Upper airway patency during apnoea of prematurity

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Abstract

Twenty four preterm infants (median birth weight 1120 g and gestation 29 weeks) were studied on 83 occasions by measuring upper airway airflow. Airway patency was detected by the transmission of cardiac impulse up the airway and airway closure by its absence. A total of 309 apnoeas of at least five seconds' duration were recorded. One hundred and eighty (58·0%) were central, 109 (35·5%) mixed, and 20 (6·5%) obstructive.

Airway closure was noted in 47% of apparently central apnoeas. Airway closure occurred as apnoea lengthened; the airway remained patent in 38% of apnoeas of 5–9 seconds, 17% of those 10–14 seconds, and 11% of those 15–19 seconds' duration. Airway closure occurred in every apnoea of ≥20 seconds. As a consequence, closed apnoeas were longer than open apnoeas (mean 9·7 *v* 6·6 seconds).

In 72% of mixed apnoeas, airway closure was recorded during the central element and this usually preceded obstructive breaths. In 20% of mixed apnoeas and 15·5% of the total group the airways closed, having previously been patent. This occurred after a mean of 3·5 seconds (range 1–17). Mixed apnoea produced a significantly greater drop in arterial oxygen saturation than central apnoea, but only because of the greater duration of mixed apnoea.

Airway closure occurs in both central and mixed apnoea and appears to be important in the pathophysiology of mixed apnoea. Central and mixed apnoea are part of a continuum of airway closure and not separate entities.

Upper airways obstruction is an important factor which predisposes to the development of apnoea in preterm infants.[1] Pure obstructive apnoea is rare, however, occurring in 10–12% of apnoeas in published series.[1–3] Mixed apnoea, with both central and obstructive elements, is more common and its prevalence increases, relative to pure central apnoea, as apnoea duration lengthens.[2 3] It is not known, however, whether these two types of apnoea have different aetiologies, with mixed apnoea being intrinisically longer, or whether they are part of a spectrum, with initially central apnoeas becoming mixed as the apnoea continues.

Our group has previously reported that airway closure may occur during apparently central apnoea.[4] If airflow is measured at the mouth and nose during tidal breathing an artefact, produced by the transmission of the cardiac impulse up the patent airway, is also recorded. This cardiac artefact is usually present during central apnoea in preterm infants but disappears when airway closure occurs.

It has been demonstrated previously that the presence of the cardiac artefact is a reliable indicator of upper airway patency. All apnoeic episodes with a cardiac artefact present on the flow trace began at end expiration and if the artefact persisted until the end of the episode, the first respiratory effort always produced a tidal volume. In the absence of the artefact, apnoea could begin at other points in the respiratory cycle and in over half of these episodes the first respiratory effort did not result in a resumption of flow.[4]

We postulated that airway closure during central apnoea could result in mixed apnoea, and be detected by the absence of cardiac artefact. We have therefore serially studied a group of preterm infants to analyse this phenomenon in more detail and to determine its importance in the aetiology of mixed apnoea.

Patients and methods

METHODS

Infants were studied in the right lateral position in their own cot or incubator, usually within an hour of a feed. No sedation was used. A flow of air of 3 l/minute from a cylinder was connected to one port of a Bennett face mask in order to eliminate dead space. The other port of the mask was connected by tubing to a Fleisch O pneumotachograph. Efferent flow, modified by the infant's inspiratory and expiratory effort, was recorded by the pressure gradient along the pneumotachograph, which was measured by a Validyne MP45 differential pressure transducer (range ±0·9 cm H_2O) and a transducer amplifier (P K Morgan No 076). The performance of the transducer was excellent and enabled accurate recording of the cardiac artefact in infants as small as 720 g. The 63% response time of the pneumotachograph and transducer, measured by a sudden closure of the barrel of a syringe connected to the apparatus, was 5 ms, giving a 3 dB/octave loss at 32 Hz. The total resistance of the mask system was 5·8 cm H_2O/l/second, measured at a flow of 3 l/minute.

Once the infant was asleep, the mask was placed over the mouth and nose, the seal being helped by the application of petroleum jelly to the rim of the mask. The flow signal was recorded on to tape (Racal, store 4) throughout the study, together with an electrocardiogram from a Life-Trace 12 monitor, arterial oxygen saturation (Sao_2) from an Ohmeda Biox 3700 monitor, and abdominal respiratory inductive

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plethysmography from a locally constructed model (Respivest). Additionally, the flow signal was recorded on to a chart recorder (Devices) together with the signal from a thoracic impedance monitor (Simonson and Weal respiratory 8061). Two channels representing respiratory effort were used to improve detection,[5] and the system has been described in more detail elsewhere.[6] Flow was recorded for between 20 and 30 minutes, as tolerated by the infant. Apnoeic episodes were later played on to a Gould chart recorder and analysed manually.

For the purposes of the study, apnoea was defined as cessation of airflow for 5 seconds or longer, and was regarded as central if there was no respiratory effort on the impedance and inductance traces. Apnoea was regarded as mixed if there was at least one obstructed breath and a central element of at least 3 seconds. If respiratory efforts continued, and/or the pause between efforts was less than 3 seconds, then obstructive apnoea was diagnosed. For each apnoea the presence or absence of cardiac artefact, the point in the respiratory cycle at which apnoea began and the drops in oxygen saturation were recorded.

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

PATIENTS

The infants were not preselected for the presence of apnoea. The only entry criteria were a gestational age at birth of 32 weeks or less and being clinically stable in air at the time of study. Twenty four infants were studied, many longitudinally, on a total of 83 occasions. Median gestation was 29 weeks (range 25–32) and birth weight 1120 g (range 710–1700). Median day of study was 16 (range 2–55) at a median postconceptional age of 32 weeks (range 26–36). Thirteen boys and 11 girls were included and 41 studies were performed while receiving methylxanthine treatment for apnoea. Eight of the infants had received mechanical ventilation for up to 10 days before entering the study, but none had respiratory symptoms at the time. Three infants had ultrasound evidence of intraventricular haemorrhage but only one had any parenchymal changes and all were asymptomatic.

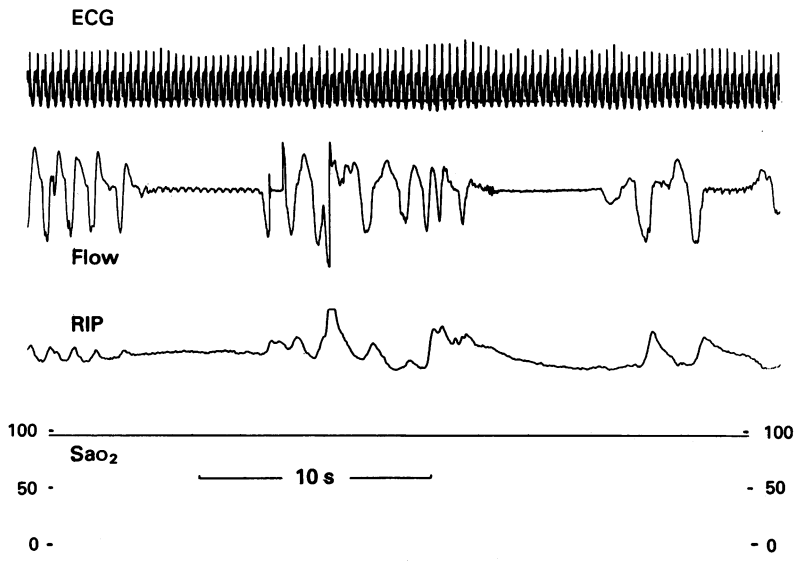

Figure 1 Two short central apnoeic episodes, the first with a patent and the second a closed upper airway. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

Results

AIRWAY PATENCY

Infants commonly became apnoeic during application of the mask and also during arousal, when they often strained against a closed glottis, as described by others.[7] Such episodes were excluded from analysis, leaving 309 apnoeic attacks for analysis. Episodes occurred in 60 of the 83 studies, with a median two apnoeas per study (range 0–19). A total of 180 apnoeas (58·0%) were central, 109 (35·5%) mixed, and 20 (6·5%) obstructive.

Two short central apnoeas are shown in fig 1. During the first episode the cardiac artefact is seen clearly throughout, indicating airway patency. However, during the second episode, which is also apparently a central apnoea, the cardiac artefact is not seen, indicating upper airway closure.

The relationship between apnoea classification and upper airway patency is shown in table 1. During only 53% of central apnoeas was upper airway patency maintained, and the airway was closed throughout during 30%. Nonetheless, this is not always the case. In fig 2 the cardiac artefact is not seen during the apnoea, and when breathing efforts resume after 12 seconds tidal exchange does not occur for a further 12 seconds and a mixed apnoea results.

The airway was closed throughout in 72% of mixed apnoeas, and this airway closure was evident even during the central element of the apnoea.

It is common, also, for airway patency to change throughout an apnoeic attack. This is usually a patent upper airway becoming closed as seen in fig 3, where the apnoea is classified as central, as tidal breathing resumes with the first respiratory effort. However, this pattern may also produce a mixed apnoea, as seen in fig 4. A patent airway closing was seen on 48 occasions (15·5% of the total), and approximately half of these were central and half mixed. This pattern was consistent with the commonest type of mixed apnoea, where the central element precedes obstructive breaths. This was seen in 69 of 109 mixed apnoeas, with obstruction prceding the central element on 40 occasions.

Table 1 Upper airway patency with respect to apnoea classification. Figures are numbers (%)

Upper airway patency	*Apnoea classification*		
	Central	*Mixed*	*Obstructive*
Open	96 (53)	5 (5)	1 (5)
Closed	54 (30)	78 (72)	18 (90)
Open→closed	25 (14)	22 (20)	1 (5)
Closed→open	5 (3)	4 (4)	0

The difference in the distribution is significant (χ^2, p=0·0001).

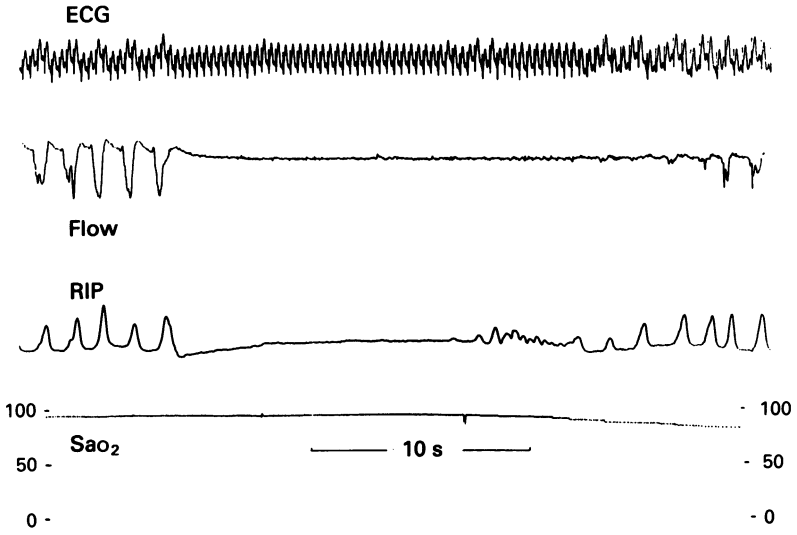

Figure 2 Prolonged mixed apnoea with airway closure even during the central element. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

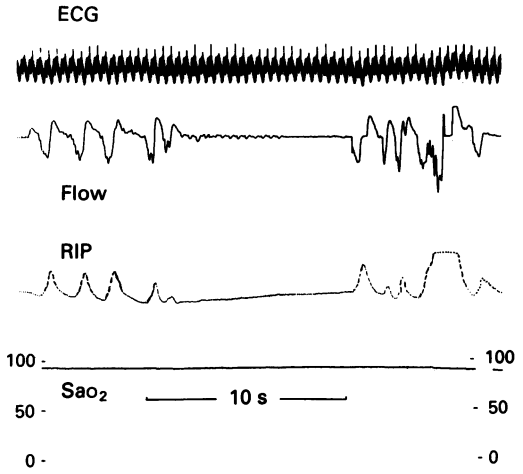

Figure 3 Central apnoea with a patent airway becoming closed. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

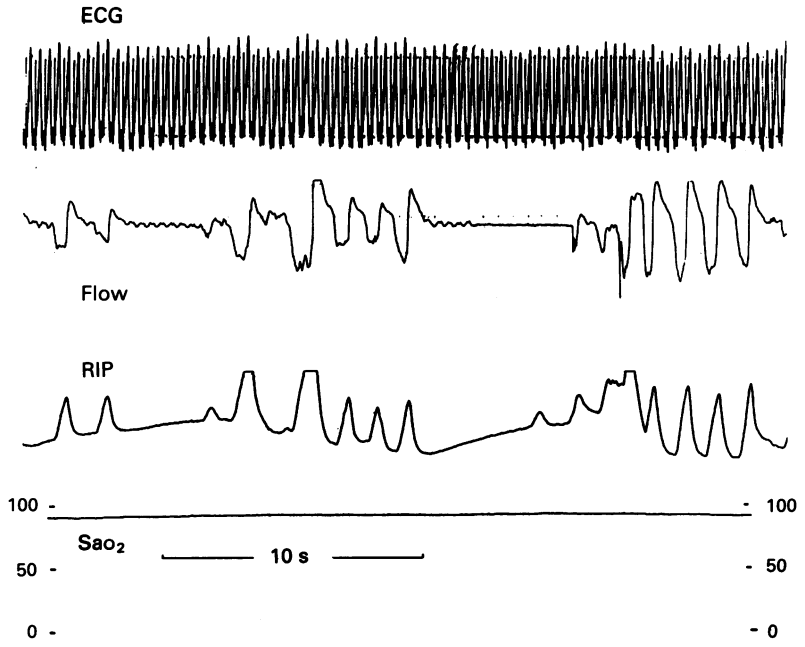

Figure 4 A patent airway closing and resulting in mixed apnoea. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

This was a significant difference ($p<0{\cdot}01$, χ^2 test).

A closed airway becoming patent without a resumption of breathing was also seen, as in fig 5, but was rare, occurring in only 2% of total apnoeas. Pure obstructive apnoea, usually with a closed airway throughout as shown in fig 6, was also rare. One apnoea with an open airway was classified as obstructive. This apparent paradox is explained by the difficulty in distinguishing breathing effort from body movement, even with two signals representing respiratory effort.

Confusion between respiration and body movement also explains the five mixed apnoeas with a patent airway. In retrospect, these few episodes with an apparently contradictory pattern have a high amplitude and disorganised trace on both respiratory signals, and almost certainly represent body movement rather than breathing effort. The difficulty in distinguishing the two is already well recognised.[7] Apart from these, when respiratory effort resumed with an open upper airway, tidal exchange occurred immediately.

As reported previously, apnoea usually begins at end expiration,[4] as seen in 284 of 309 apnoeas in this study. This was always the case when the upper airway was initially patent. On 19 occasions apnoea started in mid-expiration and on six occasions in mid-inspiration, with both these patterns resulting from airway closure.

Apnoea tends to become less common with increasing age, but the degree of airway closure did not appear to alter with age. There was no significant change in the percentage of episodes in which closure occurred with respect to either postconceptional or postnatal age. However, no infants were studied beyond 36 weeks' postconceptional age and improvement may have occurred later.

APNOEA DURATION

Mean apnoea duration recorded was 8·3 seconds (range 5–51 seconds). Apnoea duration divided by apnoea classification and airway patency is shown in table 2. Mixed apnoea was slightly longer than both central ($p<0{\cdot}0001$) and obstructive ($p<0{\cdot}02$) apnoea. Central and obstructive apnoea durations were not significantly different.

These observations are explained by the changing degree of airway patency at different apnoea durations. Airway closure becomes more common as apnoea continues. Complete airway patency was seen in 38% of apnoeas of 5–9 seconds, 17% of those 10–14 seconds, and 11% of those 15–19 seconds' duration. Airway closure occurred in every apnoea of 20 seconds' duration or greater. Consequently, closed apnoeas were significantly longer than open apnoeas ($p<0{\cdot}0001$). Airway closure *per se* appears to have an effect on apnoea duration. Episodes of central apnoea with airway closure tended to be longer than those which remained patent. There was a small but significant difference (mean 7·3 *v* 6·4 seconds, $p<0{\cdot}02$).

In the 48 episodes in which a previously

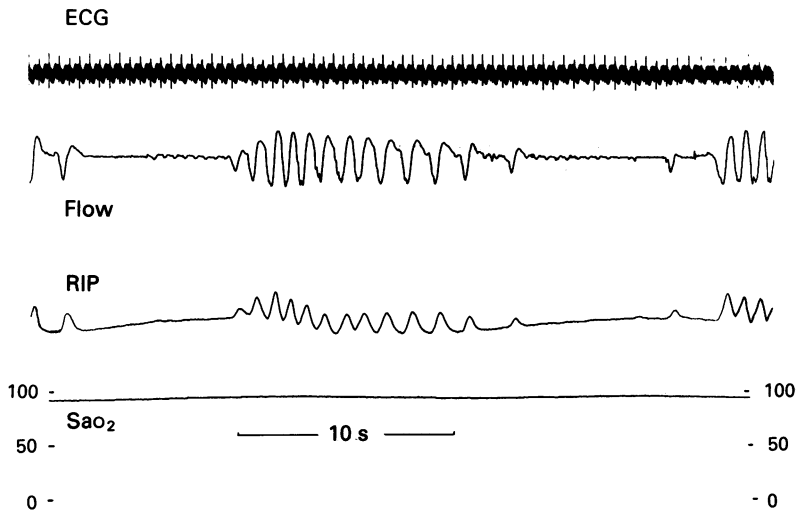

Figure 5 During the first episode here the closed airway becomes patent without apparent respiratory effort occurring. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

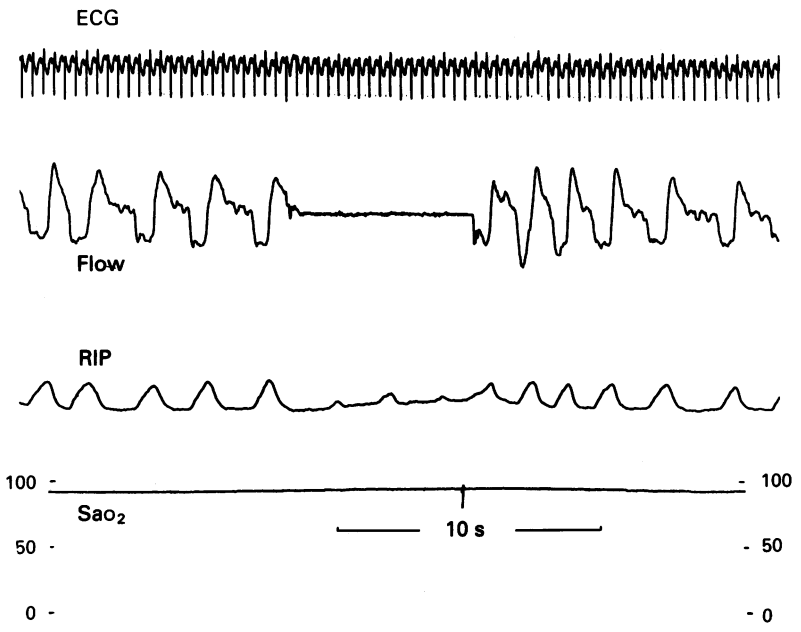

Figure 6 A short obstructive episode with closed airway throughout. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

Table 2 Apnoea duration (seconds) with respect to apnoea classification and airway patency

	Mean (SD)	*Median*	*Range*
Apnoea classification:			
Central (n=180)	6·8 (2·2)	6	5–19
Mixed (n=109)	11·0 (8·3)	8	5–51
Obstructive (n=20)	7·6 (3·4)	6·5	5–20
Airway patency:			
Open (n=102)	6·6 (2·0)	6	5–19
Closed (n=150)	9·7 (7·2)	7	5–51
Open→closed (n=48)	8·2 (4·6)	7	5–33
Closed→open (n=9)	6·0 (0·8)	6	5–7

patent airway closed the airway remained patent for a mean of 3·6 seconds (range 1–17); this was followed by a mean closed element of 4·6 seconds (range 1–16). Total apnoea duration during such episodes was not significantly different from closed apnoeas as a whole, but significantly longer than open apnoeas ($p<0·002$).

OXYGEN SATURATION

There was a close overall positive correlation between the Sao_2 drops during apnoea and apnoea duration (Sao_2 drop=(apnoea duration $\times 0·67)-1·0$, $r=0·75$, $p<0·0001$). The Sao_2 drops during mixed apnoea were significantly greater than that during central apnoea (Median 5% *v* 2%, $p<0·0001$). However, this was purely a function of the longer duration of mixed apnoea because when the slopes of Sao_2 against duration for each class of apnoea were compared there was no significant difference.

To elucidate this further we performed a stepwise multiple regression analysis to look at the effects of apnoea duration, initial Sao_2 before the onset of apnoea, apnoea classification, and airway patency on the Sao_2 drop produced. As previously stated, apnoea duration was strongly related to Sao_2 but additionally there was a negative correlation between initial Sao_2 and Sao_2 drop ($p<0·0001$). Those with a low baseline Sao_2 desaturated further with apnoea than those who were well oxygenated. This negative correlation could have been predicted from the knowledge of the haemoglobin dissociation curve. However, neither the classification of apnoea nor the degree of airway patency had any significant effect on the drop in Sao_2.

Discussion

By serially studying a group of preterm infants we have been able to clarify the importance of patency of the upper airway and its closure, which may occur during apnoea. In roughly half of our apparently central apnoeas, airway closure was recorded. In 72% of mixed apnoeas the airway was also closed during the central element. That this same phenomenon is seen in both central apnoea and the central element of mixed apnoea is strong evidence that these two types of apnoea are part of the same pathophysiological process. Furthermore, closure of an airway that had previously been patent is also seen in both types. This pattern has only been reported once before,[4] but the use of a sensitive pressure transducer has enabled us to show that it is present in 15·5% of apnoeas. Airway closure occurs more commonly, though, at end expiration at the beginning of the apnoea. We have also noted that apnoea usually precedes obstructed breaths during mixed apnoea and that as apnoea continues the airway is increasingly less likely to be patent. In fact, airway closure always occurred in apnoeas of 20 seconds' duration or greater.

All these observations lead us to a unified hypothesis by which mixed apnoea may be explained. Central apnoea occurs at end expiration and in half of these episodes the airways remains patent. Spontaneous recovery then commonly occurs, although some infants go on to develop airway closure. Of those episodes with airway closure the first respiratory effort may overcome the obstruction, in which case the episode is still outwardly central in appearance. However, a proportion are not terminated by the first respiratory effort and mixed apnoea results.

Clearly, during the minority of mixed apnoeas in which obstructive breaths precede the central element, and also obstructive apnoea itself, a different mechanism is in operation. Obstruction, for whatever reason, occurs first and in a proportion of these precipitates apnoea, during which the airway is usually closed. That obstruction may precipitate a cessation of respiratory effort in infants is well documented.[8 9]

Our results and the above hypothesis fit well with previously published observations.[1-3] The one major difference is the smaller number of pure obstructive apnoeas which we have detected. Care needs to be taken in applying a facemask over an infant's mouth and nose, particularly to avoid neck flexion which may precipitate obstructive apnoea.[10] However, we were careful to study infants with their necks in a neutral position. Indeed, if the mask had affected our number of apnoeas, then we would have expected an increase in the relative proportion of obstructive apnoeas. Infants are not obligatory nose breathers,[11] and it is possible that some infants in our study used oral breathing in response to nasal obstruction. The studies of Butcher-Puech *et al*[2] and Muttitt *et al*[3] used nasal flow and may have classified episodes of oral breathing as obstructive apnoea. However, this was not noted to be important in the study of Dransfield *et al*,[1] nor in older infants with apnoea.[7] We have included short apnoeas of 5–9 seconds' duration in our study in order to look at airway closure. This is not likely to affect the proportion of obstructive apnoeas as these are usually short and, in fact, if only apnoeas of $\geq$10 seconds are considered the relative proportion of obstructive apnoeas drops to 5%. The most likely difference between our study and others is that we used two signals of respiratory effort, which helped us distinguish this from body movement. The previous studies each used only one signal and may have classified mixed or central apnoea with body movement as obstructive apnoea.[1-3] This has been discussed in detail by Van Someren and Stothers.[7] The prevalence of obstruction may have been even lower if we had used oesophageal pressure measurements as in our previous study[4]: although the total number of apnoeas was smaller, there were no episodes of pure obstructive apnoea.

Mixed apnoea is clearly more common than obstructive apnoea. It is also more significant, as it results in a larger fall in Sao_2. This greater Sao_2 drop, however, is purely a consequence of the greater duration of mixed apnoea, rather than any direct effect of obstruction on the rate of fall of Sao_2. This is supported by the study of Muttitt *et al*,[3] but is in contrast to work in older infants,[12] although the number of obstructive episodes in this latter study was very small.

This study has elucidated the role of airway closure in apnoea in general, and mixed apnoea in particular. Two important questions remain unanswered, though: What is the mechanism by which airways closure occurs? and Where is the site of obstruction?

Closure of the airway could simply be a passive phenomenon, with tone being lost in the upper airway when flow ceases during central apnoea. The greater predisposition of preterm infants to airway closure with apnoea would then be explained by the narrower lumen making complete closure more likely.[13] However, studies on animals under anaesthesia compared with studies postmortem have shown that there is active maintenance of upper airway patency, mainly by genioglossus and geniohyoid, which prevents upper airway closure.[14] Additionally, genioglossus activity is linked closely to that of other respiratory muscles,[15] and there is evidence that flow through the upper airway results in feedback from airway receptors to maintain genioglossus tone.[16] Therefore, it is possible that both the relaxation of other respiratory muscles and the cessation of upper airway flow may actively inhibit genioglossus activity, resulting in airway closure. Although passive forces may play a part in this, the fact that we have occasionally seen upper airway patency being restored in the absence of respiratory effort, would tend to support the concept that airway patency and closure are actively determined.

The site of airway obstruction has yet to be defined. From our initial study we postulated that laryngeal closure was likely,[4] but work using pressure sensitive pharyngeal catheters has suggested that upper pharyngeal closure is responsible.[17] One criticism of the use of such catheters is that placement has to be precise, making interpretation of results difficult. We are now performing direct upper airways endoscopy in infants with apnoea in order to visualise the site of airway obstruction. Preliminary studies have suggested that closure of the arytenoid masses and aryepiglottic folds across the vocal cords may be important.[18]

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