Original Article

Reference values of respiratory impedance with impulse oscillometry in healthy Chinese adults

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Background: Impulse oscillometry (IO) is a non-invasive pulmonary function test for measuring respiratory impedance. Available reference equations of IO indices for adults are limited. The aim of this study was to develop reference equations of IO indices for Chinese adults.

Methods: In a multicentral, cross-sessional study of IO in Chinese adults, IO data from healthy subjects were collected from 19 general hospitals across China between 2016 and 2018. Oscillometry measurements were conducted in accordance with recommendations of the European Respiratory Society (ERS). Multiple linear regression was performed to develop sex-specific reference equations of IO indices.

Results: IO measurements were performed in 1,318 subjects, of which 567 subjects were defined as healthy individuals with acceptable IO data and were included in the final analysis. Reference equations and limits of normal [lower limit of normal (LLN)/upper limit of normal (ULN)] of IO indices were developed separately for males and females. Height but not age was shown to be the most influential contributor to IO indices. The reference equations currently used in lung function laboratories predicted higher $R5$ and $X5$. Normal ranges of $R5$ and $X5$ recommended by the equipment manufacturer were clearly different from the ULN/LLN derived from the reference equations.

Conclusions: Reference equations of IO indices for Chinese adults from a wide region were provided in this study. It is necessary to update new IO reference equations and adopt ULN/LLN as normal ranges of IO indices.

Trial Registration: This study was registered at www.clinicaltrials.gov as part of a larger study NCT03467880.

Keywords: Reference values; respiratory impedance; impulse oscillometry (IO); forced oscillation technique (FOT); adult

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Introduction

Impulse oscillometry (IO) is one of the techniques of respiratory oscillometry that measures respiratory impedance non-invasively (1). IO is regarded as a complementary tool to conventional lung function tests due to its minimal demand for cooperation and sensitivity in the evaluation of small airway function (2). Reports of IO as a useful tool in the assessment of asthma (3-6), chronic pulmonary obstructive diseases (7) and bronchiectasis (8) have increased its application in research and clinical settings.

In accordance with other lung function tests, choosing optimal reference values is crucial for the interpretation of IO. The first and also the most widely used reference equation of respiratory impedance with IO is the one proposed by Vogel *et al.* in 1994 (9). The sample population of Vogel's equations was from a German industrial city that suffered from air pollution and included smokers, which obviously did not meet the American Thoracic Society (ATS) recommended criteria for the data source of lung function reference values (10). Furthermore, the study only used age as predictor of the respiratory impedance, where later studies (11-17) have demonstrated that respiratory impedance is more associated with height and weight rather than age. This may have an impact on the predictive values and normal ranges of IO indices, thus decrease the capacity for IO to identify respiratory abnormality. Although some studies had focused on developing new reference equations of respiratory impedance by oscillometry, the available reference equations of IO indices for adults are limited (11-16,18-21). The lack of appropriate reference equations and normal ranges of IO have hindered the application of oscillometry in clinical practice.

The aim of the present study was to develop reference equations of IO indices that: (I) are based on data of healthy Chinese adults collected from a wide region and under standardized quality control; (II) provide normal limits of IO indices with up-to-date criteria for clinical use. We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/jtd-20-3376).

Methods

The study of IO in Chinese was a multicenter, cross-sectional and observational study, and collected IO and spirometry reports from healthy subjects and patients with respiratory diseases in 20 general hospitals from 15 provincial regions throughout China between 2016 and 2018 (details of these hospitals are shown in Figure S1). IO data of healthy subjects were used to develop reference equations of IO in the present study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2015-37) and informed consent was taken from all individual participants.

Subject

Subjects were recruited mainly from individuals who have regular check-ups in hospitals, volunteer students at colleges and the relatives of hospital patients. Self-reported questionnaire was used to collect medical history, history of smoking and occupational exposures, respiratory symptoms, and results of chest radiography within the last 6 months. Subjects who met the following criteria were included as healthy subjects: no history of smoking or smoked <100 cigarettes in their lifetime; no occupational exposures; no respiratory tract infections in the last 4 weeks; no chronic or recurrent respiratory symptoms including cough, expectoration, wheezing, or shortness of breath; reported no severe cardiopulmonary diseases or systematic diseases. Those who had abnormalities on chest radiography or spirometry were excluded.

Oscillometry measurement

A Masterscreen Impulse Oscillometry System (CareFusion, Hoechberg, Germany) was used for oscillometry measurements in this study. Oscillometry measurements were conducted following the official technical recommendations for oscillometry from the European Respiratory Society (ERS) (22). Verification of impedance was performed daily and a criterion of error ≤10% or 0.1 $kPa \cdot s \cdot L^{-1}$ was adopted.

Measurements were performed in the sitting position with head in a neutral or slightly extended position, and the nose was closed by a nose clip. The cheeks were firmly supported by hands to reduce the effects of upper airway shunt. The subject was instructed to breath quietly at functional residual capacity level for 45–60 s. Measurements were repeated until three acceptable measurements were achieved, and the average of the three measurements was used for analysis. An acceptable measurement should have a data acquisition of at least 30 s and included five normal breaths without obvious artifacts like spikes in *Z*-time tracing or drifts in the volume-time tracing. The coherence of each measurement was ≥0.8 at 5 Hz and ≥0.9 at 20 Hz. Unacceptable data were excluded from the analysis.

Based on the fundamentals of forced oscillation technique (FOT), oscillometry measures respiratory impedance (*Z*) by superimposing pressure wave on the normal breathing (1). *Z* includes resistance (*R*) and reactance (*X*). *R* represents the resistive properties of respiratory system, and *X* represents the capacitive and inert properties of respiratory system. IO indices analyzed in this study included *R* and *X* at different frequencies (5–35 Hz), the difference between and *R*5 and *R*20 (*R*5–*R*20), resonant frequency (*f*res), and low-frequency reactance area (AX). The key indices for the normal limits analysis were *R*5 and *X*5, which are respectively recognized as total resistance and capacitance of respiratory system.

Spirometry

Spirometry (CareFusion, Hoechberg, Germany) was performed immediately after the oscillometry measurements as per the ATS/ERS guideline for spirometry (23). If spirometry was performed before the oscillometry, at least 3 min of rest was allowed for rest (22). Three acceptable measurements that met the quality control criteria of the ATS/ERS guidelines (24) were acquired and the best one was used in the analysis. Spirometric indices analyzed in this study were forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and maximal mid-expiratory flow (MMEF). Reference values of spirometry were derived from the study of reference values for spirometry in Chinese aged 4–80 years (25).

Statistical analysis

As IO indices exhibited skewness distribution, the results were presented as median with interquartile range. Mann-Whitney U tests were performed for the comparisons of continuous indices. A P values <0.05 was considered statistically significant.

Reference equations were calculated separately for males and females using multivariate linear regression analysis. Scatter plots (see Figure S2) were drawn to observe the linear relationship between IO indices and predictor variables. Normal P-P plots and residual plots were drawn to examine the normality and equal variance of the residuals. As the residuals of *f*res and AX only displayed normality and equal variance after *f*res and AX were log transformed, thus *f*res and AX were calculated as $\log_{10}$ transformation (lg*f*res and lgAX) in the equations. Predictor variables (height, weight and age) were selected using the stepwise method, in which predictors would enter the model if P<0.05 and were removed if P>0.10. Fitness of the model was assessed by the coefficient of determination (R^2). Normal limits of IO indices were calculated as followed: upper limit of normal (ULN) of *R* = predictive value + 1.645 × residual standard deviation (RSD), lower limit of normal (LLN) of *X* = predictive value – 1.645 × RSD.

For the development of prediction models with multivariate regression analysis, according to the rule of ten events per variable, assuming that the number of predictors of the equation is 3, then the sample size would be at least 30 for male and female subjects. Subjects with missing data would be excluded from the analysis.

Results

In this study, a total number of 1,318 of subjects were recruited and finished the oscillometry measurements between 2016 and 2018 in 19 hospitals across China, 567 subjects from 13 hospitals were included in the final analysis (*Figure 1* and Table S1). The baseline characteristics are presented in *Table 1* and *Figure 2*. Height range was 154–186 cm in males and 142–176 cm in females. The spirometric indices FEV_1, FVC, FEV_1/FVC and MMEF of the analyzed population were all within normal limits.

For the whole population, the median (interquartile range) of *R*5 was 0.29 (0.09) $kPa \cdot s \cdot L^{-1}$, *R*20 was 0.27 (0.08) $kPa \cdot s \cdot L^{-1}$, and *X*5 was –0.10 (0.04) $kPa \cdot s \cdot L^{-1}$. Resistance at all frequencies in females were significantly higher than those in males, while reactance at all frequencies (except for *X*15) were more negative in females than in males (details are shown in Table S2).

Results of the reference equations for main IO indices are shown in *Table 2* (complete results of other IO indices

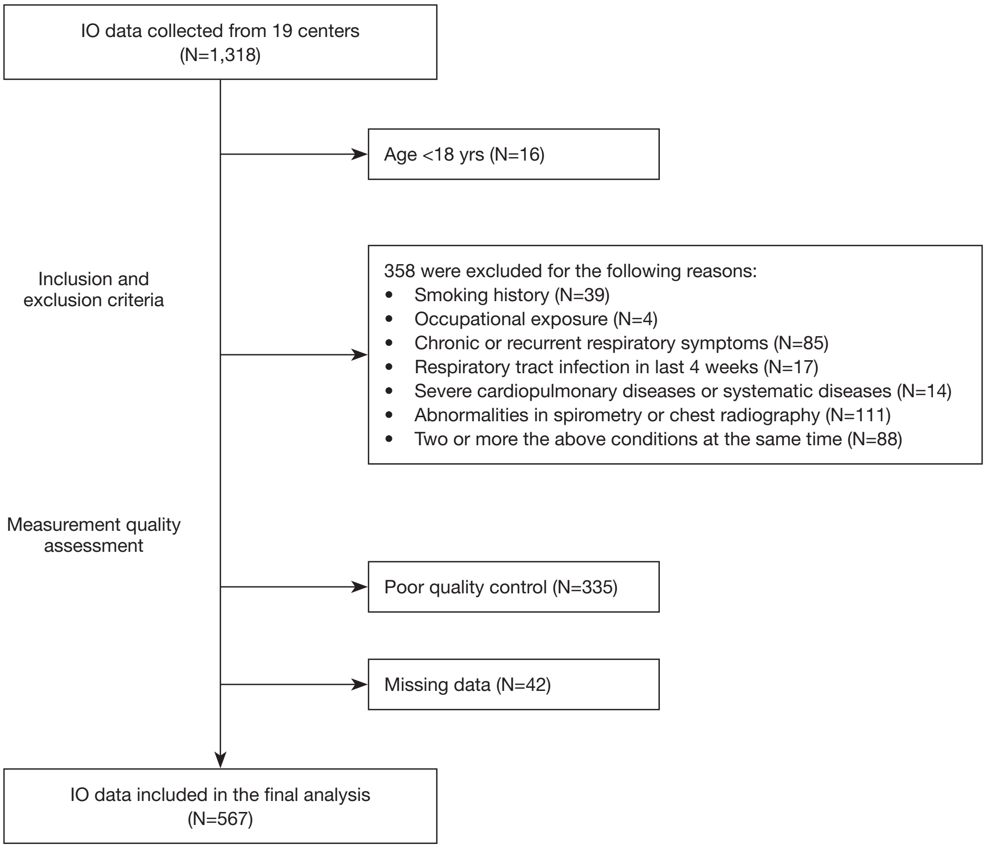

Figure 1 Flow chart of the inclusion and exclusion criteria for analyzed data. IO, impulse oscillometry.

Table 1 Baseline characteristics of the study population

Baseline characteristics	Male (N=270)	Female (N=297)	P value
Age (years)	36.0 (23.8)	34.7 (23.0)	0.065
Height (cm)	170.0 (9.0)	159.0 (7.0)	<0.001
Weight (kg)	69.0 (15.1)	56.0 (12.0)	<0.001
BMI (kg/m^2)	23.7 (4.4)	21.9 (4.4)	<0.001
FEV$_1$ (L)	3.88 (0.87)	2.86 (0.55)	<0.001
FEV$_1$ z score	0.28 (1.24)	0.16 (1.16)	0.213
FVC (L)	4.66 (0.99)	3.34 (0.62)	<0.001
FVC z score	0.23 (1.31)	0.17 (1.27)	0.211
FEV$_1$/FVC	0.83 (0.07)	0.84 (0.07)	0.002
FEV$_1$/FVC z score	–0.05 (1.10)	–0.05 (1.17)	0.839
MMEF (L/s)	3.86 (1.51)	2.95 (1.21)	<0.001
MMEF z score	0.12 (1.23)	0.05 (1.26)	0.461

Data are presented as median (interquartile range). BMI, body mass index; FEV$_1$, forced expiratory volume in the first second; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow.

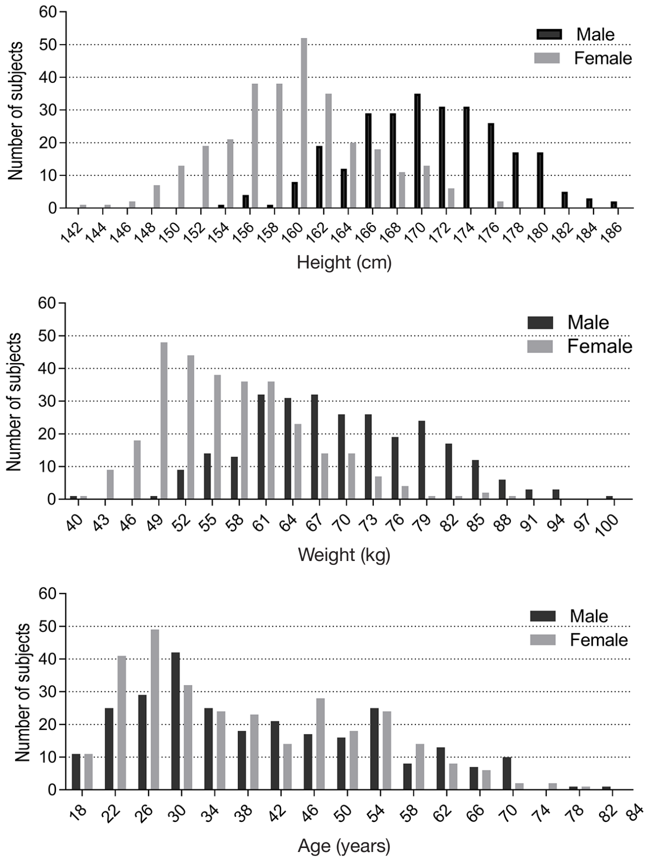

Figure 2 Distribution of height, weight and age of the study population by gender.

are shown in Tables S3,S4). Except for *R*35 in males, all IO indices in this study derived significant reference equations with height and/or weight as predictors. R^2 of the equations ranged from 0.0154 to 0.250 and tended to be smaller in equations of the impedance at higher frequencies.

In the equations of most IO indices, height was shown to be the most influential predictor as it contributed the largest R^2 changes in the prediction models. Height was negatively associated with *R*, *f*res and AX, and positively associated with *X*. On the contrary, weight showed a positive association with *R*, *f*res and AX, and negative association with *X*. Age was shown to be predictor to some indices including *X*5, *X*25, and *X*35 in both genders and *Z*5, *R*5, and lgAX in females (Tables S3,S4). However, the scatter plots (Figure S2) between these indices and age did not display notable linear relationships.

For further comparisons of reference values of previous studies [Vogel *et al.* (9), Newbury *et al.* (15), and Schulz *et al.* (18)] and the present one, reference values of *R*5 and *X*5 were compared as a function of height, with age fixed at 50 years, and weight was calculated by a fixed body mass index (BMI) of 23 kg/m^2 (the median of our study subjects). Results are in *Figure 3*. Also, differences between the actual values and the reference values by different equations in healthy subjects were compared in Figures S3-S5.

Discussion

Sex-specific reference equations for respiratory impedance were developed based on large-scale data of healthy Chinese adults from a wide region in a multicenter IO study.

Contributors to the respiratory impedance

As pulmonary function is associated with physiological changes during growth and aging, reference equations of

Table 2 Reference equations of the main IO indices

IO indices	Equations	RSD	R^2
*Z*5	M: 0.6811 – 0.0032 × H + 0.0019 × W	0.0415	0.1877
	F: 0.9110 – 0.0042 × H + 0.0023 × W – 0.0008 × A	0.0493	0.1673
*R*5	M: 0.6275 – 0.0030 × H + 0.0019 × W	0.042	0.1789
	F: 0.8103 – 0.0038 × H + 0.0024 × W – 0.0005 × A	0.0491	0.1606
*R*20	M: 0.5038 – 0.0019 × H + 0.0010 × W – 0.0004 × A	0.0401	0.0668
	F: 0.5042 – 0.0013 × H	0.0442	0.0282
*R*5–*R*20	M: 0.2485 – 0.0018 × H + 0.0010 × W	0.0205	0.2249
	F: 0.2360 – 0.0019 × H + 0.0017 × W	0.0306	0.1865
*X*5	M: –0.3100 + 0.0013 × H + 0.0002 × A	0.0195	0.1105
	F: –0.3605 + 0.0015 × H + 0.0004 × A	0.0236	0.1233
lg*f*res	M: 1.9238 – 0.0068 × H + 0.0033 × W	0.0801	0.1963
	F: 1.8261 – 0.0067 × H + 0.0051 × W	0.0805	0.2505
lgAX	M: 1.3268 – 0.0142 × H + 0.0043 × W	0.2124	0.1179
	F: 1.6639 – 0.0166 × H + 0.0089 × W – 0.0029 × A	0.2037	0.1540

IO, impulse oscillometry; RSD, residual standard deviation; R^2, coefficient of determination; *Z*5, total respiratory impedance at 5 Hz; *R*5, resistance at 5 Hz; *R*20, resistance at 20 Hz; *R*5–*R*20, *R*5 minus *R*20; *X*5, reactance at 5 Hz; *f*res, resonant frequency; AX, low-frequency reactance area; M, male; F, female; H, height; W, weight; A, age.

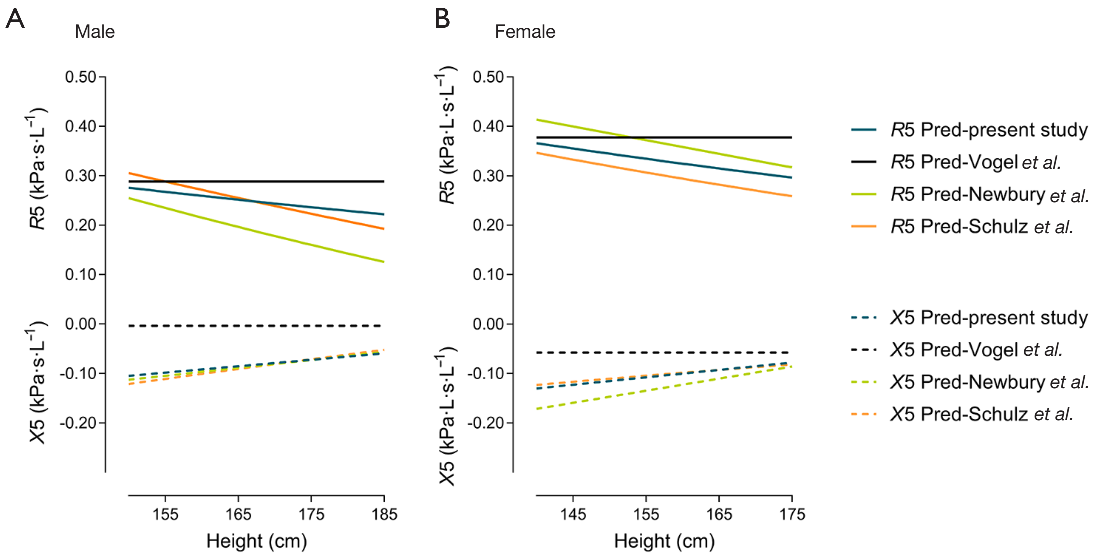

Figure 3 Comparison of the Pred of *R*5 and *X*5 predicted by different equations. Results are shown as a function of height, with age fixed at 50 years, and weight was calculated by a fixed BMI of 23 kg/m^2 (the median of our study population). Solid lines indicate Pred of *R*5, and dashed lines indicate Pred of *X*5. Pred, predictive values; BMI, body mass index.

pulmonary function commonly include anthropometric variables such as sex, age, height and weight, in order to justify the contributory effects of these factors to lung function. Our study found that height was the most influential contributor to respiratory impedance measured with IO, with that taller individuals had higher *R* and less negative *X*. This finding is consistent with the previous studies (11-17,19,21,26). As shown in *Table 3*, though the coefficients or forms of the predictors in the IO equations are different, the tendency of the effect of predictors in most equations remains the same; that is, height is negatively correlated with *R*5 and *R*20, and positively correlated with *X*5. The association between height and respiratory resistance can be explained by the effect that height contributes to the diameter of the airways and lung volume. This could also explain the discrepancies of respiratory impedance between males and females. In contrast, weight displayed a positive association with *R*. The decreased lung volume and ventilation heterogeneity reported in the obese subjects (27,28) may account for the higher respiratory resistance in the obese. However, the mechanism behind how body weight affects respiratory impedance in subjects with normal weight is still not clear since most studies have focused on overweight or obese individuals. Although age did not appear to be a marked contributor to *R* in adults in our study, a negative dependence on age for *R* has been reported in studies of children and adolescences (29,30). Thus, the effect of age on *R* may be related to the rapid physiological changes during growth, especially on the growth of the respiratory system in children and adolescences.

Reference equations of respiratory impedance with IO

Since age is shown to have little impact on respiratory impedance in adults, it is no surprise that in *Figure 3*, marked differences of predictive values were found between the Vogel's equations and the equations from other three representative studies [Newbury *et al.* (15), Schulz *et al.* (18) and the present study], as age is the only predictor in Vogel's equations (9). Given that many lung function laboratories are still using Vogel's equations, it is important for the physicians to note that Vogel's equations predict higher *R*5 and *X*5 than other equations, especially for *X*5, and the differences are greater in tall subjects for *R*5 and in short subjects for *X*5. Undoubtedly, developing a more appropriate equation is imperative.

As summarized in *Table 3*, since Vogel's equations were developed, 10 studies have developed new equations of IO indices in adults, and 7 of these were from China. However, most of these studies have limitations such as lack of quality control of IO data or small sample sizes [Fang *et al.* (12), Shiota *et al.* (13), Newbury *et al.* (15), Ni *et al.* (14), Wang *et al.* (16)]. Among these studies, only 6 studies had mentioned the number of IO measurements for each subject, only 4 studies [Wang *et al.* (16), Schulz *et al.* (18), Zhang *et al.* (19), Shu *et al.* (20)] had mentioned the requirements of repeatability, and 3 studies [Shiota *et al.* (13), Newbury *et al.* (15), Schulz *et al.* (18)] had mentioned the acceptable criteria for the IO measurements. As the variations of oscillometry are greater than spirometry (31), multiple measurements and strict quality control are particularly important in oscillometry measurements to ensure the repeatability and reliability of the data. Regarding sample size, studies from Shiota *et al.* (13) and Newbury *et al.* (15) were based on small sample sizes, with 166 and 125 subjects, respectively. This may decrease the reliability and applicability of their equations as a study have shown that at least 150 males and 150 females are required to validate reference equations of lung function tests in individual laboratories (32). Also, Shiota's equation did not take sex into account, whereas sex-related differences in IO indices have been reported in the present and former studies (21). Schulz's study (18) was based on data from a relatively large sample size and with clear quality control criteria. Similar values of *R*5 and *X*5 produced by Schulz's study and the present study in *Figure 3* provide evidence of the reliability of our reference equations.

Although 7 studies from China have developed reference equations of IO indices (11,12,14,16,19,20,26) (*Table 3*), all of these studies were based on local sample populations, which may be less representative of the whole population of China, as China is a country with large territory and population. Heterogeneity in the inclusion criteria of participants and quality control also hinder the integration of these databases. Our study was a multicenter study that included data from a wide region across China, with uniform inclusion criteria and standardized quality control. Therefore, this study is more representative of the general population and produces more reliable data.

Normal ranges of IO indices

Despites the fact that ERS had published official recommendations for the application of oscillometry in the clinical practice (22,33), there are no acknowledged

Table 3 Summary of the reference equations of IO indices for adults

Equations	Area	N	F/M	Age range (years)	Ethnicity	Predictors				
						Sex	*R*5	*R*20	*X*5	*f*res
Present study	China	567	1.10	18–82	99.3% Han	M	–H, W	–H, W	H, A	–H, W
						F	–H, W, –A	–H,	H, A	–H, W
Vogel *et al.* (9), 1994	Germany	506	0.70	18–69	NA	M	A	A	–A	NA
						F	A	A	–A	NA
Zhao *et al.* (11), 2002	Xinjiang, China	457	0.80	16–81	Han, Uygur	M	W, –H	W, –H, –A	H	W, –H
						F	W, –H	–H, –A	H, W	W, –H
Fang *et al.* (12), 2005	Kunming, China	185	0.73	19–68	NA	M	–W *H	–W *H	NA	$-e^{H}$
						F	$-e^{W}$	$-e^{W}$	NA	–LogH, LogW
Shiota *et al.* (13), 2005	Japan	166	1.40	20–83	NA	–	–LogH	–LogH	LogH, –A	–
Ni *et al.* (14), 2006	Nantong, China	120	0.69	20–79	Han	M	–H, W, A	–H, W, A	H, W, A	H, W, A
						F	H, W, A	H, W, –A	H, W, A	H, W, A
Newbury *et al.* (15), 2008	Australia	125	1.12	25–74	Caucasian	M	–H, W, –A	–H, W, –A	H, A	NA
						F	–H, A	–H, A	H, –A	NA
Wang *et al.* (16), 2011	Shenyang, China	100	0.69	19–80	NA	M	–lgH, –lgA	$-H^{2}$, $-e^{A}$	$-A^{2}$	A^{2}
						F	–lgH	$-H^{2}$	H^{2}, $-e^{A}$	–lgH, A*W
Li *et al.* (26), 2012	Lanzhou, China	920	1.04	>18	NA	M	–lgH, W	–H, W	$-A^{2}$	–H, W
						F	–H, W	W	$-A^{2}$	–H, W
Schulz *et al.* (18), 2013	Germany	397	1.58	45–85	Caucasian	M	–H, W, –A	–H, W, –A	H, –W, –A	–H, W, A
						F	–H, W, –A	–H, W, –A	H, –W, –A	–H, W, A
Zhang *et al.* (19), 2015	Macau, China	362	1.02	18–78	Han	M	W, –H	–H	H	A, –H
						F	CW, –W, A	–H	H, A	A, CW, –W
Shu *et al.* (20), 2016	Jianghan Plain, China	431	1.03	18–79	NA	M	–AH, A, $-A^{2}$, e^{W}, $-e^{A}$	–AH, A, $-A^{2}$, –lgA	A*H, –A	$-H^{2}$, W^{2}
						F	$-H^{2}$, W, $-e^{W}$	W, $-H^{2}$	H^{2}	W, $-H^{2}$, $-e^{W}$

H, W, A respectively indicate height, weight and age as predictors of the equations; "–" indicates a negative effect of the predictor; M: equations for males; F: equations for female. IO, impulse oscillometry; N, the number of the study sample; F/M, ratio of female subjects to male subjects; *R*5, resistance at 5 Hz; *R*20, resistance at 20 Hz; *X*5, reactance at 5 Hz; *f*res, resonant frequency; NA, information was not available in the published paper.

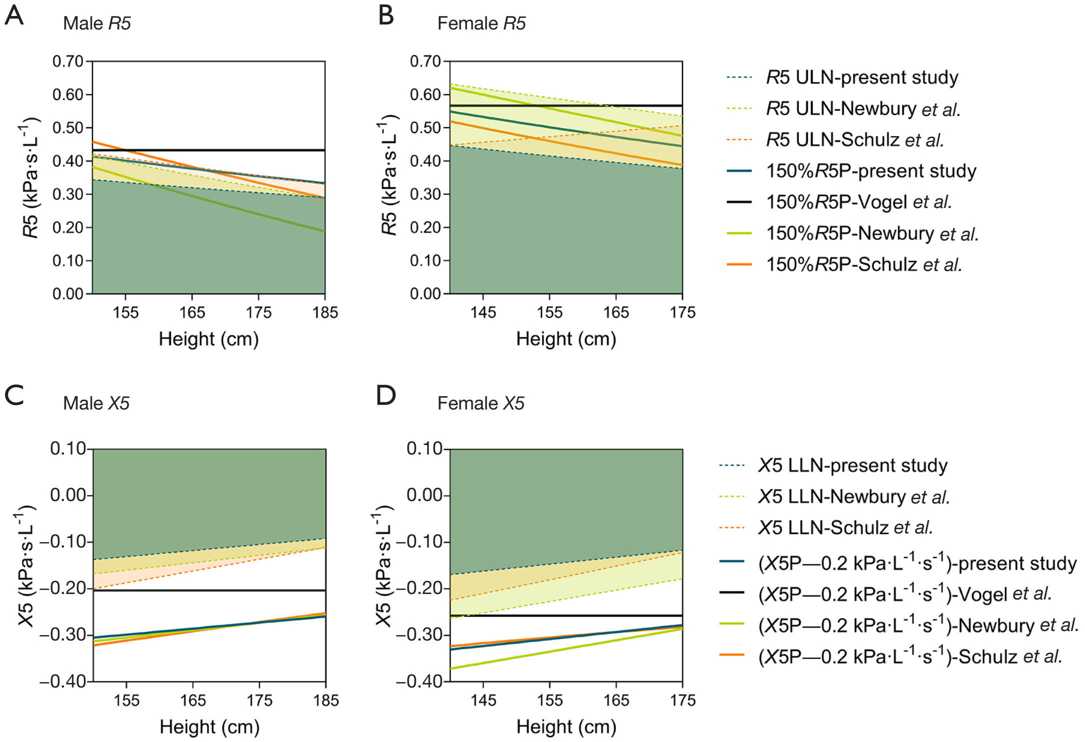

Figure 4 Comparisons of the normal ranges of *R5* and *X5* derived by different equations. Colored area under the dotted lines indicates ULN of *R5* or LLN of *X5*. Solid lines indicate 150% *R5*P or the predictive values of *X5* minus 0.2 kPa·s·L^{-1} (*X5*P–0.2 kPa·s·L^{-1}). As the RSD of Vogel's equations is not available, the ULN/LLN with Vogel's equations is not shown. ULN, upper limit of normal; LLN, lower limit of normal; 150% *R5*P, 150% of the predictive values of *R5*; RSD, residual standard deviation.

criteria for the normal ranges of respiratory impedance with oscillometry, probably due to the lack of systematic studies concerning on normative values of respiratory impedance. The IO equipment manufacturer recommends using 150% of the predicted value as the normal limit for *R5* and *R20*, and predicted value minus 0.2 kPa·s·L^{-1} as the normal limit of *X5*. The former was derived from the report of a bronchial challenge test study showing that a 20% decrease in FEV$_1$ was comparable to a 50% increase in airway resistance (1). However, ATS guidelines for pulmonary function tests reported in 2017 have recommended using LLN/ULN as the criteria of abnormal of pulmonary function (10). As is shown in *Figure 4*, predicted *X5* minus 0.2 kPa·s·L^{-1} (*X5*P–0.2 kPa·s·L^{-1}) was significantly more negative than the LLN of *X5*, regardless of the equation used. The 150% of predicted *R5* (150% *R5*P) was much higher than the ULN of *R5* produced by our equations, and marked differences were also shown in the comparison of ULN of *R5* and 150% *R5*P produced by Newbury' equations in males and Schulz's equations in females. The above differences between the ULN/LLN and the normal limits currently used in laboratories will apparently increase the risk of misdiagnosis. Under the increasing application of oscillometry in clinical practice, it is necessary to update new equations and normal ranges of oscillometry. The validation of our new equations and normal ranges of IO in patients with respiratory diseases will be further analyzed and discussed in our later reports.

Limitations

There were limitations to the present study. First, due to the practical limitations, our study population was not a random sample and may be less representative of the whole healthy population. Nevertheless, multicenter sources of data and strict inclusive criteria for healthy subjects in this study provide a guarantee of the representativeness of a healthy population. To date, our equations are the most representative and reliable for healthy Chinese adults. Second, our equations are based on the data of Chinese population, its use in other populations or ethnicities may be limited. However, we believe that these data may be a foundation or promotion to the development of multiethnic reference equations of oscillometry in the future, and our findings about the inappropriateness of the current normal ranges of IO indices may provide evidences for the update of the internationally technical standards. Third, as the IO data from children and adolescents in multicenter study of IO in Chinese were not enough to develop reference equations, we failed to develop continuous reference equations with a full age range. Studies containing a larger number of healthy children and adolescents with a randomized sample are needed in the future.

Conclusions

In summary, based on the data of a large-scale healthy population in the multicenter IO study in China, we developed new reliable reference equations of respiratory impedance with IO. Also, we found that the normal ranges of IO indices wildly used in laboratories were clearly different from the ULN/LLN derived from the reference equations. It is necessary to update new IO reference equations and adopt ULN/LLN as normal ranges of IO indices for better use of osicllometry in clinical practice.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2015-37) and informed consent was taken from all individual participants.

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