Circulatory effects of fast ventilator rates in preterm infants

A C Fenton, D J Field, K L Woods, D H Evans, M I Levene

Abstract
High frequency positive pressure ventilation has been suggested to result in a lower incidence of respiratory complications in preterm infants with idiopathic respiratory distress syndrome compared with ventilation at conventional rates. A possible disadvantage is compromise of the infant’s cardiovascular condition secondary to inadvertent positive end expiratory pressure (PEEP). In a group of 20 such infants treated with high frequency positive pressure ventilation (rates of up to 100/minute) and paralysed, changes in arterial blood pressure and cerebral blood flow velocity were largely influenced by changes in arterial blood gases, and no effect could be attributed to inadvertent PEEP. In addition, the observed fall in both arterial carbon dioxide and oxygen tensions could be readily predicted for theoretical reasons. Under certain conditions at the fastest rates used, cerebral blood flow velocity was significantly influenced by changes in blood pressure, which may indicate impaired cerebrovascular regulation. Though other factors (such as the severity of the infants’ illness or the use of paralysis) may have been responsible for this apparent blood pressure passivity, the role of high frequency positive pressure ventilation in such infants warrants further study.

During recent years the type of infant treated in neonatal units has changed, and the extremely immature infants now encountered regularly are at great risk from the respiratory complications of idiopathic respiratory distress syndrome. In addition, neonatal ventilators are now more sophisticated and these factors have led to different patterns of ventilation being tried in attempts to minimise the complications of respiratory support.

The use of one such alternative, high frequency positive pressure ventilation, has been increasing in neonates, because of a reported reduction of harmful interaction with the infant’s own respiratory efforts, as well as an improvement in oxygenation in unparalysed infants. Concerns about high frequency positive pressure ventilation have centred around the production of inadvertent positive end expiratory pressure (PEEP), resulting from insufficient time for the lungs to empty during the expiratory phase. This may lead to harmful secondary effects on both the lungs and the cardiovascular system. The former effect may impair blood gases and the latter may produce a number of secondary problems, for example decreased venous return, or restriction of left ventricular filling.

Several factors are likely to influence the occurrence of inadvertent PEEP and whether its effects are transmitted to the cardiovascular system. Theoretically, it is more likely to occur in paralysed infants who cannot expire actively, and also if the degree of air leak around the endotracheal tube is relatively small. Mechanical transmission of inadvertent PEEP to the cardiovascular system will be affected by lung compliance, which will vary with the stage of idiopathic respiratory distress syndrome.

To assess the magnitude of these potential cardiovascular effects we have studied the changes produced by high frequency positive pressure ventilation on arterial blood pressure and cerebral blood flow velocity in a group of paralysed infants in the acute phase of idiopathic respiratory distress syndrome to see whether any of the changes that occurred could be attributed to inadvertent PEEP.

Patients and methods
The study was carried out on the neonatal unit at the Leicester Royal Infirmary between June 1988 and August 1989. Twenty infants were studied on one occasion each. Their birth weights ranged from 720–2420 g (median 1480 g) and their gestational ages from 25–34 weeks (median 30 weeks). The median age at the time of study was 54–5 hours. Median peak inspiratory pressure at the time of the study was 24 cm H₂O and median inspired oxygen concentration was 0·73. Full details of the infants are given in the table.

Infants were considered eligible for the study if they were being ventilated for respiratory distress syndrome and were paralysed with pancuronium to facilitate ventilation. The decision to use pancuronium was based on the inability to ventilate the infant satisfactorily at either slow or fast rates and was made independently by the clinicians responsible for the infants’ care. All infants had indwelling arterial catheters (either umbilical or radial) for clinical reasons and were intubated orally with shouldered endotracheal tubes. An infant was excluded if a pneumothorax was present, if there was pre-existing intraventricular haemorrhage, or if the infant’s condition was unstable.

The study was approved by the Leicestershire district ethics committee. Informed parental consent was obtained before all studies and parents were encouraged to be present for the duration of the study. The following variables were recorded:
Circulatory effects of fast ventilator rates in preterm infants

Details of infants at time of study

<table>
<thead>
<tr>
<th>Case No</th>
<th>Gestation (weeks)</th>
<th>Birth weight (g)</th>
<th>Age at study (hours)</th>
<th>Fractional inspiratory oxygen</th>
<th>Peak inspiratory pressure (cm H2O)</th>
<th>Positive end expiratory pressure (cm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>900</td>
<td>124</td>
<td>0.86</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>1500</td>
<td>77</td>
<td>0.75</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>2000</td>
<td>66</td>
<td>0.60</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>2070</td>
<td>66</td>
<td>0.80</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>1990</td>
<td>73</td>
<td>0.70</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>1700</td>
<td>14</td>
<td>1.00</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>1280</td>
<td>81</td>
<td>0.98</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>1360</td>
<td>43</td>
<td>0.78</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>2070</td>
<td>20</td>
<td>0.58</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>880</td>
<td>57</td>
<td>0.96</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>1790</td>
<td>21</td>
<td>0.94</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>1550</td>
<td>49</td>
<td>0.70</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>27</td>
<td>1100</td>
<td>216</td>
<td>0.55</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>1400</td>
<td>22</td>
<td>0.58</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>750</td>
<td>16</td>
<td>1.00</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>31</td>
<td>1450</td>
<td>38</td>
<td>0.58</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>27</td>
<td>1060</td>
<td>144</td>
<td>0.65</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>30</td>
<td>720</td>
<td>86</td>
<td>0.50</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>31</td>
<td>1600</td>
<td>23</td>
<td>0.46</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>34</td>
<td>2420</td>
<td>52</td>
<td>1.00</td>
<td>32</td>
<td>3</td>
</tr>
</tbody>
</table>

Cases 6, 10, and 15 died of idiopathic respiratory distress syndrome.

CEREBRAL BLOOD FLOW VELOCITY AND ARTERIAL BLOOD PRESSURE

In three of the infants cerebral blood flow velocity and arterial blood pressure recordings were made from the anterior cerebral artery using an ATL 600 duplex Doppler system with a 724A probe (pulse echo 7.5 MHz, Doppler frequency 5 MHz). One anterior cerebral artery was visualised in the sagittal plane through the anterior fontanelle and signals were recorded from a point midway between the most inferior border of the corpus callosum and the vessel's origin in the circle of Willis. Care was taken to ensure that the angle of insonation of the vessel was less than 10°.

For these recordings the Doppler sample value was set to 3 mm and the high pass wall filter at its lowest value (100 Hz). Doppler signals were recorded on to digital audiotape and subsequently replayed through a fast Fourier transform analyser. The maximum frequency envelope of 20 or more consecutive beats was extracted and calibrated in terms of velocity using the Doppler equation. The mean velocity over the cardiac cycle was estimated by halving the mean value of the maximum velocity over the cycle. In these infants, a permanent record of blood pressure was made on a chart recorder.

The remaining 17 infants studied had cerebral blood flow velocity measurements recorded from one middle cerebral artery using a miniature probe attached to the infant's skin, which we have previously described. This system also collects data about blood pressure from the indwelling arterial line and displays the information graphically at the bedside. This obviates the need to handle the infant repeatedly to make estimations of cerebral blood flow velocity. Results may also be retrieved off line at a later stage. In all infants, mean arterial blood pressure was recorded at each stage of the study.

RESPIRATORY RECORDINGS

Ventilator pressures were recorded from the endotracheal tube through a 19 gauge needle connected to a pressure transducer. Tidal volumes were recorded using a Gaeltec pneumotachograph (with a bias flow system to eliminate dead space) combined with a differential pressure transducer and integrator as described previously. All signals were recorded on a chart recorder for later analysis.

STUDY PROCEDURE

After the recording apparatus had been attached, a period of 15 minutes was allowed for stabilisation of the infant's condition. All infants were then studied at three ventilator rates: 30-40, 50-60, and 100/minute, using a Sechrist ventilator (model IV-100B). Peak inspiratory pressure, PEEP, and inspiratory: expiratory ratio were kept constant. The rate change sequence was initially an increase in all cases, as all infants entered the study while being ventilated at either 30-40 or 50-60/minute. Infants entering at 30-40/minute had their rate increased by at least 20/minute as a first step. Those entering at 50-60/minute were increased to 100/minute and then reduced to 30/minute as a last stage before returning to their baseline rate.

At 100/minute, a second set of recordings were made with the pneumotachograph bias flow switched off. This manoeuvre was performed to enable comparison of the cardiovascular effects of the rate change at different arterial carbon dioxide pressure (PaCO2). A 12 minute stabilisation period was allowed after each rate change before measurements were made of mean arterial blood pressure, cerebral blood flow velocity, tidal volume, peak inspiratory pressure, and PEEP. Even at the fastest rates, the ventilator pressure wave flattened out. At each stage 0.1 ml of blood was taken through the arterial line for measurement of PaCO2 and arterial oxygen pressure (PaO2).

STATISTICAL ANALYSIS

Parametric statistical tests were used. Paired t tests were used to compare observed values of PaO2, PaCO2, mean arterial blood pressure, and cerebral blood flow velocity at the four ventilator settings. No adjustment was made for
multiple comparisons. The principal findings would not have been altered by this adjustment, which was judged unnecessary because of the small number of comparisons being made. Linear regression analysis was used to examine the factors influencing changes in cerebral blood flow velocity. A step down analysis was used, incorporating PaCO₂, PaO₂, and mean arterial blood pressure as potential explanatory variables. The adequacy of the linear model was checked by plotting residuals.

**Results**

PaO₂ changed little at the different ventilator settings, but was significantly lower at 100/minute than at 30/minute (p=0.043) (fig 1). PaCO₂ was significantly lower at 60/minute (p=0.003), and at 100/minute (p=0.016), than at 30/minute (fig 2). With the bias flow turned off at 100/minute, however, PaCO₂ was not significantly different from that observed at 30/minute (p=0.7). There was a substantially higher PaCO₂ at 100/minute with the bias flow turned off than at the same rate with the pump on (p=0.004).

There was a slight downward trend in mean arterial blood pressure at increasing ventilation rates, which was significant at 100/minute compared with 30/minute (p=0.043). Turning the bias flow off at 100/minute, however, resulted in a clear increase in mean arterial blood pressure (p=0.003) compared with the same rate with the pump on (fig 3). The statistical analysis suggested that this did not depend significantly on the accompanying changes in blood gases.

Cerebral blood flow velocity fell as ventilator rate was increased from 30 to 60/minute (p=0.0017), but showed no further fall on further increasing the rate to 100/minute (p=0.74). Removal of the bias flow at this rate resulted in a clear rise in cerebral blood flow velocity (p=0.008) to the level observed at 30 breaths/minute (fig 4). Stepwise linear regression indicated that two separate factors were associated with the observed changes in cerebral blood flow velocity. Firstly, as ventilator rate was changed from 30 to 100/minute, the change in cerebral blood flow velocity was closely associated with the change in PaCO₂ (p=0.008), but was independent of changes in PaO₂ or blood pressure. The variation in PaCO₂ alone was sufficient to account for 30% of the variability in the change of cerebral blood flow velocity.

Secondly, the rise in cerebral blood flow...
velocity on removal of the bias flow at 100/
minute was not related to the change in PaCO2,
but was significantly dependent on the change
in mean arterial blood pressure (p=0.014).
Once the change in mean arterial blood pressure
had been included in the regression model, the
effect of the change in PaCO2 was not signific-
ant (p=0.14); neither was the effect of the
change in PaO2 (p=0.9). Twenty nine per cent
of the variability in the change in cerebral blood
flow velocity resulting from the removal of the
bias flow was attributable to the associated
change in mean arterial blood pressure.

Discussion
There is relatively little data on the effects of
inadvertent PEEP in preterm infants which
occurs even at relatively slow ventilator rates.4
Our findings indicate that the use of high fre-
quency positive pressure ventilation in para-
lysed infants with stable idiopathic respiratory
distress syndrome does not result in adverse
haemodynamic effects or changes in blood gases
that might be attributable to inadvertent PEEP.

In a study such as this, standardisation of
patients by stage of disease is clearly important.
The criteria for the use of pancuronium were
well defined and all the infants were studied
when their ventilatory requirements were stable.

Important factors determining the produc-
tion of inadvertent PEEP are lung compliance
and the amount of air leak around the endo-
tracheal tube.⁴ We attempted to measure static
compliance in all of our infants using a pro-
longed inspiration technique, but were unable
to prevent significant air leaks in 18 of the
infants studied, despite the use of shouldered
endotracheal tubes. The two infants in whom
successful measurements were made had compli-
cances of 0.5 and 0.6 mLCm⁻¹H₂O, respec-
tively. As major leaks around the endotracheal
tubes occurred in most of our infants, it seems
likely that this effect limits the tendency to
develop inadvertent PEEP. As our clinical prac-
tise in regard to type and size of endotracheal
tube used is similar to that in many neonatal
units, we believe that inadvertent PEEP does
not pose a clinically important problem in para-
lysed infants.

A potential criticism of our method in view of
the air leak is that rather than measuring tidal
volumes, we were in fact merely recording
changes in air leak. Though this may be true to
some extent, the rise in minute volumes we
recorded (fig 5) were accompanied by concur-
rent falls in PaCO₂ between 30 and 60 breaths/
minute, which would not have occurred if the
changes measured had merely represented alter-
ations in air leak. The subsequent rises in
PaCO₂ between 60 and 100 breaths/minute
despite further rises in minute volume probably
resulted from the fall in tidal volume at the
higher rate (fig 5) rendering it less effective.

The significant fall in PaO₂ between slow
and fast rates may also be predicted from theo-
retical principles, as increasing ventilator rate
alone (that is, producing an increased number
of ventilator up strokes/unit time) will result in
a fall in mean airway pressure, thus directly
affecting oxygenation.

Our findings are in contrast to those of
Greenough et al, who found that the use of high
frequency positive pressure ventilation did not
result in significant changes in arterial blood
gases.¹³ We suspect that these findings result
from differences in methods. Firstly, half the
infants in this study were ventilated with
Bourns ventilators, which in our experience are
less efficient at rates of 100/minute. Secondly,
flow rates were altered to maintain mean airway
pressure while keeping inspiratory:expiratory
ratios and peak inspiratory pressure constant.
To do this, an increase in PEEP must have been
required (not stated in the paper), which would
have negated the changes in PaCO₂ and PaO₂
that we observed.

It has been recognised in animal studies since
the last century that changes in blood gases have
an important influence on the cerebral vasculature,¹⁴
but the full extent of this effect on cerebral blood
flow had to await reliable methods of estimating
cerebral blood flow in humans.¹⁵ Models for cerebral injury in
preterm neonates have hypothesised that there is
impaired cerebrovascular regulation,¹⁶ with vas-
cular ‘watershed’ regions notably in the periven-
tricular white matter most at risk from ischaemia. If the normal regulatory mechanisms
fail to operate, ‘pressure passive’ blood flow
may result, but evidence for this is scanty and
has been obtained from heterogeneous groups
of infants.¹⁷

The finding that in particular circumstances
changes in mean arterial blood pressure seemed
to exert more influence on cerebral blood flow
velocity (and thus actual cerebral blood flow)¹⁸
than PaCO₂ was unexpected. Though care must
be taken in attaching clinical importance to sig-
ificant results generated unexpectedly from
statistical analysis, several points are of note.
Firstly, for this apparent relationship to have
resulted from the statistical analysis alone is
unlikely, as not only was the significance of the
effect of mean arterial blood pressure gained,
but that of PaCO₂ lost. Secondly, an effect
secondary to the order of rate changes during
the study would have been expected to have an
opposite effect to that seen. Thirdly, this effect
was observed at carbon dioxide tensions
encountered at other times in the study and it is

Figure 5 Mean (SEM)tidal (□) and minute (△) volumes
with increasing ventilator rates. Open symbols represent bias
flow on, shaded symbols represent bias flow off.
therefore unlikely that maximal cerebrovascular dilatation secondary to changes in PaCO₂ had been achieved. Were this the case, changes in blood pressure may indeed have had a more prominent influence on cerebral blood flow, resulting in pressure passive cerebral blood flow.

Finally, this group of infants represents some of the illiest treated in our unit, and the apparent dependence of cerebral blood flow velocity on mean arterial blood pressure may actually represent impaired cerebrovascular regulation. It is, however, important to bear in mind that PaCO₂ acts both by direct and indirect (that is, sympathetically mediated) mechanisms on the cardiovascular system, and thus may still be the governing factor in the responses observed. In addition, we may have been observing the effect of other factors—for example, those secondary to the use of paralysing agents.

The rise in PaO₂ observed with the bias flow turned off was also unexpected. We suspect that this too may have resulted from an indirect effect of the change in PaCO₂ mediated by changes in mean arterial blood pressure. This would in turn raise left atrial pressure and alter shunting. Interestingly, none of the surviving infants subsequently developed ultrasound evidence of preterm cerebral injury. In summary, the use of high frequency positive pressure ventilation in paralysed infants does not seem to result in adverse cardiovascular effects that are attributable to inadvertent PEEP. In addition, it results in statistically significant (though not necessarily clinically relevant) changes in arterial blood gases, which would appear to be readily predictable from theoretical considerations. Under certain conditions these changes in cerebral blood flow velocity that may have been to a certain degree dependent on changes in blood pressure. The use of ventilator rates greater than 50 or 60 breaths/minute in paralysed infants seems to confer no advantage and may in fact be detrimental. Clearly their role in such infants requires further study.

ACF was supported by the Spastics’ Society.

5 Morgan BC, Martin WE, Hornbein TF, Crawford EW. Guntheroth WG. Haemodynamic effects of intermittent positive pressure respiration. Anesthesiology 1966;27:584–90.
Circulatory effects of fast ventilator rates in preterm infants.

A C Fenton, D J Field, K L Woods, D H Evans and M I Levene

*Arch Dis Child* 1990 65: 662-666
doi: 10.1136/adc.65.7_Spec_No.662

Updated information and services can be found at:
http://adc.bmj.com/content/65/7_Spec_No/662

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/