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Airway responsiveness following wheezy bronchitis in infants

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ABSTRACT: The study was undertaken to assess the airway function and its response to carbachol and salbutamol in infants recovering from wheezy bronchitis. In 82 children aged 3–33 mths, free from wheeze at the time of testing, and in 14 healthy infants, airway resistance (Raw) and thoracic gas volume (TGV) were measured using a body plethysmograph. Specific airway resistance (sRaw=Raw × TGV) was calculated. Increasing doses of nebulized carbachol were applied to challenge the airways. After a positive reaction had been achieved, 0.1 mg of nebulized salbutamol was administered. Raw was monitored during the whole procedure. In 23 of the 82 children the study was repeated after nine months on average. Within this period Raw remained elevated, whereas TGV and sRaw fell considerably (TGV from 37.9 to 28.2 ml·kg^{-1}, p<0.01; sRaw from 0.78 to 0.63 kPa·s^{-1}, p<0.01). Airway responsiveness also dropped during the observation period (mean log provocation dose producing 50% fall (PD_{50}) 0.026 and 0.358, p<0.01). In comparison with controls the study infants responded to lower doses of carbachol (mean log PD_{50} 0.610 and 0.031, respectively, p<0.01). Airway responsiveness was not related to baseline airway calibre or to signs of atopy. sRaw returned to baseline 2–5 min following salbutamol. The results suggest that airways of children in a symptom-free period following wheezy bronchitis have reduced patency and reveal hyperresponsiveness to carbachol.
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It was shown that the major physiological abnormality in wheezy bronchitis in infants is an increased airway resistance [1, 2], similar to that found in older children and adults with asthma.

The concept of bronchial hyperresponsiveness plays an important role in the pathophysiology of asthma in older children [3, 4] and adults [5, 6]. However, very little is known about airway function in wheezy infants. The failure of wheezy infants to respond to nebulized sympathomimetic agents, in contrast with older subjects [7, 8], suggests that different mechanisms may be responsible for airway narrowing.

Recent studies have shown that infant airways can respond to an inhaled bronchoconstrictor agent [9–11], suggesting that wheezy infants may be able to respond in a similar way to older children.

The study was performed in an attempt to assess airway function, airway responsiveness and the effect of a nebulized β_2-agonist in wheezy infants who were asymptomatic at the time of the study in comparison to the group of healthy nonatopic infants.

Patients and methods

Subjects

Eighty two children aged 4–33 mths (mean 17±7 mths) entered the study. All of them were born at term. Following birth, none required mechanical ventilation or supplemental oxygen. All children suffered from wheezy bronchitis (recurrent dyspnoea and wheezing). Twenty had a first degree family history of atopy and in 24 atopic eczema was found. The infants had been free from wheeze and clinically stable at the time of testing for at least 4 wks. There was no medication administered to the children for at least 2 wks before the study.

The control group included 14 healthy infants aged 10–28 mths (mean 19±3.9 mths). None of these children had positive family history of atopy or signs of allergy (including first- and second-degree relatives), no viral respiratory tract infections in the preceding 4 wks and no recent drug history.

Measurements

Baseline bronchial function and response to bronchoconstricting and bronchodilatating agents was measured using body plethysmography technique.

Thiopentone sodium 30–40 mg·kg^{-1} per rectum was administered 15 min before the test.

When asleep, the infant was placed supine in a whole body plethysmograph with a heated humidified rebreathing bag (volume constant Baby Plethysmograph, E. Jaeger, Germany). When thermal equilibrium had been reached within the plethysmograph, baseline measurements of thoracic gas volume (TGV) and airway resistance (Raw) were obtained in triplicate. Mean values were used to compute specific airway resistance (sRaw=Raw × TGV) as a measure of baseline airway function [12].

After baseline values had been obtained, each infant inhaled saline aerosol (0.45% phosphate buffered saline (PBS)), delivered by an ultrasonic nebulizer (IU-2, Poland) through a face mask during tidal breathing for 2 min. The nebulizer had a mean output of 0.5±0.08 ml·min^{-1} at 1.5–3.5 *l*·min^{-1} minute ventilation. Mean mass diameter of droplets was 3 μm. Immediately after administration of the aerosol, at least three Raw and TGV measurements were repeated. The same sequence was followed for each dose of carbachol starting with 625 μg. The dose of carbachol was doubled until sRaw increased at least 50% from baseline (positive reaction), or up to 5,000 μg. Raw and TGV were measured immediately after each dose. After a positive reaction had been achieved, 0.1 mg of nebulized salbutamol was administered. Two and five minutes after the completion of this aerosol, the measurements of Raw and TGV were repeated in triplicate.

Twenty three children were reassessed after 4–24 mths (study II).

Data processing

Carbachol is slowly metabolized by cholinesterase [13, 14] and, therefore, cumulative doses were calculated. Mean within-subject variability of Raw and TGV was 11% and 7%, respectively, and the highest within-subject variability of sRaw was 22%. Therefore, for analysis of airway responsiveness the cumulative dose of carbachol causing a 50% increase of sRaw (PD_{50}sRaw) was calculated. PD_{50} values were log transformed in order to obtain a normal distribution and to calculate the mean and standard deviation. Statistical analysis was performed by means of a two-tailed Student's t-test.

The study was approved by the Ethical Committee and informed consent from the parents was obtained.

Results

Mean baseline Raw and TGV in wheezy and control children are given in table 1. There is no difference in baseline airway function between these two groups of children. Only normalized TGV in wheezy infants is significantly higher than predicted. Nevertheless, log PD_{50} in wheezy infants was significantly lower than in the control group indicating higher airway responsiveness. Table 2 shows that in 23 infants who were studied twice, after several months, TGV significantly fell into the range of predicted values [15]. Also,

Table 1. – Baseline airway function and logPD_{50} in wheezy and in control children (mean±SD)

	Raw % pred	TGV % pred	TGV ml·kg^{-1}	sRaw kPa·s^{-1}	logPD_{50} n=70
Wheezy n=82					
mean	128	112	35.2*	0.72	0.031**
±SD	45	44	13.8	0.25	0.385
Control n=14					
mean	125	104	32.4	0.72	0.610
±SD	24	30	9.4	0.31	0.440

*: the value is higher ($p<0.02$) than the predicted (30.1±3.77 ml·kg^{-1}) elaborated in the same laboratory [15]; **: the value is significantly lower ($p<0.001$) than in control children. PD_{50}: provocation dose producing a 50% increase in airway specific resistance; Raw: airway resistance; TGV: thoracic gas volume; sRaw: specific airway resistance.

Table 2. – Comparison of airway function in 23 children studied twice (mean±SD)

	Age mths	Raw % pred	TGV % pred	TGV ml·kg^{-1}	sRaw kPa·s^{-1}
Study I	16	131	121	37.9	0.78
	±5	±50	±51	±16.1	±0.25
Study II	25	132	91	28.2	0.63
	±7	±39	±22	±6.7	±0.14
t (paired) test		NS	3.22 p<0.01	3.17 p<0.01	3.46 p<0.01

For abbreviations see legend to table 1.

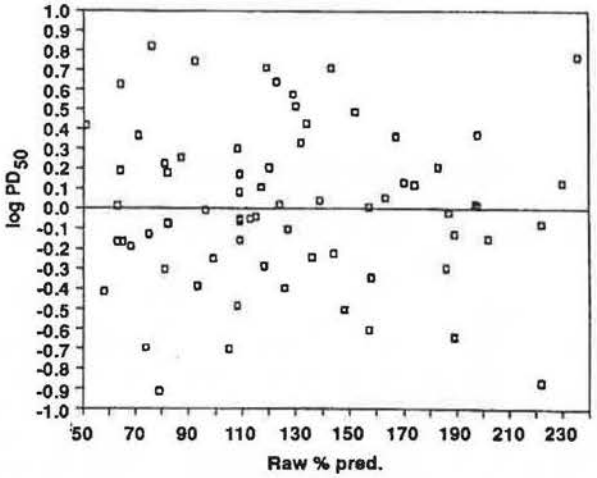

Fig. 1. – The graph showing no relationship between baseline airway resistance and log PD_{50}. PD_{50}: provocation dose producing 50% increase in airway specific resistance; Raw: airway resistance.

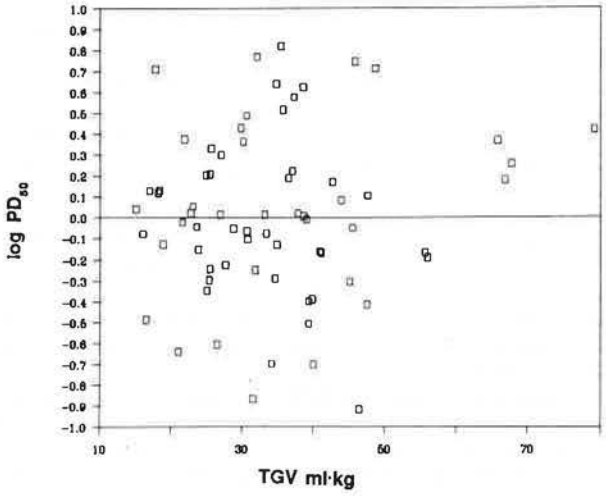

Fig. 2. – The graph showing no relationship between baseline TGV and log PD_{50}. PD_{50}: provocation dose producing 50% increase in airway specific resistance; TGV: thoracic gas volume.

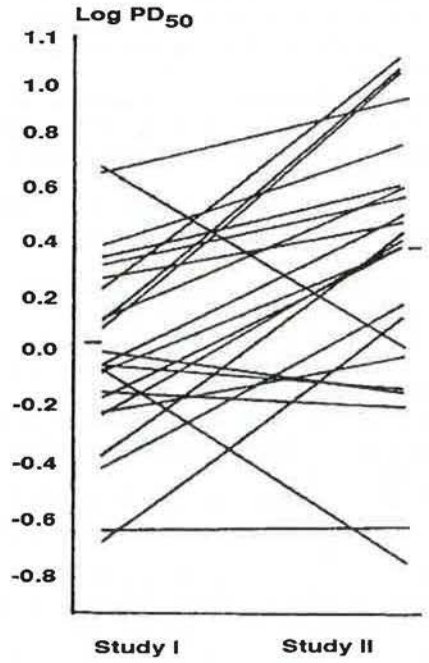

Fig. 3. – Individual data points of log PD_{50} obtained on two occasions in 23 infants. The horizontal bars refer to the mean values (0.026 and 0.358; $p<0.01$). PD_{50}: provocation dose producing 50% increase in airway specific resistance.

sRaw was significantly reduced. Only airway resistance was elevated on both measurements.

PD_{50} to carbachol was measured in 70 infants. Eight of the 82 children failed to finish the test because of arousal before the test had been completed, and in four PD_{50} was greater than 5 mg.

In order to assess whether bronchial responsiveness in infants depended on bronchial calibre, individual log PD_{50} values were related to baseline values of Raw and TGV. There was no relationship between airway responsiveness and baseline airway resistance or TGV (figs 1 and 2).

In 23 children who were studied twice, airway responsiveness was lower on the second occasion than on the first (fig. 3). sRaw returned to baseline within 2–5 min after salbutamol in all infants.

Discussion

The results of this study indicate the presence of airway hyperresponsiveness in infants with wheezy bronchitis who were symptom free at the time of study. The doses of carbachol causing bronchoconstriction were similar to those applied to older asthmatic children [16]. Moreover, an increase of airway calibre after salbutamol following challenge was observed.

The first question to be discussed is whether specific airway resistance is an appropriate technique to study changes in intrathoracic airways.

As a result of bronchial challenge in infancy we have found hyperinflation [10]. Because of the concomitant increase in airflow resistance and TGV it is recommended that specific airway resistance be used to assess bronchial changes during bronchoprovocation [17]. Any increase in the level of functional residual capacity (FRC) could influence the response. Increased elastic recoil of the lung at higher volumes tends to increase the flow and, therefore, underestimate Raw. In severe airway obstruction, the plethysmographic method often underestimates alveolar pressure changes and, therefore, airway resistance is often underestimated by body plethysmography. On the other hand, lung volume is overestimated. When using sRaw this potential error can be overcome [18, 19].

Airway resistance, if measured plethysmographically, includes the upper (nasal passages and larynx) and the intrathoracic airways. Although the nasal passages account for about 50% of the total airway resistance [20], the present results provide evidence that carbachol-induced, as well as salbutamol-induced, changes of the resistance concern intrathoracic airways. It is an accordance with β-receptor distribution in the bronchial tree [21].

In contrast to the present results, other workers have reported that airway responsiveness to histamine increased in infants when baseline airway obstruction became more severe [11]. To explain this contradiction, the difference between both methods should be stressed. In our group of infants only moderately increased airway resistance was observed, whereas among 11 wheezy infants studied by PRENDVILLE *et al.* [11] almost half suffered from severe airflow limitation. It seems, therefore, very likely that bronchial responsiveness depends on baseline airway calibre only if this is considerably reduced. Indeed, the relationship between starting airway conductance and bronchial hyperresponsiveness has been shown to be weak [22]. The question can be raised why the majority of children were hyperresponsive whereas a few were not. Decreasing responsiveness after several months might suggest that in children there is an

age-dependent airway responsiveness which is not related to disease. Bronchial responsiveness in healthy children was found to be much higher than expected from surveys of adults [23]. These findings are consistent, with the increased airway responsiveness that TEPPER [24] reported in asymptomatic healthy infants below 15 mths of age. Bronchial responsiveness might thus decrease with age, probably corresponding to the fact that many children "grow-out" of their tendency to cough and wheeze.

In all infants salbutamol administered after challenge caused airway relaxation, whereas the clinical experience is rather disappointing. PRENDVILLE *et al.* [25] have shown after salbutamol the reduction of airway responsiveness to histamine in wheezy infants indicating the presence of functional β_2-receptors. The reduction in forced expiratory flow rate after bronchodilator observed by the same authors [26] depends on the relative effects of the drugs on airway compliance and on airway calibre. An increase in airway compliance due to a decrease in airway smooth muscle tone will tend to diminish maximum flow rates at low lung volumes.

In conclusion, the airways of children in a symptom free period following wheezy bronchitis have reduced patency. Moreover, in these children, airway hyperresponsiveness to carbachol was demonstrated. It does not depend on baseline airways calibre or on atopy signs, but on decreases in time course. The airway constriction resulting from carbachol challenge is easily reduced by the β-adrenergic agonist (salbutamol).

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Réactivité des voies aériennes aprés bronchite spastique chez les enfants. P. Gutkowski.

RÉSUMÉ: Cette étude vise à apprécier la fonction des voies aériennes et sa réaction au carbachol et au salbutamol chez de petits enfants (3–33 mois) convalescents d'une bronchite spastique. Chez 82 enfants sans sibilances au moment du test

et chez 14 enfants bien portants, la résistance des voies aériennes (Raw) et le volume gazeux intrathoracique (TGV) ont été mesurés par pléthysmographie corporelle, la résistance spécifique des voies aériennes étant calculée selon la formule sRaw = Raw × TVG. Des doses croissantes de carbachol ont été appliquées lors d'une provocation par aérosol: aprés obtention de la réaction positive, l'on a administré 0.1 mg de salbutamol. La Raw a été suivie pendant l'ensemble de expérience. Chez 23 des 82 enfants, l'étude a été répétée en moyenne après 9 mois. Au cours de cette période, Raw est resté élevée, mais TGV et sRaw ont franchement diminué (TGV de 37.9 à 28.2 $ml \cdot kg^{-1}$, $p<0.01$; sRaw de 0.78 à 0.63 $kPa \cdot s^{-1}$). La réactivité des voies aériennes a également diminué pendant la période d'observation (log moyen PD_{50} 0.026 et 0.358, $p<0.01$). Par comparaison avec les contrôles, les enfants de l'étude ont répondu à des doses plus faibles de carbachol (log moyen PD_{50} 0.610 et 0.031, respectivement, $p<0.01$). La réactivité des voies aériennes est sans relation avec leur calibre ou avec des signes d'atopie. sRaw revient aux valeurs basales 2 à 5 minutes après salbutamol. Ces résultats suggèrent que la période asymptomatique faisant suite à une bronchite spastique, les voies aériennes des enfants ont un calibre réduit et sont hyperréactives à l'égard du carbachol.
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