CURRENT PROBLEM

Pathophysiology of apnoea in preterm infants

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Apnoea is usually divided into three main types: central, obstructive, and mixed, the last of which contains elements of the first two. Recent investigations, however, have suggested that this division is less clear cut, and may be both artificial and misleading in terms of aetiology and therapeutic approaches. This division may be more a reflection of the inadequacies of the monitoring equipment that is used to detect apnoea in infants than of any real difference in the underlying pathophysiological processes.

The upper airway

INCREASING EVIDENCE FOR AN IMPORTANT ROLE
Although pure obstructive apnoea (defined as continued respiratory efforts with no flow of air) is relatively uncommon—about 12% among preterm babies—if those infants with mixed apnoea are included then about 70% of preterm infants with apnoea have episodes of airway obstruction.[1] Recent work has shown that airways are closed during the 'central' part of mixed apnoea during which respiratory efforts are absent as well as during apparently 'pure' central apnoea. When flow is detected by a face mask system that incorporates a pneumotachograph and sensitive pressure transducer, a cardiac artefact can be detected on the recorded flow trace. When the upper airway closes this artefact disappears, so it can therefore be used as an indirect indicator of the patency of the airway. Using this method closed airways have been detected in about half the cases of apparently 'central' apnoea (unpublished observations). It is therefore clear that closure of the airway is common to all forms of apnoea, and possibly

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has a central role in the pathophysiology of apnoea. The figure shows diagramatically how airway closure, and the infant's response to it, may give rise to the apparently different types of apnoea.

SITE OF OBSTRUCTION
The two most likely sites of loss of upper airway patency on anatomical and physiological grounds are the larynx and pharynx.

Larynx
The larynx of a newborn infant has been described as 'a grossly enclosing composite of skeleton and musculature and a more discretely mobile, internal composite'.[2] The laryngeal vestibule of the infant is small in all diameters, particularly in relation to the lumen of the trachea, making it anatomically a likely site for obstruction.

It is often difficult to intubate apnoeic infants, because instead of finding the cords widely open as one might expect in a hypoxic, 'flat' baby they are often quite tightly adducted on laryngoscopy. Resumption of respiratory efforts against such a closed glottis has also been described. This may indicate that the larynx is the site of upper airway obstruction in apnoeic preterm infants.[3] Using an ultrafine fibreoptic endoscope passed transnasally we have seen obstruction at the laryngeal level in some preterm infants with problematical apnoea. The obstructing structures seem to be disproportionately large arytenoid masses and aryepiglottic folds. We have seen such obstruction not only in obstructive apnoea but also in the central part of mixed apnoea and in apparently pure central apnoea, which correlates with the findings of indirect indicators of airway patency (unpublished observations).

'Laryngeal chemoreflex' in preterm infants is well known[4]; this can be stimulated with boluses of fluid of as little as 0·01–0·1 ml instilled into the oropharynx. The response seems to be chemosensitive, there being a greater response to water than saline rather than simply a mechanoreceptor reaction in response to the presence of the bolus.[5] Stimulation of this reflex produces swallowing, airway obstruction, and apnoea that may at times be prolonged. This reflex is thought to protect the airway, and many features of it are similar to spontaneous apnoea seen in preterm infants.[6] It has been suggested that apnoea represents an exaggeration of this protective reflex in preterm infants.

Infants with malformations of the central nervous system such as meningomyelocele,
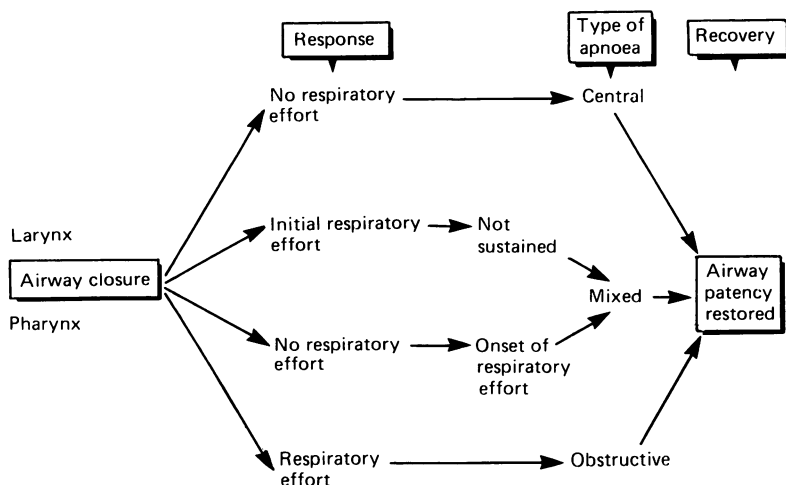
Obstruction of airways giving rise to apparently different types of apnoea.

Arnold-Chiari deformity, and hydrocephalus, which result in paralysis of the abductor cord secondary to raised intracranial pressure, commonly get apnoea and upper airway obstruction.[7] Direct electrical stimulation of the superior laryngeal nerve also produces glottic closure that is followed by prolonged apnoea in monkeys. This is a reflection of the degree of maturation, with preterm and newborn monkeys having more extreme apnoea after stimulation than older monkeys.[8]

Pharynx

The pharynx is a muscular tube without any rigid support. When subject to negative intraluminal pressure (as during inspiration) the tendency is for the walls of the pharynx to collapse. The upper airway muscles, such as the genioglossus and geniohyoid, are important in counteracting this tendency and in maintaining pharyngeal patency.[9] Reduced tone in these muscles, as one might expect in preterm infants or during rapid eye movement sleep, may predispose to upper airway obstruction. The oropharynx has been identified by radiography, electromyography, and laryngoscopy as the site of airway obstruction in adults and older infants with obstructive sleep apnoea.[10][11]

A catheter filled with saline and placed in the pharynx has been used to monitor pharyngeal pressure changes in preterm infants with apnoea.[12] Results have suggested that airway obstruction occurs high in the oropharynx and above the catheter tip in over 90% of episodes. The position of the catheter tip in these studies is critical and it was judged only by the pressure changes seen in normal breathing and swallowing and not confirmed laryngoscopically or radiologically. There is, however, good evidence of the importance of the function of muscles of the upper airway such as the genioglossus in the recovery of apnoea,[13] as increased electromyographic activity is recorded at the end of an episode, which leads to restoration of airway patency.[14] Infants with mixed and obstructive apnoea may respond to occlusion by reducing the activity of these muscles.[15]

There is therefore evidence to suggest that in apnoeic episodes airway patency may be lost at either laryngeal or pharyngeal level. It is also possible that obstruction at one of these sites may, by causing cessation of airflow, produce the collapse of the other.

Central immaturity

Immaturity in the control of respiratory activity clearly plays an important part in the pathophysiology of apnoea of prematurity. There is now accumulating evidence of adaptation of higher centres—including those of respiratory control—that are gestation dependent. The ventilatory response to carbon dioxide shows a striking difference in preterm infants with apnoea when compared with controls. Infants with apnoea have depressed ventilatory responses to hypercapnia and other measures, suggesting that there is a reduced respiratory centre output that is independent of overall pulmonary function.[16] When the effect of increasing anatomical dead space was examined by analysing the response to tube breathing, however, it was found that although most immature infants had poor respiratory adaptation, there was no deficit in control in babies with apnoea once correction for postconceptional age had been made (unpublished observation).

Further evidence of brain stem immaturity comes from measures of neuronal function in preterm infants with apnoea. Auditory evoked responses have been used to measure brain stem conduction times, which were significantly increased in babies with apnoea compared with controls matched for gestational age.[17] Apnoea also resolved once the brain stem conduction times fell to the same level as babies without apnoea. Similarly, when the glabellar tap response and its augmentation by auditory stimuli was investigated, a group of infants with problematical apnoea showed significantly reduced augmentation, which implied immaturity of brain stem neuronal function and organisation.[18]

Assessment of peripheral chemoreceptor reflexes showed that they have little part to play in the onset of apnoea in preterm infants. There is evidence they are active by 28 weeks' gestation, and responses to high and low inhaled oxygen concentrations do not seem to change significantly with increasing gestational age.[19]

Periodic breathing—a respiratory pattern consisting of recurring cycles of breaths and respiratory pauses—is a common finding in preterm infants who spend up to 40% of the time breathing in this way.[20] It decreases with gestational age, being less common in more mature babies, and is therefore another marker of immaturity of respiratory control, although it is generally agreed to be of no pathological importance. It seems that periodic breathing is not a precursor of apnoea,[21] although it decreases in frequency with advancing gestational age and responds to treatment with one of the xanthine group of drugs. Upper airway obstruction is also common in periodic breathing.[22] Similar pathophysiological processes therefore seem to be operating in periodic breathing as in apnoea of prematurity, although the occurrence of one does not necessarily lead to the other.

There are also differences in respiratory reflexes in preterm infants and in those experiencing apnoea. In response to increased respiratory loads infants with apnoea maintain inspiratory efforts poorly with shorter inspiratory times.[23] Airflow obstruction can cause apnoea in preterm infants,[24] either spontaneously when the neck is in certain positions[25] or experimentally by occlusion with a mask.[26] We should be cautious about extrapolating from the response to an experimentally induced occlusion compared with naturally occurring obstruction during apnoea, however, as there may be differences in the responses of the respiratory muscles.[14]

The chest wall becomes more stable with increasing gestational age and dynamic measurements of diaphragmatic function are achieved. The improved stability seems to parallel the resolution of apnoea of prematurity and

it may be that reduced diaphragmatic work may contribute to this.[27] Preterm infants also show immature responses to stimulation of irritant receptors in the bronchial mucosa, which often result in reduced respiratory efforts and apnoea rather than the facilitatory response seen in mature infants.[28]

There is now, therefore, well documented evidence of the immaturity of respiratory control mechanisms and other brain stem functions in preterm infants and in particular in those with apnoea.

Management of the infant with apnoea

The first aspect of management is to identify and treat any underlying causes of apnoea such as sepsis, anaemia, and patent ductus arteriosus in an infant who is having frequent episodes. Tactile stimulation and other forms of vestibular proprioceptive stimuli such as those provided by waterbeds and ventilated mattresses may well reduce apnoea significantly.[29] The position in which the baby is nursed is important, as excessive neck flexion may precipitate upper airways obstruction and apnoea.[25] Nursing babies prone with the head tilted upwards may reduce gastro-oesophageal reflux and help the few infants who have xanthine resistant apnoea that may be associated with reflux.[30]

When apnoeic attacks are frequent, severe, and associated with episodes of hypoxia and bradycardia other treatment is required.

PHARMACOLOGICAL TREATMENT

The xanthine based drugs are effective in reducing the frequency of attacks of apnoea of prematurity although they may not eliminate them, and may fail to prevent severe apnoeic spells.[31] Some units use theophylline; others, however, use caffeine, which seems to be equally effective in therapeutic doses and perhaps better tolerated.[32] Some theophylline resistant apnoea does respond to treatment with caffeine. Xanthine based drugs seem to reduce the frequency of attacks of all types of apnoea including those with associated airway obstruction.[31] Their site of action is thought to be predominantly on the respiratory centre, increasing minute ventilation and sensitivity to hypercarbia.

In apnoea that does not respond to xanthine based drugs, an infusion of doxapram—another centrally acting respiratory stimulant—may be effective. Studies have shown an additional increase in minute ventilation and tidal volume when doxapram is added in infants who already have therapeutic concentrations of theophylline, with a corresponding reduction or abolition of the apnoea.[33] Treatment does, however, require a continuous intravenous infusion and blood pressure must be monitored closely for evidence of hypertension. Irritability of the central nervous system and convulsions are worrying possible side effects.

CONTINUOUS POSITIVE AIRWAY PRESSURE

The mechanism by which continuous positive airway pressure (CPAP) reduces apnoea is still a matter for some debate. Its effect on the lung function of infants is to reduce minute ventilation by reducing tidal volume, and to reduce respiratory frequency mainly as a result of prolongation of expiratory time, whether or not they have lung disease.[34] This has the effect of improving oxygenation and may be one reason why apnoea may be reduced. The beneficial effects of CPAP seem to be selective for mixed and obstructive apnoea, however, and it is ineffective for central apnoea.[35] This has lead to the idea that CPAP may either passively splint the upper airway or activate its dilator muscles. It has already been suggested that the airway may close in up to half of the episodes of central apnoea, yet this does not seem to be reduced by CPAP. One common factor in cases of apnoea that are helped by CPAP is the respiratory drive that is present in both obstructive and part of mixed apnoea, and this may be an important prerequisite for its effectiveness.

CPAP may also affect respiratory reflexes and seems to improve infants' ability to respond to increased respiratory loads.[36] This may be the result of elimination of the Hering-Breuer reflex. It may also stabilise the rib cage as instability of the chest wall has also been implicated in the aetiology of apnoea.[27] CPAP does not alter the ventilatory response to carbon dioxide, so reduction in apnoea does not seem to be related to an increased sensitivity to carbon dioxide while being treated with CPAP.[34]

Monitoring

The inadequacies of apnoea monitors are well known, the most important being the failure to detect obstructive episodes both in research and clinical practice.[37] There is still no reliable and practical method of monitoring airflow that can be used routinely on the neonatal unit. Monitors detecting respiratory efforts have the problems of attachment, movement artefact, and the inability to detect obstruction. Even further away is a practical way of determining airway patency in the absence of air flow.

At present the emphasis must be on monitoring the resultant effects of apnoea by detecting bradycardia and hypoxia. Transcutaneous oxygen monitors and pulse oximetry are usually reliable and we are all becoming increasingly familiar with them and their limitations. They do at least indicate the cardiovascular consequences of problematical apnoea, and alert us to the need to intervene and treat. It is probably less important to try and define the type of apnoea as it is becoming more likely that the same pathophysiological factors underly their aetiologies.

Conclusion

The distinctions between obstructive, central, and mixed apnoea are becoming less obvious as evidence accumulates that suggest similarities in their underlying pathophysiology. Airway patency seems to be an important part of this, together with immaturity in the control of respiratory activity. This suggests that we should not be too dogmatic in our approach to

treatment (by—for example, reserving theophylline for central apnoea and CPAP for obstructive apnoea) but should be prepared to try different treatments alone or in combination. We hope that as more details of the important pathophysiological factors are brought to light, new therapeutic options will be suggested.

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