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Timing and Nature of Wheezing at the Endpoint of a Bronchial Challenge in Preschool Children

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Summary. Bronchial reactivity to inhaled agents in preschool children can be undertaken by auscultating the lungs to detect wheezing, but there is a lack of information on when wheeze first appears at the endpoint of the challenge and on the acoustic characteristics of the wheeze. We recorded breath sounds continuously during tidal breathing inhalation challenges with adenosine 5′-monophosphate, using sensors attached over each upper lobe in 80 preschool children. In 35 children, the challenge was considered positive by a pediatrician who determined the endpoint by detecting wheeze on auscultation after an inhalation. Using acoustic analysis, we determined that the first wheeze appeared during the 2-min period of nebulization in 31% of positive challenges; it was unilateral in 37%, and only inspiratory in 46%. A running window of 6 sec was used to detect at least two wheezes without reference to phase of breathing, and this index had a sensitivity of 97.6% and specificity of 99.7% for determining the endpoint of a challenge. Detecting wheeze acoustically adds safety to the technique by enabling the challenge to be stopped earlier, while the lack of a need to document the phase of breathing simplifies the technique. **Pediatr Pulmonol. 2005; 39:262–267.** © 2005 Wiley-Liss, Inc.

Key words: preschool children; inhalation provocation tests; characteristics of wheezing; sound spectrography.

INTRODUCTION

The assessment of bronchial reactivity to inhaled agents such as methacholine and adenosine 5′-monophosphate (AMP) in preschool children can be undertaken simply and with minimal equipment by auscultating the lungs and listening for the appearance of wheezing.[1–3] We previously showed that wheeze alone or in combination with mild hypoxia or tachypnea appeared in 81% of 146 young asthmatic children undergoing this type of challenge, which we have termed the ''PCwheeze'' technique.[4] Other investigators reported similar incidence of wheezing in such challenges.[5,6] Using an electronic stethoscope to auscultate the lungs during the PCwheeze challenge, we compared the performance of a pediatrician experienced in this type of test with the objective measurement of wheeze by acoustic analysis of recorded breath sounds.[7] We found that with an acoustically measured wheeze rate (total duration of wheeze/total duration of breath) of 10%, the detection of wheezing by the pediatrician had a sensitivity of 100% and a specificity of 91%. In this study, it was apparent that wheeze could be unilateral (in 9 of 22 children) and was sometimes only present during inspiration. In this study, auscultation and acoustic recording were performed by listening for a few breaths over each lung at the end of nebulization, in conformity with the normal way of conducting a challenge.

In our previous studies[1–4,7] and as far as we can determine in all similar studies in the literature,[8–10] no attempt was made to record breath sounds continuously during and after the period of nebulization. Thus there appear to have been no studies using acoustic recording to address the important questions of when wheeze first appears at the endpoint of a challenge, or of what the essential features are in an acoustic recording which define a positive challenge. This information is critical if objective acoustic measurements of wheeze are to be used to determine the endpoint of a challenge, and even more so if the lengthy and often tedious challenge as currently performed is to be speeded up by using fewer steps with higher concentrations of challenge agent. The present study was designed to determine whether wheezing occurred during nebulization, its acoustic characteristics, and to what extent it was intermittent.

MATERIALS AND METHODS

The patients were chiefly preschool children with unexplained cough referred for a bronchial provocation

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challenge because of a possible diagnosis of asthma. Bronchial challenges were performed using 2 min of nebulization during tidal breathing with auscultation replacing lung function measurement, as described previously.[1,3,4,7,11] For the present study, the diaphragm of an acoustic sensor (see below) was attached with adhesive tape over each upper lobe anteriorly, and an inductance belt (Respitrace, Ambulatory Monitoring, Inc., Ardsley, NY) was placed around the chest to record the phase of respiration. The study was approved by our institutional Ethics Review Board. Doubling concentrations of adenosine 5′-monophosphate (AMP) were administered, beginning with 0.39 mg/ml and increasing every 5 min until the endpoint or maximal concentration (200 mg/ml) was reached. Chest auscultation of each upper lobe was performed by an experienced pediatrician, using a regular stethoscope for at least 5 breaths between 15–60 sec after the end of each period of nebulization. Respiratory rate and oxygen saturation measured by pulse oximetry were recorded. The pediatrician determined that the challenge was positive if definite wheezing for at least 5 breaths, not necessarily consecutive, was heard over either or both upper lobes, if there was a fall in oxygen saturation of $\geq$5% from baseline, or an increase in respiratory rate of $\geq$50% from baseline. If he felt unsure about the signs, he continued with the next dose of challenge agent, provided there was no desaturation or tachypnea as defined above.

Breath sounds over both lungs were recorded continuously throughout the bronchial challenge, using sensors prepared by inserting a sensitive microphone (Sennheiser ME104-ANT, Wedemarg, Germany) into the tubing 1 cm from the metal portion of a standard bell and diaphragm stethoscope (Yamasu Double Stethoscope, Kezmedico Co. Ltd., Saitama, Japan). The signals from each sensor were preamplified (SM PRO Audio PR8, Melbourne, Australia), fed into a computer (Steinberg Nuendo Audiolink 96, Hamburg, Germany), digitized at a rate of 44.1 KHz, and stored for analysis. We tested our stethoscope-microphone systems by applying sinusoidal signals to a loudspeaker between 50–5,000 Hz and measuring the outputs from the microphones with the computer. The responses of the sensors showed a decline of about 10 dB between 50–1,000 Hz, followed by a return to baseline until a further progressive decline began at approximately 1,500 Hz. The signal from the Respitrace was used to vary the pitch of an oscillator so that it could also be fed into the computer with the acoustic signals. The breath sounds were analyzed offline in the frequency time domain (Cool Edit Pro, version 2.0, Syntrillium Software Corp., Phoenix, AZ) and scanned manually by the investigators for the presence of wheeze, defined in accordance with the CORSA report[12–14] as musical monophonic or polyphonic sounds with a duration of at least 100 msec within the frequency range of 150–800 Hz (Fig. 1). The duration of wheeze divided by the duration of the breath (Tw/Ttot) was calculated for breaths with wheeze as originally described by Baughman and Louden.[15] The complete acoustic record was analyzed for all challenge steps, with wheeze reported by the pediatrician from observations after each period of nebulization or heard by a technician listening continuously to the real-time breath sound recording throughout the challenge. The site, timing, and intensity were determined for the first breath with wheeze, the first two consecutive breaths with wheeze, the first three consecutive breaths with wheeze, and the first breaths with both inspiratory and expiratory wheeze.

RESULTS

Positive and Negative Challenges

In total, 80 children entered the study, but 2 were wheezing before the challenge could start and were not challenged, and 2 children had a positive challenge but did not wheeze. In 1 of these 2, there was a fall in saturation of 7.2%, and in the other a fall in saturation of 8.2%. These 4 children were excluded from further analysis. Of the 76 remaining children, 35 had a positive challenge in which the pediatrician noted wheezing at the endpoint.

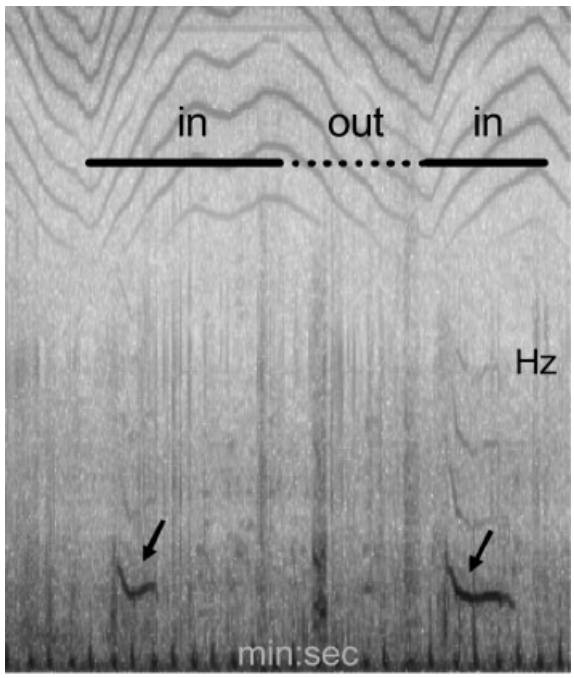

Fig. 1. Fast Fourier transformation of sonogram with signal derived from Respitrace belt superimposed above to show phase of respiration. Oscillator controlled by Respitrace generated a signal with many harmonics. Acoustic record shows monophonic inspiratory wheezes (arrows), with faint harmonics on two consecutive breaths. Scale on vertical axis is in Hz, and on horizontal axis in minutes and seconds.

These children comprised 27 boys and 8 girls with a mean age of 4.9 years, of whom 10 were less than 4 years of age and 8 were 6 years of age or older. In 4 children, the endpoint occurred at the highest concentration of AMP (200 mg/ml), in 8 it occurred after 100 mg/ml, in 6 after 50 mg/ml, and in the remaining 17 children at a concentration of 25 mg/ml or less. Oxygen saturation at the endpoint fell in 27 children (77%), with a fall of less than 7% in all but 3 children and of less than 10% in all but 1 child, who had a fall of 11%. None of these children had a fall in oxygen saturation >5% at the concentration preceding the endpoint concentration. Forty-one children with a negative challenge completed the final dose (200 mg/ml) of AMP without any wheeze, desaturation, or tachypnea being detected by the pediatrician. In one of these children, the acoustic analysis detected brief, unilateral inspiratory wheeze at an AMP concentration of 50 mg/ml which was not detected by the pediatrician, and the challenge continued without any further wheeze clinically and acoustically until the 200 mg/ml dose had been completed. The children with negative challenges comprised 31 boys and 10 girls with a mean age of 4.5 years, of whom 15 were less than 4 years of age and 8 were 6 years of age or older.

Acoustic Findings at the Endpoint of Positive Challenges

The results of the acoustic analysis of wheeze at the endpoint in the 35 children with a positive challenge are summarized in Table 1. The first wheeze was detected acoustically during the 2-min period of nebulization in 11 (31%), and in 5 children (14%) this was during the first minute of nebulization. In 13 children (37%), the first wheeze was unilateral, and in 16 children (46%) it was only inspiratory. The first wheeze was monophonic in nature in 19 children (54%), and in 10 children (29%) it was both monophonic and inspiratory in nature. In 34 of 35 children (97%), the Tw/Tot of the first wheeze was >10%, and in 27 (77%) it was greater than 15%. In 34 children (97%), there were at least two consecutive breaths with wheeze recorded at the endpoint concentration, but 3 consecutive breaths with wheeze were recorded in only 23 (66%), and the presence of any breath in which wheeze occurred during both inspiration and expiration was recorded in only 23 (66%). Wheezing was detected acoustically between 20–60 sec after the end of nebulization in all 35 children (100%), even when the first wheeze had occurred during nebulization, and was also detected more than 60 sec after the end of nebulization in 29 (91%). Because a bronchodilator was administered once the pediatrician determined that the endpoint had been reached, we were unable to determine how long wheezing would have persisted in the absence of treatment. The pattern with 2 or 3 consecutive breaths with wheeze was similar to that found with the first breath as far as the timing and unilateral and monophonic nature were concerned. Isolated inspiratory wheeze was less common, with 2 and 3 consecutive breaths compared with the first wheeze (18% and 9%; $P = 0.02$ and 0.01, respectively, by chi-square analysis).

TABLE 1—Changes and Characteristics of Wheeze at Endpoint Stage

	Number	%
Total	35.0	100
Time to first wheeze after start of nebulization		
<1 min	5	14
1–2 min	6	17
2–3 min	23	66
>3 min	1	3
Site of first wheeze		
Right	7	20
Left	6	17
Both	22	63
Timing of first wheeze		
Inspiratory	16	46
Expiratory	9	26
Both	7	20
Right and left different	3	9
Characteristic of first wheeze		
Monophonic	19	54
Polyphonic	6	17
Right and left different	10	29
Maximum Tw/Ttot		
>10%	34	97
>15%	27	77
>20%	20	57
>30%	12	34
At least 2 consecutive wheezy breaths	34	97
At least 3 consecutive wheezy breaths	23	66
Two wheezy breaths in any 6-sec window	35	100
Change in saturation		
Any fall	27	77
>5% fall	12	34
>10% fall	1	3
Change in respiratory rate		
>10% rise	27	77
>20% rise	16	46
>50% rise	1	3

Acoustic Findings With Wheeze at Stages Other Than the Endpoint

In 10 children, wheeze was detected acoustically in a total of 13 stages of the challenges other than that at which the pediatrician decided the endpoint had occurred. In 3 children, wheeze was detected in 2 stages in addition to the endpoint stage. In 10 of 13 stages, the pediatrician also recorded wheeze, but in 9 he was not convinced that this was enough to call the endpoint and he continued with the challenge, while in one child the additional stage was administered in error after the pediatrician had already decided that the previous stage was the endpoint. In this extra stage, there was both clinical and acoustic wheeze

but no desaturation or other adverse effects. In the other 3 stages, the technician detected wheeze which was not heard by the pediatrician, and consequently he did not designate it as the endpoint stage. In one of these children, the challenge continued to the highest concentration without any further wheeze and was considered negative. The sound recordings from all 10 stages in which the pediatrician noted wheeze but did not consider it sufficient to be the endpoint were reviewed offline by all 3 authors who were experienced in the technique. This panel concluded that in 6 children, wheeze was sufficient to determine the endpoint at the earlier stage, while in 4 children the offline review decided that these earlier stages were indeed negative. An analysis of all 13 stages with wheeze detected acoustically, which were not originally considered by the pediatrician to be the endpoint stage, showed a very similar pattern to the endpoint stages as far as the timing and nature of the wheeze were concerned.

Endpoint According to Acoustic Findings

From the analysis of the acoustic findings of all 48 stages with wheeze (35 endpoint stages plus the additional 13 stages not considered to be the endpoint originally), it was apparent that the large majority were characterized by at least 2 consecutive breaths, with a Tw/Ttot of at least 10% and no particular preference with respect to site of wheeze, breath phase, or tonal characteristic. The mean duration of the first wheezy breath in these positive stages was 2.27 sec, so that at least 2 breaths could reasonably be expected to occur in any 6-sec period of observation. A running window of 6 sec was used to scan the complete records of all stages with acoustically documented wheeze to determine whether there were at least 2 individual wheezes, without any reference to site or breath phase, in any 6-sec period with a Tw/Ttot of at least 10%. Using these criteria, 34 of 35 stages (97%) at which the pediatrician originally decided the endpoint had been reached were positive, as well as the extra stage performed in error after the endpoint and all 6 other stages which were considered to meet endpoint criteria after the offline review of the sonograms. There were 2 false-positive results: one in the child who completed all stages of the challenge without reaching the endpoint, and the other in another child at 3 stages before the endpoint was reached. Using the presence of endpoint wheeze reported by the pediatrician and including the offline positive results as ''truth'' and taking into account all stages without wheeze in both the positive (207) and negative (409) challenges, the sensitivity of this 6-sec scan was 97.6%, and its specificity was 99.7%.

Central vs. Two-Lung Acoustic Recording

In order to determine whether it was necessary to record wheeze from both lungs, an additional sensor was attached over the manubrium sterni in 10 children from whom wheeze was detected during the 12 stages. The wheeze rate (Tw/Ttot) of wheeze for the first breath recorded from the central sensor was expressed as a percentage of the wheeze rate from the lung sensor with the highest wheeze rate. As seen in Figure 2, the central sensor failed to detect any wheeze in 2 instances, and in 3 instances the central sensor Tw/Ttot was less than 70% of the value from the lung sensor. When the Tw/Ttot from two consecutive breaths with wheeze were compared, the value from the central sensor was less than 70% of that of the lung sensor in 7 of 12 stages.

DISCUSSION

This study showed that in a positive bronchial challenge with AMP in a young child using the 2-min tidal breathing method, the first wheeze occurred during nebulization in 31% of subjects, it was unilateral in 37% of children, it was only inspiratory in 46%, and it was monophonic in 54%. While the breath phase and acoustic characteristics of the wheeze are therefore unimportant, it is essential to record from both lungs, since the wheeze was often unilateral, and a single central sensor picked up less intense wheeze or missed the wheeze compared with the lung sensor in a substantial proportion of children. The acoustic detection of 2 wheezes within any 6-sec period having a Tw/Ttot greater than 10% had very high sensitivity and specificity for detecting a positive response, as judged clinically by an experienced pediatrician auscultating the lungs after nebulization. Although all children whose wheeze began

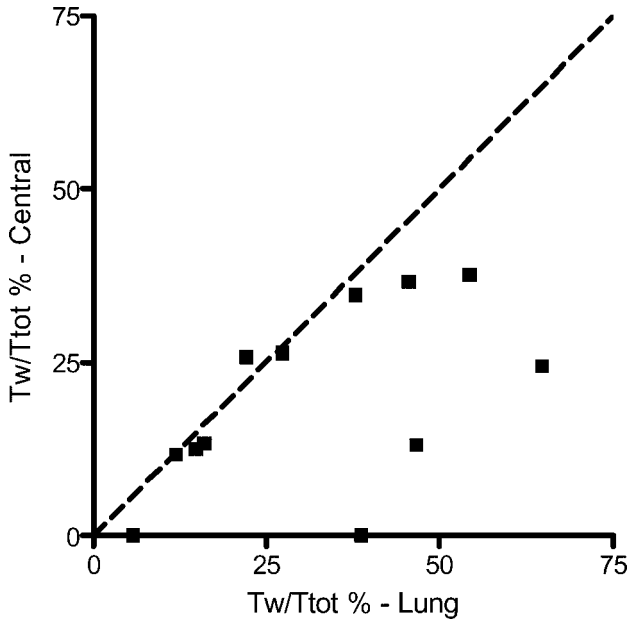

Fig. 2. Relationship between wheeze rate (Tw/Ttot) recorded by sensor placed over manubrium sterni to greatest wheeze rate recorded simultaneously from either right or left lung. Dashed line is line of identity.

during nebulization continued to do so afterwards, had the endpoint been taken as the presence of this wheeze during nebulization, the challenge could have been stopped before the completion of the 2-min inhalation period in 31% of positive challenges. Bronchial challenges in healthy preschool children are difficult if not impossible to justify ethically, at least in our society, and as we were not interested in the use of acoustic recording as a population screening test for bronchial reactivity, we did not include a control group in the present study. We were interested in the safety aspect of the very simple auscultation method for measuring bronchial reactivity in preschool children, and we therefore studied a population most likely to provide data on positive challenges.

The simple system we developed for the acoustic recording of breath sounds was based on a stethoscope to duplicate the normal clinical method of bronchial challenges in young children, together with equipment and software from the world of music. There is very little information available on the acoustic performance of stethoscopes for clinical use. Kindig et al.[16] were mainly interested in heart sounds, and compared different types of bell and diaphragm instruments to generated signals from 30–500 Hz. They found a small but progressive fall of in response as the frequency increased. Abella et al.[17] undertook a similar study over a frequency range of 37.5–1,000 Hz, and showed a similar small decline in sensitivity as frequency increased. They reported a fall of about 10 dB between 100–800 Hz in the relative response of a diaphragm stethoscope similar to that used in our study, which is very similar to the performance we found with our own system. A 10-dB change represents approximately a halving of the perceived loudness of a sound, and so the higher frequencies in the range of wheezes (150–800 Hz) detected both by the clinician and acoustically may have been somewhat underestimated. However, the mean fundamental frequency of the first wheeze detected acoustically in our study was 425 Hz and 85% of the fundamental frequencies were below 600 Hz, so that we believe that the performance of the system was adequate for the recording and analysis of data. Fortunately, the noise generated by the nebulizer had the characteristics of white noise in the frequency range of wheezing, and did not interfere with the acoustic detection of wheeze during nebulization. A greater difficulty was posed by the talking of the child or, more often, the mother or the investigators, since the frequency of speech overlaps with that of wheeze, although speech can be recognized by its characteristic multiple harmonic pattern.

Wheezing in patients with asthma is traditionally described as mainly expiratory, with a musical or polyphonic character. We were somewhat surprised to find that the wheeze during a bronchial challenge was often monophonic and often inspiratory, and indeed in 29% of children the first wheeze was a monophonic inspiratory sound. However, others reported similar findings. In a study by Sanchez et al.[9] of methacholine challenges in children with cystic fibrosis, the pattern of wheeze was quite variable, and wheezing was as common during inspiration as expiration. Another study from the same investigators,[8] this time in children with suspected asthma, also reported that wheeze was found only on inspiration in 4 of 20 children (20%). The physiologic basis of wheeze solely during inspiration is unclear. We were naturally concerned that this wheeze might have been of laryngeal or extrathoracic origin, even though it did not sound like typical laryngeal stridor to the clinical ear. However, in 17 of 23 (74%) stages (endpoint plus others) in which the first wheeze was only inspiratory, there were subsequent breaths in which wheeze was expiratory or both inspiratory and expiratory. This suggests that isolated inspiratory wheeze during a bronchial challenge indicates the start of the response, which progresses to more severe wheeze as the response develops. It is also possible that in some instances the challenge agent induces bronchospasm, which is relieved by the reduction in bronchial tone which occurs due to the increase in lung volume during inspiration,[18] so that there is no expiratory wheeze. However, the lowering of tone was demonstrated with deep inspirations and not with tidal breathing as used in the present study.

The intermittent or variable nature of the induced wheeze was also noted before,[8,9] and in only about one third of our children were there at least 3 consecutive breaths with wheeze at the endpoint. Like the inspiratory wheeze, this appears to be more a feature of bronchial challenge wheeze than wheezing during an attack of asthma. It does imply, however, that continuous auscultation or acoustic analysis should be better at determining the endpoint than intermittent auscultation after the inhalation is complete. This should be even more important if an attempt is made to quantify severity of response in terms of the amount of wheeze in a given time period. Our technician was very experienced, but it is possible that she missed some transient wheeze which had disappeared by the time the pediatrician auscultated the lungs. Continuous auscultation by a physician with a stethoscope throughout the whole of a bronchial challenge is simply not practical, and in any case most young children would object to such a procedure. By attaching the two sensors to the chest underneath the child's shirt and providing some appropriate distraction in the form of video films, we had no problem in making acoustic records for up to 45 min continuously in challenges which continued right through the last concentration of challenge agent. Because of the problem of cooperation in young children, we could not rely on them to take standardized deep breaths or control the inspiratory or expiratory flow rate. This means that our study using quiet tidal breathing differs from the usual type of bronchial challenge in older subjects in which forced

expiration is normally performed, and our results may not be applicable to challenges using forced expiration.

In conclusion, we believe that this study showed that the continuous recording and acoustic analysis of breath sounds is a practical and reliable method of determining the endpoint in a bronchial challenge in preschool children. The detection of wheeze during nebulization adds safety to the technique, and could allow the investigator to halt the nebulization once wheeze has appeared. Since the timing of wheeze in relation to breath phase is unimportant, there is no need to record breathing during the challenge, which substantially simplifies the procedure. Using a running window of 6 sec to detect at least 2 wheezes with a wheeze rate greater than 10% has very high sensitivity and specificity for detecting the endpoint, and could be used in real time during shortened challenges which employ higher concentrations of challenge agent. It may be possible to develop an algorithm which would be able to detect 600 msec of wheeze (10% of 6 sec), which would enable the endpoint wheeze to be detected automatically in 97% of children, similar to those children in the present study.

REFERENCES

1. Avital A, Bar-Yishay E, Springer C, Godfrey S. Bronchial provocation tests in young children using tracheal auscultation. J Pediatr 1988;112:591–594.
2. Avital A, Springer C, Bar-Yishay E, Godfrey S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. Thorax 1995; 50:511–516.
3. Avital A, Picard E, Uwyyed K, Springer C. Comparison of adenosine 5′-monophosphate and methacholine for the differentiation of asthma from chronic airway diseases with the use of the auscultative method in very young children. J Pediatr 1995; 127:438–440.
4. Springer C, Godfrey S, Picard E, Uwyyed K, Rotschild M, Hananya S, Noviski N, Avital A. Efficacy and safety of methacholine bronchial challenge performed by auscultation in young asthmatic children. Am J Respir Crit Care Med 2000;163:857–860.
5. Sprikkelman AB, Schouten JP, Lourens MS, Heymans HSA, Van Alderen WMC. Agreement between spirometry and tracheal auscultation in assessing bronchial responsiveness in asthmatic children. Respir Med 1999;93:102–107.
6. Yong SC, Smith CM, Wach R, Kurian M, Primhak RA. Methacholine challenge in preschool children: methacholine-induced wheeze versus transcutaneous oximetry. Eur Respir J 1999;14:1175–1178.
7. Godfrey S, Uwyyed K, Springer C, Avital A. Is clinical wheezing reliable as the end-point for bronchial challenges in preschool children? Pediatr Pulmonol 2004;37:193–200.
8. Sanchez I, Avital A, Wong I, Tal A, Pasterkamp H. Acoustic vs. spirometric assessment of bronchial responsiveness to methacholine in children. Pediatr Pulmonol 1993;15:28–35.
9. Sanchez I, Powell RE, Pasterkamp H. Wheezing and airflow obstruction during methacholine challenge in children with cystic fibrosis and in normal children. Am Rev Respir Dis 1993;147: 705–709.
10. Spence DP, Graham DR, Jamieson G, Cheetham BM, Calverley PM, Earis JE. The relationship between wheezing and lung mechanics during methacholine-induced bronchoconstriction in asthmatic subjects. Am J Respir Crit Care Med 1996;154:290–294.
11. Noviski N, Cohen L, Springer C, Bar-Yishay E, Avital A, Godfrey S. Bronchial provocation determined by breath sounds compared with lung function. Arch Dis Child 1991;66:952–955.
12. Sovijarvi ARA, Dalmasso F, Vanderschoot J, Malmberg LP, Righini G, Stoneman SAT. Definition of terms for applications of respiratory sounds. Eur Respir Rev 2000;10:597–610.
13. Sovijarvi ARA, Malmberg LP, Charbonneau G, Vanderschoot J, Dalmasso F, Sacco O, Rossi M, Earis JE. Characteristics of breath sounds and adventitious respiratory sounds. Eur Respir Rev 2000; 10:591–596.
14. Sovijarvi ARA, Vanderschoot J, Earis JE. Computerized respiratory sound analysis (CORSA): recommended standards for terms and techniques. ERS Task Force report. Eur Respir Rev 2000;10:585–649.
15. Baughman RP, Loudon RG. Quantilation of wheezing in acute asthma. Chest 1984;86:718–722.
16. Kindig JR, Beeson TP, Campbell RW, Andries F, Tavel ME. Acoustical performance of the stethoscope: a comparative analysis. Am Heart J 1982;104:269–275.
17. Abella M, Formolo J, Penney DG. Comparison of the acoustic properties of six popular stethoscopes. J Acoust Soc Am 1992;91: 2224–2228.
18. Nadel JA, Widdicombe JG. Reflex control of airway size. Ann NY Acad Sci 1963;109:712–723.