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New aspects of airway mechanics in preterm infants

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Abbreviations:

$f_{ar,1}$:	the frequency at which the first anti-resonance of high frequency impedance occurs, defined by the first zero crossing in the imaginary part in the presence of a relative maximum in the real part of the impedance spectrum
HIT:	high speed interrupter technique
v :	wave propagation velocity = wave speed
$Z_{in}(f)$:	impedance as a function of frequency
$Z_{in_{re}}$:	impedance of the real part of the impedance spectrum
$Z_{in_{re}}(f_{ar,1})$:	impedance of the relative maximum in the real part of the impedance spectrum at $f_{ar,1}$

Abstract:

High frequency respiratory impedance data measured non invasively by the high speed interrupter technique (HIT), particularly the first anti-resonance ($f_{ar,1}$), is related to airway wall mechanics. The aim of this study was to evaluate the feasibility and repeatability of HIT in unsedated preterm infants, and to compare values of $f_{ar,1}$ from 18 preterm (postconceptional age 32-37 weeks, weight 1730-2910 g) and 18 term infants (42-47 weeks, 3920 - 5340 g). Among the preterm infants, there was good short term repeatability of $f_{ar,1}$ within a single sleep epoch (mean (SD) CV: 8 (1.7)%, but 95% limits of agreement for repeated measures of $f_{ar,1}$ after 3-8 hours were relatively wide (-41 Hz; 37 Hz). $f_{ar,1}$ was significantly lower in preterm infants (199 versus 257 Hz, $p \leq 0.001$), indicating that wave propagation characteristics in preterm airways are different from those of term infants. We 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 (v) and airway cross-sectional area, we hypothesize that the physical ability of the airways to carry large flows is fundamentally different in preterm than in term infants.

Introduction

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 fetal or early postnatal life (4). Factors implicated in 'programming' of the respiratory system include fetal nutrition (7), fetal exposure to maternal smoking during pregnancy (8), preterm delivery and exposure to environmental allergen or viral respiratory infections during infancy (3;9). Little is known about the impact of preterm 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). Preterm 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 preterm 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 w of gestation and 8 months postnatal age, true alveoli do not begin to develop until around 30 weeks gestation with subsequent rapid increase in number, size and complexity during the first 3-4 years of life (10). Different growth patterns of the airways and parenchyma (dysanaptic growth) during fetal and early postnatal 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 airway narrowing and closure during tidal breathing, and have increased vulnerability to wheezing disorders. This emphasizes the complex structure-function relationships in the developing lung, including the fact that expiratory flows are related not only to airway dimensions, but 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 preterm infants during the first months of life.

In 1998, a novel method was proposed to measure high frequency respiratory impedance in vivo: the high speed interrupter technique (HIT) (26). As explained later (see discussion) it has been shown in both adults and infants, that high frequency respiratory impedance data, particularly the frequency at which the first anti-resonance ($f_{ar,1}$) occurs, is influenced by the propagation velocity (v) of pressure waves (i.e. wave speed) within the airways and is related to airway wall mechanics (26-28). In preterm 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 preterm infants, the aims of this study were i) to evaluate the feasibility and repeatability of applying the HIT in unsedated preterm infants, and ii) to assess

developmental changes in airway wall mechanics by comparing values of $f_{ar,1}$ in healthy preterm and full term infants.

Materials and Methods

The study was performed in two stages. In the first stage, the feasibility and within subject variability of using the high speed interrupter technique to measure high frequency impedance ($Z_{in}(f)$) between 32 and 512 Hz were analyzed in a group of healthy preterm infants, focusing particularly on the first anti-resonance ($f_{ar,1}$), 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 preterm infants was compared with that from healthy term infants measured under the same conditions.

Subjects

Preterm infants from the Neonatal Unit at the Homerton University Hospital, London were eligible for recruitment if they were born ≤ 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 hours 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 preterm infants were compared to a group of healthy term infants recruited antenatally at the Department 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 and the East London & City Research Ethics Committees. 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, 0.5 to 1 hour 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, Avon, 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, Mid Glamorgan, Wales). 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 minimize dead space and CO₂ re-breathing. Measurements were repeated between 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 hours to assess repeatability of measurements.

High frequency impedance measurements $Z_{in}(f)$

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 5 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 frequency of the first anti-resonance ($f_{ar,1}$), defined by a zero crossing in the imaginary part in the presence of a relative maximum in the real part ($Z_{in_{re}}(f_{ar,1})$) of the impedance spectrum was extracted from the impedance spectrum, assessed between 32 to 512 Hz (Fig. 1). Data were not accepted for analysis if: a) multiple peaks occurred, b) the relative maximum of $Z_{in_{re}}$ did not occur at the zero-crossing

in the imaginary part, c) the coherence was below 0.9 or d) oscillatory pressures changes were less than 0.15 kPa (26). After separate primary analysis at each centre (MH in London, IB in Bern), all data were reviewed by the same person for acceptability (UF). Within each test occasion, the first 10 technically acceptable manoeuvres were taken for further analysis.

Statistics

Short-term repeatability of $f_{ar,1}$ of 10 technically acceptable measurements within each test occasion was expressed as the coefficient of variation ($CV\% = 100 \times SD / \text{mean}$). Bland and Altman analysis was used to assess within-subject between-occasion repeatability on the same day (33). Comparison of results between preterm infants and full term healthy term infants were undertaken using the Wilcoxon 2-sample test.

Results

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

Among the healthy term infants, 24 data sets with technically acceptable coherence were obtained initially. However, in 6 of these infants, the impedance spectra did not show a consistent single first anti-resonance 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 preterm infants together with those of the 18 term infants are summarised in Table 1. As expected, the preterm infants were younger, lighter and shorter than those born full-term. A relatively high proportion of boys were studied, but there was no difference in sex distribution between the groups. The proportion of babies in whom both parents were White Northern European Caucasians was, however, considerably lower among the London preterm group than the Swiss full term group ($p < 0.001$). In the preterm infants one infant received CPAP-therapy (20 hours – $f_{ar,1}$ 157 Hz), while two had brief supplemental oxygen (1 d – $f_{ar,1}$ 195 Hz and 11 hours – $f_{ar,1}$ 177 Hz, respectively).

The standard deviation of repeat measurements of $f_{ar,1}$ on a single test occasion was less than 30 Hz in all but three infants (maximum 55 Hz) and was similar in preterm and 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 coefficient of variation of 8 and 10% in the two groups. Technically acceptable, repeated measurements on two occasions were obtained after an interval (mean (SD)) of 5.4 (1.7) hours in 8 of the preterm 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, (mean $f_{ar,1}$ on the first and second test occasion being 210 Hz and 208 Hz respectively). However, the 95% limits of agreement for individual subjects were relatively wide: - 41 Hz to 37 Hz.

$F_{ar,1}$ was significantly lower in the preterm than in the term infants (mean (95% CI) difference, preterm - 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.

Discussion

Results from this study showed that it is feasible to apply the high speed interrupter technique to preterm infants in unsedated sleep and that values of $f_{ar,1}$ were significantly lower among apparently 'healthy' preterm than their full term counterparts. Once the infants were spontaneously sleeping, anti-resonant frequencies could be detected in all unsedated infants without disturbance during a short measurement period of 4 - 15 minutes. There was a low failure rate, with only three preterm infants showing less than 10 technically acceptable manoeuvres. The short-term variability of the first anti-resonance within a single sleep epoch was very acceptable and comparable with previous studies from healthy 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 8 preterm infants in whom this could be measured, there was marked within subject variability between results collected after an interval of 3 - 8 hours.

Interpretation of the findings and model hypothesis

Investigation of factors determining airway function in immature infants is essential to further improve our understanding of the impact of preterm 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 wave propagation velocity (v) of travelling pressures waves, and hence are related not only to diameter, but 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 hours - $f_{ar,1}$: 157 Hz), while two had brief supplemental oxygen (1 d - $f_{ar,1}$:195 Hz and 11 hours - $f_{ar,1}$:177 Hz). Visual inspection of results indicated no bias with respect to data from these 3 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 has to 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 anti-resonant 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 anti-resonance 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, it is possible to speculate, based on the theory of simplified elastic tube models and animal models (36;37).

We found a significantly reduced $f_{ar,1}$ among the preterm group, who were not only more immature but younger and smaller than the 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), we could have expected mean airway path length to be ~30% lower and thus $f_{ar,1}$ to be ~30% higher in the preterm 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 about 30% higher in preterm than in term infants (17), a corresponding diameter scaling factor would only decrease $f_{ar,1}$ by < 10% (36). Based purely on length and diameter, we would therefore expect $f_{ar,1}$ 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 preterm infants. The latter would be consistent with structural findings (22;34).

Even though we can not quantitatively separate the impact of the different components on $f_{ar,1}$, we can still conclude that differences in $f_{ar,1}$ probably reflect differences in v in the airways of preterm compared with term infants. This has crucial implications. Maximal flows through a compliant tube are related to wave propagation velocity in the tube. The wave propagation velocity 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 non-linear (26;30;36-40). Nevertheless, based on these findings we hypothesize that the ability of airways to carry large flows is very different in the preterm than full term infant.

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 preterm 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 we found for high frequency input impedance in this study.

Limitations to the study and concomitant factors

The main limitation of this study was the fact that measurements were made through a face mask. The smaller the child, the larger the contribution of the shunt compliance of the face mask (30). We 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 preterm 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 we cannot distinguish their influence 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-conceptual age of the preterm infants at time of study was due both to shortened gestation and the fact that, for pragmatic reasons, they were measured at an earlier postnatal age than their fullterm counterparts. Differences in postnatal age could therefore have contributed to developmental differences of $f_{ar,1}$ between term and preterm infants. While a much larger, preferable longitudinally studied, population would be required to investigate the separate effects of gestational versus postnatal immaturity, it should be noted that since the preterm infants were studied *before* the expected date of delivery, the effects of preterm 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 Berne group, which partly reflected local population characteristics, but was greater than had been anticipated when planning this study. In retrospect, given the characteristics of the Swiss population, data collection in London should have been limited to preterm 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 preterm infants during the first weeks of life (44;45). While such differences could reflect differences in intra-thoracic airway calibre, they more likely 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 preterm group (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 boys, but as the proportion was similar between the two groups, this should not have introduced any bias (Figure 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 boys compared with girls 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 Zin measurements, and a very large population study (in the order of 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. It is therefore likely that airway wall mechanics and thus $f_{ar,1}$ could be altered in tobacco exposed infants. The current study was not sufficiently powered to undertake sub group analysis and specific details regarding prior environmental tobacco smoke exposure were not recorded, although all the preterm infants were studied in hospital and thus prior to any postnatal exposures.

Conclusions and clinical implications of findings

The high-speed interrupter technique is applicable in unsedated preterm infants. In common with other infant lung function tests, the first anti-resonance frequency has a 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 preterm than in term infants, suggesting that differences in $f_{ar,1}$ probably reflect differences in wave propagation velocity in the airways of preterm infants when compared with term infants.

Because of the complex nature of wave physics in compliant tubes and the limits of the study, we can not quantitatively separate the impact of the different components on $f_{ar,1}$. Based on qualitative considerations, however, our 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 wave propagation velocity and airway cross-sectional area (19), we hypothesize that the physical ability of the airways to carry large flows is fundamentally different in preterm than 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 then energy is transversally dissipated into the walls. Based on our findings it is likely that these wheezing phenomena in preterm infants occur in a different frequency range than in older children and adults.

Based on these findings, it is likely that flow limitation in preterm 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 PEEP, 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, we stabilise their airway walls with increasing end-expiratory level, and 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 preterm than in healthy 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 since they may potentially

cause adverse effects in such infants (53;54). This study has emphasised the importance of airway wall mechanics in preterm infants; future studies are required to investigate whether factors such as post-inflammatory airway wall remodelling, sex, ethnic group, postnatal age or tobacco exposure have additional effects on airway wall mechanics in these immature infants.

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Table 1: Infant Details

	Mean (SD) *		p-values
	preterm infants (n=18)	term infants (n=18)	
% male	72%	78%	0,7
% both parents Caucasian	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
Postnatal age (days)*	7 (4.5 - 10)	34 (29 - 38)	<0.001
Postconceptional 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

*for postnatal age median and inter-quartile range

Figure Legends

Figure 1:

Example of one measurement of a high-frequency impedance spectrum from a single infant. The anti-resonant 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.

Figure 1

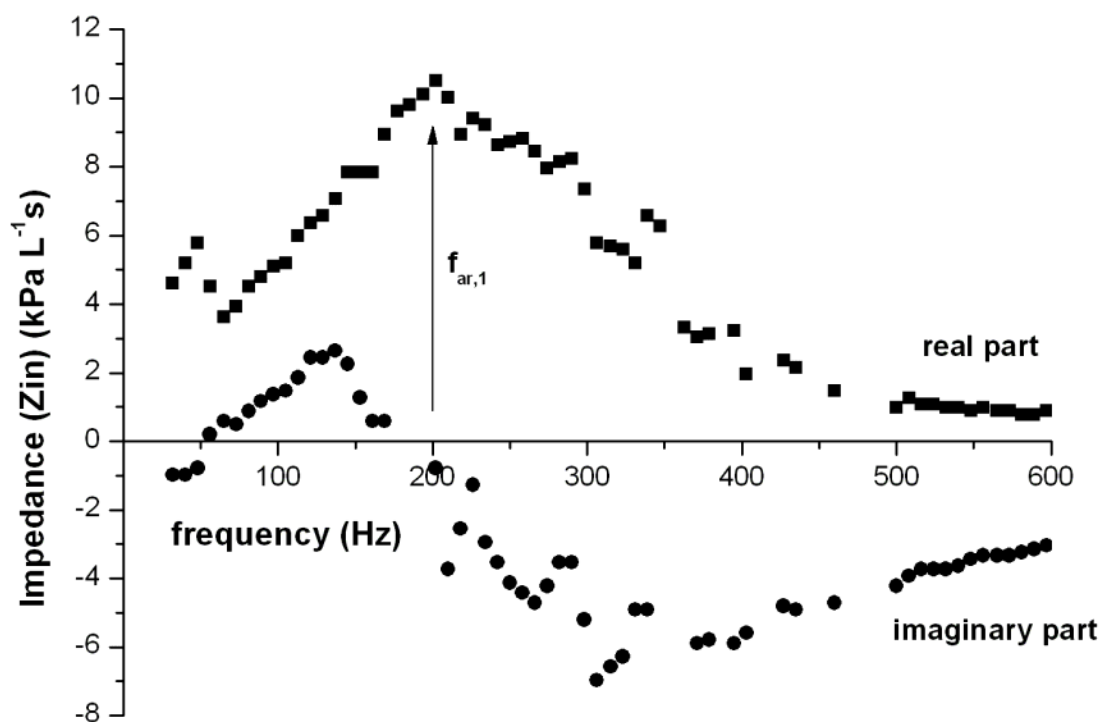
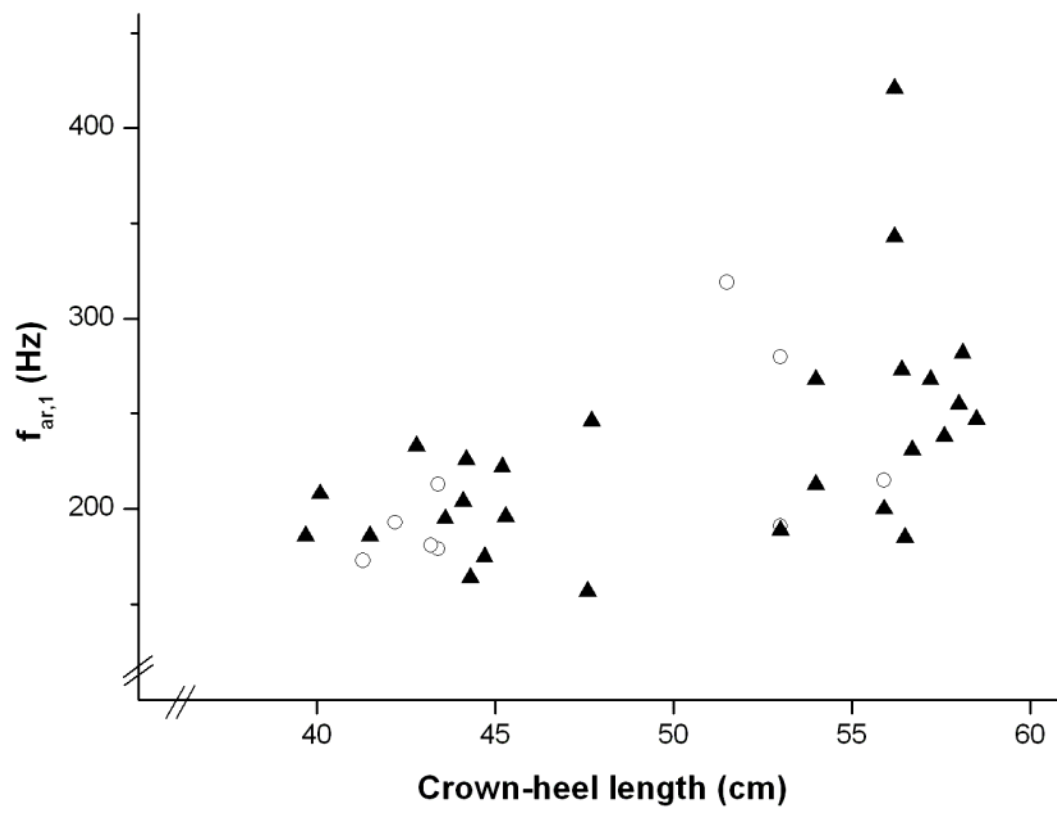


Figure 2:

Plot of $f_{ar,1}$ against crown-heel-length comparing female (\circ) and male (\blacktriangle) infants.

Figure 2



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