



Published in final edited form as:

J Perinatol. 2010 October ; 30(10): 683–687. doi:10.1038/jp.2010.27.

Characterization of Cardiorespiratory Events following Gastroesophageal Reflux (GER) in Preterm Infants

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Abstract

Objective—To characterize cardiorespiratory events in preterm infants following both acid and non-acid GER as detected by pH and multiple intraluminal impedance (MII).

Study Design—Twelve hour overnight studies were performed in 71 preterm infants (gestational age 29.4±3.0 wks, birth weight 1319±496 gm). Apnea 10 seconds in duration, bradycardia 80 bpm and oxygen desaturation 85% that occurred within 30 seconds after the initiation of GER were classified as associated with GER.

Result—12,957 cardiorespiratory events and 4164 GER episodes were documented. Less than 3% of all cardiorespiratory events were preceded by GER constituting 3.4% of apnea, 2.8% of oxygen desaturation and 2.9% of bradycardia events. GER did not prolong cardiorespiratory event duration or increase severity. In contrast, GER was associated with a shorter duration of oxygen desaturation events (7.8±4.6 vs 6.3±5.6 sec, $p<.05$).

Conclusion—GER is rarely associated with cardiorespiratory events, and has no detrimental effect on cardiorespiratory event duration or severity.

Background

Preterm infants commonly exhibit apnea, bradycardia, oxygen desaturation and gastroesophageal reflux events. As all of these events occur during early postnatal life, often a causal relationship is assumed, resulting in widespread use of anti-reflux medications to reduce the occurrence of cardiorespiratory events. Recent documentation has shown that 25% of all extremely low birth weight infants are discharged on promotility and/or antacid therapy¹ with one of the most common indicators being apnea, bradycardia and oxygen desaturation². Pharmacologic treatment for acid suppression and gastric motility have been associated with a wide range of adverse consequences^{3,4}, including late-onset sepsis⁵,

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The authors report no conflicts of interest.

necrotizing enterocolitis^{6,7}, respiratory infections⁸, dystonia and irritability⁴. Hence, characterization of a relationship between cardiorespiratory events and GER is imperative in order to address the risk benefit ratio of this treatment modality.

The evidence for an association between GER and cardiorespiratory events remains controversial^{1,9-13}. Early studies finding no relationship between apnea and GER have been limited by the use of a pH probe, allowing only for the detection of acid GER. With frequent feeds and resultant non-acid refluxate, use of a pH probe may underestimate the true incidence of GER in preterm infants¹⁴. More recent studies have employed multiple intraluminal impedance (MII) for detection of both acid and non-acid GER, again with conflicting results^{11-13,15,16}. Guidelines for detection of GER by MII¹⁷ alone have shown that MII underestimates the number of acid GER events¹⁸. As limitations of using only pH or MII in detecting GER may account for discrepancies between studies, the aim of this study was to characterize cardiorespiratory events in preterm infants following both acid and non-acid GER as detected by pH and MII.

Methods

Twelve hour overnight studies were performed in preterm infants who were referred for cardiorespiratory and GER overnight monitoring by the attending physician. Inclusion criteria included infants 34 wks gestational age at birth and a post menstrual age of less than 44 weeks at the time of study. Exclusion criteria included clinically significant congenital malformations and need for ventilator support (mechanical ventilation or CPAP) at the time of study.

Each overnight study consisted of monitoring of respiration via respiratory inductance plethysmography (SomnoStar PT, Cardinal Health, Yorba Linda, CA) which provides an estimate of flow and volume, heart rate and oxygen saturation (Masimo Radical SET, Masimo, Irvine, CA). SaO₂ data were acquired with pulse oximeter monitor settings of 2 second averaging and 2 second sample rate. GER was detected using both MII and pH (Sleuth, Sandhill Scientific Inc., Highlands Ranch, Colorado) technology. The method of detection of gastroesophageal reflux differs between pH and MII technologies. The pH probe measures changes in esophageal acidity, whereas the MII probe detects the presence of liquid in the esophagus. A 6.4 French catheter was placed in the esophagus between T7 and T9 and verified by chest radiograph. The impedance catheter contained 7 electrodes placed 1.2 cm apart corresponding to a total of 6 channels. A pH electrode was located 1 cm from the tip of the catheter corresponding to impedance channel six. GER events were defined by MII as a fall in impedance to 50% of the baseline on 2 or more sequential channels followed by stratification as acid with a pH <4, minor acid with a drop in pH of 1 or more unit but remaining above 4, or non-acid with a pH of 4¹⁷. In addition, pH only acid GER events were identified by a drop in pH <4 for 5 seconds when no event was identified by MII.

Cardiorespiratory events were defined as apnea 10 seconds in duration, bradycardia 80 bpm and oxygen saturation 85%. Apnea type was classified as: 1) central apnea-no flow with no rib cage or abdominal excursions 2) obstructive apnea-no flow with persistent rib

cage and abdominal excursions and 3) mixed apnea-elements of both central and obstructive apnea. Cardiorespiratory events were classified as being associated with GER if they occurred within 30 seconds after the initiation of a GER event. Excluding periods of motion artifact, all cardiorespiratory and GER events (ie periodic breathing and those occurring with feeds) were included in the analysis. A paired t-test was used for comparisons of duration and magnitude of cardiorespiratory events between those preceded and not preceded by GER. As caffeine has been shown to stimulate gastric acid secretion ¹⁹, a Wilcoxon Rank Sum test was used for comparisons of the number of GER events between infants receiving and not receiving caffeine at the time of study. GER events occurring within 30 seconds of the initiation of a cardiorespiratory event were also documented. A p value of <0.05 was used for statistical significance. This study was approved by the Institutional Review Board and parental consent was obtained.

Results

Seventy one preterm infants with a mean gestational age of 29.4±3.0 wks and birth weight of 1319±496 gm were enrolled in the study. The mean post menstrual age and weight at the time of study were 37.3±2.6 wks and 2395±505 gm, respectively. Forty three infants were male, 38 infants were Caucasian, and 24 were black. Five infants were receiving caffeine, three infants were receiving supplemental oxygen, and three infants were receiving anti-flux medications(Ranitidine-3 infants, Metoclopramide-1 infant) at the time of study.

There were 12,957 cardiorespiratory events with 2118(16%) apnea, 456(4%) bradycardia and 10,383 (80%) oxygen desaturation events. Sixty-seven percent of the apnea were central, 31% were mixed and 2% were obstructive. There were a total of 4164 GER events with 931(22%) acid bolus MII events, 1709(41%) non-acid bolus MII events, 341(8%) minor acid bolus MII events and 1183(29%) acid events detected by pH alone. There was no significant difference in the number of GER events between infants with (n=5) and without (n=66) caffeine (p=0.34).

Cardiorespiratory Events Preceded by GER

Combining all events for all infants, less than 3% of all cardiorespiratory events were preceded by GER with a similar percentage for apnea, desaturation episodes and bradycardia events(Figure 1). Sixty percent of the apneic events preceded by GER were central and 40% were mixed. In an attempt to identify individual infants who may have a high percentage of cardiorespiratory events initiated by GER, the percentage of cardiorespiratory events preceded by GER was calculated for each infant (Figure 2). More than 80% of infants had fewer than 4% of cardiorespiratory events preceded by GER with an over all median of 1.4%. However, three infants had >12% of all cardiorespiratory events preceded by GER. The first infant had 1 of 7 cardiorespiratory events preceded by GER which included an apnea of 11 seconds in duration. The second infant had 4 of 21 cardiorespiratory events preceded by GER. All were oxygen desaturation events ranging from 78–84% and were accompanied by respiratory pauses of <10 seconds. The third infant had 11 of 91 cardiorespiratory events preceded by GER. All were apneic events ranging from 10–14 seconds in duration.

Gastroesophageal reflux did not increase cardiorespiratory event duration. In contrast, desaturation events preceded by GER were of shorter duration than those not preceded by GER (7.8 ± 4.6 vs 6.3 ± 5.6 sec, $p<.05$, Table). Gastroesophageal reflux had no effect on desaturation or bradycardia severity.

GER Preceded by Cardiorespiratory Events

The percent of GER events that were preceded by cardiorespiratory events was also determined. Overall 9.1% of all GER events were preceded by a cardiorespiratory event with percentages based on the type of GER and mode of detection (Figure 3). This included 4.9% of acid bolus MII events, 9.3% of non-acid bolus MII events, 6.5% of minor acid bolus MII events and 12.6% of acid GER events detected only by pH. Oxygen desaturation was the predominant cardiorespiratory event preceding GER (18%), followed by apnea (15%) and bradycardia (5%).

Discussion

This study has shown that although cardiorespiratory and gastroesophageal events both commonly occur in preterm infants, fewer than 3% of cardiorespiratory events follow a GER event. In addition, GER is not associated with increased cardiorespiratory event duration or severity. Lastly, it is more common for GER to follow cardiorespiratory events, which occurs in approximately 9% of GER events.

Our study revealed an extremely small percentage of cardiorespiratory events were preceded by GER. This is in agreement with previous studies showing no association between GER and apnea^{10,13,15}. Studies finding an association between GER and apnea^{11,12} included apnea of shorter duration (< 5 seconds) than the current study protocol. As 96% of the apneic events reported by Wenzl¹¹ et al were less than 10 seconds, only 4% of those events would have been included in this study. These differences in apnea duration may explain discrepancies between studies. Midesophageal provocation with liquid profusion has been shown to initiate deglutition within 5 seconds of stimulation in preterm infants²⁰. As a swallow would rapidly clear the refluxate and initiate termination of a reflux induced apnea, it may be that GER is associated with respiratory pauses of shorter duration than documented in this study. This phenomenon may also explain the decrease in duration of oxygen desaturation events when preceded by GER as described in this study.

As the consequence of a respiratory pause of any length may be a clinical concern, oxygen desaturation and bradycardia events were included regardless of the duration of accompanying respiratory pause. In addition, all events associated with feeds or periodic breathing were included in the analysis to provide the most accurate representation of overall clinical status when considering treatment with anti-reflux medications. Thus, approximately 13,000 cardiorespiratory events were documented, and this enabled us to cast the widest possible net in search of potential detriment associated with GER. Although the absolute number of apnea, desaturation and bradycardia varied greatly, our study has demonstrated a surprisingly similar percentage (~3%) of events preceded by GER regardless of event type.

Previous studies addressing the relationship between apnea and GER have presented data in terms of both the percent^{11,13} and rate of apnea¹² associated with GER. As changes in rate can be difficult to interpret in terms of clinical relevance, we characterized the percent of cardiorespiratory events associated with GER which defines the best-case expectations for treatment with anti-reflux medications to prevent cardiorespiratory events. Our overall finding that <3% of cardiorespiratory events were preceded by GER and that only three infants had >12% of cardiorespiratory events preceded by GER, all of short duration and relatively low severity, casts considerable doubt on the effectiveness of anti-reflux medication to treat apnea of prematurity.

Criticism of studies that have found no association between GER and cardiorespiratory events has been the limitation in detection of GER in infants. This generally corresponds to non-acid GER that occurs due to frequent feeds. Although MII technology has improved the detection of non-acid GER, it is also has limitations in its ability to detect acid GER¹⁸. Detection of both acid and non-acid events has been maximized in this study by documentation of GER by both MII and pH technologies. By combining these modes of GER detection, 9% of all GER events were preceded by a cardiorespiratory event. This rate may occur by chance due to the high incidence of both GER and cardiorespiratory events detected in this study. However, as apnea has been associated with a reduction in lower esophageal sphincter tone²¹, it is possible that cardiorespiratory events trigger some GER²³.

Although 656 mixed apnea and 43 obstructive apnea were detected, a limitation of this study is the possibility that the use of respiratory inductance plethysmography may have missed short intermittent obstructive events. RIP has been found to have good agreement with the gold standard of nasal mask pneumotachograph²⁴ and discrepancies in apnea detection have been shown between all additional modes of respiratory monitoring²⁵. Although it is possible that a limited number of short intermittent obstructive apnea may have gone undetected, laryngeal stimulation, the hypothesized mechanism by which GER initiates apnea, has been predominantly associated with central apnea in piglets²⁶. In addition, the majority of apnea associated with GER in infants have also been found to be central in nature¹¹. Therefore, it is unlikely that clinically meaningful obstructive events were missed in this study and, if a respiratory event was undetected, any associated changes in heart rate or saturation would have been recorded under the scoring criteria for bradycardia and/or desaturation.

This was not a random sample of infants as only infants referred for cardiorespiratory or GER monitoring by the attending physician were included in this study. This infant cohort may not represent the general population and may be at higher risk for persistent apnea, a high incidence of GER and corresponding increased chance of GER being associated with a cardiorespiratory event. Even in this at risk cohort the association of these events was rare. The mean post menstrual age of 37 weeks may have limited the ability of this study to apply to younger convalescing preterm infants. However, previous findings in infants of 33 weeks post menstrual age were unable to show a temporal relationship between cardiorespiratory events and GER¹⁵.

In conclusion, less than 3% of all cardiorespiratory events were preceded by GER with a median of 1.4% per infant. The findings of this study have important implications pertaining to the administration of anti-reflux medications for the treatment of apnea, bradycardia and desaturation. If every cardiorespiratory event preceded by GER in this study could be resolved by anti-reflux medications, this would only decrease the incidence of cardiorespiratory events by 3%. Given the modest impact in this best case scenario, and the potential side effects of pharmacologic therapy, careful consideration should be given to the risk-benefit ratio of anti-reflux medications before administration of these treatments.

Acknowledgments

Supported by National Institute of Health grant K23-HD056299.

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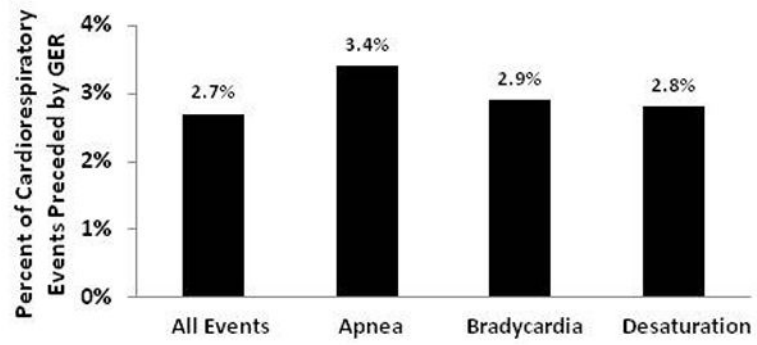


Figure 1. Independent of the type of cardiorespiratory event, approximately 3% of cardiorespiratory events were preceded by GER.

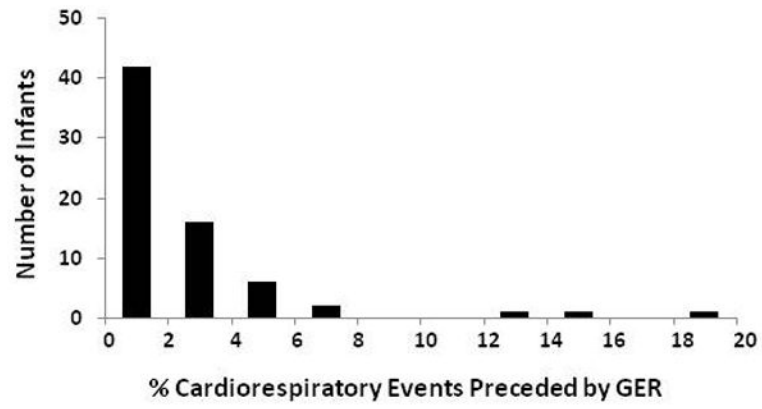


Figure 2. Greater than 80% of infants had 4% of cardiorespiratory events preceded by GER with 3 infants having >12% of events preceded by GER.

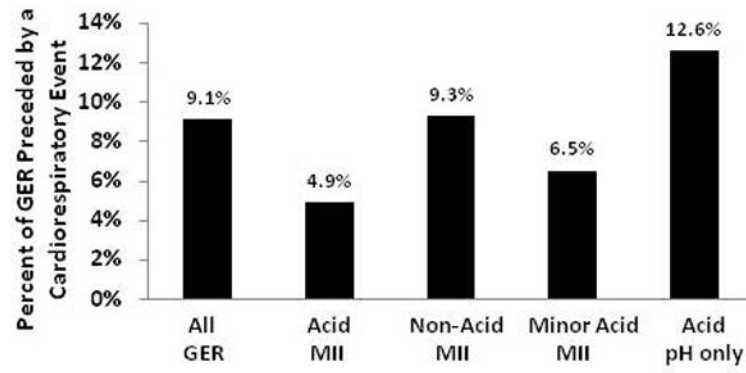


Figure 3.

Overall 9% of GER events were preceded by a cardiorespiratory event with the percent of GER events dependent on the type and modality of detection.

Table

The Relationship between GER and Cardiorespiratory Event Duration and Severity

	Preceded by GER	Not Preceded by GER
Apnea Duration (sec)	11.6±2.5	11.4±0.9
Bradycardia Duration (sec)	4.7±1.9	6.7±2.5
Desaturation Duration (sec)	6.3±4.6	7.8±5.6*
Bradycardia (bpm)	66.2±11.1	64.7±8.2
Desaturation (%)	79.5±4.9	78.8±4.0

*
p<0.05

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