Infant Apnea and Gastroesophageal Reflux: A Critical Review and Framework for Further Investigation

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Current Gastroenterology Reports 2007, **9:**219–224
Current Medicine Group LLC ISSN 1522-8037

Gastroesophageal reflux and apnea of prematurity are both common occurrences in premature infants. However, a causal relationship between the two remains controversial. Strong physiologic evidence indicates that a variety of protective reflex responses may elicit laryngeal adduction and apnea. Although a potential link between gastroesophageal reflux and apnea may exist through this pathway, clinical studies can be cited to either support or refute such a link in premature infants. The majority of gastroesophageal reflux episodes do not appear to be related to apnea. In a specific subset of events, a causal relationship may exist. Whether this is related to the character of the reflux episode or to a predisposition in a subpopulation of infants is unclear. This review presents the evidence for and against an association between gastroesophageal reflux and apnea, discusses techniques used in their evaluation, and identifies approaches for future investigation.

Introduction

Gastroesophageal reflux (GER) occurs commonly in infants, but the extent to which it is physiologic or pathologic (ie, gastroesophageal reflux disease [GERD]) is a matter of great debate. Excessive or abnormal reflux has been implicated in disorders such as apnea, sudden infant death syndrome, asthma, and chronic lung disease [1–3]. This review focuses on the association of reflux and apnea of prematurity.

A causal relationship between reflux and apnea of prematurity is commonly proposed. Several early studies suggest that such an association might exist [1,4,5]. Subsequent investigations, however, have yielded conflicting results [6–9]. Despite uncertain evidence, premature infants frequently undergo diagnostic evaluation for GERD and are widely prescribed antireflux medications. Metoclopramide and ranitidine are among the most highly used medications in the neonatal intensive care unit [10], and 48% of infants with extremely low birth weight who require prolonged hospitalization are discharged on antireflux therapy [11].

Gastroesophageal Reflux

GER occurs in all individuals. Asymptomatic infants exhibit a mean of eight episodes of acid reflux in 24 hours during the first month of life [12]. When both acid and nonacid reflux events are considered in preterm infants, the rate is even higher—from three to five events per hour [7,13]. Several physiologic factors may contribute to the high incidence of reflux episodes in infants [14]. Infants are typically placed in a supine body position, resulting in the gastroesophageal junction being continually submerged in gastric contents. They also consume a very high volume of fluid. A standard intake of 180 mL/kg/d corresponds to almost 14 L/d in an adult [15]. Central autonomic neural pathways may be immature and prone to perturbation by afferent stimulation. Thus, infants may have a predisposition to reflux episodes, and particularly to volumetric reflux episodes that reach high in the proximal esophagus, not present in other populations.

The major mechanism of reflux episodes in infants, as in adults, is transient lower esophageal sphincter relaxation (TLESR). TLESR is a sudden decrease in lower esophageal sphincter (LES) pressure that is unrelated to swallowing and thus allows gastric material to enter the esophagus unopposed by esophageal peristalsis. In a series of studies, Omari et al. [16–20] used a micromanometric sleeve assembly to measure esophageal pressures in conjunction with reflux monitoring. TLESR was consistently associated with 82% to 86% of reflux episodes [16,17]. Such episodes of TLESR appear to be equally common in symptomatic and asymptomatic infants, although

symptomatic infants demonstrate more acid reflux [18]. Feeding tubes, often required for the care of premature infants, increase the rate of reflux episodes, most likely by impairing the competence of the LES [21].

Several other proposed mechanisms for reflux do not appear to contribute importantly in infants. Upper esophageal sphincter function appears to be well developed by 33 weeks gestational age (GA) [19], and esophageal clearance mechanisms are well developed by 31 weeks [20]. Gastric emptying rates have not been shown to affect the incidence of reflux in premature infants [18,22].

Monitoring Techniques for Reflux

A wide variety of techniques have been used to detect reflux episodes during apnea investigations. Scintigraphic, sonographic, and radiologic techniques are typically short in duration and do not adequately detect the frequency of reflux episodes. Studies may be limited to either a feeding or fasting period, for example, and do not monitor a long enough period to capture a representative range of reflux or cardiorespiratory events in a particular infant. Continuous measurements are more likely to capture an adequate number of events, facilitating the identification of any temporal relationships between reflux and apnea.

Esophageal pH monitoring, a conventional continuous measure, has crucial limitations when applied to infants. Relatively few reflux episodes actually cause esophageal acidification in neonates [23]. Infants receive frequent milk-based feedings, which continually buffer stomach acid and induce a weaker acid-secretory response than that produced in older individuals. Reflux may be neutral or even alkaline in such cases. Esophageal pH may therefore significantly underestimate the frequency of reflux episodes in neonates and may not identify cardiorespiratory events resulting from nonacid reflux [24–26].

Multichannel intraluminal impedance (MII) provides a continuous, more comprehensive measure of reflux. MII technology uses esophageal measurements of electrical impedance between multiple closely spaced electrodes to identify fluid in the esophagus [27•]. Performing MII in conjunction with pH measurement increases the specificity of reflux detection and allows the identification of both acid and nonacid reflux. In addition, multiple impedance channels permit detection of the height and the location of a reflux bolus as it travels in either an antegrade (swallow) or retrograde (reflux) manner. MII is highly sensitive to very small fluid bolus volumes [28], and inter- and intra-observer agreement has been found in infants [29].

MII has several important limitations. Descriptive and normative data in infants are currently limited, which may hinder interpretation of studies. Semi-autonomous evaluative tools need to be improved and validated for this population because interpretation can be time consuming. Some studies have noted pH changes without accompanying impedance detection of a reflux bolus. The implications of these events, which are sometimes characterized by a prolonged fall in esophageal pH, are unclear. Although further experience is needed, MII may prove to be useful as a means to identify a precise temporal relationship between apnea and reflux episodes.

Apnea of Prematurity

Premature infants exhibit immaturity of respiratory control that may lead to respiratory pauses of variable duration. Apnea is most frequently defined as cessation of breathing for greater than 20 seconds or a period of shorter duration if associated with significant desaturation hypoxemia or bradycardia [30]. However, pauses not meeting this definition may be clinically important. Apnea is traditionally classified as central or obstructive depending on the absence or presence, respectively, of obstructed respiratory efforts. A third classification, mixed apnea, includes episodes with both central and obstructive components. Mixed apnea typically accounts for more than 50% of long apneic events [31•].

Although the exact cause of apnea of prematurity is not known, premature infants demonstrate immature respiratory control patterns. They exhibit enhanced inhibitory respiratory reflexes, diminished hypercapnic responses, and hypoxia-induced respiratory depression [32]. The ventral surface of the medulla and adjacent areas appears to play a crucial role in ventilatory responses, with modulation by inputs from peripheral chemoreceptors and laryngeal afferents. Excessive afferent input, likely mediated by the superior laryngeal nerve, may destabilize respiratory patterns leading to apnea [31•].

Apnea Monitoring

Apnea may be monitored in infants by a variety of techniques that measure air flow, volume, or both. Pneumotachography provides the most accurate measurement but uses a cumbersome sealed mask that is most suited to short studies. Impedance monitoring detects pulmonary volume changes through electrical impedance from two surface electrodes on the chest wall. It cannot distinguish obstructive apnea from normal respiration or quantify tidal volume. Respiratory inductance plethysmography can estimate tidal volume and therefore detect all forms of apnea using two coil bands placed around the chest and abdomen. A thermocouple detects airflow and can be used in conjunction with chest wall motion sensors to detect all forms of apnea. Because apnea of prematurity may be central, obstructive, or mixed, it is important for any technique investigating a relationship between reflux and apnea to be able to detect all three forms.

Laryngeal Reflexes That Might Link Reflux and Apnea

A variety of physiologic protective reflex responses provide a plausible link between reflux and apnea of prematurity. Reflex responses may be classified by their sensory stimulus types (eg, chemoreceptors or mechanoreceptors), specific stimulus (eg, acid, milk, water, saline, or distention), sensory location (eg, epiglottis, vocal cords, arytenoids, or even esophagus), or motor response (eg, simple cord closure or cessation of the respiratory cycle). Apnea related to protective reflex responses may be due to reflex vocal cord closure (obstructive apnea) or central cessation of respiration (central apnea) or have features of both (mixed apnea).

Several of the most interesting known reflexes for our purposes include the esophago-glottic closure reflex, the aryepiglottic closure reflex, glottic closure induced by epiglottal chemoreceptors, and laryngeal chemoreceptor reflexes (LCR), which have both their sensory and motor arms at the vocal cords. Other LCRs include those with motor arms that produce swallowing, cough, respiratory pauses, and bradycardia.

Thus, one could postulate that obstructive apnea may be produced by several mechanisms inducing glottic closure. The potential stimuli for glottic closure thus include 1) esophageal distention by a large volume of refluxate without upper esophageal sphincter relaxation and regurgitation (the esophago-glottic closure reflex), in which esophageal distention stimulates glottic closure (eg, by a large volume of refluxate without adequate upper esophageal sphincter relaxation and subsequent regurgitation); 2) the pressure of misdirected fluid of any acidity or salinity at the posterior margin of the glottis (aryepiglottic closure reflex); 3) activation of epiglottal chemoreceptors by nonsaline fluid (eg, milk acid, or water) at the anterior margin of the glottis (epiglottal closure reflex); or 4) activation of laryngeal chemoreceptors closer to the introitus of the cords (LCRs) performing in a similar manner. Central apnea, as well as the related bradycardia seen in many infants, could also be induced by afferent stimulation originating from any of these areas.

These possible links between reflux and apnea have been examined in a number of experimental studies. Animal models have demonstrated that fluid stimulation of the laryngeal mucosa can inhibit normal respiratory patterns [33,34]. Factors that might vary widely among reflux episodes, such as fluid tonicity and acidity, appear to be important in determining whether apnea occurs. In anesthetized piglets, instillation of water or cow's milk, but not saline, into the laryngeal area elicits profound apnea leading to death [34]. These responses are reproduced by electrical stimulation of the superior laryngeal nerve, whereas sectioning of the nerve abolishes the response [34]. Gamma-aminobutyric acid (GABA)–ergic neural pathways in the brainstem appear to be involved in mediating inhibitory reflex responses [35].

Studies in human infants support these findings in animal models. Investigators in an early experiment in infants found that acid (but not milk or other neutral fluids) infused into the esophagus provoked apnea in predisposed infants [1]. However, the locus of the stimulus was not clearly defined. Instillation of water into the pharynx may trigger apnea and bradycardia in infants [36], and instillation of warm saline elicits a variety of other reflex responses [37]. Altered laryngeal sensitivity may play a role in this process. In infants who had the laryngeal adductor reflex provoked by forced air (likely via the aryepiglottal closure reflex), individuals with a history of apnea counterintuitively required a higher level of stimulation to trigger the reflex [38].

In an effort to examine whether the esophago-glottic closure reflex might be involved in infants with apnea, we studied 10 term infants who presented to the hospital after an apneic episode (Unpublished data, SRO). We used cardiorespiratory monitoring, including a nasal thermistor, to detect obstructive apnea during rapid infusions of graded volumes of air into the esophagus through a multiport esophageal manometry catheter. We were unable to induce any apnea in any infant during this procedure, although it is possible that characteristics of the stimuli or of the infants produced our negative results.

Rationalization of Conflicting Data Linking Reflux and Apnea

Plausible mechanisms linking reflux to apnea could include some of these reflex responses. A causal relationship remains controversial, however, and a variety of alternative relationships may exist (Fig. 1). The numerous clinical studies described earlier that refute an association are joined by others in which medical treatment of GERD with either cisapride or metoclopramide does not reduce the frequency of apnea in affected infants [39]. It is clear that the majority of reflux episodes do not cause apnea in infants. Furthermore, in most infants with apnea, reflux episodes may not be the inciting event. In a specific subset of apneic events, however, reflux may be causal. Whether this is true and what determines the association in some cases, such as characteristics of the stimulus or predisposition in a particular infant, remain unclear. In critically evaluating any clinical study of the reflux-apnea relationship, it is crucial to search for several flaws that are frequently present. First, many of these studies use techniques that are inadequate to document obstructive or mixed apnea, the most likely types of apnea to be involved. Techniques to identify nasal air flow are required.

Second, many of these studies use techniques that are inadequate for detection of nonacid reflux, which is the most likely type of reflux to occur in postprandial infants. MII studies may be useful in this regard, and combined MII and pH monitoring has now been used in several small studies exploring the relationship between reflux

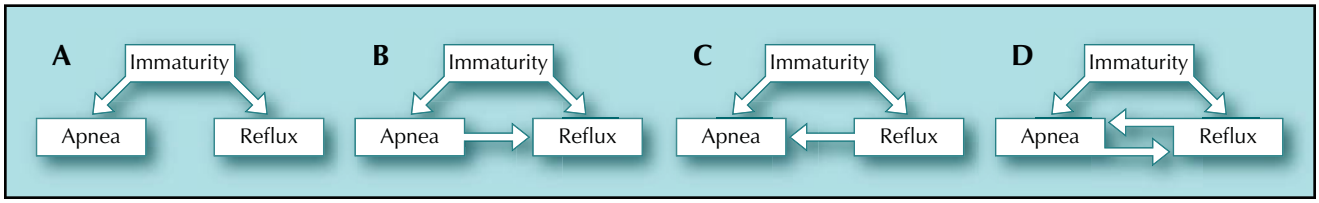

Figure 1. Possible causal relationships leading to an apparent association between apnea and reflux in infants. **A,** Immaturity leads to both apnea and reflux, although there is no direct causal relationship. In this scenario, apnea and reflux events may coincide by chance, at times with apnea preceding reflux and at times with reflux preceding apnea. **B,** Although immaturity leads to some reflux events directly, apnea is also an important cause of reflux. For instance, hypoxia may trigger lower esophageal sphincter relaxation. In this scenario, apnea would precede or coincide with reflux. **C,** Although immaturity leads to some apnea events directly, reflux is also an important cause of apnea. This pathway could be mediated by laryngeal chemoreflexes. In this scenario, reflux would precede or coincide with apnea. **D**, Mechanisms **B** and **C** both occur to a degree, depending on the characteristics of the patients and/or the apnea and reflux events themselves. Future research will be needed to identify which pathways occur in which patients.

and apnea. An early investigation in 22 infants found a greater mean time spent apneic during reflux (40 s/h) than during nonreflux time (6.8 s/h, $P<0.001$); a greater association with apnea of long reflux episodes (>30 s) than shorter reflux episodes; a significant correlation between time spent apneic and reflux episodes, although apnea either preceding or following a reflux episode by 30 seconds was included; and no difference between the number of apneas preceding or following a reflux episode [9]. These findings suggest a temporal, but not causal, relationship. Two more recent studies with MII have not supported an association in infants [7,8]. When further developed, MII should allow a more precise temporal correlation to be established between reflux episodes and apnea events, and future studies may clarify these contradictory findings.

Third, studies rarely use techniques that could experimentally investigate some of the postulated mechanisms in affected children; fiberoptic endoscopic evaluation of swallowing with sensory testing (FEESST) of the aryepiglottic closure reflex is beginning to prove a useful modality in this regard.

Fourth, it is important to remember that studies using pharmacotherapy as the intervention and apnea cessation as the outcome of interest have generally been flawed by the incomplete efficacy of all existing antireflux pharmacotherapy and by a lack of controls (eg, placebo) in the study design.

Even if a temporal association between reflux events and apneic episodes is demonstrated convincingly, this does not necessarily establish a causal relationship. Control of both respiratory patterns and esophageal function (including the LES) is regulated by central neural pathways. A defect or perturbation of central neural output may allow reflux and apnea to occur simultaneously. This may be particularly important in neurologically impaired infants. Furthermore, anatomic and functional relationships exist between ventilatory and autonomic neural output, and significant afferent inputs can influence either system [40,41]. For example, hypoxia and hyperoxia modulate LES pressures in a piglet model, reversing the usual direction of the hypothesized reflux-apnea link [42]. These alternative hypotheses could be resolved by experimental clinical studies in which reflux is induced or mimicked and apnea is sought as an outcome variable.

Future Directions

One interpretation of the studies showing no association between reflux and apnea in premature infants is that no such link exists. Another is that reflux triggers apnea only under certain circumstances that remain to be identified. Only certain types of refluxed material may induce apnea. The acidity, volume, or pressure of the refluxed material could determine the respiratory response. The anatomic structures reached by the refluxate may also play a role. For example, higher reflux that escapes through the upper esophageal sphincter and reaches the pharynx or larynx may be more likely to trigger airway closure reflexes. Furthermore, effect modification may occur, with reflux only causing apnea in a specific subset of patients with certain characteristics. The developmental predispositions in particular infants might be sensory, motor, or clearance and include heightened sensitivity to the reflexes, prolongation of physiologic protective glottic closure responses, or immaturity of refluxate clearance functions (ie, swallow or cough). Developmental maturity and other comorbidities, including neurologic injury, respiratory disease, or congenital anomalies, could make infants more or less susceptible to experiencing reflux-induced apnea.

Future studies assessing the putative link between reflux and apnea will need to be designed to capture any differential impact of certain types of reflux on specific subsets of infants. This objective could be accomplished with large studies sufficiently powered for stratified analyses based on candidate characteristics of both the reflux and the patients. Alternatively, inclusion could be restricted to focus on very specific patient populations or types of reflux. Characterization of developmental maturity is particularly challenging in the premature population, as there is no direct measure available. Genetics, comorbidities, post-menstrual age, GA at

birth, and post-natal age may all play a role. Although both are now 33 weeks GA, a 10-week old boy born at 23 weeks GA with multiple comorbidities may have very different reflux patterns and responses to reflux than an otherwise healthy 3-week-old girl born at 30 weeks GA. Premature patients with specific characteristics and comorbidities may be rare and difficult to enroll in sufficient numbers for adequately powered studies, and analyses may be confounded by the fact that patient characteristics may influence both the quality of reflux events and the patient responses to those events. Thus, the design of future studies must explicitly and scrupulously address these issues to ensure that meaningful results are obtained. Preliminary exploratory descriptive studies identifying specific patients for whom certain types of reflux episodes trigger apnea could aid in narrowing the scope of more definitive studies.

Finally, if research identifies types of reflux events that trigger apnea in certain patients, more effective antireflux therapies will then need to be developed and rigorously tested. The efficacy and toxicity of therapies for reflux in premature infants remain disputed, in part due to the lack of clear endpoints or morbidities in this population [15,39,43–47]. If an infant subpopulation is established for whom apnea is a morbidity of reflux, it will also serve as an ideal population for studies of antireflux therapies.

Conclusions

Currently available evidence suggests that most reflux events do not cause apnea in most infants but that some reflux may cause apnea in some infants. Reflexes with afferents in the esophagus or laryngo-pharynx and with efferents in the larynx or central pattern generators for respiratory processes provide plausible mechanisms linking reflux and apnea. Future investigations that carefully avoid the pitfalls of previous studies may help to define specific reflux characteristics or patient populations at risk for reflux-induced apnea and thus permit a more judicious use of more appropriate therapy for this vulnerable group.

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