Episodic bradycardia in preterm infants

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Abstract

To analyse factors likely to precipitate bradycardia, 27 preterm infants born at 32 weeks' gestation or less were studied on 89 occasions. Polygraphic recordings of electrocardiography, oxygen saturation, and respiratory effort were made. Subsequently, upper airway flow was measured by a mask and pressure transducer.

In 605 episodes detected during initial recordings, time of onset of bradycardia correlated positively with apnoea duration, with bradycardia often occurring as respiratory effort resumed. Airway closure occurred in 88% of apnoeas associated with bradycardia during flow measurements, and was significantly more common than in apnoea without bradycardia (64%). We suggest that bradycardia is most commonly a reflex response to the resumption of respiratory effort against a closed upper airway as apnoea is terminated, and that this reflex is potentiated by hypoxaemia.

Bradycardia in preterm infants is extremely common and is often considered as simply a minor inconvenience. This view was encouraged by work in the 1970s which suggested that blood pressure¹ and central blood flow² were well maintained during bradycardic episodes in all but the most immature and sick babies. Clearly though, less mature babies are now surviving and more recent work has cast doubt on the benign nature of bradycardias. Using transcutaneous Doppler techniques, Perlman and Volpe demonstrated a fall in anterior cerebral artery flow velocity with bradycardia, which was most dramatic when the heart rate fell below 80 beats/minute.³ Livera *et al* measured an appreciable fall in total intracerebral haemoglobin concentration during bradycardia using near infrared spectroscopy and an occasional rebound above resting values after recovery.⁴ They postulated that such swings in cerebral perfusion may predispose towards the development of periventricular leucomalacia. This may explain why apnoea and bradycardia was found to be an independent risk factor for later morbidity in very low birthweight infants.⁵

When one considers such data it is surprising that so little is known about the aetiology

of bradycardia. A direct effect of hypoxia on the heart was originally considered the most likely explanation.¹ Bradycardia often starts during the early stages of apnoea, however, and most authors now consider that a reflex response is more likely.^{2 6 7} Our group originally postulated that reflex bradycardia was most commonly related to respiratory effort against a closed glottis during upper airway obstruction.⁷ This view has been challenged by Henderson-Smart *et al*, who suggested a peripheral chemoreceptor response to falling oxygen saturation (SaO₂) was the most likely explanation.⁸ Experiments on immature animals, however, have shown that heart rate changes occur at the beginning of respiratory pauses before any change in arterial blood gases.⁹

Oxygenation would appear to exert an important influence, though. We have recently reported that initial SaO₂ before the onset of apnoea is significantly lower in those episodes which result in bradycardia.¹⁰ This study was therefore designed to analyse the relative importance of apnoea, SaO₂, and upper airway patency on the onset of bradycardia in a group of preterm infants.

Methods

Initial polygraphic recordings were made of SaO₂, electrocardiography (ECG), and two signals of respiratory effort, thoracic impedance and abdominal respiratory inductive plethysmography. A total recording time of 353 hours was analysed with a median study time of 3.96 hours (range 2.19-5.29). The recordings were viewed on a storage oscilloscope and suspicious episodes were played on to a chart recorder and analysed manually. Bradycardia was defined as an instantaneous heart rate of 90 beats/minute or less, as calculated from the R-R distance on the recordings. Full details of the methodology for these initial recordings have been described previously.¹⁰

Subsequently upper airway flow was measured with the infants in the right lateral position, usually within an hour of a feed. Sedation was not given. A facemask was applied over the infant's mouth and nose, with a bias flow of air of 3 l/minute conducted by tubing to one port of the mask, to eliminate dead space. The other port was connected to a pneumotachograph which could

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record the infant's respiratory flow by the use of a sensitive pressure transducer. Full details of the system for measuring upper airway flow have also been described previously.¹¹

Recordings of upper airway flow, together with SaO_2 , ECG, and respiratory effort, continued for about half an hour as tolerated. All data were recorded on to tape and analysed manually. In addition to bradycardias, apnoeic episodes of at least 5 seconds' duration, as detected on the flow trace, were analysed for comparison. Using a sensitive pressure transducer an artefact can be recorded during normal tidal breathing which is produced by transmission of the cardiac impulse up the patent airway. This is usually present during central apnoea in preterm infants but disappears when airway closure occurs. The presence or absence of the cardiac artefact is a reliable indicator of the patency of the upper airway, even in the absence of respiratory effort against a closed airway.^{11 12} Using this system, therefore, we were able to correlate the occurrence of bradycardia with upper airway patency and oxygen saturation.

Statistical analysis was performed using simple and stepwise multiple regression analysis and the χ^2 test. Approval for the study was given by the Nottingham ethics committee and informed parental consent obtained.

Patients

Infants born at 32 weeks' gestation or less were included and were not preselected for the presence of apnoea or bradycardia. Eighty nine polygraphic recordings were made on 27 infants. Median birth weight was 1140 g (range 710–1700) and gestational age 29 weeks (range 25–32). Median day of study was 15 (range 1–55) and postconceptional age 32 weeks (range 26–36). There were 16 boys and 11 girls. Eight of the infants had received mechanical ventilation for up to 10 days before entering the study but all were stable in air by the time of recording. Three infants had ultrasound evidence of intraventricular haem-

orrhage, although only one had parenchymal changes and all were asymptomatic. Infants were receiving treatment with theophylline for apnoea during 45 of the 89 studies. Because of the failure of some babies to settle during upper airway flow measurement, flow recordings were only possible on 83 occasions in 24 infants. The characteristics of these infants were very similar to the group as a whole.¹¹

Results

Six hundred and five bradycardic episodes were analysed from the initial polygraphic recordings. We have previously reported that 86% of these were associated with apnoea and that the relationship between apnoea duration and minimum heart rate was poor.¹⁰ Not surprisingly the duration of bradycardia, expressed by the number of bradycardic beats, was positively correlated with apnoea duration in seconds (number of beats = $3.39 + 0.47 \times \text{apnoea duration}$, $r = 0.49$, $p < 0.0001$).

There was enormous variability in the time of onset of bradycardia from the beginning of the apnoeic episode, with a range from one to 55 seconds. It seemed, though, that bradycardia commonly began as respiratory effort resumed at the end of the apnoea. This impression was confirmed by simple regression analysis with a significant positive correlation between apnoea duration and time of onset of bradycardia (onset of bradycardia = $4.86 + 0.37 \times \text{apnoea duration}$, $r = 0.55$, $p < 0.0001$). In other words, the longer the apnoea, the later bradycardia tends to start.

Forty one bradycardias were recorded during airway flow measurements and all were associated with apnoea. Analysis confirmed that bradycardia occurred at variable times, but often as apnoea was being terminated. Fig 1 shows a mixed apnoeic episode with a total duration of nearly 30 seconds. However, respiratory effort against a closed upper airway resumes at approximately five seconds, just as bradycardia begins. Apnoea was present on the flow trace in all 41 episodes in which bradycardia occurred. Median apnoea duration was 14 seconds (range 2–51) with bradycardia occurring after a median 11 seconds of apnoea (range 1–34). The relationship between the time of onset of bradycardia and apnoea duration for these episodes is shown in fig 2. This confirms a strong positive correlation ($r = 0.73$, $p < 0.0001$).

We have previously reported the effect of SaO_2 on the onset of bradycardia during the polygraphic recordings. Median baseline SaO_2 was lower and the fall in SaO_2 with apnoea was greater during bradycardia compared with non-bradycardic episodes.¹⁰ However, it is difficult to understand how the temporal relationship between the termination of apnoea and onset of bradycardia could be explained on the basis of falling SaO_2 and therefore later onset of bradycardia. This suggests that the fall in SaO_2 is not the primary factor which precipitates bradycardia. To analyse this further we performed stepwise multiple regres-

Figure 1 A prolonged mixed apnoea, with both resumption of respiratory effort and bradycardia, marked by arrow, occurring after five seconds (flow=upper airways flow, RIP=abdominal respiratory inductive plethysmography).

Figure 2 Time of onset of bradycardia from the beginning of apnoea(s) plotted against apnoea duration(s). Onset of bradycardia = $4.54 + 0.39 \times \text{apnoea duration}$, $r = 0.73$, $p < 0.0001$.

sion analyses on both polygraphic recordings and airway flow data. This showed no effect of either baseline Sao_2 or the fall in Sao_2 with apnoea, on the timing of bradycardia, once allowance had been made for apnoea duration.

Upper airway patency, however, is a potentially important factor. We therefore compared the 41 bradycardias with 277 episodes of apnoea lasting at least five seconds on the flow trace during which no bradycardia occurred. Upper airway closure, as detected by the absence of the cardiac artefact, occurred during 36 of 41 apnoeas associated with bradycardia (88% of the total). It occurred only in 178 of 277 episodes without bradycardia (64% of the total). Upper airway closure, therefore, occurred significantly more frequently during bradycardia ($p = 0.005$, χ^2 test). Apnoea associated with bradycardia was consequently more likely to be mixed in character with 61% in the bradycardic and 36% in the non-bradycardic group being mixed episodes ($p < 0.01$, χ^2 test).

Discussion

The inter-relationships between apnoea, Sao_2 , airway patency, and bradycardia are clearly complex. Henderson-Smart *et al* suggested that a fall in Sao_2 was the main precipitant of reflex bradycardia.⁸ Using a conventional six seconds averaging time on our oximeter, we were unable to study the temporal relationship between the fall in Sao_2 and the onset of bradycardia. However, it is difficult to explain the relationship between the onset of bradycardia and termination of apnoea on the basis of falling Sao_2 : bradycardia occurs later in longer apnoea where the Sao_2 drop is greater. However, the data of Henderson-Smart *et al* do confirm that bradycardia tends to occur later with longer apnoea; at a mean of 6.2 seconds in apnoeas of 10–14 seconds and at 11.85 seconds in apnoeas of greater than 20 seconds.⁸ They did not discuss why this should be. It is possible that both bradycardia and the fall in Sao_2 are reflex responses to respiratory effort against a closed upper airway. It has been demon-

strated in older infants that episodes of apnoea with an obstructive element produce more rapid desaturation than central apnoea.¹³ In common with others,¹⁴ however, we have been unable to confirm this in preterm infants.¹¹

In 86% of bradycardias in the polygraphic recordings apnoea was present, as detected by the absence of respiratory effort. The true figure is probably much nearer 100%, as many bradycardias in this part of the study were associated with disorganised and high amplitude respiratory effort which we have seen is common during mixed or obstructive apnoea.¹¹ Indeed, all bradycardias recorded with airway flow measurements were associated with apnoeic episodes, which were often very short. This was also noted previously in the study of Vyas *et al*.⁷

Vyas *et al* first suggested that airway closure was important in the pathogenesis of bradycardia. We have confirmed this, showing airway closure is significantly more common during apnoeas with bradycardia than those without. We have also demonstrated that there is a close temporal relationship between the onset of bradycardia and the resumption of respiratory effort. It would appear that the original observations of Vyas *et al* are substantially correct: that bradycardia is common when respiratory effort resumes against a closed upper airway.

Sao_2 is clearly important, though, as demonstrated by the fact that a low baseline Sao_2 is more likely to produce bradycardia during apnoea. It has also been shown that laryngeal chemoreflex bradycardia, another vagal reflex, is potentiated in conditions of relative hypoxia, at least in older infants.¹⁵ We therefore postulate that reflex bradycardia as a result of respiratory efforts against a closed upper airway is potentiated in the presence of relative hypoxaemia.

Mixed apnoea occurs in the presence of a closed upper airway and, being generally longer than central apnoea, commonly produces desaturation. It is, therefore, particularly likely for mixed apnoea to result in bradycardia. We suggest that the patency of the upper airway is much more important than has previously been realised in the prevention of morbidity from apnoea and bradycardia in preterm infants. Continuous positive airway pressure, which seems to act by splinting open the upper airway,¹⁶ should therefore be considered in all preterm infants with problematical apnoea and bradycardia.

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