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Apnea, bradycardia and desaturation in preterm infants before and after feeding

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Abstract

Objective—A common clinical impression is that both gastroesophageal reflux (GER) and cardiorespiratory events increase after feeding in preterm infants. We aimed to measure objectively the effects of feeding on GER, apnea, bradycardia and desaturations.

Study Design—We conducted a retrospective review of premature infants with a gestational age of 23 to 37 weeks at birth and a post-conceptional age of 34 to 48 weeks, who were referred for multichannel intraluminal impedance (MII), pH probe and 12-h apnea evaluation. Cardiorespiratory and GER event rates during pre- and post-feeding intervals were compared.

Result—Thirty-six infants met the inclusion criteria. More GER events occurred after a feed than before ($P = 0.012$). After feeds, reflux was less acidic and higher in the esophagus ($P<0.05$). In contrast, the rates of apnea, bradycardia and desaturations were not altered by infant feeding. Apnea of >5 s occurred at a median frequency of 0 (range 0 to 3) events per hour before a feed and 0 (0 to2) events per hour after a feed ($P = 0.61$).

Conclusion—The frequency, height and pH of GER are significantly altered by feedings in preterm infants. However, the common clinical impression that apnea, bradycardia and desaturations are more prevalent after feeding is not supported.

Keywords

gastroesophageal reflux; apnea; esophageal pH monitoring; multichannel intraluminal esophageal impedance

Introduction

A causal relationship between gastroesophageal reflux (GER) and apnea at prematurity continues to be a topic of significant debate and investigation. Although early studies suggest that such an association might exist, subsequent investigations have yielded conflicting results.[1–8] Nevertheless, premature infants frequently undergo diagnostic evaluation for GER, and are widely prescribed anti-reflux medications.[9,10]

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Disclosure

The authors have no financial disclosures or conflict of interest to report.

A common clinical impression is that GER may be more severe and apnea may be more significant in some infants after feeding. In this scenario, a recently fed infant who may or may not have clinical evidence of reflux, experiences an apnea, bradycardia or desaturation. A causal relationship between GER and apnea is inferred, and the practitioner is called upon to initiate anti-reflux therapy. Although periods of prolonged airway closure have been shown during active bottle feeding, and measurable changes in pulmonary mechanics may occur during or after feeds, it remains unclear whether these physiological changes translate into increased cardiorespiratory instability after feeding.[11–13]

We aimed to empirically assess the putative increase in cardiorespiratory events in preterm infants after feeds by comparing GER, apnea, bradycardia and desaturation frequencies before and after feeding. We hypothesized that feeding will alter GER patterns owing to acid buffering and gastric distention as follows: incidence of GER will increase after feeds, acidic reflux will predominate before feeds, non-acidic reflux will predominate after feeds, and the bolus height of refluxate will increase after feeds. Similarly, we hypothesized that the incidence of apneas, bradycardias and desaturations would increase after feeds.

Methods

This study is a retrospective review of 36 inpatient preterm infants, who were referred, owing to clinical indications, for a 12-h bedside apnea monitoring study with multichannel intraluminal impedance (MII) and pH monitoring at the Rainbow Babies and Children's Hospital from January to November 2006. Inclusion criteria were a gestational age of 23 to 37 weeks and a post-conceptional age of 34 to 48 weeks. Infants with major congenital anomalies were excluded. The sample size was determined by the number of clinical studies performed at our institution before the review.

Cardiorespiratory monitoring was carried out by inductance plethysmography (Respitrace, Viasys Respiratory Care, Yorba Linda, CA, USA), in conjunction with electrocardiogram and oxygen saturation (Ohmeda, Boulder, CO or Masimo, Irvine, CA, USA) recording. GER monitoring was conducted using a combined MII and pH system (Sleuth Monitoring System, Sandhill Scientific, Highlands Ranch, CO, USA). MII utilizes esophageal measurements of electrical impedance between multiple closely spaced electrodes to identify fluid in the esophagus, and enables one to detect reflux regardless of acidity.[14] The impedance/pH catheter was initially placed by measuring the nasal–ear–xiphoid distance. Placement was verified by chest radiography, with adjustment as needed to position the catheter tip approximately 1 cm above the gastroesophageal junction. Apnea monitoring, MII and pH studies were reviewed and manually scored by a single trained reviewer, with the interpreter blinded to infant feeding times. A chart review was conducted to obtain demographic information.

Common definitions for GER and respiratory events were used. A pH probe event was defined as pH <4 for >5 s. An MII event was defined as a 50% reduction in baseline impedance detected by at least two sequential channels, and was classified as acidic (pH<4) or non-acidic (pH>4). To obtain the total number of acidic events, those detected by impedance and acid events detected only by pH were totaled. The height of refluxate toward the proximal esophagus was approximated from the impedance/pH catheter tip through imbedded electrodes spaced at 1.5-cm intervals. The height of the most proximal electrode to identify a reflux bolus was recorded. An apnea of >15 s was scored and classified as central, obstructive or mixed, depending on the absence or presence of obstructed respiratory efforts. Bradycardia at <85 beats min^{-1} and desaturations of <85% were recorded. These values were selected as they may indicate a potentially clinically significant cardiorespiratory event, and are commonly reported in neonatal literature. Shorter respiratory pauses of 10 and 5 s in length were also evaluated as alternative measures.

One-hour windows before and after feeding were identified for each infant and used for the analysis. The period of time during which the infant was actually feeding was excluded from this analysis, as the goal of the study was to compare cardiorespiratory stability and GER with the stomach in its most full state post-feed versus in its most empty state post-feed, but not to compare the feeding versus non-feeding states, which have been described earlier.[15,16] All infants were on full enteral bolus feeds at the time of study. Nasogastric or orogastric tubes, if utilized for feeding, remained in place for the duration of the study. The Wilcoxon signed rank test for paired non-parametric data was used to compare average pre- and post-feeding cardiorespiratory and GER event rates for each infant.

This study was approved by the University Hospitals institutional review board and a waiver of consent was granted for chart review without patient contact.

Results

Thirty-six infants met the inclusion criteria and none of them were excluded. Apnea monitoring data were unavailable for three infants who were included in the GER analysis. One infant was evaluated twice, and only the first evaluation is included in the analyses. The average gestational age was 30.7 ± 4.3 weeks, with a birth weight of 1617 ± 834 g (Table 1). The average post-conceptional age at the time of study was 38.6 ± 3.0 weeks, with a weight of 2766 ± 720 g. The primary reasons for referral for evaluation were apnea (n = 4), bradycardia (n = 10), desaturations or cyanosis (n = 12), acute life-threatening event (n = 6), suspected reflux (n = 3) and others (n = 1). Twenty-two infants were evaluated during their intitial hospitalization after birth, and 14 were studied during a subsequent admission. Only one infant was being treated with anti-reflux medications at the time of study. That infant was on both ranitidine and metoclopramide, but still had a pH <4 for over 30% of the tracing. No infants were on proton-pump inhibitors or other histamine blockers or prokinetics. One infant was receiving caffeine therapy. The average duration of monitoring was 14.0 ± 1.8 h, with 3.2 ± 0.9 clearly defined feedings per infant.

The character of GER was markedly altered by infant feeding (Table 2). Significantly more GER events, as detected by either MII or pH probe, occurred after a feed than before. Acidic GER events were more frequent before a feed, whereas non-acidic GER events were more frequent after a feed. The median percentage of reflux events that were acidic fell from 100 (0 to 100%) during the prefeeding period to 4 (0 to 100%) during the post-feeding period (P<0.001). The average height of refluxate toward the proximal esophagus, as measured from the impedance/pH catheter tip, was higher after feeding than before.

In contrast, the rates of apnea, bradycardia and desaturations were not altered by infant feeding (Table 3). An apnea of >15 s occurred at a frequency of 0 (0 to 3) events per hour before a feed and 0 (0 to 2) events per hour after a feed (P = 0.61). As no difference in apnea of 15 s duration was detected, shorter respiratory pauses were also analyzed. Apnea of >10 s and >5 s also did not occur at statistically different rates. Similarly, the rates of bradycardia at <85 beats min^{-1} and desaturations of <85% were not affected by feeding.

Discussion

We hypothesized an increase in the rates of GER, apnea, bradycardia and desaturations after feeding. As predicted, feeding significantly increased the frequency, pH and bolus height of GER in preterm infants. Nevertheless, concomitant increases in apnea, bradycardia or desaturation were not found.

The increase in the median bolus height of refluxate after feeding is a new finding. As the sensors on the MII probe are spaced 1.5 cm apart, a median height increase from 6 (0 to 9) cm

before feeding to 6.75 (3.75 to 9) cm after feeding simply corresponds to an increase in the proportion of reflux boluses hitting higher sensors. In smaller infants, this may mean that the refluxate more frequently reached the level of the larynx; however, we were unable to pinpoint the anatomical location of the reflux in individual infants in this retrospective study. The anatomical height of the refluxate may be relevant in triggering certain morbidities. For example, perhaps only a refluxate reaching the laryngeal area triggers apnea via protective reflex pathways. This could theoretically account for the increased symptoms noted in a subset of infants after feeding. Nevertheless, in the group of infants studied, even though the higher post-feed reflux height after feeds likely meant that more reflux reached the upper esophagus after feeds, we did not find evidence of increased apnea, bradycardia or desaturations.

Although not statistically significant, we found a higher rate of apnea before feeding. In some studies, the acidity and osmolality of fluid instilled into the laryngeal area have been found to be an important factor in triggering apnea.[17,18] Furthermore, a recent investigation of the temporal relationship between reflux and apnea of prematurity noted a significant relationship with weakly acidic reflux events.[19] If acidic reflux were a more potent trigger than non-acidic events, this could explain the non-significantly higher rate of apneic events before feeds when acidic reflux is most prevalent.

We found a marked change in the acidity of reflux events from pre- to post-feeding periods. A high percentage of reflux events, particularly after feeding, were non-acidic, and may have been missed by traditional pH monitoring. This finding agrees with previously published studies in infants showing that 53 to 73% of reflux events are non-acidic and that gastric pH may be >4 for 69 to 75% of the total monitoring time.[20–22] Feeding appears to be a principal factor for the high rates of non-acidic reflux given the marked change in acidity from pre- to post-feeding intervals.

The population for this study consisted of inpatient preterm infants who were primarily referred for cardiorespiratory events and clinical suspicion of GER. If a selection bias were present in this retrospective cohort, one would expect an overestimation of the association between feeding and cardiorespiratory events. However, no increases in apnea, bradycardia or desaturations after feeds were seen. There was some heterogeneity in the population with regard to such characteristics as the presence of a nasogastric tube, diagnoses and severity of early neonatal illness. However, the analytic approach was to compare each infant's post-feed values with his/her own pre-feed values. Each infant served as his/her own comparator, thereby limiting the potential bias and confounding from other patient characteristics. This does not rule out the possibility that a particular subset of patients are predisposed to increased cardiorespiratory events after feeds.

Furthermore, because the aim of this study was to compare cardiorespiratory stability and reflux in the pre-feed state, when the stomach is most empty, with those in the post-feed state, when the stomach is most full, we excluded the active feeding period itself from the analysis. Other studies have shown increased desaturations during feeding, particularly in infants with bronchopulmonary dysplasia.[15,16] As our study was not designed to address the physiology of feeding and specifically excluded this time period, our finding that cardiorespiratory stability was not increased after feedings should not be interpreted as a claim that the infants did not have events during the active feeding period itself. Other factors, such as pulmonary reserve with exertion and possible aspiration, are likely to impact the active feeding period more significantly than the resting pre- and post-feed periods addressed in this study.

Another limitation of this study may be the power. In a *post-hoc* power calculation, assuming alpha 0.05, power 0.8 and the standard deviation of the difference in pre- and post-feeding rates ranging from 0.050 to 0.50 events per hour, the detectable difference ranged from 0.024 to

0.24 events per hour. However, we found a non-significantly higher rate of apnea before feeding, suggesting that we would not have found a significant post-feed increase in apnea with a larger sample size.

These findings argue against the common clinical impression that cardiorespiratory events are more frequent in preterm infants after feeding. Although an increase in the rate and height of GER was observed after feeds, a corresponding increase was not found in apnea, bradycardia or desaturations. The discrepancy between these findings and a clinical impression of increased cardiorespiratory events after feeding may stem from clinicians interpreting post-feeding events differently from those occurring at other times. Anecdotal accounts of increased cardiorespiratory events following feeds are commonly treated by anti-reflux therapies. As there is no difference in the incidence of cardiorespiratory events before and after feeding, these findings suggest that routine treatment of post-feeding cardiorespiratory events with anti-reflux therapies is not warranted.

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Table 1

Demographic statistics for the study population (n = 36)

Gestational age (weeks)	30.7 ± 4.3
Post-conceptional age (weeks)	38.6 ± 3.0
Birth weight (g)	1617 ± 834
Study weight (g)	2766 ± 720
Race	
White	22 (61%)
Black	14 (39%)
Male sex	18 (50%)
Supplemental oxygen at study	5 (14%)
Breast milk at study	8 (22%)
NG or OG feeds during study	8 (22%)
Caffeine at study	1 (3%)
IVH ≥3 (n = 29)	2 (7%)
PVL (n = 29)	3 (10%)
History of necrotizing enterocolitis or perforation	6 (19%)

Abbreviations: IVH, intraventricular hemorrhage; NG, nasogastric; OG, orogastric; PVL, periventricular leukomalacia.

Table 2

Rates of reflux events before and after feeding, median (range)

	Total GER (events per hour)	Acidic GER (events per hour)	Non-acidic GER (events per hour)	Median height of GER (cm)
Before feed	2 (0–11)	2 (0–11)	0 (0–4)	6 (3–9)
After feed	4 (0–16)	0 (0–10)	4 (0–11)	6.75 (3.75–9)
P-value	0.012	<0.001	<0.001	0.025

Table 3

Rates of cardiorespiratory events during pre- and post-feeding intervals, median (range)

	Apnea ≥15 s (events per hour)	**Apnea >10 s (events per hour)**	**Apnea >5 s (events per hour)**	**Bradycardia <85 beats min^{-1}**	**Desaturations <85% (events per hour)**
Pre-feed	0 (0–3)	0 (0–23)	7 (0–86)	0 (0–4)	0 (0–25)
Post-feed	0 (0–2)	0 (0–6)	6 (0–60)	0 (0–4)	0 (0–40)
P-value	0.61	0.22	0.30	0.42	0.23