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# Adenosine Bronchial Provocation With Computerized Wheeze Detection in Young Infants With Prolonged Cough\*

## Correlation With Long-term Follow-up

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**Background:** Chronic cough in babies is often associated with bronchial hyperreactivity (BHR). The objective documentation of BHR in babies is difficult, and acoustic methods have been described (provocative concentration of a substance causing wheeze) for conducting bronchial provocation tests (BPTs). We conducted a study to evaluate automatic computerized wheeze detection (CWD) in determining BHR in young infants with prolonged cough, and its correlation with the subsequent development of wheezing.

**Methods:** Infants aged < 24 months with prolonged cough (*ie*, > 2 months) underwent acoustic BPTs with the response determined by CWD and auscultation by a physician. Telephone interviews with parents were conducted after 1 month and yearly for the next 3 years.

**Results:** A total of 28 infants who were 4 to 24 months old with prolonged cough were included in the study. Twenty of these infants (71.4%) had BHR as determined by a positive acoustic BPT result. In 11 of these 20 tests, the CWD occurred earlier, and in 9 tests it occurred at the same step as auscultation by a physician. Rhonchi or whistles often preceded wheezes. Seventeen of the 20 patients with BHR completed 3 years of follow-up. Of these, 14 had recurrent episodes of wheezing and shortness of breath, and 3 were well. Six of the eight adenosine-negative patients completed 3 years of follow-up and had no symptoms of BHR.

**Conclusions:** Acoustic BPT is a technically feasible test for the detection of BHR in young infants. CWD provides an earlier detection of wheeze than stethoscope auscultation. In our group of infants, a positive acoustic BPT result had high correlation with symptoms compatible with BHR over the next 3 years.  
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**Key words:** adenosine; bronchial provocation; chronic cough; computerized wheeze detection; infants

**Abbreviations:** AL = axilla left; AR = axilla right; BHR = bronchial hyperreactivity; BL = base left; BR = base right; BPT = bronchial provocation test; CWD = computerized wheeze detection; GER = gastroesophageal reflux; NPV = negative predictive value; PC<sub>20</sub> = provocative concentration of a substance causing a 20% fall in FEV<sub>1</sub>; PCwheeze = provocative concentration of a substance causing wheeze; PND = postnasal drip; PPV = positive predictive value; TR = trachea; Tw = tracheal whistles; Wz% = wheeze rate

Prolonged or recurrent cough is a common troublesome symptom in early childhood and a common reason for health-care visits.<sup>1,2</sup> Bronchial hyperreactivity (BHR), gastroesophageal reflux (GER), and post-

nasal drip (PND) are the common etiologies. In young children, cough (in contrast to wheeze) is common as a manifestation of BHR, which sometimes is also called *cough-variant asthma*.

BHR is an established measure of asthma control and response to treatment in children and adults. However, the significance of BHR in infancy and its

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relation to the future development of asthma is still under debate.<sup>3,4</sup> BHR is measured by bronchial provocation tests (BPTs), in which the provocative concentration of a substance causing a 20% fall in FEV<sub>1</sub> from baseline (PC<sub>20</sub>) is considered as the end point and as proof of BHR. Spirometry assessment of BHR in pre-school age children is difficult to achieve. Therefore, the detection of wheezing has been suggested as an alternative end point to BPT (*ie*, provocative concentration of a substance causing wheeze [PCwheeze]) in young children. Avital et al<sup>5</sup> conducted methacholine BPTs in 15 asthmatic children aged 6 to 15 years while recording breath sounds over the trachea (TR). In 11 of 15 patients, the methacholine concentration at which wheezing appeared was identical to that at which FEV<sub>1</sub> fell by  $\geq 20\%$ . They concluded that PCwheeze is reliable and in good correlation with PC<sub>20</sub>.<sup>5</sup> Wheeze detection can be accomplished by auscultation with a stethoscope or by automatic computerized lung sounds analysis.<sup>6</sup>

This study describes the use of automatic wheeze detection in BPT studies in young infants with prolonged cough and correlates the results with a 3-year clinical follow-up.

## MATERIALS AND METHODS

### Patients

Over a 6-month period, 30 consecutive children who had been referred to the Pediatric Pulmonary Clinic for the evaluation of prolonged cough were recruited into the study. The Ethics Review Board of Rambam Medical Center approved the study. The study procedures were explained to the parents, and informed consent was signed prior to enrollment into the study. A sample size of 26 patients was calculated to detect a difference of 0.5 SD between wheeze detection by auscultation and computerized wheeze detection (CWD) with a power of 80% ( $\alpha = 0.05$  [one-tailed test]).

### Inclusion Criteria

Children aged  $< 24$  months with prolonged cough for  $> 2$  months, who were referred for evaluation by the pediatrician or family physician, were recruited for the study.

### Exclusion Criteria

Eligible patients were excluded if they had an established diagnosis of respiratory disease, had a history of prematurity, had any chronic illness, had undergone treatment with inhaled steroids within 4 weeks of enrollment into the study, had received bronchodilators within 2 weeks of enrollment into the study, or had experienced any acute illness (of any type) within 4 weeks of enrollment into the study.

### Study Procedures

Acoustic BPTs with adenosine 5'-monophosphate (*ie*, determination of PCwheeze) were performed. Children with positive

BPT results were treated with inhaled budesonide (200  $\mu\text{g}$  twice daily) by puffer and spacer (AeroChamber; Trudell Medical International; London, ON, Canada) for 4 weeks. Follow-up by telephone interview occurred at 1 month, 1 year, 2 years, and 3 years after the start of treatment (see below). A comparison of adenosine concentration at positive response by CWD vs auscultation was performed using a paired *t* test following logarithmic transformation.

### Adenosine Bronchial Provocation

BPTs were performed by the inhalation of nebulized solutions of adenosine 5'-monophosphate (adenosine) in doubling doses.<sup>7</sup> Fresh solutions of adenosine (Sigma Chemical Company; St. Louis, MO) were prepared, starting at 0.39 mg/mL to a maximum of 200 mg/mL. Nebulized adenosine solutions (Up-Draft nebulizer; Hudson RCI; Temecula, CA) with a flow of 5 L/min O<sub>2</sub> were inhaled via facemask for 2 min, followed by a 30-s recording of lung sounds and analysis with CWD, and parallel auscultation with a stethoscope by a physician (over apices and bases bilaterally). The provocation dose was doubled at 5-min intervals until wheezes were detected (PCwheeze) or a concentration of 200 mg/mL was reached (negative result). Oxygen saturation and pulse were monitored throughout the procedure with a pulse oximeter (Biox 3700e; Datex-Ohmeda; Louisville, CO), with standby nebulized bronchodilator available to ensure safety. At the end of the test, a nebulized  $\beta_2$ -agonist was administered to all patients. The procedure was conducted in a special designated quiet room with the parents present to reassure the child.

### CWD

The recording and analysis of respiratory sounds were conducted according to standardized methods, as previously described.<sup>8,9</sup> Respiratory acoustic signals were recorded from five phonopneumography piezoelectric contact sensors (PPG Sensors; Karmel Medical Acoustic Technologies Ltd; Yokneam Illit, Israel) applied over the TR above the sternal notch, the axilla right (AR), and the axilla left (AL), and both posterior bases (*ie*, base right [BR] and base left [BL]) of the lungs. The sensors are coin-shaped piezoelectric elements with a linear  $\pm 3$ -decibel frequency response from 75 to 2000 Hz, a resonance at 2.7 kHz, a useable range that extends beyond 4 kHz, and a built-in passive ambient noise-rejection capability. The sensors were attached to the chest with adhesive foam pads that further reduced ambient noise interference and eliminated contact noise. All sensors were connected to the automatic wheeze detection device (PulmoTrack model 1010; Karmel Medical Acoustic Technologies Ltd) where signal conditioning (amplification,  $\times 3,000$ ; band pass filtration, 80 to 40,00 Hz at 24 decibels per octave) was performed prior to the analog-to-digital conversion (11,025 samples per second per channel). Two other signals were tracked. Ambient noise was recorded with an air-coupled microphone placed near the patient, and chest impedance was recorded for the measurement of breathing activity (*ie*, respiratory rate, phase, and amplitude).

Lung sounds were continuously recorded and analyzed for wheezes at the five sensor positions simultaneously using all data received from the sensors. Wheeze rate (Wz%) was quantified in real time as the percentage of wheezing time during breathing time in both inspiration and expiration ( $\text{Tw}/\text{TrOT} = \text{Wz\%}$  [where Tw is the breathing time with wheezing and TrOT is total breathing time]).<sup>10</sup> Wheeze detection was performed by a fast Fourier transform-based algorithm that was previously verified and found to have a sensitivity of 91% and a specificity of 89% in wheeze detection when compared to consensus assessment by a

panel of pulmonary experts who performed auscultation of the same respiratory sounds.<sup>11,12</sup> Speech, crying, and other vocal cord sounds were identified by the system and discarded.<sup>11,12</sup> In addition, an auditory audit of the data was performed to verify the detection accuracy. The detected wheezes are shown continuously (Wheezogram; Karmel Medical Acoustic Technologies Ltd; Yokneam Illit, Israel) as a plot of wheeze frequency vs time (Fig 1, *top*), along with the chest impedance signal (Fig 1, *middle*). In addition, a chart (Acoustic Vector; Karmel Medical Acoustic Technologies Ltd) continuously shows the timing of wheezes that are detected at the different sensor sites (Fig 1, *bottom*). The automatic wheeze detection algorithm identified continuous adventitious breath sounds in frequency ranges of 80 to 4,800 Hz in the tracheal channel and 80 to 2400 Hz in the chest wall channels. These frequency ranges include low-frequency wheezes and rhonchi<sup>13</sup> as well as high-pitched Tw.<sup>14</sup> As healthy children have a Wz% of < 5% with the above-described technique,<sup>12</sup> a Wz% of > 10% at any of the channels was chosen as the positive end point of BPTs by CWD.

### Follow-up

Parents were contacted yearly for 3 years, and details were gathered regarding respiratory symptoms over the past year. The interview was conducted by the same investigator (LB) with the same caretaker (usually, the mother) at all interviews. The

interviewer asked the following questions, based on the International Study of Asthma and Allergies in Childhood questionnaire<sup>15</sup>: "Since the last interview, has your child: 1. Suffered two or more episodes of wheezing and/or shortness of breath, 2. Received bronchodilator inhalers or nebulizers with improvement in wheezing and shortness of breath, 3. Required emergency department visits or hospitalization for wheezing and shortness of breath?"<sup>16</sup>

### Statistical Analysis

A comparison between the mean adenosine concentration for CWD vs auscultation was performed using a paired *t* test after logarithmic transformation. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of positive or negative BPT results, and the future development of wheezing after > 3 years of follow-up were calculated.

## RESULTS

### Patient Demographics

Thirty infants and children (20 male patients and 10 female patients), aged 4 to 24 months (mean

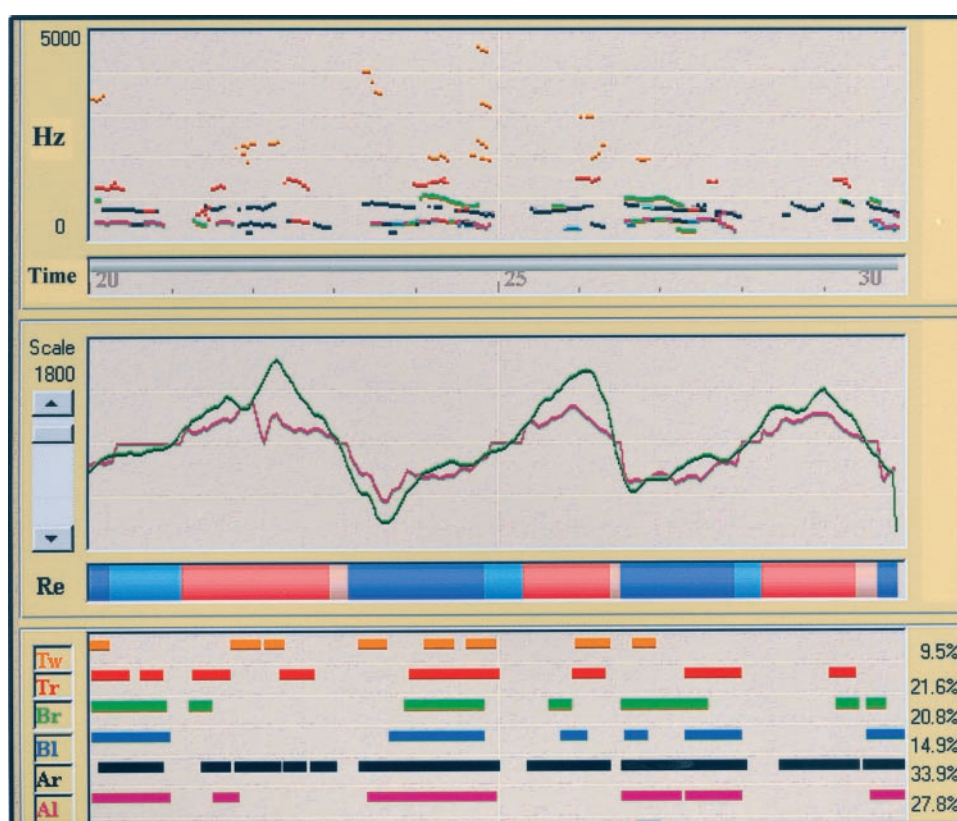


FIGURE 1. The spectral display of wheezes detected with the automatic wheeze detection device (PulmoTrack) in an infant with positive BPT results. The display (the Wheezogram) in the *top* panel displays the wheezes by their frequency (y-axis) and duration (x-axis). The wheezes are color-coded by their pick-up site (*bottom*). The *middle* panel displays the plethysmographic respiratory signal, from which inspiration (blue) and expiration (red) are displayed in the bar below it. The *bottom* panel displays the different wheezes detected by their location and duration. AL, pink; AR, black; BL, blue; BR, green; TR, red; Tw, orange. Wz% values for each channel are displayed on the right.



[ $\pm$  SD] age,  $8.3 \pm 4.2$  months) were recruited. Twenty-eight of them (19 male patients and 9 female patients) completed the acoustic BPT study. In two patients, BPTs could not be performed because of excessive crying. All infants failed therapeutic trials by their family doctor, which included dietary manipulation, positioning, and therapy with cisapride, decongestants, or cough suppressants. Although inhaled corticosteroids were prescribed to several of the patients, these were not administered. Exposure to cigarette smoke was present in 11 of the patients (39%), and family atopy was present in 10 (36%). The proportion of these was similar in the BPT-positive and BPT-negative groups. All therapy had been stopped for at least 2 weeks prior to the study.

### Bronchial Provocation With CWD

Twenty patients (71.4%) had a positive adenosine BPT result, as determined by both CWD and auscultation. An example of a positive adenosine BPT result with CWD is shown in Figures 1 and 2 (the latter being a block diagram of the Wz%). There was no consistency as to the sites where wheezing was detected first. Figure 2 shows marked wheezing that appeared after the 12.5 mg/mL dose of adenosine, with the highest wheezing detected over the TR. The mean adenosine concentration for response with CWD was  $15.6 \pm 25.2$  mg/mL (range, 0.78 to 100 mg/mL), and with auscultation it was  $64.7 \pm 68.1$  mg/mL (range, 3.12 to 200 mg/mL;  $p = 0.0002$ ). In 17 of these patients, positive BPT results were

detected at an adenosine concentration of  $\leq 25$  mg/mL by CWD, compared to the positive BPT results detected at the same concentration in 9 patients by stethoscope. In 11 patients, the response detected by CWD was positive at one to two steps lower concentration than that with auscultation (Fig 3), and in 9 patients the positive response was detected at the same step by both methods. In most cases, rhonchi or whistles preceded the wheezes during response. No adverse events were noted during the BPTs. Cough, wheeze, and tachypnea were not considered to be adverse events, as they are part of the positive response to adenosine, and the condition of all patients improved back to baseline levels following the routine administration of an inhaled bronchodilator at the end of the BPT.

### Follow-up

Twenty-seven patients were available for follow-up at 1 year. At 3 years, 17 of 20 BPT-positive and 6 of 8 BPT-negative patients were available (total, 23 of 28 patients). The results of follow-up in relation to the initial BPT results are shown in Table 1. One of the BPT-positive patients was found to have tracheomalacia. Of the eight BPT-negative patients, four were well at 1 month, one had GER, one had prolonged post-respiratory syncytial virus cough, and two had PND and hypertrophied adenoids. At 3 years, all six available BPT-negative patients were well, including the patient in whom hyperreactive airways had been diagnosed earlier.

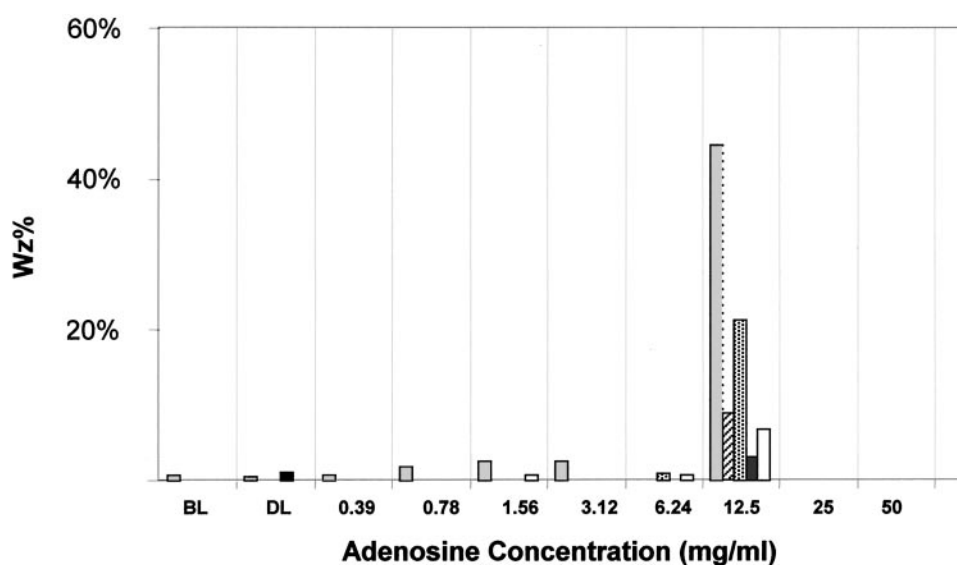


FIGURE 2. Depiction of an adenosine BPT with a CWD in a 1-year-old infant. Wz% values (see Materials and Methods section) at the different pick-up sites are shown with the corresponding adenosine concentrations. Note the marked rise in Wz% values at the 25 mg/mL step, signifying a positive PCwheeze at that point. Pickup sites are as follows: TR, gray bar; BR, diagonal bar; BL, dotted bar; AL, black bar; AR, white bar.

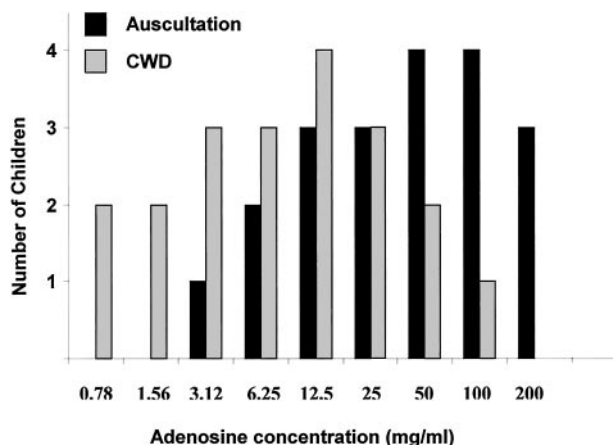


FIGURE 3. Comparison of PCwheeze by CWD and by stethoscope auscultation in 20 infants with positive PCwheeze results. Note the shift to the left (*ie*, for earlier detection) in favor of the CWD.

An analysis of these results showed that a positive BPT result at a young age had a sensitivity of 100% for the development of recurrent wheeze within the next 3 years, but the specificity was only 66.6%. The PPV was 82.3%, and the NPV was 100%.

## DISCUSSION

This study demonstrates the feasibility of conducting BPTs with a CWD in young infants. In our group of young infants with prolonged cough, we found a high correlation of a positive adenosine BPT result with recurrent episodes of wheeze and shortness of breath over the next 3 years.

The assessment of bronchial reactivity is an important tool for the assessment of children with recurrent or persistent respiratory symptoms. In young children who are unable to perform spirometry, the

detection of wheeze over the TR (*ie*, PCwheeze) has been described as an acceptable end point for BPTs, which is in good correlation with PC<sub>20</sub>.<sup>17</sup> In our study, the CWD was able to detect wheezes one or two steps earlier than with auscultation, thus limiting exposure to the provocative agent. This may be due to the higher sensitivity of the sensors, the high amplification, the improved signal-to-noise ratio, and the inability to detect high-pitched wheezes (*ie*, whistles) with the stethoscope (filtered out). Springer et al<sup>17</sup> in their study of methacholine BPTs and PCwheeze by auscultation in young asthmatic children reported that 15% of their patients did not wheeze at the end point, but had either oxygen desaturation or tachypnea. Our study was conducted in much younger patients (mean age, 9.8 months vs 4.8 years, respectively), and we decided for safety reasons to nebulize adenosine with oxygen, so that desaturation was averted, and we could not detect and compare these end points to ours.

A number of studies addressed the issue of BHR in young children. Tepper and Steffan<sup>3</sup> found positive reactivity to methacholine in healthy infants, measuring maximal flow from functional residual capacity. Lesouef et al<sup>4</sup> found a similar response to inhaled histamine. They concluded that BHR is present in most healthy infants, and that this reactivity declines with age.<sup>18</sup> Weist et al<sup>19</sup> found that, compared to healthy adults, healthy infants have heightened airway reactivity and that there is a smaller effect of deep inspiration on airway responsiveness. In contrast, Saga et al,<sup>20</sup> in a 10-year follow-up study of babies with wheeze whose mean age was 2.3 years, performed methacholine BPTs in which the end point was a fall in transcutaneous PO<sub>2</sub>. They reported that positive BPT results had a high association with the later development of asthma. Nishimura et al<sup>21</sup> performed methacholine BPTs in a large group of children who were aged 1 to 13 years, and observed them for ≥ 10 years. They found that children with chronic cough developed chronic asthma, with young children being more prone to develop asthma than older ones. They further concluded that children with chronic cough and BHR are more likely to develop asthma than those with negative BPT results. These findings are in agreement with our present results. The discrepancies in the findings of these various studies could be ascribed to the different methods used to measure airway response. It is still not fully established how the different parameters measured by these techniques compare, and whether a positive BPT determined by maximal flow from functional residual capacity (which requires sedation) is the same as that by arterial oxygen saturation, transcutaneous PO<sub>2</sub>, auscultation, or CWD. Also, the different provocative agents used might act through different path-

**Table 1—Results of 3-Year Follow-up by Clinical Outcome in BPT-Positive and BPT-Negative Infants\***

Variables	1 mo	1 yr	2 yr	3 yr
BPT-positive patients				
Asthma	19	17	16	14
Tracheomalacia	1	1		
Well		1	2	3
Total	20	19	18	17
BPT-negative				
Asthma		1		
Post-RSV	1			
PND	2			
GER	1			
Well	4	7	6	6
Total	8	8	6	6

\*RSV = respiratory syncytial virus.

ways. Adenosine is regarded as more "asthma-specific,"<sup>12</sup> whereas methacholine and histamine are "nonspecific" airway stimulators.

Although the family physician and parents were not formally informed of the results of the BPT, parents had to be present during BPTs and in some cases could see the response to adenosine. Also, patients with adenosine-positive BPT results were prescribed inhaled steroids. These two factors could potentially influence the results of short-term follow-up. However, it was explained to parents that this result does not necessarily have any long-term implication. Therefore, we think that the results of our 3-year follow-up are unlikely to be affected by these factors. Our study was also not designed to assess the possible contribution of exposure to cigarette smoke, family atopy, or other environmental factors on the development of airways hyperreactivity.

A difficulty related to this study exists in the definition of *asthma* in young patients. Data from the Tucson cohort study<sup>22</sup> and other studies have shown that there are a number of other entities, which may overlap, that can cause repeated wheezing in young infants, such as transient wheezing or viral-associated wheezing. Their exact definition and nomenclature are still the subjects of research and debate. In our study, positive BPT results were associated with repeated episodes of wheezing and shortness of breath. These infants may not have chronic asthma and may actually belong to one of the other categories. We did not perform repeat BPTs in our patients, and our follow-up was limited to 3 years. However, the high sensitivity of positive BPT results for having recurrent wheeze in the next 3 years is in line with the observations by Saga et al<sup>20</sup> and Nishimura et al.<sup>21</sup> Importantly, our study also shows a very high NPV for negative BPT results for developing wheezing over the next 3 years.

## CONCLUSIONS

The acoustic BPT is a technically feasible test for the detection of BHR in young infants. CWD often provided earlier detection of wheeze than stethoscope auscultation. In our group of infants with prolonged cough, a positive acoustic BPT result had a high PPV, while a negative BPT result had an even stronger NPV, for recurrent episodes of wheeze and shortness of breath within the next 3 years.

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