Respiratory impedance in healthy subjects: baseline values and bronchodilator response

Ellie Oostveen[1], Krisztina Boda[2], Chris P.M. van der Grinten[3], Alan L. James[4], Sally Young[4], Hans Nieland[5] and Zoltán Hantos[2]

Affiliations: [1]Dept of Respiratory Medicine, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium. [2]Dept of Medical Physics and Informatics, University of Szeged, Szeged, Hungary. [3]Dept of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, and [5]Dept of Lung Function, Medisch Spectrum Twente, Enschede, The Netherlands. [4]Dept of Pulmonary Physiology, Sir Charles Gairdner Hospital, Nedlands, Australia.

Correspondence: E. Oostveen, Antwerp University Hospital, Wilrijkstraat 10, Edegem-Antwerp, B-2650, Belgium. E-mail: ellie.oostveen@uza.be

ABSTRACT Because of the minimal demand for cooperation by the subject, the forced oscillation technique is increasingly employed in routine lung function testing. However, comprehensive and device-independent values of respiratory impedance at baseline and after bronchodilation have not been established for healthy adults.

The aim of this multicentre study was to collect impedance data from 4 to 26 Hz in healthy Caucasian subjects between 18 and 80 years of age. Five different devices were employed to assess baseline values and the bronchodilator response.

Altogether, 368 subjects were examined. Despite adjustment for anthropometry, the impedance spectra differed in frequency dependence between the centres, and hence could not be pooled. However, resistance at all frequencies except 20 and 25 Hz, and the low-frequency ($\leqslant$14 Hz) values of reactance did not exhibit a centre dependence. The regression equations for resistance reflected a greater height dependence in males and a greater weight dependence in both males and females than those published previously. Bronchodilation resulted in a statistically significant decrease (11%) in resistance and a 95th percentile equal to a 32% decrease in resistance at low frequency.

We conclude that rigorous calibration procedures should be developed to ensure data compatibility. Furthermore, new reference equations based on different setups are recommended to replace those established with a single device.

@ERSpublications
New prediction equations for respiratory impedance in adults have been developed based on multiple devices http://ow.ly/p9t4e

For editorial comments see page 1435.

This article has supplementary material available from www.erj.ersjournals.com

Received: Aug 10 2012 | Accepted after revision: Feb 06 2013 | First published online: April 18 2013

Conflict of interest: None declared.

Introduction

Measurement of the mechanical properties of the respiratory system using the forced oscillation technique (FOT) is increasingly employed in lung function laboratories. The main advantage of the FOT is ease of application: the oscillatory signal is superimposed on spontaneous breathing and, hence, no special breathing manoeuvres are required.

This minimal demand for cooperation has made the FOT especially attractive in paediatric lung function testing, where a number of studies have been performed to establish normative data using various FOT devices [1, 2], the results proving largely coherent. In contrast, there have been only a few reports on normative respiratory impedance (Z_{rs}) data in healthy adults, and some involved only relatively young or only elderly subjects [3, 4], or only a small number of oscillation frequencies were investigated [5]. Moreover, the criteria for selection of the subjects were not always reported or the sample population was limited to a rather narrow specific subgroup of subjects [3, 6]. Equally important, most such normative studies were conducted in the same laboratory, using the same forced oscillation setup, the Oscillaire, developed by LÀNDSÉR and co-workers [3, 6–8], which is no longer available.

Although international guidelines have been developed concerning use of the FOT in clinical practice [1], appropriate reference data derived from a healthy population must be available prior to clinical use, preferably obtained by using equipment and measurement procedures similar to those employed in the clinical setting. Additionally, data on the bronchodilator response in healthy subjects should be collected for the appropriate evaluation of reversibility tests in patients.

The goal of the present study was therefore to collect baseline values of Z_{rs} and the bronchodilator response with different FOT devices, and to develop reference ranges of respiratory resistance and reactance as a function of frequency (f) for healthy subjects aged 18–80 years. With this aim, three commercial FOT devices and two custom-made FOT setups were used in this five-centre (C1–C5) study for the measurement of Z_{rs}.

Methods

Subjects

The healthy, nonsmoking Caucasian adults ($\geqslant$18 years of age) included in the study had no history of pulmonary or cardiac disease, and no current wheezing, breathlessness, cough, phlegm production, hyperresponsive airways or recent respiratory tract infection. Ex-smokers with a smoking history of $>$10 pack-years were excluded. Each centre was requested to include at least five subjects of each sex per decade of age, with a total number of $\geqslant$60 subjects per centre. Except for Perth (Australia), where the invited subjects had previously taken part in the Busselton Health Studies [9], all the centres recruited subjects from among the local hospital or university staff and their family members. All subjects gave their written informed consent and the protocol was approved by the local ethical committees.

Measurements

Impedance measurements

Z_{rs} was measured using two home-made setups in Antwerp, Belgium (C1) and Szeged, Hungary (C3), while ROS Oscilink (SensorMedics, Bilthoven, the Netherlands), i2M (Chess mT, Ghent, Belgium) and IOS (Jaeger, Würzburg, Germany) devices were used in Enschede, the Netherlands (C2), Perth, Australia (C4) and Maastricht, The Netherlands (C5). The measurements were made in accordance with recent European Respiratory Society (ERS) guidelines [1]. The averages and standard deviations of three to five technically acceptable Z_{rs} measurements from each subject were retained for further analysis. Specifications on the oscillatory signal type, frequency content and recording time of the different setups are summarised in table 1.

TABLE 1 Characteristics of the different forced oscillation technique devices

Centre	Setup	Signal type	Frequency range Hz	Frequency resolution Hz	Recording time s
C1	Custom-made	Pseudorandom	4–32	2	16
C2	ROS Oscilink[#]	Pseudorandom	4–30	1	16
C3	Custom-made	Pseudorandom	2–26	2	20
C4	i2M[¶]	Pseudorandom	4–48	2	8
C5	IOS[+]	Train of impulses	5–35	5	30

C1: Antwerp, Belgium; C2: Enschede, the Netherlands; C3: Szeged, Hungary; C4: Perth, Australia; C5: Maastricht, the Netherlands. [#]: SensorMedics, Bilthoven, the Netherlands; [¶]: Chess mT, Ghent, Belgium; [+]: Jaeger, Würzburg, Germany.

DOI: 10.1183/09031936.00126212

Spirometry

The subjects performed repeated spirometric manoeuvres that met the American Thoracic Society standards [10] in C4 or the ERS standards [11] in C1–C3 and C5.

Z_{rs} data were collected prior to spirometry. The measurements of the baseline values of Z_{rs} and forced expiration were repeated after 15 min to assess short-term repeatability. Subsequently, 400 μg of salbutamol was administered through a spacer and the lung function measurements were repeated 15 min thereafter.

Reference impedance

A high-resistance (8.9 $hPa \cdot s \cdot L^{-1}$) reference impedance was circulated among the centres to check the accuracy of the different FOT setups.

The different FOT devices and calibration methods, the spirometers, and the measurements of the reference impedance are described in the online supplementary material.

Statistical methods

Anthropometric data

The intercentre comparisons of anthropometric and spirometric data were performed with one-way ANOVA with Fisher's *post hoc* least significant difference analysis.

Impedance data

The intercentre comparisons of the Z_{rs} spectra were made with repeated-measures ANOVA. Because of the skewed distributions, resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system were analysed after logarithmic transformations: $\ln(R_{rs})$ and $\ln(4–X_{rs})$, respectively. To take into account the different sets of oscillation frequencies included in the different FOT setups and to model the covariance structures of the simultaneously measured data, mixed-model ANOVA [12] was employed. Prediction equations were derived from multiple linear regression models.

From the short-term variability of the lung function data, the repeatability measure defined as the within-subject within-occasion variability was assessed in 302 subjects (82% of the total population; 150 male and 152 female). This variability was expressed as the coefficient of repeatability, defined as twice the standard deviation of the difference of the two baseline measurements made 15 min apart [2]. The coefficient of repeatability defines the limits within which 95% of the differences between two measurements will lie if the bias is zero. Coefficient of repeatability was used to estimate the number of responders to the bronchodilation administration. Since the largest changes in Z_{rs} occur in asthmatic patients at low frequency [1], this part of the analysis was restricted to R_{rs} and X_{rs} at low frequency in order to compare with the change in forced expiratory volume in 1 s (FEV_1). The 95th percentile of the bronchodilator response in our population was also calculated.

Results

A total of 368 subjects (88% lifetime nonsmokers) were included in the study; the ex-smokers had an average smoking history of 4.4 pack-years. The ex-smokers and never-smokers, corrected for anthropometry, were not different in terms of spirometry results and Z_{rs} data. The anthropometric characteristics of the studied subjects are listed in table 2; the only significant intercentre differences were that the subjects from C2 were younger, taller and lighter, and the subjects from C4 were older than those from the other centres.

As expected from the anthropometric data, higher absolute spirometric values were observed in the subjects from C2, but they were not significantly different when the results were expressed relative to the predicted value (table 2). In contrast, the C4 subjects displayed significantly lower spirometric volumes than those from all other centres. The ratios of FEV_1/vital capacity (VC) were slightly lower for the C5 subjects than for those from the other centres.

Quality control of the FOT equipment

The impedance of the reference device was assessed with the different FOT setups and proved to be within 5% and 5° of the expected magnitude and phase shift, respectively, at all frequencies for all devices except that of C4, where a deviation of >5% from the expected magnitude was observed at frequencies ⩾10 Hz (online supplementary fig. S1).

Centre dependence of Z_{rs} data

Mean values of R_{rs} and X_{rs} at the different centres after adjustment for the covariates height, age and weight are plotted in figure 1; some systematic intercentre differences are apparent in the frequency dependences of

TABLE 2 Anthropometric characteristics and baseline lung function data for the subjects included at each centre

	Centre				
	C1	C2	C3	C4	C5
Subjects n (% male)	66 (52)	61 (46)	71 (49)	108 (50)	62 (47)
Age years	47.9±17.3	42.6±15.2*	49.1±17.4	54.8±15.7*	49.5±17.3
Height cm	171.8±9.9	174.7±9.0*	170.3±10.8	170.5±9.8	170.8±9.2
BMI kg·m^{-2}	26.3±4.2	24.0±3.1*	25.4±4.2	26.5±4.6	25.5±3.6
FEV1 L	3.6±1.0	3.8±0.9$^{\#}$	3.4±0.9	3.1±0.9*	3.4±0.9
FEV1 % pred	105±13	102±12	102±12	95±13***	104±13
FEV1 z-score	0.39±0.95	0.15±0.93	0.17±0.90	-0.33±0.88***	0.30±0.93
VC L	4.4±1.2	4.7±1.1$^{\#}$	4.2±1.2	3.9±1.1*	4.4±1.1
VC % pred	104±12	103±10	101±12	95±12***	107±12$^{\#}$
VC z-score	0.25±0.87	0.19±0.77	0.04±0.88	-0.36±0.82***	0.43±0.83$^{\#}$
FEV1/VC %	81±5	80±7	82±6	79±6¶	78±6^{+}
FEV1/VC z-score	0.16±0.72	-0.08±1.07	0.17±0.83	0.00±0.78	-0.28±0.74§

Data are presented as mean± SD, unless otherwise stated. The Global Lungs Initiative reference equations [13] were used to express the spirometry data as percentages of those predicted (% pred) and as z-scores. C1: Antwerp, Belgium; C2: Enschede, the Netherlands; C3: Szeged, Hungary; C4: Perth, Australia; C5: Maastricht, the Netherlands; BMI: body mass index; FEV1: forced expiratory volume in 1 s; VC: vital capacity. *: p<0.05; ***: p<0.001 *versus* all the other centres; $^{\#}$: p<0.01 *versus* the data from C3; ¶: p<0.05 *versus* the data from C1 and C3; $^{+}$: p<0.05 *versus* the data from C1, C2 and C3; §: p<0.05 *versus* the data from C1, C3 and C4.

*R*rs and *X*rs. As described in detail in the online supplementary material, mixed-model analysis was applied to choose the autoregressive covariance structure with which to model the correlation between spectra. Mixed models with the interaction centre × frequency and the covariate combinations height–age–weight and height–age–body mass index (BMI) were addressed. Since the latter combination did not improve the model performance, height, age and weight were retained for the subsequent analysis. The dependences of the *R*rs and the *X*rs data on sex, frequency and centre were analysed on ln(*R*rs) and ln(4–*X*rs). Linear interpolation of *Z*rs values between some frequency values was necessary to facilitate the combination of data from the different centres. The frequency dependence of *Z*rs was significantly different in the various centres, thus the full set of *Z*rs spectra from all the centres could not be combined; however, data pooling was possible for *R*rs (with the exceptions of 20 and 25 Hz in the females and 25 Hz in the males) and for *X*rs up to 14 Hz in both sexes. Exclusion of the data from C5 eliminated the significant differences in *R*rs, but not in *X*rs. The C5 data were retained for further analysis.

Prediction equations

Values of single-frequency *R*rs and *X*rs, the resonant frequency (*f*res), the reactance curve area (*A*X) [14] and the mean *R*rs (*R*mean) were included in the predictions on height, age and weight. The coefficients of the prediction equations and the residual standard deviations for ln(*R*rs) and ln(4–*X*rs) are listed in tables 3 and 4, respectively. Although age did not prove to be a significant contributor to the *R*rs values at high frequency (>12 Hz) for the females, it was not omitted from the model for reasons of consistency of the predicted *R*rs as a function of frequency. However, age did not contribute significantly to the prediction of the *X*rs values for the males at any frequency, and was therefore omitted from this particular prediction. Unlike the frequency dependence of *R*rs, the *R*mean values were not statistically different between the centres, and the *A*X calculated either between 4 Hz and *f*res (*A*X4) or between 5 Hz and *f*res (*A*X5) were also centre-independent. Although there was a centre dependence in *f*res, the differences between the centres were small (the largest difference was <2 Hz) and considered clinically irrelevant. Calculation examples for the predicted median values and upper/lower limits of the normal values are given in the online supplementary material.

*Baseline variability of Z*rs

The variability in *R*rs, expressed in both absolute and relative terms, did not differ between the centres or between the sexes. Furthermore, no systematic differences were found between the two baseline measurements in *R*rs and in *X*rs. The coefficient of repeatability values of *R*rs at low frequency (n=302) and that of FEV1 (n=179) are reported in table 5. Bland–Altman analysis [15] revealed that the absolute difference between the repeated baseline measurements was related to the magnitude of the baseline value of *R*rs. The relative difference between the two baseline measurements, however, was independent of the magnitude of *R*rs (fig. 2).

DOI: 10.1183/09031936.00126212

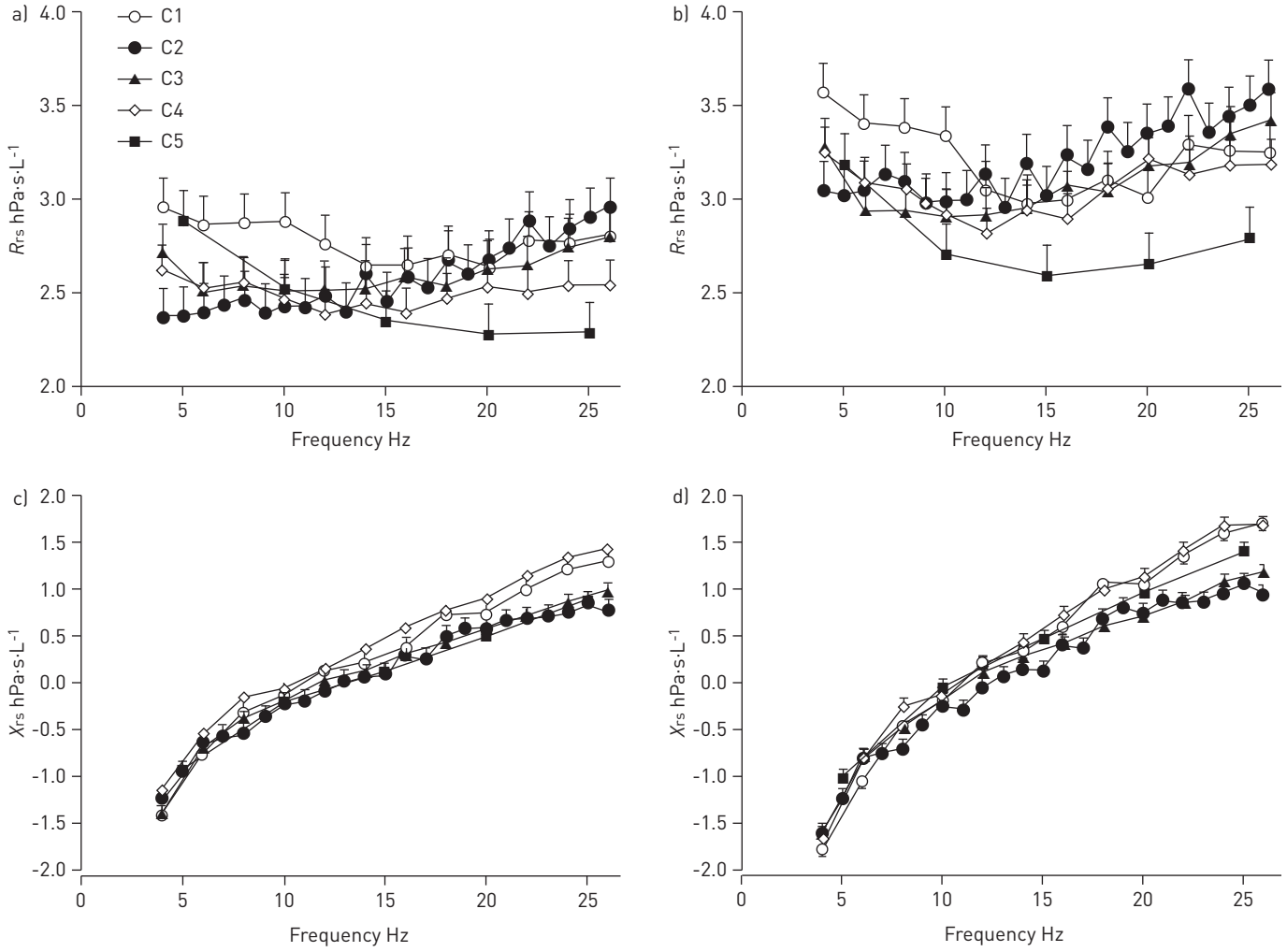

FIGURE 1 Mean±SEM values of respiratory a, b) resistance (*R*rs) and c, d) reactance (*X*rs) obtained from healthy adult males (a, c) and females (b, d) through the use of different forced oscillation technique devices at five different centres (C1: Antwerp, Belgium; C2: Enschede, the Netherlands; C3: Szeged, Hungary; C4: Perth, Australia; C5: Maastricht, the Netherlands), adjusted for height, age and weight in the mixed-model analysis.

Bronchodilator response

There was no centre dependence of the bronchodilator effect as assessed with FOT. Bronchodilation induced a significant decrease in *R*rs at all frequencies (mean decrease 11%) and an increase in *X*rs at 4, 5 and 6 Hz and FEV_1 ($p<0.001$, mixed-model ANOVA), whereas vital capacity did not change. The changes in *R*rs were more pronounced than those in *X*rs (fig. 3).

The relative coefficient of repeatability was used to identify responders to bronchodilation. *R*rs at 5 Hz identified 36% of the healthy subjects as positive responders to salbutamol and 3% of the subjects as contraresponders. By contrast, FEV_1 identified 17% of the studied subjects as positive responders and 1% as contraresponders (online supplementary table S1). Only 28 (8%) subjects were positive responders according to both methods. *X*rs at low frequency was markedly less sensitive for detection of the bronchodilator response compared to *R*rs at low frequency (online supplementary table S1).

In order to help define a positive response in asthmatic patients, the 95th percentile of the bronchodilator response in healthy adults was established. The 95th percentiles for the absolute and relative changes in *R*rs and *X*rs at low frequencies due to bronchodilation are reported in table 5. For example, the 95th percentile response in *R*rs at 4 Hz was 1.41 $hPa \cdot s \cdot L^{-1}$, corresponding to a relative decrease of 33% (table 5).

Discussion

As far as we are aware, this is the first study in which baseline and post-bronchodilator *Z*rs data were collected from healthy adult subjects at multiple centres. The *R*mean values found in our study are close to the published data [3, 4, 6, 8]. In accordance with earlier findings, females displayed larger values of *R*rs than

TABLE 3 Prediction equations for respiratory resistance (R_{rs}) at the different frequencies (f), and the average resistance (R_{mean}) for males and females

f Hz	Males					Females				
	a	b	c	d	RSD	a	b	c	d	RSD
4	5.621	-3.230	-0.00430	0.01492	0.2789	2.828	-1.643	0.00405	0.01254	0.2637
5	5.327	-3.032	-0.00381	0.01390	0.2803	2.591	-1.461	0.00279	0.01221	0.2657
6	5.454	-3.079	-0.00482	0.01366	0.2662	2.556	-1.464	0.00310	0.01222	0.2648
8	5.256	-2.972	-0.00418	0.01352	0.2669	2.642	-1.488	0.00351	0.01119	0.2681
10	4.964	-2.794	-0.00347	0.01251	0.2746	2.572	-1.441	0.00248	0.01123	0.2672
12	4.924	-2.734	-0.00420	0.01202	0.2674	2.344	-1.264	0.00321	0.00980	0.2637
14	4.402	-2.393	-0.00382	0.01091	0.2618	2.338	-1.213	0.00266	0.00936	0.2528
15	4.181	-2.286	-0.00328	0.01066	0.2649	2.426	-1.245	0.00144	0.00927	0.2562
16	4.373	-2.337	-0.00429	0.01033	0.2609	2.423	-1.198	0.00169	0.00861	0.2486
18	3.961	-2.052	-0.00422	0.00937	0.2609	2.203	-1.027	0.00199	0.00798	0.2522
20[#]	3.540	-1.824	-0.00330	0.00888	0.2638	2.482	-1.122	0.00135	0.00695	0.2467
22	3.768	-1.834	-0.00457	0.00771	0.2561	2.259	-0.951	0.00086	0.00682	0.2501
24	3.672	-1.778	-0.00480	0.00796	0.2457	2.368	-0.967	0.00086	0.00571	0.2383
26	3.578	-1.662	-0.00491	0.00689	0.2457	2.437	-0.953	-0.00002	0.00524	0.2335
***R*mean**	4.261	-2.297	-0.00355	0.01058	0.2592	2.409	-1.193	0.00143	0.00907	0.2522

$\ln(R_{rs}(f)) = a + b \times height + c \times age + d \times weight$. Units: R_{rs}: hPa·s·L^{-1}; height: m; age: years; weight: kg. Males: age range: 18–84 years; height range: 1.59–1.97 m; weight range: 54–128 kg. Females: age range: 19–81 years; height range: 1.47–1.88 m; weight range: 43–111 kg. The residual standard deviation (RSD) was calculated from the regression of transformed data. [#]: data on females from C5 omitted.

those of males. The impedance data of our healthy adult subjects were described by variables similar to those used previously in prediction equations: sex, height, age and weight.

Study population

The age and sex distributions of the population were well controlled; males and females contributed virtually equally, and the participants of each sex were evenly distributed between 18 and 80 years of age. All subjects included participated in spirometry. The FEV_1 and VC values of the subject population were close to the expected values (table 2). The baseline spirometry data from the individual centres were essentially similar, with one exception: the C4 subjects furnished values which were significantly lower than those at the other centres, but still within the expected range [13].

Obesity was not an exclusion criterion in our study. The average BMI was 25.3 and 26.1 kg·m^{-2} for females and males, respectively; values close to those reported by the World Health Organization for adults [16]. R_{rs}

TABLE 4 Prediction equations for reactance (X_{rs}) data at the different frequencies (f) for males and females

f Hz	Males					Females				
	a	b	c	d	RSD	a	b	c	d	RSD
4	2.974	-0.828	0	0.00185	0.0809	2.649	-0.716	0.00184	0.00261	0.0918
5	2.683	-0.703	0	0.00190	0.0728	2.373	-0.607	0.00150	0.00312	0.0814
6	2.407	-0.606	0	0.00234	0.0701	2.212	-0.577	0.00144	0.00373	0.0806
8	2.180	-0.497	0	0.00187	0.0654	1.916	-0.396	0.00074	0.00293	0.0848
10	2.207	-0.561	0	0.00244	0.0680	1.790	-0.392	0.00134	0.00328	0.0870
12	2.145	-0.568	0	0.00264	0.0740	1.647	-0.363	0.00158	0.00346	0.0995
14	2.265	-0.679	0	0.00310	0.0891	1.500	-0.351	0.00228	0.00405	0.1088
ln(*f*res)	5.070	-1.904	0	0.00864	0.2498	3.415	-1.104	0.00354	0.01001	0.2549
ln(*A*X4)	9.034	-5.288	0	0.01719	0.5670	5.778	-3.785	0.00960	0.02220	0.5673
ln(*A*X5)	9.730	-6.107	0	0.02122	0.7266	5.490	-4.122	0.00960	0.02836	0.6942

$\ln(4 - X_{rs}(f)) = a + b \times height + c \times age + d \times weight$. Units: X_{rs}: hPa·s·L^{-1}; height: m; age: years; weight: kg. Males: age range: 18–84 years; height range: 1.59–1.97 m; weight range: 54–128 kg. Females: age range: 19–81 years; height range: 1.47–1.88 m; weight range: 43–111 kg. f_{res}: resonant frequency; A_{X4} and A_{X5}: area under the reactance curve from 4 and 5 Hz, respectively. f_{res}, A_{X4} and A_{X5} data were logarithmically transformed to take into account the skewness of the data. The residual standard deviation (RSD) was calculated from the regression of transformed data.

DOI: 10.1183/09031936.00126212

TABLE 5 The short-term repeatability and the bronchodilator response for respiratory resistance and reactance at low frequency and forced expiratory volume in 1 s (FEV1), as observed in 368 healthy adult subjects

	R_4 hPa·s·L^{-1}	R_5 hPa·s·L^{-1}	R_6 hPa·s·L^{-1}	R_{10} hPa·s·L^{-1}	X_4 hPa·s·L^{-1}	X_5 hPa·s·L^{-1}	X_6 hPa·s·L^{-1}	AX_4 hPa·L^{-1}	AX_5 hPa·L^{-1}	FEV1 L
Short-term repeatability										
CR absolute	1.03	0.94	0.90	0.83	0.67	0.49	0.48	5.30	4.79	0.22
CR relative %	18.4	17.4	16.8	17.0	33.6	36.7	69.5	55.3	71.5	6.8
Bronchodilator response										
Absolute change	-1.41	-1.37	-1.26	-1.21	0.67#	0.55#	0.46#	-4.43	-3.90	0.34
Relative change %	-32.8	-31.5	-31.6	-31.2	-33.8	-43.5	-67.8	-56.0	-65.4	10.7

The coefficients of repeatability (CR) and 95th percentile of the change in resistance and reactance at low frequency and FEV1 are expressed in absolute and relative terms. For the bronchodilator response, the absolute change was expressed as post-bronchodilator value minus pre-bronchodilator value and the relative change as absolute change/pre-bronchodilator value. R_4, R_5, R_6 and R_{10}: respiratory resistance at 4, 5, 6 and 10 Hz, respectively; X_4, X_5 and X_6: respiratory reactance at 4, 5 and 6 Hz, respectively; AX_4 and AX_5: area under the reactance curve calculated from 4 and 5 Hz, respectively. #: the fifth percentile was determined.

is expected to rise and X_{rs} to fall with the level of obesity [17, 18], but BMI did not seem to be a stronger predictor than weight in our study.

Comparison with earlier predictions

Our predicted values for R_{mean} are compared with previous predictions in figure 4. The current equations predict higher values of R_{mean} than most of the earlier predictions [4, 5, 6, 8, 19] for short and young males, and lower values for tall males, the predicted R_{mean} therefore exhibiting a larger height dependence, whereas lower values of R_{mean} for young females were found, but with a similar height dependence, compared to most previously published equations.

A comparison of the present and previous predictions for R_{rs} and X_{rs} at individual frequencies is difficult, since in most of the literature reports Z_{rs} data were described by polynomials of frequency [3, 6, 8, 20] or linear regression determining the frequency dependence of R_{rs} and its extrapolated zero-frequency value [21]. A similar comparison of R_{rs} as a function of weight with earlier predictions is presented in online supplementary figure S6.

The present study allows the prediction of R_{rs} between 4 and 26 Hz and X_{rs} at $\leqslant$14 Hz on the basis of data pooled from the five centres. Z_{rs} data, and especially those measured at low frequency, are sensitive to bronchial obstruction and constriction [1], and the newly derived prediction equations adequately cover these frequency ranges. Measured data can be considered abnormal if the values of R_{rs}, AX or f_{res} is greater or X_{rs} is lower than the corresponding 95% confidence limit, *i.e.* the reference value $\pm 1.64 \times$ residual standard deviation (tables 3 and 4, and the online supplementary material).

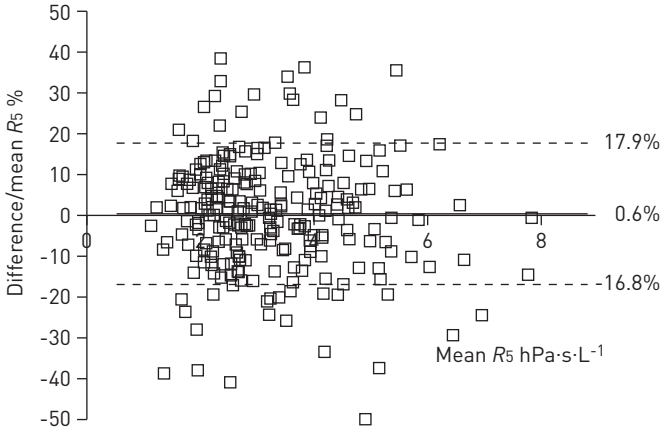

FIGURE 2 Bland–Altman plot [15] of the repeatability of two baseline measurements of the resistance at 5 Hz (R_5), made 15 min apart. Data are plotted as the relative difference between the two measurements *versus* the mean value of the two measurements. The solid line indicates the bias and the dashed lines indicate the upper and lower limits of agreement.

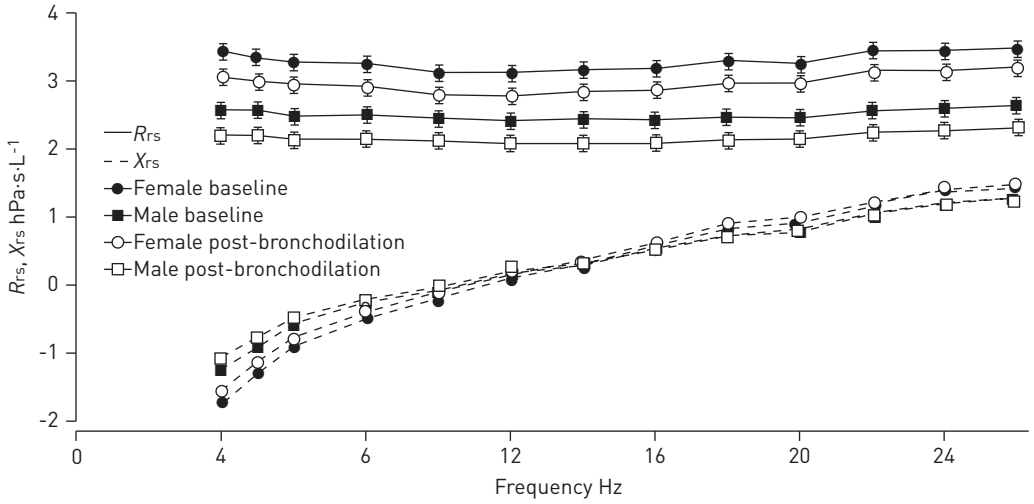

FIGURE 3 Mean ± SE values of the respiratory resistance (*R*rs) and reactance (*X*rs) in healthy females (n=188) and males (n=180) at baseline and after bronchodilation.

Equipment dependence

Whereas all manufacturers stress the uniqueness of their devices, their users expect all FOT setups to comply with the ERS guidelines [1] and that the results obtained with the various setups should be comparable. Thus, it was an underlying assumption of the current study that the *Z*rs data measured in the different centres could be pooled. To test this assumption, a reference impedance was first sent to each of the centres in order to test the accuracy of the equipment. While all setups recovered the reference value more or less accurately, it should be noted that routine calibration devices usually have much lower impedance values (~2 hPa·s·L^{-1}), which allow only a less rigorous testing.

The possibility of a device dependence in the *Z*rs data was tested next. The statistical analysis demonstrated that the frequency dependence of the *R*rs data on these healthy subjects differed in the various centres (fig. 1). However, despite anthropometry adjustment, there still might have been differences between the studied populations. This possible effect cannot be distinguished from the impact of device differences. The device at C5 was found to provide outlying *R*rs data at 20 and 25 Hz, and their *R*rs data therefore exhibited a more marked negative frequency dependence than those from the other centres. Omission of C5 data from the regression changed the coefficients in the prediction equations of *R*rs to a negligible extent (data not shown). However, it is important to point out that the interpretation of the negative frequency dependence of the *R*rs data in terms of the function of the small airways (*R*5–*R*20) and that of the large airways (*R*20) has been associated in the literature with this particular device [22, 23]. The present finding, that the frequency dependence of *R*rs is device-dependent, seriously challenges this simplistic interpretation.

The *X*rs data at frequencies above *f*res were also centre dependent, although there was no single outlying centre or device; the centres rather differed pairwise (online supplementary fig. S1). The most probable explanation for this deviating *X*rs at high frequency is a difference in the inertance of the connecting tubes/mouthpiece. These differences in construction and the correction procedures, which are not always transparent for the users, have less influence on the *X*rs data at low frequencies.

A too-low common mode rejection ratio of the flowmeter may be an important determinant of a distorted measurement of the flow at high frequency [24]. Unfortunately, the common mode rejection ratio of the commercial devices was not specified and, in most cases, could not easily be checked by the users. However, all setups accurately measured the high reference resistance at all frequencies (online supplementary fig S1). Nevertheless, the frequency dependence of *R*rs of healthy subjects after adjustment for anthropometry was shown to be centre, and thus device, dependent (fig. 1). This discrepancy might then result from differences in instrumentation and signal/data processing procedures, whose details are unavailable for the commercial devices. Perhaps most importantly, we implemented a calibration check procedure without pressure and flow fluctuations similar to those from spontaneous breathing, and hence the possibly different nonlinear performances of the FOT setups were not tested.

Previous studies have suggested that the frequency dependence of *R*rs is a markedly sensitive index that permits differentiation between health and disease and an assessment of the disease severity [7, 25–27].

DOI: 10.1183/09031936.00126212

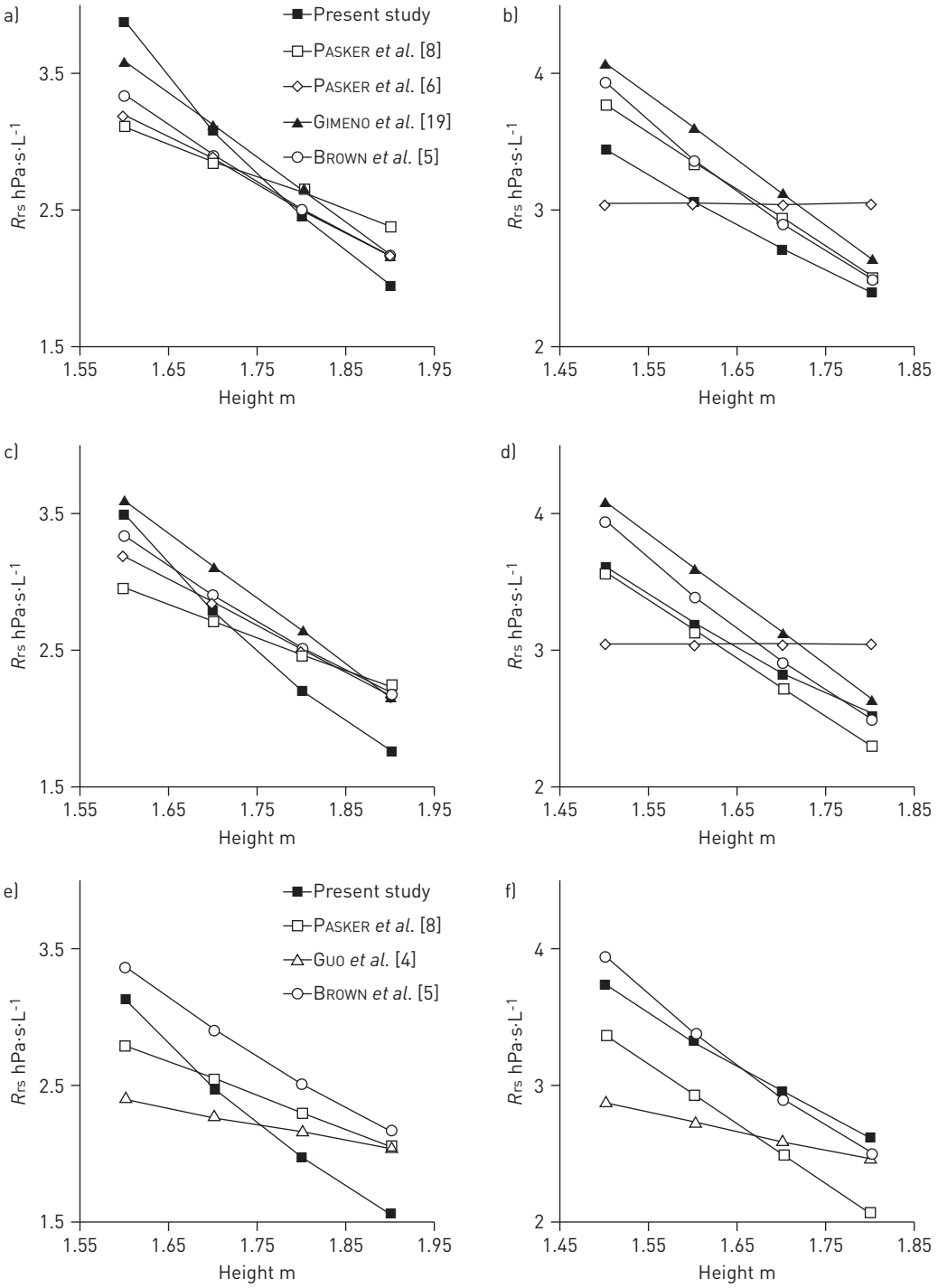

FIGURE 4 Comparison of the predicted mean values of respiratory resistance (R_{rs}) (R_{mean}) for males and females from the present study and those from previously published studies [4, 5, 6, 8, 19], as functions of height at different ages. a) male, 20 years; b) female, 20 years; c) male, 50 years; d) female, 50 years; e) male, 80 years; f) female, 80 years. Weight was fixed at 80 and 65 kg in males and females, respectively. Predictions for R_{rs} at 19 Hz were computed from BROWN *et al.* [5], since R_{rs} at 20 Hz was closest to R_{mean} in our dataset.

However, as noted above, our results indicate that this index is device dependent. We therefore suggest that the optimum way to describe abnormalities in Z_{rs} is to look for an increase in R_{rs} and a decrease in X_{rs} at low frequency only. *AX* and *f*res are additional indices *via* which to characterise abnormal X_{rs}.

Baseline variability and bronchodilator response

Use of the coefficients of repeatability as threshold values to define a positive (or negative) response to bronchodilation implies that, by definition, 5% of the studied subjects are expected to be marked as positive or negative responders if the intervention has no effect. The number of positive responders was much larger than 5%, indicating that the bronchomotor tone changed in a significant proportion of our healthy adults. R_{rs} at low frequency detected twice as many positive responders than FEV_1 did (36% *versus* 17%). The number of contra-responders with either index was <5%, but R_{rs} detected more contra-responders than FEV_1 did (online supplementary table S1). Being more sensitive than FEV_1 for detection of a change in bronchomotor tone in the clinical setting, R_{rs} has been proposed for broncho-challenge testing, but not for reversibility testing [1].

Perhaps the most important result of the bronchodilation part of our study is the 95th percentile of the response in our group of healthy adult subjects, which was equal to ~32% for R_{rs} at low frequency. The bronchodilator response of healthy adults is largely unknown. We are aware of only one study in which subjects screened in an allergy and asthma clinic were assigned to a healthy control group [23]. They exhibited an average decrease of 15% in R_5 after bronchodilation, a value close to the decrease of 11% in the present study. The 95th percentile of the response in our group of healthy adults is slightly lower than the values previously reported for healthy preschool children: 42% [28] and 43% [29].

Conclusions

In summary, our multicentre, multidevice study on normative respiratory impedance data for adult subjects revealed that FOT devices yield systematic differences in R_{rs} at 20 and 25 Hz and in X_{rs} at frequencies >14 Hz. This indicates that the standardisation rules of the Z_{rs} measurements should be complemented with more rigorous calibration procedures in order to ensure data compatibility at all frequencies. However, for the lower-frequency Z_{rs} measures, the present prediction equations allow the comparison and interpretation of adult impedance data relating to Caucasians worldwide, and our data also provide information on the baseline variability of Z_{rs} and the bronchodilator response in healthy adults. The use of our baseline Z_{rs} data and the bronchodilator response should be evaluated prospectively to establish their ability to aid in the diagnosis and management of adult patients with asthma or chronic obstructive pulmonary disease.

References

1 Oostveen E, MacLeod D, Lorino H, *et al.* The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22: 1026–1041.
2 Beydon N, Davis SD, Lombardi E, *et al.* An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; 15: 1304–1345.
3 Làndsér FJ, Clément J, Van de Woestijne KP. Normal values of total respiratory resistance and reactance determined by forced oscillations: influence of smoking. *Chest* 1982; 81: 586–591.
4 Guo YF, Herrmann F, Michel JP, *et al.* Normal values for respiratory resistance using forced oscillation in subjects >65 years old. *Eur Respir J* 2005; 26: 602–608.
5 Brown NJ, Xuan W, Salome CM, *et al.* Reference equations for respiratory system resistance and reactance in adults. *Respir Physiol Neurobiol* 2010; 172: 162–168.
6 Pasker HG, Mertens I, Clément J, *et al.* Normal values of total respiratory input resistance and reactance for adult men and women. *Eur Respir Rev* 1994; 4: 134–137.
7 Clément J, Làndsér FJ, van de Woestijne KP. Total resistance and reactance in patients with respiratory complaints with and without airways obstruction. *Chest* 1983; 83: 215–220.
8 Pasker HG, Schepers R, Clément J, *et al.* Total respiratory impedance measured by means of the forced oscillation technique in subjects with and without respiratory complaints. *Eur Respir J* 1996; 9: 131–139.
9 James AL, Knuiman MW, Divitini ML, *et al.* Associations between white blood cell count, lung function, respiratory illness and mortality: the Busselton Health Study. *Eur Respir J* 1999; 13: 1115–1119.
10 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
11 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
12 Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester, John Wiley & Sons, 2001.
13 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
14 Goldman MD. Clinical application of forced oscillation. *Pulm Pharmacol Ther* 2001; 14: 341–350.
15 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement, *Lancet* 1986; 1: 307–310.
16 World Health Organization. Obesity and Overweight Fact Sheet. www.who.int/mediacentre/factsheets/fs311/en Date last accessed: July 2009. Date last updated March 2013.
17 Zerah F, Harf A, Perlemuter L, *et al.* Effects of obesity on respiratory resistance. *Chest* 1993; 103: 1470–1476.
18 Yap JCH, Watson RA, Gilbey S, *et al.* Effects of posture on respiratory mechanics in obesity. *J Appl Physiol* 1995; 79: 1199–1205.

DOI: 10.1183/09031936.00126212

19 Gimeno F, van der Weele LT, Koëter GH, *et al.* Forced oscillation technique. Reference values for total respiratory resistance obtained with the Siemens Siregnost FD5. *Ann Allergy* 1992; 68: 155–158.
20 Govaerts E, Cauberghs M, Demedts M, *et al.* Head generator *versus* conventional technique in respiratory input impedance measurements. *Eur Respir Rev* 1994; 4: 143–149.
21 Zerah F, Lorino AM, Lorino H, *et al.* Forced oscillation technique *vs* spirometry to assess bronchodilatation in patients with asthma and COPD. *Chest* 1995; 108: 41–47.
22 Skloot G, Goldman M, Fischler D, *et al.* Respiratory symptoms and physiologic assessment of ironworkers at the World Trade Center disaster site. *Chest* 2004; 125: 1248–1255.
23 Nair A, Ward J, Lipworth BJ. Comparison of the bronchodilator response in patients with asthma and healthy subjects using spirometry and oscillometry. *Ann Allergy Asthma Immunol* 2011; 107: 317–322.
24 Peslin R, Jardin P, Duvivier C, *et al.* In-phase rejection requirements for measuring respiratory input impedance. *J Appl Physiol* 1984; 56: 804–809.
25 Van Noord JA, Clément J, Van de Woestijne KP, *et al.* Total respiratory resistance and reactance in patients with asthma, chronic bronchitis, and emphysema. *Am Rev Respir Dis* 1991; 143: 922–927.
26 Pham QT, Bourgkard E, Chau N, *et al.* Forced oscillation technique (FOT): a new tool for epidemiology of occupational lung diseases? *Eur Respir J* 1995; 8: 1307–1313.
27 Pairon JC, Iwatsubo Y, Hubert C, *et al.* Measurement of bronchial responsiveness by forced oscillation technique in occupational epidemiology. *Eur Respir J* 1994; 7: 484–489.
28 Thamrin C, Gangell CL, Udomittipong K, *et al.* Assessment of bronchodilator responsiveness in preschool children using forced oscillations. *Thorax* 2007; 62: 814–819.
29 Oostveen E, Dom S, Desager K, *et al.* Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes. *Eur Respir J* 2010; 35: 865–872.