Incidence and mechanism of bradycardia during apnoea in preterm infants

D J HENDERSON-SMART, M C BUTCHER-PUECH, AND D A EDWARDS
Perinatal Medicine, King George V Memorial Hospital, Sydney, Australia

SUMMARY Bradycardia occurred during 363 of 1520 apnoeas of 10 seconds' duration recorded in 28 preterm infants. The incidence increased with increasing duration of apnoea (10% of 10-14 seconds, 34% of 15-20 seconds, and 75% of >20 seconds, p<0.001). This was similar for each type of apnoea—central, mixed, and obstructive. During 133 apnoeas in five infants the time from the start of the apnoea to the onset of the fall in oxygen saturation (mean 6.9 seconds) was significantly related to the onset of the fall in heart rate (mean 9.3 seconds) (r=0.67, p<0.001). Recovery in heart rate coincided with resumption of air flow rather than breathing efforts and preceded the recovery in oxygen saturation. These results suggest that bradycardia occurs during apnoea as a response to falling oxygen saturation, probably through a peripheral chemoreceptor reflex that is manifest when breathing efforts are absent or ineffective.

Episodes of bradycardia occur fairly often in preterm infants. They have been reported to occur in association with apnoea,1-4 during upper airway suction,5 as well as during gavage feeding.6 During apnoea, bradycardias are more common in longer episodes,1 2 and various mechanisms for their occurrence have been postulated. Earlier studies suggested that they were due to a chemoreceptor reflex as a result of the rapid development of hypoxaemia during apnoea.1-4 More recently others have suggested that the bradycardia occurs too early in the course of apnoea for hypoxaemia to be the cause7 8 and that other peripheral reflexes, possibly related to upper airway obstruction, may be responsible.7 This study examines the occurrence of bradycardia during polygraphic studies of different types of apnoea in preterm infants and investigates the possibility that hypoxaemia may be the cause.

Methods
Polysgraphic recordings were carried out in 28 infants born at less than 35 weeks' gestation (mean 29.5 weeks, range 27-34 weeks). Gestation was usually assessed from the menstrual history. Where deficient, an ultrasound examination before 20 weeks or a Dubowitz assessment9 after birth was used. Sixty three recordings were made at 28-44 weeks' post-menstrual age, with a total recording time of 242.8 hours. The mean total recording time for each infant was 8.6 hours (range 2.8-20.5 hours). Each individual recording lasted from 1.5 to 8 hours (mean 3.9 hours). Fifteen of the infants had multiple recordings.

Studies were carried out in the newborn nursery in the infants' usual neutral thermal environment. Most infants had an indwelling 5 French gauge orogastric tube. Beat to beat heart rate was recorded from the electrocardiogram leads through a Grass-7P4F tachograph. Breathing efforts were recorded from a mercury in rubber strain gauge around the abdomen at umbilical level. Nasal airflow was recorded from a thermistor in the upper nostril (infant lying on the side). Infants were continuously observed during the recordings and comments recorded on the polygraph. During 30 recordings in 15 infants supplemental oxygen was administered through a plastic head box as part of their clinical management. Theophylline was being administered during 15 of the 63 recordings (10 babies).

In five infants oxygen saturation was measured with a rapid response (0.1 sec) ear oximeter (Waters 200). As this instrument has problems with slow zero drift the recordings were only used to time the changes in oxygen saturation, and the magnitude is not reported. The time from the onset of apnoea to the beginning of the fall in oxygen saturation and to the onset of the fall in heart rate was recorded.
during 133 apnoeas of >10 seconds in these five infants.

Bradycardia was defined as a fall in heart rate of more than 30% below the baseline before the event. The duration of apnoea was determined from the nasal flow trace, and all events of 10 seconds or more in duration were noted. The end of an apnoea was defined by the resumption of two or more breaths within three seconds. The apnoea was deemed to be central in type if both abdominal breathing movements and air flow ceased. Where breathing efforts continued without nasal air flow the apnoea was called obstructive. A combination of central and obstructive (at least three obstructive breaths) was classified as mixed apnoea. If the predominant component of mixed apnoea was central then this was a mixed central event. If predominantly obstructive the apnoea was defined as mixed obstructive. Episodes of generalised body movements associated with irregular breathing movements, diminished nasal air flow, and acceleration in heart rate were excluded from analysis.

Statistical analysis was carried out using the $\chi^2$ test for comparison of proportions, unpaired $t$ test for mean values, and linear regression for the relation between bradycardia onset and the fall in oxygen saturation.

### Results

During the 243 hours of recording in these 28 preterm infants there were 1520 apnoeas of over 10 seconds in duration. Details of these apnoeas have been reported elsewhere.\textsuperscript{10} Briefly, they consisted of 1055 central, 205 mixed central, 100 mixed obstructive, and 160 obstructive apnoeas. Apnoea duration was 10–14 seconds in 1002, 15–20 seconds in 311 and more than 20 seconds in 207. Overall, 363 of these apnoeas were associated with bradycardia. Additional bradycardias were recorded with apnoeas less than 10 seconds in duration (n=18), shallow breathing (three), intragastric tube feeding (two), and after generalised body movements (five).

The major factor influencing the incidence of bradycardia was duration of apnoea (Fig. 1). For each apnoea type there was a significant increase in the incidence of bradycardia as duration of apnoea increased (p<0.001 in each case). At duration of apnoeas of 10–14 seconds and 15–20 seconds bradycardia was more common in all apnoeas with an obstructive component compared with central apnoeas. This difference was highly significant (p<0.001) in the 10–14 seconds group and only just reached significance at 15–20 seconds (p<0.05). In apnoeas over 20 seconds in duration there was no

![Incidence of bradycardia in apnoeas of different types and durations.](http://adc.bmj.com/)

**Fig. 1** Incidence of bradycardia in apnoeas of different types and durations.
difference in the incidence of bradycardia between apnoea of each type.

During apnoeas recorded while infants were being treated with theophylline (n=367) the incidence of bradycardia was higher (34%) than when there was no such treatment (20%, p<0.001). This was weighted by the majority of apnoeas (1002 of 1522) being of 10–14 seconds' duration where the incidence of bradycardia was significantly higher with this treatment (p<0.001). In the 15–20 second apnoeas the incidence was the same (31%), while in those over 20 seconds in duration bradycardias were less common when infants were being treated with theophylline (61% v 81%, p<0.01).

Analysis of 133 apnoeas in the five infants who had continuous traces of oxygen saturation showed a close association between the fall in oxygen saturation and the onset of bradycardia (Fig. 2). Overall, the mean (SD) time to the onset of the fall in oxygen saturation was 6.9 (3.4) seconds, and the mean (SD) time to the onset of the fall in heart rate was 9.3 (4.3) seconds (Table 1). Linear regression of these two variables (Fig. 3) gave a significant correlation (r=0.67), p<0.001. Similar analysis in apnoeas of different types (Table 1) showed significant correlations for each type, although this was only weak for central apnoeas. Strongest correlations were found with mixed obstructive and obstructive apnoeas. In apnoeas of different duration (Table 2) the linear regression of time to onset of fall in oxygen saturation and to heart rate deceleration showed significant correlations in each case.

The mean times to the onset of the fall in oxygen saturation and to the onset of bradycardia became longer with increasing apnoea duration (Table 2). There were also differences in these means when
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Fig. 3 Relation between the onset of the fall in oxygen saturation and the onset of bradycardia, measured from the beginning of apnoea in seconds. Line of identity and linear regression line shown.

apnoeas of different types were compared (Table 1). There were, however, a larger number of longer apnoeas in the groups with the longest times to fall in oxygen saturation and bradycardia (mixed apnoeas). When apnoeas of different types were compared for the same duration group of 20 seconds there were no significant differences between the times to the onset of bradycardia. In this duration group the mean (SD) time to fall in oxygen saturation was longer in mixed obstructive apnoea (10-4 (3-2) sec) compared with central (5-6 (2-6) sec, p<0-01) and mixed central apnoea (7-4 (3-2) sec, p<0-01).

There were 54 apnoeas in four infants in which there was an abrupt and clear resumption of airflow, allowing timing of the recovery in heart rate and oxygen saturation. In each case the onset of the recovery in heart rate occurred within 1-5 seconds and most commonly coincided exactly with the resumption of airflow (61%), and 89% occurred within 0-5 second. The recovery in oxygen saturation commenced between two and four seconds after the beginning of airflow, with a mode of three seconds.

Table 1: Relation between fall in oxygen saturation and bradycardia in apnoeas of different types

<table>
<thead>
<tr>
<th>Type of Apnoea</th>
<th>Time to Fall in Oxygen Saturation (s)</th>
<th>Time to Onset of Bradycardia (s)</th>
<th>Correlation Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>17 (5)</td>
<td>2 (1)</td>
<td>0.85 (0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructive</td>
<td>35 (10)</td>
<td>5.4 (2.3)</td>
<td>0.88 (0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed Central</td>
<td>11 (8.3)</td>
<td>7.7 (3.2)</td>
<td>0.84 (0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed Obstructive</td>
<td>23 (18)</td>
<td>9.3 (3.3)</td>
<td>0.83 (0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>44 (35)</td>
<td>11.3 (4.0)</td>
<td>0.85 (0.34)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Mean (SD) values are reported for time to fall in oxygen saturation and time to onset of bradycardia. The correlation coefficients are calculated using Pearson's correlation coefficient. The P values are calculated using a two-tailed t-test.
Table 2  Relation between fall in oxygen saturation and bradycardia in apnoeas of different durations

<table>
<thead>
<tr>
<th>Duration of apnoea (secs)</th>
<th>10–14</th>
<th>15–20</th>
<th>&gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of episodes</td>
<td>35</td>
<td>44</td>
<td>54</td>
</tr>
<tr>
<td>Mean (SD) time to onset</td>
<td>5.6</td>
<td>6.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.51</td>
<td>0.62</td>
<td>0.60</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Linear regression equations</td>
<td>y=0.46x+3.61</td>
<td>y=0.67x+4.51</td>
<td>y=0.85x+4.87</td>
</tr>
</tbody>
</table>

* Time from onset of apnoea (see Methods).

**Time to onset of fall in oxygen saturation; y= time to onset of bradycardia.

**Discussion**

In this study almost all episodes of bradycardia were associated with apnoea or hypventilation. As noted by others they were more common in apnoeas of longer duration. Previous studies have not examined the effects of both duration and apnoea type on the incidence of bradycardia. A notable finding in this study was the similar increase in the incidence of bradycardia with increasing duration in each type of apnoea (Fig. 2). At shorter apnoea durations there was a higher incidence of bradycardia in mixed and obstructive apnoeas compared with central apnoea. This supports the finding of Vyas et al., who mainly studied shorter events and emphasised the association between obstructive breaths and the onset of bradycardia. They suggested that this was due to a peripheral mechanism possibly due to a vagal reflex stimulated during obstructed breathing.

The reflexes responsible for apnoeic bradycardia have been reviewed and shown in the newborn. Carotid body stimulation, predominantly by hypoxia, augments peripheral respiratory efforts and causes tachycardia. The primary reflex bradycardia, mediated by vagal efferents, is masked by brain stem inspiratory activity and by vagal afferents signalling lung inflation. During apnoea in preterm infants the full diving reflex is observed with peripheral vasoconstriction as well as the bradycardia. These reflex interactions explain why bradycardia can occur early in an apnoea (even at onset) when there is already significant chemoreceptor drive before the onset of apnoea. The presence of considerable resting hypoxic drive to breathing in preterm infants has been shown by the immediate fall in ventilation by about 40% when oxygen is administered. The association between obstructed breaths and the onset of bradycardia during mixed apnoea observed by Vyas et al. and here could be explained by the simultaneous chemoreceptor stimulation of breathing efforts and vagal bradycardia. As the lungs are not inflated during the obstructed breaths the bradycardic reflex would be observed.

For all apnoeas there was not a clinically important difference in the incidence of bradycardia with treatment with theophylline, and results were combined for analysis here. As suggested previously by Southall et al., however, there was a lower incidence in apnoeas of more than 20 seconds in duration, and this might be clinically important. This was true even when the threshold for bradycardia was adjusted to the baseline heart rate here, compared with a fixed level of 80 beats per minute used previously.

Measurements of oxygen saturation using a rapidly responding ear oximeter showed a significant association between the onset of fall in oxygen saturation and the onset of bradycardia. This suggests that chemoreceptor drive might be responsible for the bradycardia and supports the earlier suggestions by others. Due to zero drift on the instrument used here we were unable to determine the precise level of oxygen saturation and only used the instrument as a timer. If levels were known an even better correlation might have been obtained. Furthermore, irregularities in the relation are not unexpected as carbon dioxide drive was unknown and likely to be variable.

Oxygen saturation levels have been shown to decrease rapidly in newborn infants with apnoea. This can be explained by a higher metabolic oxygen consumption in relation to lung oxygen stores in babies nearer to the steep part of the oxygen dissociation curve. Others have claimed that the onset of bradycardia is too early in apnoea to be due to hypoxaemia.

It is not clear why there were significant differences between the times to the fall in oxygen saturation in apnoeas of different types (Table 1). The longest time occurred in mixed obstructive events, and possibly a small amount of air flow during the obstructive component may have delayed...
the fall in saturation. Regression analysis of the time to the onset of bradycardia on the time to the fall in saturation indicated, however, that this was significant for each type of apnoea.

The close association between the onset of air flow and the recovery in heart rate, despite a later recovery in oxygen saturation due to the circulation delay, suggests that lung inflation overrides the reflex bradycardia as shown in adult animals. Furthermore, recovery in heart rate before oxygenation makes direct hypoxic myocardial depression an unlikely cause of the bradycardia in fairly well infants, as studied here. Storrs found a much more variable recovery period, with bradycardia being sustained despite a resumption of breathing efforts in some infants. This could be explained by the fact that only breathing movements and not air flow was measured, so that no distinction could be made between central and mixed apnoea. In the present study recovery in heart rate did not occur in mixed apnoea when breathing efforts were obstructed but occurred promptly with the resumption of air flow.

These findings confirm that bradycardia is an important sign in preterm infants as it represents a marker of deteriorating blood gases in the absence of effective breathing efforts. The likely associated changes in haemodynamics may have deleterious effects. Repeated episodes of splanchnic vasoconstriction and fluctuations in cerebral blood flow are two such possibilities. The cardiovascular reflex responses to apnoeic hypoxia, however, are presumably meant to conserve oxygen, at least in essential organs such as the heart and brain. To do this the full reflex response is required. Where it is modified, as in ill preterm infants, blood pressure can fall and these infants often need active resuscitation. It has recently been suggested that there might also be a fall in cerebral blood flow due to the loss of autoregulation and that these repeated cerebral ischaemic events could lead to periventricular leukomalacia. There is no evidence that similar changes occur in fairly well preterm infants.

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Correspondence to Dr D J Henderson-Smart, Perinatal Medicine, King George V Memorial Hospital, Missenden Road, Camperdown, NSW 2050, Australia.

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D J Henderson-Smart, M C Butcher-Puech and D A Edwards

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