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Neonatal apnoea

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Premature infants have immature respiratory control that predisposes them to apnoea, haemoglobin oxygen desaturation and bradycardia. Apnoeas are loosely classified, according to the presence or absence of respiratory effort, into central, obstructive or mixed.

There are a variety of conditions, in the perioperative period, that predispose an infant to apnoea, including: central nervous system (CNS) lesions, infections and sepsis, ambient temperature fluctuations, cardiac abnormalities, metabolic derangements, anaemia, upper airway structural abnormalities, necrotising enterocolitis, drug administration (including opiates and general anaesthetics) and possibly gastro-oesophageal reflux.

Various monitoring techniques are discussed; the mainstay are pulse oximetry and abdominal-pressure transduction. There is some evidence of both short- and long-term complications of repeated apnoeas in the neonatal period, but the causal relationship is difficult to establish.

Continuous positive airway pressure and caffeine therapy (up to 10 mg kg^{-1}) are the most common treatments of neonatal apnoea. The less soluble volatile agents and regional anaesthetic techniques (without concurrent sedation) are associated with a lower incident of postoperative apnoea.

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Apnoea of prematurity

The physiological changes required to progress from foetus to neonate are large. There are complex physiological mechanisms that facilitate the transformation from dependence on maternal placental circulation to life as a separate stand-alone organism. Being born prematurely throws the evolved transformational process into disarray; previously physiologic reflexes become detrimental and certain reflexes needed for independent living have not yet developed.

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Premature infants have immature respiratory control resulting in a propensity for respiratory apnoeas, which increases with increasing prematurity and improves as the infant reaches term-corrected age. Apnoeas can occur spontaneously in premature infants but can be provoked, or the frequency or duration increased, with certain physiological insults. There are some reports that apnoeas >20 s may be associated with impaired neurodevelopmental outcome.[1]

There are a number of questions of particular relevance to the anaesthetist involved in the care of these infants:

- What are apnoeas and why do they occur?
- What conditions are associated with apnoea?
- Do apnoeas matter and if so, how can we minimise the perioperative risk?

Classification of apnoea

Neonatal apnoea is usually defined as a cessation of respiratory flow and is considered to make a classical triad of signs with oxygen desaturation and bradycardias, but is also commonly associated with sudden onset of palor and hypotonia. Exact definitions vary as to the required duration of airflow cessation to constitute an apnoea, which reflects the uncertainty of the significance of apnoea duration. The American Academy of Pediatrics defines apnoea as a respiratory pause of >20 s; however, a more common definition is a pause of >15 s or <15 s if the apnoea is associated with a desaturation or bradycardia. The definition of a significant desaturation or bradycardia is similarly inconsistent and includes a haemoglobin saturation falling to <90%, <80% or a change of >20% of the pre-existing value; a bradycardia is most commonly defined as heart rate <100 beats per minute (bpm).

Apnoeas have been subclassified into central, obstructive or mixed, depending on the presence of respiratory effort and upper-airway obstruction (Figs. 1 and 2). These distinctions are becoming less clear-cut as, for example, there is evidence that central apnoeas can occur with airway obstruction: 'silent obstruction'. Pure-central apnoeas and obstructive apnoeas account for approximately 20% each of all causes with the majority (over 50%) of all apnoeas being of mixed origin.[2]

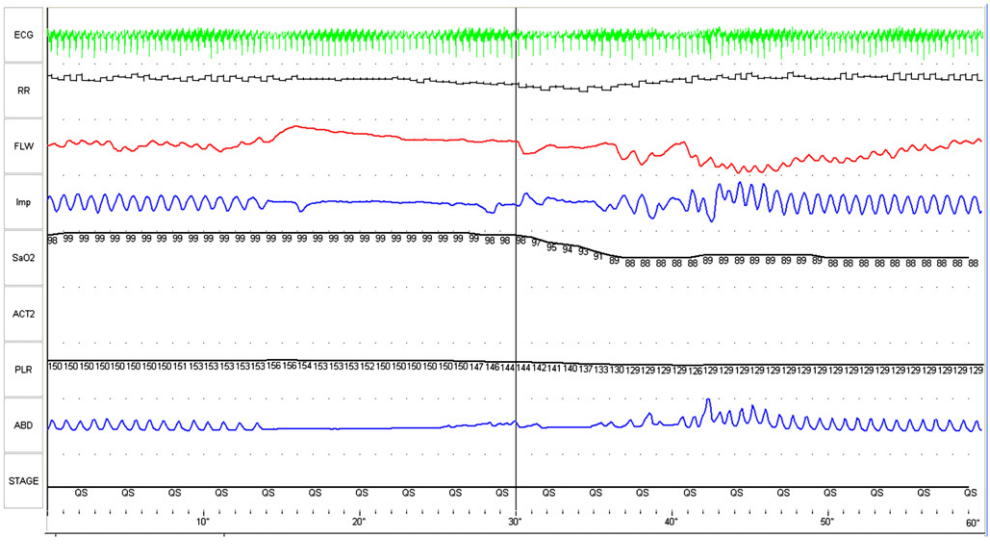

Fig. 1. Central apnoea. FLW, imp and ABD all cease. After 15 seconds the patient begins to desaturate. There is spontaneous resolution but delayed resolution of the desaturations. Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

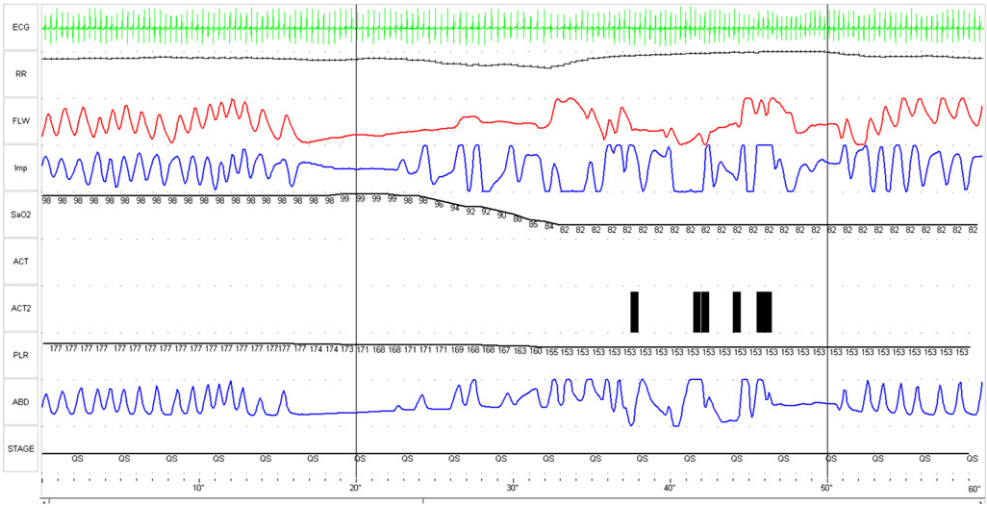

Fig. 2. Mixed apnoea. There is initial central apnoea lasting approximately 6 seconds after which there is respiratory effort (imp and ABD channel activity) but no flow until at least 15 seconds (FLW channel), the patient desaturates to 82% and becomes aroused (movement demonstrated via ACT2 channel). Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

Apnoeas occur in 7% of babies born between 34 and 35 weeks, 14% born between 32and 33 weeks, 54% between 30 and 31 weeks and in 80% of neonates born <30 weeks gestation.[3] While most apnoeas resolve by the time the infant reaches 37 weeks post-conceptional age (PCA), 80% of very low birth-weight infants, in one study, still had significant apnoeas at 37 weeks.[1]

Central apnoea occurs when airflow ceases in the absence of respiratory effort. In obstructive apnoea, there is no flow but the infant attempts to breathe throughout the pause, that is, has continuous thoracic and abdominal movement throughout the apnoea. Mixed apnoeas usually start with a central apnoeic phase, followed by upper-airway obstruction. The site of obstruction is not entirely understood, but is a combination of passive pharyngeal collapse and either active or passive laryngeal closure.[2]

Ruggins and Milner used a fibre optic scope to visualise the larynx of 12 infants having apnoeic episodes and found the larynx to be closed in some central apnoeas.[4] Al-Sufayan et al. used a different method of determining upper-airway closure: they used the presence or absence of magnified cardiac-airflow oscillations to infer whether the airway was open or closed. They found that 'silent' airway closure occurred in 20% central apnoea and preceded 59% of mixed apnoeas.[2] Closed glottis during a central apnoea may confer benefit by maintaining lung volume and providing auto-peep, thereby maintaining oxygenation, although this was not found to be the case in the 15 neonates observed by Al-Sufayan. Conversely, return of spontaneous ventilation with a closed airway (turning a central apnoea into a mixed apnoea) may trigger inhibitory cardio-respiratory reflexes prolonging the apnoea and worsening the hypoxaemia. Purely obstructive apnoea is usually associated with an anatomical or positional cause and is otherwise unusual.

Another breathing pattern often observed in infants is periodic breathing, consisting of three or more respiratory pauses of >3 s with <20 s of normal respiration between the pauses (Fig. 3). This is considered normal in term infants, but can be associated with hypoxaemia in premature infants.[5]

Physiology of control of breathing

The purpose of the respiratory control system is to maintain normal partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and hydrogen ion concentration (pH) in the face of

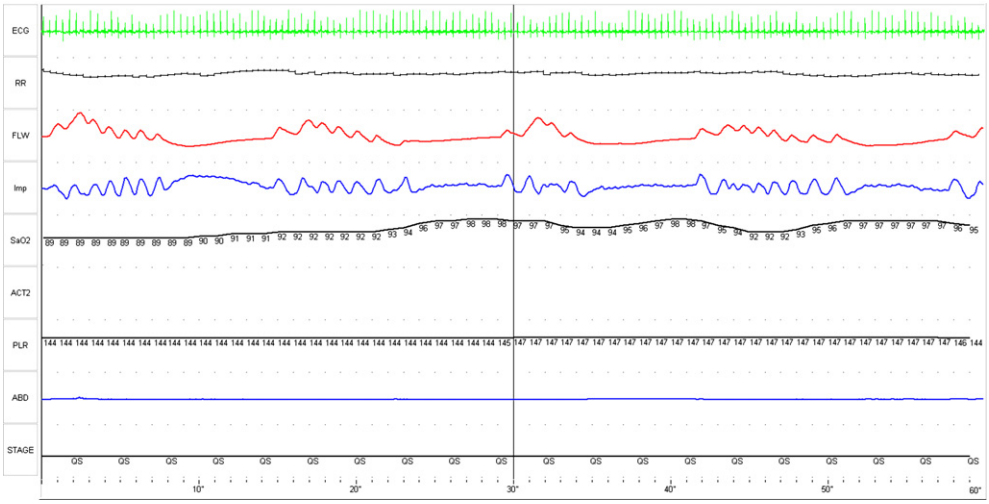

Fig. 3. Periodic breathing. Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

large changes in oxygen (O_2) consumption and carbon dioxide (CO_2) production. This complex control involves central and peripheral chemoreceptors, irritant and mechanoreceptors and central brainstem processing.

Central control of breathing starts in the inspiratory centre in the medulla oblongata and operates as a negative feedback system. The brainstem controls the periodicity of respiration and receives afferent input from the upper airways, the lungs and the peripheral and central chemoreceptors, through the vagus and glossopharyngeal nerves. It controls respiration by oscillating between three distinct respiratory phases: inspiration, post-inspiration and expiration. Efferent control occurs through the vagus (laryngeal nerves), the phrenic and the intercostal nerves. Various endogenous neuroregulators either stimulate or inhibit the respiratory centre, including adenosine, gamma-aminobutyric acid (GABA), serotonin, endorphins and prostaglandin. It is through these neuroregulators that drugs administered to the infant will affect breathing.[6,7]

Central and peripheral chemoreceptors located in the aorta, the carotid arteries and the brain, further control the basic respiratory pattern. Peripheral chemoreceptors in the carotid body contain specialised cells that detect oxygen. The chemoreceptors are sensitive to CO_2, pH, glucose, osmolality and temperature changes. The laryngeal mucosa is sensitive to chemical or mechanical stimulation, which will cause a strong inhibitory reflex – the laryngeal chemoreflex.

There is a complex coordination of upper-airway muscles of the pharynx and larynx, the diaphragm and the chest-wall muscles that ensures that the airway and larynx dilate during inhalation, thereby improving airflow. This complex control is also responsible for the protective laryngeal chemoreflex, which causes glottic closure by the laryngeal adductors in response to laryngeal stimulation. Glottic closure is also important for maintaining lung volume through end expiratory braking or 'glottic stop'.[8]

Stretch receptors in the lungs cause reflex negative feedback to respiration. The Herring–Breuer inflation-stretch reflex results in a decrease in respiratory drive whilst the deflation reflex leads to an increased respiratory rate.

The change from foetus to neonate

The foetal milieu is markedly different from that of the neonate: foetal respiratory efforts result in no change in arterial O_2 and CO_2; the foetus will become apnoeic when hypoxic, which confers some

advantage by decreasing oxygen consumption, but may be a detrimental reflex as a neonate; partial pressure of oxygen in arterial blood (PaO_2) changes from 25 mmHg as a foetus to 50 mmHg in the first few breaths of extra-uterine life, rising to 70 mmHg in the first few hours. Consequently, this relative excess of oxygen renders the carotid bodies insensitive to oxygen changes until they get reset.

Foetal breathing movements begin at about 10 weeks of gestation and increase as the foetus develops towards term. These movements are paradoxical and asynchronous and, as the foetus approaches term, occur only in rapid eye movement (REM) sleep. The foetal response to hypoxia is a decrease in respiratory effort and to hypercapnia is an increase in breathing depth, but not frequency.[8] These foetal reflexes change over the first few weeks of life to become more like the normal adult reflex: hypoxia and hypercapnia both causing reflex increase in respiration. It is during this maturation phase that both term and pre-term infants are at risk of apnoeas, following a hypoxic stimulation. The pre-term neonate will show foetal respiratory characteristics such as periodic breathing and paradoxical ventilation. Poor synchronisation of the respiratory phase and respiratory muscular control, combined with weak, easily fatigable muscles, predisposes the neonate to airway obstruction (as the diaphragm contracts, creating a negative intrathoracic pressure, the chest-wall is unable to be stabilised effectively causing paradoxical inward-chest movement and higher likelihood of obstructive apnoea).

Neonates exhibit a biphasic response to hypoxia; if they receive a hypoxic gas mixture they will initially have increased respiratory drive; however, this drive will subsequently diminish and the neonate will become apnoeic. This late ventilatory depression is possibly mediated through descending inhibitory-pontine tracts.[9] This response continues for about 3 weeks in term neonates. Hyperoxia, by silencing the carotid body, can induce irregular respiratory patterns and apnoeas.

The neonatal response to hypercapnia, unlike the response to hypoxia, is similar to adults. The central chemoreceptor response is initially down-regulated in pre-term neonates, more so in those pre-term neonates that exhibit frequent apnoeas, when compared with age-matched controls. The degree of the increased ventilatory drive, to raised PCO_2, increases with both gestation and postnatal age and reaches adult levels by about 4 weeks of age. The response to hypercapnia increases with increasing postnatal age and with increasing gestational age. These responses are impaired in apnoeic infants.[10]

Physiological features

Apnoea is the end result of immaturity of the regulation of breathing, immature response to hypoxia and hypercapnia and an exaggerated response to stimulation of the upper airway. There is poor myelination of the brainstem with reduced dentritic arbourisation and fewer synaptic connections.[11] The pre-term brain is more sensitive to the inhibitory neurotransmitters such as GABA and adenosine; up-regulation of the GABA receptor seems to have an important role in apnoea, resulting from hypoxia and hypercapnia.

All types of apnoea are usually preceded by a period of ventilatory disruption with short apnoeas and periods of hypoventilation preceding a prolonged clinically significant apnoea. Central apnoeas and mixed apnoeas are closely related; the occurrence of either results from failure of the coordination of the diaphragmatic stimulation and upper-airway dilation. Central apnoeas occur either following stimulation of the laryngeal or mechano-stretch receptors or as a result of hypoxia, hypercapnia or acidosis – the second phase of the biphasic reflex. Upper-airway closure occurs in up to 47% of central apnoeas and in all central apnoeas >20 s.[12] This is as a result of loss of upper-airway tone; mixed apnoeas occur when the central apnoea is prolonged by airway obstruction, thereby speeding up the onset of hypoxaemia and bradycardia.

Whatever the exact aetiology, the neonate's low functional residual capacity, coupled with a relatively high metabolic rate ensures that onset of hypoxaemia is rapid, following apnoea.

Oral and pharyngeal receptors have afferent input through the superior laryngeal nerve and, in response to low chloride-containing fluid, will elicit a powerful airway protective reflex of glottic closure, swallowing and apnoea. This reflex is exaggerated in the pre-term.[6]

Associated conditions causing apnoea

Immature respiratory control is the primary underlying cause of apnoea of prematurity; however, there are many co-existing conditions that may either predispose or worsen apnoea (Table 1). These should be specifically excluded in any infant with apnoeas being considered for theatre. Prudent screening investigations to be considered in such an infant will include lumbar puncture, urinalysis, viral screen, serum electrolytes, calcium, haemoglobin, chest X-ray and cranial ultrasound.

The relationship between gastro-oesophageal acid reflux (GOR) and apnoea is much discussed in the literature, but remains confused. GOR is very common in newly born infants. This is presumed to be due to decreased gastric compliance, increased oesophageal compliance and immature motor control of gastric emptying. There is some evidence that supports the link between GOR and apnoeas[13], but there is more suggesting a lack of causal relationship that concludes that they are both frequently occurring events and will co-exist in the majority of pre-term infants.[14–16] Many of these studies use pH monitoring with a $pH < 4$ considered as evidence of reflux; some evidence suggests that higher pH reflux occurs and is temporally associated with apnoeas and bradycardias through vagal reflex. Paul and colleagues investigated 29 infants born before 36 weeks gestation. They used comprehensive polygraphic monitoring to investigate the cause of apnoeas in infants, who had not responded positively to aminophylline therapy. They found a temporal relationship between the onset of apnoea and electroencephalographic (EEG) and electromyographic (EMG) signs of arousal, rather than inhibition. They also found that bradycardias were frequently not associated with hypoxaemia and thus were symptoms of vagal reflex. Anti-reflux treatment improved apnoeas in the subgroup of infants, who had not demonstrated an improvement following methylxanthine therapy.

Any central nervous system (CNS) lesion can predispose to apnoeas, including intracranial haemorrhage, seizures and hypoxic ischaemic encephalopathy. Apnoea may also be associated with infection and may be the presenting sign, prior to the development of other systemic manifestations. It is associated with systemic sepsis, bacteraemias from colonised intravenous catheters or localised infections such as abscesses.

Several drugs are known to predispose the infant to apnoea. General anaesthetic agents, magnesium, prostaglandin (PGE1) and opioid drugs (used for analgesia or sedation of the ventilated infant) have all been implicated in the aetiology of apnoeas.

Anaemia has been considered to increase the risk of apnoea; Cote, in his combined analysis of available studies investigating the effects of anaesthesia on postoperative apnoea, found a haemoglobin less than 8 g/dL to be a significant risk factor, particularly in infants over 43 weeks post-conceptual age. It is assumed that the lower oxygen carrying capacity of the anaemic patient leads to a hypoxia-induced respiratory depression and red-cell transfusions have been found to reduce short respiratory pauses.[17] However, recent investigations have not corroborated this assumption. Poets studied 21 preterm infants (median gestational age 28 weeks) and found that red cell transfusion made no difference to the frequency of significant apnoeas although there was a trend to shorter apnoeas.[18]

Neonates, when compared to older infants, have softer, more compliant soft tissues in their upper airway and neck that makes positional obstruction more likely. Therefore care needs be taken with

Table 1
conditions associated with increased prevalence of apnoeas in the preterm infant.

Gastro-oesophageal reflux
Central nervous system lesions: intracranial haemorrhage, seizures
Infection: systemic or localized, NEC, meningitis
Ambient temperature fluctuations: hyperthermia, hypothermia
Cardiac abnormalities: patent ductus arteriosus, heart failure
Post immunization
Metabolic derangements: glucose and electrolyte imbalances
Drug administration: opioids, prostaglandin (PGE1), magnesium, general anaesthesia
Anaemia
Upper airway obstruction: macroglossia, micrognathia, choanal atresia
Abdominal distention: NEC
Chronic lung disease of prematurity

positioning, avoiding excessive flexion of the head and neck; this can occur easily if care is not taken. Special vigilance needs be taken in the postoperative period when the infant is recovering from anaesthesia and is at a much higher risk. Neonates are predominately nasal breathers but will breathe through the mouth if the nose is blocked with tubes or oedema; however, in the preterm, the oral-airway resistance is higher than the term infant, which may contribute to apnoeas. Upper airway secretions can stimulate the laryngeal chemoreflex causing glottic closure.

Gastric and abdominal distension can cause respiratory compromise and predispose to apnoeas and bradycardias either through vagal stimulation or as a direct mechanical effect leading to a decrease in lung volume and accelerated hypoxaemia.

Chronic lung disease of prematurity predisposes infants to apnoeas; decreased lung compliance and increased lowerairway resistance contribute to poor oxygenation and are associated with a decreased responsiveness of the peripheral chemoreceptors. One explanation for this unresponsiveness is that during the first few weeks of life the infant is exposed to a hyperoxic environment causing abnormal maturation of the peripheral chemoreceptors.[5]

Monitoring techniques

Monitoring for apnoeas with at-risk infants is essential. There are a variety of monitoring techniques available. The most simple is an abdominal pressure sensor: a diaphragm taped to the anterior-abdominal wall transmits a small pressure change to a sensing box that alarms if abdominal movement stops for a defined period. Most neonatal unit cardio respiratory monitors utilise transthoracic impedance pneumonography: electrodes are placed on either side of the infant's chest, above and below the diaphragm; as air flows into and out of the chest, the electrical impedance between the electrodes changes as air has low impedance. The monitor can then display a live respiratory waveform and a calculated respiratory rate. This monitoring technique will usually be used in conjunction with (SpO_2) monitoring. SpO_2 monitoring alone is usually insufficient as it is associated with a high degree of movement related false alarms; desaturation events have been excluded as alarm triggers in many studies using home pulse oximetry.[19] However, newer movement resistant pulse oximeters may prove to be more reliable indicators of true hypoxaemic events.[20]

A major problem with impedance pneumonography is that it is unable to identify obstructive apnoeas; chest and abdominal movement in the absence of upper-airway airflow will cause intrapulmonary gas flows and will result in similar impedance changes to normal respiration. Nasal thermistry can be used to detect oral or nasal gas flow and will identify both central and obstructive apnoeas. Nasal thermisters or thermocouples are devices that detect the temperature changes during both inspiration and expiration. These devices are surprisingly well-tolerated being attached above the upper lip. They have a non-linear relationship to flow and cannot be relied on to provide any quantitative measurement of flow.

Respiratory inductance plethysmography measurements can estimate the tidal volume using coil bands around the infant's chest and abdomen. The chest and abdominal excursions are then summated and, following calibration, a tidal volume can be derived. However, the calibration of the bands is very sensitive to positional change; every time the infant moves, calibration needs to be repeated. This monitoring method is more useful as a qualitative measurement: it has the advantage of being able to distinguish between central and obstructive apnoeas. During an obstructive apnoea, the paradoxical chest and abdominal movements will summate to approximately zero. It is to be noted that some degree of paradoxical breathing is a normal physiological feature of REM sleep in newborns due to the inhibition of postural muscles and the increased chest-wall compliance.

Consequences of apnoeas

Short term

Apnoeas, by themselves, do not pose any threat to the neonate. However, the associated cardio-respiratory manifestations can cause detrimental outcome, especially in the pre-term neonate. These manifestations include hypoxaemia, hypercarbia, bradycardia and changes in blood pressure.

If apnoea is the first event and is significant for that neonate, then hypoxaemia may follow, associated with a reflex bradycardia, mediated by the peripheral chemoreceptors in the carotid body. The speed of onset and severity of the hypoxaemia will depend on the baseline haemoglobin oxygen saturations, the functional residual capacity and the degree of intrapulmonary shunting. When the neonate's saturation and lung volumes are both low to begin with, then, an apnoea will result in accelerated hypoxaemia and cause further loss in lung volume.

Bradycardia can also occur simultaneously with the apnoea, prior to hypoxaemia, as the result of a direct inhibitory vagal reflex following pharyngeal and laryngeal stimulation (such as insertion of a laryngoscope) or following tracheal or pharyngeal suction. Bradycardia may initially be associated with an increase in stroke volume and pulse pressure; however, if it persists, then the blood pressure will fall resulting in a reduction of major-organ perfusion, including the brain.

Near-infrared spectroscopic examination of neonates' brains has shown a relationship between apnoeas associated with bradycardia and desaturation below 85%, and reduced cerebral oxygenation and blood volume.[21] Heart rates below 80 bpm decrease blood-flow velocity in the anterior-cerebral arteries. Following severe prolonged apnoea, the associated hypoperfusion and the subsequent potential compensatory hyperperfusion may contribute hypoxic-ischaemic injury to the pre-term neonatal brain.[22]

Long term

The long-term consequences of recurrent apnoea remain controversial. A problem with many studies of premature neonates is establishing causal relationships in patients with severe co-existing medical problems. Linking recurrent apnoeas with poorer neurodevelopmental outcome is difficult. Janvier, in a study of 175 pre-term, very low birth weight (VLBW) neonates found an increased number of apnoeas to be associated with neurodevelopmental impairment defined by either a Bayley Mental Developmental Index <70 or Psychomotor Index <70, blindness or cerebral palsy. However, this study could not identify whether the apnoeas were the cause of the neurological impairment or a result of neurological damage by an undetermined cause.[23]

The other important question is whether neonatal apnoeas predispose the infant to other cardio-respiratory complications. Although infants born before 32 weeks gestation have a three-times- higher risk of sudden infant death syndrome (SIDS), there appears to be no link with history of apnoeas in these infants. Incidence of SIDS in the formerly premature infants is closely associated with socio-economic and demographic factors such as maternal age, tobacco smoking and number of previous pregnancies and is not associated with infants, who have had pre-existing respiratory-control abnormalities.[24]

Established preventative therapies

Methylxanthines

Methylxanthines have been used in clinical practice for over 30 years and are still very popularly prescribed drugs in the neonatal period. Caffeine is the most commonly used methylxanthine; it has a safer profile with a wider therapeutic window than theophylline and aminophylline; consequently, blood levels are not routinely monitored. Caffeine has an elimination half-life of 100 h compared with 30 h for theophylline.[5]

Methylxanthines reduce the severity of apnoeas and the requirement for intermittent positive pressure ventilation for treatment of severe apnoeas in the 2–7 day period after starting treatment.[25] They block two sub-types of adenosine receptors; however, the exact mechanism by which they reduce apnoea is not known.[26] Recent work by Abu-Shaweesh and colleagues suggests that the mechanism of apnoea reduction of methylxanthines is through central blockade of the adenosine A_{2A} receptors on GABAergic neurons, thereby preventing the release of GABA and diminishing respiratory inhibition.[11] Possible mechanisms include improved respiratory muscle function, generalised CNS stimulation and enhanced chemoreceptor responsiveness to CO_2. Several systematic reviews of methylxanthine effects have been published in the Cochrane library supporting the efficacy of methylxanthines for the treatment and prevention of apnoeas.[27–29]

The long-term safety is also little understood; there is some evidence that non-specific adenosine blockade in the very premature infant has some deleterious effects on neurological and cognitive development in later childhood and can result in behavioural problems.[30] It is known that methylxanthines increase energy expenditure and oxygen consumption; in a small pre-term infant, this may be enough to decrease growth.

Adenosine has been found to be neuroprotective during acute hypoxia and ischaemia and as methylxanthines block adenosine receptors, it is possible that they may actually worsen the hypoxic–ischaemic injury in high-risk pre-term neonates. A large prospective trial is underway with over 2000 VLBW infants having been recruited into the caffeine for apnoea of prematurity (CAP) trial that is following up the infants for 5 years with outcomes to include tests of cognition, neuromotor function and higher executive function. An interim 18-month follow-up of these children has revealed that those treated with caffeine as neonates had significantly improved survival without neurodevelopmental disability.[31]

Caffeine and general anaesthesia

There are three small studies investigating the efficacy of caffeine at reducing postoperative apnoea and hypoxaemic events following general anaesthesia; they all compared a single intra-operative dose of caffeine (either 5 or 10 mg kg^{-1}), to placebo.[32–34] All infants were born between 30 and 32 weeks of gestation and received the anaesthesia at 40–44 weeks of postmenstrual age. The Cochrane meta-analysis of these studies found that the absolute risk difference for postoperative apnoea was −0.58, indicating that less than two infants needed to be treated with a single dose of caffeine to prevent one postoperative apnoea. However, the clinical significance is not certain as no infant in any trial required intubation and mechanical ventilation and no adverse incidents were reported in either treatment group.[27]

Doxapram

Doxapram, similar to the methyl xanthines, stimulates breathing. Its action is on both the central and peripheral chemoreceptors and causes an increase in tidal and minute ventilation and inspiratory flow.[35] It is usually used as an intravenous preparation as the bioavailability after oral preparations is only 50%. Short-term side effects include hypertension, gastrointestinal disturbances, heart block and excessive CNS stimulation. Sreenan observed an association between the dose and duration of doxapram administration for severe apnoeas in infants weighing under 1250 g and isolated mental developmental delay.[36] Although the causal relationship is unclear, the underlying cerebral dysfunction may be presenting in these infants as apnoea and be unrelated to the doxapram administration. Only one study compares doxapram with placebo. There was some short-term benefit in the doxapram treatment group, but this benefit was not sustained beyond 48 h and the numbers were too small to draw conclusions either way as to the benefit or harm of doxapram.[37] There are insufficient data to recommend doxapram for the treatment of apnoeas in infants, and more research is needed.

Carnitine

Carnitine is a quaternary amine that is essential for the transport of fatty acids across the mitochondrial membrane for beta-oxidation metabolism. It is synthesised from the amino acid, lysine. Carnitine deficiency results in reduced mitochondrial availability of long-chain fatty acids and consequent decreased energy production in the muscles.[38] Pre-term infants have been observed to have lower carnitine levels than term infants. This seems to be related to immature biosynthesis pathways and reduced dietary intake from breast milk and parenteral nutrition solutions. Iafolla noticed a reduction in episodes of apnoea and periodic breathing following 48 h oral carnitine treatment in a report of two infants.[39] However, there is insufficient evidence to recommend the use of carnitine currently.

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) at 4–6 cm H_2O reduces the incidence of obstructive and mixed apnoeas, but not central apnoea. CPAP can be delivered through nasal prongs, nasal cannulae or a nasal mask with low bulk, portable equipment. The most common anatomical sites for airway obstruction in the neonate are the upper pharynx and the entrance to the larynx; CPAP will distend the upper airways preventing anatomical obstruction. The incidence of pure central apnoeas will not be reduced by CPAP but the obstructive component that can occur silently at the end of the central pause will be reduced. Longer central apnoeas are mostly associated with an obstructive contribution prolonging the apnoeic period. CPAP will also increase functional residual capacity and may reduce intrapulmonary shunting by distending and recruiting alveolar units; these combine to improve oxygenation and provide more oxygen reserve such that hypoxaemia onset is delayed if an apnoea does occur. The use of high-flow nasal cannulae therapy is increasingly used as a convenient, more portable alternative to CPAP delivery devices but the safety of the unregulated high flow has not been fully investigated.

Treatment

Most apnoeas are self-limiting and require no intervention. However, additional intervention may be required to avoid harmful consequences. Tactile stimulation is the first intervention, which will often terminate the apnoea by providing general CNS stimulation. When tactile stimulation is insufficient, rapid progression to more invasive interventions such as positive pressure ventilation is needed. Increased fraction of inspired oxygen may be needed in the acute treatment of a prolonged apnoea, but should be used cautiously as fluctuations in PaO_2 and relative hyperoxia may contribute to post-apnoea respiratory instability.

Anaesthesia

For over 10 years, it has been the understanding and common teaching in paediatric anaesthesia that formerly premature infants, following a general anaesthetic, have a higher risk of postoperative ventilatory complications. Furthermore, having a regional anaesthetic technique (either spinal and/or caudal anaesthesia) without the use of sedative agents may confer some protection from these respiratory complications. There is evidence that this is correct for the older volatile general anaesthetic agents including halothane, enflurane and isoflurane, but the evidence is controversial for the newer less-soluble anaesthetic agents, sevoflurane and desflurane.[40] Respiratory complications are the most frequently occurring anaesthesia-related complications in this age group with hypoxaemia, airway obstruction and apnoeas being much more common than in the older infant.[41]

General anaesthetic agents, inhalational and intravenous, produce a dose-dependent depression in conscious level and produce a similar depression of ventilatory control. Inhalational anaesthetics produce a dose-dependent flattening and right shift of the CO_2-ventilation response: with increasing Anaesthetic concentration a higher partial pressure of carbon dioxide in arterial blood ($PaCO_2$) results in the same ventilation.[42–44] Anaesthesia may also enhance the primitive reflexes that result in a greater susceptibility to apnoeas.

Cote performed a combined analysis of the original data from all available studies investigating apnoeas in infants prior to 1995. He included eight studies and concluded that the main determinants of risk of postoperative apnoea were gestational age and PCA, the presence of continuing apnoeic episodes at home and anaemia (haematocrit $<30\%$), especially in the older infants. Infants with a gestational age of 35 weeks had a risk of postoperative apnoea of more than 5%, up to a PCA of 48 weeks. Infants, who are 'small for dates' had a lower incidence of apnoea compared with gestation–matched infants, who had an appropriate weight.[45]

Unlike volatile anaesthesia, awake regional anaesthesia does not appear to exacerbate this background incidence of ventilatory disturbance[46,47], but spinal anaesthesia has a significant failure rate of 10–20% and has not been widely adopted as a technique.[48–50] Caudal anaesthesia, in awake

infants, has been described, but is technically difficult and has problems of limited duration.[51] An alternative technique is to use light general anaesthesia and a caudal epidural block with local anaesthesia. The newer inhalational agents, desflurane and sevoflurane, have enhanced recovery characteristics compared with other volatile agents, including isoflurane. Desflurane confers the fastest emergence time with sevoflurane, up to 50% slower, and isoflurane, twice as long, following an anaesthetic duration of less than 1 h.[52–54] There is some evidence that this difference in emergence times will become even more pronounced after longer duration anaesthetics as desflurane does accumulate in the tissues as readily as the more fat-soluble agents, sevoflurane and isoflurane.[55]

Opioids produce a dose-dependent respiratory depression with decreased responsiveness to CO_2, characterised by a right shift of the CO_2-response curve without the flattening. Opioids also interfere with the periodicity of breathing and may cause respiratory pauses, periodic breathing and apnoeas.[42]

The author, along with colleagues, studied 30 premature infants having inguinal herniorrhaphies under general anaesthesia. The infants were randomly allocated to receive either desflurane or sevoflurane as the sole centrally acting agent for their procedure. Comprehensive polysomnographic monitoring was applied to the infants for a 12-h period before surgery and for the first 12 h postoperatively.[53] The monitor recording was then analysed in 30 s windows and all desaturations, bradycardias and apnoeas were confirmed and classified (Figs. 1–3 were obtained from this study). We were unable to demonstrate differences between the two groups in terms of postoperative apnoea, or the relationship of pre- and postoperative respiratory events within the groups. This lack of change, associated with surgery and anaesthesia, was interesting and unexpected. Despite comprehensive monitoring, we could not show a relationship with either desflurane or sevoflurane in terms of an increase in postoperative respiratory events, as previously demonstrated. While several patients had a considerable increase in apnoea rate in the postoperative period, a large proportion had a reduction in observed apnoea. Also of note was the lack of temporal relationship between the events and the timing of the anaesthetic. The events were scattered throughout the 12-h observation period. If there were a significant link between general anaesthesia and respiratory events, it would be expected that the events would, as in previous studies, be grouped early in the postoperative period. However, this was not the case. Whilst it is not advisable to draw conclusions from such a small study, this does support the hypothesis that the newer insoluble anaesthetic agents provide a safer perioperative course for these high-risk infants.

While there are currently no large, prospective, population studies in this field, there are two recent retrospective institutional audits that add much interest to this debate. Kim and colleagues from the Children's Hospital of Eastern Ontario,retrospectively studied a series of 133 pre-term infants having inguinal herniorrhaphies.[50] A total of 63 infants had a successful spinal anaesthetic, without sedation; a total of 60 infants had a general anaesthetic and nine infants had a spinal anaesthetic, but subsequently required a general anaesthetic as the spinal anaesthetic was inadequate. The overall incidence of apnoea was 10.5% with an incidence of 6.3% in the spinal group and 10% in the general anaesthesia-alone group (no statistical difference between the groups). Of the nine infants, who had failed spinals, four had apnoeas (44.4%); it has been postulated that the sedative effect of neuroaxial blockade acts synergistically with the additional sedation.[56] This has the effect that these infants are at much greater risk of postoperative apnoea than either of the other groups. Davidson and colleagues conducted a similar retrospective audit of 127 infants and used logistic regression to identify risk factors for 'early' (within 1 h) and 'late' apnoea.[48] They concluded that, while it is difficult to predict which infants are at risk of early apnoeas, spinal anaesthetic alone confers low risk and, similar to Kim, they found that a failed spinal with subsequent general anaesthesia confers high risk. They found late apnoeas to be more strongly associated with low post-menstrual age (PMA) than either the type of anaesthesia, the gestation at birth or the weight. As these studies were both retrospective, they relied on case-note recording of significant apnoeas by the post anaesthesia care unit (PACU) and ward staff; the overall number of apnoeas in both studies was considerably lower than the author's study using comprehensive polysomnographic monitoring; this calls into question the clinical significance and validity of such sensitive monitoring. It is uncertain whether clinically unrecognised apnoeas are important to the developing infant.

Practical management options

Several questions should be answered when considering a neonate for surgery:

- What are the risks associated with anaesthesia?
- Would delaying the procedure decrease the risks?
- What is the safest anaesthetic technique?
- What postoperative monitoring is required?
- Which infants can be discharged on the day of surgery?

Each patient should be assessed individually and the risk associated with anaesthesia balanced with the cumulative risk of delaying surgery. The most common infant procedure is inguinal hernia repair that, for the premature infant, is often the final event in a long inpatient course, delayed until just prior to discharge home; for these patients, the benefit of increased ventilatory maturity has to be balanced with the risk of bowel incarceration with any delay in surgery. If feasible, elective surgery should be delayed in infants less than 46 weeks' PMA. The patient's risk of apnoea in the perioperative period will depend on:

- PMA;
- gestation;
- bull; history of apnoea; and
- lung function and oxygen requirements.

It is important with all infants to be vigilant for associated perioperative triggers for apnoea and treat appropriately:

- hypoglycaemia;
- hypoxia;
- hypercarbia;
- sepsis;
- anaemia;
- hypocalcaemia and
- ambient temperature fluctuations.

After deciding the appropriate timing of surgery, the next consideration is the safest choice of anaesthesia technique. Lower-body procedures, such as inguinal herniotomy, can be readily performed with regional anaesthesia either as a sole technique or as a supplement to general anaesthesia; both methods reduce the requirements for opiate drugs and therefore have a less-detrimental effect on ventilatory control. Spinal anaesthesia alone is a very effective technique but has a significant failure rate (reference review on regional techniques in this journal). General anaesthesia with fat-insoluble, modern volatile agents, such as desflurane, provide rapid emergence characteristics with a possibly reduced incidence of postoperative apnoea when compared with the more fat-soluble volatile agents (isoflurane and halothane). Local anaesthesia administered through the caudal route is easy to administer, provides good intra- and postoperative analgesia and does not increase the risk of apnoea, as long as local anaesthetic agents are used alone (Clonidine, ketamine and opiates administered neuroaxially, have all been associated with increased risk of apnoea). While alternative airway devices, such as the laryngeal-mask airway, are available in sizes to fit neonates, tracheal intubation provides the safest airway control; tracheal extubation is safest when the infant is wide awake with vigorous purposeful movement. Particular care should be taken when ventilating the infant to avoid hyper or hypo-ventilation or oxygenation. Preoperative SaO_2 and PCO_2, if available, can be used as a guide for intra-operative SaO_2 and end-tidal CO_2.

All infants under 62 weeks PMA should be monitored in the postoperative period with a minimum of: haemoglobin saturation and an abdominal pressure transducer. Infants over 62 weeks PMA should

be assessed and those with a significant history of apnoea or respiratory disease should be similarly monitored.

Infants over 62 weeks PMA can be discharged home after an appropriate period of recovery (4 h minimum) if: the surgery is minor, they have an uneventful recovery period and if they are otherwise medically well. Appropriate discharge of infants under 60 weeks must be dictated by the infants' risk factors for apnoea; the risk for apnoea, following general anaesthesia, will return to the preoperative risk over the subsequent 12 h, with the greatest risk in the immediate recovery period. High-risk infants will need overnight monitoring.

Research agenda

- Further research is required to finally decide whether a general anaesthetic or a spinal block is safest in neonates at risk of apnoea. Research should ideally target both short-term (1st postoperative day) and long-term (several years) outcome measures.
- The long-term safety of methyl xanthines is not established.

Conflict of interest statement

None.

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