Gastroesophageal Reflux and Apnea of Prematurity: No Temporal Relationship

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ABSTRACT. *Objective.* **A relationship between gastroesophageal reflux (GER) and apnea of prematurity (AOP) has long been suspected but is difficult to prove because most GER in this age group is nonacidic and thus undetectable by pH monitoring, the current standard for GER detection. The new multiple intraluminal impedance (MII) technique allows pH-independent reflux detection via changes in impedance caused by a liquid bolus inside the esophagus. We used this technique to investigate whether there is a temporal relationship between GER and AOP and whether GER occurs predominantly before a cardiorespiratory (CR) event.**

Methods. **Nineteen infants with AOP (median gestational age at birth: 30 weeks; range: 24–34; age at study: 26 days [13–93]) underwent 20 6-hour recordings of MII, breathing movements, nasal airflow, electrocardiogram, pulse oximeter saturation, and pulse waveforms. MII signals were analyzed, independent of CR signals, for reflux episodes (RE), defined as a fall in impedance in at least the 2 most distal channels. CR signals were analyzed for CR events, ie, apneas of ≥4-second duration, desaturations to ≤80%, and falls in heart rate to ≤100/min. A temporal relationship between an RE and a CR event was considered present if both commenced within 20 seconds of each other.**

Results. **There were 2039 apneas (median: 67; range: 10–346), 188 desaturations (6; 0–25), 44 bradycardias (0; 0–24), and 524 RE (25; 8–62). The frequency of apnea occurring within ± 20 seconds of an RE was not significantly different from that during reflux-free epochs (0.19/min [0.00–0.85] vs 0.25/min [0.00–1.15]); the same was true for desaturations and bradycardias. Also, RE occurred similarly often within 20 seconds before as after an apnea (2; 0–14 vs 1; 0–17). A minority of apneas (3.5%) was associated with an RE reaching the pharyngeal level; of these, significantly more (45 vs 26; median: 1; 0–10 vs 1; 0–7) occurred after rather than before an RE.**

Conclusion. **Both CR events and GER were common in these infants but, with few exceptions, did not seem to be temporally related.** *Pediatrics* **2002;109:8–11;** ***control of breathing, laryngeal chemoreflex, hypoxemia.***

ABBREVIATIONS. AOP, apnea of prematurity; GER, gastroesophageal reflux; RE, reflux episode; MII, multiple intraluminal impedance; CR, cardiorespiratory; Spo_2, pulse oximeter saturation; EKG, electrocardiogram; F, French.

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The pathophysiology of apnea of prematurity (AOP) is incompletely understood. One of the factors potentially involved is gastroesophageal reflux (GER). This is because of 1) the observation that AOP occurs frequently in the immediate postprandial period, ie, when GER is most likely to occur[1]; 2) data from animal studies that show that apnea can be induced by the instillation of small amounts of liquid into the larynx, resulting in stimulation of the laryngeal chemoreceptors[2]; and 3) the observation that apneas are more likely to occur after episodes of regurgitation, documented via pH monitoring and manometry.[3] The last observation is further supported by anecdotal reports of apneic spells occurring immediately after a reflux episode (RE).[4,5]

Most studies that attempted to document a temporal relationship between apnea and GER, however, failed to do so.[6–12] In the few studies that did observe such a relationship, all infants had been specifically selected because of a history of apneic spells and frequent regurgitations.[3,4] The majority of prolonged apneic spells even in these infants, however, was not associated with regurgitation. Nevertheless, because of a widely presumed relationship between GER and AOP, the use of prokinetics became popular in infants with AOP; 19% of very low birth weight infants admitted to US teaching hospitals received these according to a recent survey.[13]

One of the reasons that it may have been difficult to demonstrate a relationship between GER and AOP is that the method applied to identify GER, namely pH monitoring, will only detect acidic reflux, whereas most reflux in infants is nonacidic.[14,15] This potential caveat can be avoided by using a new method for reflux detection, the multiple intraluminal impedance (MII) technique. This technique is based on the intraluminal measurement of electrical impedance between a number of closely arranged electrodes during a bolus passage. It allows the reliable detection of fluid boluses that occur in an antegrade (swallows) as well as in a retrograde (GER) manner.[16,17]

In this study, we recorded the MII in conjunction with cardiorespiratory (CR) parameters in a group of preterm infants with AOP to investigate whether GER is involved in the pathophysiology of AOP. We wanted to test the following hypotheses: 1) there is a close temporal relationship between GER and AOP (because this would be a prerequisite for a causal relationship), and 2) reflux episodes usually precede

rather than follow apneas (assuming that GER causes apnea via stimulation of the laryngeal chemoreflex).

METHODS

Nineteen infants (13 boys) were enrolled in this study; 1 infant was studied twice. All had been born at <37 weeks' gestation; had received >50% of their fluid intake orally and still via nasogastric tube; were not on mechanical ventilatory support; and had clinical evidence of AOP, defined as the occurrence of at least 2 episodes of apnea (>20 seconds), bradycardia (<100 beats per minute), and/or hypoxemia (pulse oximeter saturation [Spo_2] ≤80%) over a 2-hour period as documented in their nursing charts. Infants who had conditions resulting in secondary apnea, such as sepsis or intraventricular hemorrhage, or any congenital anomalies were excluded.

All infants underwent 6-hour recordings of MII (z-lab; Sandhill Scientific, Highlands Ranch, CO), breathing movements via thoracic impedance, electrocardiogram (EKG), nasal airflow, pulse oximeter saturation in beat-to-beat mode, and pulse waveforms (Nellcor N-200; Mallinckrodt, St. Louis, MO). The purpose-built impedance catheter consisted of 7 metallic cylinders placed 1.5 cm apart from each other around an 8 French (F) feeding tube, with the latter also containing a 5 F feeding tube through which the infants received either expressed breast milk or formula. Catheters were positioned by advancing them first into the stomach and pulling then them back until the impedance measured between the lowest 2 electrodes increased, indicating that they had reentered the esophagus. At this position, at least 1 electrode always remained visible inside the pharynx, allowing the identification of RE that had reached up to the pharyngeal level. The study was approved by the hospital's ethics committee, and written informed parental consent obtained.

Recordings were analyzed in 2 phases by one of the authors (N.S.). First, CR signals were analyzed for cessations in breathing efforts and/or nasal airflow for ≥4 seconds (central and obstructive/mixed apneas; further separated into episodes lasting ≤20 seconds and >20 seconds and excluding periodic apnea, see below), falls in heart rate to ≤100 beats per minute (bradycardias), and falls in Spo_2 to ≤80% (desaturations).[1,18] These analyses were done blinded to the esophageal impedance signals. When the EKG signal was disturbed or faulty, the pulse wave form signal was used to determine heart rate. Periods with disturbed pulse wave form signal indicating motion artifact were excluded from desaturation analysis. Periodic apnea was defined as the occurrence of 3 or more apneas, each separated by <20 breaths.[18] Second, the impedance signals were analyzed, blinded to the CR signals, for RE, defined as a decrease in impedance starting in the most distal channel and extending over at least 2 channels (Fig 1).[19] All RE were then analyzed for any temporal association with a CR event (apnea, bradycardia, or desaturation), which was considered present if the CR event commenced within ± 20 seconds of the onset of an RE; this interval was arbitrarily defined from pilot data.

Data are presented both as cumulative values and as medians and ranges of individual measurements. The frequency of apneas associated with GER was calculated by dividing the number of pauses during these reflux epochs by the total time of these epochs and comparing the resulting values with those calculated for reflux-free epochs using the Wilcoxon's matched pairs test.[3] Correlations were calculated using the Spearman's rank correlation test.

RESULTS

Clinical Data

Median gestational age at birth was 30 weeks (range: 24–34 days) and at study was 33 weeks (29–37); postnatal age at study was 26 days (13–93 days), birth weight was 1150 g (600–1865 g), and weight at time of study was 1595 g (1000–2320 g). Five infants had been ventilated after birth, and 9 were still receiving additional inspired oxygen via nasal cannulae (22%–35%) for residual lung disease; 9 received caffeine (2.5 mg/kg/d) and 2 doxapram as treatment for AOP. Infants had a median of 1 episode of clinically evident regurgitation or vomiting (range: 0–8) noted in their nursing charts for the last 48 hours before the onset of recording.

Recording Results

During 118 hours of recording (median: 6.0; range: 4.9–6.6 hours), a total of 524 RE occurred, with a median rate of 25 per recording (range: 8–62). This compared with 2039 apneas (67; 10–346; 314 [median: 9; range: 0–101] of these being obstructive/mixed apneas), 188 desaturations (6; 0–25), and 44 bradycardias (0; 0–24).

Apnea frequency during epochs with reflux was not significantly different from that found during reflux-free epochs (0.19/min [0.00–0.85] vs 0.25/min [0.00–1.15]; $P > .05$). Also, there was no correlation between apnea, bradycardia, or desaturation and RE,

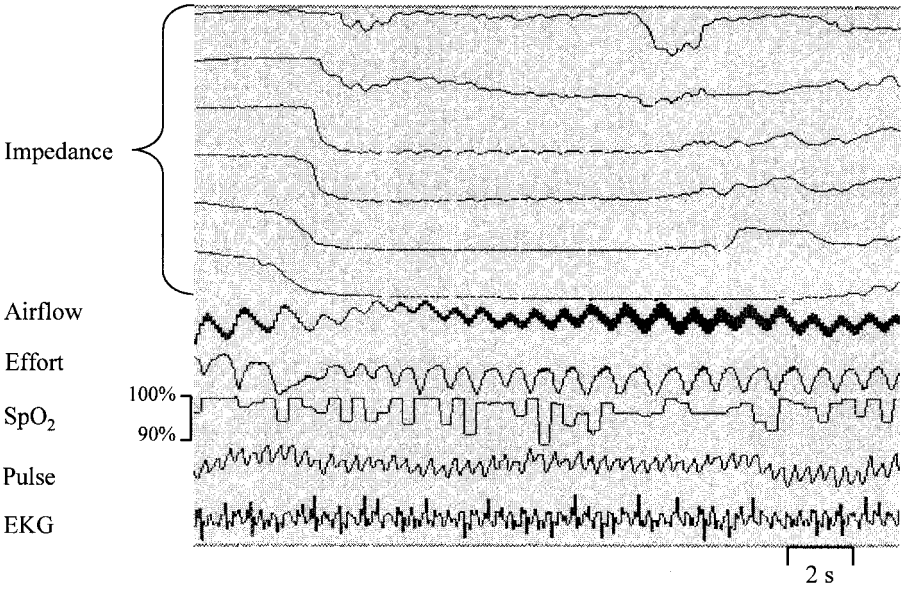

Fig 1. Example of an RE with the refluxate reaching the pharyngeal level but occurring without any change in cardiorespiratory signals. The RE is characterized by a decrease in impedance starting in the most distal channel and subsequently extending orally until reaching the uppermost electrode located in the pharynx as determined by pharyngeal inspection. The second deflection, starting in the uppermost impedance channel, represents as swallow. Note that Spo_2 was recorded in the beat-to-beat mode, where breath-by-breath changes in Spo_2 are common in preterm infants, and that the EKG looks artifactual as a result of insufficient graphics resolution; in the study, the latter signal was therefore analyzed using a different time frame.

ie, infants who exhibited high numbers of any of these events were not more likely to have frequent RE ($r \leq 0.2$, $P > .05$). Finally, among those apneas that did occur within 20 seconds of an RE, similar numbers occurred before as well as after an RE (2; 0–14 vs 1; 0–17; $P > .05$).

The situation was similar for desaturations. Only 9 of these (4.8%; in 7 recordings) were associated with an RE, and the frequency of desaturation that occurred with GER was again not significantly different from the desaturation that occurred during reflux-free epochs (0.00; 0.00–0.12 vs 0.00; 0.00–0.07; $P > .05$). All 9 desaturations, however, occurred after an RE, with the reflux reaching the pharyngeal level in 6 of these 9 episodes. Finally, only 1 of 44 bradycardias occurred within ± 20 seconds of an RE; which was too small a number to interpret.

When analysis was restricted to those 345 RE that reached the pharyngeal level (median: 17 per recording; range: 3–35), the frequency of apnea that occurred in conjunction with these RE was again not significantly different from that found during reflux-free epochs (0.17/min [0.00–1.00] vs 0.19/min [0.00–0.97]; $P > .05$). However, of those 71 apneas that were associated with an RE reaching the pharyngeal level, significantly more (45 vs 26; median: 1; 0–10 vs 1; 0–7; $P < .05$) occurred after rather than before an RE.

DISCUSSION

Both CR events and GER were common in these infants but occurred independent of each other. Apnea, bradycardia, or desaturation did not occur more frequently with reflux than during reflux-free epochs. Thus, in this group of preterm infants with recurrent episodes of "idiopathic" AOP, the AOP primarily seemed to be unrelated to GER, although there was a minority of RE, particularly among those in which the refluxate reached the pharyngeal level, that may have resulted in apnea and/or desaturation.

We chose to investigate the relationship between GER and AOP from a respiratory viewpoint, ie, by addressing the question of whether a significant proportion of these respiratory events is triggered by GER. For this reason, we enrolled infants with AOP irrespective of whether they had a history of frequent regurgitations. The lack of a relationship between GER and AOP found in these infants cannot suggest that such a relationship does not exist in individuals. However, our results clearly do not support the hypothesis that GER is a mechanism involved in a large proportion of apneas in preterm infants and would, therefore, argue against the indiscriminate use of antireflux measures (eg, treatment with prokinetics) in infants with AOP and occasional regurgitations.[13]

Even those RE that reached the pharyngeal level were not more likely to be associated with apnea, which is in contrast to other work in this field.[3] Nevertheless, our findings are in line with those from Page and Jeffery,[20] who observed that preterm infants studied at term-equivalent age responded to the pharyngeal infusion of small volumes of 0.9% saline or water during sleep with a volume-dependent increase in swallowing frequency, but not with an increased apnea rate. These authors suggested that apnea and bradycardia are predominantly evoked if the larynx rather than the pharynx is stimulated, which does not usually occur during regurgitation of small amounts of liquid.[20] Alternatively, they speculated that the response is age dependent, with apnea being more likely to occur in less mature infants (<37 weeks). This potential explanation, however, is not supported by our data because all but 2 of our patients were studied at <37 weeks' postconceptional age.

Several studies in older infants also failed to demonstrate a consistent relationship between acidic GER and apnea.[5–11] However, a potential shortcoming of these studies was that they used pH monitoring to document GER, which will identify only acidic reflux (pH <4). Gastric acidity depends on the intervals at which neutralizing milk is fed. It has been shown that in term infants fed in 4-hour intervals, gastric pH is <4 for only 42% of the time.[15] Although we could not measure pH, it is likely that this proportion was even lower in our patients, who were fed in 2-hour intervals. In fact, Wenzl et al,[14] also using the MII technique, showed that only 11% of RE in term infants with recurrent regurgitation or respiratory symptoms had a pH of <4. These authors also observed that a high proportion of RE (85.7%) were accompanied by "breathing irregularities" and that 29.7% of apneas (>5 seconds) were associated with GER. However, they did not identify control periods, ie, they did not determine whether GER was significantly more likely to occur with apneas and/or irregular breathing (both of which are common in this age group[18]) than without these respiratory patterns.

Limitations

We excluded periodic apnea because there is evidence that the underlying pathomechanism for this pattern is different from that causing isolated apneas[21] and even less likely to be reflux related. We did not record esophageal pH because it was technically impossible to combine a feeding tube, the impedance electrodes, and a pH electrode so that they would fit into an 8 F feeding tube, which was the maximum diameter we considered acceptable for preterm infants, as we were concerned that a thicker tube would increase airway resistance, thereby interfering with respiratory control.[22] However, such a study has been performed in term infants, showing that almost 90% of RE in this age group are nonacidic, suggesting that MII is more sensitive for GER detection than pH monitoring.[14] One infant was studied twice, with recordings being 2 months apart, because AOP symptoms recurred after they had temporarily ceased, and, therefore, entry criteria were met again. Finally, MII is a relatively new technique, and there is little experience with it in preterm infants. One theoretical concern is whether it is sensitive enough to detect the small liquid boluses that typically occur in this age group. Recent work from our group, however, has shown that even volumes of 0.1 mL, instilled into the pharynx of preterm infants, are reliably detected with this technique (unpub-

lished observation). Also, MII allows reliable GER detection in older individuals,[16,17] and there is no reason that its underlying physical principle should cause age-dependent differences in its ability to identify GER.

CONCLUSION

This study has shown that GER does not play a significant role in the pathophysiology of "idiopathic" AOP. This finding may be relevant to the practice of giving prokinetics to infants with AOP. The effectiveness of this practice has never been proved, is difficult to maintain after the withdrawal of cisapride from the market, and, as our results suggest, lacks a pathophysiological basis.

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THE HYPING OF DRUGS

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Fryhofer SA. Prescription pitches. *New York Times.* August 21, 2001

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