Methacholine-induced volume dependence of respiratory resistance in preschool children

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Methacholine-induced volume dependence of respiratory resistance in preschool children. F. Marchal, N. Loos, P. Monin, R. Peslin. ©ERS Journals Ltd 1999.
ABSTRACT: Enhanced negative volume dependence of airway resistance is associated with bronchoconstriction in tracheostomized paralysed open-chest animals. Significant upper airways responses may be associated with bronchoconstriction and could thereby alter the pattern of volume dependence in spontaneously breathing subjects. The aim of the study was to test whether volume dependence of respiratory resistance (Rrs) could be demonstrated in preschool children undergoing routine methacholine challenge.

The volume dependence of respiratory oscillation resistance at 12 and 20 Hz (Rrs,12 and Rrs,20) was examined in eight 4–5.5-yr-old children showing a positive response to methacholine. Multiple linear regression analysis was also used to account for flow dependence during tidal breathing (Rrs,12 or Rrs,20=$K$1+$K$2|V′|+K3V).

Rrs,12 and Rrs,20 yielded similar results. Negative volume dependence was present at baseline and significantly enhanced by methacholine (p<0.01). For instance, the mean± SD inspiratory $K$3 at 20 Hz was -4.1±1.3 hPa·s·L^{-2} at baseline and -15.0±4.3 hPa·s·L^{-2} after methacholine, in which case it was also larger on expiration than on inspiration (p<0.05), possibly as a result of upper airway responses.

A significant increase in the negative volume dependence of respiratory resistance may thus be shown in preschool children in response to methacholine. The volume dependence ($K$3) during inspiration may be particularly useful in detecting bronchoconstriction, because it is less likely to be affected by upper airway mechanisms than during expiration.
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Bronchial hyperresponsiveness is frequently evaluated in preschool children with recurrent cough episodes in order to assess whether a diagnosis of asthma should be made. The usual lack of cooperation with forced expiratory manoeuvres at this age precludes measurement of forced expiratory volume in one second (FEV1). Respiratory resistance (Rrs) is an alternative and may be measured non-invasively during tidal breathing. In routine lung function studies, significant variations in Rrs after pharmacological challenge are taken as evidence of bronchoconstriction. However, several reports indicate that contraction of the upper airways may be asssociated with the bronchoconstriction evoked by histamine or methacholine (Mch) stimulation in adult animals and humans [1–7] and may contribute to the measured increase in resistance.

Data on the respective contributions of upper and lower airways responses to Mch are scarce in the preschool child, although the information may be even more relevant to Rrs than to FEV1 measurement. Indeed, upper airway constriction is likely to be more apparent during tidal breathing than during voluntary forced expiration, a co-ordinated motor activity that includes dilation of the glottis [8]. Furthermore, maximum expiratory flow is independent of the extrathoracic airways. Data obtained in tracheostomized and paralysed animals show that the bronchoconstriction resulting from airway challenge is associated with complex alterations in lung mechanics [9–12]. Some

of the changes are reflected in the negative volume dependence of airway resistance (Raw), *i.e.* an increase in Raw with decreasing volume of the lung [10, 13]. There is hardly any evidence that the volume dependence of Raw induced under such experimental conditions may also be detected in spontaneously breathing young children undergoing Mch inhalation tests.

The forced oscillation technique, using a single sinusoidal pressure signal, provides a number of Rrs values, which may be used to describe within-breath variations in Rrs, provided the excitation frequency is high enough relative to the respiratory frequency to ensure adequate temporal resolution. Multiple linear regression analysis of Rrs against tidal flow and volume represents an elegant method of estimating the change in Rrs with lung volume while also taking into account its expected flow dependence. Algorithms based on this approach have been described and validated in normal adult subjects (*e.g.* [14, 15]). This type of analysis has already been applied to other fields of paediatric respiratory mechanics, for instance in studying the relationship between transrespiratory pressure, flow and volume in children undergoing artificial ventilation [16].

The aim of the present study was to describe the pattern of within-breath variations in Rrs in preschool children exhibiting a positive response to Mch aerosol challenge with special attention to volume dependence.

Materials and methods

Subjects

Eight children (two males and six females) aged 4–5.5 yrs referred for lung function measurements were included in this study. Seven had a history of chronic cough and one of recurrent upper respiratory tract infections. All had been free of respiratory infection for ≥4 weeks prior to the study. None received bronchodilators or inhaled steroids at the time of the study. All subjects had a normal baseline R_{rs} at 12 Hz ($R_{rs,12}$). Normal values for input respiratory impedance had previously been determined during a collaborative study performed in 127 healthy children aged 2.8–7.4 yrs recruited from kindergartens and schools in Rabka, Poland, using equipment similar to that described here. The prediction equation for $R_{rs,12}$ (in hPa.s·L^{-1}) based on height (in m) is: in $(R_{rs,12})$=2.4914 - 2.4425ln height and the SD for lnR_{rs} is 0.2052.

The subjects included in this study were selected on the basis of a positive airway response to Mch challenge. The criteria were based on an increase in $R_{rs,12}$ of ≥50% associated with a statistically significant decrease in reactance at that frequency. The characteristics of the children are presented in table 1. The study was approved by the regional committee for human subject experimentation.

Respiratory impedance measurement

The apparatus for measuring respiratory impedance (Pulmosfor; SEFAM, Vandoeuvre les Nancy, France) was in conformity with the recommendations of the European Working Group on Forced Oscillations [17]. This system has been described in detail previously except for slight modifications in the software for more convenient use and improved handling of data.

Briefly, input pressure was delivered by a loudspeaker around the subject's head enclosed in a canopy. Pressure difference and hence flow across the upper airway wall were thus significantly reduced. The child wore a noseclip and breathed through a mouthpiece connected to a Fleisch no 1 pneumotachograph (Metabo, Hepalinges, Switzerland) attached to a differential pressure transducer (Micro 176PC14HD2 Honeywell±35 hPa, Scarborough, Canada). The input pressure was measured with an identical transducer, matched to the first within 1% of amplitude and 2°

of phase up to 32 Hz. The common mode rejection ratio of the flow channel was 60 dB at that frequency. Sinusoidal pressure signals at 12 and 20 Hz were applied successively for 10–20 s.

Protocol

Two series of control measurements of respiratory impedance (Z_{rs}) were obtained ~30 min apart. Each series consisted of at least two periods of acquisition at each frequency. Repeated measurements were also obtained after Mch.

Mch chloride (Laboratoire Allerbio, Varennes-en-Argonne, France) was administered using a De Vilbiss nebulizer (model 5610D; Health Care Worldwide, Somerset, PA, USA) and a dosimeter (Mediprom FDC 88; Mediprom, Paris, France) at the following cumulative doses: 50, 100, 200, 400, 800 and 1200 µg. When $R_{rs,12}$ had increased by ≥50%, the next dose was given and the test stopped thereafter. The Mch dose with the largest $R_{rs,12}$ was analysed as the maximum response. Reversibility was obtained at the end of the test by inhalation of 2 puffs of Bronchodual® a mixture of fenoterol bromhydrate (50 µg·dose^{-1}) and ipratropium bromide (20 µg·dose^{-1}) delivered through an inhalation chamber.

Respiratory impedance processing and data analysis

Pressure and flow signals were low-pass filtered at 32 Hz using analogue filters and digitized at a sampling rate of 320 Hz. The signals were analysed oscillation cycle by oscillation cycle, providing 12 or 20 Z_{rs} measurements per second, depending on the excitation frequency. The breathing component of the signals was eliminated using a digital high-pass filter with a corner frequency of respectively 6 and 10 Hz. The Fourier coefficients of pressure and flow at the excitation frequency were computed and combined to obtain R_{rs} and respiratory reactance (X_{rs}) according to the usual equations [18]. The data were corrected for the 2.1 ms time constant of the pneumotachograph. Each dataset was then filtered to eliminate aberrant Z_{rs} values, usually associated with rapid-flow transients. The filtering procedure consisted of eliminating those points lying outside the 99% confidence interval, i.e. lower or higher than the mean±3SD and was repeated three times.

Table 1. – Anthropometric and lung function data of infants studied

Subject No.	Diagnosis	Sex	Age yrs	Height cm	Weight kg	$R_{rs,12}$ hPa·s·L^{-1}	CV %	$R_{rs,12}$ % pred	PD50 µg
1	URTI	F	4.0	108.0	20.0	12.3	11.3	122	50
2	Cough	M	4.0	103.0	17.0	12.7	11.9	113	470
3	Cough	F	4.7	108.0	20.0	12.2	4.7	122	280
4	Cough	M	4.0	101.0	15.0	12.8	11.1	109	700
5	Cough	F	4.0	108.0	18.0	8.3	5.5	83	68
6	Cough	F	4.0	110.0	19.0	11.3	10.3	118	160
7	Cough	F	5.5	122.0	22.0	8.3	14.2	112	500
8	Cough	F	4.5	111.0	23.0	8.9	9.1	95	450
Mean			4.3	108.9	19.3	10.9	9.8	109	335
SD			0.5	6.3	2.6	1.9	3.2	14	233

$R_{rs,12}$: respiratory resistance at 12 Hz; CV: coefficient of variation (of $R_{rs,12}$); PD50: methacholine dose provoking a 50% increase in $R_{rs,12}$; URTI: upper respiratory tract infection; F: female; M: male.

The time courses of tidal flow and volume, R_{rs} and X_{rs} were then displayed on the computer screen and the overall R_{rs} mean for the acquisition epoch obtained.

The data were stored on disk for off-line multiple linear regression analysis in order to describe the within-breath variations in R_{rs} separately for inspiration and expiration and assuming linear flow and volume dependence. The following equations were used:

$$R_{rs,I} = K_1 + K_2|V'| + K_3 V \qquad (1)$$

$$R_{rs,E} = K_1 + K_2|V'| + K_3 V \qquad (2)$$

where $R_{rs,I}$ and $R_{rs,E}$ are R_{rs} during inspiration and expiration respectively V' and V are the flow and volume means during the corresponding oscillation cycle, K_1 is the resistance at functional residual capacity (FRC) and zero flow, and K_2 and K_3 account for the flow and volume dependence of R_{rs} respectively. The statistical significance of the multiple linear regression coefficients was assessed from their corresponding F ratio. Only those coefficients with F ratios significant at $p<0.05$ were retained. Data were compared using a paired t-test and expressed as mean±SD unless otherwise indicated.

Results

Baseline

Representative trace of flow, $R_{rs,12}$ and R_{rs} at 20 Hz ($R_{rs,20}$) at baseline are displayed in figure 1. Large fluctuations in $R_{rs,12}$ and $R_{rs,20}$ may be seen and the resistance was minimal at zero flow. The flow dependence of $R_{rs,20}$ is depicted in figure 2a, in which there appears to be a slight hysteresis during expiration. In this example, the values of K_2 during inspiration and expiration (K_{2I} and K_{2E}), as determined from equations 1 and 2, are res-

pectively 18.1 and 27.3 $hPa·s^2·L^{-2}$. Corresponding values at 12 Hz are respectively 13.8 and 26.7 $hPa·s^2·L^{-2}$. The "zero flow" $R_{rs,20}$, i.e. $R_{rs,20} - K_2|V'|$ plotted against tidal volume in figure 2b, shows slight negative volume dependence on expiration but not on inspiration.

The mean baseline data at 12 and 20 Hz are summarized respectively in tables 2 and 3. R_{rs} at both frequencies showed flow dependence with significant K_2 in all children $R_{rs,12}$ was significantly greater during expiration than during inspiration. The difference appeared to be related to the nonlinear component of the resistance since K_2 but not K_1 was larger during expiration than during inspiration. A similar difference in K_2 was observed at 20 Hz. K_3 was less systematically significant, particularly during inspiration, during which only six of eight subjects showed significant values, which were usually negative. K_3 during expiration (K_{3E}) tended to be more negative than K_3 during inspiration (K_{3I}) at both frequencies, but the difference did not reach statistical significance ($p= 0.08$ at 12 Hz and 0.06 at 20 Hz).

Methacholine

At maximum response to Mch. $R_{rs,12}$ and $R_{rs,20}$ were markedly increased and the periodic variations were not strictly in phase with flow (fig. 3). This was more easily detected with $R_{rs,20}$ than $R_{rs,12}$, because of better time resolution. The $R_{rs,20}$/flow diagram shows marked hysteresis (fig. 4a). This expresses striking volume dependence, occurring during both expiration and inspiration (fig. 4b). Similar findings were observed for $R_{rs,12}$.

A representative dose/response curve for R_{rs} and K_3 at 12 and 20 Hz is shown in figure 5. There was an increasingly negative K_3 with cumulative Mch dose, together with an increase in R_{rs}. The variability appears to increase after Mch, in relation to the mean amplitude of
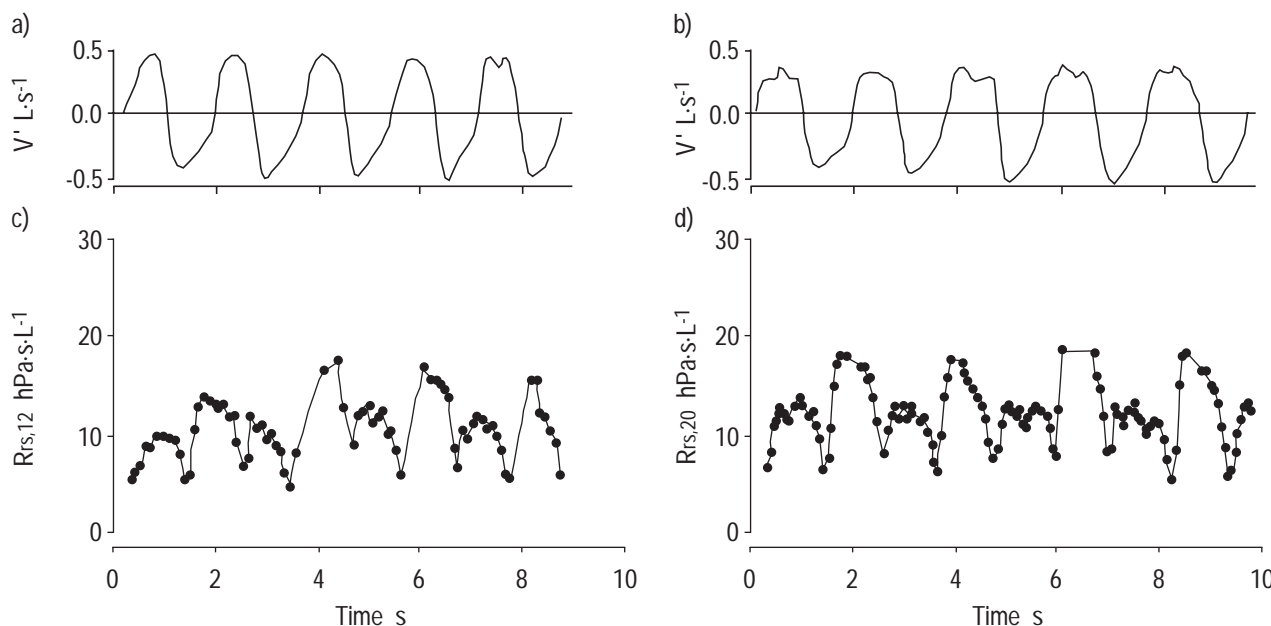

Fig. 1. – Representative time courses of: a, b) tidal flow (V') and c, d) respiratory resistance (R_{rs}) at 12 ($R_{rs,12}$) and 20 Hz ($R_{rs,20}$) at baseline. Flow values are negative during expiration. Both $R_{rs,12}$ and $R_{rs,20}$ show periodic within-breath fluctuations. Most of the R_{rs} variation is reflected in the absolute value of the tidal flow.
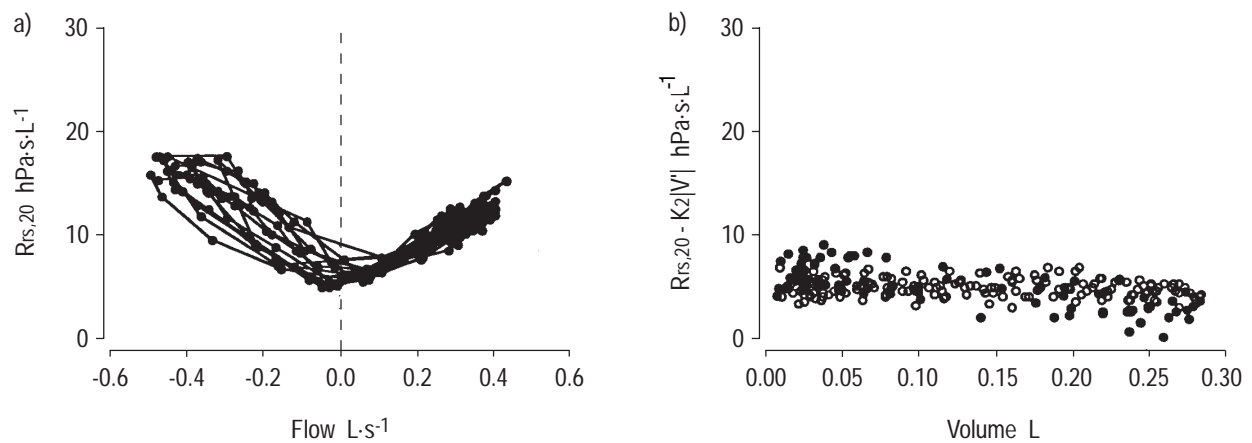
Fig. 2. – Plot of: a) respiratory resistance at 20 Hz ($R_{rs,20}$) against tidal flow; and b) flow-corrected $R_{rs,20}$ ($R_{rs,20} - K2|V'|$) against volume at baseline, during inspiration (○) and expiration (●). Note the obvious flow dependence of $R_{rs,20}$ (a). Some degreee of negative volume dependence during expiration is suggested by the slight hysteresis of the $R_{rs,20}$/flow relationship (a) and indicated by the negative slope of the flow-corrected $R_{rs,20}$ volume relationship (b).

corresponding parameter. The population mean coefficients of variation for $K3I$ and $K3E$ after Mch were 26.9 and 23.5% at 12 Hz and 24.6 and 25.1% at 20 Hz respectively.

The mean Mch data at maximum response are given in tables 2 and 3 at each frequency. All coefficients of flow or volume dependence were significant. Furthermore, all values were significantly different from baseline, so that $R_{rs,12}$ and $R_{rs,20}$ not only were greater than control values but also more flow- and volume-dependent. There was also more flow-dependence during expiration than inspiration, as already found at baseline. $K3$ was also larger during expiration than inspiration at both frequencies. There was no significant difference between 12 and 20 Hz for any parameter.

Finally, the percentage change in R_{rs} and change in $K3$ were computed for the last five Mch doses, as shown in figure 6. A decrease in $K3$ was consistently associated with the increase in R_{rs}. The decrease in $K3$ appeared larger on expiration than on inspiration at the last two doses, the difference being statistically significant for the data at 12 Hz.

Discussion

This study demonstrates that preschool children exhibit significant tidal flow and volume related variations in R_{rs} that may differ during inspiration and expiration and be markedly altered by aerosol Mch.

The subjects were selected according to the magnitude of their $R_{rs,12}$ response and the significant decrease in X_{rs} at 12 Hz ($X_{rs,12}$) at the corresponding Mch dose. It has, indeed been, previously reported that the Mch-induced decrease in $X_{rs,12}$ calculated from Z_{rs} measurements using a head generator significantly correlated to the percentage change in $FEV1$ [19]. A head generator was used because it minimizes upper airway wall motion [20, 21] and has been shown to improve the estimation of Z_{rs} in children with airway obstruction [22] as well as the sensitivity of the forced oscillation technique in describing within-breath variations in R_{rs} in adult subjects [23]. When discussing the physiological implications of the changes in R_{rs}, it is important to bear in mind that the coefficients defined in equations 1 and 2 describe a temporal association with flow or volume which does not necessarily imply causality. This may be of particular importance in understanding the contribution of the upper airways.

R_{rs} showed significant flow dependence and Mch was associated with an increase in $K1$ and $K2$, which are both determined by Reynolds number [24]. The latter increases with induced airway obstruction, and turbulent flow extends to parts of the airways in which it was previously laminar [25]. Thus, although a coefficient accounting for flow dependence must be included to properly describe the within-breath variations in R_{rs}, changes in $K1$ or $K2$ do not help to locate the response within the airways. Accordingly, the $K2:K1$ ratios appeared similar at baseline and after Mch.

Table 2. – Respiratory resistance at 12 Hz ($R_{rs,12}$) and derived coefficients of flow and volume dependence

		$R_{rs,12,I}$ hPa·s·L^{-1}	$R_{rs,12,E}$ hPa·s·L^{-1}	$K1I$ hPa·s·L^{-1}	$K1E$ hPa·s·L^{-1}	$K2I$ hPa·s^2·L^{-2}	$K2E$ hPa·s^2·L^{-2}	$K3I$ hPa·s·L^{-2}	$K3E$ hPa·s·L^{-2}
Baseline	Mean	10.3	11.4[+]	6.7	6.9	12.4	20.5[+]	-6.8	-10.5
	SD	1.5	2.5	0.6	0.8	3.3	7.3	1.9	6.0
	n	8	8	8	8	8	8	6	7
Methacholine	Mean	17.6*	18.7*	11.4*	11.6*	23.9*	34.4*,[+]	-16.0*	-30.1*,[+]
	SD	1.4	1.7	2.4	3.2	6.0	5.7	2.7	18.6
	n	8	8	8	8	8	8	8	8

$R_{rs,12,I}$: $R_{rs,12}$ during inspiration; $R_{rs,12,E}$: $R_{rs,12}$ during expiration; $K1I$ and $K1E$: $R_{rs,12}$ at zero flow and constant volume during inspiration and expiration; $K2I$ and $K2E$: coefficient of flow dependence of $R_{rs,12}$ during inspiration and expiration; $K3I$ and $K3E$: coefficient of volume dependence of $R_{rs,12}$ during inspiration and expiration; n: number of significant coefficients. *: $p<0.05$ versus baseline; [+]: $p<0.05$ versus inspiration.

Table 3. – Respiratory resistance at 20 Hz (Rrs,20) and coefficients of flow and volume dependence

		Rrs,20,I hPa·s·L^{-1}	Rrs,20,E hPa·s·L^{-1}	K1I hPa·s·L^{-1}	K1E hPa·s·L^{-1}	K2I hPa·s^2·L^{-2}	K2E hPa·s^2·L^{-2}	K3I hPa·s·L^{-2}	K3E hPa·s·L^{-2}
Baseline	Mean	10.8	11.4	6.8	6.7	14.4	22.8[+]	-4.1	-9.6
	SD	1.6	2.3	1.0	1.3	3.9	6.9	1.3	5.0
	n	8	8	8	8	8	8	6	8
Methacholine	Mean	18.2*	19.1*	12.1*	12.0*	24.0*	38.5*,[+]	-15.0*	-28.6*,[+]
	SD	2.0	2.5	1.7	2.4	7.1	11.1	4.3	21.2
	n	8	8	8	8	8	8	8	8

Rrs,20,I: Rrs,20 during inspiration; Rrs,20,E: Rrs,20 during expiration; K1I and K1E: Rrs,20 at zero flow and constant volume during inspiration and expiration; K2I and K2E: coefficient of flow dependence of Rrs,20 during inspiration and expiration; K3I and K3E: coefficient of volume dependence of Rrs,20 during inspiration and expiration; n: number of significant coefficients. *: $p<0.05$ *versus* baseline; [+]: $p<0.05$ *versus* inspiration.

The experimental evidence in animals is that Rrs measured at frequencies $\geq$12 Hz is little influenced by lung [9, 26] and chest wall tissues [26]. Conversely, the chest wall has been estimated to contribute nearly 50% of the Rrs in adult humans [27] in whom Zrs also showed significant $K$3 values within the tidal range [14, 15]. The partitioning of Rrs, however, indicated that chest wall tissues did not show consistent volume-related variations [28]. Plethysmographic measurements in normal adults have demonstrated the hyperbolic relationship between Raw and lung volume in the range of the total lung capacity [25]. In infants, plethysmographic studies have shown variation in Raw during the respiratory cycle, alinearities of the pressure/flow relationship [29] and hysteresis of this curve on expiration in the presence of airways obstruction [30]. Recently, volume dependence of Raw estimated from model fitting of input Zrs data was demonstrated in eight infants during an induced apnoea [31]. The significant K3s observed in the current study are thus likely to be attributed to the airways. This negative volume dependence of Raw, as demonstrated in a variety of ani-

mal species ventilated through a tracheostomy (*e.g.* [9, 13]) may, in a simplified manner, be explained by the increasing stretch on intraparenchymatous airways related to elastic lung recoil, which increases with lung volume [25].

The consistent and large increase in the negative volume dependence of Rrs after Mch is a major finding of the present study. There are a few reports of the volume dependence of Rrs in adult subjects with airways obstruction [3, 32], but the authors are unaware of such analysis in young children. Spontaneous breathing is a condition which does not allow control of variations in end-expiratory lung volume and represents a possible confounding factor. Nevertheless, the present observation is in keeping with studies in paralysed artificially ventilated animals, in which the experimental design allowed relative control of lung volume, the variations in which were imposed by application of graded levels of positive end-expiratory pressure [10, 13]. The mechanisms involved in explaining the increased negative volume dependence of Rrs after Mch include partial airway closure at
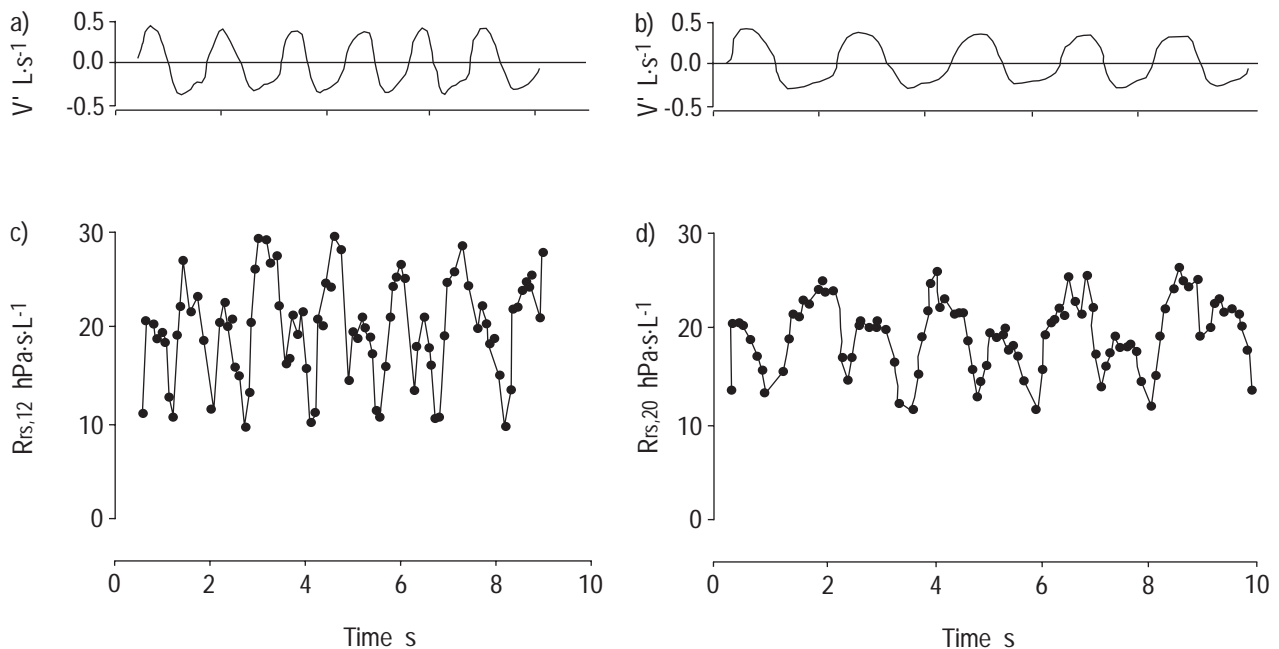

Fig. 3. – Representative time courses of: a, b) tidal flow (V') and c, d) respiratory resistance (Rrs) at 12 (Rrs,12) and 20 Hz (Rrs,20) at maximum response to methacholine. Note the altered pattern of within-breath variations in Rrs at both frequencies. Rrs variations are less strictly in phase with flow, compared with control. The amplitude of the periodic Rrs variation, particularly at 12 Hz in this example, was also increased, whereas there was little change in flow amplitude compared with baseline.
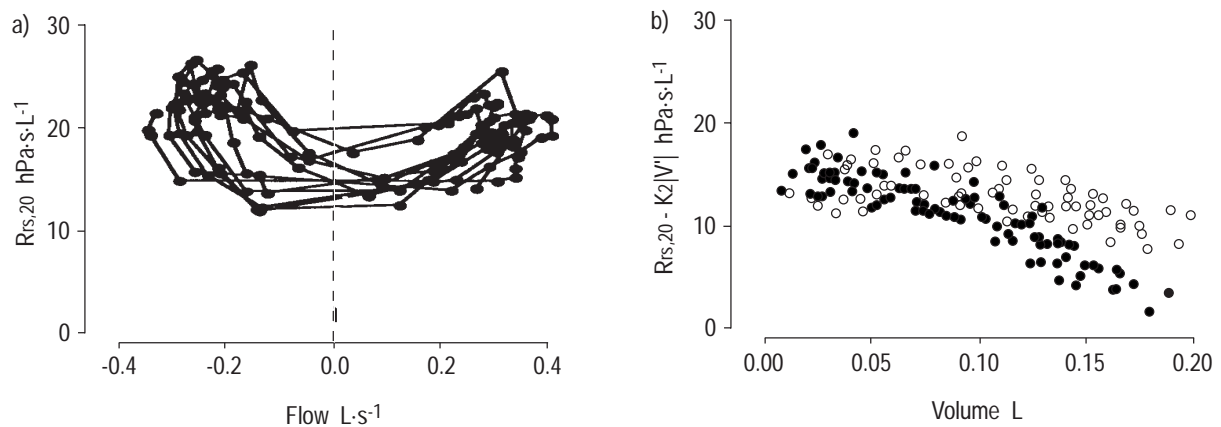
Fig. 4. – Plot of: a) respiratory resistance at 20 Hz ($Rrs,20$) against tidal flow; and b) flow-corrected $Rrs,20$ ($Rrs,20 - K2|V'|$) against volume at maximum response to methacholine, during inspiration (○) and expiration (●). A marked increased in the volume dependence of $Rrs,20$ occurs, during both inspiration and expiration and is shown by the hysteresis of the $Rrs,20$/flow relationship (a) and the negative slope of the flow-corrected $Rrs,20$/volume relationship (b). Note the difference from the corresponding relationships at baseline in figure 2.

low lung volume (in the present case near the FRC), increased coupling of airways and parenchyma related to the bronchoconstriction and/or to stiffening of lung tissue [10, 12, 33]. The current study cannot however provide evidence as to the mechanisms involved.

$K3$ tended to be larger during expiration than inspiration at baseline, and the difference was significant after Mch (tables 2 and 3), indicating that flow-corrected Rrs,I and Rrs,E may differ at the same lung volume. This difference may point toward a contribution of the upper airways. Indeed, in normal adults, the glottic diameter has been shown to be smaller during expiration than during inspiration at a given volume and to frequently exhibit progressive narrowing throughout expiration, abrupt widening at the onset of inspiration and little change further throughout this part of the cycle [34]. Adding the effects of the upper airways and the lower respiratory system would then yield a larger apparent volume dependence of total Rrs during expiration than during inspiration. Fibreoptic studies have documented increased glottis narrowing after inhaled or intravenous histamine in normal adults [7] and after inhaled Mch in normal adults [6] and asthmatics [5]. This observation was extended to both the glottis and pharynx of normal subjects challenged with Mch by studying the pattern of acoustic reflections in the

proximal airways [4]. Altogether, the glottis adduction was reported to be more pronounced during expiration than inspiration (*e.g.* [5, 7]) which may explain why $K3E$ was more negative than $K3I$ after Mch (tables 2 and 3). Thus, during both control and Mch measurements, the volume dependence of Rrs is less likely to be affected by the upper airways during inspiration than during expiration.

To summarize these findings, in preschool children breathing spontaneously, significant fluctuations in Rrs reflect changes in the characteristics of the pressure/flow relationship and in airways calibre throughout the respiratory cycle. Of clinical relevance is the enhanced negative volume dependence of Rrs when the airway response to Mch is positive. The mechanisms may involve different levels of the respiratory system. Increased interdependence between intraparenchymatous airways and lung tissues and/or partial closure of the airways may relate the phenomenon to mechanical alterations of the lung and the intrathoracic airways. Conversely, the pattern of expiratory change in laryngeal dimensions and the reflex laryngeal response that may be associated with the bronchoconstriction may to some degree cause volume dependence of Rrs during expiration. Because the inspiratory phase is likely to be free of progressive laryngeal narrowing, $K3I$ is expected
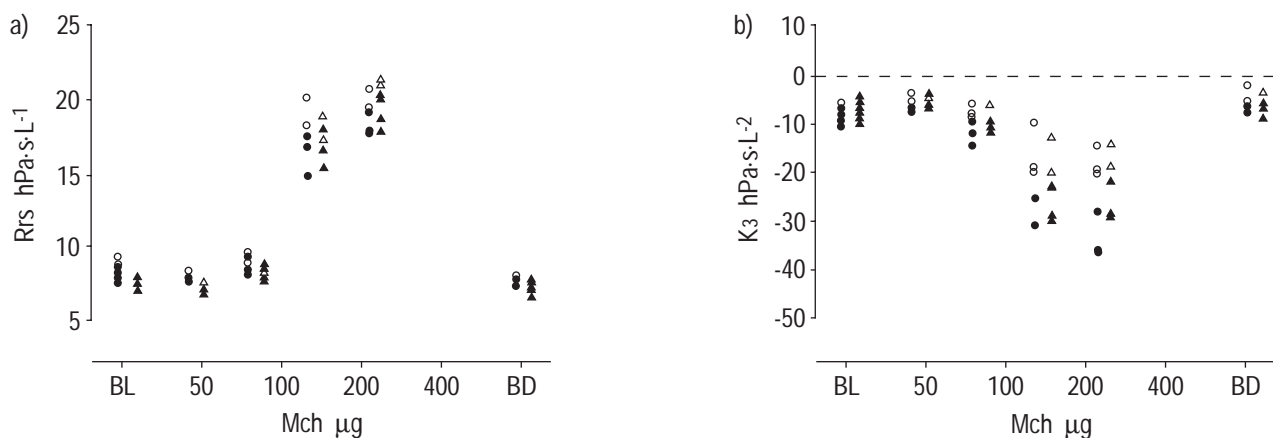

Fig. 5. – Representative methacholine (Mch) dose/response curves for: a) respiratory resistance (Rrs) and b) the coefficient of volume dependence of Rrs ($K3$) in one child. The raw data are shown for 12 (●, ○) and 20 Hz (▲, △) during inspiration (○, △) and expiration (●, ▲) at baseline (BL) and at different cumulative Mch doses; reversibility by bronchodual (BD) is also shown.
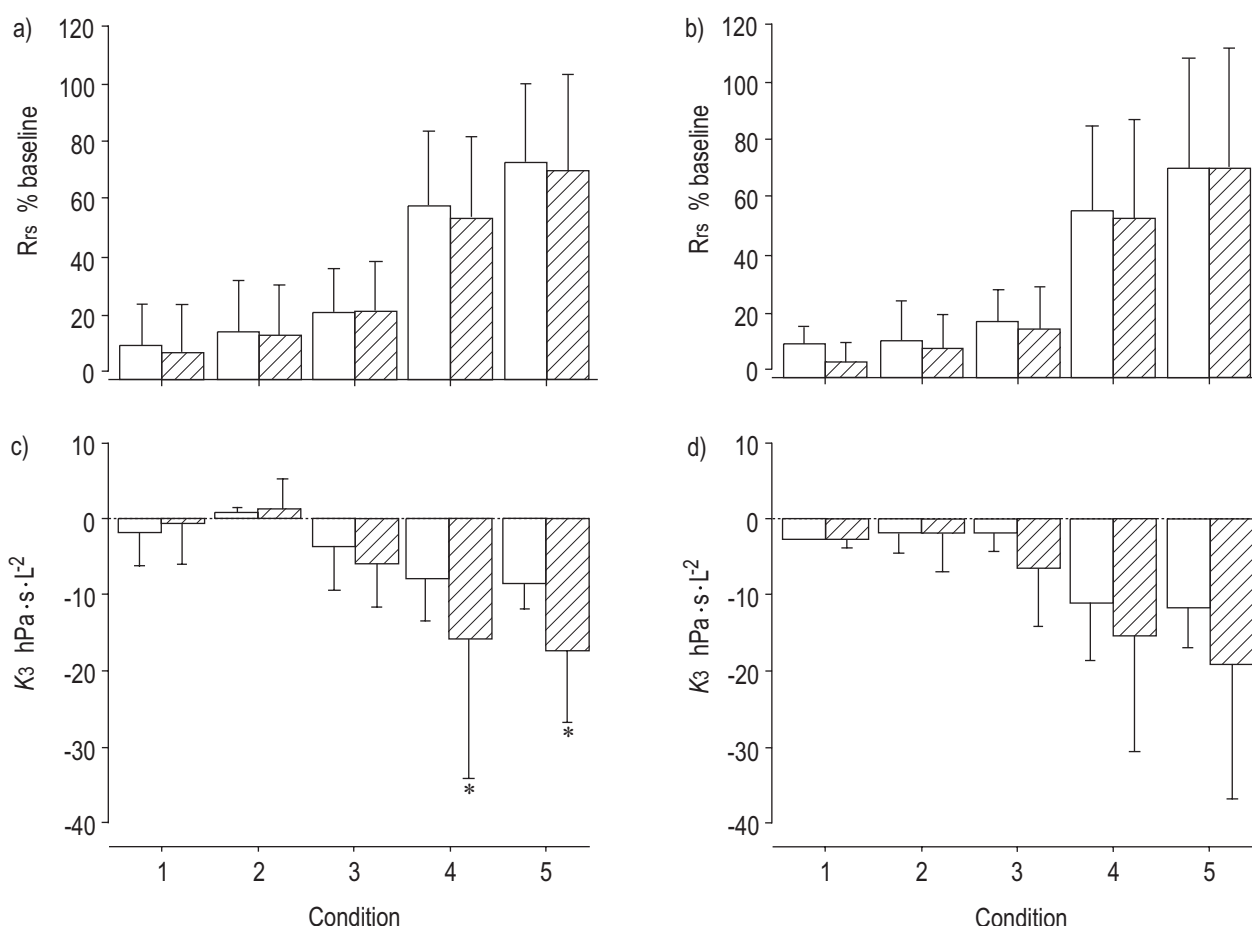
Fig. 6. – Change (Δ) in: a, b) respiratory resistance (R_{rs}); and b) the coefficient of volume dependance of R_{rs} (K_3) from baseline in response to methacholine in the study population at: a, c) 12 Hz; and b, d) 20 Hz during inspiration (□) and expiration (▨). Data are presented as mean±SD and pooled for the maximum response (condition 5) and the four preceding doses (conditions 1–4). *: $p < 0.05$ versus inspiration.

to more specifically reflect alterations at the level of the intrathoracic airways.

From a practical point of view, it is speculated that the volume dependence of R_{rs} during inspiration can potentially be used to detect the response of intrathoracic airways during Mch challenge. Further studies are, therefore, needed to establish the correspondence of this parameter with more conventional indices, such as forced expiratory volume in one second, and to assess its practical usefulness in the routine interpretation of airway challenge test results.

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