ORIGINAL ARTICLE

Association between gastroesophageal reflux and dips in the oxygen transcutaneous saturation of the hemoglobin in infants with chronic obstructive ventilatory disease

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Abstract

Objective: to verify the association between oxygen desaturation episodes and the dips in pH in infants with chronic obstructive respiratory symptoms.

Method: cross-sectional study with children 24 months old or younger hospitalized for investigation of chronic obstructive respiratory symptoms from 1997 to 1999. The patients underwent esophageal pH monitoring associated with transcutaneous oxygen saturation during the night. The patients were included in the study according to their need to be hospitalized and availability of equipment. The indices used to measure this association were reflux index, total number of refluxes, number of refluxes longer than 5 minutes, Euler index, ZMD index, 24-hour mean pH, and mean pH of desaturation.

Results: we studied 44 children. The mean age was 7.5 months, and 20% had desaturation below 93% during pH monitoring. We used the t test to compare the occurrence of desaturation with the pH monitoring parameters. We found higher significance with the reflux index (RI), number of episodes longer than 5 minutes, ZMD index, 24-hour mean pH, and mean pH of desaturation. The bivariate analysis, taking into account possible confounding factors and RI, showed PR equal to 6.61 (IC 95% 1.67 – 26.12) for an RI higher than 4%.

Conclusion: oxygen saturation monitoring associated with pH monitoring may be a useful tool to establish an association between GER and respiratory problems in patients with chronic or recurrent wheeze.


Introduction

Gastroesophageal reflux (GER) is a very frequent clinical condition in pediatric patients and it usually occurs during the first year of life. The association between GER and several complications of the digestive tract is widely known. Currently, our attention should also be directed to manifestations outside the digestive tract, such as those of pulmonary, cardiac, and pharyngeal-laryngeal nature - among which the pulmonary complications are probably the most widely discussed.1-5 The association between GER and pulmonary problems often goes unsuspected, leading patients to suffer from the disease for a long time without receiving proper treatment; in addition, patients are subjected to frequent and long-term hospitalizations, thus increasing morbidity and mortality considerably.2,5,6 Despite the fact that a lot of research has been carried out in this area, the causal relationship between gastroesophageal reflux and respiratory symptoms is not well established, especially for cases within the first two years of life.

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Pulmonary function assessment - considered by some authors as an excellent method for verifying possible alterations caused by gastroesophageal reflux, is neither readily available nor easily implemented for Brazilian infants and preschool children. An alternative way to evaluate the association between GER and chronic obstructive pulmonary disease is through transcutaneous measurement of oxygen saturation. Many studies carried out with premature babies who suffer from apnea showed that there were cardiorespiratory alterations triggered by gastroesophageal reflux. Highly significant reductions in heart rate, airway flow, and oxygen saturation were noted after the simulation of gastroesophageal reflux in animal models. Since 1974, esophageal pH monitoring has been used for the diagnosis of acid reflux in GER. This is the most reliable diagnostic test for detecting silent GER and, in some cases, for establishing a time relationship between episodes of GER and the symptoms presented during examination. Esophageal pH monitoring offers specificity and sensitivity higher than 90%. In this study, we used transcutaneous oxygen monitoring and esophageal pH monitoring concomitantly in an attempt to demonstrate possible associations between fall in esophageal pH and desaturation episodes.

Material and methods

All patients with up to 24 months of life who had been hospitalized at least once due to obstructive respiratory symptoms, and who were submitted to esophageal pH monitoring between January 1997 and July 1999 were eligible for the study. Patients presenting respiratory tract malformations, cystic fibrosis, or immunodeficiencies were excluded. Our population was submitted to 24-hour esophageal pH monitoring and transcutaneous oxygen monitoring for 8 hours together with pH monitoring. The study was carried out according to the recommendations of the medical staff and to equipment availability. All patients were staying in the hospital at the time of examination.

We considered a reduction in transcutaneous measurement of hemoglobin oxygen saturation during pH monitoring (desaturation) as a clinical outcome. Saturation measurements of less than 93% were established as the criterion for desaturation. Data related to the medical history of patients were collected during pH monitoring and from the guardian of the infant. Emphasis was given to data related to sex, age, personal history of atopy, personal history of allergic rhinitis, family history of asthma, family history of allergic rhinitis, frequency of wheezing episodes, and number of hospital admissions. During physical examination, we carried out measurements of hemoglobin oxygen saturation, of breathing frequency, and of cardiac frequency. We examined patients for cyanosis; activity of the alae nasi; retraction (subcostal, intercostal and suprasternal); crackles; wheezing; and rhonchi.

A Synectics monitor, model Digitrapper MD, with a recording channel and semi-disposable antimony catheter was used for measurement of esophageal pH. Prior to each test, the equipment was gauged at pH 7.01 and pH 1 with buffer solutions supplied by the manufacturer and according to the equipment’s program. The use of antireflux medications such as antiemetics, antacids, prokinetics, and H2 blockers was discontinued at least 48 hours before the measurements. The location of the catheter tip, between T8 and T9, was calculated using the formula presented by Stroebel and confirmed through frontal chest x-ray. After placing the catheter precisely, the equipment was switched on. Following a minimum of 20 hours and a maximum of 24 hours after the beginning of pH measurement, the equipment was switched off. There were no dietary restrictions during measurements (feeding on demand); also, there were no restrictions to normal activities and no sedatives were used. The only restriction was that patients could not be in upright position. We asked the guardian of the patient to register, in a standardized log book, the meals, changes in position, wakefulness, and symptoms such as cough, wheezing, cyanosis, apnea, vomiting, and desaturation. At the end of the test, the collected data were transferred into a computer and assessed using the software supplied with the equipment. The relevant data obtained with the exam were: total reflux index (RI), total number of reflux episodes, number of episodes longer than 5 minutes, duration of longest episode, Euler score, mean duration of reflux during sleep (ZMD), occurrence of reflux episode during sleep, and association of reflux episodes with symptoms.

Transcutaneous oxygen saturation monitoring was carried out using Ohmeda 3700 pulse oxymeter with a skin sensor for infants. This equipment measures saturation and cardiac frequency every 12 seconds. Results are saved into its memory and can be retrieved for the previous 8 hours. The skin sensor was fastened onto one of the upper or lower limbs with sticking plaster and a splint was occasionally used for better fixation. The location was chosen according to the best signal possible for measurement of saturation. The esophageal pH monitoring was always nocturnal, since respiratory symptoms associated with GER occur more frequently at night. The patient’s guardians also logged the time of conclusion of the exam in order to later calculate the precise moment of desaturation. The data were transferred into a computer equipped with software specifically designed for this purpose.

Due to the possibility of false episodes of desaturation occurring while patients change positions - due to loss of signal - the saturation and cardiac frequency data were reassessed according to logged events of change in position. To do so, the data were entered into Excel software and assessed using superposed line graphs with different colors for each line, thus allowing for the identification of situations of change in position. Next, the time of actual desaturation events was registered. Later on, these data were entered into
the pH-metry software as desaturations, and the association between GER episodes and desaturation was verified.

Statistical analysis was carried out using the variables considered relevant for characterizing gastroesophageal reflux: 1) total reflux index (RI) - interval of time with reflux pH less than 4; 2) total number of episodes (reflux pH less than 4); 3) number of episodes longer than 5 minutes; 4) Euler score - number of reflux pH less than 4 + 4 times the number of reflux episodes of more than 5 min; 5) ZMD - mean duration of reflux pH less than 4 of the late postprandial period during sleep. Four new variables were created in order to try to establish a correlation between GER and desaturation: 24-hour average esophageal pH of the immediate postprandial and late postprandial periods, and average desaturation pH of these same periods. The immediate postprandial period is the time period between the last meal up to 120 minutes after the meal, and the late postprandial period starts 120 minutes after the meal.

With the objective of assessing strong and moderate associations between desaturation and other variables, we determined that a preliminary study would require a minimum population size of approximately 20 patients per group, with α = 5% and β = 20%.

We considered the significance level of α = 0.05. Data were processed and analyzed using SPSS v8.0, Epi-info v6.04p, and PEPI v3.0 software. This study was approved by the Scientific Committee of the Hospital da Criança Santo Antônio, according to recommendations of the Brazilian National Health Council. Our data was collected by means of questionnaires, interviews with family members or guardian, and physical examination. All research procedures used are considered routine protocols and of minimal risk according to the Health Research Norms (Normas de Pesquisa em Saúde) issued by the Brazilian National Health Council. Parents or guardians of patients signed an informed consent form after receiving brief information on the disease, study objectives, and possible risks for the children.

Results

Our study included 44 children aged 1 to 24 months; 90% of patients aged 1 to 6 months; the age average was 7.5 months and the median 7 months for a standard deviation of 5 months. Male patients represented 66% of our population.

Patients were most frequently indicated for esophageal pH-metry due to wheezing of unknown cause (73%) and bronchiolitis obliterans (11%). The average age at onset of respiratory symptoms was 3 months. The frequency of wheezing episodes was established in 79% of patients, out of which 57% had, at least, monthly wheezing episodes. Eighty-three percent of patients were hospitalized up to 3 times due to respiratory symptoms, with 3 months as the average age at onset of symptoms. Gastrointestinal symptoms were diagnosed in most patients: vomiting in 52%, nausea in 16%, and choking in 30%. Sixty-percent of patients had family history of asthma. Patients were divided into 2 groups according to the presence or not of desaturation during pH-metry (Table 1). In both groups, 9 patients were being administered O2 therapy due to oxygen saturation below 95% in ambient air. There were no significant differences between the groups regarding the use of oxygen. Values of less than 93% were considered as desaturation, with or without oxygen therapy. The desaturation group included 9 patients (20.5%), whereas the group without desaturation included 35 patients. There was no significant difference between the average age of the two groups (P = 0.856).

We calculated the average values of the variables commonly used for assessment of GER and of the variables created for this study - 24-hour average esophageal pH of the immediate postprandial and late postprandial periods, and average desaturation pH of these same periods. These values were compared using Student’s t test. There were significant differences in almost all the parameters assessed (Table 1).

The correlation between desaturation and GER episodes was calculated using Pearson correlation coefficient. We observed a moderate correlation of reflux index, number of reflux episodes of more than 5 minutes, and average 24-hour esophageal pH with the total number of desaturations (r = 0.6134, 0.6462, and -0.6297, respectively; P < 0.001). A moderate correlation of the number of reflux episodes of more than 5 minutes and of the average 24-hour esophageal pH of the late postprandial period with the number of desaturations in the late postprandial period was also observed (r = 0.6122 and -0.6330, respectively; P < 0.001). We carried out a bivariate analysis of the reflux index, frequency of episodes, number of hospitalizations, and breathing frequency. A statistically significant difference was found between reflux index and the outcome. There were no statistically significant differences for the other variables. These results are shown in Table 2.

Discussion

GER is very common among infants and occurs in approximately 8% of them during the first year of life. During this period, wheezing is also very frequent. It is estimated that 25 to 30% of children present wheezing as infants. Given the high prevalence of GER and wheezing during the first years of life, it is possible that in a random population of infants there may be, coincidentally, children with concomitant GER and wheezing. Thus, it is important to know not whether these diseases or symptoms occur at the same time, but rather if they are related to one another.

Our objective was to establish an association between GER and chronic or recurrent wheezing in a selected population of infants and with the proper methodology.
**Table 1** - Comparison between presence or absence of reductions in oxygen saturation below 93% according to pH monitoring findings*

<table>
<thead>
<tr>
<th></th>
<th>With Desaturation</th>
<th>Without Desaturation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 9</td>
<td>n = 35</td>
<td></td>
</tr>
<tr>
<td>RI†</td>
<td>16.4 (7.0 - 26.3)</td>
<td>3.4 (2.1 - 6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># reflux episodes</td>
<td>132 (104 - 236)</td>
<td>85 (46 - 143)</td>
<td>0.024</td>
</tr>
<tr>
<td># reflux episodes longer than 5 min.</td>
<td>9 (3 - 15)</td>
<td>1 (0 - 2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Euler ‡</td>
<td>144 (130 - 328)</td>
<td>93 (50 - 147)</td>
<td>0.007</td>
</tr>
<tr>
<td>ZMD §</td>
<td>1.45 (0.5 - 1.86)</td>
<td>0.50 (0 - 0.90)</td>
<td>0.025</td>
</tr>
<tr>
<td>Average 24-hour pH in IPP</td>
<td></td>
<td>5.08±0.59</td>
<td>5.70±0.50</td>
</tr>
<tr>
<td>Average 24-hour pH in LPP ¶</td>
<td>4.92±1.01</td>
<td>5.77±0.45</td>
<td>0.036</td>
</tr>
<tr>
<td>Average desat pH. in IPP</td>
<td>5.13±1.00</td>
<td>5.87±0.72</td>
<td>0.034</td>
</tr>
<tr>
<td>Average desat pH. in LPP</td>
<td>4.92±1.35</td>
<td>5.69±0.66</td>
<td>0.038</td>
</tr>
</tbody>
</table>

* Data presented as mean ± standard deviation or median (interquartile range, 25th-75th percentile)
† Reflux index
‡ Euler score
§ ZMD
|| IPP = immediate postprandial period (<120 minutes)
¶ LPP = late postprandial period (>120 minutes)

Despite the high prevalence of GER and wheezing, the results of our study should not be affected since we did not consider the diagnosis of pathological or nonpathological GER; but rather, we assessed the association between fall in esophageal pH and desaturation.

**Table 2** - Bivariate analysis with prevalence ratio for the association between desaturation < 93% and Index of Reflux, frequency of episodes, number of hospital admissions, and respiratory frequency, in the study “Association between gastroesophageal reflux and desaturations”

<table>
<thead>
<tr>
<th>Variable</th>
<th>PR</th>
<th>CI 95%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR &gt; 4%</td>
<td>7.30</td>
<td>0.99 - 53.59</td>
<td>0.227</td>
</tr>
<tr>
<td>Frequency of episodes &lt; fifteen days</td>
<td>1.25</td>
<td>0.39 - 4.05</td>
<td>1.000</td>
</tr>
<tr>
<td>Number of hospitalizations &gt; 3</td>
<td>1.55</td>
<td>0.49 - 4.92</td>
<td>0.464</td>
</tr>
<tr>
<td>Respiratory frequency &gt; 50</td>
<td>1.33</td>
<td>0.40 - 4.50</td>
<td>0.700</td>
</tr>
</tbody>
</table>

It was not possible to establish that GER causes desaturation; however, it was possible to verify an association between them.

We chose a 93% desaturation value based on the average saturation of the study population, which was 95%, and on the hemoglobin dissociation curve.

The expected PaO₂ for a 95% saturation is of 80 mmHg, whereas for a 93% saturation, it is of 65 mmHg. Despite the small percentile difference in saturation, there is a significant reduction in oxygenation, which is clinically significant.19

The most frequent reason for indication of esophageal pH-metry were, first, infants with wheezing of unknown cause and, second, bronchiolitis obliterans, which was diagnosed using patient clinical status and CT scanning of the chest. The high frequency of patients diagnosed with bronchiolitis obliterans is explained by the fact that our services are a center of reference for this disease. Though bronchiolitis obliterans had been previously diagnosed in our population, at our services pH-metry is a routine protocol for these patients due to possible therapeutic and causal relations.

It is important to indicate when pH-metry was carried out, since the occurrence of breathing effort or intense wheezing may result in increased GER.17 We observed, thus, that not all patients were in optimal conditions to undergo esophageal pH monitoring. Some patients showed
signs of use of accessory muscle and a great number of patients required oxygen therapy during examination. There were more signs of breathing distress in the group of patients who required O2 therapy in comparison to that of the group who did not; however, the breathing frequency of the earlier was not different from that of the latter (P=0.392).

Oxygen saturation monitoring through pulse oximetry is a simple, noninvasive, and accurate method for measuring arterial oxygen saturation. However, pulse oximetry has a series of limitations that might affect final results.20,21 We tried to reduce such limitations by carrying out measurements during nighttime, when children spend most of the time sleeping. Occasional measurement errors can be reduced by eliminating desaturation episodes that occur during loss of signal. In this sense, with the software for assessment of oxygen saturation it is possible to identify these errors and exclude them.

The most important parameters of pH-metry for assessing GER are reflux index (RI) and number of episodes of more than 5 minutes.22 In our study, the RI and number of episodes of more than 5 minutes were higher in the group with desaturation, indicating that GER was more severe in this group (P<0.05); the total number of reflux episodes and the Euler score were also higher in this group (P<0.05). The ZMD was almost three-fold higher in the group with desaturation than in the group without desaturation (P<0.05). However, our average ZMD values were different from those described in the literature. Perhaps, this response is related to the age of patients and their neurological maturity. In a study of ZMD values in groups with respiratory symptoms and according to age, the authors found higher ZMD in patients aged 0 to 6 months than in those aged 6 to 12 months or older than 12 months; these differences were statistically significant.23 This suggests that ZMD may be related to immaturity of the central nervous system.

In a recent study associating pH monitoring and polysonography and that was aimed at studying the association between GER and apnea in infants, the author observed that infants with sleep apnea presented higher reflux index, number of episodes of more than 5 minutes, and 18-24 hour ZMD in continuous esophageal pH monitoring (P<0.05). The total number of episodes and the Euler score did not distinguish between patients with or without apnea. Patients with apnea had higher ZMD values and age average significantly lower than that of patients without apnea.24

The objective of using average 24-hour pH measurement was to determine whether or not patients with desaturation had esophageal acidity higher than that of patients without desaturation. As a result, we observed that the earlier did have acidity higher than the latter (P<0.05), with no difference between the immediate postprandial and the late postprandial periods. Assessment of average pH during desaturation of the immediate postprandial and late postprandial periods indicated a lower pH in the group with desaturation (P<0.05) and in this same group in the late postprandial period, thus suggesting more severe GER in these patients. Vandenplas et al.25 suggests that assessment of GER be carried out during sleep, awake, immediate postprandial, and late postprandial periods, since patients with altered pH-metry have gastroesophageal reflux more frequently during sleep, and predominantly in the late postprandial period. Healthy children only present GER when they are awake and predominantly up to 2 hours after meals. Sondheimer, in 1980,26 showed that it was possible to differentiate symptomatic patients by late postprandial GER through pH monitoring.

The association between GER and respiratory symptoms is controversial. Numerous methods have been employed in the attempt to establish this association; however, up to the present moment, none of these methods can be considered the gold standard. Experimental evidence support the association between GER and alterations in cardiopulmonary function. Kenigsberg et al.,27 in an experiment with animal models, observed reflex bradycardia after reduction in esophageal pH. Wright et al.11 showed a reduction in cardiac frequency, forced expiratory volume in the first minute, and oxygen saturation in humans after intra-esophageal infusion of acid.; the same result was obtained, however, after infusion of saline.

In our study, we found a significant correlation between the total number of desaturations in the immediate postprandial and late postprandial periods with the reflux index, the number of episodes of more than 5 minutes, and the average 24-hour pH. The number of desaturations increased according to the increase in the reflux index and the number of episodes longer than 5 minutes and according to the reduction of average pH during pH monitoring.

Since the respiratory status of patients in this study was not optimal for pH monitoring, we determined whether the clinical status or factors that indicated more severity (respiratory frequency, number of hospital admissions, frequency of episodes, and reflux index) were associated with the clinical outcome. The cutoff point for respiratory frequency was set at 50 mrpm - the maximum normal value for the age range of up to 24 months.28 The international literature indicates that reflux indexes of up to 4% are considered normal; and those higher than 4% indicate abnormal GER.17 The cutoff points for the number of hospital admissions and frequency of reflux episodes were determined by the author since there were no studies that could be used in comparison to ours.

The bivariate analysis showed that respiratory frequency, number of hospital admissions, and frequency of reflux episodes are not separately associated to the clinical outcome. Only RI is significantly associated with the outcome. Our results may be assessed with a few limitations due to the sample size; however, results indicate that the study could
be successfully applied to a larger population, despite the fact that there are no studies described in the literature that could be used for comparative purposes.

Conclusion

There was a significant association between fall in esophageal pH and occurrence of desaturation in infants with chronic or recurrent obstructive pulmonary symptoms. The GER of patients with desaturation, which was assessed via pH monitoring parameters, was more severe. Although our study presents limitations due to the reduced size of the population and to not having a gold standard test for diagnosing the association of respiratory diseases and GER, we understand that the present study offers an additional parameter for the assessment of this association.

References


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