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New aspects of airway mechanics in pre-term infants

M. Henschen*,#,¶, J. Stocks#, I. Brookes+ and U. Frey§

ABSTRACT: High-frequency respiratory impedance data measured noninvasively by the high-speed interrupter technique (HIT), particularly the first antiresonance frequency ($f_{ar,1}$), is related to airway wall mechanics.

The aim of this study was to evaluate the feasibility and repeatability of HIT in unsedated pre-term infants, and to compare values of $f_{ar,1}$ from 18 pre-term (post-conceptional age 32–37 weeks, weight 1,730–2,910 g) and 18 full-term infants (42–47 weeks, 3,920–5,340 g).

Among the pre-term infants, there was good short-term repeatability of $f_{ar,1}$ within a single sleep epoch (mean (SD) coefficient of variance: 8 (1.7)%), but 95% limits of agreement for repeated measures of $f_{ar,1}$ after 3–8 h were relatively wide (-41 Hz; 37 Hz). $f_{ar,1}$ was significantly lower in pre-term infants (199 *versus* 257 Hz), indicating that wave propagation characteristics in pre-term airways are different from those of full-term infants. The present authors suggest that this is consistent with developmental differences in airway wall structure and compliance, including the influence of the surrounding tissue.

Since flow limitation is determined by wave propagation velocity and airway cross-sectional area, it was hypothesised that the physical ability of the airways to carry large flows is fundamentally different in pre-term than in full-term infants.

KEYWORDS: Infant, interrupter technique, pre-term, respiratory function tests

There is a significant body of evidence from epidemiological studies confirming a link between childhood lower respiratory illness and wheezing and the development of adult chronic respiratory disease [1–6]. The nature of this link, the biological mechanisms which mediate it, and the genetic, developmental and environmental factors which influence its expression have been the focus of considerable research effort in recent years. One concept evoked to explain this association is that of ''programming'', the permanent alteration of the structure and function of organs and tissues by factors operating during sensitive periods in foetal or early post-natal life [4]. Factors implicated in programming of the respiratory system include foetal nutrition [7], foetal exposure to maternal smoking during pregnancy [8], pre-term delivery and exposure to environmental allergen or viral respiratory infections during infancy [3, 9]. Little is known about the impact of pre-term delivery on airway development, although it has been shown that this may result in a relative increase in the amount of bronchial smooth muscle and number of goblet cells, particularly among those who require mechanical ventilatory support [10]. Pre-term delivery, even in the absence of any neonatal respiratory disease or ventilatory support, may have an adverse effect on subsequent lung growth and development, which persists and may even worsen throughout the first years of life [11–15].

To evaluate the impact of pre-term delivery on airway development, it is essential to understand the effect of developmental structural differences on airway function. While all conducting airway generations are formed by 16 weeks' gestation, with a linear increase in airway diameter between 22 weeks' gestation and 8 months post-natal age, true alveoli do not begin to develop until ~30 weeks' gestation, with subsequent rapid increase in number, size and complexity during the first 3–4 yrs of life [10]. Different growth patterns of the airways and parenchyma (dysanaptic growth) during foetal and early post-natal life result in airways that are relatively large in relation to lung volume at birth [16]. This has been reflected by functional measurements which indicate relatively low airway resistance [17] and an increased expiratory rate constant (change in flow divided by the change in volume between 50 and 75% of expired forced vital capacity) in early life [18]. Nevertheless, young infants, particularly those delivered prematurely, who are often born early for some abnormal reason, are prone to

AFFILIATIONS
*Dept of Paediatrics and Adolescent Medicine, University Hospital of Freiburg, Freiburg, Germany.
#Portex Respiratory Unit, Institute of Child Health,
¶Neonatal Unit, Homerton University Hospital, London, and
+Dept of Child Health, University of Leicester, Leicester, UK.
§Paediatric Respiratory Medicine, Dept of Paediatrics, University Hospital of Bern, Inselspital, Bern, Switzerland.

CORRESPONDENCE
M. Henschen
Schwarzwald-Baar Klinikum
Villingen-Schwenningen GmbH
Vöhrenbacher Straße 23
D-78050 Villingen-Schwenningen
Germany
Fax: 49 7721933599
E-mail: matthias.henschen@sbk-vs.de

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airway narrowing and closure during tidal breathing, and have increased vulnerability to wheezing disorders. This emphasises the complex structure–function relationships in the developing lung, including the fact that expiratory flows are related not only to airway dimensions, but also to the compliance of the airway wall [19] and of the surrounding parenchyma and chest wall [16]. It has been shown in an animal model, that structural differences of immature airways may result in a markedly increased airway wall compliance [20]. In addition, developmental changes in the properties of the lung parenchyma [21, 22], dynamic control of end-expiratory lung volume [23], high chest wall compliance [24] and diminished airway–tissue coupling [25] influence elastic recoil of the respiratory system with subsequent impact on functional airway diameter and airway wall mechanics. Due to the complexity of these interactions, it is extremely difficult to assess the potential impact of altered airway wall mechanics on measured values of resistance or forced expiratory flows in pre-term infants during the first months of life.

In 1998, the high-speed interrupter technique (HIT) was proposed as a novel method to measure high frequency respiratory impedance *in vivo* [26]. As explained later (see the discussion section), it has been shown in both adults and infants, that high frequency respiratory impedance data, particularly the frequency at which the first antiresonance ($f_{ar,1}$) occurs, is influenced by the wave propagation velocity (v) of pressure waves (*i.e.* wave speed) within the airways and is related to airway wall mechanics [26–28]. In pre-term infants, particularly during respiratory distress when higher intrathoracic pressures occur, airway wall mechanics will become increasingly important for flow limitation. To better understand flow limitation, and thus wave propagation and airway wall properties in pre-term infants, the aims of this study were: 1) to evaluate the feasibility and repeatability of applying the HIT in unsedated pre-term infants, and 2) to assess developmental changes in airway wall mechanics by comparing values of $f_{ar,1}$ in healthy pre- and full-term infants.

MATERIALS AND METHODS

The present study was performed in two stages. In the first stage, the feasibility and within-subject variability of using the HIT to measure high frequency impedance ($Z(f)$) between 32 and 512 Hz were analysed in a group of healthy pre-term infants, focusing particularly on the $f_{ar,1}$, which is mainly determined by wave propagation properties of pressure waves in the airways (see discussion). During the second stage, values of $f_{ar,1}$ from this group of pre-term infants were compared with those from healthy full-term infants measured under the same conditions.

Subjects

Pre-term infants from the Neonatal Unit at the Homerton University Hospital, London, UK, were eligible for recruitment if they were born at $\leqslant$36 completed weeks of gestation without major congenital abnormalities and required minimal ventilatory assistance (defined as continuous positive airway pressure (CPAP) and/or supplemental oxygen for $<$24 h after delivery). Gestational age was assessed from mothers' date of last menstrual period and from obstetric ultrasound scans performed at or before 20 weeks of pregnancy. The pre-term infants were compared with a group of healthy full-term infants recruited antenatally at the Dept of Paediatrics, University Hospital of Berne, Switzerland. Infants were ineligible for recruitment if they had experienced any respiratory problems, including upper or lower respiratory illnesses prior to testing. The study was approved by the University of Berne, Berne, Switzerland and the East London and City Research Ethics Committees, London, UK. Informed written consent was obtained from the parents, who were usually present during the measurements.

Study design

All infants were studied unsedated in natural sleep, 30 min to 1 h after a feed. In both centres, infants were measured using an identical protocol and equipment [26, 29]. Respiratory data were collected during consecutive periods of relatively quiet regular breathing in room air, with the infant settled in the supine position, while heart rate and oxygen saturation were monitored. Impedance measurements were performed prior to any other lung function measurements. A transparent Rendell–Baker face mask (size 0; Ambu International, Bath, UK) was held over the infant's mouth and nose. A leak-free seal and reduction of dead space was created using therapeutic silicone putty (Carters, Bridgend, UK). The effective dead space volume of the face mask was ~6 mL, as described previously [30], while that of the tube with the propeller valve was 7 mL. Between the short sets of measurements, the tube was detached to minimise dead space and CO_2 rebreathing. Measurements were repeated 10–25 times within each test occasion, provided the child remained undisturbed. Where possible the entire protocol was repeated on the same day after an interval of 3–8 h to assess repeatability of measurements.

High frequency impedance measurements Z(f)

The principles and technical details of the HIT have been described in detail previously [29]. Identical custom-built equipment was used in both centres. Briefly, high-frequency respiratory input impedance was measured with a propeller valve that rapidly (within 1 ms) occluded the airway opening five times within a period of 0.15 s (duration of each period of closure and opening being 15.5 ms) during tidal breathing without disturbing the infant. The resulting pressure and flow oscillations were measured by the wave tube technique [31] using two piezo-electric transducers (EuroSensor; Model 33, London, UK). Spectral analysis was used to calculate respiratory input impedance from the pressure and flow signals [32]. The $f_{ar,1}$, defined by a zero crossing in the imaginary part in the presence of a relative maximum in the real part of the impedance spectrum ($Z_{re}(f_{ar,1})$) was extracted from the impedance spectrum, assessed between 32 and 512 Hz (fig. 1). Data were not accepted for analysis if: 1) multiple peaks occurred; 2) the relative maximum of Z_{re} did not occur at the zero-crossing in the imaginary part; 3) the coherence was $<$0.9; or 4) oscillatory pressures changes were $<$0.15 kPa [26]. After separate primary analysis at each centre (M. Henschen in London, UK; I. Brookes in Bern, Switzerland), all data were reviewed by the same person for acceptability (U. Frey, Bern, Switzerland). Within each test occasion, the first 10 technically acceptable manoeuvres were taken for further analysis.

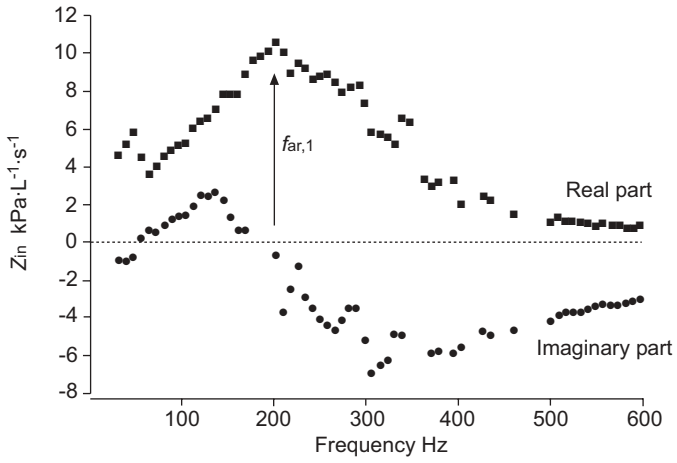

FIGURE 1. Example of one measurement of a high-frequency impedance spectrum from a single infant. The antiresonant frequency ($f_{ar,1}$) is defined by the relative maximum in the real part ($Z_{in,re}(f_{ar,1})$) in the presence of a zero crossing in the imaginary part. Z_{in}: respiratory input impedance.

Statistics

Short-term repeatability of 10 technically acceptable measurements of $f_{ar,1}$ within each test occasion was expressed as the coefficient of variation (CV %=100×SD/mean). BLAND and ALTMAN [33] analysis was used to assess within-subject between-occasion repeatability on the same day. Comparison of results between pre-term infants and healthy full-term infants were undertaken using the Wilcoxon two-sample test.

RESULTS

Measurements of high-frequency input impedance during tidal breathing were attempted in 21 healthy pre-term infants. None of the infants woke up during the short measurement period (range 4–15; median 6 min), but a sufficient number of technically acceptable measurements could be obtained in only 18 infants. The mean±SD number of attempted measurements was 18±3 and that of technically acceptable measurements 17±4.

Among the healthy full-term infants, 24 data sets with technically acceptable coherence were obtained initially. However, in six of these infants, the impedance spectra did not show a consistent single first antiresonance but a multiple peak resonance pattern. These data were excluded from further analysis, because a dominant peak could not be determined (see discussion).

Details of the remaining 18 pre-term infants together with those of the 18 full-term infants are summarised in table 1. As expected, the pre-term infants were younger, lighter and shorter than those born full-term. A relatively high proportion of males were studied, but there was no difference in sex distribution between the groups. The proportion of babies in whom both parents were northern European white people was, however, considerably lower among the London pre-term group than the Swiss full-term group ($p<0.001$). In the pre-term infants one infant received CPAP therapy (20 h, $f_{ar,1}$=157 Hz), while two had brief supplemental oxygen (1 day, $f_{ar,1}$=195 Hz and 11 h, $f_{ar,1}$=177 Hz, respectively).

The SD of repeat measurements of $f_{ar,1}$ on a single test occasion was <30 Hz in all but three infants (maximum 55 Hz), and was similar in pre-term and full-term infants (mean±SD: 16±3 and 23±13 Hz, respectively). While this was relatively independent of the absolute values, it equated to a mean CV of 8 and 10% in each of the two groups, respectively. Technically acceptable repeated measurements on two occasions were obtained after an interval (mean±SD) of 5.4±1.7 h in eight of the pre-term infants. Within-occasion variability during the second set of recordings was virtually identical to that observed in the initial set of measurements. There was minimal bias between repeated measures (the mean $f_{ar,1}$ on the first and second test occasions were 210 and 208 Hz, respectively). However, the 95% limit of agreement for individual subjects were relatively wide: -41–37 Hz.

$f_{ar,1}$ was significantly lower in pre-term than in full-term infants (mean (95% confidence interval)) difference, pre-term–full-term: -58 (-28– -88) Hz). On inspection of the data, there was overlap according to both sex and ethnic group (data not shown), although formal statistical comparison was precluded by the small sample size.

TABLE 1 Details of infants included in the study

	Pre-term infants	Full-term infants	p-value
n	18	18	
Male %	72	78	0.7
Both parents white northern Europeans %	17	100	<0.001
Birth weight kg	2.01±0.35	3.55±0.35	<0.001
Gestational age weeks	34±2	40±1	<0.001
Post-natal age days#	7 (4.5–10)	34 (29–38)	<0.001
Post-conceptional age weeks	35±1	45±1	<0.001
Test weight kg	2.12±0.26	4.55±0.43	<0.001
Crown–heel length cm	43.6±2.2	55.7±2.1	<0.001
$f_{ar,1}$ Hz	199±24	257±60	<0.001

Data are presented as mean (SD), unless otherwise indicated. #: data presented as median (interquartile range). $f_{ar,1}$: first antiresonance frequency.

DISCUSSION

The results of the present study show that it is feasible to apply the HIT to pre-term infants in unsedated sleep and that values of $f_{ar,1}$ were significantly lower among apparently healthy pre-term infants than their full-term counterparts. Once the infants were spontaneously sleeping, antiresonant frequencies could be detected in all unsedated infants without disturbance during a short measurement period of 4–15 min. There was a low failure rate, with only three pre-term infants showing <10 technically acceptable manoeuvres. The short-term variability of the first antiresonance within a single sleep epoch was very acceptable and comparable with previous studies from healthy full-term infants between 6–24 months of age [26, 30]. However, while there was no systematic group difference between the two sets of measurements of $f_{ar,1}$ on the same day in the eight pre-term infants in whom this could be measured, there was marked within-subject variability between results collected after an interval of 3–8 h.

Interpretation of the findings and model hypothesis

Investigation of factors determining airway function in immature infants is essential to further improve understanding of the impact of pre-term delivery on the subsequent development of airway structure and function. From a structural point of view, airways are relatively large in relation to lung volume during early life, but the maximal flows that can be conveyed through such airways may be somewhat less than anticipated, since such flows are a function of the v of travelling pressures waves; hence, they are related not only to diameter, but also to airway wall compliance [19]. One hypothesis is that the structural immaturity of the airway walls results in highly compliant airways, crucially determining flow limitation in immature airways of prematurely born infants. The high compliance of the airway walls in immature animals has been demonstrated *in vitro* [22, 34], but the situation might be different *in vivo* and/or in human infants, depending on the strength of airway–parenchyma attachments and the relationship between lung and chest wall compliance [24]. This relationship will be further complicated by the tendency of young infants to dynamically elevate their end-expiratory volume, thereby further regulating airway patency and elastic recoil, and by changes in sleep state, which may affect both lung volume and upper airway tone [16, 23]. A true picture of the role of these complex interacting structural and functional systems can therefore only be estimated *in vivo*. Since increased transmural pressures may affect airway compliance [20, 35], infants who had received mechanical ventilation were excluded from this study. Only one infant received CPAP therapy (20 h; $f_{ar,1}$=157 Hz), while two had brief supplemental oxygen (1 day, $f_{ar,1}$=195 Hz and 11 h, $f_{ar,1}$=177 Hz). Visual inspection of results indicated no bias with respect to data from these three infants, and identical conclusions were reached, whether or not they were excluded from the analysis.

The interpretation of these results in terms of their physiological meaning must be very cautious and can only be undertaken by reference to simplified models. At higher frequencies, pressure waves follow the physical laws of acoustics. In a large-diameter, simple, rigid straight tube, v corresponds to the first harmonic acoustic antiresonant frequency, comparable to the sound pitch of a flute. The frequency of this resonating sound is dependent on wave speed, which in turn is mainly dependent on gas density and the length of the tube. In a branching network of compliant small tubes (such as the airways), the frequency at which this antiresonance occurs is still dependent on v but, in such a system, v does not correspond to the free field sound wave speed, *i.e.* the wave speed in a simple, rigid straight tube. Under such circumstances, v is no longer dependent simply on length and gas density, but also on the airway wall mechanics (compliance) and, to a minor extent, by airway diameter in very small tubes. In the terminal airways of human adults where the diameter is <1 mm, v is 62% of the free-field speed of sound [28]. Thus, in very peripheral airways, v is significantly reduced. A reduction in v in these distal airways would cause them to resonate at a lower frequency. More important, however, is the influence of airway wall compliance. Airway wall compliance strongly influences v and, thus, $f_{ar,1}$ in compliant airways. The relationship between airway path length, diameter, wall compliance, v and $f_{ar,1}$ is highly complex and the influence of their components cannot easily be distinguished. Nevertheless, speculation is possible, based on the theory of simplified elastic tube models and animal models [36, 37].

A significantly reduced $f_{ar,1}$ was found among the pre-term group, who were not only more immature, but also younger and smaller than the full-term infants. Since mean airway path length must be shorter the smaller the infant, one might have expected $f_{ar,1}$ to be higher in this group. Indeed, assuming a certain proportionality between crown–heel length and mean airway path length [10], the mean airway path length would be expected to be ~30% lower and, thus, $f_{ar,1}$ to be ~30% higher in the pre-term group. Theoretically, airway diameter also has a certain influence on wave propagation in small tubes and, therefore, $f_{ar,1}$. However, based on published animal model estimations [36, 37], and assuming that airway resistance was ~30% higher in pre-term than in full-term infants [17], a corresponding diameter scaling factor would only decrease $f_{ar,1}$ by <10% [36]. Based purely on length and diameter, $f_{ar,1}$ would therefore be expected to be higher in younger, smaller infants. This suggests that increased airway wall compliance due to immaturity must have a significant influence on $f_{ar,1}$ and hence v in pre-term infants. The latter would be consistent with structural findings [22, 34].

Even though the impact of the different components on $f_{ar,1}$ cannot be separated quantitatively, it can still be concluded that differences in $f_{ar,1}$ probably reflect differences in v in the airways of pre-term compared with full-term infants. This has crucial implications. Maximal flows through a compliant tube are related to v in the tube. v is the speed at which a small disturbance travels in a compliant tube filled with gas. The maximal flow in a compliant tube (V'_{max}) is the product of velocity and tube area [19]. Thus, $f_{ar,1}$, velocity and V'_{max} are related. These considerations can, however, only be qualitative and not quantitative, since the relationship between $f_{ar,1}$, airway path length, airway wall compliance and the frequency of the travelling pressure waves is highly nonlinear [26, 30, 36–40]. Nevertheless, based on these findings, the present authors hypothesise that the ability of airways to carry large flows is very different in pre-term than in full-term infants.

Repeatability of $f_{ar,1}$

Despite the consistency of measurements within any one testing session, the within-subject variability of $f_{ar,1}$ when measurements were repeated after several hours limits the potential clinical usefulness of this technique. The reasons for such variability are manifold, but include the fact that airway wall compliance is part of a complex regulatory system maintaining balanced flow through the airways. Other parts of this regulatory system may be lung volume, elastic recoil and airway diameter. The degree of between-occasion variability observed in the pre-term infants in this study is similar to that published previously in 10 healthy unsedated full-term infants on two different days within the same week [30]. There are very limited data describing between-occasion repeatability for lung function tests in infants with which to compare the current results. Due to the difficulties in undertaking such studies, most are based on very small numbers of subjects and all have used different approaches to reporting ''repeatability'' [41–43], which complicates comparisons. Nevertheless, most appear to reflect a similar degree of between-occasion variability for forced expiratory flows in infancy, as was found for high frequency input impedance in the current study.

Limitations to the study and concomitant factors

The main limitation of the current study was the fact that measurements were made through a face mask, and the smaller the child, the larger the contribution of the shunt compliance of the face mask [30]. The present authors tried to overcome or at least partially compensate for this potential error by using the same face mask and filling it with silicon putty to reduce the dead space, but this could have contributed to the lower values of $f_{ar,1}$ among the pre-term infants since the ''effective'' dead space would have been relatively large in relation to body size in this group. Similarly, input impedance measurements include the upper airways, and their influence cannot be distinguished from the lower airways [25, 29, 40]. On the other hand, study design was strengthened by the fact that measurements were undertaken during spontaneous unsedated sleep, thereby reflecting the complexities of the real dynamic situation.

The lower post-conceptional age of the pre-term infants at time of study was due both to shortened gestation and the fact that, for practical reasons, they were measured at an earlier post-natal age than their full-term counterparts. Differences in post-natal age could, therefore, have contributed to developmental differences of $f_{ar,1}$ between full- and pre-term infants. While a much larger, preferably longitudinally studied population would be required to investigate the separate effects of gestational *versus* post-natal immaturity, it should be noted that since the pre-term infants were studied before the expected date of delivery, the effects of pre-term birth *per se* are likely to have made an important contribution. A further potential limiting factor was the difference in ethnic background between the London and Bern groups, which partly reflected local population characteristics, but was greater than had been anticipated when planning the current study. In retrospect, given the characteristics of the Swiss population, data collection in London should have been limited to pre-term infants born to White mothers to avoid any confounding. In reality, given the available resources and the prolonged period of recruitment this would have entailed, this was not feasible. It has been shown that forced expiratory flows are higher in black than white pre-term infants during the first weeks of life [44, 45]. While such differences could reflect differences in intrathoracic airway calibre, they are more likely to reflect transient differences in breathing pattern during the neonatal period among black babies, in whom a lower nasal resistance [17, 46] and increased expiratory braking during tidal breathing [44, 45] has also been noted. While statistical analysis of the effect of ethnicity in this study was precluded both by the sample size and by the heterogeneity of the pre-term group (with almost half the infants being of mixed ethnic origin (table 1)), visual inspection of the data revealed complete overlap according to ethnicity.

In the current study, there was also an unexpected preponderance of males, but as the proportion was similar between the two groups, this should not have introduced any bias (fig. 2). Numerous studies have shown that after correction for body size, the sex of an infant has a marked effect on airway function, though not on lung volumes, with lower maximal expiratory flows at low lung volumes being observed in males compared with females at any given height during infancy [45, 47–49] and later childhood. To date, nothing is known about the influence of factors such as ethnic background, sex or body size on high frequency $Z(f)$ measurements, and a very large population study (~200 infants) would probably be required to determine such effects [50].

A further concomitant factor may be tobacco exposure. ELLIOT *et al.* [51] suggested that airway wall mechanics and airway tissue coupling is altered in tobacco-exposed newborn animals. Therefore, it is likely that airway wall mechanics and, thus, $f_{ar,1}$ could be altered in tobacco-exposed infants. The current study was not sufficiently powerful to undertake subgroup analysis, and specific details regarding prior environmental tobacco smoke exposure were not recorded, although all the pre-term infants were studied in hospital and thus prior to any post-natal exposures.

Conclusions and clinical implications of findings

The HIT is applicable in unsedated pre-term infants. In common with other infant lung function tests, the $f_{ar,1}$ has a

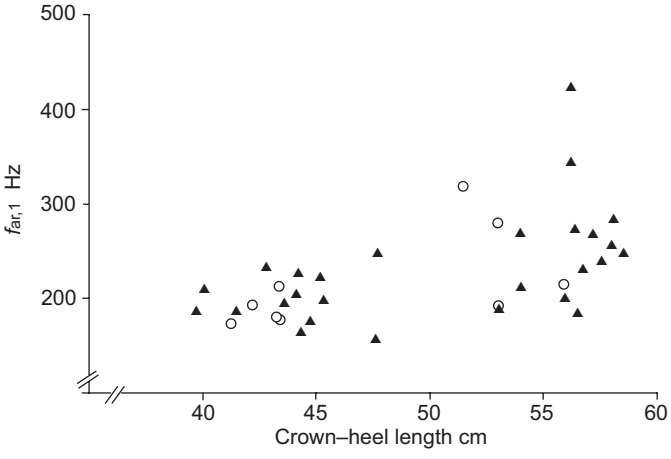

FIGURE 2. Plot of $f_{ar,1}$ against crown–heel length comparing female (○) and male (▲) infants.

good short-term variability within a single test occasion, but shows considerable within-subject variation when tests are repeated some hours later. Despite the presence of shorter airways, the $f_{ar,1}$ of the high frequency impedance spectrum was significantly lower in pre-term than in full-term infants, suggesting that differences in $f_{ar,1}$ probably reflect differences in v in the airways of pre-term infants when compared with full-term infants. Due to the complex nature of wave physics in compliant tubes and the limits of the study, it was not possible to quantitatively separate the impact of the different components on $f_{ar,1}$. Based on qualitative considerations, however, the present findings suggest that developmental differences in airway wall mechanics and airway–parenchyma coupling influencing airway wall compliance may play a critical role in determining $f_{ar,1}$. The latter would be consistent with morphological data in published animal models, showing higher compliance in immature airways [37].

This has important physiological, clinical and research implications. Since flow limitation is determined by v and airway cross-sectional area [19], the present authors hypothesise that the physical ability of the airways to carry large flows is fundamentally different in pre-term and full-term infants, and that this probably cannot be accounted for simply by the absolute reduction in airway dimensions found in such infants. Interestingly, wave propagation and mechanical properties of the airway walls determine when the airway walls start to resonate (wheezing), since it is then that energy is transversally dissipated into the walls. Based on the present findings, it is likely that these wheezing phenomena in pre-term infants occur in a different frequency range than in older children and adults.

Based on these findings, it is likely that flow limitation in pre-term infants is not only determined by airway diameter and airway obstruction, but additionally by the mechanical properties of the airway walls. Clinically, this means that ventilation strategies using positive end-expiratory pressure, which affects end-expiratory level, elastic recoil and thus airway wall elasticity, will have a large impact on airflow through the immature airways in these very young infants. In simple clinical terms, if their airway walls are stabilised with increasing end-expiratory level, this will subsequently facilitate flow through the airways. Furthermore, it implies that flow limitation in respiratory distress with high intrathoracic pressure during active expiration might limit the airways more dramatically in pre-term than in healthy full-term infants. Drugs such as bronchodilators, which not only cause airway dilation but also increase airway wall compliance [52], may therefore reduce the flow in these collapsible immature airways. Bronchodilators thus need to be used with care, as they may potentially cause adverse effects in such infants [53, 54]. This study has emphasised the importance of airway wall mechanics in pre-term infants; future studies are required to investigate whether factors such as post-inflammatory airway wall remodelling, sex, ethnic group, post-natal age or tobacco exposure have additional effects on airway wall mechanics in these immature infants.

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