Pediatric esophageal motility disorders: studies on (patho)physiology, diagnosis and management

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CHAPTER 3

Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review

Marije Smits, Michiel van Wijk, Miranda Langendam, Marc Benninga and Merit Tabbers

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ABSTRACT

Background
In infants, apneas can be centrally mediated, obstructive or both and have been proposed to be gastroesophageal reflux (GER) induced. Evidence for this possible association has never been systematically reviewed.

Purpose
To perform a systematic review using PubMed, EMBASE and Cochrane databases to determine whether an association between GER and apnea in infants exists. Studies with n>10 infants, aged <12 months, were included. GER had to be studied by pH-metry or pH-impedancemetry. GER episodes were defined as pH <4 for ≥5 s and/or a drop of >50% of baseline in impedance signal in distal channels. An apneic event was defined as a cessation of breathing for ≥20 s, or ≥10 s with hypoxemia or bradycardia. An epoch of ≥2 min was used to define temporal relation between GER and apnea. Methodological quality of studies was assessed with Newcastle Ottawa Scale (NOS). Of 1959 abstracts found, 6 articles met the inclusion criteria. All studies had poor methodological quality. A total of 289 infants were included. The temporal association of GER followed by apnea was assessed in all studies, with epochs varying from 10 s to 2 min. One study found an increase of apneic events after GER, the remaining 5 studies did not find an association. Two studies assessed apnea followed by GER as well, but did not find sufficient evidence for association.

Conclusion
This systematic review showed insufficient evidence for an association between GER and apneas in infants. High quality studies using uniform inclusion criteria, definitions according to accepted guidelines, and patient relevant outcome measures are needed.
INTRODUCTION

Gastroesophageal reflux (GER) is the passive movement of gastric contents into the esophagus. This occurs primarily during transient lower esophageal sphincter relaxation (TLESR). TLESR is a relaxation of the lower esophageal sphincter (LES) not preceded by a swallow and is mediated by a vago-vagal pathway.

Apnea is the cessation of respiratory airflow and can be central (no respiratory effort), obstructive (respiratory effort present but not resulting in airflow due to upper airway obstruction) or mixed in nature (no respiratory effort followed by obstruction-like respiratory efforts). Clinically significant apnea lasts \( \geq 20 \) s, or for a period of \( \geq 2 \) breaths accompanied by significant desaturation, hypoxemia or bradycardia. The Nucleus Tractus Solitarius (NTS) in the brainstem plays a large role in pathogenesis of apneas by expressing a paradoxical overriding inhibitory response to signals from peripheral afferents. These afferents are excited by, for example, hypoxia, hypercapnia, and stimulation (e.g. obstruction) of the upper airways and may lead to respiratory pauses of variable duration.

Apneas, irrespective of their nature, have been proposed to be GER induced. The persuasion that GER and apnea are causally related is embedded in guidelines for the treatment of GER disease (GERD) and pathological apneas. It is hypothesized that GER-induced esophageal distension as well as pharyngeal penetration of GER can activate local vagal stretch and chemical receptors. In animal models, distension of the esophagus can indeed induce apnea and it is established that laryngeal chemoreceptor reflexes (LCR) can trigger central apneas in infants. Thus, vagal afferents triggered by GER seem to be able to induce apneas through pathways mediated by the brain stem. However, a recent study found no effect of feed thickening, which significantly reduced GER episodes reaching the proximal esophagus, on the frequency and duration of apnea episodes.

Another hypothesis is that apneas cause GER episodes. In a retrospective physiologic study, it has been shown that all clinically relevant apneas (\( \geq 20s \)) identified, were followed by a decrease in LES pressure. Although only manometry was performed in this study and occurrence of GER episodes was not assessed, this decrease in LES pressure putatively allows GER to occur after apnea. This likelihood further increases when abdominal pressure rises, e.g., during arousal and straining after apnea. Furthermore, obstructive respiratory efforts and repetitive swallowing are long known manifestations of previously mentioned LCR. Apart from inducing apneas, LCR also causes decrease in LES pressure. LCR can elicit coughing (as occurs after arousal from apnea) which increases abdominal pressure, and therefore the chance of GER occurring in the presence of low LES pressure.

Finally, given the close proximity of the GER pattern generator and breathing control centers in the brain stem, it could be hypothesized that GER episodes and apneas temporally relate as result of a common central pathway.
A substantial amount of studies and non-systematic reviews have attempted to pinpoint the relationship between GER and apneas. However, their conclusions contradict each other. Therefore, we systematically reviewed evidence for an association between GER and apneas, and vice versa, in infants.

METHODS

Search strategy
We searched Medline, Embase, Cochrane electronic database, and Cochrane Controlled Trials Register for prospective studies and systematic reviews from 1980 up to June 2014. The following key terms were used: gastro(-o)esophageal reflux, apn(o)ea, Apparent Life Threatening Event, and infant. No language restriction was applied. Obtained reviews and articles were hand searched for additional studies. The full search strategy is available from the corresponding author.

Inclusion criteria
Two reviewers (MS, MvW) independently judged articles as shown in Figure 1. Full length articles were included if the study met our inclusion criteria: (i) Prospective study or case-control study, (ii) n > 10 study subjects per patient group investigated with a corrected age <12 months and suspect for GER related symptoms, GERD, apnea and/or apparent life-threatening events (ALTE), (iii) Simultaneous GER investigation (pH-metry or pH-impedance (pH-MII) measurement and/or manometry) and apnea assessment (cardiorespiratory monitoring), (iv) Apneic events defined as a cessation of breath ≥20 s or ≥10 s with significant desaturation and/or bradycardia, (v) GER events were defined as pH<4 for ≥5 s and/or a drop of >50% of baseline in impedance signal in the distal two channels, (vi) Epoch (time window) between GER and apnea or vice versa was defined ≥2 min, (vii) Study aim was to determine any relation between GER and apnea.

Quality assessment
Before data extraction, included full length articles were judged by two assessors (MS, MvW) for quality, using the Newcastle Ottawa Scale (NOS). This scale is a validated tool for scoring the methodological quality (risk of bias) of comparative observational studies. As the NOS is aimed at comparative studies and most included studies were expected to be patient series, we adjusted the outcome question: 'was follow up time long enough for the outcome to occur?' into 'was study time long enough to assess outcomes?'. Also, only in studies incorporating two or more groups, the latter were divided into an exposed and non-exposed cohort. Definition of an exposed cohort was chosen as defined by authors (e.g. treatment/no treatment or presence/absence of symptoms at start of study). Similarly, outcome definitions were chosen as defined by authors (e.g. a decrease in GER, apnea and/or symptoms). Comparability of cohorts was only scored for studies with two or more patient groups. Furthermore, we added three scoring items that could be answered with 'A', 'B' or 'C'. This modified version of the NOS consists of 11 questions (Table 1). Depending on the answer,
questions are rated with one star per item, mapping the methodological quality of the article. There are no cut-off values for this scale, therefore no summary scores were calculated. In general, the more stars, the higher the quality of the article (range 0-11 stars).

Data extraction
Two assessors (MS, MvW) independently performed structured data extraction. The data extracted from each article included author and year of enrollment, study setting, methods, type and number of subjects, method of GER and apnea assessment, potential follow-up, outcome measures, and results. If disagreement between the two reviewers existed, consensus was found where possible, or a third reviewer (MT) made a final judgment.

RESULTS

Literature search and quality assessment
The search strategy generated 1959 titles. No systematic reviews were found. Based on title and abstract, 41 studies were selected to potentially meet inclusion criteria (Figure 1). After retrieving full text articles and scoring in- and exclusion criteria, an additional 35 articles were excluded. Reasons for exclusion were: (i) n < 10 patients included (n=3), (ii) Definition of GER and/or apnea did not meet the inclusion criteria or no definitions were given (n=20), (iii) Duration of epochs used to define a temporal association between GER and apnea, or vice versa, was unclear or >2 min (n=9), (iv) Retrospective study or non-systematic review (n=2) and (v) other (n=1). Finally, six studies could be included for our systematic review.23-28 Of these, two had a case-control design,24,25 the other four were patient series. Data from 289 infants (five studies reported gestational age: range 24-43 weeks, one reported postnatal age: range 1-34 weeks23) were included. Studies were conducted in tertiary centers in The United States of America23,24,26-28 and Europe.25

The two assessors initially agreed on 56 of 66 scored quality items, with a Cohens Kappa agreement of 0.77 (0.61-0.8=substantial agreement). Agreement after discussion was reached in 100% of cases. NOS scoring items per article are described in Table 1. Overall quality was considered to be poor. Outcome assessment was blinded in none of the studies and only three of six define outcome measures. Since only two of six studies studied >1 patient group, not all NOS scoring items were applicable for the other four studies.24,25 Due to heterogeneity in design, outcome measures, and analysis, pooling of results was impossible. Therefore, studies are discussed separately.

Patient demographics
All but one study included prematurely born infants (Table 2).23 In general, included infants were suspected of having apneas and/or GER related symptoms. One study included a group of ‘symptomatic’ (apneas and/or bradycardias present or GER after feed) and a group of ‘asymptomatic’
infants\textsuperscript{25} (no GER symptoms or apneas present). One study assessed infants after near-miss sudden infant death syndrome (SIDS).\textsuperscript{23}

\textbf{GER assessment}

All studies using esophageal measurements had a metric cutoff to determine the presence of GER (e.g. a pH drop below 4 for 5-15 s; Table 3).\textsuperscript{23-27} The study using pharyngeal pH-metry defined GER as appearance of gastric contents into the mouth, supported by pH changes measured with pharyngeal recording.\textsuperscript{28}

\textbf{Apnea assessment}

Ariagno et al. did not report the absolute number of apneas but the number of apneas per hour (Apnea Index; Table 3).\textsuperscript{24} Di Fiore et al. also did not report on absolute numbers, but displayed results graphically in the article.\textsuperscript{26} The other four studies reported on overall numbers of apneas that may or may not be classified into central, obstructive and/or mixed or prolonged and short. For this review only prolonged, presumed clinically significant, apneas were considered. De Ajuriaquerra et al. assessed both symptomatic and asymptomatic infants and found only one asymptomatic infant to have apneas (mixed and obstructive). All other apneas were recorded in symptomatic infants.\textsuperscript{25}

\textbf{Association of GER and apnea}

\textbf{GER causing apnea (n=6)}

Only one study found a significant increase of apneic events after GER,\textsuperscript{28} the other five studies did not find an association (Table 4). Of the latter five, Ariagno et al. report one of 45 infants to have an apneic event associated with GER (<2min following GER). In this infant, 24 of the total recorded study apnea (n=31) were recorded.\textsuperscript{23} De Ajuriaquerra reported one apnea occurring <1 min after a GER episode. In this study, no correlation between apnea and GER was found in either the symptomatic infant group (n=14) or the entire study population (n=20). No further details for association in the six asymptomatic infants were reported.\textsuperscript{25} The two studies by Di Fiore et al. found neither apneas nor cardiorespiratory events to be associated with GER, nor did GER increase the duration of apnea episodes.\textsuperscript{26,27} Ariagno et al.\textsuperscript{24} reported reflux associated apneas (RAAP) in 24 infants, i.e., the number of apneas occurring within 1 min after a GER event, which were found in 62% of infants. Cisapride treatment administered in this study did not significantly reduce RAAP. Authors stated that, although acid GER and mixed apneas were reduced in the cisapride group, not enough evidence was present to claim GER is causally related to apnea, nor that treatment of GER related symptoms will significantly improve management of infants with persistent apneas.\textsuperscript{24}

\textbf{Apnea causing GER and assessment of common etiology (n=2)}

Di Fiore et al. assessed GER induced by apneas. Nine percent of GER events were preceded by a cardiorespiratory event.\textsuperscript{27} The other study from Di Fiore et al. found 85% of apneas related to GER were followed by arousal within 30 s and significant more apneas of >10 s occurred before or during GER as compared to apneas immediately after GER. Authors concluded these findings suggest that
arousal is associated with termination of GER, rather than that apneas are able to induce GER.\textsuperscript{26} None of the included studies specifically searched for a common etiology of GER and apnea.

Medical therapy in studies (n=4)

Three out of six studies reported on medical therapy that infants received during the study, whereas apnea therapy was abated prior to the commencement of one study.\textsuperscript{25} Ariagno et al.\textsuperscript{24} found that 8 days of cisapride therapy significantly reduced the number of GER episodes of $\geq 5$ min ($p=0.026$), the RI ($p=0.017$) and overall mixed apneas compared to baseline, but it did not reduce RAAP.\textsuperscript{24} The effect of administered ranitidine or metoclopramide on GER or apnea parameters was not reported in the studies by Di Fiore et al.\textsuperscript{26,27} There was no significant difference in the number of GER events ($p=0.34$) or reflux index (RI, $p=0.94$) between infants with or without caffeine and/or theophylline therapy.\textsuperscript{26,27} Accordingly, Ariagno et al.\textsuperscript{24} stated that caffeine therapy had no effect on GER parameters (no $p$-values reported).\textsuperscript{24}

DISCUSSION

This systematic review shows insufficient evidence for any association between GER and apneas in infants. Most available studies addressing this topic are methodologically inadequate in terms of sample size, design, outcome measures, and analysis, or use techniques that are no longer state of the art. Therefore, we only included a small number of studies with clinically relevant criteria for GER and apnea that met internationally accepted standards and had a clear definition of temporal relation, with epochs of 2 min maximum.\textsuperscript{4,9,29} Even with these strict inclusion criteria, data from the six included studies were too heterogeneous to be pooled.

In general, all included studies have methodological limitations. Firstly, not all GER events are same in terms of acidity, proximal extent, and volume and could, therefore, trigger other neuroregulatory mechanisms through different mechano- and chemoreceptors. Five of six included studies used pH-metry to evaluate GER instead of pH-MII technology, which enables differentiation between these different types of GER.\textsuperscript{27} pH-metry, as compared to pH-MII measurements, misses out on non-acid ($pH >7$) and weakly acid ($4 < pH < 7$) GER episodes, while the latter have been shown the predominant type of GER in infancy.\textsuperscript{30-32}

Secondly, all but one study\textsuperscript{25} did not categorize the apneas into central, obstructive or mixed for their analysis. It might be that central and obstructive apneas are differently related to GER, as immaturity of the central nervous system and LCR, respectively, are considered the most likely underlying mechanism in infants.

Thirdly, administration of medication modulating GER and apnea could have influenced results of the included studies. This has been shown in several pediatric and adult studies.\textsuperscript{33,34} Nevertheless, only three studies did report on the effect of medication administered.\textsuperscript{24,26,27} Of those, cisapride is unavailable nowadays due to associated cardiac side effects and metoclopramide is no longer
advocated for infant GERD after being linked to tardive dyskinesia. From the studies reporting on medication, apnea therapy (caffeine and/or theophylline) appeared to have no effect on GER parameters, nor did anti-GER medication seem to influence GER related apnea, implying GER and apnea are not associated. Still, considering the lack of data provided, no firm conclusions can be drawn. Finally, statistical analysis of the association between GER and apneas was very poor across included studies. None of the studies used a GER or apnea-specific association index, whereas mean values and standard deviations were sparsely provided. This makes interpretation of the data difficult. Although current available association indices for GER-related symptoms all have their limitations, it is indispensable to prove the presence of association between GER and apneas. New association indices specifically aimed at the relation between GER and respiratory events might proof suitable alternatives for future research. However, no gold standard exists yet.

One study that showed a positive association between GER and apnea used pharyngeal pH-metry to assess GER. Due to its position, the catheter is unable to detect distal GER events not reaching the pharynx, which can theoretically trigger apnea through esophageal distension and subsequent vagal activation. In addition, simultaneous recording time of GER and apneas in the study of Menon et al. was very short, with a mean of 1.4h for six children and 2-3h for the remaining four infants. For clinical use, a minimum of 18 h recording of GER is commonly used to reliably associate symptoms with GER. Recently, the influence of recording time on the association found was clearly shown, confirming the need for prolonged monitoring.

In general, GER is universally present in infants, with 50% of infants of 0-3 months having visible regurgitation at a daily basis. Normative values of the total amount of acid and weakly/non-acid GER not reaching the mouth are unknown, but the amount of distal acid GER episodes alone in healthy infants can reach up to 56 episodes. Apneas are a relative rare phenomenon in mature infants, especially after the first days of life. With a large physiological amount of GER episodes (further enhanced by posture, frequent liquid feeds, and anatomical properties of the infants upper gastrointestinal tract) and little apneas, association can be found as a result of chance - especially with small sample sizes and with inadequate definitions of GER, apneas and association indices. Moreover, even if a causal relation exists, a reduction in apneas does not necessarily reduce the number of GER events significantly, because most GER events will occur simply because all infants, including completely healthy babies, experience GER events frequently. In addition to the paucity of high quality evidence on this topic, a recent study even states that GER is associated with interruptions of sleep in infants (arousals), which implies nocturnal GER episodes are likely to amplify respiratory reflexes.

A better understanding of the association of GER and respiratory mechanisms (i.e., apneas) in infants will have great diagnostic and therapeutic consequences for this group of patients and could potentially lead to shortened hospital stay and a reduction in healthcare costs. GERD is diagnosed in up to 50% infants admitted for recurrent apneas and frequently accompanied by costly and invasive
diagnostics and even therapeutic approaches like anti-reflux surgery. Thus, there is a clear need for well-powered studies.

One of the challenges when conducting research addressing the association between GER and apnea in symptomatic infants is the lack of consensus regarding criteria which are needed to identify an infant as ‘symptomatic’. According to clinical guidelines, GERD is defined as GER causing troublesome symptoms and complications, with apneas mentioned as one of those possible complications. Similarly, only when the number of apneas per hour exceeds a threshold is a patient is classified into one of the apneic sleeping disorder syndromes (either central, obstructive or mixed). However, theoretically, every single GER episode could trigger a significant apneic event and vice versa. Therefore, when defining inclusion criteria, it is of importance to realize that assessing the association between GER and apnea is different from diagnosing GERD or an apnea syndrome in clinical practice.

More generally, successful execution of randomized clinical trials is often obstructed by difficulties of recruiting research groups of sufficient size due to ethical dilemmas both for medical ethical committees and parents.

We suggest future studies assess premature and mature infants separately, to distinguish the possible different pathophysiological mechanisms of apnea of prematurity and persistent apneas after reaching full term. Furthermore, the use of state-of-the-art techniques that include at least pH-MII for the detection of all GER episodes is essential to find an association between a normal and ubiquitous physiological phenomenon as GER and a relatively rare phenomenon as pathological apneas. Additional esophageal manometry further enables assessment of predominant neurological mechanism behind GER: TLESRs. For apnea, a clear cut definition according to the latest standards should be used, dividing apneas into central, obstructive, and mixed. Calculations on association of GER and apneas must be based on best available association indices and a well described epoch for association. To sufficiently power studies, Barriga et al. demonstrated that a prolonged measurement increases the possibility to detect an association. Indeed, in recordings of <12 hrs or with <70 GER episodes and <10 symptoms (apneas) per 24 h, finding an association between GER and symptoms is mathematically impossible. This problem might be partially overcome by elongating the measurements artificially with a mathematical algorithm generated by computer systems. While a recent study showed that GER distributions can indeed be reproduced in silico, future research will need to show if symptoms such as apneas can be predicted by computer models in a similar way.

In conclusion, despite substantial literature on the association between GER and apnea in infants, this systematic review identified only six articles that met our inclusion criteria and were suitable for data extraction. This indicates there is a lack of high quality data addressing this topic. We found insufficient evidence for an association between GER and apnea in infants. Nevertheless, it might be that GER is causally related to apnea in a selected group of infants. To adequately identify if this group exists and what the nature of this hypothesized GER-apnea association is, there is a need for
high quality, well-powered studies using uniform inclusion criteria, definitions according to accepted guidelines, state-of-the-art techniques, reliable symptom association indices, and patient-relevant outcome measures.

Figure 1. Flow chart of included studies.
### Table 1. Quality of articles using Newcastle Ottowa Scale including added items by the authors.

Depending on the answer, questions are rated with a star. There are no cut-off values for this scale. In general, more stars mean a higher methodological quality.
<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects (n)</th>
<th>Age At birth (GA wks)</th>
<th>Age At study (wks)</th>
<th>Male n (%)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Medication during study</th>
<th>Recording (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariagno et al. 1982 (23)</td>
<td>45</td>
<td>-</td>
<td>10 ± 8 PNA</td>
<td>25 (56%)</td>
<td>near miss SIDS term infants</td>
<td>failure to thrive</td>
<td>Nr</td>
<td>17.95 ± 3.25</td>
</tr>
<tr>
<td>Ariagno et al. 2001 (24)</td>
<td>24</td>
<td>28.8 ± 3.1</td>
<td>35.6 ± 4 GA</td>
<td>16 (67%)</td>
<td>hospitalized infants suspect for GER, apnea and/or feeding intolerance.</td>
<td>negative baseline pH study (n=12)</td>
<td>caffeine n=12 before Cis</td>
<td>2 recordings of 15-16</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>positive pH study*</td>
<td>surgery during treatment (n=1)</td>
<td>caffeine n=9 after Cis</td>
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<td></td>
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<td>8 days therapy with Cis (0.10mg/kg/6hrs)</td>
<td>repeat measurement &gt;8 days after start Cis (n=4)</td>
<td>nasal O₂ suppl n=12 before Cis</td>
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<td></td>
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<td></td>
<td>PSG/pH study before + after Cis</td>
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<tr>
<td>De Ajuriaquerra et al. 1991 (25)</td>
<td>20</td>
<td>31 (27.5-36.5)</td>
<td>38.7 (73-43) PCA</td>
<td>11 (55%)</td>
<td>hospitalized premature born infants &gt;37 wks PCA</td>
<td></td>
<td>caffeine abated &gt;7 days prior to study</td>
<td>6.18 (3.95-6.80)</td>
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<td></td>
<td>asymptomatic infants (n=6)</td>
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<tr>
<td>Di Fiore et al. 2005 (26)</td>
<td>119</td>
<td>28 ± 2</td>
<td>37 ± 4 PCA</td>
<td>nr</td>
<td>hospitalized premature infants</td>
<td>congenital malformations</td>
<td>xanthine n=26‡</td>
<td>12 overnight</td>
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<td></td>
<td>Symptoms of GER</td>
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<td>nasal O₂ suppl n=40</td>
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<td></td>
<td>apneas, bradycardia and/or desaturations</td>
<td>&lt;1500 g at birth</td>
<td>Ranitidine and/or Metoclopramide n=15</td>
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<tr>
<td>Di Fiore et al. 2010 (27)</td>
<td>71</td>
<td>29.4 ± 3</td>
<td>37.3 ± 2.6 GA</td>
<td>43 (61%)</td>
<td>hospitalized premature infants &lt;44 wks at measurement§</td>
<td>congenital malformations</td>
<td>Caffeine n=5*</td>
<td>12 overnight</td>
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<td></td>
<td>referred for cardiorespiratory and GER overnight monitoring</td>
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<td></td>
<td></td>
<td>Ranitidine and/or Metoclopramide n=3</td>
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<tr>
<td>Menon et al. 1985 (28)</td>
<td>10</td>
<td>28-40</td>
<td>1-4 PCA</td>
<td>Nr</td>
<td>hospitalized infants</td>
<td></td>
<td>nr</td>
<td>1.4 (n=6) 2-3 (n=4)</td>
</tr>
</tbody>
</table>

Table 2. Patient demographics. *Reflux index within 2SD of mean according to criteria Vandenplas et al. †No effect on GER values. ‡Effect on RI ns p=0.94. §<34 weeks GA at birth. ¶No effect on number of GER events (ns, p=0.34). PNA, postnatal age; PCA, postconceptional age; GA, gestational age; SIDS, sudden infant death syndrome; PSG, polysomnography=cardiorespiratory monitoring; GER, gastroesophageal reflux; AOP, apnea of prematurity; Cis, cisapride; nr, not reported.
**Table 3. GER and apnea parameters**

<table>
<thead>
<tr>
<th>Author</th>
<th>GER test</th>
<th>GER and GERD definition</th>
<th>number of GER episodes (% of all)/RI</th>
<th>Apnea test</th>
<th>Apnea definition</th>
<th>No. Of apnea or Apnea Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariagno et al. 1982 (23)</td>
<td>pHmetry</td>
<td>pH4 ≥15s</td>
<td>n=566</td>
<td>Resp effort ECG</td>
<td>ApC</td>
<td>n=314*</td>
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<tr>
<td>Ariagno et al. 2001 (24)</td>
<td>pHmetry</td>
<td>pH4 ≥5s</td>
<td>na</td>
<td>Resp effort ECG</td>
<td>Nasal airflow ECG O2 saturation</td>
<td>n=26</td>
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<td>RI &gt;2SD</td>
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<tr>
<td>De Ajuriaquerra et al. 1991 (25)</td>
<td>pHmetry</td>
<td>pH4 ≥15s</td>
<td>n=134</td>
<td>Resp effort ECG</td>
<td>ApC</td>
<td>n=26</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>RI &gt;10.4%</td>
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<tr>
<td>Di Fiore et al. 2005 (26)</td>
<td>pHmetry</td>
<td>pH4 ≥5s</td>
<td>pH4 per 12h</td>
<td>na</td>
<td>Resp effort ECG</td>
<td>Heart rate O2 saturation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RI (cut-off nr)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Di Fiore et al. 2010 (27)</td>
<td>pH/MII</td>
<td>pH4</td>
<td>+ 50% fall MII baseline line 2 distal channels</td>
<td>Resp effort ECG</td>
<td>Heart rate O2 saturation</td>
<td>n=42</td>
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<tr>
<td></td>
<td></td>
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<td>n=530</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ no MII event</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td>n=183 (29%)</td>
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<td>n=1419</td>
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<tr>
<td>Menon et al. 1985 (28)</td>
<td>Pharyngeal pHmetry</td>
<td>Visibility of GER in mouth, ΔpH= support</td>
<td>n=44</td>
<td>Resp effort ECG</td>
<td>Nasal airflow ECG</td>
<td>n=100</td>
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</table>

*In 46 measurements (1 subject studied twice). †As compared to standard values reflux index according to Vandenplas et al. §Not matching our apnea definition, therefore not displayed here. RI, reflux index (% of time esophageal pH<4); GER, gastroesophageal reflux; GERD, GER disease; WA, weakly acid GER; NA, non-acid GER; Cis, Cisapride; Resp effort=respiratory effort; Ap, apnea; ApC, central apnea; ApO, obstructive apnea; ApM, mixed apnea; AI, apnea index: no of apneas per hour; CR event, cardiorespiratory event; ECG, electrocardiogram; ΔpH, change in pH; brady, bradycardia; bpm, beats per minute; desat, desaturation; nr, not reported; na, not applicable; SD, standard deviation.
<table>
<thead>
<tr>
<th>Author</th>
<th>GER followed by apnea</th>
<th>Apnea followed by GER</th>
<th>Association GER-Apnea according to authors?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epoch</td>
<td>Measure</td>
<td>Outcome</td>
</tr>
<tr>
<td>Ariagno et al. 1982 (23)</td>
<td>≥ 2 min</td>
<td>Aps after GER/ total Aps</td>
<td>1/341 (0,2%)</td>
</tr>
<tr>
<td>Ariagno et al. 2001 (24)</td>
<td>≥ 1 min</td>
<td>Infants with ≥ 1 Ap after GER (RAAP)*</td>
<td>14 (62%)</td>
</tr>
<tr>
<td>De Ajuriaguerra et al. 1991 (25)</td>
<td>≥ 1 min</td>
<td>Aps after GER/ total Aps</td>
<td>1/139 (0,7%)</td>
</tr>
<tr>
<td>DiFiore et al. 2005 (26)</td>
<td>≥ 30s</td>
<td>Number of Aps &gt;10s before, during or after acid GER</td>
<td>532/6255 (8,5%)</td>
</tr>
<tr>
<td>DiFiore et al. 2010 (27)</td>
<td>≥ 30s</td>
<td>Aps after GER/all Aps</td>
<td>72/2118 (3.4%)</td>
</tr>
<tr>
<td>Menon et al. 1985 (28)</td>
<td>10s post GER periods</td>
<td>Mean freq Aps in post GER periods vs freq Aps during GER free periods</td>
<td>8/100 (8%)</td>
</tr>
</tbody>
</table>

Table 4. Association of GER and apnea. *RAAP, reflux associated apnea, cisapride treatment reduced RAAP (not significant, p=0.12). †No exact numbers or calculations reported. GER, gastroesophageal reflux; Ap, apnea; Aps, apneas; ApsC, central apneas; ApsO, obstructive apneas; ApsM, mixed apneas; CR event, cardiorespiratory event (including all apnea, solitary bradycardia and solitary oxygen desaturations); nr, not reported.
REFERENCES


Chapter 3

Contributors' statement

Marije Smits: conceptualized and designed the study, scored all abstracts and full text articles, drafted the initial manuscript, and approved the final manuscript as submitted.

Michiel van Wijk: was second rater of abstracts and full text articles for systematic review, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Miranda Langendam and Marc Benninga: reviewed and revised the manuscript, and approved the final manuscript as submitted.

Merit Tabbers: was deciding rater of full text articles for systematic review, senior author, reviewed and revised the manuscript, and approved the final manuscript as submitted.