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Gastro-oesophageal reflux and apnoea – is there a temporal relationship?

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Short title: Gastro-oesophageal reflux and apnoea

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ABSTRACT

Background: Gastro-oesophageal reflux (GOR) and apnoeas 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, particularly the frequency of obstructive apnoeas and if the frequency of GOR episodes correlated with apnoea frequency once maturity at testing was taken into account.

Methods: Polysomnography and pH/multichannel (pH/MII) intraluminal impedance studies were performed. Apnoeas were classified as central, obstructive or mixed. MII events were classified as acidic ($\text{pH} < 4$) or weakly acidic ($4 < \text{pH} < 7$). Apnoea frequency in the five minute period after a reflux event was compared to the five minute period preceding the event and in a five minute reflux free period (control period).

Results: Forty infants (median gestational age 29 (range 24-42) weeks) were assessed at a post-conceptual 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 reflux events were detected by the pH probe only. Apnoeas were not more frequent following GOR than during control periods. Both the frequency of apneas ($p=0.002$) and GOR episodes ($p=0.01$) were inversely related to post-conceptual age at testing, but not significantly correlated with each other when controlled for post-conceptual 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 on neonatal units receive anti-reflux medications. Yet, the evidence for a causative link is limited. Studies [1-3] using a pH probe have not found a temporal association between apnoea and GOR, 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 thus may precipitate an obstructive rather than a central apnoea.

Multichannel intraluminal impedance (MII) using allows detection of GOR irrespective of pH and thus may be a better method to detect if there is a temporal association of GOR and apnoea. Previous studies examining the relationship between MII/pH detected reflux events and apnoeas, however, have yielded conflicting results but have been in different populations, used different criteria to diagnose reflux or have not related GOR to different types of apnoea. Our primary aim, therefore, was to test the hypothesis, using a pH/multichannel intraluminal impedance probe, that there was 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 compared to children [6, 7] but a correlation with gestational age has not been assessed. It may be that the apparent association of apnoea and GOR episodes is explained by them both having 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.

METHODS AND MATERIALS

Subjects were recruited from the neonatal intensive care unit at King's College Hospital NHS Foundation Trust between March 2013 and September 2015. Infants having recurrent apnoeas, at a frequency of more than three in an eight hour period, clinically suspected to be due to GOR were eligible for entry into the study. Reasons for suspecting GOR were frequent overt regurgitation, post-prandial apnoea, discomfort or back-arching. 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 study.

Protocol

Infants were studied when on full enteral feeds. They were studied for a minimum of two hours when in a postprandial 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 was detected using a thermistor which utilised 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, Bognor Regis, UK) 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 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 with the recordings stored on the PC. These recordings were used during analysis of the sleep studies to identify artefact caused by handling or infant movement.

A custom built synchronisation box provided a synchronisation signal to an auxiliary input to the Alice sleep system and the multichannel intraluminal impedance system (see below).

Apnoeas were defined as cessation of respiratory airflow for a minimum of five seconds. For each apnoea, associated changes in heart rate and oxygen saturation were recorded. The apnoeas were classified as central if there was a cessation of respiratory airflow and thoraco-abdominal movements for at least five seconds; obstructive apnoea if there was a cessation of respiratory airflow with persistence of thoraco-abdominal movements for at least five seconds;

mixed apnoea if there was a central apnoea and at least one respiratory effort without airflow preceding or following the central apnoea. An apnoea index, that is the number of apnoeas per hour, was calculated for all apnoeas and for obstructive apnoeas.

Combined multichannel intraluminal impedance and pH study

A single use combined pH/MII probe (Zin51 probe, Sandhill Scientific, Highland Ranch, Colorado, USA) was used. It incorporated seven impedance bands allowing measurement of impedance across six channels each with a width of 1.5cm. In between the distal two channels was an antimony pH sensor. Prior to each study, the pH sensor was calibrated with pH buffer solutions of pH 4.0 and pH 7.0 and an automated impedance check was performed by the Zephyr Sleuth system (Sandhill Scientific). The infant's length was measured and oesophageal length was estimated according to Strobel's formula for infants over 40cm [8] and from a nomogram for those under 40cm [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 confirmation of probe position recording was commenced. The Zephyr Sleuth system (Sandhill Scientific) 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 Zephyr system produced by Sandhill Scientific has two 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 provided a customized software patch which allowed a rectangle wave synchronization signal from the aforementioned box via this 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 recognised the synchronization signal in the recordings of both the zephyr and the Alice sleep system, and allowed synchronization. The software patch and synchronization box were provided by Sandhill Scientific who had validated the system and provided further software for system clock checking using repeat synchronization signals at the beginning and end of each study.

An acid reflux event was defined as an oesophageal pH less than four for more than five seconds [11]. The total number of acid events per 24 hours 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 four to rising above four) were determined. The mean ACT (the total duration with a pH less than four divided by the number of acid reflux events) was calculated and the maximum ACT

identified. The acid index was the total time spent with the oesophageal pH less than four as a percentage of the total study time.

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

Analysis

An apnoea was considered to result from GOR if it occurred in the five minute period following the start of a reflux event. The frequency of apnoeas in the five minutes following a reflux event was compared to the frequency of apnoeas in the five minutes preceding the reflux event and to a reflux free control period. The reflux free control period included all periods of the recording which were more than five minutes before or after a reflux event.

A post-hoc analysis was performed using a two-minute window of association [12] (see supplementary Table 1) and performed using the American academy of sleep medicine criteria [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 hours, and post-conceptual age. The analyses with regard to correlations between apnoea and GOR frequencies were subsequently repeated controlling for post-conceptual age.

RESULTS

Forty infants were recruited to the study born at a median gestation of 29 (range 24 to 42) weeks studied at a median postnatal age of 53 (range 2 to 212) days, with a median post-conceptual age of 37 (range 30-54) weeks. The median study duration was three (range two to five) hours.

A total of 123 hours of recordings were analysed. There were 900 central apneas, 580 obstructive apneas and 452 mixed apneas. One hundred and fifty-three reflux events were detected only by the pH probe; 37 acid MII events, 344 weakly acid events and 19 weakly alkali MII events were recorded. Of the 1938 apnoeas, 745 occurred in the five minutes preceding reflux events, 754 occurred in the five minute period 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. (Table 1) The frequency of obstructive apnoeas was higher before reflux events compared to 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 apneas was higher before compared to 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-conceptual 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 ($r=0.34$, $p = 0.030$), but obstructive and mixed apnoea indices did not significantly correlate with the total number of reflux events. After controlling for post-conceptual 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 compared to before, suggesting that apnoea is not precipitated by reflux.

Obstructive apnoeas, but not apnoeas overall, were commoner prior to an acid reflux event, however this was not significant when corrected for multiple comparisons. Nunez et al. studied preterm infants who had persistent cardio-respiratory disturbances post term and found a subject specific association between MII events and obstructive apnoeas in three infants who subsequently required a fundoplication or had worse clinical GOR, but their results may not be representative as only seven patients in total were studied [14]. In another study, 21 infants aged less than six months were referred for investigation with pH study and polysomnography for apparent life-threatening events. Although the majority of 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 apnoea being associated with reduced lower oesophageal sphincter tone [15] increasing the likelihood of subsequent reflux and regurgitation events. Omari retrospectively reviewed manometric and physiological monitoring studies in prematurely born infants and found that prolonged apnoea (more than 20 seconds) was frequently associated with relaxation of the lower oesophageal sphincter [15]. 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 –

70 cm H₂O [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 MII/pH detected reflux events and apnoeas overall detected by polysomnography have come to conflicting results. Peter et al. studied nineteen infants with a diagnosis of apnoea of prematurity at a median post-conceptual age of 33 weeks and found no temporal association [19]. Di Fiore studied 71 prematurely born infants [20] and found that 3% of cardio-respiratory events (apnoea, desaturation or bradycardia) followed reflux events, 9% of reflux events were preceded by a cardiorespiratory event, but they did not specify if certain types of apnoeas were more likely to precede GOR. Funderburk et al. studied 40 preterm and 18 term infants suspected to have GOR. and found no correlation between reflux events and apnoea, reflux event. Reflux events, however, were only recorded by a symptom diary completed by nursing staff and parents [21]. Corvaglia et al. demonstrated a significantly higher frequency of apnoeas following both pH detected and non-acid MII detected reflux events, compared to prior to those events in infants with apnoea of prematurity [22]. Their study population, however, differed from ours in that it included a preterm population selected by reports of at least two apnoeas in a two hour period.

In a study using MII and pH and cardiorespiratory monitoring in prematurely born infants on 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 (greater than 30 seconds) [23]. There were, however, no significant differences in the frequency of apnoeas in the epochs either

preceding or following a reflux event but only six preterm infants were investigated. A further study suggesting that GOR does not cause apnoea is 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 receiving alternatively formula thickened with amylopectin or 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 maturation of lower oesophageal motility [26] and the lower oesophageal sphincter [27] or improved gastric emptying with advancing gestational age [28]. Importantly after controlling for gestational age we found no significant correlation between apnoeas and GOR, further supporting the concept that GOR does not cause apnoeas.

This study has strengths and some limitations. Infants were monitored with video polysomnography rather than relying on manual recording of events and hence this allowed detected of all apnoeic episodes as well as the exclusion of artefacts. In addition, we were able to differentiate the apnoeas into central, mixed and obstructive. Furthermore, use of a synchronization signal between the polysomnograph and pH/II recorder ensured accuracy in the correlation of

respiratory and reflux events. The use of 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 we would have expected [29]. In addition to automated analysis, the traces were visually inspected ensuring all impedance reflux events were detected. Our population was heterogeneous with regards to gestational age at birth, but were selected on the basis of a high clinical suspicion of GOR and thus were very relevant to answer our key question of whether there was a temporal relationship of GOR and apnoea. We undertook further analysis using the AASM criteria to diagnose a significant apnoea [13] and this did not highlight any further significant association (see supplement). We had used a five minute window to determine if there was any causal relationships between apnoea and GOR. This window duration was chosen as it was based on the observation by Upton et al. that pooling of refluxate in the pyriform fossa was seen up to five minutes after reflux episodes [30]. Glen et al [12] suggested that a temporal relationship was strongest when using a window of two minutes. Hence, we reanalyzed our data using a window of two minutes and our conclusions remained the same.

In conclusion, our data provide no evidence that apnoeas resulted from GOR.

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Table 1: Frequency of apnoeas by reflux status

Data expressed as median (range)

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

Table 2: Frequency of apnoeas by MII detected weakly acid reflux status

Data are expressed as median (range)

	Pre MII weakly acid reflux	Post MII weakly acid reflux	Reflux free	p (pre versus post reflux)	p (post reflux versus reflux free period)
Central apnoea	0.21 (0- 3.4)	0.27 (0- 2.4)	0.35 (0-2.4)	0.52	0.29
Mixed apnoea	0.1 (0-1)	0.23 (0- 1.25)	0.17 (0- 1.19)	0.05	0.56
Obstructive apnoea	0.46 (0- 2.63)	0.14 (0- 2.27)	0.17 (0- 1.60)	0.04	0.51
All apnoeas	1 (0-5.18)	0.93 (0- 4.45)	0.87 (0- 4.04)	0.29	0.82

Table 3: Frequency of apnoeas by MII detected acid reflux status

Data are expressed as median (range)

	Pre MII acid reflux	Post MII acid reflux	Reflux free	p (pre versus post reflux)	p(post reflux versus reflux free period)
Central apnoea	0.25 (0-4)	0 (0-4.5)	0.35 (0-2.4)	0.86	0.24
Mixed apnoea	0 (0-1)	0 (0-1)	0.17 (0- 1.19)	0.14	0.81
Obstructive apnoea	0 (0-1.5)	0 (0-1)	0.17 (0- 1.60)	0.61	0.87
All apnoeas	1 (0-6)	0.75 (0-5)	0.87 (0- 4.04)	0.92	0.80