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Pulmonary Acoustics and Esophageal pH Monitoring in Infantile Nocturnal Cough

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ABSTRACT

The aim of this study was to determine the feasibility of overnight computerized acoustic respiratory monitoring (ARM) conducted simultaneously with lower esophageal pH monitoring in infants with nighttime cough, and correlate findings with one-year clinical follow-up. Infants aged under 18 months with nocturnal cough of at least two months' duration were studied. Each child underwent 18–24 h of esophageal pH monitoring and concurrent 8–10 h nocturnal ARM. Anti-reflux therapy or inhaled corticosteroids (ICS) were prescribed according to the results. Telephone interviews with parents were conducted after one month and one year to determine respiratory symptoms and response to therapy. Eighteen infants were studied. Two had significant GER, and improved with anti-reflux therapy. ARM revealed continuous adventitious breath sounds (CABS)—wheezes, rhonchi, whistles—in 14 infants. Nine improved with ICS. Three others whose CABS had a temporal relation to short reflux "events" had incomplete response, and improved with added anti-reflux therapy. One year later, 10/14 subjects with CABS had symptoms compatible with airway hyperreactivity. ARM is a noninvasive objective method of evaluating nighttime cough in infants. In our group of infants with nocturnal cough, GER was infrequent. The most common acoustic finding was CABS, which may suggest airway hyperreactivity. Simultaneous esophageal pH monitoring may enable better discrimination between primary airway hyperreactivity and GER-associated symptoms.

INTRODUCTION

NIGHTTIME COUGH is a common and troublesome symptom in small children. Airway hyperreactivity and gastro-esophageal reflux (GER) are the most common etiologies,[1–3] whereas post-nasal drip, upper airway obstruction and tracheo-bronchomalacia are less common.

Objective measurements of airway and pulmonary function during sleep are difficult to perform, and require invasive instrumentation. Wheezing lung sounds have been shown to correlate with measurements of airway obstruction. Pasterkamp et al.[4] and Boughman et al.[5] have documented correlation between sever-

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ity of wheezing and airway obstruction indices such as FEV1.0 and mid-expiratory flows. Reliable measurements of cough and related phenomena during sleep in young children are difficult to make. A number of studies that investigated nocturnal cough in children used parental questionnaires, bedside monitoring by parents or medical personnel, or cough recording via microphone and tape recorder.[6,7] Subjective reporting as manifested in diary cards was found to be unreliable.[6] Recent improvements in computer and digital recording technology now make possible overnight recording and analysis of respiratory sounds, thus enabling objective documentation and quantification of the nocturnal acoustic events.[8]

The aim of this study was to determine the feasibility of performing overnight recording and analysis of lung sounds concurrent with lower esophageal pH monitoring (pH-metry) in infants with nighttime cough, and characterize the nocturnal acoustic phenomena, their temporal relation to GER, and their correlation with clinical outcome 1 year later.

MATERIALS AND METHODS

Patients

Infants referred to the Pediatric Pulmonary Clinic for evaluation of prolonged nocturnal cough were recruited. Rambam Medical Center's Ethics Review Board approved the study. The study procedures were explained to the parents and informed consent was obtained prior to enrollment.

Inclusion criteria. The inclusion criteria were as follows:

1. Age <18 months
2. Prolonged cough > two months
3. Cough predominantly or exclusively nocturnal and unresponsive to treatment by the pediatrician or family physician prior to referral

Exclusion criteria. The exclusion criteria were as follows:

1. Previous established diagnosis of specific respiratory disease other than the symptoms for which they were studied
2. Presence of another chronic illness
3. Any acute illness within 1 month of enrollment

Study procedures. In-hospital 18–24-h esophageal pH monitoring (pH-metry) and 8–10-h of nocturnal acoustic respiratory monitoring (ARM) were conducted concurrently, so that the acoustic and pH events could be time-matched.

Controls. Six infants, aged 2–12 months, with no respiratory symptoms had ARM studies performed overnight.

Esophageal pH monitoring

Esophageal pH monitoring was performed according to a standard protocol, with a flexible pH electrode placed in the distal one-third of the esophagus. Position of the pH electrode was verified with a chest x-ray. Recording of pH was performed continuously for 18–24 hours, while various events (e.g., feeding, sleep, crying) were being documented. The data was then analyzed using designated computer software (Digitrapper MKIII OS version 1.30 co 3, Synectics Medical Corp., Stockholm, Sweden).[9]

The categories of pH data analysis were as follows: *Significant GER* was defined as pH of <4.0 for more than 6% of the time.[9] In addition, we defined *GER events* as periods of pH of <4.0 that lasted at least 1 min and had a "physiological" pattern (i.e., rapid pH drop with gradual recovery), taking into account that even short episodes of acid reflux may induce cough.

ARM procedure

Recording and analysis of respiratory sounds were conducted according to standardized methods previously described.[8,10,11] Respiratory acoustic signals were measured with five phonopneumography piezoelectric contact sensors that were applied over the trachea (TR), right and left axillae (AR; AL) and posterior bases (BR; BL) of the lungs.[8] They were connected to a digital recorder (PulmoTrack® model 1010, Karmel Medical Acoustic Technologies Ltd., Yokneam Illit, Israel), where signal conditioning (amplification X3000; band pass filtration 80–4000 Hz at 24 dB/oct) was performed prior to analog-to-digital conversion (11,025 samples/sec/channel). The sensors and wires posed no restriction on the infants who moved freely during sleep. The system had been previously validated[8] and shown to detect no abnormal acoustic signals or artifacts in healthy subjects during sleep.

Wheezing and CABS were continuously measured at the five sensor positions simultaneously using all data received from the sensors, and were quantified in real time as percent of wheezing time to breathing time (Wheeze Rate, Wz%).[8] Wheeze and CABS detection was performed by an FFT-based algorithm that was previously verified and found to have sensitivity of 91% and specificity of 89% when compared to consensus assessment by a panel of experts.[12] Speech, crying and other vocal cord sounds were identified by the system and discarded.[8] In addition, auditory review of the data was also performed to verify the detection accuracy. Figure 1 shows a typical 30-sec ARM data recording from an infant with multiple CABS.

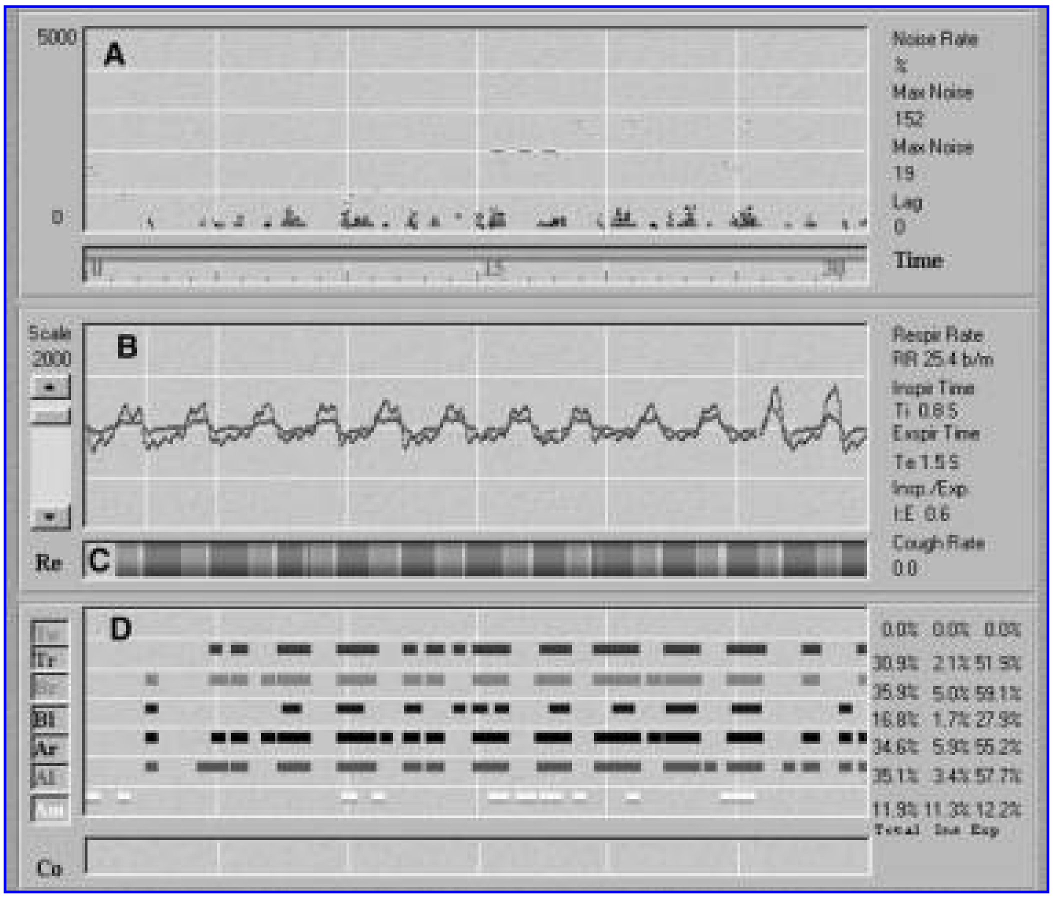

FIG. 1. Example of PulmoTrack display of a 30-sec data segment from a wheezing patient. The detected wheezes or CABS are shown continuously as a Wheezogram®, a plot of wheeze frequency versus time (*top panel*), along with the chest impedance signal (*middle panel*), and a bar below it showing inspiration (*lighter band*) and expiration (*darker band*). In addition, an Acoustic Vector™ continuously shows the timing of wheezes detected at the different sensor sites, while the white bars indicate ambient noise (*bottom panel*). The total (Tot.), inspiratory (In.), and expiratory (Ex.) wheeze rates are shown on the right of the bottom panel.

The automatic wheeze detection algorithm identifies CABS from 80 to 4800 Hz in the tracheal channel and 80 to 2400 Hz in the chest wall channels. These frequency ranges include low frequency wheezes and rhonchi as well as high pitch tracheal "whistles."[13]

The subjects were studied for one whole night, from the time they were put to sleep until they woke up in the morning (8–10 h), while esophageal pH monitoring was also being performed. Digital acoustic respiratory measurements were taken simultaneously from all five sensor sites. Coughs were detected automatically and verified by auditory review. CABS such as wheezes, whistles, and rhonchi were quantified and stored in real time by the PulmoTrack,® and off-line auditory review was conducted. Timing of low pH events, CABS, and coughs was recorded and matched.

Treatment and follow-up

Treatment was prescribed according to the following guidelines: Patients with "significant" GER were prescribed dietary manipulation (Enfamil AR), oral cisapride and cimetidine; patients with CABS were treated with inhaled budesonide 200 mcg twice daily. At follow-up 1 month later, response to therapy was evaluated by parental report and physical examination. Therapy was adjusted if necessary according to clinical judgment. Patients were then returned to the care of their pediatrician. A structured telephone interview was conducted 1 year later. Questions were asked about the following: (1) episodes of cough or wheeze in the past year, (2) present cough or wheeze, (3) therapy prescribed by family doctor, (4) current treatment, (5) response to bronchodilators and/or ICS, if taken, and (6) diagnosis of asthma or HRAD given by a physician. Patients were regarded as having reactive airways if they had repeated episodes of wheeze and shortness of breath responsive to inhaled bronchodilators or ICS, or if a diagnosis of HRAD was given by a physician.

RESULTS

Twenty-four infants aged 4–18 months were recruited. 18 patients completed the study. Reasons for disqualifications were inability to insert the esophageal pH probe (four patients), and parental refusal to participate after enrollment (two patients).

Patient demographics

There were five girls and 13 boys, whose ages ranged from 4 to 18 months (mean age 9.2 ± 3.7). Mean symptom duration was 4.1 ± 1.9 months (range 2–12 months). All failed dietary manipulation, positioning or therapeutic trials with either inhaled bronchodilators, cisapride or cough suppressants prescribed by their family doctor. None of the subjects received an adequate trial of ICS. All therapy had been stopped more than 2 weeks prior to the study.

Combined nocturnal esophageal pH monitoring and ARM

Only two patients were found to have *Significant GER*. The 16 other infants had esophageal pH of <4.0 for less than 4% of the time (normal), but 10 of them had brief *GER events* during the night with nine having CABS on ARM.

Nocturnal cough was demonstrated in three patients: one patient with *Significant GER* had coughing spells associated with reflux periods (Fig. 2), one with *GER events* and one with esophageal pH of >4.0 all night. However, the main acoustic finding was the presence of CABS (wheezes, rhonchi, whistles), illustrated in Figure 1, in 14 patients. Figure 3 shows an example of an all-night tracing of lower esophageal pH combined with ARM. A *Significant GER* episode occurred around 4 a.m. with simultaneous appearance of wheezing/CABS. Five of the 10 patients with *GER events* had episodes of CABS that demonstrated a temporal association between a *GER event* and acoustic findings (Fig. 3). In these patients, the *GER events* always preceded the acoustic phenomena. Overall, however, most CABS were not associated with esophageal pH changes (Fig. 4). Off-line auditory review of the acoustic data confirmed the findings of the

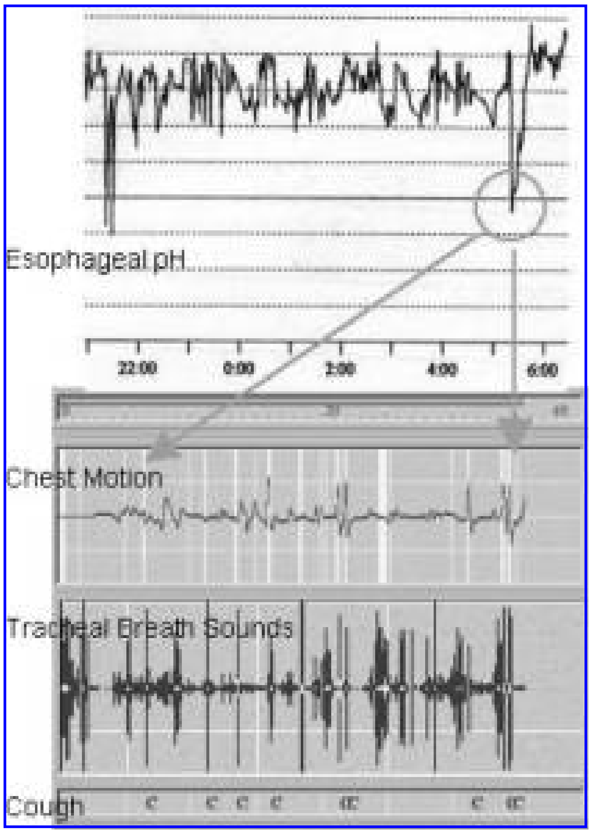

FIG. 2. Whole night trend of esophageal pH in a 12-month-old infant, demonstrating an episode of "significant" GER associated with repeated coughing. Lower panel shows 30 sec of acoustic tracings during the circled GER episode. There are numerous coughs, most of which are identified by the automatic "cough detector" algorithm, indicated by the "C"s at the bottom.

computerized analysis, as described above. No abnormal acoustic events were found in the ARM studies of the six control subjects.

Treatment

The two infants with *Significant GER* were prescribed anti-reflux therapy (cisapride, H_2 blockers, dietary manipulation) and reported significant improvement in their symptoms. Thirteen patients with CABS and two with cough, all without *Significant GER*, were treated with ICS. At 1 month, 11 reported improvement or resolution of symptoms. Of these, three subjects with CABS related to *GER events* reported a partial response, and improved further with addition of anti-reflux therapy. One patient reported no response and was diagnosed on bronchoscopy as tracheobronchomalacia.

Follow-up

One year after the study time, the two subjects with *Significant GER* were well and not receiving any therapy. Of the five with CABS related to *GER events*, two were well and three had intermittent wheezing and were diagnosed as having hyperreactive airways disease (HRAD). Of the other eight subjects with CABS, five had repeated episodes of wheezing and shortness of breath and were diagnosed as having HRAD, two had intermittent wheezing and were using inhaled bronchodilators and one had tracheobronchomalacia. Of the three remaining subjects (two with cough and one with normal nocturnal studies), two developed repeated episodes of wheezing and shortness of breath responsive to bronchodilators and were diag-

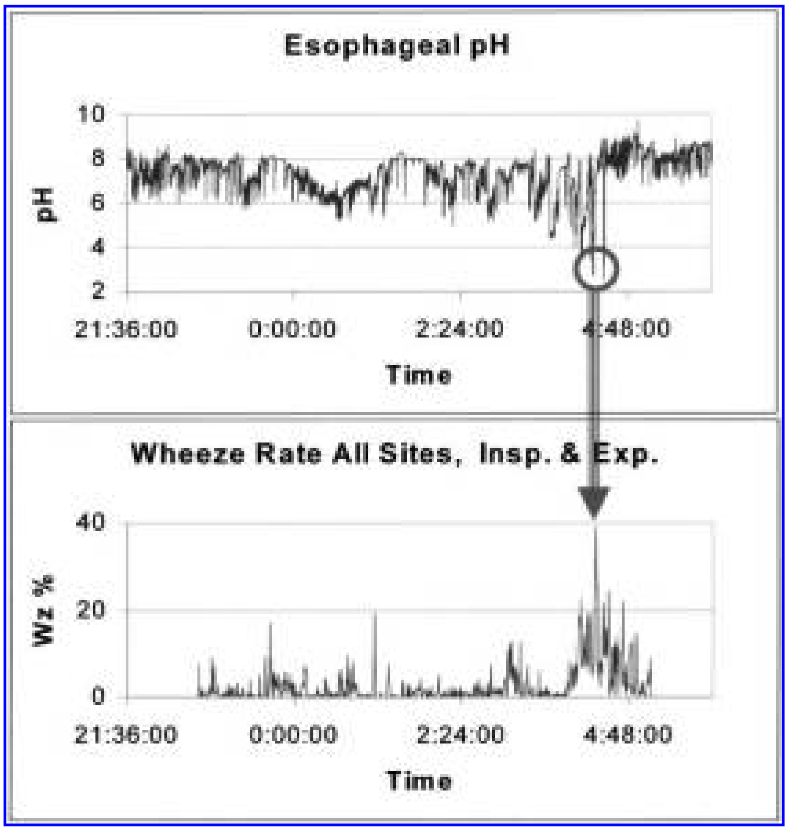

FIG. 3. Whole night trend tracings of esophageal pH and wheeze rate in a 9-month-old infant. Note appearance of marked wheezing in association with GER "events" starting around 4 am.

nosed as having HRAD and one was healthy. Overall, 15 patients were treated with ICS; of 13 CABS-positive subjects, nine had good resonse to ICS and all had HRAD at 1 year. Three subjects had partial response, of which two were well and one had HRAD at one year. One subject with no response had tracheomalacia. Of 14 patients with CABS, 10 had HRAD at 1 year, whereas of four infants without CABS one had HRAD. Four of the asthmatic subjects required ER visits and two were hospitalized due to exacerbation of wheezing and shortness of breath. They were all treated with asthma medications and responded well. The results are summarized as a block diagram in Figure 5.

DISCUSSION

Nighttime acoustic monitoring of lung sounds is feasible and provides objective acoustic information in infants with nocturnal respiratory complaints/symptoms. Concurrent pH-metry may help discriminate between HRAD and GER. In our group of young infants presenting with prolonged nocturnal cough, we found frequent abnormal acoustic events during sleep, mostly rhonchi and wheezes, while GER was infrequent.

GER is considered a major cause of respiratory symptoms in children[14–17] and has been documented in many studies. A GER incidence of 64% was reported in a group of infants with uncontrolled wheezing.[14] A study of infants with recurrent respiratory symptoms found that 25% had abnormal esophageal pH studies,[15] whereas in our group of infants with nocturnal cough, the incidence of GER was only 11.1%. This apparent discrepancy may be explained by the different study populations: our infants had cough vs. uncontrolled wheeze as their main symptom.

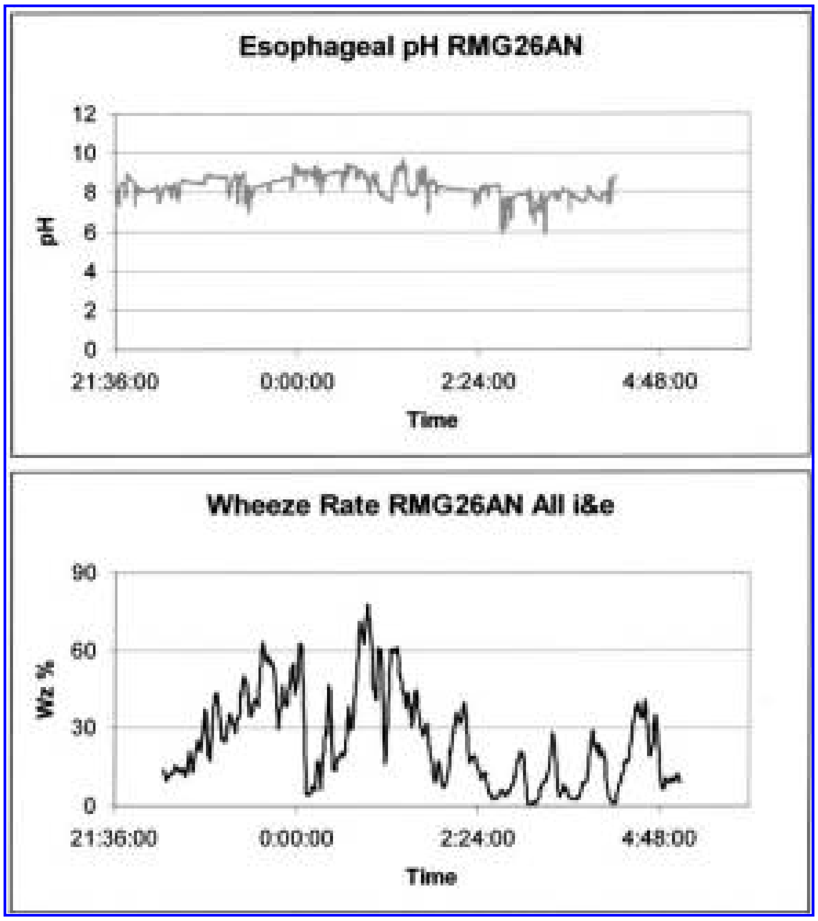

FIG. 4. Whole night trend of esophageal pH and wheeze rate in a 5-month-old infant with a history of nocturnal cough, revealing marked wheezing and normal esophageal pH.

Asthma and GER are both common medical conditions, and often coexist.[16,17] Furthermore, asthma and cough may precipitate GER. Thus, the co-existence of the two conditions does not imply a cause and effect relationship. There is still controversy regarding the role of GER in exacerbating asthma symptoms. A number of studies have shown a high incidence of GER in asthmatic patients.[18,19] Instillation of acid into the esophagus resulted in exacerbation of nocturnal asthma[20] and bronchoconstriction, and a recent study employing esophageal balloon and face mask pneumothachograph found significant increase in airway resistance during GER episodes.[21] Medical or surgical treatment of GER resulted in improvement of asthma control.[16,22,23] Conversely, other studies reported no association between GER and nocturnal asthma,[24,25] and treatment with omeprazole did not improve asthma symptoms.[26] A critical review of the literature[27] concluded that there is no conclusive evidence for the role of acid reflux in asthma exacerbation. These contrasting results might be due to differences in methodology and patient selection in the different studies. Many of the negative studies relied on daytime PFT measurements, as there is difficulty in assessing airway function during sleep. A recent review[28] still concludes that anti-reflux therapy produces improvement only in a small subset of asthmatic patients, and the Cochrane review[29] states that a subgroup of subjects might benefit from GER therapy, but it appears difficult to predict responders.

Our present study indicates that combining nocturnal acoustic monitoring of breath sounds and lower esophageal pH monitoring can help identify infants who are likely to benefit from anti-reflux therapy. GER in our patient population was uncommon. This was a small group and an uncontrolled study, therefore exact correlations cannot be made. However, infants in whom CABS were temporally associated with acid

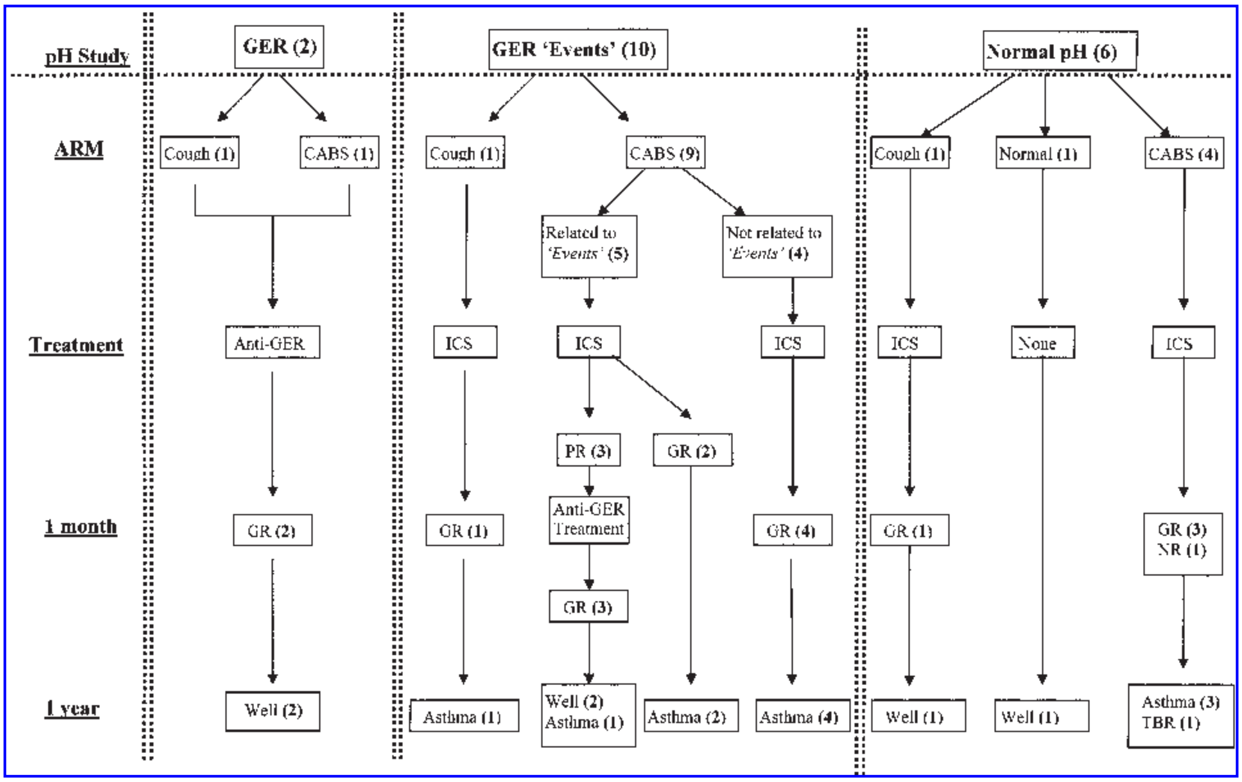

FIG. 5. Block diagram of the results. Bold numbers in parenthesis indicate number of subjects. GR, good response; PR, partial response; NR, no response; TBR, tracheobronchomalacia.

reflux seemed more likely to benefit from anti-reflux therapy. Therefore, similar to adults, in most pediatric patients GER and cough are not related. In individual cases, however, temporal studies of cough and GER may confirm this relationship, and these patients can benefit from specific anti-reflux therapy, as did these patients in our study.

In our group of infants with nocturnal cough, the most common nocturnal acoustic finding was CABS-rhonchi and wheezes, which were not associated with episodes of GER. This was not a controlled trial, response to ICS was judged by parents' reports, and cough is known to have a significant period effect.[30] Therefore, the improvement after 1 month cannot be definitely ascribed to ICS therapy. However, many of these infants developed overt wheezing and episodes of shortness of breath responsive to bronchodilators in the next year. The nature of the recorded acoustic sounds, with follow-up history of recurrent episodes and response to anti-asthmatic therapy could suggest that these patients had HRAD as the major cause for their cough. The Tucson cohort data[31] and other studies showed that there are a number of entities, which may overlap, that can cause repeated wheezing in young infants (transient wheezing, viral-associated wheezing, hyperreactive airways disease, asthma). Their exact definition and nomenclature are still the subject of research and debate. In our study we defined infants who had repeated episodes of wheezing and shortness of breath as having HRAD, since treatment for all these entities is with asthma medications. These infants may not be long term asthmatics and may actually belong to one of the other categories.

CONCLUSION

Nighttime acoustic monitoring of lung sounds is technically feasible and practical in infants with nocturnal respiratory complaints/symptoms, and concurrent pH-metry may help discriminate between HRAD and GER. Acoustic monitoring is noninvasive and provides objective, quantitative information on the status of infants' airways. In our group of infants with persistent nocturnal cough, most patients had abnormal acoustic findings (wheezes, rhonchi, whistles), which may be suggestive of underlying bronchial hyper-reactivity. Concurrent esophageal pH monitoring with ARM may enable better discrimination between HRAD and GER.

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