Upper airway reflexes in response to gastric reflux

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SUMMARY

Gastric reflux, and especially laryngopharyngeal reflux, occur several times a day in every infant. Most often, this does not pose any problem. However, in certain conditions, the contact between the refluxate and the upper airway mucosa can trigger several reflexes leading to cardiorespiratory inhibition. This is especially true for the laryngeal chemoreflexes, which are triggered by laryngeal penetration of gastric refluxate. The laryngeal chemoreflexes are held responsible for a subset of apnoeas of prematurity, many apparent life-threatening events, and probably some cases of sudden infant death syndrome. Although a number of experiments in newborn animals, as well as a few clinical studies in human infants, have been performed in the last 40 years to evaluate laryngeal chemoreflexes, their true role in neonatal cardiorespiratory events is still highly debated. In addition, many uncertainties persist with regard to treatment and prevention of their potentially dramatic consequences.

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INTRODUCTION

Laryngopharyngeal reflux, or gastric reflux reaching the upper airway, can lead to a number of otorhinolaryngologic problems in the pediatric population. Chronic rhinitis, recurrent otitis media and otalgia, dysphonia, globus pharyngeus, chronic cough, recurrent spasmodic croup, worsening of obstructive sleep disordered breathing, and subglottic or supraglottic stenosis have all been linked to laryngopharyngeal reflux as the main or additional pathogenetic factor in children. Beyond this constellation of common ENT problems, the laryngopharyngeal reflex can trigger important upper airway reflexes such as the laryngeal chemoreflexes (LCR), whose vagal component can be responsible for major cardiorespiratory inhibition in certain circumstances, especially in the newborn mammal. It is generally accepted that the LCR are involved in major cardiorespiratory control disorders in the early postnatal period, which include the frequent apnoeas of prematurity and apparent life-threatening events of infancy (ALTE) as well as the dramatic sudden infant death syndrome (SIDS). While the LCR have been studied since the 1970s and have been the subject of numerous publications in the scientific literature, many uncertainties persist with regard to their exact involvement in relation to cardiorespiratory events, and appropriate treatment in daily practice. The aim of this review is to present a summary of current knowledge on LCR and their proposed involvement in apnoeas of prematurity, ALTE and SIDS.

ORIGINS OF THE LARYNGEAL CHEMOREFLEXES

Phylogenetically, according to Negus,3 the primitive larynx appeared with the first lungfish, some 350 million years ago, as a necessary sphincter to protect the lungs from drowning while diving. While evolution has transformed the larynx into a sophisticated organ capable of performing complex functions, lower airway protection has remained its most important raison d’être. Throughout life in today’s mammals, reflex closure of the larynx will indeed prevent liquids from entering the trachea. Beginning in foetal life, the larynx must defend future airways against penetration of amniotic fluid, which contains potentially harmful debris such as skin cells, lanugo and vernix caseosa. While the future airways are filled with chloride-rich liquid secreted by the respiratory epithelium, the amniotic liquid is poor in chloride. Hence, laryngeal receptors sensitive to low chloride-containing liquids are thus responsible for foetal LCR, which include forceful laryngeal closure, apnoea, bradycardia and blood flow redistribution towards the brain and heart.4 While such LCR appear very nicely adapted to the foetus, whose blood gas homeostasis is ensured by the mother via the placenta, these same foetal-type LCR may however be potentially dangerous after birth, when the newborn mammal depends on regular respiration and high cardiac output to ensure sufficient oxygen delivery to its organs. Perinatal maturation of the LCR is thus of utmost importance to ensure a smooth transition from foetal to extra-uterine life. Compared to foetal LCR, mature LCR primarily include short apnoea, laryngeal closure, expiratory reflex, cough and swallowing, as well as arousal...
if it occurs during sleep. While postnatal maturation of the LCR has been described in newborn mammals, \(^4\) current data suggest that LCR in the healthy, full-term neonate do not include clinically significant cardiorespiratory inhibition. \(^5\) In contrast, foetal-type LCR with apnoeas, bradycardias and haemoglobin desaturations, which can at times be life-threatening, are observed in certain abnormal neonatal conditions, especially in premature newborns. \(^4,5\)

**LIQUIDS AND LARYNGEAL RECEPTORS RESPONSIBLE FOR POSTNATAL LARYNGEAL CHEMOREFLEXES**

While ontogenetic considerations and various studies conducted in the early postnatal period clearly link the LCR to chloride-poor liquids, a number of studies have shown that LCR can be triggered by other solutions in the newborn lamb. \(^6\) Laryngeal chemoreflexes in response to milk and acidic solutions are of direct relevance to laryngopharyngeal reflux. \(^7,9\) Interestingly, hydrochloric acid solution at a pH of 2, which corresponds to the gastric pH a few days after birth in preterm newborns, \(^10\) most often triggers the strongest LCR-related cardiorespiratory events, at least in lambs. \(^9\) This is obviously relevant to cardiorespiratory events observed in the neonatal period, such as apnoeas of prematurity and ALTE, which have been linked to laryngopharyngeal reflux. \(^11–13\)

Several candidate laryngeal receptors have been targeted as being responsible for the LCR. It is generally acknowledged that laryngeal taste buds, which are densely present on the laryngeal surface of the epiglottis, the aryepiglottic folds and the cuneiform process of the arytenoid cartilages, are involved in the LCR. \(^14\) Beyond these well-defined chemosensitive formations, various other laryngeal chemoreceptors can likewise be involved. These receptors include all mucosal receptors, such as irritant receptors, water receptors and C fibre endings, which can be stimulated by exposure to chemical compounds. Laryngeal irritant receptors correspond to the nerve endings of small diameter myelinated A\(\delta\) fibres, which are present within the laryngeal mucosa, similar to the irritant receptors observed all along the tracheobronchial tree. \(^15\) Unmyelinated C fibre endings are also embedded in the laryngeal mucosa, with extensions to the submucosa. The TRPV1 (transient receptor potential cation channel subfamily vanilloid member 1) present on C fibre endings is activated by a large array of noxious agents, including extracellular H\(^+\) ions. Involvement of TRPV1 in the LCR, especially in response to acid laryngopharyngeal reflux, is likely, and may lead to new treatments aimed at decreasing TRPV1 activity. \(^16,17\) Conversely, while the TASK-1 channel, an acid-sensitive two-pore domain potassium channel, is also present in the laryngeal mucosa of the newborn lamb (unpublished observations), its role in the LCR triggered by acid reflux is doubtful, given its pH sensitivity in the physiological range (pK\(_a\) = 7.3). Overall, it must be recognized that the morphological or electrophysiological characteristics of the laryngeal chemoreceptors responsible for LCR, as well as their transduction mechanisms, are still largely unknown.

**NEURAL CIRCUITRY INVOLVED IN LARYNGEAL CHEMOREFLEXES**

Nerve fibres originating from the laryngeal mucosa are contained in the two superior laryngeal nerves, which convey the vast majority of laryngeal sensory information. A lesser contingent of sensory information travels through the two recurrent laryngeal nerves via the Galen nerve, a communicating nerve between the ipsilateral superior and recurrent laryngeal nerves. All primary afferents pass through the nodose ganglion, where the neuron somata are located, and enter the caudal part of the nucleus tractus solitarius to release glutamate onto second-order neurons and initiate the LCR. Numerous neuromediators/neuromodulators and interneurons are involved in this process and allow integration of the huge amount of afferent information entering the nucleus tractus solitarius. Once integrated into the nucleus tractus solitarius, the information from the laryngeal mucosa is relayed to motoneurons of the C3 phrenic nucleus (apnoea) and to preganglionic cardiac vagal neurons (bradycardia) and laryngeal motoneurons (laryngeal closure) in the nucleus ambiguus (Figure 1).

**POSTNATAL CONDITIONS WHICH ENHANCE LCR-RELATED CARDIO-RESPIRATORY INHIBITION**

Various conditions have been shown to enhance LCR-related cardiorespiratory inhibition, primarily in the early postnatal period.

**Prematurity**

Results from experiments in non-sedated, preterm lambs as well as clinical observations strongly suggest that prematurity is responsible for foetal-type LCR, with prominent apnoeas, bradycardias and episodes of desaturation, which may be life-threatening. \(^9,18\) Further enhancement of LCR-related cardiorespiratory inhibition has been reported during sleep in one study. \(^18\) Interestingly, enhanced LCR-related cardiorespiratory inhibition in preterm lambs was shown to be prevented by caffeine treatment in addition to being largely decreased with postnatal maturation, \(^9\) mimicking clinical observations of apnoeas of prematurity.

**Reflex laryngitis**

Most relevant to the present review are our recent observations that LCR-related respiratory inhibition is enhanced in an ovine newborn model of reflux laryngitis (unpublished observations). This is consistent with results from a pilot study in preterm newborns showing that dexamethasone treatment of laryngitis
largely prevented cardiorespiratory events resistant to usual interventions.19

Sedation

While most studies on the LCR have been performed under various sedative or anaesthetic agents, the latter have been shown to enhance LCR-related respiratory inhibition in piglets. This important observation is significant, especially when interpreting results from most animal studies on LCR, as well as for avoiding unnecessary sedation in infants, such as antihistamine medications for promoting sleep.20

Hyperthermia

In a series of recently conducted experiments in piglets, hyperthermia was shown to enhance LCR-related respiratory inhibition.21 Of interest, this was further related to specific heating of the caudal nucleus tractus solitarius, where primary SLN afferents synapse with second-order neurons.22 Moreover, infusion of gabazine, a GABAk inhibitor, prevented the enhancement of LCR-respiratory inhibition by hyperthermia.21

Exposure to cigarette smoke

Postnatal exposure to cigarette smoke or intravenous nicotine has been shown to enhance LCR-related cardiorespiratory inhibition in lambs.24 In addition, gestational exposure to cigarette smoke further enhances LCR-related respiratory inhibition observed with hyperthermia in piglets.25 Such results may be especially relevant to the pathogenesis of SIDS, for which hyperthermia and cigarette smoke exposure are well-known risk factors.

Respiratory syncytial virus infection

Respiratory syncytial virus infection increases LCR-related respiratory inhibition in lambs and human infants.26,27 Such observations may have significant relevance to SIDS pathogenesis and to central apnoeas associated with viral respiratory infection in very young infants.12,28

Anaemia, hypoxia, hypercapnia and acidosis

Anaemia enhances LCR-related respiratory inhibition.29 Furthermore, the presence of hypoxia30 or pre-test hypercapnia or acidosis is associated with a more severe LCR-related cardiorespiratory inhibition, such that fatal LCR in anaesthetized piglets may be predicted by the level of PaCO2 or pH a priori to LCR.8

NEONATAL CONDITIONS OR TREATMENTS WHICH DECREASE LCR-RELATED CARDORESPIRATORY INHIBITION

Perinatal maturation

Clinical observations and animal data suggest that prenatal maturation generally prevents clinically significant LCR-cardiorespiratory inhibition (foetal-type LCR) in healthy, full-term newborns before the first postnatal hours, if no additional risk factors are present.5,31–33 ALTE related to foetal-type LCR are indeed observed in only a very small subset of healthy full-term newborns, when additional factors, such as upper airway infection, are transiently present. Furthermore, as mentioned above, foetal-type LCR observed in preterm newborns will disappear with postnatal maturation.9,33

Medications

Various treatments have been reported to blunt LCR-related cardiorespiratory inhibition. The adenosine receptor antagonists, caffeine and aminophylline, have been shown to decrease LCR-related cardiorespiratory inhibition, including in premature lambs.9 Other drugs such as acetazolamide,34 β-adrenergic agonists,35 calcitonin gene-related peptide antagonists,36 topical or intravenous diphenhydramine37 and topical lidocaine38 are also able to blunt the apnoeic component of the LCR in animal experiments. These findings should form the basis for further studies aimed at the therapeutic prevention of LCR-related cardiorespiratory inhibition.

CLINICAL IMPLICATIONS

As highlighted above, animal experiments and daily clinical observations strongly support the contention that LCR-related cardiorespiratory inhibition is an important component in the pathogenesis of cardiorespiratory control disorders in early postnatal life.

Apnoeas of prematurity

Laryngeal chemoreflexes have been frequently held responsible for cardiorespiratory events observed in preterm newborns. Clinicians regularly witness apnoeas, bradycardias and/or desaturations triggered by common oral medications, such as domperidone or vitamins, most likely via laryngeal penetration and LCR, due to swallowing immaturity in premature infants. The same mechanism is also at play for cardiorespiratory events occurring during breast- or bottle-feeding.

The role of gastric reflux in apnoea of prematurity pathogenesis has been widely debated in the last decade, as elegantly reviewed by Slocum et al.29 Part of the controversy has been fuelled by the observation that, while anti-reflux medications have not been shown to alleviate apnoea of prematurity,30 many clinicians have used these medications in virtually all cases of cardiorespiratory events occurring in the neonatal period. In addition, multichannel cardiorespiratory and oesophageal pH / impedance recordings have led to discrepant results with regard to the temporal link between cardiorespiratory events and gastric reflux, both acidic and non acidic.39

Overall, while some experts believe that LCR, most frequently secondary to laryngopharyngeal reflux, are responsible for 70% of apnoeas of prematurity,4 others contend that they are much less often involved, and probably only in a small subset of preterm newborns.19 While the jury is still out on this issue, clinical experience suggests that LCR are nevertheless involved in a significant number of apnoeas of prematurity, especially in the presence of additional exacerbating conditions, such as reflux laryngitis.19 Clearly, further well-designed clinical studies are needed to answer this important question.

Aside from the LCR, distension of the oesophagus by gastro-oesophageal reflux can also trigger the oesophageal glottic reflex, which is responsible for apnoea, laryngospasm and heart rate slowing.11,39,41 The potential relevance of this reflex in the pathogenesis of apnoeas of prematurity is currently unknown.

Apparent life-threatening events of infancy and sudden infant death syndrome

Overall, ALTE’s occur in 1–2% of infants.13 Many reports in the literature conclude that a number of ALTE’s are linked to gastric reflux, especially to choking on laryngopharyngeal reflux contents during wakefulness.42 It thus appears that the LCR are responsible
for many ALTE’s, especially when additional conditions, such as mild respiratory infections, transiently heighten LCR-related cardiorespiratory inhibition.

It is now accepted that the vast majority of ALTE infants do not die from SIDS.13 The “triple risk theory” states that 3 factors need to be present for SIDS to occur: 1) a preexisting anomaly, e.g., a dysfunction of the brainstem neural networks controlling cardiorespiratory function; 2) a developmental window of susceptibility, between 2-4 months of age, and 3) a triggering event, which challenges vital function controllers during sleep. As convincingly presented by Leiter,43 the laryngopharyngeal reflux-related LCR represent such a trigger, which can initiate a chain of events ultimately leading to death if the multiple recovery mechanisms (arousal, anoxic gasping) fail (Figure 2).

Significant LCR-related respiratory inhibition in children and adults

While LCR-related cardiorespiratory events are mostly observed in newborns and young infants, severe and at times life-threatening “sleep-related laryngospasm” has been reported in children and adults. The frequent dramatic effect of anti-gastric reflux treatment44–46 has led to a linking of these conditions to gastric reflux. While vagal reflexes originating from stimulation of oesophageal receptors during gastro-oesophageal reflux may be sufficient to trigger laryngospasm,47 the presence of laryngopharyngeal reflux and LCR is most often suggested. Regardless of the originating site of the reflexes, the presence of hyperactive vagal reflexes with local inflammation (reflux oesophagitis or laryngitis) is deemed important. Of note, gastric reflux-related laryngospasm has been reported to be more frequent in neurologically impaired children.1

CONCLUSION

Current knowledge suggests that gastric reflux can be a major cause of cardiorespiratory events in early postnatal life, especially via the triggering of foetal-type laryngeal chemoreflexes. However, although the latter were first described nearly 40 years ago, their exact involvement in the pathogenesis of common and/or dramatic disorders of cardiorespiratory control in the newborn is far from being fully understood. In addition, when suspected, responses to treatment can be deceiving. Further studies are needed to truly understand the role of gastric reflux plus laryngeal chemoreflexes, especially in apnoeas of prematurity, thereby enabling us to design a more consistently effective treatment.

References


Figure 2. Chain of events triggered by laryngeal chemoreflexes leading to sudden infant death syndrome. HR: heart rate; decr. BP: decrease in blood pressure; incr. CO2: increase in CO2; decr. O2: decrease in O2. Modified from ref 41.


