left pulmonary artery velocity, colour Doppler diameter of ductus arteriosus shunt and size, and Doppler of the middle cerebral arteries (MCAs) were performed according to previously published methods.[9 10] Doppler assessment of pulmonary artery pressure was also performed using the time to peak velocity divided by the right ventricular ejection time (TPV/RVET).[11] All measurements were performed by one investigator (KW).

Abbreviations: FiO_2, fractional inspired oxygen; MCA, middle cerebral artery; $PaCO_2$, arterial carbon dioxide pressure; PEEP, positive end expiratory pressure; RVO, right ventricular outflow; SVC, superior vena cava; TPV/RVET, time to peak velocity divided by the right ventricular ejection time

Blinding at the time of measurement was achieved by allocating each study a random number drawn from a sealed envelope. This number was the only identifier on the ultrasound screen. The scans were recorded to different magnetic optical disks, and measurements were done as a batch away from the bedside at a later time. The intervention was carried out and the data collected, if possible, between 3 h and 9 h of age. Echocardiographic and other parameters were recorded at the initial setting of 5 cm H_2O PEEP, after an increase of PEEP to 8 cm H_2O for 10 min and 10 min after PEEP was returned to 5 cm H_2O. An arterial blood gas was drawn just before the start of the protocol and before the intervention measurement. If no arterial line was in place, transcutaneous measurements of $PaCO_2$ and PaO_2 were noted. Respiratory function variables (dynamic lung compliance, mean airway pressure, minute volume, FiO_2) were measured using the Babylog 8000 ventilator (Dräger, Germany) and were collected together with physiological variables (heart rate, blood pressure) from the Agilent monitor (Phillips, The Netherlands). Average respiratory function variables were calculated from 30 s interval measurements. Respiratory function measurements were excluded if the tube leak was more than 25%. Exit criteria to stop the intervention were an increase in FiO_2 more that 30% from baseline or a drop in mean blood pressure of 20% from baseline.

Statistical analysis

Our hypothesis was that an increase in PEEP would not result in a remarkable change in SVC flow of more than 25% from baseline. The cut-off of 25% was chosen to allow for measurement error that was documented in previous studies and to allow for clinically unimportant changes in SVC flow. We statistically analysed the data with SPSS (version 12.0) for Windows.

General linear models with repeated measurements were performed for normally distributed outcomes to test the within subjects effects at the three measurement time points. Friedman test was used for non-parametric outcomes, paired t test was used to estimate mean differences in normally distributed outcomes and Wilcoxon signed rank test was used for non-parametric outcomes after the increase in PEEP compared with baseline. Linear regression was used to identify risk factors for changes in flow before and after the increase in PEEP and to evaluate the possible interaction or confounding effect of gestational age, postnatal age and $PaCO_2$ on the relation between PEEP increase and flow changes. Statistical significance was set at 5%. One-way analysis of variance was used to identify risk factors for changes in compliance. Groups were divided on the basis of a clinically relevant change in compliance of 10% (no clinically relevant change, difference $>10\%$ or $\leqslant 10\%$). The association between severity of lung disease (mean airway pressure, compliance, resistance, FiO_2) and flow changes was evaluated with linear regression analysis.

RESULTS

The study included 50 infants (40 preterm and 10 term) with a median gestational age of 30 weeks and a median weight of 1612 g. Of the preterm infants, 22 were less than 30 weeks' gestation. All preterm infants were ventilated because of respiratory distress syndrome (RDS) and received surfactant. Two of the term infant were ventilated for meconium aspiration, five for non-specific lung disease with a positive click test for surfactant function, two for pneumonia/sepsis and one infant for mild perinatal asphyxia. Nine infants had their first study after 24 h or 48 h of life because they were transported to our centre or they were not ventilated in the first 24 h of life.

Tables 1 and 2 show the cardiovascular and pulmonary function measurements before, during and after the increase in PEEP. In eight infants, some indices of flow were not measurable due to poor windows, but SVC flow was always measurable. Pathologically low measures of SVC and RVO are defined as less than 40 ml/kg/min and 120 ml/kg/min, respectively.[12] No infant met the exit criteria during the study.

Effect of higher PEEP on SVC flow and RVO

A change in SVC flow of more than 25% from baseline was found in 18 (36%) infants, with 9 infants having increased flows and 9 decreased flows (fig 1). Overall, after the increase in PEEP there was a non-significant difference in SVC flow of −5 ml/kg/min (95% CI −12 to 3 ml/kg/min) or −0.7% (95% CI −10.7% to 9.2%) due to a small but significant decrease of 1.6 mm (95% CI 0.3 to 2.9 mm) in SVC diameter. The intervention caused a significant reduction in RVO with a mean of 17 ml/kg/min (95% CI 5 to 28 ml/kg/min) or 5% (95% CI 0% to 10%). Gestational age was not found to be an interaction factor or confounding factor in these analyses.

Gestational age, birth weight, baseline RVO, mean airway pressure, FiO_2, lung compliance or resistance did not predict the direction of the change in SVC flow or RVO. There was a negative association between baseline SVC flow and change in SVC flow after the increase in PEEP (linear regression coefficient −0.3 ml/kg/min; 95%CI −0.5 to −0.1 ml/kg/min). Postnatal age (hours) was positively associated with change in RVO after the increase in PEEP (regression coefficient 0.8 ml/kg/min; 95% CI 0.1 to 0.5 ml/kg/min).

Table 1 Cardiovascular response to an increase in positive end expiratory pressure (PEEP) in all 50 infants*

	Baseline PEEP 5 cmH_2O	Intervention PEEP 8 cmH_2O	Return to PEEP 5 cmH_2O	p Value
Right ventricular output (ml/kg/min)	234 (103)	218 (95)	224 (87)	0.014
SVC (ml/kg/min)	92 (36)	87 (36)	86 (34)	0.207
SVC diameter (mm)	3.7 (1.0)	3.6 (1.1)	3.6 (1.0)	0.040
SVC velocity time integral (m/s)	0.093 (0.032)	0.097 (0.035)	0.090 (0.029)	0.172
Left pulmonary artery velocity (m/s)	0.33 (0.11)	0.32 (0.13)	0.32 (0.12)	0.669
Duct diameter (mm)	2.2 (1.6–3.0)	2.2 (1.9–28)	2.1 (1.8–3.1)	0.628
Ductal shunt (%RL)	14 (0–25)	12 (0–27)	15 (0–28)	0.760
Middle cerebral artery mean (m/s)	0.13 (0.09–0.17)	0.14 (0.10–0.18)	0.12 (0.09–0.16)	0.190
Heart rate (beats/min)	143 (17)	141 (20)	143 (19)	0.198
Systolic blood pressure (mm Hg)	47 (9)	48 (9)	47 (9)	0.265
Diastolic blood pressure (mm Hg)	30 (7)	30 (6)	30 (6)	0.602

%RL, percentage of cardiac cycle with right to left shunt; SVC, superior vena cava flow; Vti, velocity time integral.
*Values expressed as mean (SD) or median (IQR) where appropriate.

Table 2 Pulmonary response to an increase in positive end expiratory pressure (PEEP) in all 50 infants*

	Baseline PEEP 5 cm H_2O	Intervention PEEP 8 cm H_2O	Return to PEEP 5 cm H_2O	p Value
Mean airway pressure (cm H_2O)	8.5 (7.3–10.0)	11.0 (9.6–12.3)	8.6 (7.2–10.0)	0.000
Tidal volume† (ml/kg)	4.1 (3.4–4.9)	3.3 (2.7–4.3)	4.1 (3.5–5.3)	0.000
Compliance† (ml/cmH_2O/kg)	0.43 (0.36–0.69)	0.53 (0.33–0.81)	0.45 (0.30–0.67)	0.409
Resistance† (cmH_2O/l/s)	96 (41)	78 (33)	93 (40)	0.000
Partial pressure of carbon dioxide (mmHg)	44 (12)	47 (11)	NA	0.002
Partial pressure of oxygen (mmHg)	75 (63–99)	80 (63–99)	NA	0.884
Fractional inspired oxygen (%)	25 (21–34)	25 (21–31)	25 (21–30)	0.043

NA, not available.
*Values expressed as mean (SD) or median (IQR) where appropriate.
†Tidal volume, compliance and resistance are reported for 36 infants with less than 25% tube leak.

Effect of higher PEEP on other haemodynamic measurements

In 40 infants the ductus arteriosus was patent, with a median ductal diameter of 2.2 mm. The increase in PEEP had no significant effect on the ductal size or the proportion of ductal flow going right to left, a marker of relative pressure between the systemic and pulmonary system. The intervention also did not significantly change the left pulmonary artery mean velocity. As an assessment of pulmonary pressure, we calculated the time to peak velocity divided by the right ventricular ejection time (TPV/RVET). It showed no significant change with the intervention and there was no association between the change in RVO or LPA mean velocity and the change in TPV/RVET. The change in MCA mean velocity after the increase in PEEP was not significant (median difference 0.003 m/s; $p = 0.337$).

Effect of higher PEEP on respiratory function

Valid analysis of respiratory outcomes was possible in 36 infants who had a tube leak less than 25% (see table 2). Dynamic lung compliance showed a non-significant increase (median difference 0.02 ml/cm H_2O/kg; $p = 0.093$), but lung resistance was significantly decreased after 10 min of higher PEEP (mean difference at 10 min −18 cm H_2O/l/s; 95% CI −26 to −10 cm H_2O/l/s). Both compliance and resistance returned to their baseline values within 10 min of the PEEP returning to 5 cm H_2O.

Significant associations were found between the following baseline characteristics and change in compliance with the intervention: mean airway pressure ($F_{(2,35)} = 3.3$, $p = 0.049$), minute volume ($F_{(2,27)} = 6.3$, p 0.006) and resistance ($F_{(2,35)} = 3.8$, $p = 0.032$). Infants who showed a decrease of more than 10% with the intervention had a higher mean airway pressure, higher minute volume and a lower resistance. This may point to overdistension as the cause for the decrease in compliance with an increase in PEEP.

An increase in PEEP resulted in a significant increase in $PaCO_2$ (mean difference 3.0 mm Hg; 95% CI 1.2 to 4.8 mm Hg). Linear regression showed no significant effect of $PaCO_2$ changes on changes in RVO, MCA mean velocity or ductal shunting. An increase in $PaCO_2$ was, however, associated with a small but significant increase in SVC flow (regression coefficient 1.3 ml/kg/min; 95% CI 0.0 to 2.5 ml/kg/min).

Respiratory function and flow

We explored the relationship between changes in respiratory function and changes in flow and found two weak associations. First, an increase of 1% in compliance was associated with a 0.4% (95% CI 0.1% to 0.6%) increase in SVC flow (fig 2). Second, there was a positive association between $PaCO_2$ and MCA mean velocity (regression coefficient 0.002 m/s; 95% CI 0.001 to 0.004 m/s), but the association between changes in $PaCO_2$ and MCA mean velocity with the intervention was not statistically significant (regression coefficient 0.001; (95% CI −0.001 to 0.003).

DISCUSSION

We have shown that an increase of PEEP from 5 cm H_2 to 8 cmH_2O for 10 min did not lead to a clinically relevant change in upper body and brain blood flow (SVC flow) in most of the infants in the present study. It was associated with a significant decrease in RVO but there were no clinically relevant changes in any of the other haemodynamic measurements. Improvements in SVC flow were associated with improvements in lung

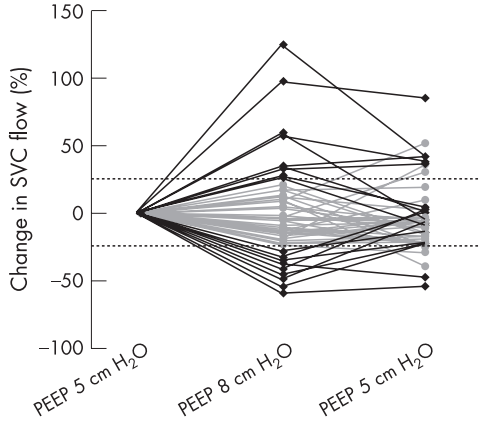

Figure 1 Change in superior vena cava (SVC) flow (%) with the intervention. Black lines show more than 25% change between 8 cm H_2O of positive end expiratory pressure (PEEP) and baseline.

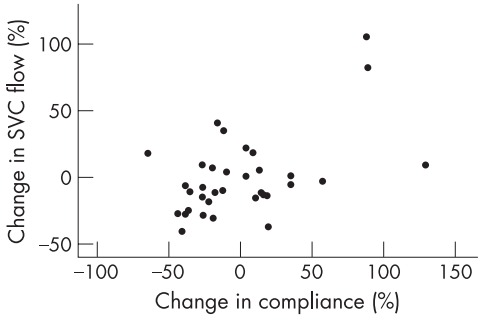

Figure 2 Partial regression scatterplot of change in superior vena cava (SVC) flow (%) and change in lung compliance (%) if corrected for $PaCO_2$ changes with 8 cm H_2O of positive end expiratory pressure (PEEP) compared with baseline.

compliance, although this analysis is sensitive to the method of analysis.

In contrast to the literature, our study found relatively little consistent change in the haemodynamic measurements overall.[13 14] Potential reasons for this include our heterogeneous study population, or the impact of our intervention. Possibly, an increase of 5 cm H_2O to 8 cmH_2O in PEEP was not large enough to cause consistent negative effects on blood flow as reported in the literature. Few infants had low systemic blood flows. We expected that infants with low baseline flow would show a larger decrease in flow with the intervention, but they were more likely to have an increase in SVC flow at 8 cmH_2O of PEEP. This may be a regression to the mean.

The decrease in RVO of −17 ml/kg/min was significant, but we are not sure if this is of clinical importance considering the normal baseline RVO in this population. In six of the seven babies with low baseline RVO (<120 ml/kg/min) the intervention resulted in no detectable change, but a potential adverse effect of higher PEEP should be evaluated more thoroughly with further research, especially in infants with low flow.

Probably the most important haemodynamic effect of PEEP in preterm infants with respiratory distress syndrome is through the direct effect on alveoli. When PEEP is set too low, blood will be shunted away from collapsed alveoli which produce a regional increase in pulmonary vascular resistance. With optimal lung volume, lung vascular resistance will be at its lowest point, thus maximising RVO and cardiac input. PEEP is capable of optimising lung volume by keeping open (partially) collapsed alveoli. The intervention performed in this study is not considered a lung recruitment manoeuvre, and we can only speculate about lung volumes in the studied infants.[15] Lung volume is also related to airway resistance. At low lung volumes due to insufficient PEEP, airway resistance and the work of breathing are high.

In this study compliance increased with the maximum increase after 10 min of PEEP of 8 cmH_2O. It can take up to 14 min for the alveoli to stablise after a change in PEEP.[16] However, the evidence on the effect of PEEP on compliance is conflicting.[17–19] Compliance can only be used as a measurement to optimise ventilation without decreasing blood flow, if it is combined with information on lung volume. Two studies investigating lung compliance and blood flow simultaneously in newborn infants showed a progressive decrease in cardiac output with less decrease in the infants with low compliance.[13 14] We found a reduction in RVO, but we did not find a significant positive association between an increase in compliance and an increase in RVO as we did for SVC flow. This could be caused by differences in flow measurements. In RVO, we looked at the change in velocity and assumed the diameter did not change, whereas change in SVC depended on change in diameter. This suggests that RVO, although perhaps not such a consistent measure of systemic blood flow as SVC, is less vulnerable to measurement error if only change in velocity is assessed. It may be a better method to detect short-term changes such as in this study.[20]

Although our intervention seems to be only a minor increase in mean airway pressure, modest changes in PEEP can result in a clinically important decrease in tidal volume or functional residual capacity.[21] This could explain the increase in $Paco_2$ found in our study. Other studies suggest that the increase in $Paco_2$ is responsible for an increase in cerebral blood flow.[22 23] The relationship between $Paco_2$ and cerebral blood flow is exponential and a normal $Paco_2$–cerebral blood flow reactivity is about 4% per mm Hg.[24] In this study, the increase in $Paco_2$ was associated with an increase in SVC flow, but not with an increase in RVO or MCA mean velocity which makes the $Paco_2$–SVC flow relationship difficult to interpret. The potential negative effect of PEEP on RVO could have been balanced by the potential positive effect of a higher $Paco_2$ on cerebral blood flow and SVC flow.

What is already known on this topic

- Higher PEEP can optimise lung inflation and improve oxygenation in ventilated newborns.
- Higher PEEP can diminish venous return, hence cardiac output and consequently cerebral blood flow.

What this study adds

- A short-term modest increase in PEEP reduces RVO but does not lead to a remarkable change in systemic blood flow in most infants.
- Infants with improvements in compliance in response to higher PEEP tend to have improvements in SVC flows.

CONCLUSION

A short-term modest increase in PEEP reduces RVO, but does not lead to a clinically important change in systemic blood flow in most infants. In the present study, clinically significant changes (both positive and negative) in systemic blood flow were found in 36% of the infants. Improvements in lung compliance were associated with improvements in SVC flow. The association between ventilation and blood flow is a complex one that needs more study. Future research should focus on more sick infants, especially those with low blood flows, and on the effect of a larger intervention, such as lung recruitment manoeuvres.

ACKNOWLEDGEMENT

We thank Dr J H vd Lee, Deparment of Pediatric Clinical Epidemiology Emma Children's Hospital AMC, Amsterdam, for statistical advice.

Authors' affiliations

Koert A de Waal, RPA Newborn Care, Royal Prince Alfred Hospital, Sydney, Australia
Nick Evans, David A Osborn, RPA Newborn Care and University of Sydney, Sydney, Australia
Martin Kluckow, Department of Neonatology, Royal North Shore Hospital and University of Sydney, Sydney, Australia

Funding: Koert A de Waal was partially funded by the Ter Meulen Fund, Royal Netherlands Academy of Arts and Sciences.

Competing interests: None.

REFERENCES

1 **Meek JH**, Tyszczuk L, Elwell CE, *et al*. Low cerebral blood flow is a risk factor for severe intraventricular haemorrhage. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F15–8.
2 **Kluckow M**, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F188–94.
3 **Osborn DA**, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics* 2003;**112**(1 Pt 1):33–9.
4 **Mirro R**, Busija D, Green R, *et al*. Relationship between mean airway pressure, cardiac output, and organ blood flow with normal and decreased respiratory compliance. *J Pediatr* 1987;**111**:101–6.
5 **Mundie TG**, Easa D, Finn KC, *et al*. Effect of baseline lung compliance on the subsequent response to positive end-expiratory pressure in ventilated piglets with normal lungs. *Crit Care Med* 1994;**22**:1631–8.

6 **Ranieri VM**, Eissa NT, Corbeil C, *et al*. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1991;**144**(3 Pt 1):544–51.
7 **Michna J**, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. *Am J Respir Crit Care Med* 1999;**160**:634–9.
8 **Osborn DA**, Jeffery HE, Bredemeyer SL, *et al*. Targeted early rescue surfactant in ventilated preterm infants using the click test. *Pediatrics* 2000;**106**:E30.
9 **Evans N**, Kluckow M, Simmons M, *et al*. Which to measure, systemic or organ blood flow? Middle cerebral artery and superior vena cava flow in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2002;**87**:F181–4.
10 **El Hajjar M**, Vaksmann G, Rakza T, *et al*. Severity of the ductal shunt: a comparison of different markers. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F419–22.
11 **Su BH**, Watanabe T, Shimizu M, *et al*. Doppler assessment of pulmonary artery pressure in neonates at risk of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F23–7.
12 **Evans N**. Which inotrope for which baby? *Arch Dis Child Fetal Neonatal Ed* 2006;**91**:F213–20.
13 **Hausdorf G**, Hellwege HH. Influence of positive end-expiratory pressure on cardiac performance in premature infants: a Doppler-echocardiographic study. *Crit Care Med* 1987;**15**:661–4.
14 **Trang TT**, Tibballs J, Mercier JC, *et al*. Optimization of oxygen transport in mechanically ventilated newborns using oximetry and pulsed Doppler-derived cardiac output. *Crit Care Med* 1988;**16**:1094–7.
15 **De Jaegere A**, van Veenendaal MB, Michiels A, *et al*. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. *Am J Respir Crit Care Med* 2006;**174**:639–45.
16 **Thome U**, Topfer A, Schaller P, *et al*. 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**:831–7.
17 **Philips JB**, Beale EF, Howard JE, *et al*. Effect of positive end-expiratory pressure on dynamic respiratory compliance in neonates. *Biol Neonate* 1980;**38**:270–5.
18 **Dinger J**, Topfer A, Schaller P, *et al*. Effect of positive end expiratory pressure on functional residual capacity and compliance in surfactant-treated preterm infants. *J Perinat Med* 2001;**29**:137–43.
19 **Dimitriou G**, Greenough A, Laubscher B. Appropriate positive end expiratory pressure level in surfactant-treated preterm infants. *Eur J Pediatr* 1999;**158**:888–91.
20 **Tsai-Goodman B**, Martin RP, Marlow N, *et al*. The repeatability of echocardiographic determination of right ventricular output in the newborn. *Cardiol Young* 2001;**11**:188–94.
21 **Bartholomew KM**, Brownlee KG, Snowden S, *et al*. To PEEP or not to PEEP? *Arch Dis Child Fetal Neonatal Ed* 1994;**70**:F209–12.
22 **Shortland DB**, Field D, Archer LN, *et al*. Cerebral haemodynamic effects of changes in positive end expiratory pressure in preterm infants. *Arch Dis Child* 1989;**64**:465–9.
23 **Mullaart RA**, Hopman JC, Rotteveel JJ, *et al*. Influence of end expiratory pressure on cerebral blood flow in preterm infants. *Early Hum Dev* 1995;**40**:157–65.
24 **Greisen G**. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;**81**:423–8.