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High-frequency respiratory input impedance measurements in infants assessed by the high speed interrupter technique

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ABSTRACT: High-frequency input impedance ($Z(f)$) measurements, including antiresonances, provide useful noninvasive information on airway geometry and especially airway wall mechanics in the canine and human adult respiratory system. A knowledge of airway wall mechanics would be particularly important in understanding flow limitation phenomena in infants. High-frequency $Z(f)$ has not been measured in infants above 256 Hz, because the high impedance of the infantile respiratory system would be expected to result in low amplitudes of oscillatory flow at higher frequencies. The aim of this study was to develop a technique to measure high-frequency $Z(f)$ in infants and to elucidate the nature of the antiresonance phenomena in the $Z(f)$ spectrum in infants.

$Z(f)$ was measured from 32–900 Hz during rapid airflow interruption by the high-speed interrupter technique (HIT) in 18 infants (aged 24–149 weeks) with wheezing disorders. The HIT enables the excitement of higher flow amplitudes at high frequencies using a pseudostep forcing function.

In all infants $Z(f)$ showed a mean (SD) first antiresonance ($f_{ar,1}$) of 172 (35) Hz (real part of $Z(f)$ at $f_{ar,1}$ ($Z(f)$re($f_{ar,1}$)): 4.9 (1.1) kPa·L^{-1}·s) and in five infants a second antiresonance ($f_{ar,2}$) of 564 (51) Hz ($Z(f)$re($f_{ar,2}$): 2.0 (0.7) kPa·L^{-1}·s). The antiresonances were found to be related to wave propagation in the airways (acoustic antiresonances), because they increased by a factor of ~2 when He-O_2 was inhaled. This implies that $f_{ar,1}$ and its harmonics are a function of airway wall compliance.

In conclusion, the first and second antiresonances may be helpful in understanding flow limitation in wheezing disorders in infants, because flow limitation is related not only to airway diameter but also to airway wall compliance.

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In infants and toddlers suffering from wheezing disorders, lung function testing for diagnosis and the monitoring of therapy is technically difficult and patients usually need to be sedated. The rapid thoracic compression (RTC) technique has been shown to be a simple and reproducible method to assess flow limitation in infants [1]. Maximum flows achieved during expiration are directly related to airway cross-sectional area (calibre) and inversely related to airway wall compliance [2], so that the technique cannot determine the contribution of these two properties to overall airway function. For instance, bronchodilator agents can cause both an increase in airway calibre and, by removing airway smooth muscle tone, an increase in airway wall compliance. Their effect on maximum expiratory flow would be determined by both the baseline conditions of airway calibre and airway wall compliance and the relative changes induced, since an increase in calibre and airway wall compliance will have opposite effects on maximum flow rates. The RTC can therefore sometimes lead to paradoxical results when the effect of inhaled bronchodilators is tested in infants [3]. In order to understand better the role of physiological development of the airways in foetal life and infancy for later airway disease [4] and to understand wheezing disorders and drug action in infancy, there is a need for a noninvasive lung function technique that provides a measure of airway wall properties independent of airway calibre.

Measurements of respiratory input impedance ($Z(f)$) can be made noninvasively over a wide range of frequencies within seconds without patient cooperation. The technique has been used to measure lung function in dogs [5–9] and in human adults [10–14]. Even though $Z(f)$ measurements were proposed several years ago as a potentially useful test of infant lung function, until recently, only $Z(f)$ data at frequencies <100 Hz have been reported in infants [15–18]. If information regarding airway wall properties is required, $Z(f)$ data should be measured at higher frequencies [19, 20]. An important feature of the high-frequency impedance spectrum is the presence of an antiresonance, defined by the zero-crossing in the imaginary part in the presence of a relative maximum in the real part. In infants, the exact nature of these antiresonances has not been completely elucidated. In human adults it is known that $Z(f)$ at frequencies >100 Hz (in particular antiresonances) is influenced by airway resistance and airway wall properties and little by tissue properties.

Even though one can infer changes in airway wall properties from $Z(f)$ at frequencies that include only the first

antiresonance [19, 20], $Z(f)$ at frequencies that include additional antiresonances are needed before quantitative estimates of airway wall properties can be obtained [8, 9, 14]. Measurements of $Z(f)$ with loudspeaker-generated forced oscillations applied at the airway opening are problematic because infant airways are small and the respiratory system has a relatively high impedance. Therefore, if pressure waves are applied at the airway opening, the amplitude of the resulting flow will be small and the signal-to-noise ratio will be low. This is particularly true for higher frequencies because of the capacitative shunting into the gas compression compliance of the loudspeaker dead-space.

To overcome these problems a new technique was developed, the high-speed interrupter technique (HIT) [21], which uses a pseudostep flow-forcing function and enables much higher flow amplitudes at high frequencies than the forced oscillation technique (FOT).

The aim of the current study was to determine whether it is technically possible to measure coherent high-frequency $Z(f)$ in infants using the HIT and whether the baseline variability of the antiresonance features is similar to the variability of a reference lung function technique such as RTC. A further aim was to determine whether these antiresonances were related to wave propagation phenomena in the airways as in adults, which would imply that the frequency of the first antiresonance was a function of airway wall properties independent of airway calibre. A final aim was to measure whether patency of the upper airways might influence high-frequency $Z(f)$.

Physiological background

$Z(f)$ data have been analysed either using systems identification techniques [5–8, 11, 14–16, 18, 22] or by considering changes in specific features of the $Z(f)$ spectra [12, 13, 17]. For example, in adults the level of airway obstruction is directly related to the amount of negative frequency dependence in the real part of $Z(f)$ ($Z(f)$re) and the frequency of the resonance (where the $Z(f)$re is a relative minimum and the imaginary part $Z(f)$im crosses zero) as well as inversely related to the frequency of the antiresonance (where the $Z(f)$re is a relative maximum and $Z(f)$im crosses zero) [12]. Unlike feature analysis, systems identification techniques provide estimates of physiological parameters by fitting a model to the $Z(f)$ data. One such model, the Dubois six-element model [22] provides separate estimates of airway (R_{aw}) and tissue resistance (R_{ti}), as well as thoracic gas volume (V_{tg}). However, this model can be used only if the $Z(f)$ data include an antiresonance that is related to the tissue inertance (I_{ti}) and the alveolar gas compression compliance (C_g). There is such an antiresonance in dogs [5–7] and rabbits but not in adult humans [10, 11]. Instead, the antiresonances in adults are due to wave-propagation phenomena and are thus related to inertance of the gas within the airways and the compliance of the airway walls [10, 11] Since the antiresonances are related to wave propagation, estimates of R_{aw} and V_{tg} are not possible in human adults but inferences about airway wall properties are possible [10, 11]. Even though the phenomena that contribute to antiresonances in infants are not clearly understood, preliminary results have indicated [19] that antiresonances could be related to the total respiratory system inertance (I_{rs}) but also partly due to the gas compression compliance in the face mask. In order to determine whether anti-resonances are related to I_{ti} and C_g or to wave-propagation phenomena, measurements of high-frequency impedance have to be taken using gases of different density [10, 11]. So far, this has never been done in infants.

Methods

Subjects

The main study (part 1) was performed in 18 infants and young children (11 females and 7 males, aged 24–149 weeks) with a history of episodic or recurrent wheeze, who had been referred from the outpatient clinic for lung function tests as part of their clinical investigation (table 1). Physiological and technical aspects (parts 2 and 3) were studied in a separate group of six infants (three males and three females, aged 1–18 months). Infants with other severe diseases and infants with upper respiratory tract infection within the previous 3 weeks were not included in the study. The infants and toddlers were sedated using a maximum oral dose of 150 $mg \cdot kg^{-1}$ triclofos sodium and lung function was measured during behaviourally defined quiet sleep. The additional HIT measurements were approved by the Ethics Committee of the Royal Postgraduate Medical School, Hammersmith Hospital, London, UK. Written consent was obtained from parents.

Study design

The study was performed in three parts. First, in 18 infants it was determined whether it was technically possible to measure high-frequency impedance. In these infants the variability (10 measurements) of the frequency and relative maxima in the real part at the antiresonances was determined, and compared to the variability of the maximal flow at functional residual capacity (FRC) (V'_{maxFRC}) by the RTC. Secondly (part 2), in three additional infants measurements of $Z(f)$ breathing a gas mixture of 21% oxy-

Table 1. – Physical characteristics of subjects

Group	Weight kg	Height cm	GA weeks	PNA weeks	V'_{maxFRC} mean±SD $mL \cdot s^{-1}$	Pred. for age %	Pred. for length %
Mean	9.7	75.6	38.9	51.5	213.6±11.6	77.5	72.3
SD	1.7	8.2	2.8	19.6	89.5±5.4	36.8	39.0
Minimum	6.8	63.0	30.0	24.0	78.9±6.5	14.5	17.7
Maximum	16.0	95.6	41.0	148.6	409.0±23.7	152.1	184.8

GA: gestational age; PNA: postnatal age; V'_{maxFRC}: maximal flow at functional residual capacity; V'_{maxFRC}: maximum flow at functional residual capacity; Pred: predicted values from Ref [1].

gen and 79% helium (Heliox; He-O_2) were taken to elucidate the physiological basis of the antiresonances. If antiresonance in infants were related to wave-propagation phenomena, then the frequency at which antiresonance occurred would increase as a function of gas density. In a gas of lower density wave-propagation velocity would be faster and the frequency of the antiresonance in a tube would be higher. Thirdly (part 3), it was questioned whether the upper airways significantly influenced the antiresonances. This hypothesis was tested in three infants by measuring five sets of HIT measurements before and after occluding one nostril.

High-speed interrupter technique for infants

The principle of the HIT (fig. 1) has been described elsewhere [21] and is thus only described briefly here. The HIT is based on rapid multiple interruptions of airflow. If flow interruption were to occur instantaneously, the input flow signal applied to the lungs would be a step function, the frequency (f) content of which varies as $1/f$. The less rapidly the interruption occurs, the lower the amplitudes of the flow at higher frequencies. This interrupter is driven by a stepper motor (start speed 1,200 Hz, maximal speed 7,500 Hz, ramp time 13 ms). The shutter consists of a rotating blade which closes the airway opening within 1 ms, remains closed for 15.5 ms, then opens for another 15.5 ms. Thus the complete interruption-closure cycle occurs once every 31 ms. The motor is controlled by a digital-to-analogue converter (Model AT-MIO-16; Natio-nal Instruments, Tx, USA). The position of the shutter valve (open or closed) was measured by a photo-optic resistor to ensure that the shutter was reopened after an interruption so that the subject was able to breathe between the measurements. Whenever the interrupter was enabled, it triggered only at inspiratory flow rates of less than 0.1 $L \cdot s^{-1}$ producing five separate interruptions. The shutter mechanism was connected to the mouthpiece by a tube 14 cm in length of 1 cm internal diameter.

$Z(f)$ was measured using the wave tube technique described in detail elsewhere [8, 14, 21, 23]. In brief, in this technique pressures are measured at two locations (6.7 cm apart) along the tube between the shutter mechanism and the mouthpiece. The first pressure transducer (P_1) was placed 3.3 cm and the second pressure transducer (P_0) 10 cm from the airway opening (face mask). A

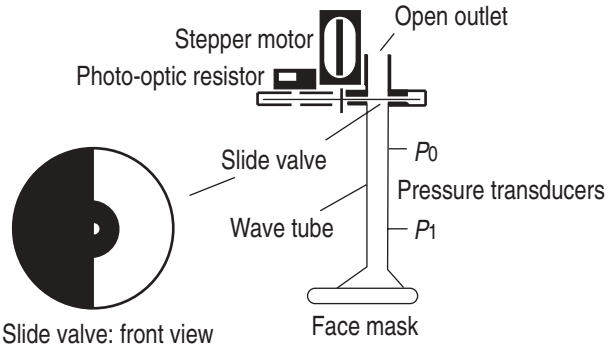

Fig. 1. – Using the noninvasive high-speed interrupter technique (HIT) high-frequency input impedance can be measured using a quickly rotating interrupter valve which generates a pseudo-step flow function. The resulting pressure and flow oscillations can be assessed using the wave tube technique [17].

Rendell Baker Soucek face mask (size 1; Ambu International, Bath, UK) was chosen because its dead space was small. In the process of study design different face masks were tried and their effect on high-frequency $Z(f)$ data studied. The dead space in the face mask was minimized to 10–15 mL by filling it as much as possible with putty (Therapeutic Putty, Carter's, Bridgend, UK). $Z(f)$ was computed as the load impedance of the tube by:

$$Z(f) = \frac{Z_c \cdot \sinh\gamma L}{P_1/P_0 - \cosh\gamma L} \quad (1)$$

where L is the distance between the two pressure transducers (6.7 cm), Z_c is the characteristic impedance of the tube, and γ is the propagation coefficient of the tube. P_1 and P_0 were measured with piezoelectric pressure transducers that were matched within <2% in magnitude and <2° of phase (EuroSensor, Model 33; UK). The electrical output of these transducers was band-pass filtered (8–2,000 Hz) and converted from analogue to digital at 8,258 Hz (Model AT-MIO-16; National Instruments). Data were stored during five complete cycles of the interrupter (five times 31 ms = 155 ms, with a sampling rate of 8,258 Hz). The ratio of P_1/P_0 was estimated from the cross-power spectra of P_0P_1 and the auto power spectra of P_1 [24]. The length of the FFT window was 1,024 points. Control of the interrupter shutter, data acquisition, and computation of the cross-power and autopower spectra and their ratio were performed using Labview for Windows (National Instruments).

Thoracic compression technique

Partial expiratory flows at FRC (V'_{maxFRC}) were measured using the RTC technique [1, 3, 25]. The supine infants wore an inflatable polythene thoracoabdominal jacket (Medical Engineering Dept, Royal Postgraduate Medical School, London, UK) with the arms out. Flow was measured using a face mask (size 1, Rendell Baker Soucek, Ambu International) and Fleisch No. 1 (Gould, NE, USA) pneumotachograph and differential pressure transducers (Validyne MP45, Northridge, CA, USA). The linearity was estimated to be accurate within 2%. The flow signals were converted from analogue to digital and assessed using RASP software (Physiologic, Newbury, UK). After a series of RTC measurements to determine the optimal jacket pressure, 10 RTC measurements were performed at end-tidal inspiration using this optimal jacket pressure. The mean value of all technically satisfactory values was determined. Transcutaneous oxygen tension (P_{O_2}) (TMC3; Radiometer, Copenhagen, Denmark), and transcutaneous oxygen saturation (S_{a,O_2}) (Biox 3740; Omeda, Omaha, NE, USA), were observed. The head position was standardized based on the experience of DESAGER *et al.* [17] but, for safety reasons the mouth was not taped. The head position was not changed between measurements using different techniques. The same face mask and putty filling were used for both techniques.

Part 1: Description and repeatability of high-frequency impedance phenomena

In order to test the short-term repeatability within a period of 10–15 min, 10 sets of $Z(f)$ measurements were performed during quiet, regular tidal breathing. Each measurement

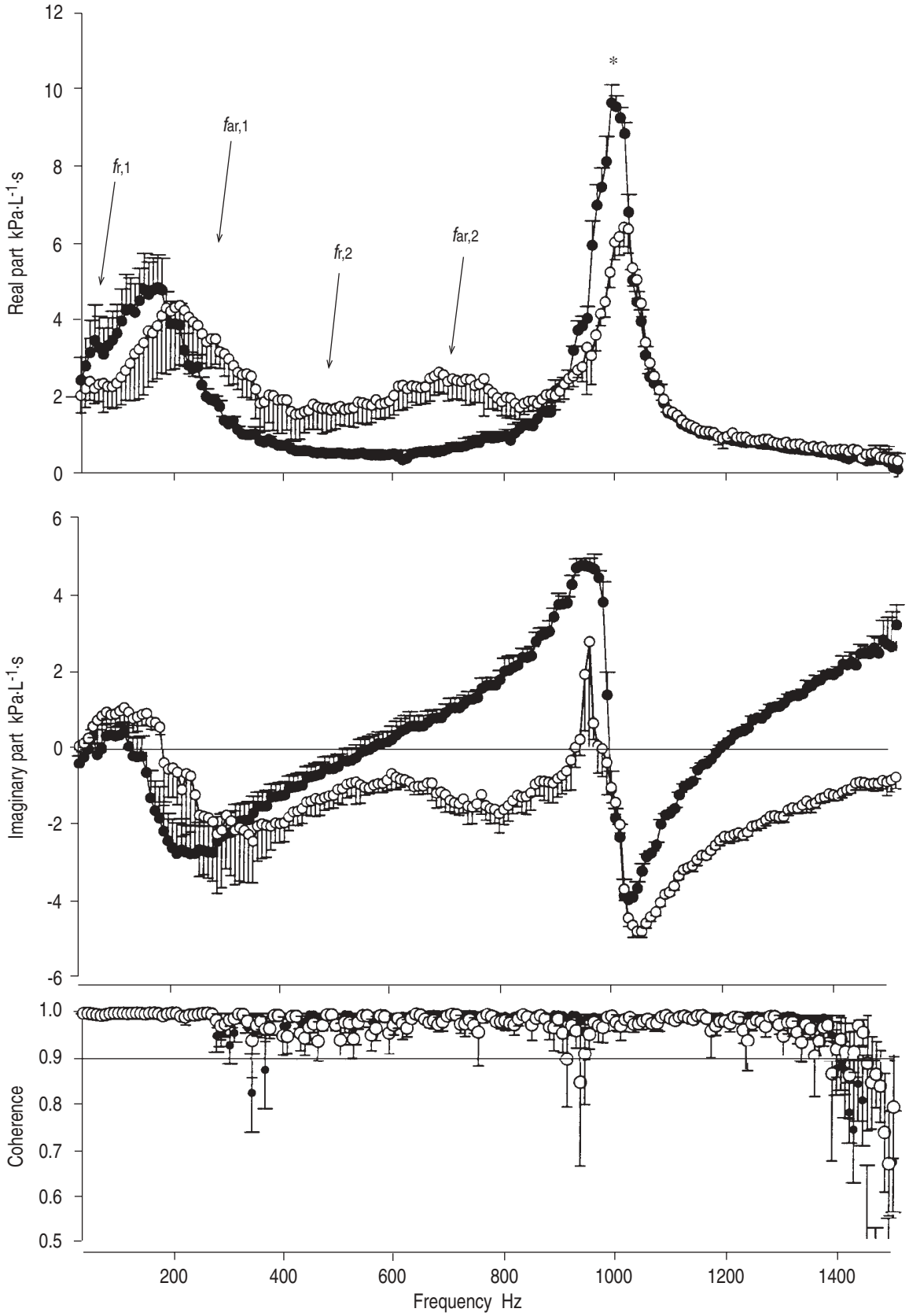

Fig. 2. – Mean impedance spectrum, SD (bars) and coherence from 10 input impedance measurements assessed by the high-speed interruptor technique in two representative infants (●: subject 11; ○: subject 5). Both infants showed a first and second resonance frequency ($f_{r,1}$ and $f_{r,2}$) and a first antiresonance ($f_{ar,1}$). Subject 5 showed a second antiresonance ($f_{ar,2}$). A third antiresonance($f_{ar,3}$) at ~1,000 Hz occurred in both infants, but was dependent on the set-up and the type of face mask (artefactual). Apart from single frequency points, which were excluded from the spectrum, the coherence was >0.9 from 32 to ~1,300 Hz. *: upper airway artefact.

took 0.15 s at the beginning of inspiration. Airflow interruptions that did not show peak pressure changes of Š0.15 kPa were not accepted. None of the infants was disturbed in sleep by the measurements, no symptoms occurred, and P_{O_2} and S_{a,O_2} remained stable. Thereafter, the inflatable jacket was wrapped around the infant's chest and 10 forced expirations were performed. From each of the 10 sets of five airflow interruptions, $Z(f)$ and coherence γ were calculated. The 10 sets were assessed during a period of 10–15 min to determine short-term repeatability. Only $Z(f)$ data with coherence >0.90 were accepted. If the coherence of the whole set of measurements was low the set was rejected. If the coherence of a few data points was <0.9, these particular frequency points were rejected and excluded from the spectrum. From the sets that fulfilled the criteria mentioned above, the mean and SD of the $Z(f)$ was calculated from 32 Hz to the maximal frequency with $\gamma > 0.90$ ($f_{max}\gamma$). The $Z(f)$ was presented by complex numbers (real and imaginary part): short-term repeatability of frequency ($f_{ar,1}$) and the relative maximum in the real part at $f_{ar,1}$ ($Z(f)$re($f_{ar,1}$)) at the antiresonances were expressed by their coefficient of variation (CV).

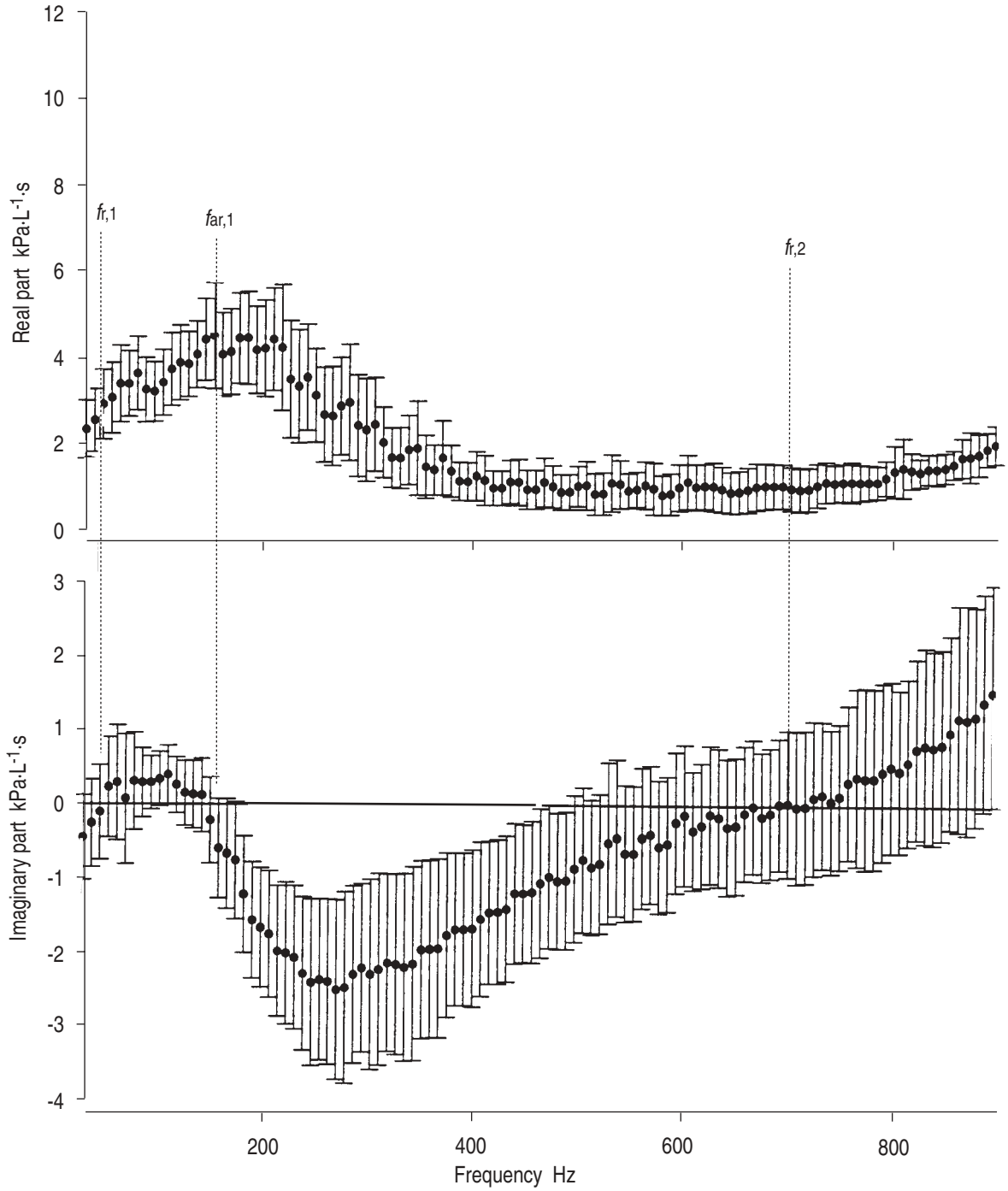

Fig. 3. – Impedance spectra (mean and SD for all 18 infants) from 32 to 900 Hz, showing the first resonance frequency, $f_{r,1}$ (53±14 Hz), the first antiresonance, $f_{ar,1}$ (172±35 Hz) and the second resonance frequency, $f_{r,2}$ (762±158 Hz).

From the 10 forced expiratory manoeuvres the mean and SD of V'_{maxFRC} were calculated as well as percentage predicted (for age) based on the reference values of TEPPER *et al.* [1]. Short-term repeatability V'_{maxFRC} was expres-sed by the CV. The differences in CV between the diff-erent parameters were compared using a nonparametric Wilcoxon test.

Part 2: Measurements during Heliox (He-O_2) breathing

Five sets of $Z(f)$ measurements were collected in three infants (aged 1, 9 and 12 months) during air breathing and during humidified Heliox (He-O_2) breathing after 8–10 min of equilibration.

Part 3: Influence of nasal patency on Z(f)

In another three infants (aged 12, 12 and 18 months) the possibility was examined that high-frequency $Z(f)$ data were influenced by the upper airway patency. In each of these three infants, five sets of $Z(f)$ measurements were performed before and after the occlusion of one nostril by gentle pressure over the alae nasae and by putting therapeutic putty inside the face mask. During this 30 s manoeuvre S_{a,O_2} was stable in all infants. With this manoeuvre the resistive and inertive properties of the upper airways were altered, without any direct alteration of the intrathoracic airway function.

Results

Part 1: High-frequency impedance phenomena

Representative examples of $Z(f)$ data in two subjects (5 and 11) are shown in figure 2. All subjects showed similar high-frequency $Z(f)$. The real part of $Z(f)$ at 32 Hz was between 1.34–3.54 (mean 2.34±0.64) kPa L^{-1}·s. In all but four of the subjects a first resonance was found above 32 Hz ($f_{r,1}$) at 53±14 Hz and in all subjects a second resonance $f_{ar,2}$ at 762 ± 158 Hz. All subjects showed a well-defined antiresonances ($f_{ar,1}$) at 172 ± 35 Hz. In three subjects the first antiresonance was split into two distinct

Table 3. – Technical quality of the high-frequency impedance measurements using the high-speed interrupter techniques

Patient	n	$f_{max}\gamma$ Hz
1	10	1322
2	9	1379
3	8	1411
4	7	1330
5	8	1395
6	10	1387
7	10	1340
8	10	1444
9	7	1315
10	10	1451
11	10	1387
12	8	1379
13	10	1370
14	10	1443
15	10	1483
16	10	1443
17	10	1443
18	10	1379
Mean	9.3	1395
SD	1	49

From 10 measurements (inclusion criterion: pressure change >0.15 kPa) n measurements showed a coherence >0.9 up to a maximal frequency ($f_{max}\gamma$).

Table 2. – Results of high frequency impedance measurements using the high speed interruptor technique

Patient	V'_{maxFRC} mL·s^{-1}		$f_{ar,1}$ Hz		$Z(f)$re kPa·L^{-1}·s		$f_{ar,2}$ Hz		$Z(f)$re($f_{ar,2}$) kPa·L^{-1}·s		Ratio
	mean	CV	mean	CV	mean	CV	mean	CV	mean	CV	$f_{ar,2}/f_{ar,1}$
1	146	5.1	117.5	3.3	2.6	7					
2	320	4.9	162	6.7	5.3	8.8	554	6.3	17.7	30.9	3.4
3	201	3.7	161	13.5	4.6	20.8					
4	149	5	218.5	4.5	6.2	7.5					
5	144	4.5	212.5	9.7	6.3	18.6	648	11.8	30.7	48.5	3.1
6	409	5	177.9	14.1	6.4	8.9	540	6.4	23.2	26.8	3.0
7	268	5.4	173	7.3	5.3	17					
8	213	6	185.8	3.8	2.9	5.3					
9	183	5.3	193	8.3	5.3	21.9					
10	128	10.5	85.6	18.2	4.0	3.5	570	5.9	10.8	5.8	6.67*
11	92	9.9	154.5	6.4	4.8	17.9					
12	79	10.4	173	10	4.7	20					
13	87	12.1	139.9	25.1	3.6	15.8					
14	89	8.4	212.9	11	6.3	6.4					
15	220	3.4	209	5.7	7.0	10.9					
16	175	4.3	198.6	11.7	4.6	16.9					
17	243	4.9	152	7.1	4.8	11.5					
18	356	6.7	162.8	8.8	3.8	15.4	511	4.9	18.2	6.9	3.1
mean	213	6.4	171.6	9.7	4.9	13	564.4	7.1	20.1	23.7	3.2
SD	90	2.6	34.8	5.4	1.1	5.9	51.4	2.7	7.4	18	0.2

Values are shown as the mean and coefficient of variation (CV) of 10 measurements. The input impedance ($Z(f)$) antiresonances (high-speed interrupter technique) were described by the frequencies of the first and second antiresonances ($f_{ar,1}$ and $f_{ar,2}$ (Hz)) and the relative maxima in the real part at $f_{ar,1}$ and $f_{ar,2}$, respectively ($Z(f)$re($f_{ar,1}$), $Z(f)$re($f_{ar.2}$)). V'_{maxFRC}: maximal expiratory flow at functional residual capacity (using rapid compression technique).

maxima but only one zero-crossing in the imaginary part (subject 8: 113/185 Hz; 10: 86/200 Hz; 12: 140/209 Hz). In five of the infants (as in subject 5, fig. 2) there was a relative maximum in the real part of $Z(f)$ at a frequency $f_{ar,2}$ = 690±180 Hz that was associated with relative maximum in the imaginary part, but the imaginary part did not cross zero as it does in a well-defined antiresonance. At 1,003±9.67 Hz ($f_{ar,3}$) a well-defined antiresonance was found in all subjects. However, this antiresonance varied within subjects, when the set-up or the face mask was changed (as discussed in more detail below). Therefore, only $Z(f)$ measurements up to 900 Hz are reported (fig. 3). The short-term repeatability of the first and second antiresonance is given by the CV (table 2). The CV of $f_{ar,1}$ (9.7±5.4%), $f_{ar,2}$ (7.1±2.7%) and V'_{maxFRC} (6.4±2.4%) in these subjects were not significantly different (p>0.01), whereas the CV of $Z(f)re(f_{ar,1})$ (13±5.9%) and $Z(f)re(f_{ar,2})$ (23.7±18%) were higher than the CV of V'_{maxFRC} (p<0.01).

The technical reliability of the HIT is described by the number of measurement sets (n out of 10) with coherence γ >0.90 and the maximal frequency up to which $Z(f)$ could be measured with coherence γ >0.9 ($f_{max}\gamma$) (table 3). In all infants the coherence was >0.9 between 32 Hz and 1,395±49 Hz, except for a few single frequency points, usually around 350 and 900 Hz. These frequency points were excluded from the analysis.

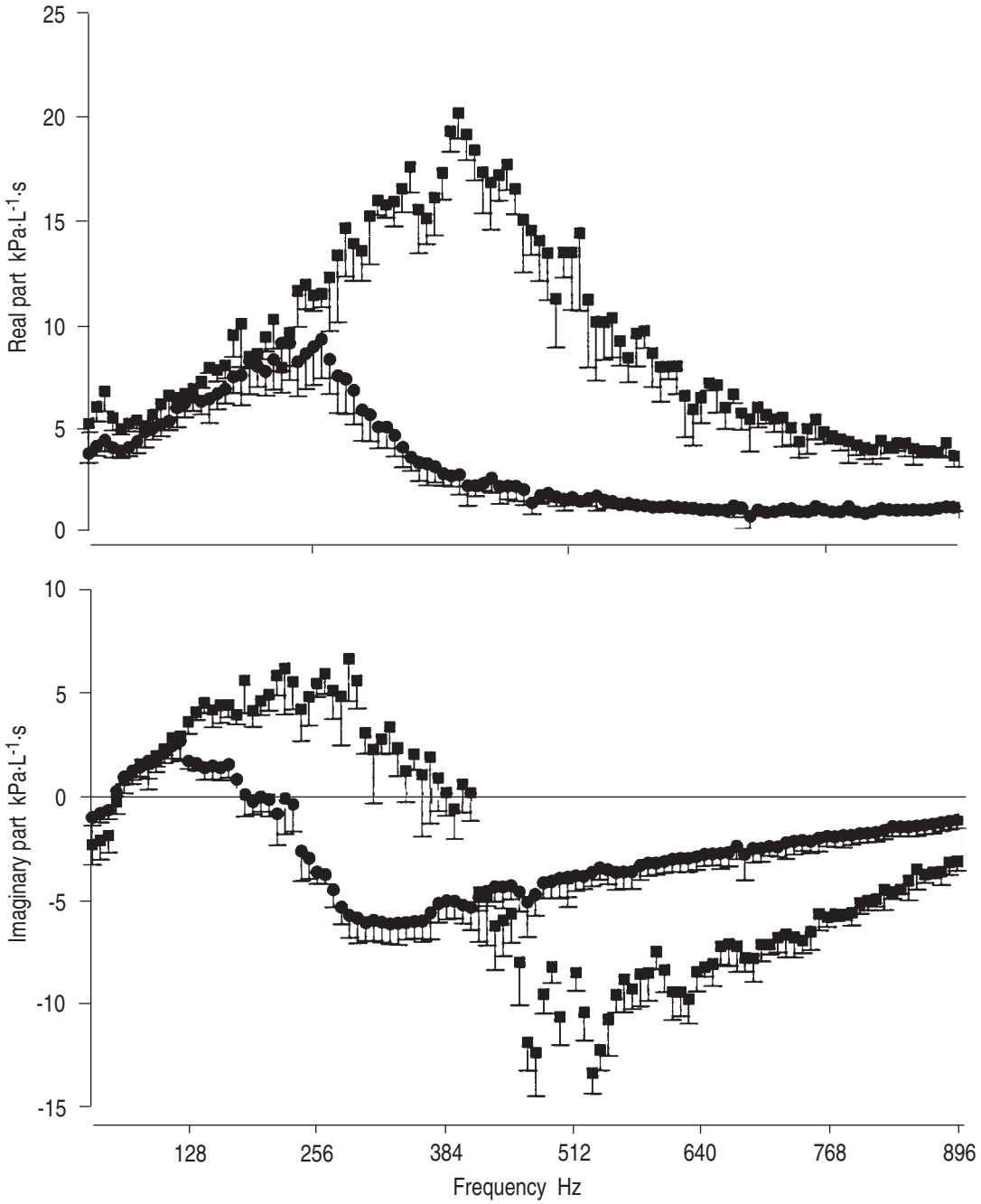

Fig. 4. – High-frequency input impedance ($Z(f)$) measurements (mean and SD of 10 measurements) during room air (●) and He-O_2 breathing (■) in one infant. The antiresonances $f_{ar,1}$ shifted from 193 Hz to 403 Hz when breathing gas of low density (He-O_2).

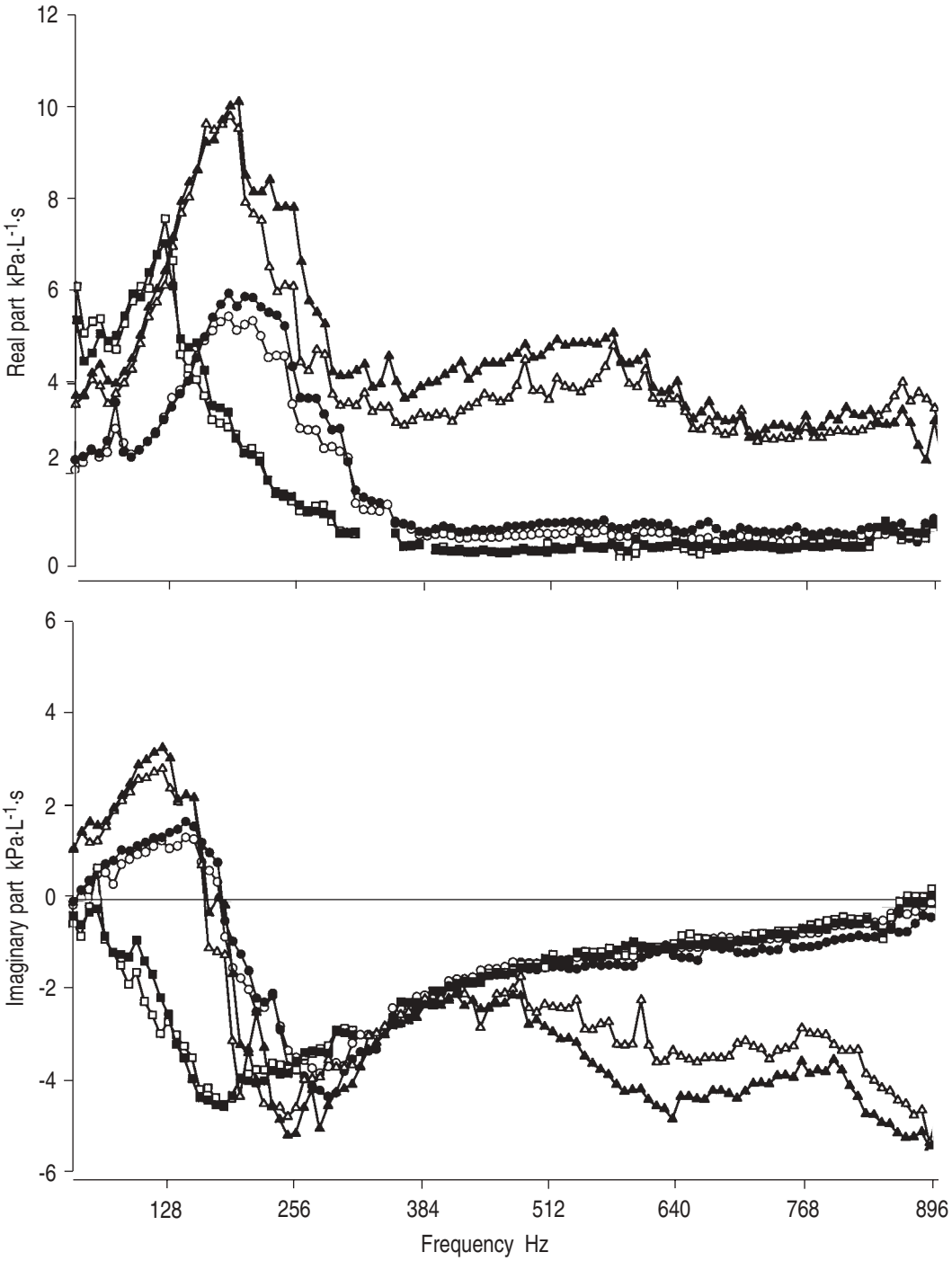

Fig. 5. – Example of five high-frequency input impedance ($Z(f)$) measurements (mean; errors quitted for clarity) in three infants (circles, squares, triangles) before (open symbols) and after (closed symbols) occlusion of one nostril, indicating that the antiresonance in the $Z(f)$ measurements was not significantly influenced by altering the upper airway patency.

Part 2: Measurements during Heliox (He-O_2) breathing

When a gas of lower density (He-O_2) was inhaled, $f_{ar,1}$ increased from 193 to 403 Hz (ratio 2.1) in one subject (fig. 4), from 112 to 274 Hz (ratio 2.4) in the second subject and from 209 to 314 Hz (ratio 1.5) in the third subject. These results are close to the theoretical value of 1.93 and provide evidence that the first antiresonance is a phenomenon related to wave-propagation velocity within the airways.

Part 3: Influence of nasal patency on Z(f)

Occluding one nostril had no significant effect on the first antiresonance in all three infants (fig. 5). The differences in $f_{ar,1}$ and $Z(f)\mathrm{re}(f_{ar,1})$ before and after occlusion for the three subjects were 0, 0 and 8 Hz and -0.5, 0.5 and 0.22 kPa·L^{-1}·s respectively.

Discussion

Two problems were addressed in this study: firstly, whether high-frequency input impedance in infants can be

measured by the noninvasive HIT and, secondly, whether high-frequency $Z(f)$ data can provide information about intrathoracic airway mechanics. For this purpose, the nature of the antiresonances in infants had to be elucidated. It has recently been demonstrated in human adults that the frequency of these antiresonances contains information about airway wall properties [8–11, 14]. The possibility of measuring airway wall mechanics *in vivo* in infants would, thus, help to elucidate flow limitation phenomena in wheezing disorders in infants, since flow limitation is influenced not only by the airway diameter but also by airway wall compliance [2]. The widely used rapid chest compression technique is not able to distinguish between the effects of airway diameter and airway wall compliance on airflow limitation. Measurement of airway wall properties would help to answer the question of whether only developmental differences in airway size [4] or possibly also developmental differences in airway wall compliance might predispose to wheezing disorders in infancy. It could also explain why bronchodilators can have paradoxical effects in infants [3], bearing in mind that they have the potential to change both airway diameter and airway wall compliance by changing airway smooth muscle tone.

Information about airway wall properties in adults has been extracted from measurements of $Z(f)$ from 5–320 Hz [11] and in more detail from 8–2000 Hz in adults [14]. In infants, $Z(f)$ data have never been measured in the frequency range >256 Hz, and the nature of antiresonance phenomena has never been elucidated. Measurement of $Z(f)$ at these high frequencies was expected to be difficult, because infant airways are small and the system has a relatively high impedance. Therefore, if pressure waves are applied at the airway opening, as in the FOT, the amplitude of the resulting flow will be small and the signal-to-noise ratio will be low. This is particularly true for higher frequencies because of the capacitative shunting into the gas compression compliance of the loudspeaker (FOT) [21]. To overcome these problems a new technique was developed, the HIT [21], which uses a pseudo-step-flow forcing function and enables much higher flow amplitudes at high frequencies than the FOT.

The interrupter technique was invented by Neergaard and Wirz [26] and has been modified many times [27–31]. The value of the standard interrupter technique is limited because it only permits the measurement of a Newtonian lung resistance [30, 31], but changes in airway opening pressure after airflow interruption can be analysed in more details. Jackson *et al.* [28, 29] showed that highly damped pressure oscillations occurred after rapid airflow interruption. Romero *et al.* [32] showed in dogs that an antiresonance in the power spectrum of the airway opening pressure occurred at ~80 Hz and a gas density-dependent antiresonance occurred at 180 Hz. They specula-ted that these antiresonances correspond to the C_g-I_{ti}-tissue resonance (80 Hz) and the first acoustic resonance (180 Hz) described by Jackson and Lutchen [7] in the $Z(f)$ spectrum. Only a single antiresonance was found in human adults which, after correction for the mouthpiece length, was close to 180 Hz [33, 34] and it was speculated in analogy that it corresponds to the wave propagation-related antiresonance in the $Z(f)$ spectrum found by Jackson *et al.* [11]. Recently, it was shown in a dog lung and in human adults that it is possible to measure high-frequency $Z(f)$ using the new HIT [21], when not only the post-occlusional pressure transients but also post-occlusional oscillatory flow transients are measured.

Measurement of Z(f) in infants using the HIT from 32 to ~1300 Hz

This was technically possible with a coherence-γ >0.9 using a pseudostep flow-forcing function generated by the HIT. Two resonances and one antiresonance was found in all of the infants, whereas a second antiresonance was detectable only in five of the subjects. At frequencies over 1,000 Hz a third antiresonance occurred which was dependent on the set-up and the face mask. The frequency and the real part at this third antiresonance changed when the set-up, the head position and the face mask were varied within the same patient. Furthermore, despite matching the pressure transducers inaccuracies were also expected at about 1,000–1,100 Hz, because the resonant frequency of the solid-state pressure transducers was expected to lie in this frequency range. For these reasons, only $Z(f)$ data up to 900 Hz were reported.

Physiological interpretation of Z(f) data below 100 Hz in infants

The first resonance frequency ($f_{r,1}$) was <32 Hz in 4 subjects and at 53±14 Hz in the others, which is slightly higher than in our previous study [20] (37±9 Hz), but similar to the studies of Desager *et al.* [17] and Jackson *et al.* [19]. Marchal *et al.* [15] did not find a resonance in their study, probably because their measurements were not taken to high enough frequencies. Marchal *et al.* [16] found $f_{r,1}$ at lower frequencies when they used the head generator technique, indicating the effects of extrathoracic airway walls on $f_{r,1}$. Also, Sly *et al.* [18] found $f_{r,1}$ to be at much lower frequencies. This might be explained by the fact that they performed measurements under conditions of raised lung volume and induced relaxation (Hering-Breuer reflex) in healthy infants. The geometry of the face mask might also have been different in their study.

In the present study, $f_{r,1}$ was inversely related to postnatal age; the older the child the lower the first resonance. Based on the Dubois model [22] $f_{r,1}$ is given by:

$$f_{r,1}={}^1/_2\cdot[C_{ti}(I_{aw}+I_{ti})]^{0.5},$$

where C_{ti} is the tissue compliance, I_{aw} the airway inertance and I_{ti} the tissue inertance. This dependence on compliance would explain the inverse correlation between $f_{r,1}$ and age. The frequency dependence of the real part of $Z(f)$ below $f_{r,1}$ was difficult to assess with the HIT because the lowest frequency measured was 32 Hz. However, this frequency dependence of resistance in infants is influenced not only by parallel inhomogeneity but also by nonrigid behaviour of the upper or central airways [19]. Recent computer predictions by Jackson *et al.* [19] suggest that since infant airways are so compliant, the real part could be frequency dependent even in healthy infants, as observed by Marchal *et al.* [15]. Using FOT this frequency dependence of resistance as well as $f_{r,1}$ was demonstrated to change in a very complex and unsystematic manner during induced airway obstruction [20].

Physiological interpretation of Z(f) above 100 Hz in infants

The most prominent features in the $Z(f)$ above 100 Hz are the antiresonances. A first antiresonance was found in

all infants and a second antiresonance in five infants. The frequencies of both the first and second antiresonance showed a CV similar to V'_{maxFRC} from the widely used RTC technique, whereas the relative maxima at the anti-resonant frequencies showed a slightly higher variability. The frequency and relative maxima in the real part were not related to age. However the patients were not healthy and so a final conclusion on age dependence cannot be drawn. The first antiresonance occurred at ~170 Hz, which is similar to the findings in adults [11] and to our previous study [20], but higher than reported in the study of JACKSON *et al.* [19] in healthy infants. The fact that higher antiresonant frequencies were found in infants with wheezing would be consistent with observations in adults with obstructive pulmonary disease [12]. However, while there was a tendency for $f_{ar,1}$ to be higher with decreasing V'_{maxFRC} and therefore increasing airway obstruction, this correlation was not significant. To understand this more information is needed on the nature of the antiresonances in infants, since in wheezy infants the airways might be very different from those of patients with chronic obstructive pulmonary disease.

The current findings support mainly the hypothesis that the antiresonances are caused by wave-propagation phenomena in the airways, as in human adults. Theoretically, the fact that the antiresonant frequency changed when a gas of lower density ($He-O_2$) was inhaled could be explained either by the interaction of C_g and I_{ti} (Dubois model) or by the influence of the average molecular weight of the gas mixture (gas density) on the wave-propagation velocity. In the first case, according to the Dubois model $f_{ar,1}$ would be inversely related to C_g and I_{ti}. I_{ti} should not be affected by a gas of different density, whereas C_g would change provided the ratio of specific heats of the two different gases are different and the compressions in the alveoli are adiabatic. The differences in specific heat between air (1.4) and $He-O_2$ (1.56) would result in an 11% increase in C_g and a 5% decrease in $f_{ar,1}$ during $He-O_2$ breathing. Similarly, if the antiresonance were purely related to the gas compression compliance in the face mask (C_m), $f_{ar,1}$ would change, but not by a factor of 2. In the second case, if the antiresonance is related to wave-propagation, $f_{ar,1}$ is proportional to the wave-propagation velocity (υ). For example, in a rigid tube, $f_{ar,1}$ would be $\upsilon/4L$, where L is the length of the tube. In a rigid tube υ is only dependent on gas density and not on diameter, whereas in a compliant tube υ is a function of gas density and wall compliance [35]. However, airway wall compliance did not change during the $He-O_2$ experiment. The ratio of υ_{He-O_2} (64.5 ms^{-1}) and υ_{air} (33.3 ms^{-1}) is 1.93. In the present study $f_{ar,1}$ increased by a factor of ~2 following $He-O_2$ breathing, which makes it likely that the antiresonance is related to wave propagation in the airways and not to tissue properties. In this concept antiresonances are often referred as acoustic antiresonances [11].

Assuming a very simple acoustic airway model consisting of a single open rigid airway, the harmonics ($f_{ar,2}$, $f_{ar,3}$, $f_{ar,4}$...) of $f_{ar,1}$ would occur at multiples of 3, 5, 7... times $f_{ar,1}$. In four of five subjects in whom a second antiresonance $f_{ar,2}$ occurred, it was found to occur at a multiple of ~3 (5 in subject 10) of $f_{ar,1}$, which would support the hypothesis. However, $f_{ar,1}$ of 171 Hz would correspond to a mean airway path length of 48.7 cm, which seems too long for an infant. In compliant tubes, $f_{ar,1}$ depends not only on airway path length and gas density, but also on the compliance of the tube. The relationship between the wave-propagation velocity in a nonrigid tube and the wall compliance is highly complex and dependent on the frequency of the travelling pressure wave [35]. This might lead to two phenomena: first, $f_{ar,1}$ is dependent on airway wall compliance and, secondly, the ratio $f_{ar,2}/f_{ar,1}$ might not simply be a harmonic function.

This new evidence that the antiresonances are dependent on wave propagation is interesting from a developmental point of view since high-frequency $Z(f)$ data in human infants correspond more closely to $Z(f)$ in human adults [10, 11] than to $Z(f)$ in animals [7] with lungs of similar size to infant lungs. However, wave-propagation-related antiresonances in human adults are much sharper and narrower. There are at least two possible explanations for this. In wheezy infants parallel inhomogeneities are expected. Since $f_{ar,1}$ corresponds to a mean airway pathlength, one would expect to see a bundle of antiresonances that are close together and might originate from different parallel segments. An alternative explanation would be that multiple peaks could occur because of the frequency dependence of wave-propagation velocity in a compliant tube [35]. Both hypotheses would also explain the occurrence of multiple peaks around $f_{ar,1}$ in three of the subjects at baseline.

Having elicudated the origin of the antiresonance phenomena, the question remains of whether the high-frequency $Z(f)$ was largely determined by intrathoracic airway geometry or whether the extrathoracic airway significantly influenced the high frequency $Z(f)$. In three subjects, after occlusion of one nostril the high-frequency $Z(f)$ did not change significantly, providing reassuring evidence that upper airway resistance had little influence on the antiresonances. The influence of extrathoracic airway wall compliance on $Z(f)$ data at frequencies below 100 Hz has been pointed out by several authors [16, 19]. The current data support the hypothesis that the antiresonances occurring above 100 Hz are related to wave-propagation phenomena, implying that its frequencies are related to airway wall properties. It must be assumed, that pressure waves are propagated along the entire airway pathlength from the airway opening to the alveolar space. The compliance of the upper airway may, therefore, partly influence wave-propagation velocity and the high-frequency impedance spectrum of the respiratory system. The influence of the upper airway was minimized in the present measurement setting by filling the face mask with putty and stabilizing the cheeks by holding the face mask firmly in place. In order to determine the relative contribution of extrathoracic and intrathoracic airway wall compliance on $f_{ar,1}$, one must selectively change one or the other. Since airway smooth muscle is the major determinant of intrathoracic airway wall compliance and cholinergic receptors in the extrathoracic airway are only located in vessels and glands [36], methacholine challenge might help to elucidate the situation. This is reported in our accompanying paper.

Conclusions

A new noninvasive lung function technique, the high speed interrupter technique has been developed, which enables the noninvasive measurement of high-frequency input impedance from 32–1,300 Hz in infants. Measurements can be performed without the cooperation of the patient within a few seconds. At frequencies between

100–900 Hz two antiresonances were found. At ~1,000 Hz there was a third antiresonance, which was artefactual and depended on the set-up and face mask. The first antiresonance was related to wave-propagation velocity in the airways, similar to the situation in human adults. This implies that the frequency of the first antiresonance is a function of airway wall compliance independent of airway diameter. The frequencies of these antiresonances show a similar variability to standard lung function parameters in this age group. The antiresonance was not significantly affected when nasal patency was altered by occluding one nostril. Since the first antiresonance is a function of airway wall compliance and not of airway diameter, it can be used to elucidate developmental differences in airway wall compliance in the first year of life and their consequences for wheezing disorders, and to explore the actions of therapeutic agents that affect airway function.

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