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Laryngeal Chemoreflexes and Development

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INTRODUCTION

The following provides some background information on the laryngeal chemoreflexes (LCR). Most of these studies have dealt with the potential involvement of the LCR in the Sudden Infant Death Syndrome (SIDS) and this will also be discussed.

ANIMAL MODELS AND LARYNGEAL CHEMOREFLEXES

In the mid-1970's, Johnson et al.[1] and Harding and colleges[2,3] discovered that when water is introduced into the larynx of the newborn lamb, the responses include startle, arousal from sleep, rapid swallowing, prolonged apnoea, bradycardia, hypertension, and constriction of the peripheral vascular bed resulting in redistribution of perfusion. On the other hand, when saline replaced water in this study, there was little or no effect. These studies comprised the first detailed description of the LCR. Later, these findings were confirmed in puppies as well as piglets, kittens and newborn monkeys.[4–7] It was shown that LCR reflexes arise from stimulation of sensory afferent nerve fibers in the superior laryngeal nerves (SLN). Anatomical and physiological studies indicate that unencapsulated, unmyelinated nerve endings terminating in the mucosal epithelium of the epiglottis, aryepiglottic folds and interarytenoid space are the sole receptors mediating these reflexes[4,8–11] (Fig. 1). The intraepithelial location of these receptors would appear to be ideal for rapidly detecting ionic changes in the overlying mucous layer.

Boggs and Bartlett determined that the chloride concentration of solutions bathing the mucosal surface is a critical factor determining receptor discharge.[4] Water and other solutions with low chloride content, such as gastric fluid and saliva had a stimulating effect proportionate to their chloride content. Isotonic saline had little effect. High potassium concentrations stimulated these "water receptors" as well. This suggested that the concentration of chloride and potassium in the thin mucous layer overlying the airway mucous caused depolarization the receptors.[4] They also found that strongly acidic or alkaline solutions stimulate the receptors even when the chloride concentration was equivalent to that of plasma. The receptors were shown to be slowly adapting, meaning that they continued to discharge as long as the liquid solution was present on the mucosal surface, and cease firing only after it is washed away by saline. The reflexes triggered by fluid contact are extremely rapid, occurring in less than 0.3 seconds. Moreover, the receptors are concentrated in the interarytenoid notch of the larynx (Fig. 1).[11] Thus, swallowing and laryngeal closure is initiated before fluid penetration can take place.

Studies of the maturation of the various reflexive components of the LCR in dogs of various ages, as well as studies of mature and immature human infants, indicate a similar pattern of maturation. Boggs and Bartlett[4] found that prolonged apnoea and, to some extent, arousal were the predominant responses to LCR stimulation in newborn puppies. Apnoea duration diminished greatly after the first week of life. In contrast, Sullivan and associates found that LCR responses in sleeping adult dogs typically produced arousal associated with coughing and swallowing.[12] Cough only occurred after cortical arousal. If the animals did not arouse, then apnoea occurred.

LARYNGEAL CHEMOREFLEXES IN INFANTS

As regards maturation of the LCR in infants, when a small bolus of water is introduced into the pharynx of the term infant, a brief respiratory pause and one or two swallows occur. This is very unlike the more exaggerated response of the premature infant. As in the newborn puppy, coughing was infrequent in both preterm and term infants[13] (Figs. 2 & 3). Prolonged apnoea, bradycardia and obstructed inspiratory efforts, often with stridor, in response to a water bolus were infrequent in infants born at term. These responses were almost exclusively found in premature infants.[13–15] Although coughing was relatively uncommon in preterm infants when the

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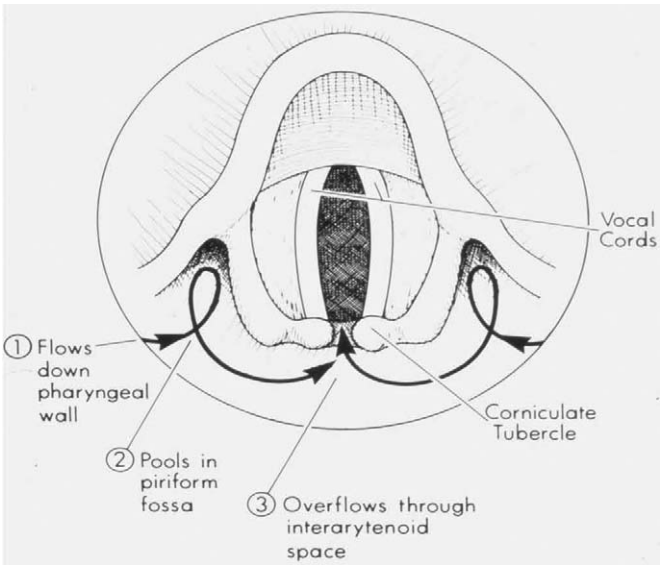

Figure 1. A stylized view of the hypopharynx illustrating the path of flowing saline when the stimulus technique used in living infants was simulated in deceased subjects. After saline pooled in the piriform fossae, the first contact with laryngeal structures was by way of a narrow channel in the interarytenoid space or notch.

reflex apnoea was prolonged it was often associated with one or more coughs[15,16] (Fig. 4).

As indicated above, the various components of the LCR are more prominent in the newborn and diminish with age.[13] Studies in animal models indicate that anaemia and hypoxemia enhance the LCR.[17] At first glance, it is unclear why these several factors are associated with increased LCR activity. Moreover, it is established that upper airway infection also increases LCR activity and this might be beneficial.[18,19] One may ask what are the evolutionary pressures that have contributed to these modulations of the LCR? For example, it seems odd that hypoxia reinforces the LCR when an important component, apnoea, results in hypoxia.[20,21]

Regarding the effect of maturation, it is noteworthy that risk for aspiration is very high at birth. Meconium or amniotic fluid aspiration is not uncommon. Therefore, it seems appropriate that LCR activity would be increased in the newborn to counteract the risk of aspiration. Regarding increase in the reflex activity during hypoxia, it may be beneficial since this might counteract the risk of aspiration of meconium since these infants are relatively hypoxic at birth. Indeed, most infants are hypoxic, to some extent, prior to taking the first breath. The more hypoxic the infant, the greater the advantage of protecting the airway from aspiration of meconium and or amniotic fluid. As in artificial resuscitation, clearing the airway of secretions is the first step.

It is unclear why anaemia is associated with increased LCR activity.[17] Physiologic anaemia peaks at two to four months of age and is more pronounced in premature infants than those born at term. Anaemia would increase the likelihood of cerebral anoxia particularly if associated with upper airway infection, which is often associated with prolonged apnoea. In this same vein, infants with upper airway viral infection are at increased risk for bacterial pneumonia resulting from aspiration of bacteria in upper airway secretions. Hence, increase LCR responses might be particularly important since the pharyngeal bacteria are usually the source of the pulmonary infections.

MATURATION OF LARYNGEAL CHEMOREFLEXES

The past history of LCR research indicates that maturation of the LCR is associated with reductions in repetitive swallows as well as apnoea duration. As maturation progresses, there appears to be an increase in cough, decrease in swallowing and an increase in arousal.[13] However, it should be pointed out that maturational

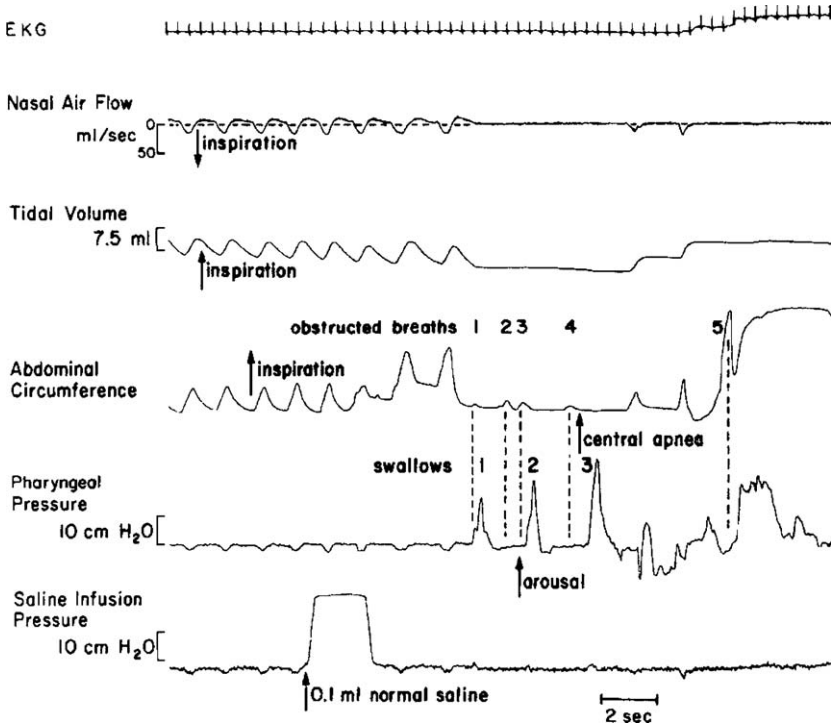

Figure 2. Polygraphic tracings illustrating an infant's responses to a 0.1 ml saline bolus, including swallows, obstructed breaths, arousal, and brief central apnoea. Obstructed breaths 1 and 3 immediately precede swallows and hence are designated "swallow breaths." Obstructed breaths 2, 4, and 5 occur between swallows and are designated "ordinary" obstructed breaths. For obstructed breaths 1 through 4, the level of obstruction is below the tip of the pharyngeal catheter. For obstructed breath 5, the level is above the tip of the catheter. Arousal was noted at the arrow and was evidenced by direct observation and then a later shift in the EKG baseline) Pressure elevation in injection catheter marks timing of saline infusion and does not reflect pharyngeal pressures. CO_2 recording (not shown) indicated absent oral ventilation during these events.