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Gastro-Oesophageal Reflux and Apnoea: Is There a Temporal Relationship?

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Keywords

Apnoea · Gastro-oesophageal reflux · Multichannel intraluminal impedance · pH

Abstract

Background: Gastro-oesophageal reflux (GOR) and apnoea are common in infants; whether there is a causal relationship is controversial. ***Objectives:*** To determine whether there was a temporal relationship between GOR and apnoea, in particular, the frequency of obstructive apnoeas and if the frequency of GOR episodes correlated with apnoea frequency when maturity at testing was taken into account. ***Methods:*** Polysomnography and pH/multichannel intraluminal impedance (MII) studies were performed. Apnoeas were classified as central, obstructive, or mixed. MII events were classified as acidic (pH <4) or weakly acidic (4 < pH < 7). Apnoea frequency in the 5-min period after a reflux event was compared to that in the 5-min period preceding the event and that in a 5-min reflux-free period (control period). ***Results:*** Forty infants (median gestational age 29 [range 24–42] weeks) were assessed at a post-conceptional age of 37 (30–54) weeks. Obstructive (n = 580), central (n = 900), and mixed (n = 452) apnoeas were identified; 381 acid reflux events were detected by MII and 153 by the pH probe only. Apnoeas were not more frequent following GOR than during control periods. Both the frequency of apnoeas (p = 0.002) and GOR episodes (p = 0.01) were inversely related to post-conceptional age at testing, but were not significantly correlated with each other when controlled for post-conceptional age. ***Conclusions:*** These results suggest that GOR does not cause apnoea.

Introduction

Apnoea and gastro-oesophageal reflux (GOR) are common in infants cared for on the neonatal intensive care unit. It has been speculated that GOR may be a cause of apnoea, and, indeed, many infants in neonatal units receive anti-reflux medications. However, the evidence for a causative link is limited. Studies using a pH probe have not found a temporal association between apnoea and GOR [1–3], but a pH probe only detects acid reflux events. Importantly, non-acid reflux events may precipitate apnoea via the laryngeal chemoreflex [4]. Triggering of the laryngeal chemoreflex results in reflex closure of the vocal cords, and thereby precipitate an obstructive rather than a central apnoea.

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Multichannel intraluminal impedance (MII) allows detection of GOR, irrespective of pH, and so may be a better method for detecting whether there is a temporal association of GOR and apnoea. Previous studies examining the relationship between MII and pH detected reflux events and apneas. Results were conflicting, but the studies were on different populations, used different criteria to diagnose reflux, or did not relate GOR to different types of apnoea. Using a pH/MII probe, our primary aim was to test the hypothesis that there is a temporal relationship between GOR and apnoeas, particularly obstructive apnoeas.

Apnoea is associated with prematurity, with an inverse relationship between apnoea frequency and maturity at birth [5]. Reflux episodes may be higher in infants than in children [6, 7], but correlation with gestational age has not been assessed. It may be that the apparent association of apnoea and GOR episodes can be explained by the fact that they both have an inverse relationship with maturity. A second aim of our study was to determine if any apparent correlation between the frequency of apnoea and GOR episodes disappeared when gestational age was taken into account.

Materials and Methods

Subjects were recruited from the Neonatal Intensive Care Unit at King's College Hospital NHS Foundation Trust between March 2013 and September 2015. Infants experiencing recurrent apnoeas, at a frequency of >3 in an 8-h period, and clinically suspected to have GOR were eligible for entry into the study. Reasons for suspecting GOR were frequent overt regurgitation, post-prandial apnoea, discomfort, or arching of the back. Infants were excluded if they had a symptomatic patent ductus arteriosus, anaemia, or sepsis. The study was approved by the London Riverside Research Ethics Committee. Written parental consent was obtained prior to the study.

Protocol

Infants were studied when on full enteral feeds. They were studied for a minimum of 2 h when in a post-prandial sleep.

Polysomnography

Polysomnography was performed using an Alice 4 sleep study unit (Profile Vio-systems, Bognor Regis, UK) with the Alice 5 firmware upgrade. Abdominal and thoracic movements were measured using stretch sensitive piezo-electric respiratory bands. Oral and nasal airflow were detected using a thermistor which utilized temperature differentials generated by airflow movement. A single channel electrocardiogram was recorded to monitor heart rate. To assess for movement artefact, activity meters (Profile Vio-systems) were attached to an arm and a leg to record limb movements. Oxygen saturation was continuously monitored using a pulse oximeter (Masimo rainbow SET Pulse CO-Oximetry) and was incorporated into the Alice sleep system using an auxiliary input. The Alice sleep system was connected to a PC which was used to display the recordings in real time and store collected data. The infant was monitored by video camera throughout the study, and recordings were stored on the PC. These recordings were used during analysis of the sleep studies to identify artefacts caused by handling or infant movement. A custom-built synchronization box provided a synchronization signal to an auxiliary input to the Alice sleep system and the MII system.

Apnoeas were defined as cessation of respiratory airflow for a minimum of 5 s. For each apnoea, associated changes in heart rate and oxygen saturation were recorded. Apnoea was classified as central if there was a cessation of respiratory airflow and thoraco-abdominal movements for at least 5 s, obstructive if there was a cessation of respiratory airflow with persistence of thoraco-abdominal movements for at least 5 s, and mixed if there was a central apnoea and at least 1 respiratory effort without airflow that either preceded or followed the central apnoea. An apnoea index, i.e., the number of apnoeas per hour, was calculated for all apnoeas and for obstructive apnoeas.

Combined MII and pH Study

A single-use, combined pH/MII probe (Zin51 probe, Sandhill Scientific, Highland Ranch, CO, USA) was used. It incorporated 7 impedance bands, allowing measurement of impedance across 6 channels (each with a width of 1.5 cm). In between the 2 distal channels was an antimony pH sensor. Prior to each study, this sensor was calibrated with buffer solutions of pH 4.0 and pH 7.0, and an automated impedance check was performed by the ZepHr sleuth system (Sandhill Scientific). The infant's length was measured, and oesophageal length was estimated according to the Strobel formula for infants >40 cm [8] and from a nomogram for those <40 cm [9]. The probe was inserted through a nostril and secured at the required length. A chest radiograph was then obtained as per the unit's routine policy to determine if the pH sensor was appropriately positioned between the seventh and ninth thoracic vertebrae [10]. The position of the probe at the nares was reassessed following completion of the study to ensure the probe had not been displaced.

Following this confirmation of probe position, recording was commenced. The ZepHr sleuth system continuously recorded impedance and pH data with a sampling frequency of 50 Hz. Analysis of the traces produced was performed using Bioview Analysis software (Sandhill Scientific) and by manual review. The ZepHr system has 2 input ports, one of which accepts the combined pH/MII probe. There is another port which can accept a pH probe using a traditional RJ45 connector. Sandhill Scientific also provided a customized software patch, which allowed a rectangle wave synchronization signal from the aforementioned box (via the RJ45 port) to be recorded in a synchronization channel alongside the MII/pH recording. A similar output from the "box" was incorporated as an auxiliary input to the Alice Sleep system. Software provided by Sandhill Scientific recognized the synchronization signal in the recordings of both the ZepHr and the Alice sleep systems, and allowed synchronization. Sandhill Scientific had validated the system and provided further software for system clock checking using repeat synchronization signals at the beginning and end of each study.

Table 1. Frequency of apnoeas by reflux status

Type of apnoea	Pre-reflux period	Post-reflux period	Reflux-free period	*p* (pre-reflux vs. post-reflux period)	*p* (post-reflux vs. reflux-free period)
Central	0.31 (0–3.44)	0.4 (0–2.50)	0.35 (0–2.4)	0.75	0.90
Mixed	0.20 (0–2)	0.20 (0–1)	0.17 (0–1.19)	0.41	0.64
Obstructive	0.26 (0–2.5)	0.15 (0–2.5)	0.17 (0–1.60)	0.03	0.98
All	0.94 (0–6)	0.97 (0–4.58)	0.87 (0–4.04)	0.38	0.77

Data is expressed as median (range).

An acid reflux event was defined as an oesophageal pH of <4 for >5 s [11]. The total number of acid events in 24 h was calculated by multiplying the number of events by 24 and dividing the result by the duration of the study. The duration of the reflux event and the acid clearance time (ACT, the time from the pH dropping below 4 to rising above 4) were determined. The mean ACT (the total duration with a pH of <4 divided by the number of acid reflux events) was calculated and the maximum ACT was identified. The acid index was the total time spent with the oesophageal pH of <4 as a percentage of the total study time.

MII reflux events were defined as a drop-in impedance to below 50% of the baseline at the most distal channel, which moved retrogradely across at least 2 channels. These were further classified as acid (pH <4), weakly acid (4< pH <7), or weakly alkaline (pH >7). A pH-only event was defined as a drop in pH of <4 without associated changes in impedance.

Analysis

Apnoea was considered to result from GOR if it occurred in the 5-min period following the start of a reflux event. Apnoea frequency in the 5 min following a reflux event was compared to that in the 5 min preceding the reflux event and in a reflux-free control period. The reflux-free control period included all periods of the recording >5 min before or after a reflux event.

A post-hoc analysis was performed using a 2-min window of association [12] (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000485173) according to the criteria of the American Academy of Sleep Medicine [13].

Statistical Analysis

Differences were assessed for statistical significance using the Wilcoxon signed-rank test. Significance was taken at the 5% level ($p < 0.05$). A Bonferroni correction was then undertaken for multivariate comparisons between apnoea frequencies, and gave an adjusted significance level of 0.2% ($p = 0.002$).

Spearman's correlation coefficients were calculated to determine the strength of the correlations between the frequencies of all apnoeas, central, obstructive, and mixed apnoeas, total reflux events in 24 h, and post-conceptional age. The analyses with regard to correlations between apnoea and GOR frequencies were subsequently repeated, controlling for post-conceptional age.

Results

Forty infants, born at a median gestation of 29 (range 24–42) weeks, studied at a median postnatal age of 53 (range 2–212) days, and with a median post-conceptional age of 37 (range 30–54) weeks, were recruited to the study. The median study duration was 3 (range 2–5) h.

A total of 123 h of recordings were analysed. There were 900 central, 580 obstructive, and 452 mixed apnoeas. One hundred and fifty-three reflux events were detected by the pH probe only; 37 acid events, 344 weakly acid events, and 19 weakly alkaline MII events were recorded. Of the 1,938 apnoeas, 745 occurred in the 5 min preceding reflux events, 754 occurred in the 5 min following reflux events, and 439 occurred during the reflux-free period.

Overall, there were no significant differences between the frequency of apnoeas pre- and post-reflux, or between the frequency of apnoeas post-reflux and during reflux-free periods; the frequency of obstructive apnoeas was higher before reflux events than post-reflux ($p = 0.03$) (Table 1). The only difference with regard to MII-detected weakly acid events and apnoea frequency was that the frequency of obstructive apnoeas was higher before than after such events ($p = 0.04$) (Table 2). This did not achieve significance when adjusted for multiple comparisons. There were no significant differences with regard to MII-detected acid events and apnoea frequency (Table 3).

Both the apnoea index and total number of reflux events were inversely correlated with post-conceptional age ($r = –0.47$, $p = 0.002$ and $r = –0.41$, $p = 0.010$, respectively). The apnoea index and total number of reflux events were significantly correlated ($r = 0.34$, $p = 0.034$). The central apnoea index correlated significantly with the total number of reflux events ($\rho = 0.34$, $p = 0.030$), but obstructive and mixed apnoea indices did not significant-

Table 2. Frequency of apnoeas according to weakly acid reflux status detected by MII

Type of apnoea	Before weakly acid reflux	After weakly acid reflux	Reflux-free period	*p* (pre-reflux vs. post-reflux)	*p* (post-reflux vs. reflux-free period)
Central	0.21 (0–3.4)	0.27 (0–2.4)	0.35 (0–2.4)	0.52	0.29
Mixed	0.1 (0–1)	0.23 (0–1.25)	0.17 (0–1.19)	0.05	0.56
Obstructive	0.46 (0–2.63)	0.14 (0–2.27)	0.17 (0–1.60)	0.04	0.51
All	1 (0–5.18)	0.93 (0–4.45)	0.87 (0–4.04)	0.29	0.82

Data is expressed as median (range).

Table 3. Frequency of apnoeas according to acid reflux status detected by MII

Type of apnoea	Before acid reflux	After acid reflux	Reflux-free period	*p* (pre-reflux vs. post-reflux)	*p* (post-reflux vs. reflux-free period)
Central	0.25 (0–4)	0 (0–4.5)	0.35 (0–2.4)	0.86	0.24
Mixed	0 (0–1)	0 (0–1)	0.17 (0–1.19)	0.14	0.81
Obstructive	0 (0–1.5)	0 (0–1)	0.17 (0–1.60)	0.61	0.87
All	1 (0–6)	0.75 (0–5)	0.87 (0–4.04)	0.92	0.80

Data is expressed as median (range).

ly correlate with the total number of reflux events. After controlling for post-conceptional age, there was no longer a significant correlation between total reflux events and either total apnoea index or central apnoea index.

Discussion

We have demonstrated that the frequency of apnoeas is no greater following reflux episodes than before episodes, suggesting that apnoea is not precipitated by reflux.

Obstructive apnoeas, but not apnoeas overall, were more common prior to an acid reflux event, but this was not significant when corrected for multiple comparisons. Nunez et al. [14] studied preterm infants who had persistent cardio-respiratory disturbances post-term, and found a subject-specific association between MII events and obstructive apnoeas in 3 infants who subsequently required a fundoplication or had worse clinical GOR; however, their results may not be representative as only 7 patients in total were studied. In another study, 21 infants aged <6 months were referred for investigation with pH study and polysomnography for apparent life-threatening events. Although most of the apnoeic events were unrelated to reflux episodes, the majority of apnoeas temporally related to reflux events preceded reflux and were of an obstructive nature [15].

The possible association of obstructive apnoeas following GOR may be explained by the fact that apnoea is associated with reduced lower oesophageal sphincter tone [15], increasing the likelihood of subsequent reflux and regurgitation events. Omari [15] retrospectively reviewed manometric and physiological monitoring studies in prematurely born infants, and found that prolonged apnoea (i.e., for >20 s) was frequently associated with relaxation of the lower oesophageal sphincter. An alternative explanation is that, during obstructive apnoea, the intra-abdominal pressure rises steeply with concurrent increases in negative intra-thoracic and oesophageal pressure, which can reach levels as low as –50 to –70 cm H_2O [16, 17]. This pressure may create a vacuum effect, leading to aspiration of the stomach contents into the oesophagus [18].

Previous studies examining the relationship between reflux events detected by MII/pH and apnoeas overall detected by polysomnography have produced conflicting results. Peter et al. [19] studied 19 infants with a diagnosis

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of apnoea of prematurity at a median post-conceptional age of 33 weeks, and found no temporal association. Di Fiore et al. [20] studied 71 prematurely born infants and found that 3% of cardio-respiratory events (apnoea, desaturation, or bradycardia) followed reflux events and that 9% of reflux events were preceded by a cardiorespiratory event; however, they did not specify if certain types of apnoeas were more likely to precede GOR. Funderburk et al. [21] studied 40 preterm and 18 term infants suspected of having GOR, and found no correlation between reflux events and apnoea; the reflux events, however, were only recorded by a symptom diary completed by nursing staff and parents. Corvaglia et al. [22] demonstrated a significantly higher frequency of apnoeas following both pH-detected and non-acid MII-detected reflux events, compared to prior to such events in infants with apnoea of prematurity. Their study population differed from ours, in that it included a preterm population selected based on reports of at least 2 apnoeas in a 2-h period.

In a study using MII and pH and cardiorespiratory monitoring in prematurely born infants in the NICU, an increased frequency of apnoeas was demonstrated during periods of GOR, particularly with weakly acid reflux events and reflux events of long duration (>30 s) [23]. There were, however, no significant differences in the frequency of apnoeas in the epochs either preceding or following a reflux event (but only 6 preterm infants were investigated). Another study, suggesting that GOR does not cause apnoea, concerned the lack of effectiveness of feed-thickening in reducing apnoeas [24]. Twenty-four infants with apnoea of prematurity underwent oesophageal pH, MII, and cardiorespiratory monitoring after alternating formula thickened with amylopectin with unmodified formula. The feed thickener was effective in significantly reducing the oesophageal acid exposure, but there was no significant difference in the frequency of clinically relevant apnoea [24]. Indeed, an editorial on the above paper suggested that apnoea of prematurity should not be treated with anti-reflux medications unless clear data proves a causal relationship [25].

We found that, as expected, apnoea was inversely related to maturity [5], but so was GOR. Possible explanations for the latter relationship are the maturation of lower oesophageal motility [26] and the lower oesophageal sphincter [27], or the improved gastric emptying with advancing gestational age [28]. Importantly, after controlling for gestational age, we found no significant correlation between apnoea and GOR, further supporting the concept that GOR does not cause apnoea.

This study has strengths and some limitations. Infants were monitored with video polysomnography rather than relying on manual recording of events, allowed for the detection of all apnoeic episodes as well as the exclusion of artefacts. In addition, we were able to differentiate central, mixed, and obstructive apnoeas. Furthermore, use of a synchronization signal between the polysomnograph and pH/MII recorder ensured accuracy in the correlation of respiratory and reflux events. The use of an pH/MII probe allowed detection of both acid and non-acid reflux events. This is particularly important in neonates and young infants as most reflux episodes are not acidic [29]. We did not find a significant correlation between acid reflux events and any type of apnoeas, but only 37 infants had acid reflux events, as to be expected [29]. In addition to automated analysis, the traces were visually inspected, ensuring that all impedance reflux events were detected. Our population was heterogeneous with regard to gestational age at birth, but infants were selected on the basis of a high clinical suspicion of GOR, relevant for answering our key question of whether there is a temporal relationship of GOR and apnoea. We undertook further analysis according to the American Academy of Sleep Medicine criteria for diagnosing a significant apnoea [13], but this did not highlight any further significant association (online suppl. material). We used a 5-min window to determine if there was any causal relationship between apnoea and GOR. This window was chosen based on the observation by Upton et al. [30] that pooling of refluxate in the pyriform fossa was seen for up to 5 min after reflux episodes. Glen et al. [12] suggested that a temporal relationship was strongest when using a window of 2 min. We therefore reanalysed our data using a window of 2 min, and our conclusions remained the same. In conclusion, our data did not provide any evidence that apnoeas result from GOR.

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Disclosure Statement

There were no conflicts of interest.

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