Apnoea & Bradycardia

Introduction

Brief pauses in breathing (five to ten seconds) are common particularly in preterm infants and when they alternate regularly with breathing efforts, this is called periodic breathing. In some infants the pauses are prolonged and rapid depletion of oxygen stores leads to hypoxaemia and reflex vagal bradycardia.\(^1\) Prolonged apnoea in the newborn infant is defined as a pause in breathing of more than 20 seconds or a shorter pause associated with bradycardia or hypoxaemia \(^2\). Where the event is associated with an absence of breathing movements, this is defined as central apnoea where breathing movements continue without air flow it is defined as obstructive. Most commonly they are mixed apnoeas, with both an initial central apnoea followed by obstructive efforts\(^1\).

Incidence and risk factors

Recurrent prolonged apnoea and bradycardia occurs in most infants born before 30 weeks gestation; in about half of those at 30-32 weeks; in only about 10% of those at 34-36 weeks; it rarely occurs at term\(^1,3\). The specific reason for this is not clear although immaturity of the brainstem has been documented to be associated with apnoea\(^4\) and in preterm infants who have apnoea, it almost always ceases by term age.

<table>
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<tr>
<th>Gestational age</th>
<th>Incidence of recurrent apnoea(^3)</th>
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<tr>
<td>&lt; 30 weeks</td>
<td>80%</td>
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<tr>
<td>30-31 weeks</td>
<td>50%</td>
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<tr>
<td>32-33 weeks</td>
<td>14%</td>
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<tr>
<td>34-35 weeks</td>
<td>7%</td>
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Although immaturity is a major underlying factor, various insults may contribute. Recognition of any underlying cause is important since specific treatment (such as antibiotics for infection) might be indicated.

Conditions causing or accentuating apnoea

- **Hypoxaemia.**
- **Central nervous system disturbances.**
  - Asphyxia
  - Intracranial haemorrhage
  - Seizures
  - Drug depression
  - Malformations
- **Systemic illness.**
  - infection
  - shock (e.g. NEC)
- heart failure (e.g. PDA)
- **Metabolic disturbance.**
  - hypoglycaemia
  - hyponataemia
  - hypocalcaemia
  - inborn error
- **Thermal disturbance.**
  - hyper- or hypothermia
- **Anatomical narrowing of airways.**
  - Choanal atresia
  - Micrognathia
  - Macroglossia
  - Tracheomalacia

### Consequences of disease

If prolonged, apnoea can lead to hypoxaemia and reflex bradycardia which may require active resuscitative efforts to reverse. There are clinical concerns that these episodes might be harmful to the developing brain or cause dysfunction of the gut or other organs. Follow up studies show that recurrent apnoea is **not an independent predictor of later abnormal neurodevelopment**\(^1,5\). Frequent episodes may be accompanied by respiratory failure of sufficient severity as to warrant intubation and the use of intermittent positive pressure ventilation (IPPV). A major concern for parents is whether their baby will have apnoea at home and die from sudden infant death syndrome (SIDS). Epidemiological studies indicate that while preterm infants are at increased risk of SIDS this is not related to apnoea of prematurity. However, an insult such as RSV infection or pertussis can cause a recurrence of apnoea in the first few months after discharge. Polygraphic studies at discharge from neonatal units do not predict future SIDS\(^6,7\).

### Diagnosis

The breathing and heart rate of infants born at less than 35 weeks gestation (or more mature infants who are very ill) are usually monitored to detect apnoea/bradycardia that may warrant clinical attention. In RPAH Newborn Care the nursing staff grade events and keep a chart.

**Grade 1** = Apnoea > 15-20 seconds &/or bradycardia &/or cyanosis associated with cessation of effective breathing efforts, which respond quickly to stimulation.

**Grade 2** = As above or more prolonged, and responding slowly to stimulation or requiring bag and mask resuscitation. If considered necessary the type of apnoea (central or obstructive) can be defined by multichannel polygraph recording, although this can often be determined by careful clinical observation of the events.

### Interventions

Management includes correction of any aggravating factors and adequate monitoring of breathing movements (impedance apnoea alarm) and heart rate. If oxygenation is inadequate between apnoeas (\(\text{SaO}_2 < 85\%\)) then a small increase in environmental oxygen (e.g. 23-25%) may reduce the severity of apnoea. Care must be taken to avoid hyperoxia since the lungs are relatively normal and these immature infants are at risk of retinopathy. If supplemental oxygen is used the target saturation level is 90 -95%\(^8\).

**Kinesthetic Stimulation**

A recent small cross over trial in 10 preterm infants showed a reduction in short pauses in breathing and duration of desaturation\(^9\). This does not change the conclusions of the review published by the Cochrane collaboration showing no benefit compared with methylxanthines and that this cannot be recommended to prevent apnoea\(^10\).
Positioning

There is less apnoea when infants are nursed in the prone position compared with supine\textsuperscript{11}. A randomised study has shown that nursing a preterm infant prone does not reduce the rate of apnoea when compared with side sleeping\textsuperscript{12}.

Continuous Positive Airway Pressure

Continuous positive airways pressure (CPAP, 4-6cm H\textsubscript{2}O) via nasal prongs will usually reduce the severity of the apnoea\textsuperscript{13}. Nasal intermittent positive pressure ventilation (NIPPV) is more effective than nasal continuous positive pressure ventilation (NCPAP)\textsuperscript{14}. Short bi-nasal prongs are more effective than single prong NCPAP\textsuperscript{15}. Only short term outcomes are reported.

L Carnitine

One randomised controlled trial has reported no effect on apnoea rate with L-carnitine supplementation\textsuperscript{16}.

Creatine

One randomised controlled trial has reported no effect on apnoea rate with creatine supplementation\textsuperscript{17}.

Blood transfusion

This has not been shown to be effective in reducing apnoea in anaemic infants\textsuperscript{18}.

Doxapram

Doxapram is as effective as methylxanthines in prevention of apnoea. However there are concerns about the side effects of doxapram and there are no long term data on this drug\textsuperscript{19}. Side effects include hypertension, QTc prolongation, seizures, respiratory distress, vomiting, diarrhoea, and urinary retention.

Methylxanthines

Caffeine is the preferred treatment for apnoea in this unit. Of the two methylxanthines in use, caffeine, which is just as effective, has potential therapeutic advantages over theophylline due to its higher therapeutic ratio and thus less side effects, more reliable enteral absorption and the longer half life allows once daily administration\textsuperscript{20, 21}. The standard dosing with caffeine citrate is 20 mg/kg load (IVI or oral) and then 5 mg/kg/day (IVI or Oral). If apnoeas persist the daily maintenance dose can be increased to a maximum of 10 mg/kg/day of caffeine citrate. Blood levels do not need to be monitored routinely. Caffeine has been proven safe and effective in large multicentre randomised controlled trials\textsuperscript{22, 23, 24}. Short term benefits, aside from the reduction in apnoea, included less need for mechanical ventilation, oxygen supplementation, chronic lung disease, and patent ductus arteriosus\textsuperscript{22}. At 18 month follow up there was a 23\% reduction in the primary outcome of death or disability outcome (OR: 0.77; 95\% CI: 0.64–0.93). The effect on cerebral palsy was a reduction to 4.4 vs. 7.3\% (RR: 0.58; 0.39–0.87). Apart from antenatal magnesium sulphate no other drug has shown an effect on reducing cerebral palsy in NICU graduates\textsuperscript{25}. A subsequent subgroup analysis of the study has shown that the improvement in the primary outcomes were confined to those infants who received caffeine and

- were on respiratory support
- were treated for apnoea
- had caffeine to facilitate extubation.

There was also evidence that caffeine given early had a greater beneficial effect\textsuperscript{26}.

Treatment with Caffeine.

When to start treatment.

Where infants do not spontaneously recover during apnoea/bradycardia alarms, cutaneous stimulation is
usually sufficient to terminate the apnoea. If the response is slow or cyanosis severe, bag and mask ventilation with the infant’s usual environmental oxygen may be needed. Avoid over-oxygenation during and after bag and mask ventilation. There are no data indicating what rate of apnea/bradycardia warrants further treatment. It is probably more important to consider the effect of events on the infant rather than the absolute number of events. If episodes are frequent (more than two to four apnoea or bradycardia alarms per hour) or the infant is slow to respond to any event, then some other assistance is usually given. Apnoea and the associated hypoventilation can be a clinical problem following extubation from IPPV and both methylxanthines and nasal CPAP are effective in reducing this, and increasing the chances of successful extubation.

At what gestation?

The CAP and other randomised trials enrolled infants less than 30 weeks gestation and less than 32 weeks gestation.

In RPAH caffeine is given to infants less than 30 weeks gestation to facilitate extubation, infants less than 30 weeks who have any apnoea, and infants greater than 30 weeks who have 2 or more apnoeas requiring intervention.

When to cease treatment

There are no trial data to support decisions about when to cease treatment. Based on experience in RPAH Newborn Care, treatment with caffeine is usually ceased when there have been no significant apnoea/bradycardia events for one week. If after a further week there are no more events, monitoring is ceased. Discharge home occurs when parents are ready and ‘criteria for discharge’ are met. In the absence of some unusual clinical indication predischarge pneumograms and use of apnoea monitors at home are discouraged, as there is no evidence of need and their use could impair the parental development of normal family relations by perpetuating an ICU attitude.

If a baby on caffeine is to be back transferred to a referring hospital in the next few days the usual practice is to stay on caffeine until stabilised in the local unit.

What dose of caffeine to use.

Caffeine has a wide therapeutic index and levels need not be checked.

A small randomised trial compared a standard loading dose of 25 mg/kg of caffeine citrate (12.5 mg/kg caffeine) followed by maintenance of 6 mg/kg caffeine citrate (3 mg/kg caffeine) compared with a loading dose of 50 mg/kg of caffeine citrate (25mg/kg caffeine) followed by 12 mg/kg caffeine citrate (6 mg/kg caffeine). Both arms showed equal reduction in apnoea with the higher dose regime having benefits in the first 8 hours.

A larger randomised trial compared three regimes of 60 mg/kg, 30 mg/kg and 6 mg/kg loading dose of caffeine citrate, followed by 30 mg/kg, 15 mg/kg and 3 mg/kg maintenance doses. This trial showed no difference in extubation failure although there were fewer failures in the lowest dose group (p=0.06). There were fewer apnoeic events in the higher dose groups and no statistically significant increase in side effects.

A further randomised trial compared a loading dose of 80 mg/kg followed by maintenance of 20 mg/kg with a loading dose of 20 mg/kg followed by 5 mg/kg/day of caffeine citrate. There were short term benefits with less extubation failure and fewer apnoeas in the high dose group. At follow up at 1 year of age there was no evidence of harm in the high dose regime.

The CAP trial used a loading dose of 20 mg/kg followed by a daily maintenance dose of 5 mg/kg of caffeine citrate (equivalent to 10 mg/kg and 2.5 mg/kg of caffeine base). The maintenance dose could be doubled but it not clear how often this happened.

In this unit the oral and intravenous caffeine preparations are presented as caffeine base. The dose is 10 mg/kg loading dose (equivalent to 20 mg/kg caffeine citrate) followed by a maintenance dose of 2.5 mg/kg (equivalent to 5 mg/kg caffeine citrate) given once daily. The dose can be increased if clinically indicated.
## Key Points

<table>
<thead>
<tr>
<th>Description</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Apnoea is usually due to cessation of breathing efforts although airway obstruction may prolong recovery in individual episodes or be the predominant problem in some infants</td>
<td>5</td>
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<tr>
<td>The accompanying bradycardia is a vagal reflex response to hypoxia</td>
<td>5</td>
</tr>
<tr>
<td>Apnoea is most common at lower gestations and usually ceases by term</td>
<td>4</td>
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<tr>
<td>Apnoea is accentuated with additional insults (hypoxia, infection etc)</td>
<td>5</td>
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<tr>
<td>Apnoea per se is not a risk for subsequent neurodevelopmental delay</td>
<td>4</td>
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<tr>
<td>Caffeine reduces apnoea and use of IPPV</td>
<td>1a</td>
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<tr>
<td>Nasal CPAP reduces apnoea</td>
<td>4</td>
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<tr>
<td>Caffeine and CPAP reduce post extubation apnoea</td>
<td>1a</td>
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<tr>
<td>NCPAP is less effective than theophylline at reducing apnoea</td>
<td>2</td>
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<tr>
<td>Caffeine reduces important short term outcomes</td>
<td>1b</td>
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<tr>
<td>Caffeine reduces death and disability</td>
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<td>Caffeine should be given to infant receiving mechanical ventilation</td>
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<td>Grade of recommendation A</td>
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<tr>
<td>Caffeine should be given to infants with recurrent apnoea</td>
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<td>Grade of recommendation B</td>
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<tr>
<td>Caffeine should be given early</td>
<td>1b</td>
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## References


5. Tudehope DI, Rogers YM, Burns YR, Mohay H, O'Callaghan MJ. Apnoea in very low birthweight infants: outcome at 2 years. Aust Paediatr J. 1986 May;22(2):131-4


10. Osborn DA, Henderson-Smart DJ. Kinesthetic stimulation for treating apnea in preterm infants. Cochrane Database of Systematic Reviews 1999, Issue 1


