Respiratory Medicine (2007) **101**, 969–976

ELSEVIER

respiratoryMEDICINE

Acid and non-acid gastro-esophageal refluxes in children with chronic pulmonary diseases

Claude Thilmany, Julia Beck-Ripp, Matthias Griese*

Department of Pediatric Pulmonology, Dr. von Haunersches Kinderspital, Ludwig-Maximilians-University Munich, Lindwurmstraße 4, D 80337 Munich, Germany

Received 3 May 2006; accepted 5 September 2006
Available online 16 October 2006

KEYWORDS
Gastroesophageal reflux;
Child;
Gastric acidity determination;
Electric impedance;
Respiration

Summary
Objectives: Acid gastro-esophageal reflux has been shown associated with chronic pulmonary diseases. The role of non-acid refluxes in these children is still unknown. Therefore we investigated the prevalence of acid and non-acid refluxes, and their association with desaturations, in children with chronic pulmonary symptoms.
Methods: In 25 children aged 6 months to 15 years with unexplained chronic cough, wheeze or sputum production, refluxes were assessed by 24 h-multiple intra-esophageal impedance measurements, simultaneous pH metry and continuous recording of oxygen saturation.
Results: pH in the proximal and distal esophagus as well as six impedance channels were evaluated in all subjects. A mean of 129.4 refluxes per day per patient was detected. Complete and technically usable readings of oxygen saturation were obtained in 14 children. In this group the subjects had a mean of 112.6 refluxes and 92.6 desaturations per day per patient. The symptom index and symptom sensitivity index for acid refluxes were 34.7% and 24.6%, respectively, for non-acid refluxes 3.0% and 66.7%, respectively.
Conclusions: We found a high prevalence of acid reflux and a very low number of non-acid refluxes in this population. The symptom index was negative for all types of reflux, whereas the symptom sensitivity index was positive for both acid and non-acid reflux. Our data support a relation between acid gastro-esophageal refluxes and chronic pulmonary symptoms; however, this study does not support a role of non-acid reflux in children with respiratory symptoms, which are not on antacid medication.

Introduction

Gastro-esophageal reflux is a common condition in patients of all age groups with chronic pulmonary diseases.[1,2] Acid gastro-esophageal reflux can be seen as physiological to a

*Corresponding author. Tel.: +49 89 5160 7870; fax: +49 89 5160 7872.
E-mail address: matthias.griese@med.uni-muenchen.de (M. Griese).

0954-6111/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2006.09.006

certain degree. However, high prevalences of GERD (Gastro-esophageal reflux disease) are found in asthma and cystic fibrosis.[3] There are several mechanisms which may lead to lung damage or pulmonary signs and symptoms, including aspiration of large amounts of gastric contents (macroaspiration),[4] microaspiration of gastric juice[5] and reflux bronchoconstriction.[6–8] A stimulation of the laryngeal chemoreceptors and induction of apneas by the instillation of liquid into the larynx has been shown.[9] On the other hand, biochemical markers of pulmonary aspiration, like fat-laden macrophages in bronchoalveolar lavages,[10] support the concept of recurrent microaspirations. However the lipid-index, derived from the assessment of fat-stained macrophages has a low sensitivity and may not very helpful in clinical practice.[11]

The diagnosis of pathological gastro-esophageal reflux in patients with chronic pulmonary diseases is important as it leads to appropriate treatment which has been shown to improve pulmonary symptoms.[12–15] Patients with pathological gastro-esophageal reflux resulting in chronic pulmonary signs may have clinically silent GERD i.e. not showing the classic reflux symptoms heartburn and regurgitation.[16] Twenty-four-hour esophageal pH testing is the gold-standard in the diagnosis of pathological gastro-esophageal reflux.[17] This method accurately diagnoses gastro-esophageal refluxes with a sensitivity and specificity of approximately 90%.[18] The frequency of false-negative results ranges between 10% and 25%.[19]

This lack of complete diagnostic accuracy may result from a failure to identify non-acid reflux episodes with conventional techniques. This hypothesis is further supported by the observation that sometimes the signs persist under appropriate medical acid suppression.[20,21] Surgical procedures seem to have a better outcome in the long term and may improve pulmonary signs in patients with severe gastro-esophageal reflux.[22,23] This can be explained by the fact that depending on the gastric secretory status and the time after meal the fundic content varies in composition and acidity.[24,25] Therefore the refluxate may be acid or non-acid. It seems plausible that non-acid reflux also provokes pulmonary signs. Bile acids for example are proinflammatory components of non-acid reflux, as shown by several in vivo and in vitro.[26–28] Obviously 24-h esophageal pH testing is not able to detect non-acid reflux episodes. This is especially problematic in infants, as they are fed at relatively short intervals, and formula neutralizes at least in part gastric acidity. The recently introduced multiple intraesophageal impedance monitoring in combination with pH measurement allows to distinguish between acid and non-acid esophageal reflux, and to determine the height reached by the refluxate in the esophagus. This technique is based on the assessment of changes in the electrical impedance in the esophagus by the refluxate, due to induced alterations of the electrical current between two of a number of closely arranged electrodes. It therefore allows to detect and analyze the anterograde (swallow) and retrograde (reflux) passage of liquid and gas bolus in hollow organs such as the esophagus.[29]

The aims of this investigation were to determine the prevalence of acid and non-acid gastro-esophageal reflux in children with chronic pulmonary diseases and not on antacid medication by combined 24-h esophageal pH and multiple intraesophageal impedance monitoring, and to study the supposed direct correlation between reflux into the distal and proximal esophagus and objectively assessed respiratory signs, i.e. oxygen saturation monitored by pulse oxymetry.

Methods

Patients

Patients attending the Children's Hospital of the University of Munich, who suffered from chronic respiratory signs (cough, wheezing, active sputum production) that were not explained by their clinical diagnosis, were enrolled. This included children with not sufficiently controlled asthma and treated with high doses of inhaled corticosteroids ($>800\,\mu g$ budenosid or equivalent per day); patients with cystic fibrosis, instable despite appropriate antimicrobial treatment, chest physiotherapy and after exclusion of other causes for instability; infants with ongoing, not steadily improving bronchopulmonary dysplasia; children with interstitial pulmonary disease of unknown origin; patients with recurrent bronchitis, recurrent pneumonia and chronic cough. All patients were seen by a pediatric pulmonologist before being considered for reflux testing.

There was a high clinical suspicion for signs possibly caused by reflux, and all examinations were clinically necessary. All investigations were made during routine clinical evaluation of the patients. All caregivers and, where appropriate, in addition the children gave their informed consent.

A total of 25 patients (11 female, mean age 6 years, range 6 months to 15 years) were examined; one infant was studied twice. Clinical data are given in Table 1. Acid suppression medication or motility agents, if present, were stopped at least 1 week before the study.

pH and multiple intraesophageal impedance measurement

All patients were admitted to the children's hospital for the 24 h pH/MII recording. Measurements of intraesophageal pH and multiple intraesophageal impedance (MII) were done using the Sandhill stationary MII-measuring setup (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA). Multiple intraesophageal impedance registration relies on the measurement of electrical impedance changes to alternating electrical current between two adjacent electrodes during the passage of a bolus inside a luminal organ. The sequential arrangement of the electrodes on the catheter allows detecting the direction of bolus movement. A reflux episode is defined as a decrease in impedance starting in the most distal channel and extending orally to the more proximal channels.

The custom-made flexible 2-mm diameter combined pH/multiple intra-esophageal impedance catheter consists of nine metallic cylindrical electrodes, each 5 mm in length, set at different intervals between 15 and 60 mm (Sandhill Scientific; Highlands Ranch, CO, USA). Because impedance is measured between adjacent electrodes, this set-up allowed for six bipolar measuring segments (channels). The measuring segments were positioned from just above the cardia (channel 6) to the hypopharynx (channel 1). Two, one

Table 1 Study subjects: leading disease, leading pulmonary and gastrointestinal symptoms.

Subject	Age (y)	Leading disease	Presenting pulmonary symptoms
1	11	Cystic fibrosis	Massive sputum production, very frequent exacerbations not appropriately responding to antimicrobial and anti-inflammatory treatment
2	7	Recurrent pneumonia*	Recurrent infiltrates on chest radiography, fever, cough†
3	2	Recurrent pneumonia*	Recurrent infiltrates on chest radiography, fever, cough†
4	11	Chronic bronchitis*	Chronic cough††
5	14	Cystic fibrosis	Massive sputum production, very frequent exacerbations not appropriately responding to antimicrobial and anti-inflammatory treatment
6	4	Agenesis of corpus callosum, peripartal asphyxia and recurrent pneumonia*	Recurrent infiltrates on chest radiography, fever, cough†
7	5	GERD	Chronic cough††
8	3	Congenital interstitial respiratory disease of unknown cause	Tachydyspnea
9	4	Recurrent pneumonia*	Recurrent infiltrates on chest radiography, fever, cough†
10§	0.5	Acute life threatening event	Apnea
11	2	Obstructive sleep apnea syndrome	Apnea, sore throat
12	2	Chronic bronchitis*	Chronic cough††
13	13	Recurrent chronic bronchitis*	Chronic cough††
14	5	Obstructive sleep apnea syndrome	Apnea
15	15	Asthma	Wheezing
16	15	Cystic fibrosis	Active sputum production
17	5	Chronic bronchitis*	Chronic cough††
18	0.3	Progressive sleep related breathing irregularities	Apnea and desaturations $<90\%$ during sleep
19	2	Recurrent chronic bronchitis and pneumonia*	Chronic cough††
20	2	Gaucher disease	Chronic cough††
21	7	Cholesterin pneumonitis	Oxygen saturation at rest $<90\%$
22	1	Alveolarproteinosis	Oxygen saturation at rest $<90\%$
23	6	Bronchopulmonary dysplasia, cerebral bleeding, microcephalia	Recurrent pneumoniae
24	4	GERD	Chronic cough††
25	4	Chronic bronchitis*	Chronic cough††, sore throat
26§	0.5	Acute life threatening event	Apnea

*Excluded were cystic fibrosis, immuno-deficiency syndrome, primary ciliary dyskinesia, airway or cardiopulmonary abnormalities, allergies, α_1-PI-deficiency or interstitial lung diseases.
†More than 3 episodes in the last year.
††Duration longer than 3 months.
§Subject examined twice.

distal and one proximal, pH-sensitive antimony electrodes, incorporated into the assembly, were used. The distal pH sensor was to be placed approximately 2.5 cm above the gastro-esophageal junction and the proximal pH sensor just below the pharynx. Three different lengths of probes with varying measuring segments, ranging from 11 to 22 cm, were used according to the height of the patient.

The pH electrode was calibrated in buffers of pH 4 and 7 at the beginning and at the end of each study. Before placement of the probe the children had to be fasting for at least 6 h. The catheter was passed transnasaly under topical anesthesia with lidocain gel into the esophagus, where it stayed for approximately 24 h. The catheter was positioned by advancing it into the stomach and then pulling it back until the pH increased, indicating that it had reentered the esophagus. The correct position of the distal pH sensor was estimated before placing the probe by calculating the distance (d) from the nose: $d = ((\text{height of patient}/4)+5) \times 0.87$. In all cases the correct probe positioning was confirmed by diagnostic chest X-rays. If needed the probe was repositioned appropriately.

The pH-impedance assembly was connected to a portable device amplifying pH and transducing impedance to voltage. pH and multiple intra-esophageal impedance were recorded

continuously by a connected personal computer running appropriate recording software (MII Acquisition; Sandhill Scientific, Inc., Highlands Ranch, CO, USA).

Patients were served a regular diet but were told to omit acid drinks. The children and their parents were asked to record food intake, drinks, physical activity and body position in a diary.

Pulse oxymetric saturation and video recording

Pulse oxymetric saturation and video recording were done using a digital sleep lab (Comlab 32; Schwarzer GmbH; Munich, Germany). Patients were monitored for pulse oxymetric saturation only during nighttime and in supine position. The signal was continuously recorded on the sleep lab device and in parallel routed from the sleep lab to the pH/impedance device where it was displayed and stored together with pH and impedance. For this purpose a conventional paper-encephalograph (EEG ED 14; Schwarzer GmbH; Munich, Germany) was used as a digital–analog transducer.

Five patients were not monitored for oxygen saturation due to technical reasons (broken sensor). In three patients due to a large number of artifacts (more than 50% of the recording time) a reasonable analysis of the respiratory data was impossible. Three patients needed oxygen supplementation during the recording and one patient showed periodic respiration with continuous desaturations. In the other 14 patients complete data sets with excellent quality of pulse oxymetry were available.

Data analysis

Reflux-related data analysis was performed using appropriate software (Bioview and Gerdcheck; Sandhill Scientific, Inc., Highlands Ranch, CO, USA).

All impedance recordings were manually analyzed and all data underwent visual validation. An impedance-detected reflux episode was defined as a drop in impedance of more than 50% from baseline in the distal two channels, progressing retrograde.[30]

The consensus conference for detection and definitions of acid, non-acid, and gas reflux recently proposed four subcategories for reflux.[31] They are based on the esophageal pH during reflux detected by MII: acid reflux (a pH fall from above to below 4), superimposed acid reflux (MII-reflux while pH$<$4, formerly named re-reflux), weakly acid reflux (MII-reflux with a pH fall to above or equal to 4 but below 7) and weakly alkaline reflux (MII-reflux with pH greater or equal to 7). For the purpose of this study we did make no difference between weakly acid and weakly alkaline reflux (both termed non-acid reflux in accordance to previous studies by other groups[29,32]). MII-refluxes were defined as a sharp impedance drop of at least 50% of the initial impedance value starting in the most distal impedance channel (channel 6), extending over at least two channels, with the tracings showing the typical reflux pattern. They were defined as acid, when the pH fell below 4, and non-acid when they occurred without a concomitant drop of pH below 4. Gastro-esophageal refluxes detected only by the pH probe, i.e. a pH fall from above to below 4 in the absence of reflux detected by impedance monitoring (so called pH-only refluxes), were counted as acid refluxes.

Pulse oxymetric saturation recordings were independently and manually analyzed for drops in SpO_2 $\geqslant$4% (desaturations) using appropriate software (Brainlab; OSG; Rumst, Belgium).

All reflux events and all desaturations were then analyzed for temporal relationship, which was considered present if a desaturation followed a reflux within a 120-s interval.[33]

Statistical analysis

Statistical analysis was performed using appropriate software (Prism; GraphPad Software, Inc.; San Diego, CA, USA). Individual data, cumulative values, mean, lower and upper 95% confidence intervals are presented. The symptom index (SI)[34] and symptom sensitivity index (SSI)[35] were calculated as following: SI = (Number of reflux related desaturations/Total number of desaturations) $\times$ 100%, SSI = (Number of desaturation associated reflux episodes/Total number of reflux episodes) $\times$ 100%.

Values above 50% for the SI and above 10% for the SSI were considered abnormal.[36] Both indices have only been validated in adults and not in children, but are routinely used in pediatrics.[21]

Statement regarding internal review board approval

The project was approved by the institutional review board of the University.

Results

Prevalence of acid and non-acid refluxes

During a total measuring time of 579 h and 44 min, 3138 reflux episodes were registered in the 25 patients (mean 5.4/h [4.0–6.8/h]). The majority, i.e. 2978, of the refluxes (94.9%) were acid, and only 160 (5.1%) of the refluxes were non-acid. Nearly one third (31.1%) of all acid refluxes reached the proximal pH measuring point. Per individual patient a mean of 5.1/h [3.7–6.6/h] for acid reflux and a mean of 0.3/h [0.1–0.4/h] for non-acid reflux were detected (Table 2).

Reflux events and desaturations (SpO_2 drop $\geqslant$4%)

During the total time of 207 h and 33 min where appropriate oxygen saturation data were available, 1080 reflux episodes (1047 acid and 33 non-acid) and 741 desaturations were recorded in 14 patients. A mean of 3.9 desaturations/h [0.9–6.8/h] was recorded (Table 3).

In this study, 290 of 1047 acid (SI 34.7%, SSI 24.6%) and 15 of 33 non-acid (SI 3.0%, SSI 66.7%) reflux episodes were associated with a desaturation. 305 of all 1080 acid and non-acid reflux episodes were associated with a desaturation (SI 37.7%, SSI 25.8%) (Table 3). The correlation between acid refluxes and desaturations was stronger for distal ones than for proximal ones (SI 31.2% vs. 3.5%; SSI 34.7% vs. 6.8%) (Table 3).

Table 2 Duration of observation and frequency of refluxes in individual subjects.

Subject	Duration of observation (h.min)	Total refluxes (number/h)	Acid refluxes (number/h)	Acid reflux time (% of total)	Proximal acid refluxes (number/h)	Distal acid refluxes (number/h)	Non-acid refluxes (number/h)
1	22.46	7.2	6.5	18.4	4.5	2.0	0.7
2	19.38	2.1	2.1	1.9	0.4	1.7	0.0
3	24.03	6.7	6.6	19.4	3.0	3.6	0.1
4	23.54	9.9	9.9	6.9	3.6	6.3	0.0
5	22.19	10.5	10.5	52.3	4.5	6.0	0.0
6	23.59	3.2	3.0	5.4	0.2	2.8	0.2
7	24.23	6.4	6.3	33.9	2.0	4.3	0.1
8	23.41	8.5	8.3	19.7	5.2	3.1	0.2
9	21.34	1.8	1.5	3.7	0.8	0.7	0.3
10	24.06	8.1	7.3	13.4	0.0	7.3	0.8
11	16.29	6.0	5.8	13.2	1.2	4.7	0.1
12	21.54	4.4	4.3	8.3	3.7	0.6	0.1
13	21.34	5.9	5.9	15.9	4.8	1.1	0.0
14	22.52	5.4	5.2	9.4	2.6	2.5	0.3
15	24.18	7.5	7.3	6.4	0.7	6.7	0.1
16	22.24	7.0	6.0	15.1	1.4	4.6	1.0
17	20.50	0.9	0.8	0.3	0.1	0.7	0.1
18	24.26	7.5	7.4	18.7	0.1	7.3	0.1
19	24.11	1.9	1.7	3.6	0.0	1.7	0.3
20	24.36	0.7	0.5	0.2	0.2	0.2	0.2
21	16.47	14.3	14.2	50.5	0.4	13.9	0.1
22	13.09	0.0	0.0	0.0	0.0	0.0	0.0
23	24.03	7.4	6.8	23.2	0.0	6.8	0.6
24	24.12	1.8	1.3	1.8	0.6	0.7	0.5
25	22.53	0.7	0.7	0.5	0.1	0.6	0.0
26	24.43	4.5	3.5	7.4	0.8	2.7	1.0
Sum	579.44						
Mean	22.05	5.4	5.1	13.4	1.6	3.6	0.3
Lower 95% CI	20.55	4.0	3.7	7.8	0.9	2.3	0.1
Upper 95% CI	23.15	6.8	6.6	19.1	2.3	4.8	0.4

Acid refluxes were defined as total number of refluxes, total number of refluxes detected by pH monitoring (pH $<$ 4) (acid), number of refluxes reaching distal measuring point (2.5 cm above LES), number of refluxes reaching proximal measuring point and number of refluxes detected by impedance technique only (non-acid).

Table 3 Desaturations and association with refluxes—pooled data.

	Total	Mean	95% CI	SI* (%)	SSI† (%)
Measuring time (h.min)	207.33	14.50	10.58–18.41		
Refluxes	1080	4.7/h	2.0–7.4/h		
Acid	1047	4.5/h	1.9–7.2/h		
Proximal	381	1.5/h	0.4–2.5/h		
Distal	666	3.1/h	0.7–5.4/h		
Non-acid	33	0.2/h	0.1–0.2/h		
Desaturations	741	3.9/h	0.9–6.8/h		
Associated with reflux	305	1.6/h	0–3.5/h	37.7	**25.8**
Associated with acid reflux	290	1.5/h	0–3.4/h	34.7	**24.6**
Associated with proximal acid reflux	48	0.2/h	0–0.4/h	3.5	6.8
Associated with distal acid reflux	242	1.3/h	0–3.2/h	31.2	**34.7**
Associated with non-acid reflux	15	0.1/h	0–0.2/h	3.0	**66.7**

Values above 50% for the SI and above 10% for the SSI were considered abnormal (data represented in bold).[36]

*SI = (Number of relux related desaturations/total number of desaturations) $\times$ 100%.

†SSI = (Number of desaturation associated reflux episodes/total number of reflux episodes) $\times$ 100%.

Discussion

We investigated the prevalence of acid and non-acid refluxes, and their association with desaturations, in infants, children and adolescents with chronic pulmonary diseases and unexplained disease activity. There was a high rate and proportion of acid reflux events, but only a few non-acid refluxes. The very low frequency of non-acid refluxes challenges their relevance in children with chronic pulmonary signs. Desaturations were common in this cohort of subjects and a close correlation between desaturations and distal (low) refluxes was demonstrated. These results support the pathophysiological role of distal refluxes, whereas no link to proximal (high) acid refluxes was observed, i.e. a SI of 31.2% for distal vs. 3.5% for proximal acid refluxes and a SSI of 34.7% for distal vs. 6.8% for proximal acid refluxes. Taken together the data support the concept that esophageal–pulmonary reflex mechanisms[6–8] and not necessarily micro-aspirations are a principal mechanism for these respiratory signs.

The most intriguing result of this study is the high rate of acid refluxes in comparison to non-acid refluxes, i.e. a ratio of 19–1, in this pediatric population with chronic pulmonary signs. As this is to our knowledge the first study assessing both types of refluxes in this age group, with patients not on antacid medication, no direct comparison to other studies can be made.

In normal adult volunteers similarly more acid refluxes were observed previously, however the ratio was only 2–1.[37] These data suggest that with the presence of symptoms the number of acid refluxes is increased. This conclusion is in line with data from adults with symptomatic gastroenterological reflux disease, where the number of acid refluxes was increased compared to healthy controls.[38]

Similarly, with omeprazol treatment of gastroenterological symptomatic reflux, during a 2-h post-prandial interval, the acid reflux episodes decreased with improvement of symptoms, whereas the overall number of reflux episodes remained the same.[32]

In contrast, in infants with recurrent regurgitation or pulmonary symptoms only 31% of all refluxes were acid, resulting in a ratio of 1–2. This inversed ratio of acid to non-acid refluxes was mainly due to frequent feeding and associated gastric acid buffering in these very young subjects.[39]

There is an ongoing discussion about the role of gastro-esophageal reflux in both adults and children with chronic pulmonary signs and symptoms. The high number of acid refluxes in our cohort supports the relevance in this group of patients. However direct evidence for a causal role may only be obtained from interventional studies[32] or proof of aspiration of gastro-duodenal content by bronchoalveolar lavage.[9] Indirect evidence may come from association studies between precisely assessed respiratory signs and reflux episodes.

In our study all desaturation events within 120 s interval after a reflux were judged as possibly related causally. From these data the symptom index and symptom sensitivity index calculated were 34.7% and 24.6% for acid refluxes and 3.0% and 66.7% for non-acid refluxes. The SI (normal $<50\%$) was negative for all types of reflux. In contrast the SSI, was positive, i.e. $>10\%$, for both acid and non-acid refluxes, supporting the view that the desaturations were indeed reflux related.

Of further interest was the observation that the distal (low) acid refluxes were much more closely linked to desaturations, than the proximal (high) acid refluxes. Thus reflex mechanisms, involving esophageal distension and vagal stimulation, and not micro-aspirations into the lungs may represent the main mechanism to evoke the pulmonary signs.[40,41] Hypothetical explanations may include reflux-induced phases of hypoventilations or hypoperfusion which result in ventilation-perfusion mismatch and reduced oxygen saturation. This result differs from those of Rosen et al. who showed that 65% of all reflux episodes that were associated with respiratory signs were high refluxes, more likely to be associated with micro-aspirations. The majority of the refluxes in that study however were non-acid, as the children were on antacid medications during the examination. Furthermore analysis of signs was not restricted to desaturations but included other respiratory symptoms.[21]

When interpreting the results of our study, several limitations must be kept in mind. This is a highly selected group of subjects with respiratory signs not otherwise explained and thus with a relatively high likelihood for gastro-esophageal refluxes. On the other hand, although the patients did not have clinical complaints of gastro-esophageal reflux disease, i.e. retro-sternal burn or regurgitation of gastric contents, the respiratory signs used for calculations and conclusions were objectively recorded by measurements of desaturations. The study cohort size was relatively small and some particular children with predominant neutral refluxes may have been missed. We had also asked the parents to protocol physical activity and food intake; however validation by inspection of the video recordings showed that these protocols were not reliable. The same was true for respiratory signs, like cough, wheezing, tachypnea, breath holding and grunting, that relied on the parents' documentation. We therefore focused in this study on pulse oxymetric saturation as these were reliably obtained, could be quality checked from the pulse curve and the other readings of the polygraphy. As the measurement of pulse-oxymetric saturation is vulnerable to artifacts due to movement, we could only monitor for desaturations during the night, the patients being in a supine position. The fraction of non-acid refluxes however was similarly low during nighttime (3% of all refluxes), as it was during the 24-h recording (5% of all refluxes). Lastly, other variables than the oxygen desaturations, e.g. continuously measured airway resistance, may be helpful to sensitively and objectively describe physiological impairments by reflux, however these are not yet readily available in a clinical setting.

To our knowledge this is the first study investigating 24-h recordings of concurrent intra-esophageal pH and impedance in patients suffering from chronic pulmonary disease and not treated by antacida. We clearly confirmed that pathological gastro-esophageal refluxes are common in all age groups, i.e. infants, children and adolescents, with chronic pulmonary diseases. Our data showed that non-acid refluxes only play a minor role in these children, because they were very infrequent. If non-acid refluxes are responsible for pulmonary signs at all, this may be the case

in subjects with a high frequency of neutral refluxes, i.e. those on treatment with acid suppressants, as suggested by Rosen et al.[21] Thus patients with persistent respiratory signs under antacid therapy should be further investigated by impedance recordings. The primary assessment of non-acid reflux activity may not be necessary during the initial evaluation of gastro-esophageal reflux disease in children with chronic respiratory symptoms.

Acknowledgments

This study was supported by a ''Förderung von Forschung und Lehre'' (FöFoLe) grant of the Ludwig-Maximilians-University, Munich, Germany.

References

1. Radford PJ, Stillwell PC, Blue B, et al. Aspiration complicating bronchopulmonary dysplasia. *Chest* 1995;**107**:185–8.
2. Harding SM, Richter JE. The role of gastro-esophageal reflux in chronic cough and asthma. *Chest* 1997;**111**:1389–402.
3. Yüksel H, Yilmaz O, Kirmaz C, et al. Frequency of gastro-esophageal reflux disease in nonatopic children with asthma-like airway disease. *Respir Med* 2006;**100**:393–8.
4. Mendelson CL. The aspiration of stomach content into the lung during obstetric anesthesia. *Am J Obstet Gynecol* 1946;**52**:191–205.
5. Boyle JT, Tuchman DN, Altschulter SM. Mechanisms for the association of gastro-esophageal reflux and bronchospasm. *Am Rev Respir Dis* 1985;**131**(suppl.):16–20.
6. Spaulding Jr HS, Mansfield LE, Stein MR, et al. Further investigation of the relationship between gastro-esophageal reflux and bronchoconstriction. *J Allergy Clin Immunol* 1982;**69**:516–21.
7. Davis RS, Larsen GL, Grunstein MM. Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. *J Allergy Clin Immunol* 1983;**72**:393–8.
8. Field SK, Evans JA, Price LM. The effects of acid perfusion of the esophagus on ventilation and respiratory sensation. *Am J Respir Crit Care Med* 1998;**157**:1058–62.
9. Davies AM, Koenig JS, Thach BT. Upper airway chemoreflex responses to saline and water in preterm infants. *J Appl Physiol* 1998;**64**:1412–20.
10. Ahrens P, Noll C, Kitz R, et al. Lipid-laden alveolar macrophages (LLAM): a useful marker of silent aspiration in children. *Pediatr Pulmonol* 1999;**28**:79–82.
11. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. *Pediatr Pulmonol* 1999;**27**:419–22.
12. Field SK, Sutherland LR. Does medical anti-reflux therapy improve asthma in asthmatics with gastro-esophageal reflux? A critical review of the literature. *Chest* 1998;**114**: 275–83.
13. Kiljander TO, Salomaa ER, Hietanen EK, et al. Chronic cough and gastro-esophageal reflux: a double-blind placebo-controlled study with omeprazole. *Eur Respir J* 2000;**16**: 633–8.
14. Kiljander T, Salomaa ER, Hietanen E, et al. Asthma and gastro-oesophageal reflux: can the response to anti-reflux therapy be predicted? *Respir Med* 2001;**95**:387–92.
15. Niklasson A, Bajor A, Bergendal L, et al. Overuse of acid suppressive therapy in hospitalized patients with pulmonary diseases. *Respir Med* 2003;**97**:1143–50.
16. Harding SM, Guzzo MR, Richter JE. The prevalence of gastro-eophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med* 2000;**162**:34–9.
17. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroeosphageal reflux disease. *Am J Gastroenterol* 1999;**94**:1434–42.
18. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastro-esophageal reflux disease. *Arch Intern Med* 1995;**155**:2165–73.
19. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992;**98**:1102–11.
20. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux esophagitis does not consistently improve asthma control: a systematic review. *Thorax* 2001;**56**:198–204.
21. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. *Am J Gastroenterol* 2004;**99**:2452–8.
22. Perrin-Fayolle M, Gormand F, Braillon G, et al. Long-term results of surgical treatment for gastro-esophageal reflux in asthmatic patients. *Chest* 1989;**96**:40–5.
23. Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999;**116**:766–74.
24. Sifrim D, Silny J, Holloway RH, et al. Composition of the postprandial refluxate in patients with gastro-esophageal reflux disease. *Am J Gastroent* 2001;**96**:647–55.
25. Wenzl TG, Silny J, Schenke S, et al. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. *J Pediatr Gastroenterol Nutr* 1999;**28**:423–8.
26. Galli J, Cammarota G, Calo L, et al. The role of acid and alcaline reflux in laryngeal squamous cell carcinoma. *Laryngoscope* 2002;**112**:1861–5.
27. Shirvani VN, Ouatu-Lascar R, Kaur BS, et al. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: ex vivo induction by bile salts and acid exposure. *Gastroenterology* 2000;**118**:487–96.
28. Sung MW, Roh JL, Park BJ, et al. Bile acid induces cylcooxygenase-2 expression in cultured human pharyngeal cells: a possible mechanism of carcinogenesis in the upper aerodigestive tract by laryngopharyngeal reflux. *Laryngoscope* 2003;**113**:1059–63.
29. Sifrim D. Patterns of gas and liquid reflux during transient lower esophageal sphincter relaxation: a study using intraluminal electrical impedance. *Gut* 1999;**44**:47–54.
30. Srinivasan R, Vela MF, Katz PO, et al. Esophageal function testing using multichannel intraluminal impedance. *Am J Physiol Gastrointest Liver Physiol* 2001;**280**:G457–62.
31. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004;**53**:1024–31.
32. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and non-acid gastro-esophageal reflux: effect of omeprazole. *Gastroenterology* 2001;**120**:1599–600.
33. Lam HG, Breumelhof R, Roelofs JM, et al. What is the optimal time window in symptom analysis of 24-h esophageal pressure and pH data? *Dig Dis Sci* 1994;**39**:402–9.
34. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-h esophageal pH monitoring. *Am J Gastroenterol* 1988;**83**: 358–61.
35. Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-h esophageal pH recording. *Am J Gastroenterol* 1991;**86**:160–4.

36. Bredenoord AJ, Weusten BLAM, Smout AJPM. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. *Gut* 2005;**54**:1810–7.
37. Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol* 2004;**99**:1037–43.
38. Sifrim D, Holloway R, Silny J, et al. Acid, non-acid, and gas reflux in patients with gastro-esophageal reflux disease during ambulatory 24-h pH-impedance recordings. *Gastroenterology* 2001;**120**:1588–98.
39. Skopnik H, Silny J, Heiber O, et al. Gastro-esophageal reflux in infants: Evaluation of a new intraluminal impedance technique. *J Pediatr Gastroenterol Nutr* 1996;**23**:591–8.
40. Oliven A, Haxhiu M, Kelsen SG. Reflex effect of esophageal distension on respiratory muscle activity and pressure. *J Appl Physiol* 1989;**66**:536–41.
41. Davis RS, Larsen GL, Grunstein MM. Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. *J Allergy Clin Immunol* 1983;**72**:393–8.