Does the outcome of the tidal breathing and dosimeter methods of assessing bronchial responsiveness in children with asthma depend on age?

D Birnie, G W S thoe Schwartzenberg, W C J Hop, E E M van Essen-Zandvliet, K F Kerrebijn

Abstract

As minute volume increases with age, a study was carried out to determine whether the measurement of bronchial responsiveness to pharmacological agents with the tidal breathing technique in children might be influenced by age. Bronchial responsiveness to histamine administered by tidal breathing was therefore compared with that produced with a dosimeter in 25 children with asthma aged 5–18 years. Bronchial responsiveness was defined as the concentration of histamine that caused a 40% rise in pulmonary resistance (PC_{40}) measured by random noise forced oscillation at 6 Hz. Values of PC_{40} measured by the tidal breathing method were lower than those obtained with the dosimeter method, presumably owing to differences in the dose administered and variations in the pattern of breathing. The difference between the two methods was not related to age, however. It is concluded that the tidal breathing and the dosimeter methods are both suitable for the measurement of bronchial responsiveness in children of various ages and that both can be used in longitudinal studies.

Increased bronchial responsiveness to histamine and methacholine is a characteristic feature of asthma. The technical aspects of aerosol generation and dose delivery have been carefully standardised.[1–4] Two methods of aerosol generation and inhalation are widely used. In the tidal breathing method described by Cockcroft *et al*[1] a Wright's nebuliser is used to generate an aerosol that is delivered continuously and inhaled by tidal breathing for two minutes. In the dosimeter method recommended by Chai *et al*[2] a DeVillbiss nebuliser and a dosimeter are used to deliver a measured dose of agonist during the first 0·6 second of each of five inspiratory capacity breaths from functional residual capacity (FRC). Ryan *et al*[3] found no differences in responsiveness or total lung dose of radiolabelled aerosol in adults between the two methods.

Reference values for minute volume in children are reported to be between < 5 and 6·5 l at the age of 6 years and to increase to more than 8 l over the age of 12.[5] As the amount of aerosol deposited in the airways is linearly related to minute volume,[6] we formed the hypothesis that aerosol delivery into the airways and hence bronchial responsiveness might vary with age with the tidal breathing method. This would be important in longitudinal studies of bronchial responsiveness in children. Aerosol delivery with a dosimeter does not depend on minute volume.

The aim of this study was to investigate whether bronchial responsiveness measured by the tidal breathing technique in children depends on minute volume and age. We therefore compared bronchial responsiveness to histamine obtained by the tidal breathing and the dosimeter methods in children of different ages.

Division of Paediatric Respiratory Medicine
D Birnie
G W S thoe Schwartzenberg
E E M van Essen-Zandvliet
K F Kerrebijn

Department of Biostatistics
W C J Hop

Erasmus University and University Hospital/Sophia Children's Hospital, Rotterdam, The Netherlands

Address for reprint requests: Dr K F Kerrebijn, Division of Paediatric Respiratory Medicine, Erasmus University and University Hospital/Sophia Children's Hospital, Gordelweg 160, 3038 GE Rotterdam, The Netherlands.

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Methods

SUBJECTS

We selected 25 subjects (nine girls) with a history of mild asthma and a documented increase in responsiveness to inhaled histamine (table). Their ages ranged from 5·0 to 18·3 years. The provocative concentration of inhaled histamine causing a 40% rise in respiratory resistance at 6 Hz (PC_{40} Rrs6) was less than 15 mg/ml histamine—that is −1·65 standard scores (lower limit of 95% confidence interval) from levels of PC_{40} Rrs6 in a reference population of healthy children.[7] All patients were atopic as judged by their reactions to one or more common allergens. Subjects were receiving inhaled beta agonists or sodium cromoglycate. Those with respiratory infections or periods of wheezing in the two weeks before the study were excluded. All medication was stopped 12 hours before the study. Informed consent was given by all parents and children.

MEASUREMENT OF LUNG FUNCTION

Respiratory resistance (Rrs) at 6 Hz oscillation frequency (Rrs6) was used to measure the response to inhaled histamine diphosphate. Rrs was measured with the forced pseudo random noise oscillation technique described by Lándsér.[8] Bronchial provocation tests were performed only if baseline Rrs was within two standard deviations of the predicted mean.[9] Each histamine challenge was preceded by five consecutive forced oscillation measurements, from which a mean baseline value and the coefficient of variation were calculated.

Characteristics of the patients

Age, sex	Height (centile for age)	Weight (centile for height)	Rrs6 (SD from predicted mean[12])
5·0, M	50	75	−0·87
6·8, M	90	30	−0·80
7·1, F	60	20	+1·37
7·5, F	60	75	+0·77
7·6, F	60	50	−0·80
7·7, F	50	50	+0·45
8·0, M	50	10	+0·15
9·4, F	10	90	+0·10
10·3, M	25	60	−0·15
10·9, M	50	50	−0·80
11·2, M	25	75	+0·18
11·3, M	70	25	−0·15
11·9, F	50	90	+0·90
11·9, M	50	>90	−1·65
12·2, M	70	50	+0·78
12·5, M	60	50	−0·15
14·6, F	75	90	+0·54
14·6, M	70	50	+1·49
14·8, M	60	40	−0·14
15·8, M	75	80	−0·20
15·9, M	50	80	−0·03
16·2, F	3	80	+1·38
17·0, M	20	70	+0·23
17·1, F	10	50	+0·17
18·3, M	10	90	+0·30

Rrs6—respiratory resistance at 6 Hz oscillation frequency.

AEROSOL GENERATION AND INHALATION

Tidal breathing method

The aerosol was generated by a DeVillbiss 646 nebuliser with its vent closed and with 3 ml solution in the vial; the gas flow rate gave an output of 100 μl/min (that is, 4–5 l/min). The aerosol was delivered directly into the central chamber of an inspiratory-expiratory valve box and inhaled through a mouthpiece that kept the lips apart, allowing a bias flow during inspiration. A noseclip was applied throughout. Histamine diphosphate in buffered saline was inhaled for two minutes in doubling concentrations (0·25–32 mg/ml). Rrs6 was measured after each provocation. The challenge was stopped when a 40% rise in Rrs6 had occurred. Histamine in the expired air passed through a breathing system filter (Pall, Portsmouth). Expiratory minute volume and breathing frequency were monitored with a pneumotachograph during each inhalation (Bear, Baar, Switzerland). Mean values were used for analysis.

Dosimeter method

The aerosol was generated from a DeVillbiss 646 nebuliser with its vent closed and primed with 3 ml solution. The nebuliser was attached to a French-Rosenthal dosimeter driven by air at 137·8 kPa (20 lb/in^2). The aerosol was delivered directly into the mouth through a mouth tube. The subject inspired as slowly as possible from FRC to TLC, after a visual signal extending over two seconds. During inspiration the dosimeter was triggered for 0·6 seconds. At the end of inspiration the child was asked to hold his or her breath for about two seconds. When aerosol is delivered in this way in the early part of inhalation virtually none is lost to the exhaled air and lung deposition should be maximal.[10] A total of 20 μl of aerosolised solution was delivered to the mouth in four consecutive breaths. Histamine diphosphate in buffered saline was given in doubling concentrations (0·25–32 mg/ml). The challenge was stopped after Rrs6 had increased 40% from baseline. The 24 hour within subject difference in repeat measurements was within one doubling dose for around 95% of measurements, a value similar to that observed with the tidal breathing technique.[11]

Both methods

Saline was inhaled before all histamine challenges to exclude a response to diluent; a response was defined as a rise in baseline Rrs6 of more than twice the coefficient of variation. Doses of histamine were given at five minute intervals, with measurement of pulmonary function for about three minutes after each dose. The maximum doses administered with the two techniques were the same.

All lung function values were expressed as standard deviations from predicted mean values according to the reference values of Duiverman *et al*[12] (table).

PC_{40} Rrs6 by tidal breathing (PC_{40} tb) and PC_{40} Rrs6 by dosimeter (PC_{40} dm) were calculated from a log dose-response plot by linear interpolation of data points, the mean values of three technically satisfactory measurements being used for each data point. In a previous study we showed that PC_{40} Rrs6 is closely and linearly correlated with PC_{20} FEV_1.[13]

STUDY DESIGN

Two challenge tests with histamine diphosphate were performed in random order on the same day. The second challenge was given at least one hour after Rrs6 had returned to within 20% of baseline (that is, within 1 SD of the within subject variability).[9]

STATISTICAL ANALYSIS

PC_{40} dm and PC_{40} tb were compared by Student's *t* test after log transformation. To check whether this test was appropriate—that is, whether tachyphylaxis and period effects were absent—the procedures given by Hills and Armitage for crossover designs were first applied.[14] Multiple regression was used to evaluate the effect of various factors on PC_{40} simultaneously.

Results

Mean (SD) PC_{40} tb values (1·65 (2·15)) were lower than PC_{40} dm (3·52 (5·28)) ($p < 0·001$). The mean difference (after log transformation) was 0·28 (SEM 0·05) log units, corresponding to a geometric mean ratio of 1·9. There was no evidence of a crossover effect (tachyphylaxis) or time trend. The scatter of the points in relation to the line of identity in figure 1 indicates that the difference between the two methods was not related to mean PC_{40} values. The mean difference between PC_{40} tb and PC_{40} dm was twofold; the variation between subjects was considerable. PC_{40} dm and PC_{40} tb did not correlate with baseline respiratory resistance, height, weight, or age. There was also no correlation between these

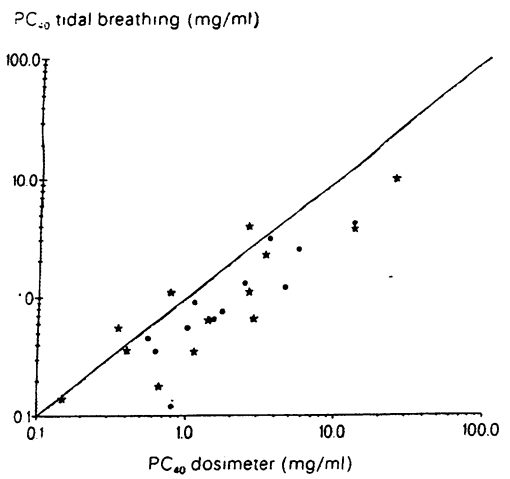

Figure 1 Relation between values for bronchial responsiveness (PC_{40}) to histamine obtained with the tidal breathing technique and the dosimeter technique. ● First measurement by dosimeter; ★ first measurement with tidal breathing.

variables and PC_{40} tb, PC_{40} dm, or their ratio when a multivariate analysis was used.

The ratio of PC_{40} tb to PC_{40} dm was not related to age (fig 2). Minute volume ranged from 7 to 21 l and breathing frequency from 14 to 33/min, which indicates that most children were hyperventilating during tidal breathing. There was no correlation between minute volume and PC_{40} tb (fig 3). There was a non-significant trend for PC_{40} tb to decrease with increasing breathing frequency.

Discussion

The purpose of this study was to compare the tidal breathing method with the dosimeter method with regard to the effect of age on the measurement of bronchial responsiveness.

Our hypothesis was that in young children, whose minute volume may be lower than the volume output of the nebuliser, less aerosol would be inhaled into the pulmonary airways than in older children. The response to inhaled histamine is highly dependent on the dose of aerosol deposited, which in turn is linearly related to minute volume.[6] Age related differences in minute volume might thus result in differences in the amount of histamine deposited in the pulmonary airways and in age dependent values of bronchial responsiveness. We therefore compared bronchial responsiveness determined by the tidal breathing method and bronchial responsiveness determined by the dosimeter method, in which histamine deposition is independent of the volume of inspired air. Our results indicate that the outcome of both methods was independent of age and minute volume. This might be explained by the unexpected finding that most of the children appeared to hyperventilate when they inhaled histamine, so that their minute volume was larger than the volume output of the nebuliser during inspiration. Furthermore, the deposition fraction of an inhaled aerosol is relatively independent of minute volume.[15] There were probably no important differences therefore in the amount of histamine inspired from the mouth into the lungs or in the fractions of aerosol deposited with the two methods of aerosol delivery.

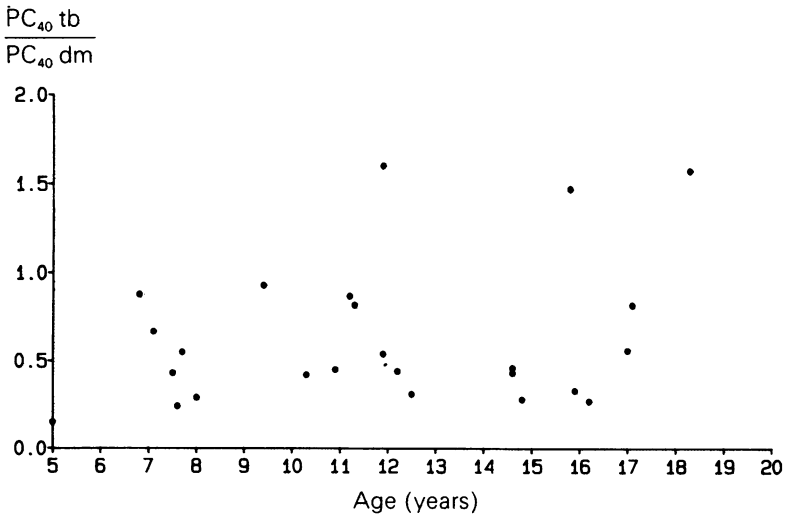

Figure 2 Ratio of values for bronchial responsiveness to histamine obtained with the tidal breathing technique (PC_{40} tb) to those obtained with the dosimeter technique (PC_{40} dm) according to age. $r = 0{\cdot}27$ ($p > 0{\cdot}10$).

The tidal breathing method resulted in a mean PC_{40} about half that obtained with the dosimeter. There was, however, a considerable variation in the ratio between subjects, though in most the absolute difference was small. Our findings are similar to those of Bennett and Davies,[16] who found significantly lower $PC_{20}FEV_1$ values with the tidal breathing method than with the dosimeter method; they differ, however, from the values published by Ryan *et al.*[3] These authors found that histamine aerosol generated by a Wright nebuliser and inhaled by tidal breathing for two minutes via a face mask gave PC_{20} values similar to those obtained by an aerosol generated by a De Villbiss 646 nebuliser attached to a dosimeter. This is surprising in view of the major variations in the pattern of ventilation between and within patients during aerosol inhalation by tidal volume breathing, which may lead to differences in the aerosol fraction entering the mouth.[17] The amount of aerosol generated during tidal breathing was about seven times the output of the dosimeter in the study of Ryan *et al*[3] and six times in the study of Bennett and Davies.[16] This is less than in our study, where the aerosol output during tidal breathing was 10 times the output of the dosimeter. Bennett and Davies[16] supposed that the differences they found between the methods were due to differences in the amount of aerosol that entered the mouth. Our findings, however, suggest that other factors play a part—for example, the site of aerosol deposition, because of within subject variation in the pattern of ventilation during aerosol inhalation by tidal breathing.[18] Minute volume has little effect on the site of aerosol deposition in the lungs[6] and no between subject relation of minute volume to PC_{40} tb was found.

It seems unlikely that the variation of responses between patients was due to the sequence of testing because the results from the second challenge did not differ systematically from those obtained after the first challenge. This is in agreement with the results of repeated histamine challenge reported by Lemire *et al*,[19] Ruffin *et al*,[20] and Gerritsen *et al*[21] and with in vitro observations on human

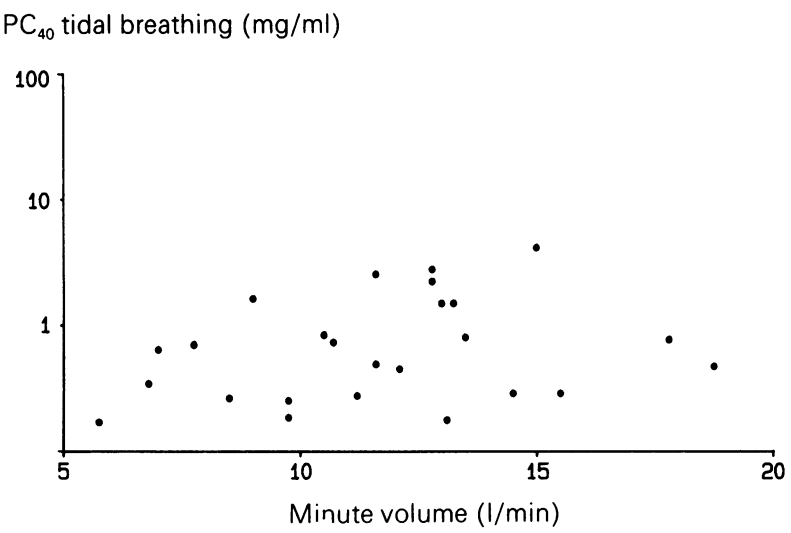

Figure 3 Relation between minute volume and bronchial responsiveness (PC_{40}) to histamine. r = 0·06 (p > 0·10).

airways,[22] but contrasts with the results of Manning *et al.*[23] These investigators observed tachyphylaxis when consecutive histamine inhalation tests were separated by one and three hours. Their study differed from ours in that they investigated asthmatic subjects with mildy hyperresponsive airways and the average dose of histamine was twice that used in our study. In two of our three patients who had a PC_{40} of 10 mg/ml or more on the first occasion the PC_{40} was lower after the second challenge than after the first. In these patients the pre-challenge Rrs was similar on the two occasions, which indicates that the airway calibre was similar.

Another factor that might have contributed to the within subject variation between the methods is the inspiratory flow rate while subjects were inhaling from the dosimeter. Ryan *et al*[24] and Laube *et al*[25] showed that larger inspiratory flow rates resulted in a higher total lung dose, more central deposition of the aerosol, and higher PC_{20} values. Although we urged our subjects to inspire as slowly as possible by asking them to follow the investigator who raised his hand over a period of about two seconds, inspiratory flow rates are difficult to regulate precisely and differences in flow rate may have influenced the results. We were unable to measure flow rates.

In conclusion, we could not confirm our hypothesis that minute volume has a role when aerosol is delivered by tidal breathing in children who differ greatly in age and size and that as a consequence values for bronchial responsiveness obtained by the tidal breathing technique are age dependent. Aerosol delivery by tidal breathing is therefore a valid technique for the measurement of bronchial responsiveness in children from 5 years of age and thus should be as suitable as the dosimeter for longitudinal studies. Our results also show that the two methods do not necessarily give similar values of bronchial responsiveness. Our observations imply that age related differences in bronchial responsiveness[26] are unlikely to be caused by the measurement technique used.

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