Management of apnoea and bradycardia in the newborn

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Abstract

Apnoea and associated bradycardia are common in preterm newborn infants. Apnoea of prematurity is a developmental disorder, which requires careful evaluation to exclude other pathological causes contributing to the apnoeas. The long-term effects of apnoea and bradycardia are unclear, but may be associated with long-term neurodevelopmental problems. Severe apnoeas may need resuscitation, mechanical ventilation or CPAP. Caffeine is currently the drug of choice for treatment of apnoea of prematurity. The effects of may other interventions, including stimulation, Kangaroo care, RBC transfusion, etc need further evaluation. Further research into the pathophysiological mechanisms underlying apnoeas, neurodevelopmental effects and long-term follow up of affected infants will help in optimizing management strategies for apnoea of prematurity.

Keywords apnoea; bradycardia; management; neonate; preterm

Management of Apnoea and Bradycardia in the newborn

Apnoea and bradycardia in the newborn is a common problem encountered in neonatal practice, particularly in preterm infants. There is debate both over the aetiology and optimal management of the condition.

Clinically significant apnoea in infants is defined as breathing pauses that last for >20 seconds or for >10 seconds if associated with bradycardia, oxygen desaturation, pallor or reduced tone.

In the term baby, apnoea usually signifies an underlying pathology. The potential causes of apnoea in this group are listed in Table 1.

In premature infants, apnoeas are much more common. In addition to the above-mentioned causes in Table 1, apnoeas in premature infants are often caused by immaturity. Such apnoeas are called apnoeas of prematurity.

The American Academy of Paediatrics defines apnoea of prematurity (AOP) as a pause of breathing for more than 15–20 seconds, or accompanied by oxygen desaturation (SpO_2 $\leq$80% for $\geq$4 seconds) and bradycardia (heart rate <2/3 of baseline for $\geq$4 seconds), in infants born less than 37 weeks of gestation.

The incidence of AOP is inversely correlated with gestational age and birth weight, and is almost universal in infants who are <1000 g or <30 weeks gestation at birth.

The causes of AOP are physiologically explained as central, obstructive or mixed.

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- Central apnoea – due to absence of respiratory drive
- Obstructive apnoea – due to airway obstruction or collapse despite continued respiratory effort
- Mixed apnoea – persisting airway obstruction leads to CNS depression due to hypoxia and acidosis resulting in mixed apnoea

For the majority of preterm infants a mixed picture is seen with both obstructive and central factors contributing to the apnoea.

Apnoea of prematurity is a diagnosis of exclusion and therefore thorough examination and appropriate investigations are essential to diagnose and treat other pathological causes.

Pathophysiology

The pathogenesis of AOP is poorly understood but immaturity plays a major causative role.

Apnoea typically leads to decrease in arterial pO_2 and oxygen saturation, although the extent of the decrease varies between infants. The apnoea and desaturation leads to bradycardia by multiple mechanisms, including hypoxic stimulation of the carotid body chemoreceptors. Severe bradycardia can lead to reduction in cardiac output and fall in systemic blood pressure and cerebral blood flow velocity. Cerebral auto-regulation is poor in premature infants, and a fall in systemic blood pressure may lead to cerebral hypo-perfusion, which might potentially exacerbate hypoxic ischaemic brain injury in these infants.

Studies of premature infants and various animal models have shown immature responses to both hypercapnia and hypoxia, which are thought to contribute to AOP. In response to hypoxia, infants exhibit a biphasic ventilatory response. There is an initial increase in ventilation followed by a decline in breathing. This late decline, called the hypoxic ventilatory depression, is prolonged in preterm infants often to below baseline ventilation. The pathophysiology behind the late depression is poorly understood, but may involve the central inhibitory neurotransmitters. In response to increased CO_2, there is a prolongation of expiratory duration in preterm infants, instead of an increase in tidal volume and frequency as seen in term neonates and adults. This is also centrally mediated at the brainstem level via inhibitory neurotransmitters. Such responses to the hypoxia and hypercapnia in preterm infants aggravate apnoea and result in delayed recovery of the infant.

Further, inhibitory upper airway responses to stimulation of airway receptors, and absence of cough and gag reflexes are also thought to contribute to AOP.

Hypoxia, toxins and other stressors can further alter postnatal maturation of the respiratory system, leading to persistence of recurrent apnoeas in premature infants.

The anatomy of premature infants is also an important contributor to apnoeas of prematurity. A large occiput, hypotonic neck muscles, neck flexion and small airways increase the risk of upper airway obstruction.

Thermoregulation may also play a role in apnoea of prematurity. In a small study of near-term infants, the frequency and duration of apnoeas were significantly inversely correlated with basal heat loss, suggesting that apnoea is related to metabolic state and environmental temperature.

Other factors like nasal oedema/obstruction with NG tube (increases nasal airway resistance), delayed gastric emptying and gastro-oesophageal reflux have also been linked to AOP.

Pathological causes of apnoea and bradycardia in the newborn

Infection	• Local or systemic
	• Bacterial or viral
Neurological	• Intracranial haemorrhage
	• Hypoxic ischaemic encephalopathy
	• Seizures
	• Congenital intracranial malformations
Respiratory	• RDS/CLD
	• Aspiration
	• Airway malformation
Cardiovascular	• Clinically significant PDA
	• Heart failure
	• Hypovolaemia/hypotension
Gastrointestinal	• NEC
	• GORD
	• Non-specific abdominal distension
Haematological	• Anaemia
Drugs (infant and maternal)	• Narcotics
	• Analgesics
	• Magnesium
	• Prostaglandins
	• Any drug withdrawal
Pain	• Acute or chronic
Metabolic	• Hypoglycaemia
	• Hypocalcaemia
	• Hypothyroidism
	• Hyponatraemia

Table 1

Anaemia may also be associated with apnoea because of lowered oxygen-carrying capacity of red blood cells that leads to hypoxia, resulting in respiratory depression.

Several neurotransmitters including GABA, adenosine, serotonin and endorphins, and cytokines involved in prostaglandin E2 production may have a role and hence are being researched upon as possible factors in pathogenesis of AOP.

A diagrammatic representation of possible pathophysiological mechanisms leading to AOP is depicted in Figure 1.

Many of the other conditions listed in the pathological causes of apnoea like glucose or electrolyte imbalance, presence of a patent ductus arteriosus with a large shunt and anaemia can be associated with apnoea of prematurity. Various neonatal diseases can play an additive role, resulting in an increased incidence of apnoea. This does not necessarily imply causation and hence care must be taken when attributing the cause and treating apnoea.

AOP—gastro-oesophageal reflux disease (GOR) relationship

Both gastro-oesophageal reflux and AOP are common in premature infants. There is no strong evidence to support the view that apnoea and reflux are temporally or causally related. Monitoring studies demonstrate that reflux and apnoea occur as unrelated events. When a relationship between reflux and apnoea is observed, apnoea may precede rather than follow reflux.

The risk factors for both AOP and GOR are present in premature infants. The relationship between GOR and AOP can be understood as a dynamic interaction that can play out in different ways.

In certain circumstances, immaturity may lead to both apnoea and reflux with no direct causal relationship between the two. In

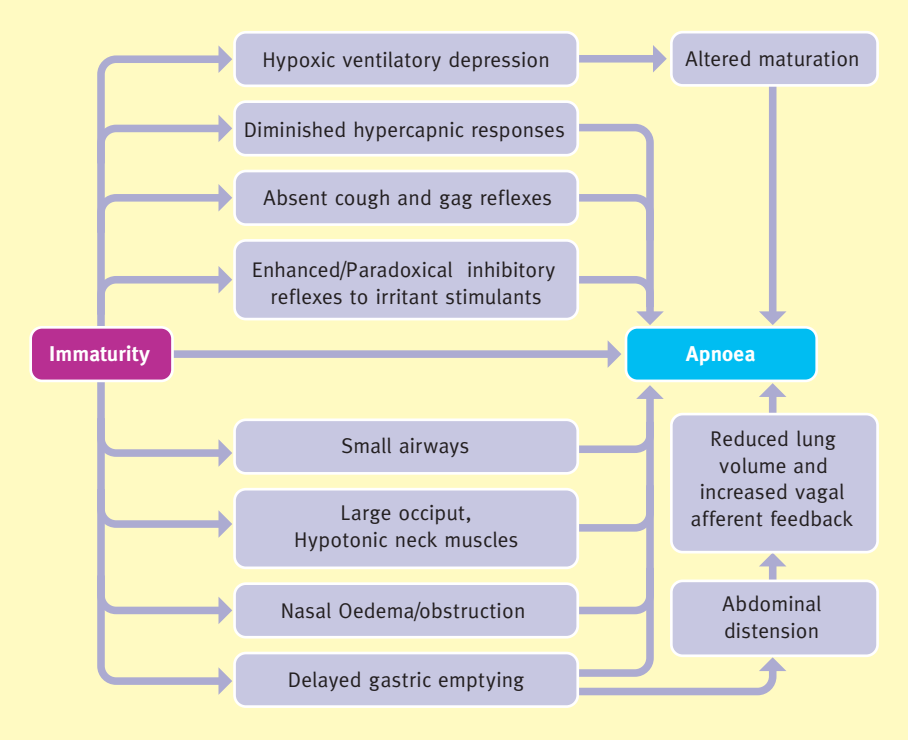

Figure 1 Proposed pathophysiological mechanisms predisposing or leading to apnoea of prematurity.