Methacholine responsiveness in infants assessed with low frequency forced oscillation and forced expiration techniques

G L Hall, Z Hantos, J H Wildhaber, F Peták, P D Sly

Abstract

***Background*—The contribution of the pulmonary tissues to the mechanical behaviour of the respiratory system is well recognised. This study was undertaken to detect airway and lung tissue responses to inhaled methacholine (Mch) using the low frequency forced oscillation technique (LFOT).**

***Methods*—The respiratory system impedance (Zrs, 0.5–20 Hz) was determined in 17 asymptomatic infants. A model containing airway resistance (Raw) and inertance (Iaw) and a constant phase tissue damping (G) and elastance (H) was fitted to Zrs data. Tissue hysteresivity (η) was calculated as η=G/H. The raised volume rapid thoracic compression technique (RVRTC) was used to generate forced expiratory volume in 0.5 seconds ($FEV_{0.5}$). Lung function was determined at baseline and following inhaled Mch in doubling doses (0.25–16 mg/ml) until the maximal dose was reached or a fall of 15% in $FEV_{0.5}$ was achieved ($PC_{15}FEV_{0.5}$). The response to Mch was defined in terms of the concentration of Mch provoking a change in lung function parameters of more than two standard deviation units (threshold concentration).**

***Results*—At $PC_{15}FEV_{0.5}$ a response in Raw, Iaw, G, and η, but not H, was detected (mean (SE) 61.28 (12.22)%, 95.43 (34.31)%, 46.28 (22.36)%, 44.26 (25.83)%, and –6.48 (4.94)%, respectively). No significant differences were found between threshold concentrations of LFOT parameters and $FEV_{0.5}$.**

***Conclusions*—Inhaled Mch alters both airway and respiratory tissue mechanics in infants.**

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Keywords: forced oscillations; airway mechanics; lung tissue mechanics; children

Division of Clinical Sciences, Institute for Child Health Research, Perth, Australia
G L Hall
Z Hantos
F Peták
P D Sly

Department of Medical Informatics and Engineering, University of Szeged, Szeged, Hungary
Z Hantos
F Peták

Department of Respiratory Medicine, University Children's Hospital, Zürich, Switzerland
J H Wildhaber

Centre for Child Health Research, University of Western Australia, Perth, Australia
G L Hall
P D Sly

Correspondence to:
Dr G L Hall, Respiratory Medicine, University Children's Hospital, Steinwiesstrasse 75, Zürich, CH-8032, Switzerland
graham.hall@kispi.unizh.ch

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Responsiveness to an administered drug or compound remains the most useful physiological test in the assessment of asthma in adults and older children. In infants the usefulness of lung function tests to assess the severity of respiratory disease or to distinguish between health and disease remains uncertain. Healthy infants have been found to exhibit hyperresponsiveness[1 2] which may then decrease with age.[3] Responsiveness has also been shown to correlate with baseline lung function in normal infants and in those with cystic fibrosis.[4] Stick *et al*[5] reported that, while infants with recurrent wheeze had significantly lower baseline lung function than normal infants, the responsivenesses of the two groups to histamine were equal. In contrast, Gutkowski[6] found that infants with a history of recurrent wheezy bronchitis exhibited increased hyperresponsiveness to inhaled carbachol when compared with healthy controls. One possible reason for these conflicting results is the methods used to assess bronchial responsiveness in infants. The rapid thoracic compression (RTC), body plethysmography, and raised volume rapid thoracic compression (RVRTC) techniques are most commonly used. These techniques are unable to provide separate information on the mechanical behaviour of the airways and the respiratory tissues. A number of investigations in animals have shown that the pulmonary tissues do, indeed, respond to inhaled bronchoconstrictors.[7–9]

Sly *et al*[10] recently demonstrated that, by using the Hering-Breuer reflex, a pause in breathing could be induced to allow the reliable measurement of the respiratory system input impedance (Zrs) at low frequencies (<2 Hz) in infants. A four parameter model of the respiratory system was then fitted to these Zrs data to allow the partitioning of the airway and respiratory tissue mechanics. Using this method Hayden and coworkers[11] observed a significant fall in airway resistance (Raw) and a decrease in tissue damping (G) following the administration of a bronchodilator, and concluded that the low frequency forced oscillation technique (LFOT) was suitable for studying the dilator response in the airways and respiratory tissues in infants. However, the LFOT has not been used in infants to measure the respiratory mechanical response to inhaled bronchoconstrictors. The aim of this study was therefore to characterise the effect of inhaled methacholine (Mch) on the airways and respiratory tissues in sedated infants using the LFOT. We compared the responses in the parameters obtained by RVRTC and LFOT by adapting the protocol used by Hayden *et al.*[12]

Methods

SUBJECTS

Seventeen infants (seven boys) were enrolled in the study. Eight had a history of three or more episodes of wheeze in the previous 12 months of life (recurrent wheeze), two had three or more episodes of cough without wheeze (recurrent cough), and the remaining seven

had no history of respiratory disease (normal). All infants had been free of symptoms or illness for a period of at least four weeks preceding the study. The mean (SE) age of the infants was 66.2 (6.9) weeks (range 5–24 months); their length was 77.9 (1.4) cm (range 67.5–86) and their weight 10.7 (0.4) kg (range 7.9–14). The infants were sedated with an oral dose of chloral hydrate (70–100 mg/kg); heart rate (HR) and oxygen saturation (Sa_{O_2}) were monitored throughout the study. They were studied in the supine position with the head supported in the midline and the neck slightly extended.

Parents gave written informed consent and were generally present during the study. The study was approved by the human ethics committee of the Princess Margaret Hospital for Sick Children.

MEASUREMENT APPARATUS

Raised volume rapid thoracic compression technique

The method of Hayden *et al*[12] was used to determine forced expiratory volume at 0.5 seconds ($FEV_{0.5}$). This technique uses a pump to raise the infant's lung volume above the tidal range. The infants were inflated three times to a transrespiratory pressure of 20 cm H_2O with passive deflations between each inflation. A jacket was connected to a positive pressure reservoir and a compression force was applied to the thorax and abdomen after the third and final inflation. Forced expiratory flow was recorded, integrated, and volume-time curves were produced from which $FEV_{0.5}$ was calculated.

Low frequency forced oscillation technique

Respiratory input impedance spectra (Zrs) were measured by LFOT during a pause in breathing induced by the Hering-Breuer reflex as described by Sly *et al.*[10] Before obtaining the oscillatory measurements three deep forced inspirations were applied by using the RVRTC pump-up device until the transrespiratory pressure reached 20 cm H_2O; the first two inflations were followed by passive expiration. At the end of the third inflation the airway was occluded at a transrespiratory pressure of 20 cm H_2O, hence inducing the Hering-Breuer reflex. In the resulting pause in breathing the low frequency pseudorandom signal containing 16 frequency components in the 0.5–20 Hz range was driven into the infant's respiratory system by the loudspeaker. Measurements were six seconds in length and examined for leak or respiratory efforts, with corrupted recordings being excluded.

Flow was measured with a screen pneumotachograph (17 mm ID) connected to an ICS 33NA002D differential pressure transducer (ICSensors Inc, Milpitas, CA, USA). An identical pressure transducer was connected to the face mask to sense Prs. The Prs and V' signals were low-pass filtered at 25 Hz, sampled at 128 Hz with a 12 bit analogue to digital converter, and stored on an IBM compatible computer for later analysis.

Following each measurement the mask was lifted and the infant allowed to exhale and breathe spontaneously. A linear model of the respiratory system[13] was fitted to the individual Zrs spectra in the 0.5–15 Hz range. The model contained a frequency independent resistance (R) and inertance (I) connected in series with a constant phase tissue compartment characterised by tissue damping (G) and elastance (H):

$$Z = R + j\omega I + (G—jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency, and α is expressed as $\alpha = 2/\pi \arctan (H/G)$. Tissue hysteresivity ($\eta$) was calculated as G/H.[14] We assumed that R and I are predominantly airway parameters—that is, the Newtonian resistance and inertance of the respiratory tissues are negligible and are therefore denoted by Raw and Iaw, respectively.

STUDY PROTOCOL

The protocol used was a modified version of that described by Hayden and coworkers.[12] Lung function was recorded using both techniques at baseline and following inhalation of nebulised saline and Mch. Three to five baseline and control (inhaled saline) measurements were recorded with each technique while, because of time constraints, three technically acceptable recordings were obtained following each inhalation. Nebulisations were given at five minute intervals for one minute of tidal breathing via a jet nebuliser at 8 l/min (Innertech Resources Inc, Bannockburn, IL, USA). The Mch concentrations started at 0.25 mg/ml and increased in doubling doses until a positive response was recorded or to a maximum of 16 mg/ml. The test was discontinued if the Sa_{O_2} dropped below 85% at any time throughout the test. 200 µg of salbutamol was administered via a pressurised metered dose inhaler and small volume metal spacer (Nebuchamber, AstraZeneca, Sweden) following the completion of the Mch study.

ANALYSIS OF DATA

Each set of RVRTC and Zrs data was analysed to produce outcomes for $FEV_{0.5}$ and oscillatory parameters (Raw, Iaw, G, H, and η), respectively. Baseline measurements of $FEV_{0.5}$ and oscillatory parameters were averaged to give mean (SD) values and the coefficient of variation was calculated (COV=SD/mean). The standardised variants (Z scores) were calculated to compare the baseline lung function values with a previously reported population of healthy infants.[15] Mean values of $FEV_{0.5}$ were calculated for each dose of Mch, with a fall in $FEV_{0.5}$ of 15% from control ($PC_{15}FEV_{0.5}$) being considered a positive response to Mch.[12] Individual Zrs spectra were examined and the highest magnitude Zrs spectrum for each Mch dose analysed and reported. Changes in oscillatory parameters were expressed as the percentage change from control. An infant was considered to have had a positive response to Mch, as determined by the LFOT parameters, if the percentage increase from control in a particular parameter—for example, Raw or G—exceeded twice the coefficient of variation—that is, the threshold concentration

Table 1 Group mean (SE) baseline lung function data for the raised volume rapid thoracic compression (RVRTC) method and the low frequency forced oscillation technique (LFOT)

Lung function parameter	*Mean (SE)*	*Z score (SE)*	*COV (SE)%*
$FEV_{0.5}$ (ml)	201.9 (12.4)	–0.28 (0.23)	3.8 (0.7)
Raw ($cmH_2O \cdot s/l$)	18.3 (1.2)	0.10 (0.25)	8.3 (1.3)
Iaw ($cmH_2O \cdot s^2/l$)	0.11 (0.01)	–	11.5 (1.7)
G (cmH_2O/l)	29.4 (3.0)	–0.41 (0.22)	14.4 (1.9)
H (cmH_2O/l)	145.8 (10.2)	0.77 (0.23)§	8.7 (1.4)

$FEV_{0.5}$ = forced expiratory volume in 0.5 seconds; Raw = airway resistance; Iaw = airway inertance; G = tissue damping; H = tissue elastance; COV = coefficient of variation.
The standardised variants (Z score) were calculated using the regression equations previously reported (Z scores are not available for Iaw).[15] With the exception of H, lung function parameters were not significantly different from normal (*p<0.01).

(TC)—and remained above that level for the remainder of the study. The magnitude of the response in oscillatory parameters at $PC_{15}FEV_{0.5}$ was expressed in terms of SD units and was calculated as the magnitude of the response divided by the SD of the control measurements.

STATISTICS

Group mean data are expressed as mean (SE) while individual data are shown as mean (SD). Threshold concentrations were not normally distributed and are presented as median and 25–75% confidence intervals (CI). To ascertain if any lung function parameter was more sensitive to changes in respiratory mechanics due to inhaled Mch, a Kruskal-Wallis one way analysis of variance on ranks was carried out. A paired *t* test was used to compare the fitting error (F%) of the model fit to the Zrs data under baseline conditions and following the maximal Mch concentration delivered. Significance was accepted at the $p<0.05$ level.

Results

FORCED EXPIRATION

The group mean (SE) baseline values for $FEV_{0.5}$ were 201.9 (12.4) ml (table 1). There were no differences between the patients with or without a history of respiratory disease. Fourteen of the 17 infants had a 15% fall in $FEV_{0.5}$ before waking up. Of the remaining three infants, one woke due to cough and/or wheeze during nebulisation while the other two woke spontaneously without obvious cause. Table 2 shows the $PC_{15}FEV_{0.5}$ data.

FORCED OSCILLATION

Figure 1 shows typical dose-response curves in terms of Zrs parameters (patient no 14). The control data are characterised by mean values and error bars. Individual peak measurements following inhaled Mch are also shown. Baseline values for the oscillatory parameters are shown in table 1. Z score data for H were significantly different from the normal population previously described ($p<0.01$).[15] The fitting error was calculated under baseline and maximally constrictive conditions. The model was found to fit the Zrs well following inhaled Mch, with no significant differences seen in fitting error from control conditions (7.6 (0.3)% and 8.1 (0.4)% for control and Mch, respectively)

Three of the 17 infants woke before completion of the test while, in a further eight, the apnoeic pause in breathing was insufficient to allow the reliable measurement of Zrs at $PC_{15}FEV_{0.5}$. Table 2 shows the $PC_{15}FEV_{0.5}$, the corresponding percentage change from control, and the magnitude of the change (expressed as SD units) of the oscillatory parameters. Of the six infants in whom LFOT could be measured at $PC_{15}FEV_{0.5}$, all had a positive response in Raw (as defined by an increase of >2 SD units), five infants exhibited a response in Iaw, three had a response in G and η, while only one infant showed a response in H.

Table 3 shows the threshold concentrations for the respective lung function parameters. No significant differences were seen in the threshold concentration of any lung function parameter.

Discussion

The aim of this study was to use the LFOT to detect changes in airway and/or pulmonary tissue mechanics following the administration of inhaled Mch. The results show that changes in both airway and parenchymal mechanics

Table 2 Concentration required to provoke a 15% decrease in $FEV_{0.5}$ ($PC_{15}FEV_{0.5}$), the corresponding response in LFOT parameters, and the magnitude of the response in SD units

Patient no	*$PC_{15}FEV_{0.5}$*	*Raw*	*Iaw*	*G*	*H*	*η*
1 (H)	1	Br	–	–	–	–
2 (D)	1	12.61 (3.3)	–3.88 (–0.3)	–3.66 (–0.5)	6.07 (0.3)	–8.85 (–0.3)
3 (D)	1	56.82 (7.8)	95.76 (113.1)	18.03 (4.4)	–19.95 (–2.5)	46.31 (8.5)
4 (H)	16	Br	–	–	–	–
5 (D)	0.5	44.53 (4.6)	48.95 (6.9)	20.86 (1.5)	9.77 (3.3)	6.54 (0.4)
6 (D)	4	Br	–	–	–	–
7 (D)	1	Br	–	–	–	–
8 (H)	0.25	76.09 (41.5)	164.47 (22.3)	62.57 (2.5)	–17.17 (–3.8)	13.96 (2.6)
9 (D)	Aw	Aw	–	–	–	–
10 (H)	16	Br	–	–	–	–
11 (H)	Aw	Aw	–	–	–	–
12 (D)	Aw	Aw	–	–	–	–
13 (D)	2	Br	–	–	–	–
14 (H)	16	82.67 (9.7)	45.35 (11.1)	149.03 (4.7)	–9.97 (–2.1)	166.11 (4.6)
15 (D)	4	Br	–	–	–	–
16 (H)	2	94.96 (24.5)	221.96 (53.6)	30.83 (1.6)	–7.66 (–1.2)	41.54 (1.7)
17 (D)	1	Br	–	–	–	–
Mean (SE)	4.7(1.7)	61.28 (12.22) (15.2 (6.1))	95.43 (34.31) (34.4 (17.5))	46.28 (22.36) (2.4 (0.8))	–6.48 (4.94) (–1.0 (1.0))	44.26 (25.83) (2.9 (1.3))

$PC_{15}FEV_{0.5}$ is expressed in mg/ml; oscillatory mechanical parameters are shown as percentage increase from control with the magnitude of the response expressed in SD units (shown in parentheses).
Raw = airway resistance; Iaw = airway inertance; G = tissue damping; H = tissue elastance; η = tissue hysteresivity; Aw = infant awoke before completion of test; Br = pause in breathing of sufficient length to introduce the low frequency oscillation could not be induced; (H) = healthy; (D) = diseased.

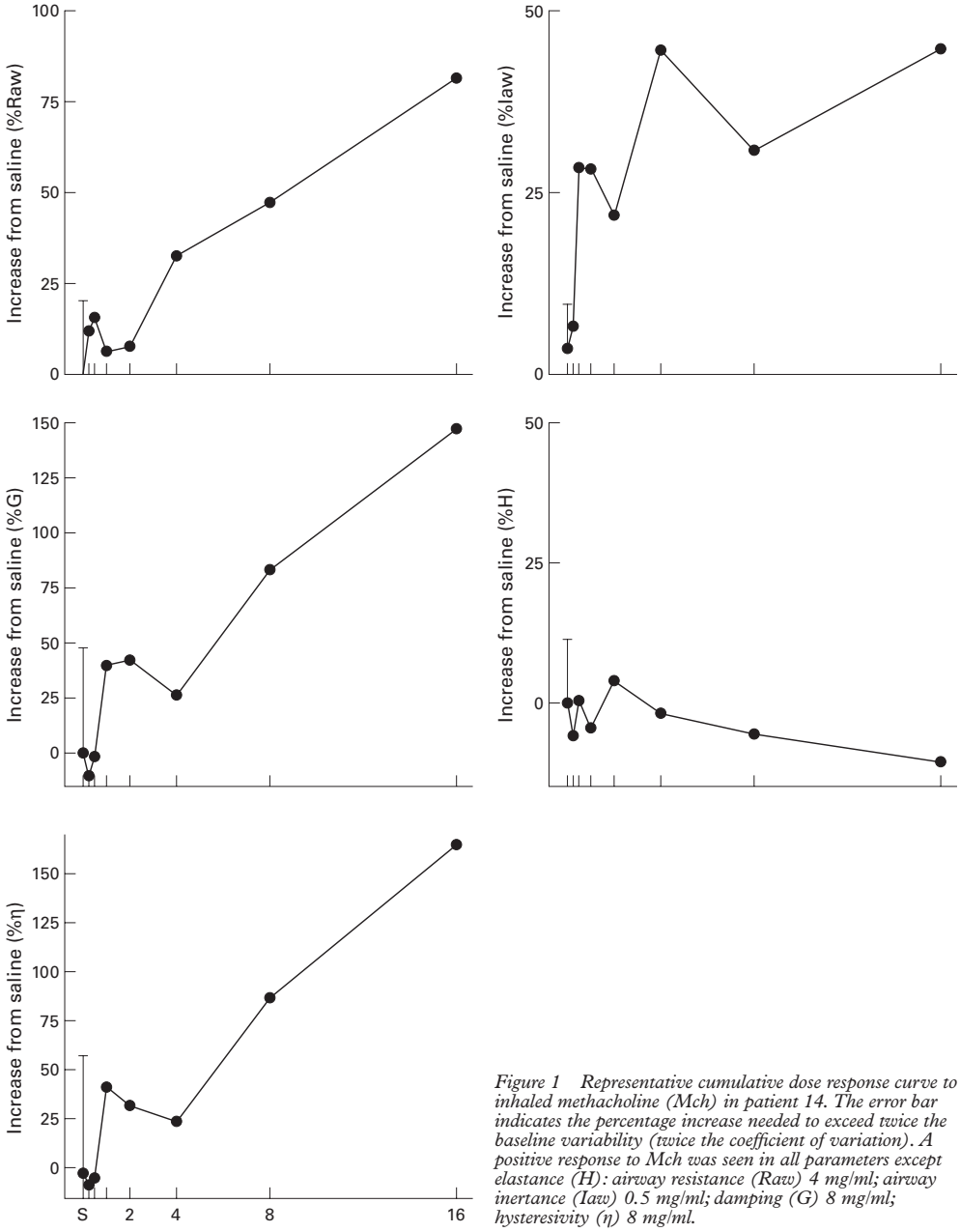

Figure 1 Representative cumulative dose response curve to inhaled methacholine (Mch) in patient 14. The error bar indicates the percentage increase needed to exceed twice the baseline variability (twice the coefficient of variation). A positive response to Mch was seen in all parameters except elastance (H): airway resistance (Raw) 4 mg/ml; airway inertance (Iaw) 0.5 mg/ml; damping (G) 8 mg/ml; hysteresivity (η) 8 mg/ml.

occur as a result of inhaled Mch and that the threshold concentration of Mch required to cause significant increases in LFOT parameters can be determined. In a number of infants in whom $PC_{15}FEV_{0.5}$ could be defined, a technically acceptable measurement with the LFOT could not be obtained (six of 14, 43%). This was because of the inability to induce a pause in breathing of sufficient length. In all cases this occurred at the concentration of Mch at which the response in $FEV_{0.5}$ was subsequently determined.

COMPARISON BETWEEN LFOT AND RVRTC

To allow comparisons between the different tests, the threshold concentration for each lung function parameter was calculated for each individual. The threshold concentrations were not significantly different, which indicates that no particular lung function parameter was more sensitive to alterations caused by inhaled Mch within this population.

The success rates between the RVRTC and LFOT were, however, different. As this study is the first to assess the response to inhaled Mch with the LFOT in infants, a previously defined and acceptable outcome variable was required. $PC_{15}FEV_{0.5}$ was therefore chosen as the primary outcome variable and priority was given to obtaining satisfactory FEV data. $PC_{15}FEV_{0.5}$ was successfully obtained in 14 of the 17 patients, with the remaining three waking before completion of the test. Of the 14 infants in whom the $PC_{15}FEV_{0.5}$ was obtained, a complete LFOT data set was collected in six infants (43% success rate). In the remaining eight infants acceptable LFOT data could not be obtained because of an insufficient pause in breathing. In all cases this occurred at the concentration at which $PC_{15}FEV_{0.5}$ was deter-

Table 3 Threshold concentration (TC) for the infant lung function parameters

Patient no	*TC $FEV_{0.5}$*	*TC Raw*	*TC Iaw*	*TC G*	*TC H*	*TC η*
1	1	–	–	0.25	–	–
2	0.25	0.25	–	–	0.25	–
3	1	1	1	–	–	1
4	4	2	2	2	–	4
5	0.5	0.5	0.25	0.25	–	–
6	2	1	1	0.25	–	0.25
7	0.25	0.5	0.5	0.5	–	0.5
8	0.25	0.25	0.25	0.25	–	0.25
9	Aw	–	–	2	–	2
10	4	–	–	4	–	4
11	1	1	–	0.25	1	–
12	2	–	0.5	–	0.5	–
13	2	–	–	0.5	–	1
14	2	4	0.5	8	–	8
15	4	–	–	–	–	–
16	2	0.25	0.25	0.25	–	1
17	0.5	–	–	–	0.5	–
Median (25% to 75% CI)	1.5 (0.5 to 2)	0.75 (0.25 to 1)	0.5 (0.25 to 1)	0.375 (0.25 to 2)	0.5 (0.375 to 0.75)	1 (0.5 to 4)

Raw = airway resistance; Iaw = airway inertance; G = tissue damping; H = tissue elastance; η = tissue hysteresivity; – = parameters not reaching threshold concentration.
One infant woke spontaneously before the end of the test (patient 9).
Threshold concentrations for each parameter are expressed in mg/ml methacholine. There were no significant differences between the threshold concentrations in any lung function parameter.

mined, suggesting that the Hering-Breuer reflex could not be induced because of alterations in lung function caused by inhaled Mch. The completion rates for both techniques were higher if the threshold concentrations were considered; 16 of the 17 infants reached $TCFEV_{0.5}$, with the remaining infant waking before completion. Of these 16 infants, the threshold concentrations for LFOT parameters were achieved in 10 (62.5% success rate). This lower success rate is due, in part, to the limited time available to obtain technically satisfactory measurements at each dose of the cumulative Mch challenge. Each successive dose was commenced within five minutes of the previous inhalation, thus only three measurements of each technique could be obtained. The use of the LFOT alone would allow more time to obtain acceptable results following inhalation and allow the responsiveness of the airways and respiratory tissues to be assessed at a higher success rate.

AIRWAY VERSUS PARENCHYMAL RESPONSIVENESS

Although evaluation of the low frequency oscillatory data provides a separate assessment of the mechanical properties of the airways and tissues, the determination of the relative responsiveness of the airways and the parenchyma was limited because of the study design. Our data nevertheless show a response to inhaled Mch in both the airways and pulmonary tissues in infants. Significant increases were seen in Raw (61.3 (12.2)%), Iaw (95.4 (34.3)%), G (46.3 (22.4)%), and η (44.3 (25.8)%) but not H (–6.5 (4.9)%). A significant decrease was seen in the resonant frequency (–18.9 (9.0)%).

Airway responses

Since in the model used in this study all the Newtonian resistive and inertial properties are represented by Raw and Iaw , respectively, the inferences to central and peripheral airway responses are not straightforward. However, the significant increase in Iaw at $PCFEV_{0.5}$ provides indirect evidence that Mch evoked significant constriction in the nasal and central airways. In addition, nine infants had a significant positive response in Iaw as defined by an increase of >2 SD units. The inertance of the nasal passages contributes most of the total inertance of the respiratory system,[16] making this parameter highly sensitive to changes in the properties of the extrathoracic airways. This response of both the central and peripheral airways to inhaled Mch has also been shown in asymptomatic adults by Ohrui *et al*[17] using a catheter tipped manometer lodged in a bronchus of 3 mm inner diameter. The response in Iaw in the present study indicates a response in the nasal and/or central pathways. Such a large increase in Iaw must be accompanied by a significant increase in the resistance of the central airways; however, we cannot determine whether the peripheral airways also contributed to this response.

The methodology for obtaining Zrs spectra requires the transrespiratory pressure to be raised to 20 cm H_2O. As such, it is conceivable that changes in airway wall compliance may be involved in the values of Raw before and after Mch challenge since contracted bronchi may be less compliant than those in the control state. The influence of the dynamic compliance of the airways and its changes before and after inhalation of Mch remains unclear since the model used did not contain a parameter structurally corresponding to airway wall properties. Hantos *et al*[13] have shown that up to marked constrictions of the peripheral airways and at low to medium oscillation frequencies, the shunt compliance of the central airways does not play any significant role in the frequency dependence of the respiratory system. However, the changes in the quasi-static pressure/area characteristics of the airways have implications for the Mch evoked increases in Raw. Our results show that administration of inhaled Mch changes the viscoelastic properties of the lungs and chest wall, increasing the resistive losses, while there were no significant alterations to the elastance of the respiratory system. The increase seen in Raw may therefore reflect

an altered equilibrium between the decreased compliance of the contracted airways and that of the subtending tissues at the same elevated transrespiratory pressure as that before the Mch challenge. Application of the LFOT at lower levels of transrespiratory pressure, which is possible although with lower success,[18] would show the impact of the altered airway wall compliance and also the sensitivity of the LFOT due to Mch challenge at a more physiological working point of the respiratory system.

Tissue responses

Interesting responses within the pulmonary tissues were seen, with an increase in G (46.43 (22.36)%) and η (44.26 (25.83)%), but not in H (–6.48 (4.94)%) at $PCFEV_{0.5}$. These increases in G and η are considerable, especially in view of the fact that the contribution of the chest wall to Zrs reduces the sensitivity of the Zrs parameters to changes in the viscoelastic properties of the pulmonary tissues. A number of investigators have shown that, if inhomogeneous constriction of peripheral airways occurs, then the increases in G that were not mirrored by increases in H were related to peripheral inhomogeneity.[8 13 19] While it is possible that the changes in tissue damping seen in the present study may be caused by peripheral airway inhomogeneities, we believe that the higher transrespiratory pressures used in the current study to obtain Zrs are very likely to counteract any tendency to develop marked heterogeneity.

A mechanism of dissociated parenchymal response has been suggested by Fredberg and coworkers[20] who showed, in isolated lung tissue strips, that the time to peak response following administration of an agonist was significantly shorter in η than in tissue elastance (Eti), with the response in tissue resistance (Rti) being governed by the product ηE. Using an open chest rat preparation Salerno *et al*[21] found that the response in Rti could be attributed to that of either Eti or η, depending upon the stimulus used. Following inhaled Mch and changes in lung volume, Eti wholly accounted for changes in Rti whereas intravenous Mch resulted in increases in Rti predominantly resulting from that in η. The early response in η has been attributed to activity in the rapidly cycling cross bridges in the parenchyma, while the changes in elastance are regulated by the slower cycling cross bridges.[20] This dissociation between the hysteresivity and elastance of the lung tissues may be responsible for the changes seen in G within the present study and may be related to increases in η.

CONCLUSIONS

The present pilot study has shown that the measurement and evaluation of low frequency Zrs data is able to detect a response in both the airways and respiratory tissues to inhaled Mch in sedated infants. This response was attributed predominantly to the airways, although the increase in tissue damping, which probably occurred via altered parenchymal hysteresivity, was also marked. Infants with a history of respiratory disease had an increased responsiveness to inhaled Mch. Further larger studies are required to determine accurately the site of this responsiveness. Forthcoming studies using the LFOT would benefit from an increased success rate if the limited time available is spent exclusively for the collection of Zrs data.

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