RESPIRATORY MEDICINE (1999) **93**, 102–107

Agreement between spirometry and tracheal auscultation in assessing bronchial responsiveness in asthmatic children

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We have recently found that changes in lung sounds correspond well with a 20% fall in the forced expiratory volume in 1 s (FEV_1) after methacholine challenge in asthmatic children. Up to now, little was known about the agreement between a 20% fall in FEV_1 and a change in lung sounds after repeated bronchial challenge.

In this study we investigated the agreement between the total cumulative histamine dose causing a fall in FEV_1 of 20% or more (PD_{20}) and the detection of a change in lung sounds ($PD_{lung\ sounds}$) after two bronchial challenges on different occasions in asthmatic children.

Fifteen asthmatic children (nine boys), mean age 10·8 years (range 9–15), were studied. All performed two histamine challenge tests on 2 days, with a 24 h to 1 week interval. Lung sounds were recorded over the trachea for 1 min and stored on tape. Lung sounds were analysed directly and also scored from the tape-recording by a blinded second investigator. Wheeze, cough, and an increase in respiratory rate were assessed. The relationship between PD_{20} and $PD_{lung\ sounds}$ was calculated by Bland and Altman's measurement of agreement.

Eleven children had a positive challenge test ($PD_{20} \leq 16{\cdot}0\ mg\ ml^{-1}$) on both test days; four had a positive challenge on one test day. In 24 out of 26 positive challenges, wheeze, cough, prolonged expiration and/or increased respiratory rate were detected one dose-step before, or at the dose-step of histamine that induced a fall in FEV_1 of 20% or more. In two challenges, PD_{20} was not detected by a change in lung sounds. In four out of four negative challenges ($PD_{20} > 16{\cdot}0\ mg\ ml^{-1}$) no change in lung sounds could be detected. Good agreement between the logarithm of PD_{20} and the logarithm of $PD_{lung\ sounds}$ was found on both test days. The mean difference was 0·04 and the limits of agreement ($d \pm 2$ SD of the differences) were $0{\cdot}04 \pm 0{\cdot}41$.

A good agreement was found between the total cumulative histamine dose causing a fall in FEV_1 of 20% or more and the detection of a change in lung sounds after two bronchial challenges on different occasions in asthmatic children.

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Introduction

Histamine or methacholine bronchial inhalation challenge is a well-known measurement for assessing bronchial responsiveness in adults and children, and has been proven to be useful in the diagnosis and evaluation of asthma. However, spirometric tests which require active cooperation in forced expiratory manoeuvres cannot be used in infants and young children because of their inability to perform these tests reliably (1). An alternative technique based on detecting audible wheeze over the trachea and requiring passive cooperation only has been described for bronchial inhalation challenge tests in children (2). In older children, a close correlation has been observed between the 20% fall in forced expiratory volume in 1 s (FEV_1) after bronchial provocation challenge and the occurrence of wheeze (2,3). Recently, we found that not only the appearance of wheeze, but also other changes in lung sounds correspond well with a 20% fall in FEV_1 after bronchial challenge with methacholine (4). Wheeze by itself was shown not to be a sensitive indicator for assessing bronchial responsiveness, but cough, increase in respiratory rate and prolonged expiration were more frequently found at the 20% fall in FEV_1.

Received 26 June 1998 and accepted in revised form 2 October 1998.
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0954-6111/99/020102+06 $12.00/0

Changes in lung sounds detected by tracheal auscultation would offer an attractive method for assessment of bronchial responsiveness in children who are not able to perform spirometry if changes in lung sounds correspond with a 20% fall in FEV_1 and do so repeatably. However, little is known about the agreement between a 20% fall in FEV_1 and the detection of a change in lung sounds after bronchial challenge on different occasions. We therefore investigated the relationship between the total cumulative histamine dose causing a fall in FEV_1 of 20% or more (PD_{20}) and the detection of a change in lung sounds after two bronchial challenges on different occasions in asthmatic children.

Methods

SUBJECTS

Fifteen children (nine boys) with mild to moderate asthma (4), without concomitant diseases and aged 9–15 years (mean 10·8 years), were recruited from the outpatient clinic of the Beatrix Children's Hospital in Groningen, The Netherlands. All children had a PD_{20}-histamine $\leq 8\ mg\ ml^{-1}$ in the year before this study was performed. All children used daily inhaled corticosteroids, with a dosage ranging from 200 to 400 μg twice daily and used bronchodilator therapy on demand. None of the children used oral corticosteroids. The mean baseline Tiffeneau index (FEV_1 vital capacity^{-1}) before the histamine inhalation challenge test was 87% of predicted (range 66–95%). All children performed two histamine challenge tests on 2 days, at the same time of day, and separated by 24 h to 1 week. The first challenge with histamine was requested as part of the children's routine evaluation. They were asked to perform a second challenge test in order to assess the repeatability of the tracheal auscultation method. No child had a history of a respiratory tract infection for at least 1 month before the challenge tests or between the two test days. Bronchodilator therapy was withheld for at least 8 h (short-acting) or 24 h (long-acting) before testing to allow histamine-induced bronchoconstriction to occur. Inhaled corticosteroids were continued. All children had normal chest auscultation before the histamine inhalation challenge test. Informed consent was obtained from the child and parents. The study was approved by the Medical Ethics Committee of the University Hospital Groningen.

INHALATION CHALLENGE TEST

The children performed spirometric tests using the Spirometry/Flow-Volume Program (version 4.34, Jaeger, Würzburg, Germany). The best result of three FEV_1 attempts was used for analysis. Histamine inhalation was preceded by baseline lung function measurements, followed immediately by the inhalation of phosphate-buffered saline as a control. After inhalation of the phosphate-buffered saline, doubling concentrations of histamine (beginning with $0{\cdot}03\ mg\ ml^{-1}$ to a maximum of $16{\cdot}0\ mg\ ml^{-1}$) were administered during four inhalations through the Asthma Provocation System nebulizer (version SA, Jaeger, Würzburg, Germany), with a calibrated output of 5 μl per puff. The aerosol was delivered into the mouth piece while the children were wearing a nose clip. During each inhalation of the aerosol, a deep breath was taken and held for 10 s. Three minutes after the fourth inhalation of the aerosol, FEV_1 measurements were performed. Successive concentrations of histamine solutions were given at 5-min intervals. The provocation tests were discontinued if the FEV_1 decreased by 20% or more from the baseline or when the maximum dose of histamine was reached. Bronchial responsiveness was defined as the total cumulative dose of histamine inducing a 20% or more fall in FEV_1 (PD_{20}).

TRACHEAL AUSCULTATION

The trachea auscultation method was performed according to the protocol as described previously (5). Lung sounds were recorded over the trachea by a microphone (Wip en Broos, Winsum, The Netherlands) placed in the suprasternal notch and attached to the skin with two-sided adhesive tape rings. Lung sounds were recorded for 1 min starting 2 min after administration of each dose of histamine (before FEV_1 measurements) during quiet respiration. Lung sounds were stored on tape (DT-120 Rn, Sony), using a digital audio tape recorder (DTC-59 ES, Sony) and were analysed by headphone (Beyer Dynamic DT 801, Badhoevedorp, The Netherlands). The lung sounds were scored directly (A.B.S.) as wheeze, cough, prolonged expiration, and increase in respiratory rate. Cough was scored if it was persistent, i.e. continuously coughing after inhalation of histamine. Prolonged expiration was scored when the duration of expiration exceeded the duration of inspiration. Increase in respiratory rate was defined as an increase of 50% or more from the baseline respiratory rate. A second analysis of the lung sounds was scored blindly from the audio tape-recordings by a senior pediatric pulmonologist, who was unaware of the patient characteristics, baseline lung function, and the histamine concentrations applied (W.M.C.A.). For this second analysis lung sounds of all subjects were recorded on tape, without indicating patient data or stage of the challenge at which the lung sounds were recorded. The total cumulative histamine dose at which a change in lung sounds was heard was defined as $PD_{lung\ sounds}$.

STATISTICAL ANALYSIS

The agreement between the PD_{20}-histamine and the $PD_{lung\ sounds}$ was calculated by Bland and Altman's (6) measurement of agreement, and the intraclass correlation coefficient (7). The logarithms of PD_{20}-histamine and $PD_{lung\ sounds}$ were used for these calculations. Those subjects who inhaled $16\ mg\ ml^{-1}$ histamine without reaching a fall in FEV_1 of 20% were considered to have a negative challenge test. For statistical analysis, they were considered to have a PD_{20} or $PD_{lung\ sounds}$ of $32\ mg\ ml^{-1}$. To account for the repeated studies and for the possible effects of the day at which bronchial challenges were performed, a maximum-likelihood method was used, based on the model

TABLE 1. Characteristics of patients and lung function testing

Patient no.	Age (years)	Test	FEV_1/VC (%)	Histamine (mg ml^{-1})		Maximum fall in FEV_1 (fall in FEV_1 at $PD_{lung\ sounds}$)# (%)	Lung sounds
				PD_{20}	$PD_{lung\ sounds}$		
1	13	1	85	8·0	>16·0	20·0	None
		2	80	16·0	16·0	41·7	Wheeze, prolonged expiration
2	9	1	88	16·0	8·0	31·6 (17·5)	Wheeze, cough, prolonged expiration
		2	89	16·0	8·0	20·0 (11·6)	Wheeze, cough
3	10	1	78	4·0	4·0	23·8	Wheeze, prolonged expiration
		2	78	8·0	4·0	39·6 (7·5)	Wheeze, cough, prolonged expiration
4	10	1	78	16·0	16·0	21·2	Wheeze, cough
		2	78	16·0	>16·0	20·0	None
5	14	1	78	16·0	16·0	40·9	Cough
		2	76	>16·0	>16·0	0·0	None
6	10	1	95	8·0	8·0	30·0	Cough
		2	95	>16·0	>16·0	18·1	None
7	10	1	90	16·0	16·0	43·3	Wheeze, prolonged expiration, increased respiratory rate
		2	90	>16·0	>16·0	17·4	None
8	9	1	95	>16·0	>16·0	9·8	None
		2	93	16·0	16·0	25·0	Wheeze
9	11	1	77	8·0	8·0	21·7	Wheeze
		2	75	16·0	16·0	30·8	Prolonged expiration
10	7	1	69	8·0	8·0	20·0	Wheeze, cough, prolonged expiration
		2	70	8·0	8·0	23·1	Wheeze, cough, prolonged expiration
11	15	1	69	8·0	8·0	27·9	Wheeze, prolonged expiration
		2	66	16·0	16·0	30·6	Wheeze
12	13	1	71	4·0	4·0	29·1	Wheeze, cough, prolonged expiration
		2	63	8·0	8·0	23·2	Wheeze, cough, prolonged expiration
13	8	1	92	16·0	16·0	25·6	Wheeze
		2	89	16·0	8·0	26·0 (18·0)	Wheeze, prolonged expiration
14	11	1	67	4·0	1·0	20·6 (13·5)	Wheeze, prolonged expiration
		2	69	4·0	2·0	25·1 (18·3)	Wheeze, prolonged expiration
15	12	1	69	0·5	0·5	22·5	Wheeze, prolonged expiration
		2	66	4·0	4·0	27·7	Wheeze, prolonged expiration

FEV_1=forced expiratory volume in 1 s; VC=vital capacity; PD_{20}=dose of histamine causing a 20% fall in FEV_1; $PD_{lung\ sounds}$=dose of histamine at which a change in lung sounds was heard; #=if PD_{wheeze} did not equal PD_{20}, the fall in FEV_1 at which a change in lung sounds was detected is shown.

described by Laird and Ware (8) and Davidian and Giltinan (9). The linear mixed-effects model implemented in S-plus (10) was used with a random effect of the intercept, with an unrestricted variance matrix, and assuming independent within-person errors with constant variance.

Results

The subject characteristics and results of the lung function tests are shown in Table 1.

Eleven out of 15 children (patient numbers 1–4 and 9–15) had a positive challenge test ($PD_{20} \leq 16{\cdot}0$ mg ml^{-1}) on both test days. Four children (patient numbers 5–8) had a positive challenge test on one test day. In 24 out of 26 positive challenges, wheeze, cough, prolonged expiration and/or increased respiratory rate were detected. In 18 positive challenges, changes in lung sounds were detected after a fall in FEV_1 of 20% or more. In six positive challenges, changes in lung sounds were detected before a fall in FEV_1 of 20% was observed. In these challenges, the

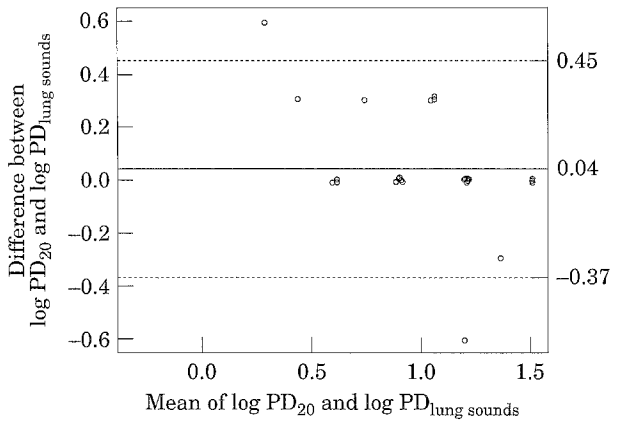

FIG. 1. Agreement between the logarithms of PD_{20}-histamine and $PD_{lung\ sounds}$ on both test days. PD_{20}=total cumulative histamine dose causing a fall in FEV_1 of 20% or more; $PD_{lung\ sounds}$=total cumulative histamine dose at which a change in lung sounds was heard; log=logarithm; $d \pm 2$ SD=0·04 ± 0·41; d=mean difference; 2 SD=standard deviation with limits of agreement.

fall in FEV_1 at which a change in lung sounds was detected ranged from 7·5 to 18·3% (patient numbers 3, 13, 14). In two positive challenge tests (patient numbers 1 and 4) no change in lung sounds could be detected despite a fall of 20% in FEV_1. In all four negative challenges (PD_{20} >16·0 mg ml^{-1}) no change in lung sounds could be detected.

None of the children showed signs of dyspnoea, cyanosis, or intercostal retractions during the challenge tests. Complete agreement was found between the lung sounds scored directly and the lung sounds scored blindly during the subsequent audio tape recording analysis.

A good agreement between the logarithm of PD_{20}-histamine and the logarithm of $PD_{lung\ sounds}$ was found on both test days (Fig. 1). The mean difference (d) was 0·04 and the limits of agreement ($d \pm 2$ SD of the differences) were 0·04 ± 0·41. The mean difference and the limits of agreement are depicted in Fig. 1. A good agreement was also found between the logarithms of PD_{20}-histamine and $PD_{lung\ sounds}$ on both the first and the second test days. The mean difference and the limits of agreement were 0·02 ± 0·48 and 0·06 ± 0·34 for the first and second test days, respectively. Moderate agreement was found between the logarithm of the PD_{20}-histamine measured on the first and second test days, and between the logarithm of the $PD_{lung\ sounds}$ measured on both days. The mean differences and limits of agreement were −0·22 ± 0·58 and −0·18 ± 0·34, repectively. The intraclass correlation coefficients of the logarithms of the PD_{20}-histamine and $PD_{lung\ sounds}$ on the first and second days were 0·56 and 0·66, respectively. A significant difference was found between the PD_{20}-histamine values measured on the first and second test days (P=0·007; likelihood ratio=7·27; difference between test days 1 and 2=0·22). A significant difference was also found between the $PD_{lung\ sounds}$ values measured on both occasions (P=0·045; likelihood ratio=4·01; difference between test days 1 and 2=0·18). No statistically significant effect of the day was found (P=0·08; likelihood ratio=3·06; difference between day 1 and 2=0·09).

Discussion

This study shows good agreement between the total cumulative histamine dose causing a fall in FEV_1 of 20% or more and the detection of a change in lung sounds after two bronchial challenges on different occasions in asthmatic children. Despite statistically significant differences between the PD_{20}-histamine measured on test days 1 and 2, and between the $PD_{lung\ sounds}$ measured on both occasions, a good agreement was found between PD_{20} and $PD_{lung\ sounds}$. No statistical effect of the day on which the bronchial challenge was performed could be found.

To our knowledge there are no published data concerning the agreement between the detection of PD_{20}-histamine and a change in lung sounds on two occasions, using the subjective tracheal auscultation method described in this and our earlier study (5). However, Sanchez *et al.*, using a computerized analysis of respiratory sounds, found a good reproducibility of acoustic meaurements during methacholine challenge in children with suspected asthma (11) and with cystic fibrosis (12). In contrast, Spence *et al.*, in a study of six adult asthmatic patients during methacholine challenge, found that the level of FEV_1 at which audible wheeze appeared was not reproducible, differing widely both between patients and also within patients on different test days (13). Moreover, they showed a lack of reproducibility of the changes in mean and median breath sound frequencies (13). Spence *et al.* also performed a computerized analysis of lung sounds. In both these studies (Sanchez *et al.* and Spence *et al.*) the sound analysis was limited to the detection of wheeze. Moreover, the subject of investigation in these studies was the repeatability of acoustic measurements in relation to airflow obstruction and not the repeatability of the agreement between the concentration of methacholine inducing a fall in FEV_1 of 20% or more and a change in lung sounds.

Our observation that the appearance of wheeze is not the only indicator of bronchial reponsiveness, but that the appearance of cough, increase in respiratory rate, and a prolonged expiration are also significant, is in accordance with our previous study (5). This is in contrast with the observations of Avital *et al.* and Noviski *et al.*, who used the occurrence of wheeze only as an indicator for bronchial responsiveness (2,3). Although Noviski *et al.* observed the occurrence of transient coughing, increase in respiratory rate, mild wheezing over the lung fields, and localized crepitations in some children, these changes in lung sounds did not correlate with either the concentration of methacholine causing wheeze or the concentration causing the FEV_1 to fall by 20% (3). Adinoff *et al.*, however, described a methacholine inhalation challenge test in which the end-point was expressed as the concentration of methacholine which induced clinical signs of cough, wheeze, respiratory distress, and/or intercostal retractions (14). Sanchez *et al.* also reported the appearance of cough at the concentration of methacholine which induced

a fall in FEV_1 of 20% or more during bronchial challenge tests (11).

In order to apply our tracheal auscultation method to younger children, further studies should be performed in this age group because it is possible that younger children may respond differently from older children to a histamine bronchial challenge test. In animal studies, increased bronchial reponsiveness has been demonstrated in immature subjects compared with mature subjects (15). In humans, increased bronchial responsiveness has been demonstrated in healthy children aged 5–11 years in comparison with adolescents, and adults (16). Also, airways reactivity has been reported in healthy infants, as demonstrated by bronchoconstriction with methacholine, and the subsequent bronchodilatation with a bronchodilator agent (17). The results of these studies show that infants and younger children can exhibit bronchial reponses which may be falsely interpreted as bronchial hyperresponsiveness. However, Avital *et al.* (2,18) have demonstrated a good correlation between the degree of bronchial reponsiveness and the severity of asthma symptoms in older as well as in younger children. In one study they investigated the use of the tracheal auscultation method during methacholine challenge in two groups of children (2). The first group included 15 children with asthma, aged 6–15 years (mean age 10 years), who performed spirometry and tracheal auscultation. The second group included 75 young children aged 1–8 years (mean age 4·6 years), who were unable to perform spirometry reliably and only performed tracheal auscultation. The children were subdivided into subgroups, within which clinical asthma was classified according to the mininmal therapeutic requirement for optimal control of symptoms. In this latter study it was demonstrated that the results of the tracheal auscultation showed a close relationship between the degree of clinical bronchial responsiveness and the severity of asthma in both groups. Interestingly, the mean methacholine concentration causing audible wheeze (the end point of the test) in both groups of children was similar to that found in adults for broadly similar therapeutic groups (19,20). In another study, Avital *et al.* (18) compared bronchial reponsiveness to methacholine in children of different age groups (aged 1–17 years), and with asthma of different severity, and found that bronchial responsiveness was independent of age, but distinguished between severity groups. Adinoff *et al.* (14) also found good agreement between positive methacholine challenge tests (defined as the occurence of respiratory distress or wheeze), and the severity of symptoms in young children aged 1–5·8 years. Very recently, Guirau *et al.* (21) have investigated the provocative concentration of methacholine causing wheeze (PC_{wheeze}) in children under 2 years of age with a history of wheeze, and in healthy children of the same age group, and correlated these data with the clinical progression of these children at admission and at follow-up. They found a significant inverse relationship between PC_{wheeze} values and the severity of clinical symptoms. Thus, it is possible that young children may respond differently from older children to bronchial challenges; however, these latter studies show a close relationship between the clinical severity of asthma symptoms and $PC_{wheeze/lung\ sounds}$, suggesting that $PC_{wheeze/lung\ sounds}$ indicates a degree of bronchial responsiveness which is independent of age.

In conclusion, this is the first study to investigate and demonstrate a good agreement between spirometry and subjective tracheal auscultation in assessing bronchial reponsiveness on different occasions in asthmatic children. The present study confirms our earlier observation that changes in lung sounds correspond well with the 20% fall in FEV_1 after a bronchial challenge test (5). Our method is simple and requires little equipment. Changes in lung sounds detected by tracheal auscultation can be used for the assessment of bronchial responsiveness in asthmatic children and would probably offer an attractive method for children who are not able to perform spirometry reliably. However, the application of the method to younger children needs to be further elucidated.

Acknowledgement

This study was supported by the Netherlands Asthma Foundation. We thank Dr P. L. P. Brand for his encouraging remarks.

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