Neonatal and Pediatric Respiratory Medicine

Edited by

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and

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Preface

In compiling this volume we invited experts from North America, the United Kingdom and Australia to write articles reviewing topics in paediatric respiratory medicine, encouraging them to provide clear personal statements with the clinician in mind. The subjects have been chosen on the grounds that they are either controversial or have changed rapidly in the last few years. This selection process obviously rests on the interests of the two editors to some extent but we hope that the ground covered, although far from comprehensive, will be of interest to neonatal, pulmonary and general paediatricians alike.

Finally, we would like to thank all the contributors for their support and time and hope that they are as pleased with the final result as we are

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R. Martin

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Resuscitation of the newborn

A. D. Milner and H. Vyas

HISTORICAL BACKGROUND

The transition from a fluid environment to an air milieu makes birth the most perilous time in a human life. Clement Smith (1967) called this hazardous period 'The Valley of the Shadow of Birth'. Failure to adapt rapidly leads to birth asphyxia and its dire consequences. This high risk situation has been recognized for a long time. Our first report on sudden death from respiratory failure in newborn infants dates back to H Wang T (2698–2599 BC), an Emperor of China. References to increased respiratory problems were also made in *Eber's Papyrus* (Egypt, circa 1552 BC). The first description of active intervention, presumably an active form of mouth-to-mouth ventilation, is to be found in the Old Testament:

> 'And he went up, and lay upon the child, and put his mouth upon his mouth, and his eyes lay upon his eyes, and his hands upon his hands: He stretched himself upon the child; and the flesh of the child waxed warm. Then he returned, and walked in the home to and fro; and went up and stretched himself upon him; and the child sneezed seven times, and the child opened his eyes'.
>
> II Kings, Chapter 4, Verses 34–35

By the fifth century BC the Chinese were managing respiratory failure by 'counter irritation'. Soon after, Hippocrates (circa 400 BC) described experimental endotracheal intubation. The Babylonian Talmud expounded on the concepts of resuscitation for the newborn, later to be written up by Moses Maimonides. Although Vesalius (1514–1569 AD) used tracheotomy for ventilatory support in a sow, it was Robert Hook in 1667 who demonstrated that it was possible to keep animals alive with mechanical ventilation for a long period. Robert Boyle (1670) performed further studies on asphyxiated kittens, giving a clear account of both resuscitation ('pinching') and primary apnoea.

Chaussier gave the final detailed description of endotracheal intubation of asphyxiated infants in 1806 (Faulconer and Keys, 1965). By the early nineteenth century mouth-to-mouth breathing was a common way of resuscitation in adults, but in 1812 the Royal Humane Society put an end to this by publishing a health warning in their annual report. The authors of the report felt that a mouthful of air used was: 'chiefly carbonic, or what arises from burning charcoal and more likely to

destroy than to promote the action of the lungs' This Society did, however, redeem itself to some extent by sponsoring the development of an intermittent positive pressure ventilator in 1845.

Although Billard's textbook of paediatrics (Billard, 1828) was retrogressive, recommending blood-letting and leeches, Evanson and Maunsell (1842) were still using mouth-to-mouth breathing in asphyxiated neonates. They describe a 'sthenic' type of asphyxia in which the infant had a good pulse and an 'asthenic' type in which the baby was virtually moribund. The description of the technique they used is a joy to read and they concluded: 'the disadvantages of using air already deteriorated by having been respired is more than counterbalanced by the other advantages of this plan'. However, their excellent advice went unheeded and there followed a whole variety of procedures recommended, including the use of slapping (still practised), tickling, applying hot and cold water and even tongue pulling!

As mentioned earlier, intermittent positive pressure ventilation had already been used in the second half of the nineteenth century. Truehead (1869) and O'Dwyer (1887) demonstrated that intubation and intermittent positive pressure ventilation could be successfully used to manage childhood respiratory failure. Egon Braun in Vienna (Doe 1889) successfully demonstrated resuscitating asphyxiated newborns using intermittent positive pressure ventilation.

Flagg (1928), in America, published details of the apparatus and technique which he had devised for direct laryngoscopy, intubation and intermittent positive pressure insufflation with an oxygen and carbon dioxide mixture, for resuscitation of asphyxiated infants. Working independently, Blaikley and Gibberd (1935) were the first to publish details of tracheal intubation and treatment of 'asphyxia neonatorum' in the UK. They were the first individuals to recommend that an insufflation pressure of 30 cm H_2O was necessary for lung expansion. Since their publication, endotracheal intubation and intermittent positive pressure ventilation was accepted as the standard method of resuscitation until 1950 when AKerren and Furstenberg introduced the idea that intragastric oxygen would be sufficient to support life. It took ten years before Coxon (1960) finally discredited their finding.

No further vogues have come into fashion and now intermittent positive pressure ventilation, either through a face mask or an endotracheal tube, is the accepted way of resuscitating asphyxiated neonates.

PHYSIOLOGICAL RESPONSES TO ASPHYXIA

Birth constitutes a severe physiological challenge. In 1964 Saling convincingly demonstrated a progressive fall in scalp blood Po_2, O_2 content and pH with a corresponding rise in Pco_2 during normal human labour, assuming that these changes were due to uterine contraction and resultant fall in placental blood flow (Saling, 1964). Dawes *et al.* (1963) in their rhesus monkey studies confirmed that there was a fall in intrauterine femoral arterial Po_2 at or after uterine contractions. Recently, catecholamine levels have been used to assess the degree of stress during labour. Fetal concentrations have been found to be increased 10-fold during normal vaginal delivery and even higher levels have been noted in complicated deliveries (Lagercrantz and Bistoletti, 1977; Eliot *et al.*, 1980; Lagercrantz, Bistoletti and Nylund, 1981).

However, whatever the cause, the principal effect of the stress of birth on the fetus is that of asphyxia with progressive hypoxia and acidosis. Extensive animal experimentations have shown that animals respond to this in a predictable way (Dawes, 1968; Hull, 1971). With the onset of acute total asphyxia, the fetal monkey starts making rhythmic respiratory effort, clonic movements and convulsions. This is followed by a profound bradycardia while the animal remains atonic and without any spontaneous movements. During this period (primary apnoea) the skin is initially cyanosed, but over a period of minutes becomes progressively paler due to intense vasoconstriction. The vasoconstriction is probably related to the outpouring of vast quantities of catecholamines. After the initial apnoeic phase the fetus starts to gasp at progressively increasing rates. By 5 min the gasping becomes weaker and around 8.5 min secondary or terminal apnoea sets in. If active resuscitation is not commenced at this stage, the animal dies. The time to the last gasp is very much dictated by the pH of the animal at delivery. If the fetus is grossly acidotic (pH <6.8), no gasps are observed at all. The course of events is very similar in the mature fetal lamb but the time to the last gasp is shorter, only 5.4 min (Dawes *et al.*, 1963).

The phenomenon of primary apnoea can be greatly extended by drugs such as morphine or even by general anaesthetic. Barbiturates have been also known to extend the period of primary apnoea (Cockburn, Daniel, Dawes *et al.*, 1969). Although often it is not possible to differentiate between primary and secondary apnoea, the former will nearly always respond to stimuli such as tactile stimulation or analeptics, with the onset of gasping. In the secondary apnoeic phase, active resuscitation with intermittent positive pressure ventilation is necessary to sustain life.

While it is often assumed that the human neonate responds in a similar manner, we should be wary of such assumptions. As stated by Hull (1971) 'it is not easy to evaluate the relevance of animal investigations to the clinical (human) situation', particularly as in the animal kingdom, labour and birth are rapid events. Only in the human is the process of labour and delivery a protracted one. This may modify the infant's responses. There is no conclusive evidence that primary and secondary apnoea occur in human infants However, occasionally babies are delivered with acute total asphyxia who do not have any spontaneous gasping. These babies do not respond to tactile stimuli and probably would only survive if rapid resuscitatory measures were taken and might represent the terminal apnoeic phase. Much more frequently the babies respond rapidly to manual resuscitation, particularly seen after Caesarean section, in a manner similar to animals in primary apnoea. The duration of this period cannot, however, be assessed properly for obvious ethical reasons.

The respiratory behaviour of the asphyxiated infant cannot be discussed on its own without reference to the corresponding cardiovascular changes. In the fetal lamb and monkey, asphyxia results in a transient rise in blood pressure and a fall in the heart rate (Dawes, 1968). As the pH continues to drop there is a simultaneous decline in the heart rate and a steady fall in the cardiac output. The blood pressure falls to a very low level at the last gasp. Cassin, Swann and Cassin (1960) recorded pressures of 9/7 mmHg in their animal studies during anoxic death. The hypoxia and acidaemia result in intense pulmonary vasoconstriction only relieved by adequate ventilation of the lungs. Adamson *et al.* (1964) have shown the importance of improving acid–base balance as well as oxygenation in accelerating recovery following asphyxia.

FACTORS LEADING TO ONSET OF RESPIRATION AT BIRTH

We now know that the fetus makes intrauterine respiratory efforts before birth. It is thus appropriate to think of extrauterine respiration as an extension of breathing activity *in utero* Thus, to understand the factors leading to onset of extrauterine breathing, the control of intrauterine activity is essential.

Ahfield (1888) was the first person to associate abdominal pulsation with intrauterine fetal breathing. However it was not until 1971 that Boddy and Robinson (1971) made direct observations using A-scan ultrasound to assess the human fetus The fetus initiates respiratory activity as early as 11 weeks' gestation: Initially the fetal breathing is irregul r and infrequent but it becomes more frequent and organized with increasing gestat on. Patrick *et al.* (Patrick *et al.*, 1978, 1980; Patrick, Natale and Richardson, 1978) have extensively investigated fetal breathing using real-time ultrasound in the last ten weeks of pregnancy. They observed fetal breathing for 31% of the time at both 30–31 weeks' and 38–39 weeks' gestation. However, fetal breathing is abolished during labour, possibly related to fetal hypoxia. Apart from labour many other factors are known to affect fetal breathing *in utero* including hypoxia, hypoglycaemia, alcohol (all reducing fetal breathing) and smoking (enhancing the rate of fetal breathing).

Animal studies have shown that the fetal breathing movements occur predominantly in 'rapid eye movement sleep' (Dawes *et al.*, 1972; Ioffe *et al*, 1980), a state in which the cortical activity heavily modifies the respiratory drive. Recent research indicates that respiration at birth is initiated by a variety of triggering factors. Some may be of primary importance whilst others serve as back-up systems. There are thus both intrinsic and extrinsic factors which are responsible for the initiation of respiration at birth.

Intrinsic factors

As mentioned earlier, the intrauterine breathing activity is inhibited towards the last stage. In sheep preparation this has been shown to be due to uterine contractions causing fetal asphyxia. The longer the contractions, the longer PaO_2 takes to return to normal levels after each contraction. Harned *et al.* (1966) observed fetal gasps following umbilical cord occlusion Biscoe, Purves and Sampson (1969) showed that carotid body chemoreceptors are inactive and insensitive to chemical or drug stimulation. Jansen *et al.* (1981) studied the effect of *in utero* carotid chemoreceptor denervation on their fetal lamb preparations after birth. Four of their carotid sinus denervated fetuses were allowed to be delivered spontaneously and all established regular respiration after birth. Their experiment indicated that fetal carotid chemoreceptors are not essential for spontaneous intrauterine breathing activity during rapid eye movement sleep (REM sleep) nor for the establishment of effective breathing at birth. However, little is known about the function of central chemoreceptors in the fetus.

Extrinsic factors

Although birth asphyxia is probably the strongest stimulus for the newborn to breathe other factors are responsible for maintaining respiration. Experimental

evidence indicates that these factors can initiate breathing in the term fetus via sensory stimulation alone.

(*a*) *Temperature.* Cooling of the fetal snout can initiate respiration. Cooling of the skin can also induce breathing and, conversely, warming lambs can induce apnoea.
(*b*) *Pain.* Painful stimuli can induce respiratory responses in the fetus though these are not often sustained This was the rationale for using varieties of 'torture' on the newborn who had failed to breathe.

Stimuli, such as touch, proprioception and audiovisual input, must play an important part in initiating and maintaining breathing but are obviously very difficult to quantify. Cordorelli and Carpelli (1975) suggested that these peripheral stimuli recruit central neurones and thus increase central arousal.

Recently, endorphins have been implicated in the pathogenesis of apnoea. These can be modified by naloxone (Chernick, Madansky and Lawson, 1980). However, the role of endogenous opiates in fetus still remains unclear.

The factors that lead to failure of respiration include.

(i) Severe birth asphyxia (usually pH <7.0)
(ii) Maternal analgesia/anaesthesia.

If the intrinsic factors fail to initiate respiration extrinsic factors should be recruited. If these too fail, active resuscitation should be commenced.

INDICATIONS FOR RESUSCITATION

The newborn baby is more tolerant of asphyxia than the adult or older child, and there are well-recorded instances of babies who have not commenced respiratory efforts for 10–15 min and yet escaped neurologically intact (Scott, 1976). However, some infants who are slow to breathe have already suffered moderately severe hypoxia by the time of birth and such an additional delay would then almost inevitably lead to death or severe neurological damage. For this reason we follow the standard criteria for commencing active resuscitation, namely·

(1) Failure of regular respiration to occur by 2 min after delivery
(2) Apnoea and a heart rate of less than 80 per min before the age of 2 min.

Inevitably, using these indications many babies (probably in the region of 85%) would have started to breathe spontaneously within the next 1–2 min. However, irreversible damage would have affected the remaining 15% more than justifying intervention at these levels.

The need for intubation seems to be falling in many units from a high in the region of 10% in the 1960s. In Nottingham the frequency of intubation has fallen from 3.3% in 1978 to 2.1% of all deliveries in 1982. We strongly suspect that this represents improvements in obstetric care.

The requirement for intubation is closely related to the type of delivery, so that less than 1% of babies born by normal spontaneous delivery require intubation, while 8% of breech deliveries and over 6% of babies born by Caesarean section will require active resuscitation (*Table 1.1*). Prematurity is also important and at least

Table 1.1 Effect of mode of delivery on need for intubation

Mode of delivery	*Percentage needing intubation*	*Percentage of all intubated*
Normal spontaneous	0.8	32
Forceps	2.5	19
Caesarean section	6.2	41
Breech	8.0	8

Table 1.2 High-risk deliveries requiring presence of a paediatric resident

Caesarean section
Breech delivery
Multiple pregnancy
Preterm delivery
Meconium staining with fetal distress
Rhesus incompatibility in moderately to severely affected fetus (as judged by antibodies)
Instrumentation: all Kielland's deliveries
Neville Barnes or Wrigleys liftout when associated with fetal distress
Prepartum haemorrhage if associated with fetal distress or bleeding

40% of babies born with a gestation of less than 32 weeks will require intubation. However, since the majority of deliveries are normal, at least one-third of all intubations are likely to be unexpected. Conversely, if the paediatric resident attends all of what are generally recognized as high risk deliveries (*Table 1.2*), there will be no delay proceeding with resuscitation in the remaining 60% at a cost of attending just over 20% of all deliveries.

PHYSIOLOGICAL EFFECTS OF RESUSCITATION

The pattern of resuscitation now generally accepted has evolved from very little information obtained from studies on stillborn babies and data collected by Karlberg and his colleagues on a small group of babies breathing spontaneously at birth (Karlberg *et al.*, 1962). We are now in a position where we can assess the babies' responses and evaluate efficacy by measuring tidal exchange with a pneumotachograph and inflation and intrathoracic pressures with suitable pressure transducers.

Babies' response to inflation

Measurements of intrathoracic pressure and tidal volume have shown that the baby may respond to the first few inflations in three ways: passive response, Head's paradoxical reflex and rejection response (Boon, Milner and Hopkin, 1979).

Passive response

In some situations the baby makes no active response. In this situation the oesophageal pressure trace mimics the change in tidal exchange to a degree which is determined by the compliance characteristics of the chest wall and respiratory muscles (*Figure 1.1*). There is an apparent 'opening pressure' due to the prolonged

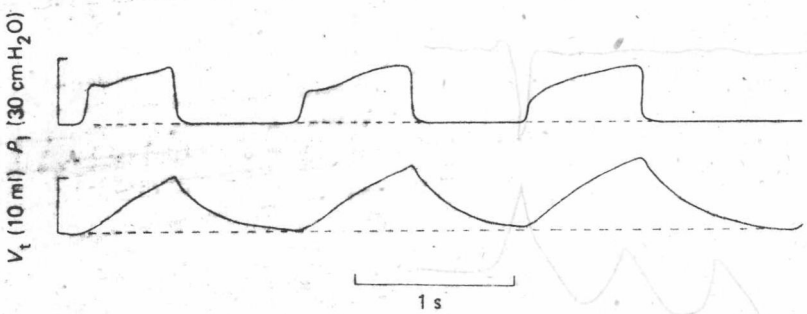

Figure 1.1 Inflation pressure (P_I) and tidal volume (V_t) at the onset of resuscitation showing a passive response. (Reproduced from Boon *et al.*, 1979, by courtesy of the Editors and Publishers, *Archives of Disease in Childhood)*

time constant of the fluid-filled lung, producing a slowly rising tidal volume in the presence of square wave inflation. This pattern was seen in 30% of the first three breaths in 20 full-term babies requiring resuscitation (Boon, Milner and Hopkin, 1979).

Head's paradoxical reflex

In a further 18% of these breaths the inflation pressure stimulated the babies to make a spontaneous inspiratory effort, often dramatically augmenting the inspiratory volume (*Figure 1.2*). As the babies tended to inspire at rates of greater than $31 \cdot min^{-1}$, the bias flow normally selected, the inflation pressure of 30 cm of water was often reversed, a situation which cannot be considered ideal (*Figure 1.3*).

Rejection response

The common pattern seen was for the baby to produce large positive intrathoracic pressures, often exceeding 90 cm of water, starting soon after the onset of the inflation. These pressures were almost always sufficient to squeeze air out of the lungs during the period of positive inflation (*Figure 1.4*). The nature of these rejection responses remains uncertain. Measurement of both intragastric and intrathoracic pressure with the dual pressure transducer system has shown that the positive pressures are generated below the diaphragm (*Figure 1.5*), presumably by the abdominal muscles. The relatively long time course suggests that these are not part of the cough reflex but represent a coordinated active expiration in response to the positive inflation.

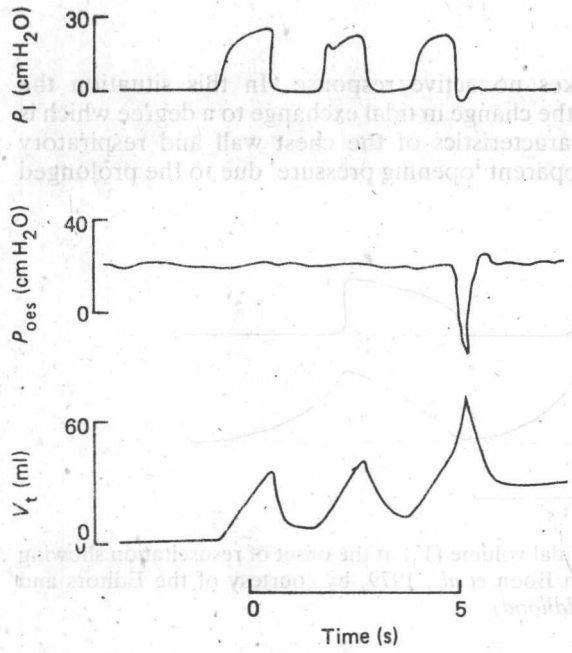

Figure 1.2 Inflation (P_I), oesophageal pressure (P_{oes}), and tidal volume (V_t) during resuscitation. On the third inflation the baby makes an inspiratory effort, increasing tidal exchange (Head's paradoxical reflex)

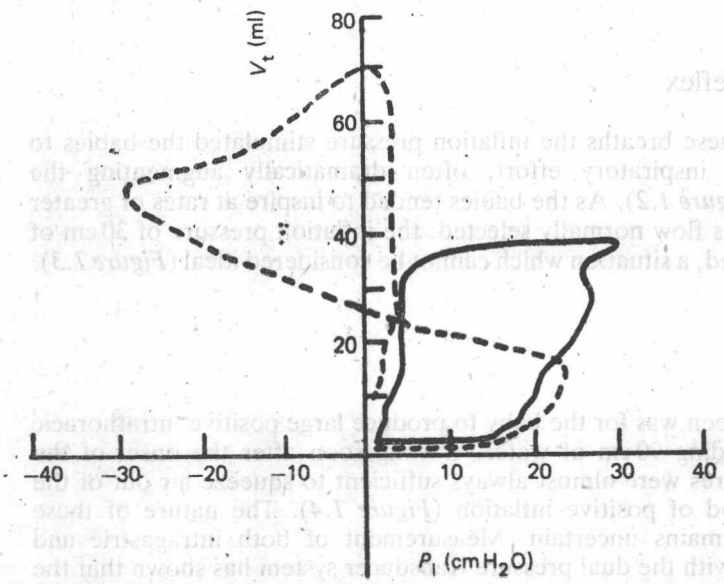

Figure 1.3 Pressure/volume loops at the onset of resuscitation. During the second inflation (dotted line) a Head's paradoxical reflex leads to reversal of the pressure within the airway. (Reproduced from Boon *et al.*, 1979, by courtesy of the Editors and Publishers, *Archives of Disease in Childhood*)