



# Correlation between Gastroesophageal Reflux and Respiratory Sounds in Children

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## Abstract

**Background:** Many children with respiratory symptoms such as wheezing and chronic cough have gastroesophageal reflux disease. However, a causal relationship of these diseases has yet to be corroborated.

**Methods:** Thirty-eight children (aged >24 months) with symptoms of gastroesophageal reflux and/or wheezing and cough were enrolled in this study. Patients underwent pH-impedance monitoring and recording of lung sounds (WHolter®). Results: The median number of cough events associated with weakly acid reflux in the group of patients with positive impedance monitoring was significantly higher than the median of cough associated with weakly acid and non-acid reflux in the group of patients with negative impedance monitoring ( $p = 0.003$ ). The median number of events of wheezing  $\geq 5\%$  associated with an episode of acid reflux was significantly higher ( $p = 0.008$ ) in the group of patients with positive 24-hr pH monitoring than those with negative 24-hr pH monitoring. Conclusion: In conclusion, we found a relationship between gastroesophageal reflux and respiratory symptoms: wheezing was associated mainly with acid reflux, whereas coughing was associated with weakly acid reflux.

**Keywords:** Gastro-esophageal reflux; Wheezing; Pulmonary sounds; pH-impedance

## Introduction

Asthma causes recurrent episodes of paroxysmal dyspnea with wheezing, cough and chest restriction. Wheezing is a continuous high-pitched expiratory sound with musical quality produced by an air flux that becomes turbulent flowing thorough the reduced airway calibre and causes an oscillation of the bronchial walls [1]. Gastroesophageal reflux is common in infants and children, and aspiration with swallowing in the absence of GER may also cause respiratory symptoms [2]. The patients may present excessive burping or emesis, coughing after meals and nocturnal cough or wheeze; crying and/or arching of the back may be the only symptoms in infants. About half of the children with asthma and abnormal esophageal pH show few or no symptoms of GERD [2].

Asthma has been related to gastroesophageal reflux in both children and adults [3]. The demonstration of a cause and effect between respiratory symptoms and GER may be difficult, since both conditions share common triggers. In a previous study, the incidence of silent GERD in children with pulmonary disease was between 46% and 75% [3]. Although acid suppression reduces acid reflux events in these patients, many continue to experience reflux symptoms or show no improvement in overall lung function [3].

In other studies, more than 40-50% of children with respiratory symptoms had GERD [4] and 60-80% of children with asthma had GERD [5].

The aims of this study were to evaluate the relationship between respiratory symptoms, wheezing and cough, and GER in children.

## Materials and Methods

This study was carried out at the Pediatrics Department of the University of Verona hospital over a period of 12 months. Children with wheezing, cough and recurrent respiratory infections and/or symptoms of gastroesophageal reflux underwent simultaneous measurements of pH-impedance monitoring and recording of lung sounds with a specifically dedicated device, the WHolter®.

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**Table 1:** Median number of events of acid, weakly acid and non-acid reflux related to coughing.

	Positive cough	Negative cough	P-value
Acid reflux (median)	34.20 (IQR 20.60-47.030)	21.55 (IQR 13.53-74.28)	0.63
Weakly acid reflux (median)	104.80 (IQR 45.88-264.10)	24.3 (IQR 15.48-89.58)	0.043
Non-acid reflux (median)	2.75 (IQR 0.00-10.50)	2.2 (IQR 0.30-7.55)	0.81

**Table 2:** Median number of liquid, mixed, gas, proximal and distal reflux related to wheezing.

	Positive wheezing	Negative wheezing	P-value
Liquid reflux (median)	2.2 (IQR 0.25-9.85)	18.9 (IQR 10.40-24.75)	0.0062
Mixed reflux (median)	39.45 (IQR 24.35-306.10)	122.8 (IQR -64.48-252.20)	0.23
Gas reflux (median)	64.5 (IQR 50.38-84.25)	64.5 (IQR 31.28-104.40)	0.98
Proximal reflux (median)	27.00 (IQR 6.75-244.50)	63.5 (IQR 25.75-99.50)	0.42
Distal reflux (median)	58.5 (IQR 30.00-327.00)	116.5 (IQR 64.50-236.80)	0.41

## Patients

The patients participated in a 24-hour study to evaluate respiratory symptoms (wheezing and cough) and/or symptoms of gastroesophageal reflux using simultaneous pH-impedance monitoring and WHolter<sup>®</sup>. Any patients over 15 years of age or under 24 months of age with acute infectious diseases, febrile diseases, cardiorespiratory malformations, allergic asthma, bronchospasm, bronchial asthma were excluded.

The study was approved by the local Ethics Committee and both the children and their parents gave informed consent. The study was approved by the Ethical Committee of Verona.

## PH-Multichannel Intraluminal Impedance (pH-MII) monitoring

The children underwent twenty-four hours of esophageal pH-impedance monitoring with an Ohmega<sup>™</sup> device (MMS, Medical Measurement Systems b.v. Enschede, The Netherlands). This method represents the gold standard for the evaluation of GERD and measure impedance, pH and/or pressure in the esophagus and stomach, noting up to 50 samples per second. Therefore, the device allows a clinician to identify all the episodes of acid, non-acid or weakly acid pH reflux using traditional measures and to distinguish between liquid, mixed and gas reflux by the analysis of the data by a specific software.

The system includes a portable "Data Recorder" with impedance amplifier and a catheter placed in the nose to the distal esophagus. The pH sensor is placed approximately 2 cm above the lower esophageal sphincter (LES), and the six impedance channels were located at 3, 4.5, 6, 7.5, 9, and 10.5 cm from the LES [6].

Liquid reflux was defined as a retrograde 50% drop in impedance that starts distally (at the level of the LES) and propagates to at least the next two more proximal impedance measuring segments. Only liquid refluxes lasting at least 3 seconds were taken into account. Gas reflux was defined as a rapid (3 kΩ/s) increase in impedance >5000 Ω, occurring simultaneously at least in two esophageal measuring segments, in the absence of swallowing. Mixed liquid-gas reflux was defined as gas reflux occurring immediately before or during a liquid reflux [7].

Reflux was defined as the presence of liquid or gas at the two most proximal segments; distal reflux was confined to the two most distal segments only [8].

The type of a single episode of reflux was evaluated by the pH sensor as follows: 1. Acid reflux: reflux of material that caused a drop in pH below 4 for 5 seconds or longer; 2. Weakly acid reflux: reflux of material that altered the pH between 4 and 6.5; 3. Non-acid reflux: reflux of material that did not change the pH (6.5-7) [7,9,10].

pH monitoring was considered positive for values on the reflux index over 5% (% of the total time during which the pH was <4) [11]. Impedance monitoring was considered positive when the acid reflux was >35, the weakly acid reflux >18 and non-acid reflux >7 [7].

## The WHolter<sup>®</sup> device

The WHolter<sup>®</sup> device was designed by KarmelSonix (Haifa, Israel) for recording, audio playback, graphical representation and automatic identification of lung sounds, wheezing and cough. The instrument allows simple, rapid continuous auscultation, especially for an objective quantification of wheezing. It is useful when monitoring a patient at home during the night or for 24 hours for the purpose of knowing the presence or absence of asthma attack symptoms to be able to quantify them and relate the respiratory symptoms to gastroesophageal reflux or other disorders. Specific analysis algorithms, special sensors and microprocessors capture and filter signals even in the presence of ambient noise. Frequency of wheezing (%), which is defined as the ratio between total time of wheezing and total time of breaths [wheeze frequency (wz %) = (wheeze time / breathing time) X 100] is the most important parameter used.

The device signals the difference between inspiratory and expiratory wheezing and determines the respiratory rate, respiratory phase and relationship between the two parameters. Wheezing was considered positive when the rate was ≥5% [12]; while cough was considered positive if a patient had at least 10 coughing events. The data and results of both recordings were compared in order to evaluate a temporal relationship. A positive temporal association between an episode of wheezing ≥5% or a coughing event and an episode of acid reflux or weakly acid or non-acid reflux was considered if it occurred within a 5-minute window (for instance, 5 minutes before or after a reflux event) [3].

## Statistical analysis

For statistical analysis we used the Statgraphics program, precisely the Kruskal-Wallis test and the Mann-Whitney (Wilcoxon) W test. A *p* value below 0.05 was considered significant.

**Table 3:** Median number of liquid, mixed, gas, proximal and distal reflux related to cough.

	Positive cough	Negative cough	P-value
Liquid reflux (median)	17.00 (IQR 9.65-24.30)	15.85 (IQR 5.50-23.78)	0.82
Mixed reflux (median)	135.00 (IQR 71.73-308.60)	55.05 (IQR 28.93-116.10)	0.0277
Gas reflux (median)	74.75 (IQR 31.28-111.90)	55.55 (IQR 35.05-70.10)	0.27
Proximal reflux (median)	70.50 (IQR 31.25-138.50)	27.5 (IQR 9.75-54.00)	0.0142
Distal reflux (median)	58.5 (IQR 30.00-327.00)	131.00 (IQR 78.00-293.30)	0.0061

**Table 4:** Median number of episodes of cough temporally associated with acid reflux in the groups of patients with positive or negative pH monitoring.

	Positive pH monitoring	Negative pH monitoring	P-value
Cough and acid reflux	8.00 (IQR 4.00-12.00)	4.00 (IQR 1.00-7.00)	0.068

In this study we considered pH monitoring to be a gold standard to evaluate the specificity and the sensibility of the WHolter<sup>®</sup> to detect reflux associated sounds.

## Results

Thirty-eight patients (20 males and 18 females) were recruited, ranging in age from 24 months to 15 years, with a mean age of 5.97 ± 3.38 SD. Of the thirty-eight children, 15 had positive pH monitoring (39.47%), 4 showed positive WHolter (10.53%), and 2 were positive (5.26%) in both cases. Twenty-six patients (68.42%) had a temporal association between an episode of wheezing ≥5% and an episode of acid reflux, whereas 30 patients (78.95%) had at least one temporal association between a cough event and an episode of acid reflux. Twenty-three patients (60.53%) had at least one temporal association between an episode of wheezing ≥5% and an episode of weakly acid reflux and non-acid reflux; whereas 30 patients (78.95%) had at least one temporal association between a cough event and an episode of weakly acid reflux and non-acid reflux. The median number of events of acid, weakly acid and non-acid reflux were compared in patients with positive and those with negative wheezing. The median number of acid reflux events in patients with positive wheezing was 18.85 (13.53-107.1), whereas in patients with negative wheezing it was 34.2 (20.6-54.4) (p=0.43).

The median number of weakly acid reflux events in patients with positive wheezing was 19.40 (IQR 9.4-198.4); in patients with negative wheezing it was 98.15 (IQR 29.38-229.7) (p=0.19).

As for non-acid reflux events, the median number of events in patients with positive wheezing was 1.5 (IQR 0-4.95), whereas it was 2.75 (IQR 0-9.6) (p 0.39) in patients with negative wheezing.

The median number of events of acid, weakly acid and non-acid reflux were compared in patients with positive cough and in those with negative cough (Table 1). The median number of liquid, mixed, and gas reflux, proximal and distal reflux were compared in groups of patients with positive wheezing and in those with negative wheezing (Table 2).

The median number of the different types of reflux within the group of patients with positive cough and the group with negative cough are shown in (Table 3).

In the group with positive cough there was a statistically significant difference between the median number of distal reflux (n=131 IQR: 78-293.3) and the median number of proximal reflux (n= 70.5) (IQR 31.25-138.5) (p=0.0142).

The median number of episodes of wheezing ≥5% associated with acid reflux in the group of patients with positive pH monitoring was 4.00 (IQR 1-9), and in those with negative pH monitoring it was 1.00 (IQR 0-2), with a statistically significant difference between the two groups (p=0.022).

The median number of cough events associated with acid reflux in the group with positive pH monitoring was 8.00 (IQR 4.00-12.00), whereas it was 4.00 (IQR 1.00-7.00) (p=0.068) in the group with negative pH monitoring.

The median number of segments with wheezing ≥5% in patients with positive pH monitoring was 39 (IQR 18.00-114.00), whereas it was 15.00 (IQR 5.00-83.00) (p 0.1) in those with negative pH monitoring. The median number of cough segments in the group with positive pH monitoring was 32 (RI 5-83), whereas it was 28 (RI 16-47) (p 0.9) in the group with negative pH monitoring.

In the group with positive MII monitoring, the median number of events with wheezing associated with weakly acid reflux was 1 (IQR 0-4.00); in those with negative MII monitoring it was 0.5 (IQR 0-1.25) (p=0.19).

In patients with positive MII monitoring the median number of cough events associated with weakly acid was 7 (IQR 2-14.5); in those with negative MII monitoring it was 0 (IQR 0-1.00) (p=0.0014).

## Discussion

A significant number of children with respiratory symptoms such as wheezing and cough have been reported to have chronic gastroesophageal reflux disease [4]. Nevertheless, a causal relationship between these two diseases has not yet been demonstrated. In a study published in 2005, Sifrim et al. [14] evaluated the relationship between acid reflux, weakly acid and cough in 22 patients with chronic cough. They found that 69.4% of the episodes of cough were independent of reflux, but about 30% of episodes of cough were temporally associated with reflux. In half of these cases the cough preceded reflux, and therefore the reflux seemed to be a consequence rather than a cause of coughing. These results support the hypothesis that coughing can induce reflux by increasing the pressure gradient between the abdomen and chest and that it can create a positive feedback between cough and GERD. In the other patients of the group, coughing was preceded by acid reflux (32%) and weakly acid reflux (17%). This was the first study showing that weakly acid reflux may be the cause of chronic cough [14].

In a further study by Kunsh et al. [13] that evaluated the

respiratory symptoms in patients with GERD, nocturnal cough was detected in 19 out of 25 patients with GERD, and almost half of the cough events coincided with reflux events. Eighty-nine percent of these cough events were preceded by reflux while reflux was rarely preceded by cough. Nocturnal wheezing was observed in only 11 of the 25 patients and 16 (41%) wheezing events coincided with reflux events; 100% of wheezing events were preceded by reflux. These 16 episodes of wheezing were associated with different types of reflux events including acid reflux (56%), biliary reflux (31%) and combined reflux (13%). This suggests that reflux events are followed by respiratory symptoms [13]. The study by Kunsh and two other studies suggest that the majority of patients with a positive association between cough and reflux have predominantly biliary reflux, while wheezing is most often preceded by acid reflux [13,16,15]. In the present study only 25% of cough events were temporally associated with reflux: 87% was preceded by acid reflux, and 13% by acid reflux. Similarly for the weakly acid and non-acid reflux, the cough events were preceded by a reflux event in 88% of cases, whereas 12% of cases were followed by weakly acid and non-acid reflux. Furthermore, the median number of weakly acid reflux events was higher in the group with positive cough than in the group with negative cough. Our study shows that the median number of events of weakly acid and non-acid reflux associated with cough was higher in the group of patients with positive MII monitoring than in the group of patients with negative MII monitoring ( $p=0.0014$ ). These results support the hypothesis that chronic cough may be partly caused by weakly acid reflux and that cough is a consequence of reflux.

The median number of episodes of cough temporally associated with acid reflux was higher in the group with positive pH monitoring compared with the group with negative pH monitoring, but the results were not statistically significant in the two groups ( $p=0.068$ ) suggesting that cough events occur mostly independent of acid reflux events (Table 4).

Only 5% of patients showed wheezing associated with reflux, and these patients presented symptoms preceded by reflux. The median number of wheezing events  $\geq 5\%$  associated with an episode of acid reflux was higher in the group of patients with positive pH monitoring than in that of those with negative pH monitoring ( $p=0.022$ ), therefore suggesting a correlation between wheezing and acid reflux.

These results induce us to speculate that weakly acid reflux may contribute to cough reflex, whereas acid reflux could be responsible for obstructive respiratory symptoms such as wheezing. A previous study by Irwin et al. [17] showed that most episodes of GER that cause cough occur mainly in the distal rather than proximal esophagus. GER was suggested to be the most common cause of chronic cough because it stimulates distal esophageal mucosal receptors, probably through an esophageal-bronchial cough reflex. The median of distal reflux events was higher than the median of proximal events in the group of patients with positive cough, supporting the hypothesis that an esophageal-bronchial reflex can contribute to respiratory symptoms.

Our study also allowed us to calculate the specificity (92%) and sensibility (24%) of the sounds recorded by the WHolter device in relation to positivity and negativity of pH monitoring. Although this instrument showed a high specificity and a fairly positive predictive value of 67%, it cannot currently be proposed as an alternative approach to pH-impedance monitoring for screening children with

respiratory symptoms and gastroesophageal reflux.

In conclusion, this study is in favour of a relationship between respiratory symptoms and gastroesophageal reflux and suggests that wheezing is mostly associated with acid reflux, whereas cough with weakly acid reflux.

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