HIGHLIGHTED TOPIC | Neural Control of Perinatal Respiration

Some aspects of clinical relevance in the maturation of respiratory control in infants

Bradley T. Thach
Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri

Thach BT. Some aspects of clinical relevance in the maturation of respiratory control in infants. J Appl Physiol 104: 1828–1834, 2008. First published April 17, 2008; doi:10.1152/japplphysiol.01288.2007.—Two reflex mechanisms important for survival are discussed. Brain stem and cardiovascular mechanisms that are responsible for recovery from severe hypoxia (autoresuscitation) are important for survival in acutely hypoxic infants and adults. Failure of this mechanism may be important in sudden infant death syndrome (SIDS), because brain stem-mediated hypoxic gasping is essential for successful autoresuscitation and because SIDS infants appear to attempt to autoresuscitate just before death. A major function of another mechanism is to protect the airway from fluid aspiration. The various components of the laryngeal chemoreflex (LCR) change during maturation. The LCR is an important cause of prolonged apneic spells in infants. Consequently, it also may have a role in causing SIDS. Maturational changes and/or inadequacy of this reflex may be responsible for pulmonary aspiration and infectious pneumonia in both children and adults.

sudden infant death syndrome; apnea; autoresuscitation; hypoxic gasping; laryngeal chemoreceptors

SOME ASPECTS OF CLINICAL RELEVANCE IN THE MATURATION OF RESPIRATORY CONTROL IN INFANTS

Two mechanisms vital for survival in developing infants will be considered. These are highly relevant to several life-threatening conditions, including infant apnea, pulmonary aspiration, and sudden infant death syndrome (SIDS). One important respiratory protective response leads to spontaneous recovery from hypoxic apnea. This requires cardiorespiratory brain stem-mediated interactions, including hypoxic gasping. This brief review will discuss the critical importance of autoresuscitation (AR) in both infants and adults and the current knowledge of respiratory and circulatory interactions that take place during AR. The second vitally important function concerns reflex mechanisms that protect the infant’s lungs from aspiration. These responses to a laryngeal fluid stimulus include swallowing, apnea, obstructed respiratory efforts, cough, hypertension, and arousal from sleep. Collectively these several responses are the components of the laryngeal chemoreflex (LCR).

Physiology of AR. The physiological adaptations to sudden severe hypoxemia have been studied extensively in animal models (58). At onset of hypoxia, ventilation rapidly increases largely due to carotid body chemoreceptor activity. During this phase, oxidative metabolism in all tissues rapidly decreases and is replaced by anaerobic glycolysis. Very soon thereafter, there is generalized loss of function in the central nervous system (CNS) resulting in arreflexia, apnea, and apparent lifelessness (“hypoxic coma”). After this, a third phase begins with the appearance of maximally large breaths with a brief inspiratory time termed “hypoxic gasps.” This begins when arterial oxygen pressure reaches 8 to 10 Torr (19, 30). If air or oxygen is available, gasps provide oxygen to the lungs, and cardiovascular function rapidly improves with an increase in heart rate and blood pressure. This is followed by a complete and rapid return of CNS function as well as that of all other organs as hypoxic redistribution of circulation resolves. (1, 21). AR has been documented in animal studies and also in observations of human infants and older individuals (1, 40, 42, 54, 56). After successful AR, there is no evidence of permanent injury to the brain or other organs. Within seconds following AR, mice are active and often start grooming (21). Infants who are otherwise healthy and who experience brief severe hypoxia also have normal behavior very soon after AR. This is particularly well documented in infants with severe breath-holding spells (13, 14).

Previously, it was believed that once hypoxic coma occurred all reflexes are abolished. However, more recent studies in mice indicate that at least some brain stem reflexes remain (25). If water is introduced into the pharynx at onset of hypoxic gasping, gasps temporarily cease and rapid swallowing occurs. These are two key elements of the LCR protective reflex. Mechanical stimulation of the pharynx and larynx has no effect on swallowing or gasp frequency in this situation. In these mice, during hypoxic coma (i.e., the gasping phase), water is more effective than saline in stimulating swallowing, again indicating LCR activation. These observations establish that the LCR remains intact and functional during hypoxic coma.
They also indicate that the brain stem centers that regulate gasping are responsive to peripheral afferent stimuli. Thus the LCR would be of obvious benefit to infants at birth because in many cases marked hypoxia with hypoxic coma is present at the time of delivery. In this case, often there is amniotic fluid, blood, or meconium in the newborn’s pharyngeal airway. If intrapulmonary aspiration is to be prevented in this situation, gasping must be delayed until swallows can clear the pharynx of foreign matter.

Another relevant observation of the importance of the LCR during hypoxic coma relates to SIDS. Aspirated gastric contents unrelated to attempted artificial resuscitation are frequently found in the lungs of infants who died of SIDS (27). This indicates that SIDS infants potentially lack adequate airway protective reflexes when AR is attempted. In this case, aspiration could be a critical event in the pathway leading to death.

Much has been learned about the physiology of AR from animal studies in several species. Studies have primarily been in rodents, although there have been studies in dogs, newborn rabbits, and lambs (1, 2, 11, 19, 21, 30, 60). In the past, it was thought that gasping efforts involved only the chest wall inspiratory muscles as well as those muscles that maximally dilate the pharynx and glottis (5). However, more recent studies have shown that expiratory muscles are also active during gasping. At peak gasp inspiration vocal cord constriction occurs (5, 60). This has the effect of eliminating or retarding expiratory airflow, thereby maintaining an increased lung volume in between gasps and in theory this should increase the efficacy of gas exchange in the lung during AR.

Studies in rodents have shown that elevated body temperature adversely affects autoresuscitation in certain situations (24, 50). In contrast, cooling prolongs gasping allowing autoresuscitation after many minutes (2). These effects are likely due to increases or decreases in metabolic rate. This would have the effect of reducing or increasing cardiac glycogen consumption during extreme hypoxia (7). It is well known that cardiac glycogen stores are critical for heart function during AR (6). Reduced consumption would preserve glycogen stores, allowing the hypoxic heart to function for a longer time (7). In addition, prior administration of theophylline, a drug that increases brain metabolic rate, reduces gasping duration in the heads of decapitated mice (20). This and other studies indicate that CNS carbohydrate stores are important in preserving medullary function during extreme hypoxia. In light of this, it would be relevant to evaluate carbohydrate stores in the medullary neurons that generate gasps or in adjacent glial cells.

The critical importance of the postnatal development of AR mechanisms has been demonstrated in mice. Young (SWR/J) mice were accidentally discovered to be unable to autoresuscitate during a narrow developmental time frame (19–22 days) (21). That is to say that after induction of hypoxic coma by breathing N2 when air is then made available to these animals, gasping takes place but recovery does not occur. This is unlike younger or older SWR mice and all other strains of mice tested so far. In these young SWR mice, gasps are initially weak and are followed by a progressive decrease in inspired volume. As gasps become progressively weaker gasping rate increases, indicating progressive failure of the brain stem centers regulating gasping. This same sequence of terminal increased rate of weak gasps occurs in all other strains of differently aged mice and rabbits after repeated successful ARs when ultimately failure of AR finally occurs (15). Once this sequence begins, spontaneous recovery is very rare.

Other observations have shown the importance of carbohydrate stores for AR in young SWR mice. Studies of other inbred mouse strains have shown that there is a nadir in cardiac glycogen content at 19–21 days of age. However, cardiac glycogen content is much lower in SWR mice than in other mouse strains when the nadir is reached (7). Anaerobic glycolysis is essential for adequate heart function during extreme hypoxia, and so inability to maintain circulation secondary to heart failure appears to be at least one of the causes of AR failure in young SWR mice. Of interest also is that pentobarbital anesthesia reverses AR failure in these SWR mice independently of its effects in lowering body temperature (22). The mechanism for this effect is unclear, although the overall slowing of metabolic rate caused by pentobarbital could preserve cardiac function and prolong gasping, thereby allowing more time for pulmonary blood to become fully oxygenated in much the same way as cooling does.

SIDS is now known to be caused by a number of pathological abnormalities. Nevertheless, the SWR mouse model of AR failure appears to be a good model for SIDS because SIDS incidence peaks during a narrow developmental time window in infants. Also, a potential benefit of this model is that it offers an opportunity to identify the gene or genes responsible for AR failure because such failure is only found in the SWR inbred mouse strain.

During the course of maturation, there are important changes in AR mechanisms in mice and rats as in other species (12, 15). Newborn mice have comparatively large glycogen stores (6). This allows AR to take place over a prolonged time period. Obviously, this would be advantageous because extreme hypoxia often occurs during labor. In the case of prolonged labor, the increased reserves of glycogen allow the newborn to survive until the opportunity for successful AR at birth is present when air finally is available. On the other hand, in older mice cardiac glycogen stores are much lower. However, these older mice successfully resuscitate when exposed to extreme hypoxic conditions (15, 21). Here the rate of gasping is more rapid than that in the newborn, and AR is accomplished in a relatively short time span, hence large cardiac glycogen stores are not needed (15). It seems reasonable to speculate that rapid recovery is beneficial for survival in certain situations. Were the adult like the newborn, delayed AR would prolong hypoxic coma and in theory, at least, reduce the opportunity to escape from or resist predators.

Brain stem centers involved in gasping. The neurons that originate gasping appear to be stimulated by hypoxia unlike all other neurons (49). For years it was believed that there had to be a “gasping center” in the brain stem. Its precise location long remained unknown. However, in the past 20 yr, its likely location has been identified. Whereas some neurophysiologists maintain that neurons in the pre-Botzinger nucleus initiate gasping, others have argued that the nucleus ambiguous, immediately adjacent to the pre-Botzinger nucleus, is responsible for gasping (49, 52, 62). The latter view is supported by the observation that hypoxic gasping can still occur after pre-Botzinger activity has been eliminated (48). Much of this controversy may be due to difficulties in defining and recognizing gasping, particularly in brain stem slices and also in
determining the precise location of pre-Botzinger neurons (52). Neurons in the pre-Botzinger nucleus stimulated by hypoxia appear to discharge in a characteristic pattern consisting of an abrupt inspiratory activation, a brief inspiratory time, and lack of a graduated inspiratory ramp (53). This is the pattern of activity in inspiratory muscles during hypoxic gasping (30). There are two mechanisms that could explain the stimulation of neurons in the gasping centers. This could either be result of a direct effect of hypoxia on these neurons or the result of hypoxic depression of other centers that inhibit gasp-generating neurons.

Recent studies suggest that both glutamate and nitric oxide are important in regulating gasping (16, 17). Both cause earlier onset of gasping and increase in gasp frequency. However, they decrease gasping duration. Therefore, it is plausible that increases in nitric oxide and/or glutamate are responsible for the decreasing strength and increasing frequency of gasping that occurs with gasping center failure preceding the last gasp. In any case, it is likely that cardiovascular regulating brain stem centers as well as normal function of cardiac pacemakers are also necessary for successful AR, particularly in situations where exposure to an hypoxic environment is prolonged (1, 2). The bradycardia and decreased cardiac output that occur at onset of hypoxic coma have long been regarded as mechanisms that lower cardiac workload, thus reducing the need for a high rate of glycolysis. This would allow for prolongation of gasping.

**Importance of AR in infants and older children.** During the neonatal period, intermittent spells of apnea lasting 20 s or longer associated with cyanosis, bradycardia, and acute severe neurologic depression are relatively common. Although a number of studies have been directed to determining factors that might precipitate spells, relatively few studies have investigated physiological mechanisms leading to spontaneous recovery from apnea. In the premature infant, the majority of apneic pauses lasting 15 s or longer resolve spontaneously. As well, most spells lasting 20 s or longer terminate when cutaneous stimulation is administered. Before the era of modern resuscitation techniques, it was believed to be potentially harmful to stimulate infants during an apneic spell. Many years ago, the developmental physiologist and pediatrician Albrecht Peiper studied hospitalized infants during prolonged apneic spells. These observations were made with motion pictures and strain gauge pneumography (42) (Fig. 1). Spontaneous recovery almost always occurred even after 3–5 min of absent eupneic respirations. Peiper observed that during prolonged apneic spells respiratory recovery was invariably initiated by a series of “gasp”s,” which were “shorter and deeper than that of normal respiration.” This pattern is the same as that seen in animal models of hypoxic gasping.

Studies of hypoxic apnea, coma, and gasping in older individuals are rare. For the most part, they consist of monitoring individual patients in whom unanticipated AR takes place in the hospital or laboratory. Occasionally, such episodes have been well documented by polygraphic recordings. One of these occurred in a 17-yr-old adolescent in whom both respiration and heart rate were recorded during successful autoresuscitation from hypoxic apnea (40). In addition, Gauk and coworkers (14) made polygraphic observations in two children with a history of cyanotic breath-holding spells. Some of these spells occurred during monitoring in the laboratory. Each child suddenly lost consciousness and became apneic and cyanotic while breath holding. The apnea was terminated by an isolated “gasp” observed by the investigators. Within several seconds following the single gasp, arterial oxygen saturation, as measured by ear oximetry, rose from 40% to 65% in one instance and from less than 30 to 55% in another. The infants appeared entirely normal within seconds of AR, which is typical of severe breath-holding spells in young children. Additionally, there are many other cases in which visual observations and recordings of respiration and heart rate indicate that AR can occur in a variety of situations, causing extreme anoxia. These include asphyxia at birth, idiopathic infantile apnea, severe infantile breath-holding spells, obstructive sleep apnea in adults, and apnea associated with pertussis and other upper respiratory infections (42, 54, 56).

Regarding relevance to SIDS, AR is a likely mechanism for recovery in many infants during severe apparent life-threatening events. These infants are pale or cyanotic, hypotonic, and arreflexic, and they appear lifeless when first noticed by caretakers. Recovery is often spontaneous, in which case slow forceful respiratory efforts typical of hypoxic gasping are not infrequently reported by parents (B. T. Thach personal observation). It has often been speculated that an apparent life-threatening spell could be a precursor to a SIDS death. Thus, based on data from animal studies, it has been suggested that SIDS may occur when an otherwise reversible condition produces transient hypoxemia, or cerebral ischemia, and AR fails (19).

**AR FAILURE AND SIDS**

In recent years, the use of cardiorespiratory monitoring in infants has become common. Analysis of monitored recordings in which the infant’s death happened before the parents were aware of the monitor alarm and the infant could be rescued has provided important information on AR in SIDS infants.

These recorded deaths have happened in infants diagnosed as SIDS as well as other infants dying of natural causes (38, 47, 51). Importantly, of the 18 or so SIDS deaths analyzed so far, there have been only two cases in which central apnea occurred before the onset of hypoxic gasping. In these recordings bradycardia occurs abruptly just before to onset of gasping. This suggests that the preceding hypoxemia was severe and
already present during the 15-s period captured in the monitor’s memory storage just before the bradycardia. The cause of the preceding hypoxia is unclear. Obstructive apnea or exposure to an asphyxiating environment when bedding covers the infant’s face cannot be excluded. Hypoxic gasping was documented in all but one of the SIDS infants. All of the non-SIDS infants also gasped terminally. It is highly relevant to note that compared with the infants dying from other causes, the SIDS infants had a markedly decreased ability to transiently increase their heart rate or recover eupneic breathing as a result of hypoxic gasping (51). Out of the five SIDS cases, only one had evidence of a transient heart rate increase following gasps, while none had evidence of complete AR. This again was significantly different from the non-SIDS infants. The latter infants with known severe health problems often repeatedly autoresuscitated (Fig. 2). The remainder usually showed some evidence of successful resuscitation with either increases in heart rate or transient eupnea. Although the number of infants was small, these differences between SIDS and non-SIDS infants were statistically significant.

These unique observations in SIDS infants are of particular interest because other investigators have reported decreased serotonergic receptors in brain stem regions possibly involved in gasping in SIDS infants compared with controls (26). Areas of the brain stem involved in regulation of circulation and heart rate, and, therefore, presumably important in AR, show similar differences in serotonergic receptors.

MATURATION OF LCR AND ITS RELATION TO PROLONGED APNEA IN INFANTS

It has often been proposed that an apneic episode resulting from airway protective reflexes could result in an infant’s death (59). These several reflexive responses are termed the LCR. The term chemoreflex was adopted because hypochloride or acidic fluid coming in to contact with laryngeal receptors is
required to elicit the reflex (4). The receptors involved appear to be unmyelinated nerve fibers located immediately beneath the laryngeal mucosal epithelium (34, 55). These nerve endings are strategically concentrated in the interarytenoid cleft at the entrance to the larynx. The LCR response has several components, which include apnea, swallowing, upper airway obstruction, coughing, hypertension and peripheral vaso-constriction (4, 18, 45). These responses are clearly functionally significant. Swallowing removes fluids from the pharyngeal airway, and vocal chord constriction combined with apnea can prevent aspiration. The hypertension and peripheral vasoconstrictive responses may be related to the redistribution of circulation that is protective during hypoxia.

Several findings have indicated that the LCR can cause prolonged apneas in infants. It has been shown that respiratory depressants such as hypoxia and anesthesia were associated with longer apnea duration in animal models (8, 9, 28, 31). In addition, increase in brain stem or body temperature increases apnea duration in piglets and rat pups (64). Respiratory stimulants such as theophylline shorten apnea duration (31). Significantly theophylline or caffeine is highly effective in treating apnea of prematurity. Up to 70% of apnea of prematurity is thought to be due to LCR reflexes (37, 44). Also relevant are studies in animal models as well as in human infants indicating that respiratory syncytial viral infection is associated with increased severity and/or prolongation of LCR apnea (32, 46) (Fig. 1). Other factors can increase LCR responses such as hypoxemia or anemia (10, 28, 63). Although it is possible that receptor sensitivity may be altered by some of these conditions, it is more likely that altered central neural processing of receptor input is the more relevant factor (29).

Studies of unanesthetized dogs of various ages as well as studies of both mature and immature human infants indicate that the LCR changes remarkably during maturation (4, 45). Apnea and to some extent arousal from sleep are predominant LCR responses in newborn puppies. However, the duration of apneas diminishes after the first week of life (4). In contrast, LCR responses in sleeping adult dogs indicate that significant apnea occurs only during rapid eye movement sleep (56). Cough, arousal, and occasional swallows are the predominant responses. Cough is dependent on prior arousal.

When sleeping infants are stimulated by minute boluses of water or saline infused into the infant’s pharynx, repeated swallowing, apnea, and airway closure resulting in obstructed inspiratory efforts are the predominant responses in young preterm infants (43, 44) (Fig. 3). In more mature infants these responses are less robust (45). In this case, a brief respiratory pause with one or two swallows occurs when water or saline is introduced into the pharynx. In infants as in the puppy, cough is infrequent. The arousal component of the LCR is also relatively infrequent in sleeping preterm infants (45). Episodes of clinically significant prolonged apnea combined with bradycardia and airway obstruction are more common in preterm compared with term infants (44). Such spontaneous apnea in preterm infants is usually associated with swallowing and intermittent airway obstruction and is identical to saline- or water-provoked LCR apnea (44). Importantly, the apnea usually occurs during sleep in the absence of any detectable stimulus except occasional regurgitation of gastric contents into the pharynx (36). These several observations suggest that endogenous stimuli from accumulated pharyngeal secretions or regurgitated gastric fluid can elicit LCR responses in preterm infants and are a significant cause of apnea of prematurity.

In summary, it appears that there is a common pattern of maturation in the LCR responses in man and other species. With maturation, there is an increase in cough and arousal responses associated with this reflex and a reduction in apnea and swallowing. Laryngeal nerve stimulation studies suggest that these changes likely result from maturation in the central processing of afferent stimuli rather than reduction in the sensitivity, reduction in the number, or change in receptor distribution within the larynx.

**RELEVANCE OF UPPER RESPIRATORY VIRAL INFECTION FOR SIDS**

As discussed above, upper respiratory viral infections as well as hypoxemia or anemia amplifies LCR responses in animal models. Of potential relevance to SIDS is that the peak in SIDS deaths (3–4 mo) occurs when physiological anemia peaks and upper respiratory viral infections become common. It has recently been shown that cytokines produced in the laryngeal mucosa during respiratory syncytial viral infection are transported retro-axoanally to brain stem centers that potentially regulate swallowing and respiratory pattern (3, 33, 35). This observation supports the concept that amplification of the LCR associated with laryngeal inflammation is a centrally mediated response. Noteworthy is that interleukins are elevated in the cerebrospinal fluid of many SIDS infant compared with controls, and a recent report suggests that interleukins are elevated in the brain stem of SIDS infants (23, 39, 61).

**RELEVANCE OF LCR REFLEXES TO PATHOLOGY IN CHILDREN AND ADULTS**

Swallowing caused by the LCR appears to be the primary mechanism whereby secretions are cleared from the pharyngeal airway of during sleep (45). Aspiration of bacterial contaminated upper airway secretions is believed to be a major cause of infectious pneumonia. In addition, it is well documented that aspiration of saliva during sleep is common and may be excessive in certain patients. As well, aspiration of refluxed gastric fluid is a threat to health throughout life and reduced LCR reflex activity that might occur with severe laryngeal inflammation due to acidic gastric fluid would be detrimental. Were this to impair LCR protective responses. Diminution of various reflexes during advanced age is common and this may be true of the LCR as well. Therefore, studies of the LCR during aging might be a fruitful area for future research.

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