Dampened ventilatory response to added deadspace in newborns of smoking mothers

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Abstract

Objective: Term newborns can compensate fully for an imposed dead space (tube breathing) by increasing their minute ventilation. We have tested the hypothesis that infants of smoking mothers would have an impaired response to tube breathing.

Design: Prospective study

Setting: Perinatal service

Patients: Fourteen infants of smoking and 24 infants of non-smoking mothers (median postnatal age of 37 (11-85) hours and 26(10-120) hours respectively) were studied.

Interventions: Breath by breath minute volume was measured at baseline and when a Dead space of 4.4ml/kg was incorporated into the breathing circuit.

Main outcome measures: The maximum minute ventilation during tube breathing was determined and the time constant (Tc) of the response calculated.

Results: The Tc of the infants of smoking mothers was longer than that of the infants of non-smoking mothers [median 37.3 (range 22.2-70.2) seconds versus median 26.2 range 13.8-51.0) seconds, p=0.016]. Regression analysis demonstrated that maternal smoking status was related to the Tc independently of birthweight, gestational or postnatal age or gender (p=0.018).

Conclusions: Intrauterine exposure to smoking is associated with a dampened response to tube breathing
Introduction

Infants whose mothers smoke during pregnancy are at increased risk for sudden infant death syndrome (SIDS) compared to infants of non-smoking mothers; the increase in risk has been reported to be between two and four fold, but as high as six fold if associated with other risk factors.[1,2,3] A possible explanation for the association is that the infants have neurodevelopmental abnormalities of the control of ventilation.[4] If that explanation was correct, infants of smoking mothers would be predicted to have a reduced ventilatory response to hypercarbia.[4,5,6] Term newborns can compensate fully for an imposed dead space (tube breathing) by increasing their minute ventilation [7]. It has been argued that hypercarbia is the most important stimulus to ventilation during tube breathing.[8,9] If then infants of smoking mothers do have neurodevelopmental abnormalities of ventilation they would be predicted to have an impaired ventilatory response to tube breathing. The aim of this study was to test that hypothesis. We therefore, compared the response to tube breathing of infants of smoking to those of non smoking mothers, all examined in the first week after birth prior to discharge from hospital.

Methods

Infants of smoking and non smoking mothers were recruited from the postnatal wards. Smoking status was determined by questioning the mothers and examining their antenatal records. Smoking mothers admitted smoking at least five cigarettes a day throughout pregnancy. Cigarette smoking was recorded to the nearest five cigarettes per day. Urinary cotinine levels were not assessed. Infants were recruited if born at term, more than six hours old, and had no obstetric or perinatal problems. Informed, written parental consent was obtained and the study approved by the King’s College Hospital Ethics Committee.

Infants were studied while awake, but quiet. Their eyes were open and the infants were breathing quietly when the measurements were made. A face mask was placed over the infant’s nose and mouth. A seven millimetre tube led from the face mask to a pneumotachograph (PK Morgan, Rainham Kent, UK) via a Y connector. The length of the tube between face mask and Y connector was adjusted such that its volume was 4.4mls/kg bodyweight, twice the anatomical deadspace. The pneumotachograph was attached to a differential pressure transducer (MP45, Validyne Corporation, Northridge CA, USA), the signal from which was recorded on a chart recorder (RS3600, Gould, Bilthoven, The Netherlands). Flow, measured from the pneumotachograph, was electronically integrated to give tidal volume and recorded on the chart recorder. From the tidal volume and the duration of inspiratory and expiratory cycle (which were used to calculate respiratory rate), the breath to breath minute volume (MV) was calculated. A second seven millimetre tube connected the face mask to a three way tap via which a bias flow of 2l/min was delivered to the circuit. A third tube connected the three way tap to the remaining part of the Y connector (Figure 1).

Baseline recordings of minute volume were made with the three way tap in the neutral position, so that the bias flow to the face mask eliminated any dead space. When the tap was rotated the bias flow was fed via the third tube directly to the Y connector and the
pneumotachograph so that the bias flow now bypassed the facemask. This resulted in the dead space of the second tube being added to the infant’s respiratory system. The infant breathed through the additional dead space until the breath by breath minute ventilation no longer increased and the maximum minute ventilation (MMV) had been reached. The breath by breath minute ventilation was plotted against time. A polynomial regression line was drawn through the data points collected from when the infant started to breath through the additional dead space. The MMV and the time constant Tc (the time taken to achieve 63%) of the increase in minute ventilation were then calculated.[10] In four infants, the study was repeated 15 minutes later; the coefficient of repeatability of Tc was 11 seconds.

**Statistical Analysis**
Differences between the groups were assessed for statistical analysis using the Mann Whitney U, the paired Wilcoxon or Chi square test as appropriate. Logistic regression analysis was then performed to determine whether the smoking status of the mother predicted the Tc independent of birthweight, gestational, age, postnatal age and gender. Analysis was performed using SPSS version 12.0, SPSS Inc, Chicago, Illinois 60606, USA.

**Sample Size**
Recruitment of 14 infants into each group allowed, with at least 80% power at the 5% level, detection of a difference in the Tc greater than six seconds, approximately 50% of the coefficient of repeatability of the measurement. In a previous study [10] the mean Tc in term infants was between 27 and 29.6 seconds, thus our sample size allowed us to detect a difference between the two groups of 25% or less of the Tc expected in term infants.[10] Recruitment continued until 14 infants were recruited into the smoking group.

**Results**
Thirty-eight infants, including fourteen infants of smoking mothers, were recruited. The median number of cigarettes per day smoked by the mother was 5 (range 5-15). The infants of the smoking and the non-smoking mothers were similar with regard to their gender distribution, birthweight and gestational and postnatal age (Table 1).
Table 1. Comparison of infants of smoking to those of non smoking mothers. Data are demonstrated as n or median (range)

<table>
<thead>
<tr>
<th></th>
<th>Infants of smoking mothers</th>
<th>Infants of non smoking mothers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>SVD*</td>
<td>10</td>
<td>16</td>
<td>1.00</td>
</tr>
<tr>
<td>gestational age</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>(weeks)</td>
<td>39 (37-42)</td>
<td>40 (38-42)</td>
<td></td>
</tr>
<tr>
<td>birthweight</td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>(kg)</td>
<td>3.44 (2.74-4.10)</td>
<td>3.40 (2.78-4.30)</td>
<td></td>
</tr>
<tr>
<td>postnatal age</td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>(hours)</td>
<td>37 (11-85)</td>
<td>26 (10-120)</td>
<td></td>
</tr>
</tbody>
</table>

*SVD – spontaneous vaginal delivery
There were no significant differences between the baseline or “dead-space added” tidal volumes, respiratory rates or inspiratory or expiratory times of the two groups. In both groups, addition of the dead-space caused significant increases in tidal volume and respiratory rate (Table 2).

The baseline MV, the MMV and the change in MV expressed as a percentage of the baseline MV did not differ significantly between the two groups. The median Tc of the infants of the smoking mothers was significantly greater than that of the infants of non-smoking mothers (p=0.016) (Figure 2) (Table 3). Regression analysis demonstrated that the smoking status of the mother was significantly related to the Tc adjusted for birthweight, gestational and postnatal age and gender (p=0.018).
Table 2  Tidal volumes, respiratory rates and inspiratory and expiratory times before (baseline) and with the added dead space (added dead space)
Data are demonstrated as median (range)

Non-smokers:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Added dead space</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>3.6 (2-6)</td>
<td>5.4 (4-8.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>42 (28-71)</td>
<td>49 (27-74)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ti (seconds)</td>
<td>0.6 (0.4-1.1)</td>
<td>0.6 (0.4-1.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Te (seconds)</td>
<td>0.8 (0.4-1.4)</td>
<td>0.7 (0.4-1.2)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Smokers:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Added dead space</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>3.8 (2.6-7)</td>
<td>6 (3.2-12)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>34 (27-59)</td>
<td>43 (25-67)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ti (seconds)</td>
<td>0.6 (0.4-1)</td>
<td>0.6 (0.4-0.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Te (seconds)</td>
<td>1.1 (0.6-1.5)</td>
<td>0.8 (0.6-1)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Ti – inspiratory time
Te – expiratory time
Table 3. Comparison of response to the added dead space of infants of smoking to those of non smoking mothers.
Data are demonstrated as median (range)

<table>
<thead>
<tr>
<th></th>
<th>Infants of smoking mothers</th>
<th>Infants of non smoking mothers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline MV (ml/min/kg)</td>
<td>150 (119-275)</td>
<td>164 (80-263)</td>
<td>0.71</td>
</tr>
<tr>
<td>MMV (ml/min/kg)</td>
<td>400 (262-631)</td>
<td>349 (192-518)</td>
<td>0.26</td>
</tr>
<tr>
<td>Change in MV (%)</td>
<td>120.8 (84.3-216.7)</td>
<td>164.3 (80-263)</td>
<td>0.09</td>
</tr>
<tr>
<td>Time constant of the</td>
<td></td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>of the response (seconds)</td>
<td>37.3 (22.2-70.2)</td>
<td>26.2 (13.8-41.9)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

We have demonstrated that infants of smoking mothers had a dampened ventilatory response to added dead space, that is the time constant of the response was longer. The infants of smoking mothers tended, although not significantly, to be older than the infants of non-smoking mothers. Maturation and a greater response to tube breathing has been demonstrated in the first ten days after birth.[10] Thus, the poorer response of infants of smoking mothers is even more marked. Results of mouth pressure measurements 100 milliseconds after an airway occlusion at the onset of inspiration (P_{0.1}) also suggested that infants of smoking mothers had a reduced ventilatory drive and there was a dose response relationship with the number of cigarettes smoked.[11 A confident conclusion regarding the strength of respiratory drive of infants of smoking mothers, however, cannot be made on the basis of P_{0.1} measurement results, as the magnitude of P_{0.1} not only reflects respiratory drive, but also respiratory muscle strength.

Although the Tc differed significantly between the two groups, their MMV and change in minute ventilation during tube breathing were similar. It is possible that, as we based our sample size calculation on the Tc results, we may have had insufficient power to confidently detect differences in the other variables. Our results, however, demonstrating a significant difference in Tc, but similar changes in MMV in the two groups are predictable from the results obtained in healthy infants. [7] Healthy infants of greater than 36 weeks of gestational age have been demonstrated to be able to fully compensate with regard to their minute volume for two additional dead spaces.[7] Hence, we predicted that the infants of smoking and non-smoking mothers would compensate for the added deadspace with similar changes in minute volume, but the time constant of their response would differ and hence based our sample size calculation on time constant data.

The mechanisms by which babies increase their minute volume to compensate for added dead space are by increasing their tidal volume and their respiratory rate. In both groups in response to the added space, their tidal volume and respiratory rate significantly increased (Table 2). In both groups, the increase in respiratory rate resulted from a significant reduction in expiratory time, but additionally in the infants of non-smoking mothers there was a shortening of the inspiratory time. The latter effect, although significant, however, was a mean difference of only 0.04 seconds.

The time constant, that is, to achieve 63% MMV during tube breathing has been noted to be faster in active compared with quiet sleep when infants were examined in the first ten days after birth.[8] Thus, although the ventilatory responses preceding hypoxia-induced arousal have not been shown to differ between sleep states [12] we took care, to always test the infants when they were awake, but quiet, and so avoid a possible confounding effect of sleep state. We assessed the infants using behavioural criteria only, but when they were measured they were breathing regularly and had their eyes open, so we do feel they were awake rather than in active, rapid eye movement sleep. Previous studies examining ventilatory control have usually examined infants when asleep, this difference needs to be remembered when interpreting our results in the context of the literature. We assessed maternal smoking status by questioning the mothers and examining their antenatal records. Urinary cotinine levels were not assessed not did we have data on the mother’s exposure to smoking by others in her workplace. Infant hair urinary cotinine measurements in an early study [13], however,
did not demonstrate overlap between a maternally declared exposure group and a control group and a good correlation ($r^2=0.63$) was found with maternal reports of smoking. Despite a lack of cotinine measurements in our study, we did find a significant difference in the response to the added dead space between infants whose mothers we classified as smokers and those as non-smokers.

Potentially, the apparatus resistance, hypoxia and hypercarbia could have stimulated the infants’ ventilation during tube breathing.[8] Experiments in which the dead space was ventilated by a fan demonstrated, however, that only 28% of the increase in minute ventilation was due to the resistive effect of the added dead space tubing.[8] In addition, measurements in air and 30% oxygen using a similar technique to that employed in our study yielded similar results.[8] suggesting hypoxia is not a major stimulus. Thus, hypercarbia would appear to be the most important stimulus to ventilation during tube breathing. Indeed, the addition of two added dead spaces has been demonstrated to increase the end-tidal CO$_2$ by only 1.8 mm Hg.[9] Thus, our data suggest that infants of smoking mothers might have a dampened ventilatory response to hypercarbia. The implications of this are that, in adverse conditions, affected infants may develop carbon dioxide retention and associated adverse consequences.

Studies examining the ventilatory response to hypercarbia in infants of smoking mothers have yielded conflicting results [4,5,6]; some studies have demonstrated an increased response [5,6], whereas in a third study [4] no significant difference was noted between infants of smoking and non smoking mothers.[4] In the first two studies [5,6], however, the response to a combined hypercapnic/hypoxic stimulus was examined, but in the third [4] the hypoxic and hypercapnic stimuli were administered separately. In that study [4], however, the infants of the smoking mothers were significantly older than the control infants and this may have influenced the results. Both groups [4] were examined between two and three months of age, whereas we assessed babies in the first week after birth, which may account for the differences in the results of the two studies. Previous studies [4,5,6] have examined infants outside the neonatal period and thus the results could have been influenced by postnatal, as well as antenatal smoking exposure. We, therefore, deliberately chose to examine infants in the first week after birth and importantly prior to hospital discharge; thus, the infants were likely to have only been exposed to antenatal smoking and allowed us to examine whether antenatal smoke exposure alone influenced ventilatory control.

Prenatal nicotine exposure results in cell death in the brainstem of animal models.[14] The abnormalities could result from fetal hypoxia, as nicotine is a powerful vasoconstrictor and reduces blood flow to the uterus, as well as having a direct vasoconstrictor effect on the fetus. [15] In addition, fetuses of smoking mothers have raised carboxyhaemoglobin levels, resulting in a decrease in fetal oxygen tension, a shift in the oxygen dissociation curve to the left and a decrease in oxygen delivery to the tissues.[16][17][18] Nicotine is also a specific neuroteratogen; exposure to nicotine during critical phases of central nervous system development has resulted in abnormalities of cell replication, cell differentiation and receptor function in rat fetuses.[19][20][21] Prolonged exposure to nicotine at low doses throughout gestation led to altered brain development, corresponding to the appearance of nicotinic receptors in the midbrain [22] and reductions in norepinephrine levels in the cerebral cortex, midbrain and hippocampus.[21] In human fetuses, high concentrations of nicotine binding sites in brainstem tegmental nuclei related to cardiopulmonary integration during mid-gestation may make those areas more susceptible to nicotine toxicity during critical periods of brain development.[23] Both peripheral and central chemoreceptor
function in lambs have been demonstrated to be altered by nicotine.[24] Such abnormalities could explain our finding of a dampened response to tube breathing in the infants of smoking mothers.

In conclusion, infants of smoking mothers had a dampened response to tube breathing when compared to infants of non-smoking mothers. The major provoking stimulus to ventilation during tube breathing in the neonate is hypercarbia. Our results are compatible with dampened chemoreceptor function in infants with in utero exposure to cigarette smoking. It is possible that this is a manifestation of neurodevelopmental abnormalities of the control of ventilation, which have been suggested to be a cause for the association of the increased rate of SIDS in infants of smoking mothers.[4] Longitudinal studies are required to further test this hypothesis.

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Competing interests
We confirm that there are no financial competing interests.

Ethics Committee Approval
This study was approved by the King’s College Hospital Ethics Committee.

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What is known on this topic?

Infants whose mothers smoke during pregnancy are at a six fold increased risk for sudden infant death syndrome. It is possible this is due to neurodevelopmental abnormalities of the control of ventilation.

What this study adds?

We have demonstrated that, in the perinatal period, infants of smoking mothers have a dampened ventilatory response to an imposed dead space. That result is compatible with dampened chemoreceptor function following in utero exposure to cigarette smoking.
Figure Legends

Figure 1
Apparatus used to measure the response to added dead space. When the three way tap is turned to be in the vertical position, this diverts the bias flow from the face mask and the infant has to breathe from the added deadspace tube as indicated.

Figure 2
A box plot of the time constant (Tc) of the response to added deadspace by maternal smoking status.
References

21. Seidler FJ, Levin ED, Lappi SE et al. Fetal nicotine exposure ablates the ability of postnatal


Time constant (Tc)

Non Smoking Mothers

Smoking Mothers