

# The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings

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► **To cite this version:**

Kathleen Blondeau, Veerle Mertens, Lieven Dupont, Ans Pauwels, Ricard Farre, et al.. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. *Pediatric Pulmonology*, Wiley, 2010, 46 (3), pp.286. 10.1002/ppul.21365 . hal-00599809

**HAL Id: hal-00599809**

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Submitted on 11 Jun 2011

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**The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings**

Journal:	<i>Pediatric Pulmonology</i>
Manuscript ID:	PPUL-09-0319.R2
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	04-Jun-2010
Complete List of Authors:	Blondeau, Kathleen; KULeuven, Center for Gastroenterological Research Mertens, Veerle; KULeuven, Center for Gastroenterological Research Dupont, Lieven; UZLeuven, Division of Respiratory Medicine Pauwels, Ans; KULeuven, Center for Gastroenterological Research Farre, Ricard; KULeuven, Center for Gastroenterological Research Malfroot, Anne; Universitair Ziekenhuis Brussel, Units of Pediatric Pulmonology De Wachter, Elke; Universitair Ziekenhuis Brussel, Units of Pediatric Pulmonology De Schutter, Iris; Universitair Ziekenhuis Brussel, Units of Pediatric Pulmonology Hauser, Bruno; Universitair Ziekenhuis Brussel, Units of Pediatric Gastroenterology Vandenplas, Yvan; Universitair Ziekenhuis Brussel, Units of Pediatric Gastroenterology Sifrim, Daniel; KULeuven, Center for Gastroenterological Research
Keywords:	Non-acid gastroesophageal reflux, chronic cough, impedance-pH, manometry



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## The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings.

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**Short title:** Reflux (acid and non-acid) and chronic cough in children with chronic cough.

**Keywords:** Children, gastroesophageal reflux, impedance-pH-manometry, cough

**ABSTRACT**

**Introduction** Assessment of the reflux-cough association in children is challenging. Esophageal (impedance-)pH recording is sensitive to recognize reflux. However, cough recorded by an event marker, possibly lacks accuracy. We **aimed** to study the exact time relationship between reflux and cough in children with chronic cough. **Methods** 26 children (12 boys;1-10.5 years) with chronic unexplained cough underwent ambulatory impedance-pH-manometry recordings. Manometry was used for precise cough recognition. Reflux was assessed with impedance-pH monitoring and defined as acid (pH<4), weakly acidic (WA) (pH 4-7), weakly alkaline (WALK) (pH≥7) or acid only (pH <4 for ≥4 sec without impedance pattern). Cough was considered “induced by” reflux, if it started ≤2 min after reflux. The Symptom Association Probability (SAP) was calculated and considered positive if >95%. Cough induced reflux if it occurred 30sec before the reflux event. **Results** Impedance-pH detected 30(21-52) reflux episodes/patient (55.2% acid, 41.5% WA and 3.3% WALK). Additionally 59 acid only events were identified [1(0-21)/patient]. Manometry detected 47(5-203) cough bursts/patient. Reflux-cough was found in 22/26 patients. Ten patients had a +SAP for reflux-cough (1 acid, 6 WA and 3 acid+WA GER), of which 9 had a normal acid exposure. 6/10 patients with +SAP using manometry had a +SAP using the event marker. Cough-reflux was detected in 19 patients [3(0-7)/patient]. Only a small fraction of the esophageal acid exposure [9.6 (0.4-31.8%)] was secondary to cough. **Conclusion** Both acid and WA GER may precede cough in children with unexplained cough, but cough does not induce GER. Objective cough recording improves symptom association analysis.

## INTRODUCTION

Both cough and gastroesophageal reflux (GER) in infants and children are common reasons for parents to seek medical attention.<sup>1</sup> Although GER has been recognized as a cause for unexplained cough, diagnosing GER related cough in children is still challenging. The presence of symptoms suggestive for GER disease, e.g. regurgitation, vomiting, failure to thrive, is often a first indication<sup>2</sup>, but the absence of these symptoms cannot exclude GER as an underlying cause of the chronic cough.

Several diagnostic techniques, including proximal pH recording and detection of lipid laden macrophages in the Broncho-Alveolar Lavage Fluid (BALF) have been used for the diagnosis of proximal reflux and aspiration of gastric contents into the lungs.<sup>3-5</sup> However, proximal reflux is not required as the presence of gastric contents in the distal esophagus might induce a vagal reflex leading to cough.<sup>6,7</sup>

Ambulatory esophageal pH-metry has long been considered an important tool for the detection of acid reflux. More recently, combined esophageal impedance-pH recordings have shown that not only acid but also non-acid reflux might be associated with respiratory symptoms such as cough.<sup>8-12</sup>

Symptom association analysis requires an accurate registration of symptoms, which previously has been performed using an event marker.<sup>10;13</sup> Since in children symptom recording is mostly controlled by the parents, the use of an event marker may imply that the timing of registration might be delayed compared to the actual occurrence of the symptom and that symptoms might be missed. Moreover, especially in patients with cough, an accurate timing of symptom recording is important since reflux may not only induce cough, but cough might also induce reflux.<sup>6;14</sup> To which extent the latter is important in children with chronic cough remains unknown.

Ambulatory 24 hours esophageal manometry has been proven a useful tool for objective recognition of cough in patients undergoing 24 hours reflux testing and for establishing the exact time relationship between reflux and cough events.<sup>8;15;16</sup>

The aim of the current study was therefore to use combined ambulatory 24 hours impedance-pH-manometry recordings to study acid and non-acid GER and its relationship to cough in children with chronic unexplained cough.

## METHODS

### Subjects

Simultaneous 24 hours ambulatory esophageal manometric-impedance-pH monitoring was performed in 26 children with chronic unexplained cough (12 boys; median age 4 years, range 1-10.5 years). The patients were recruited at the outpatient clinic of the Universitair Ziekenhuis Brussel, and presented daily cough of unclear etiology for at least 8 weeks. Those with an alternative diagnosis, such as clinical suspected asthma responding to a treatment trial during at least 4 weeks, underlying ENT problems or upper airway cough syndrome, pertussis, cystic fibrosis, tuberculosis, cardiac disease, chromosomal or humoral immunological deficiency were excluded from the study after workup as listed in Table 1.<sup>17</sup>

None of the children received acid suppressing therapy. The study was approved by the local ethical committee. Informed consent was given prior to inclusion.

### Recording equipment and technique

Cough and GER were monitored simultaneously using an ambulatory manometric-impedance-pH system. Manometry was used for accurate cough recognition whereas impedance-pH monitoring allowed detection of acid, weakly acidic and weakly alkaline reflux.

A manometric catheter with 2 solid-state pressure sensors (15 cm apart) (Sandhill Scientific, Inc; Highlands Ranch, CO, USA) (1.3 mm external diameter) was passed transnasally. The catheter was positioned so that one pressure channel was located in the esophageal body and the other in the stomach. Esophageal impedance-pH was recorded with a 2.1mm diameter catheter that comprised six electrode pairs to measure intraluminal impedance and 2 antimony pH sensors (Sandhill Scientific, Inc; Highlands Ranch, CO, USA). Two different types of age appropriate catheters were used: infant (< 75 cm of height) and pediatric (> 75 cm of height). The impedance-pH and manometric

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3 catheters were connected to a single ambulatory device containing their respective  
4 amplifiers (Sleuth, Sandhill Scientific, Inc; Highlands Ranch, CO, USA). The impedance  
5 amplifier delivered ultra-low current in a range of 1-2 KHz with resulting current flow  
6 variations in response to intraluminal impedance changes. The impedance, pH and  
7 manometric signals were digitized at 50Hz and stored in the data logger. Before the start  
8 of the recording, the pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer  
9 solutions.  
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## 11 **Study protocol**

12 The study was performed after an overnight fast. The catheters were passed trans-  
13 nasally and positioned to record pressures and pH in the stomach and pressure pH and  
14 impedance in the esophageal body. Impedance-pH catheter was positioned so that the  
15 esophageal pH sensor was at the third vertebral body above the diaphragmatic angle.  
16 The patients were encouraged to maintain normal activities, sleep schedule, and eat  
17 their usual meals at their normal times. Event markers on the data logger recorded meal  
18 times and posture changes. Between meals, patients abstained from snacks and  
19 beverages with a pH < 5. Before the study, parents were instructed to keep a careful  
20 diary and trained to use a dedicated event marker in the data logger, to record cough  
21 episodes and other events.  
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## 34 **Data analysis**

35 The manometric-impedance-pH recordings were uploaded into a personal computer and  
36 were manually analysed using dedicated software (Bioview, Sandhill Scientific, USA ).  
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### 40 Cough detection

41 The manometric tracing was independently analysed for cough episodes. Cough was  
42 defined according to Paterson et al. as phasic, short duration, rapid pressure rises (time  
43 to peak <1sec) occurring simultaneously and with the same pressure configuration at  
44 both manometric recording sites.<sup>15</sup> A “cough burst” was defined as two or more rapid  
45 simultaneous pressure peaks within 3 seconds. Only “cough bursts” were considered in  
46 the further analysis. The cough events marked in the data logger and diary information  
47 were used for comparison with objective detection of cough bursts by manometry.  
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### Reflux detection

The impedance-pH recording was analysed for GER, independently of the pressure recordings. The impedance recording was analysed using criteria described in a recent consensus report on detection and definitions of acid, non-acid, and gas reflux.<sup>18</sup> GER was defined as a sequential orally progressing drop in impedance to less than 50 % of the baseline values starting at the most distal channel and propagating retrograde to at least the next more proximal measuring segment. According to the corresponding pH change, impedance-detected reflux was classified as *acid* if pH fell below 4 for at least 4 seconds, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 seconds. *Weakly acidic reflux* was defined as a pH drop of at least 1 pH unit sustained for more than 4 seconds with the basal pH remaining between 7 and 4. Reflux was judged to be *weakly alkaline* when there was impedance evidence of reflux but the pH did not drop below 7.

*Acid only events* were defined as a drop in the esophageal pH below 4 for at least 4 sec without a characteristic reflux pattern in the impedance tracing.

For each reflux episode determined by pH-impedance, the associated gas-liquid pattern was classified as: (i) mixed reflux of liquid and gas or (ii) liquid reflux. Only gas reflux episodes (belches) were not included in the analysis. The proximal extent of each reflux event was evaluated from the impedance tracings. For each patient, the total number of reflux events (acid, weakly acidic and weakly alkaline), the number of episodes reaching the proximal esophagus (nr of episodes reaching impedance channel 1) and the exposure of the esophageal body to acid and volume were calculated.

Total 24 hours acid exposure was calculated as the percentage of time that the esophageal pH was below 4 and was considered increased if > 6% of the total recording time.<sup>19</sup> This parameter included all pH drops either related or not related to bolus reflux. For each reflux episode detected by impedance, volume exposure in impedance channel 5, was calculated as the time (sec) between the 50% drop in impedance until the 50% recovery of the impedance baseline. Total volume exposure/24 hours was obtained by addition of the volume exposures of all individual reflux events.

### Association reflux-cough

A 2 minute time interval following the start of a reflux episode was used to delimitate the time window for reflux-cough association. A 2 minute period was chosen based on



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3 previous analysis of acid reflux-chest pain association.<sup>20</sup> Thus, if a cough episode  
4 occurred in the 2 minute time period after the start of a reflux event, cough was  
5 considered “associated to reflux”. (Figure 1) If cough fell outside the 2 minutes time  
6 window after reflux, it was considered to have occurred “independent” of reflux. We  
7 calculated for each patient the symptom association probability (SAP) between cough  
8 and different types of reflux (acid and weakly acidic). (software Dr Tutuian) The entire  
9 recording was subdivided into consecutive 2 minute time intervals. Each time interval  
10 was evaluated for the presence of reflux. When reflux was detected at any point during  
11 the 2 minute period, the period was considered positive for reflux (R+). In a second step,  
12 the 2 minute periods containing a reflux episode followed by cough (R+S+), those with  
13 only cough but no reflux (R-S+) and those with neither cough nor reflux (R-S-) were  
14 counted. A contingency table was constructed containing the number of the four different  
15 types of 2 minute periods. Fisher’s exact test was used to calculate the probability (*P*  
16 value) that the observed association between reflux and cough occurred by chance. The  
17 SAP was calculated as  $(1.0-p)*100\%$ . SAP values greater than 95% were considered  
18 statistically significant.<sup>21,22</sup>  
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### 31 Association cough-reflux

32 Cough episodes preceding a reflux event were evaluated separately.

33 A reflux event was considered “induced by” cough if cough occurred in the 30 seconds  
34 preceding reflux.<sup>15</sup> (Figure 2) The total esophageal acid and volume exposures due to  
35 cough were calculated by adding the acid and volume exposures (sec) at 5 cm above  
36 the LES from the individual reflux events “induced by” cough, divided by the total  
37 recording time.  
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### 45 **Statistical analysis**

46 Data are presented as median (range) unless otherwise stated. If data were normally  
47 distributed the paired Student’s *t* test was used for comparison. If data were not normally  
48 distributed a non-parametric Mann-Whitney test was applied. Fisher’s exact test was  
49 used to calculate SAP. Statistical significance was accepted when  $p < 0.05$ .  
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## RESULTS

### Gastroesophageal reflux

4 patients had symptoms suggesting GER. Two children had heartburn and/or regurgitation, 1 had abdominal pain and 1 child had frequent vomiting.

Impedance recordings detected 967 reflux events. From the total amount of reflux detected, 55.2% was acid, 41.5% was weakly acidic and 3.3% was weakly alkaline. Overall, 32% of the reflux episodes were mixed (liquid+gas) and 68% were liquid. Of all reflux events detected by impedance, 26% reached the proximal esophagus. Reflux characteristics are displayed in table 2.

In addition to the reflux events detected by impedance, 59 acid only events were identified [1(0-21)/patient]. From the total esophageal acid exposure 6.0(2.4-62.3)% was due to acid only events. Overall, 3/26 children had an increased esophageal acid exposure. None of these children had symptoms suggesting GER. There was a significant correlation between age and the nocturnal esophageal acid exposure ( $r=0.77$ ,  $p<0.0001$ ), total number of reflux events ( $r=0.77$ ,  $p<0.0001$ ), number of acid reflux events ( $r=0.74$ ,  $p<0.0001$ ) and the esophageal volume exposure ( $r=0.79$ ,  $p<0.0001$ ).

### Cough

Gastroesophageal manometry detected 47(5-203) cough bursts/patient, of which 4(0-65) occurred during the night.

Overall 464 cough markers were recorded in 17/26 children [8(0-75) markers/child]. **There was a significant correlation between the number of coughs recorded by manometry and the number of event markers ( $r=0.73$ ,  $p=0.001$ ).** In 9 children no cough markers were recorded. (Table 3)

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3 From the 464 cough markers recorded, 388 (84%) corresponded to a cough burst  
4 identified by manometry. The event marker was pressed, 19(5-92) seconds after the  
5 start of the actual cough burst.  
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10 From the 78 event markers that did not correspond to a cough burst identified by  
11 manometry, 65 occurred in the same child. These 65 cough markers corresponded to  
12 single pressure spikes, probably representing single cough episodes.  
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17 There was no correlation between age and the number of coughs detected either by  
18 manometry or indicated by the event marker.  
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## 21 22 23 24 25 26 **Gastroesophageal reflux and cough** 27

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29 There was no correlation between any of the reflux parameters (acid exposure, volume  
30 exposure, number of reflux events and number of proximal reflux events) and the  
31 number of coughs.  
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### 34 35 Reflux-cough 36

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38 From the 1404 cough bursts detected by manometry, 140 were preceded by impedance  
39 reflux (58 acid, 77 weakly acidic and 5 weakly alkaline reflux). Only 5 cough bursts were  
40 preceded by an “acid only” event.  
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44 Ten patients had a positive SAP for reflux-cough, of which 1 exclusively for acid reflux, 6  
45 exclusively for weakly acidic and 3 patients for both acid and weakly acidic reflux.  
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49 One of the 10 patients with a +SAP had an increased esophageal acid exposure. (Figure  
50 3) One of the patients with a +SAP (acid reflux) had symptoms suggesting reflux  
51 (abdominal pain).  
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55 Patients with a +SAP were significantly older than patients with a –SAP [Mean 5.9± SD  
56 3.3 vs. Mean 3.6± SD 1.7 years, p=0.03]. All reflux parameters (acid exposure, volume  
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3 exposure, number of reflux events and proximal extent of reflux) and the number of  
4 cough bursts were similar in patients with and without a +SAP.  
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8 Six out of the 10 patients with a +SAP using objective cough detection had a +SAP  
9 using the event marker for cough recognition operated by the parents. In contrast to the  
10 SAP based on the manometric recordings, 4 of these patients had a +SAP for acid reflux  
11 and only 2 patients for weakly acidic reflux. One patient had a +SAP using the cough  
12 event marker but a –SAP using manometry. (table 3)  
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### 18 19 20 Cough-reflux

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22 Cough-reflux sequences were found in 18/26 patients [3(0-7)/patient]. From the reflux  
23 events “induced by” cough, 43% were acid, 41% weakly acidic, 4.5% weakly alkaline  
24 and 11.5% were acid only events. From the total esophageal acid 9.6% (0.4-31.8%) and  
25 bolus exposure 2.1% (0.0-28.0%) was secondary to cough.  
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28 The majority of cough-reflux events occurred during the upright period, whereas 24%  
29 occurred during a recumbent period. Thirty six percent of the cough-reflux events  
30 occurred in the first hour after the meal.  
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## DISCUSSION

GER is recognized as an important cause of respiratory symptoms in children, including chronic cough.<sup>23</sup> Reflux-symptom association during 24 hours reflux recording is an important tool for the diagnosis of GER related cough. However, in children when symptom registration is performed by the parents, the use of an event marker for cough registration might lack accuracy and the reflux-cough relationship might be misinterpreted.

The aim of the current study was to study reflux and its relationship to cough using objective techniques for both reflux (impedance-pH recording) and cough (gastroesophageal manometry) detection.

Our main findings were the following: 1) Independent of an increased esophageal acid exposure, a group of children had a statistical and clinical significant association between reflux and cough. 2) Acid reflux may precede cough. However, more frequently cough was preceded by weakly acidic reflux. Weakly alkaline reflux is rare and is unlikely to precede cough. 3) Acid only events are present in children with chronic unexplained cough and contribute to the total esophageal acid exposure. However, they were not associated with cough 4) An objective technique for cough recording is important to identify the correct time relationship between reflux and cough events. 5) Cough does not provoke reflux in children with chronic unexplained cough.

Both in adults and in children, GER has been implicated in the pathophysiology of a wide variety of respiratory symptoms and diseases including chronic unexplained cough.<sup>1;8;10-12;23-25</sup> Ambulatory 24 hours esophageal pH recording has demonstrated an increased acid exposure in a subgroup of children with respiratory symptoms such as cough<sup>10;11;23</sup>. However, 24 hours pH-metry is limited to the detection of acid reflux. In conditions during which the gastric contents is neutralized, e.g. in the postprandial period, reflux events of non-acid pH may be missed. Esophageal impedance recording allows detection all types of reflux, independent of the pH. Combining impedance with pH recording allows to classify reflux events based on their pH.<sup>18;26</sup>

The role of non-acid reflux in children with respiratory complications remains unclear.<sup>23</sup> Rosen et al. previously studied acid and non-acid reflux using combined impedance pH

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3 recording in a group of children with persistent respiratory symptoms “on” PPI therapy. In  
4 patients studied during PPI treatment, 50% of the reflux events detected by pH-  
5 impedance recordings were non-acidic<sup>10</sup>. Thilmany et al. performed a similar study in  
6 children “off” PPI therapy. They found that from the total amount of reflux detected, only  
7 5.1% was non-acidic.<sup>11</sup> In contrast to these findings we found that 44.8% of all reflux  
8 episodes was non-acidic. The reason for this large difference in prevalence of non-acid  
9 reflux remains uncertain. However, whereas our study included only children with  
10 chronic cough of unknown origin, the study of Thilmany et al included patients with  
11 different respiratory diseases including patients with cystic fibrosis.<sup>11</sup> The high  
12 prevalence of especially acid reflux in this population together with inclusion of other  
13 respiratory pathologies might be related to the higher proportion of acid reflux.  
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15 In the current study non-acidic reflux was sub classified into weakly acidic (pH 4-7) and  
16 weakly alkaline (pH $\geq$ 7). Our results showed that as in adults with chronic cough, weakly  
17 alkaline is rare and the majority of non-acidic events has a weakly acidic pH.<sup>8;16</sup>  
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28 An absence of increased reflux does not exclude an association between reflux and  
29 symptoms. Moreover, since in children normal values for impedance-pH recording are  
30 lacking, it is impossible to judge whether non-acid reflux is increased. Simultaneous  
31 symptom and reflux recording allows to determine the time association between  
32 individual reflux and cough events and to identify whether a cough is preceded, followed  
33 by or not-associated with reflux.  
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37 Thilmany et al. previously studied the time association, using a 2 min time interval,  
38 between reflux events and episodes of oxygen desaturation. They found that overall  
39 37.7% of all desaturation episodes were preceded by a reflux event of which the majority  
40 (92%) were acid.<sup>11</sup>  
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44 Rosen et al. also studied the time association between reflux and a variety of respiratory  
45 symptoms including a subgroup of children with chronic cough. They used combined  
46 impedance-pH recording, a patient diary for cough registration and a 2 minute time  
47 window for reflux-cough association. They found that overall, 37.6% of the cough events  
48 recorded were associated with reflux. Per patient analysis showed a significant  
49 association between reflux and cough in 33.3% of patients using combined impedance-  
50 pH analysis and in 5.6% of patients using only pH probe analysis.<sup>10</sup>  
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55 The use of an event marker for cough registration has a major limitation since the  
56 accuracy of this method depends largely on the patient's cooperation. This may even be  
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3 more the case in children where symptom registration is performed by the parents.  
4 Symptoms episodes may be missed (e.g. during sleep) or may be recorded later than  
5 they actually occurred. The use of an objective technique for cough recording may  
6 overcome this limitation. Gastroesophageal pressure recording has been demonstrated  
7 as a useful tool for objective cough registration and has been previously used by our  
8 group and others to study the time relationship between reflux and cough events in adult  
9 patients with chronic cough.<sup>8;15;16</sup>

10 In the current study we demonstrated in children with chronic cough that, as in adult  
11 patients, the use an objective technique for cough detection significantly increased the  
12 number of coughs recorded compared to the use of an event marker. The mean delay  
13 between the cough bursts and the event marker was approximately 20 seconds.

14 Overall 84% of the event markers corresponded to a manometric cough bursts. Although  
15 78/464 event markers did not correspond to a typical cough bursts, 65 of these were  
16 recorded in a single patient. All of the 65 markers corresponded to a single pressure  
17 spike in manometry. Since single spikes in manometry cannot be distinguished from  
18 phenomena such as sneezing, they were included in the analysis. Nevertheless, these  
19 single coughs were associated with event markers in only one child, suggesting that  
20 their clinical importance might be limited.

21 The most important aim of the current study was to evaluate the exact time relationship  
22 between reflux and cough events using objective techniques for both reflux and cough  
23 recordings. First of all we confirmed that not only acid but also weakly acidic reflux may  
24 precede cough. We remind that Rosen et al previously reported similar findings, but their  
25 study was performed in patients "on" PPI treatment and without the use of objective  
26 cough detection.<sup>10</sup> Our study showed for the first time, using an objective technique for  
27 cough recording that weakly acidic reflux may "induce" cough in children "off" PPI. A  
28 significant association between reflux and cough (+SAP) was found in 10/26 (38%) of  
29 the children, which is comparable what has been previously reported for other  
30 respiratory symptoms. Remarkable is that only 1 child had a +SAP for acid reflux,  
31 whereas all other patients had a +SAP for weakly acidic reflux either alone or in  
32 combination with acid. This finding is in line with previous observations describing that  
33 the presence of non-acid reflux was associated with an increase in reflux-symptom  
34 association.<sup>10</sup> Weakly alkaline reflux was rare and hardly ever preceded a cough event.  
35 The reason why weakly acidic reflux is more likely to be associated with cough might be  
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3 related to a different composition of the weakly acidic refluxate. The presence of specific  
4 chemical components (e.g. unconjugated bile acids) or an increased volume of the  
5 refluxate might promote stimulation of the vagal reflex associated with the reflux-cough  
6 pathway or might be more harmful when aspirated into the lungs.  
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11 Six out of the ten patients with a positive SAP for reflux-cough using manometry were  
12 also identified as SAP+ using the event marker. Interestingly, using the event marker  
13 most of these patients had an association between acid reflux and cough whereas with  
14 the manometry, cough was associated with weakly acidic reflux. The reason for this  
15 difference is unclear. Possibly acid reflux is more clearly perceived by the child and may  
16 lead to a change in behaviour (e.g. crying). This in term might make the parents more  
17 aware of the symptom and may stimulate them of pressing the event marker.  
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20 One child had a +SAP using the event marker but a –SAP using manometry, this was  
21 the child with the multiple single coughs.  
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27 Although impedance recording provides a high sensitivity of reflux detection, pH drops  
28 may occur without the typical reflux impedance pattern. These “acid only” events are  
29 found to be common, particularly in young children. In contrast to previous studies which  
30 reported a very high prevalence of acid only events, their prevalence in the current study  
31 was much lower.<sup>10-12</sup> Moreover, although acid only events may contribute to the total  
32 esophageal acid exposure, our study showed that only 4/59 acid only events preceded  
33 cough, suggesting that they do not contribute to the reflux-cough relationship.  
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40 The relationship between reflux and cough is complex, since reflux may not only induce  
41 cough but it has been suggested that cough, by increasing the abdomino-thoracic  
42 pressure gradient, can also provoke reflux. Whether and to what extent, cough provokes  
43 reflux in children is unknown. Our study is the first to report that cough is not an  
44 important cause of reflux in children with chronic unexplained cough, since only a very  
45 small proportion of the total esophageal acid and volume exposure were secondary to  
46 cough, confirming our findings in adult patients.<sup>8</sup>  
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3 The current study has some limitations, including the small number of children studied.  
4 Our study focussed primarily on children with unexplained chronic cough without clear  
5 signs of excessive reflux. In children with severe reflux, the objective relationship  
6 between reflux and cough will need to be investigated.  
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10 In order to have an optimal detection of cough, a thin catheter crossing the LES was  
11 used to record both abdominal and thoracic pressures. Although the overall prevalence  
12 of reflux in the current study was low, previous studies have reported that a catheter  
13 crossing the LES might slightly enhance reflux in children and this effect cannot be  
14 excluded from our study.<sup>27</sup>  
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18 Previous studies have shown a suboptimal reproducibility of reflux measurements using  
19 24hrs pH-recordings. Hence, it is likely that the reflux-cough association as assessed in  
20 the current study is subject to a day-to-day variability.<sup>28</sup>  
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23 Although we could establish the objective relationship between reflux and cough in this  
24 group of children with chronic unexplained cough, intervention studies will need to  
25 confirm the clinical relevance of this reflux-cough association in these patients.  
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31 In summary we can conclude that using objective techniques for reflux and cough  
32 detection, results in the observation that reflux may precede cough in a subgroup of  
33 children with chronic unexplained cough. Although acid reflux may precede cough, in  
34 most children cough was preceded by weakly acidic reflux. Weakly alkaline and acid  
35 only events are not important for the reflux-cough relationship. The use of an objective  
36 technique for cough detection increases the prevalence and accuracy of cough  
37 registration and may improve symptom association analysis. In contrast to what is often  
38 suggested, cough does not provoke a significant amount of reflux in children with chronic  
39 cough.  
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45 These findings may have important diagnostic and therapeutic implications for patients  
46 with reflux related respiratory problems. First of all our results suggested that combined  
47 impedance-pH testing is superior to pH testing alone. Secondly, other treatment  
48 strategies might need to be considered to treat patients with reflux related cough. In  
49 most of these patients reflux is treated with anti-acid medications, which insufficiently  
50 reduce weakly acidic reflux.<sup>29</sup> Anti-reflux treatments affecting all types of reflux may  
51 need to be considered. However, so far pharmacological options are limited to baclofen,  
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3 a GABA<sub>b</sub> agonist reducing the number of transient relaxations of the lower esophageal  
4 sphincter (LES).<sup>30-32</sup> In some patients anti-reflux surgery may be considered.

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6 Intervention studies will need to confirm the clinical relevance of weakly acidic reflux in  
7 children with unexplained chronic cough.  
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For Peer Review

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## Figure legends

**Figure 1:** Example of cough “induced” by weakly acidic reflux.

Impedance shows a retrograde flow of liquid up to channel 1, with the esophageal pH remaining above 4 (weakly acidic reflux). 45 seconds after the reflux, event, the manometry shows a cough burst, characterized by a rapid increase in pressure.

**Figure 2:** Example of cough provoking reflux. The manometry tracing shows a cough burst, immediately followed by a retrograde flow of liquid in the impedance tracing.

During reflux, the esophageal pH drops below 4 (acid reflux).

\* acid exposure provoked by coughing (13 sec).

\*\* volume exposure provoked by coughing (9 sec).

**Figure 3:** Flow chart displaying the different subgroups of patients identified by the study. From the patients without increased esophageal acid exposure, we identified a subgroup (n=9) that had a +SAP for reflux-cough.



**Table 1:** Work-up performed in all patients before the impedance-pH recording. Work-up showed no underlying etiological diagnosis for chronic cough, or in case of clinical suspected asthmatic cough, there was no response to a correct treatment trial of at least 4 weeks.

<b>History</b>
<b>Complete physical examination</b>
<p><b>Blood tests:</b></p> <ul style="list-style-type: none"> <li>- White blood differential cell counting</li> <li>- C-reactive protein</li> <li>- Erythrocyte sedimentation rate</li> <li>- Viral serology and anti-Mycoplasma antibodies</li> <li>- Immunoglobulins and IgG subclasses</li> <li>- Specific IgE for house dust mites, cat and dog, milk, egg, fish, peanut (RAST Phadebas)</li> </ul>
<p><b>Other tests:</b></p> <ul style="list-style-type: none"> <li>- Skin-prick testing for common allergens</li> <li>- Swab for <i>Bordetella pertussis</i> PCR and culture</li> <li>- Tuberculin test (Mantoux intradermal test)</li> <li>- Sweat testing (Gibson-Cook method)</li> <li>- Lung function testing (with peak-flow measurements) in children older than 3 years</li> <li>- Chest radiographs</li> </ul>

**Table 2:** Reflux characteristics in children with chronic unexplained cough during the total study period and in the recumbent position.

Results are expressed as median (range).

	Children with chronic cough	
	Total	Recumbent
Acid exposure (%)	2.3(0.0-15.6)	0.3(0-21.1)
Volume exposure (%)	0.8(0.0-8.0)	0.1(0.0-7.5)
Total nr of reflux events	30(5-116)	5(0-46)
Nr of acid reflux	18(0-49)	3(0-32)
Nr of weakly acidic reflux	12(3-78)	2(0-14)
Nr of weakly alkaline reflux	0(0-21)	0(0-0)
% of mixed reflux	33(3.4-82.6)	10(0-66.7)
Nr of episodes with high proximal extent	8(0-66)	1(0-25)

**Table 3:** Comparison of cough events indicated in the patient diary and objectively recorded with gastroesophageal manometry

	<b>Diary</b>	<b>Manometry</b>
Total nr of coughs	566	1424
Nr of nocturnal coughs (%)	179 (31.6)	414 (29)
Nr of coughs preceded by reflux (%)	51 (9)	145 (10.2)
Nr of patients with +SAP	6	10
+SAP acid reflux	4	1
+SAP non-acid reflux	2	6
+SAP acid + non-acid reflux	0	3

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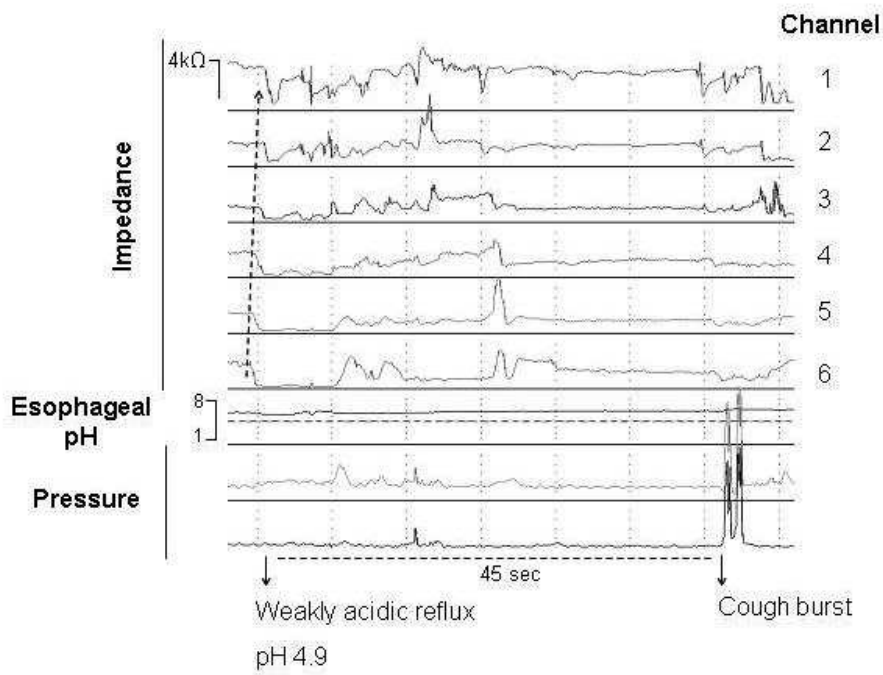


Figure 1

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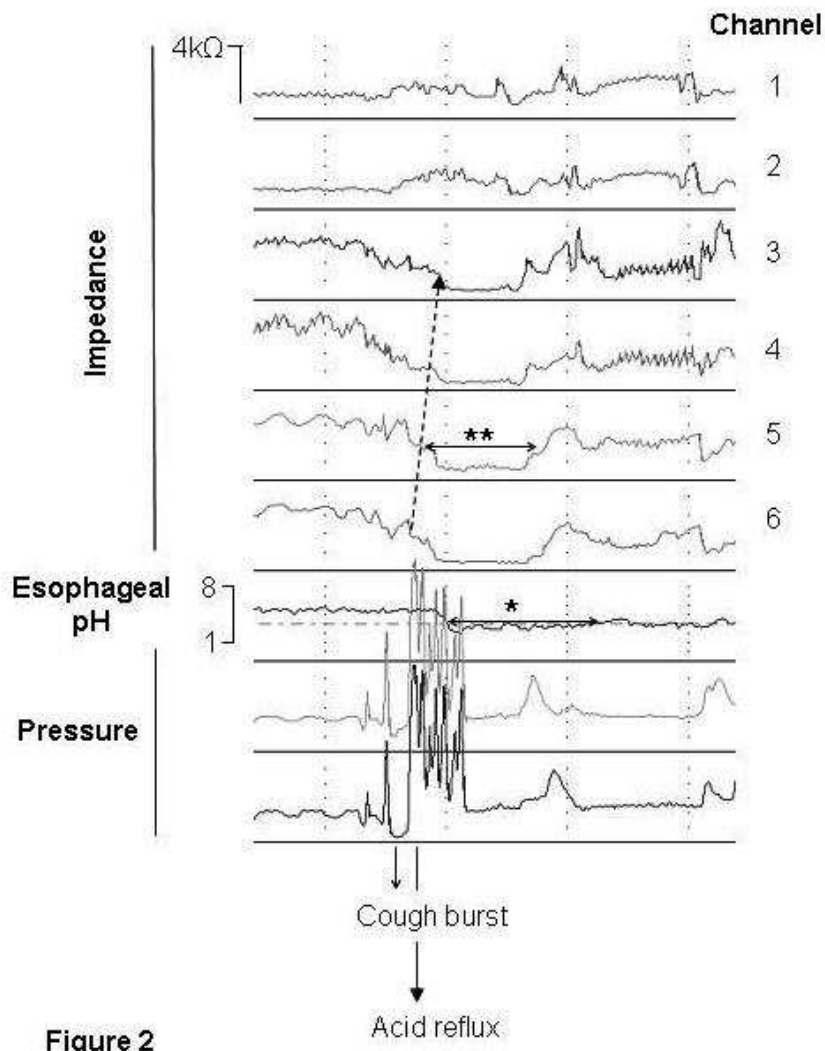


Figure 2

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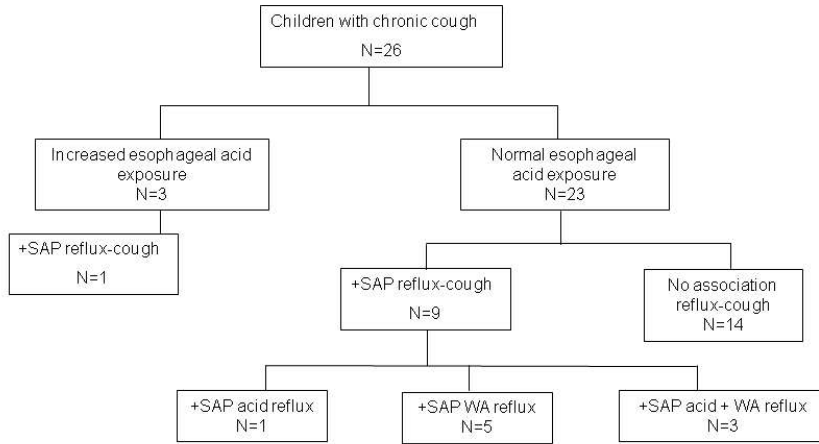


Figure 3

Figure 3  
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Review