Long-term variability of impulse Oscillometry and Spirometry in stable COPD and Asthma

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Abstract

Background: While optimizing spirometry is a challenge for all lung function labs, long-term variability is not known in stable COPD (chronic obstructive pulmonary disease) and chronic asthma. The forced oscillation technique is increasingly employed in routine lung function testing. Our aim in this study was to determine the variability in oscillometric parameters between clinic visits over weeks or months in two patient groups during a period of clinical stability (asthma patients and COPD patients). Moreover, the research assesses relationships between IOS (impulse oscillometry) parameter long-term variability and COPD severity.

Methods: We used data from 73 patients with stable COPD and 119 patients with stable asthma at the Shanghai Pulmonary Hospital Affiliated to Tongji University. Patients were included if they had three or more clinic visits where spirometry and IOS were performed during a clinically stable period. Only data recorded from the first three visits were used. The standard deviation (SDbv), the coefficient of variation (COV), intraclass correlation coefficient (ICC) and the coefficient of repeatability (COR) were calculated, Wilcoxon Mann-Whitney test was used for data that did not conform to normality of distributions, Kruskal Wallis test was used to compare with multiple groups, post hoc comparison was analyzed by Bonferroni, Spearman correlation coefficients for non-parametric data, the multiple regression analyses to determine the relationship between long-term variability and airflow obstruction.

Results: 1. the repeatability of IOS parameters were high (>0.80) ICC values in COPD and asthma, ICC values of IOS parameters were higher than for spirometry; 2. repeatability (ICC valve<0.8) of spirometry parameters was lower than IOS parameters (ICC valve>0.8) in different GOLD (the Global Initiative for Chronic Obstructive Lung Disease) stage, and the higher the stage, the worse the repeatability; 3. the severity of airflow obstruction was correlated with long-term variability of R5 (R at 5 Hz) ($P<0.05$) and R5-R20 ($P<0.05$), not with long-term variability of R20 (R at 20 Hz) ($P>0.05$).

Conclusion: IOS parameters have good long-term repeatability in asthma and COPD.
Additionally, variability is different between diseases and GOLD stages, repeatability of spirometry parameters is lower than that in IOS parameters in different GOLD stages. The greater the long-term variability seen in COPD is associated with airflow obstruction.

Introduction

IOS is increasingly receiving attention for pulmonary function examinations. The main advantage being its simplicity : the oscillatory signal is based on spontaneous breathing and, hence, no special patient cooperation is required[1].

IOS is a variant of forced oscillation technique (FOT), measures respiratory impedance at multiple frequency ranges, composed of frequencies ranging from 5 to 35 Hz and performed during tidal breathing. The principle of the maneuver is measuring the instantaneous response to pressure, using external pressure signals to measure the respiratory system impedance (resistance, reactance)[2]. R5

indicates total airway resistance, R20 mainly indicates central airway resistance, R5-R20 is considered an index of distal lung resistance, these three parameters are commonly used to evaluate airway resistance[3]. Chronic airway obstruction is a major symptom feature of COPD and asthma, forced expiratory volume in 1 s (FEV1) is the gold standard for diagnosing airway obstruction. However, FEV1 is thought to be inadequate to determine obstruction of the smaller airways[4, 5]. Some studies suggest that IOS is more sensitive than spirometry for detecting airway obstruction in patients with asthma and COPD[1, 6, 7]. Therefore, IOS is a critical detection method in detecting small airway obstruction.

As a re-emerging clinical detection technology, it is significant to study the minimal clinically important difference (MCID) for IOS in the detection of lung function in stable COPD and asthma. There has been suggestion that the ICC's (intraclass correlation coefficient) were high for all parameters in health, stable asthma and COPD, FOT measures are highly repeatable, day-to-day variability was due mostly to repeatability, which is correlated with airway obstruction[8]. Another study determined the between-visit variability of a range of IOS in a group of patients with asthma in the stable state, and between-visit variability over two-time intervals, namely in 2 weeks and 3 months. ICC values > 0.8 in the majority of cases. Therefore, they suggest that IOS parameters are stable over time and have the potential to be for clinical testing in asthma[9]. Moreover, FOT parameters have good long-term repeatability, high ICC values in health and in asthma and COPD, but also that variability differs between diseases[10]. While the short-term variability in IOS parameters is known, longer-term variability still needs more work. Understanding their variations in clinically stable patients on routine outpatient visits is necessary to estimate clinically important changes with time. Therefore, the aim of this study was to determine the variability in IOS parameters between clinic visits over weeks or months, in stable asthma and COPD patients. Moreover, the research assesses relationships between IOS parameters long-term variability and degree of airway obstruction of stable COPD.

Patients And Methods

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital. All methods including PFT (Pulmonary Function Tests) and IOS were carried out in accordance with relevant guidelines and regulations.

Patients

This study retrospectively enrolled 73 patients with stable COPD and 119 patients with stable asthma who were referred to Shanghai Pulmonary Hospital from January 2011 to December 2018. All patients were in the stable condition. The main inclusion criteria were as follows: (1) three or more clinic visits; (2) spirometry and IOS were performed; (3) no change in symptoms, no respiratory infection in the past 6 weeks and no changes in treatment. Patients be diagnosed by physicians as asthma and COPD,

and have a post-bronchodilator FEV1/FVC<70 (forced vital capacity, FVC) [10]. GOLD staging was conducted for patients with COPD according to the 2018 COPD Guidelines[11].

PFT

We performed pulmonary function tests [including spirometry and impulse oscillation (IOS)] using standard equipment (Masterscreen-PFT, Jaeger crop, Hoechberg, Germany; Masterscreen-IOS, Jaeger crop, Hoechberg, Germany). FVC, FEV1 and FEV1/FVC were determined by standard procedure[12]. R5, R20 and R5-R20 were recorded at each visit, 30 s recordings were acquired. For each patient, data were presented in absolute terms and normalized to percentage of normal predicted (% Pred).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 and GraphPad Prism 5. Data are shown as mean ± SD, median (interquartile range). A two-tailed p-values less than 0.05 is considered to be statistically significant. The Shapiro–Wilk test was used to assess normality of distributions. Long-term variability was expressed as the standard deviation of the first three visit's measurements for each subject (SDbv). The coefficient of variation (COV= SDbv/mean) was calculated and intraclass correlation coefficient (ICC; mixed-effects model, absolute agreement, mean of three raters) of IOS measurements of the three clinic visits. In addition, the coefficient of repeatability (COR) was calculated, defined as twice the standard deviation of the differences between two pairs of consecutive clinic visits from three clinical visits per patient or expressed as a percentage of close to maximal variation (pMV)[13, 14]. ICC value between 0.5 and 0.6 was considered as medium repeatability, between 0.7 and 0.8 was considered as good repeatability, and > 0.8 was considered as very good repeatability. pMV between 0 and 33% was considered decent repeatability, between 33% and 66% was considered good repeatability, and above 66% was considered poor repeatability. Age and BMI (body mass index) were analyzed by one-way ANOVA. Wilcoxon Mann-Whitney test was used for data that did not conform to normality of distributions, Kruskal Wallis test was used to compare with multiple groups, post hoc comparison was analyzed by Bonferroni. The relationships between variability (SDbv) and mean IOS parameters were examined using Spearman correlation coefficients for non-parametric data. Multiple regression analysis was used to analyze the factors that might influence the variability of IOS parameters in stable COPD patients between long-term clinic visits.

Results

Baseline demographic characteristics and lung function

The baseline demographic characteristics and lung function of COPD and asthma are provided in Table 1. 119 asthma and 73 COPD patients (n=1 Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1; n=22 GOLD stage 2; n=31 GOLD stage 3; and n=19 GOLD stage 4) were included. Since there was

only one GOLD stage 1 patient, GOLD stage 1 and Gold Stage 2 were combined for subsequent analysis. Asthma ((49.86±14.26) years) patients were younger than COPD ((62.68±9.57) years) patients (F=45.08, P<0.0001), and there was no significant difference in BMI between the two groups (F=0.93, P=0.337). There were no statistically significant differences in age and BMI among COPD GOLD1-2, GOLD3 and GOLD4 stage groups (F=0.58, P=0.562; F=1.92, P=0.155). Only R5 was not statistically different between COPD and asthma (Z=-0.28, P=0.778).

Table 1

Baseline Characteristics and Lung Function of COPD and Asthma.

	COPD-All (N=73)	COPD-GOLD1-2 (N=23)	COPD-GOLD3 (N=31)	COPD-GOLD4 (N=19)	Asthma (N=119)	P valve
Age, year	62.68±9.57	63.04±10.19	63.65±9.20	60.68±9.62	49.86±14.26	P<0.0001
M3-M1	6.1 (3.4-16.6)	6.1 (3.3-22.8)	8.4 (3.0-19.0)	4.9 (4.0-12.6)	4.9 (4.0-12.6)	
BMI, kg/m2	22.81±3.59	23.85±3.60	22.72±3.58	21.71±3.41	23.48±3.48	P=0.337
FEV1, L	0.95 (0.72-1.29)	1.51 (1.26-1.87)	0.89 (0.73-1.09)	0.69 (0.57-0.75)	2.36 (1.86-2.82)	P<0.0001
MEF 50, L	0.42 (0.30-0.71)	0.90 (0.71-0.94)	0.39 (0.31-0.54)	0.30 (0.22-0.33)	3.17 (2.56-4.03)	P<0.0001
MEF 25, L	0.19 (0.14-0.25)	0.29 (0.22-0.35)	0.19 (0.12-0.21)	0.15 (0.11-0.19)	0.85 (0.52-1.17)	P<0.0001
MMEF 75/25, L	0.37 (0.26-0.58)	0.67 (0.60-0.80)	0.35 (0.26-0.41)	0.25 (0.20-0.29)	2.16 (1.37-2.89)	P<0.0001
R5, $cmH2O \cdot s \cdot L^{-1}$	5.98 (4.64-7.64)	4.82 (4.06-6.77)	7.23 (5.55-8.51)	5.83 (4.60-7.21)	4.25 (3.13-5.11)	P<0.0001
R20, $cmH2O \cdot s \cdot L^{-1}$	3.17 (2.68-3.79)	2.97 (2.72-3.64)	3.63 (2.86-4.61)	2.69 (2.10-3.48)	3.17 (2.56-4.03)	P=0.778
R5-R20, $cmH2O \cdot s \cdot L^{-1}$	2.85 (1.89-3.9)	1.73 (0.94-3.01)	3.60 (2.60-4.03)	2.85 (2.48-4.04)	0.85 (0.31-1.59)	P<0.0001

The data are presented as mean ± SD, median (interquartile range). Age and BMI were analyzed by one-way ANOVA, post hoc comparison was analyzed by Bonferroni, Wilcoxon Mann-Whitney test was used for data that did not conform to normality of distributions. M3-M1 represents the month difference between the third and first follow-up; BMI=Body Mass Index; FEV1= forced expiratory volume in 1 s; MEF=maximal expiratory flow; MMEF=maximum midexpiratory flow; R5= R at 5 Hz; R20= R at 20 Hz; P valve COPD versus asthma.

Long-term variability in COPD and Asthma

Long-term variability of spirometry and IOS parameters are shown in Table 2. The relative between-visit variability (SDbv) for IOS were more variable than for spirometry. SDbv of FEV1, MEF 50, MEF 25, R5 and R5-R20 were statistically different in COPD and asthma (Z=-3.64, P<0.0001; Z=-8.28, P<0.0001; Z=-8.03, P<0.0001; Z=-8.50, P<0.0001; Z=-3.64, P<0.0001; Z=-5.15, P<0.0001). Between-visit variability relative to the mean (COV) for IOS parameters (R5, R20) were not statistically different between COPD and asthma (Z=-0.37, P=0.713; Z=-1.63, P=0.102), however, R5-R20 is statistically different (Z=-3.85, P<0.0001) (Fig 1).

The COR data during a period of stable disease for the two patient groups (Table 2) are novel. We show

that variations in R5 up to 35% in COPD and 36% asthma are typical of stable patients, while variations in R20 up to 47% in COPD and 46% asthma can be present, equivalent to R5-R20 up to 46% in COPD and 47% asthma. However, the repeatability of IOS parameters were high (>0.80) ICC values. Moreover, the relative CORs for IOS were more variable than for spirometry, but importantly, the ICCs were similar.

Table 2

long-term variability of spirometry and IOS parameters in COPD and Asthma.

	SDbv	COV	ICC	COR
COPD				
FEV1, L	0.15 (0.09-0.22) [a]	15% (8%-20%) [a]	0.94	0.45 (23%)
MEF 50, L	0.10 (0.06-0.19) [a]	20% (10%-31%) [a]	0.94	0.40 (26%)
MEF 25, L	0.04 (0.02-0.08) [a]	18% (11%-28%)	0.84	0.18 (45%)
MMEF 75/25, L	0.08 (0.05-0.13) [a]	17% (12%-25%) [a]	0.94	0.31 (28%)
R5, $cmH2O \cdot s \cdot L^{-1}$	0.86 (0.52-1.23) [a]	15% (10%-21%)	0.90	2.73 (35%)
R20, $cmH2O \cdot s \cdot L^{-1}$	0.40 (0.29-0.61)	13% (10%-19%)	0.84	1.62 (47%)
R5-R20, $cmH2O \cdot s \cdot L^{-1}$	0.71 (0.45-1.16) [a]	29% (20%-45%)	0.84	2.54 (46%)
asthma				
FEV1, L	0.10 (0.06-0.16)	4% (2%-7%)	0.99	0.36 (12%)
MEF 50, L	0.33 (0.20-0.48)	12% (8%-17%)	0.96	1.24 (23%)
MEF 25, L	0.12 (0.08-0.23)	16% (9%-27%)	0.95	0.72 (30%)
MMEF 75/25, L	0.24 (0.14-0.37)	12% (8%-18%)	0.96	1.03 (23%)
R5, $cmH2O \cdot s \cdot L^{-1}$	0.56 (0.33-0.90)	15% (9%-21%)	0.93	1.94 (36%)
R20, $cmH2O \cdot s \cdot L^{-1}$	0.51 (0.29-0.80)	16% (10%-23%)	0.90	1.70 (46%)
R5-R20, $cmH2O \cdot s \cdot L^{-1}$	0.40 (0.22-0.64)	46% (27%-68%)	0.83	1.42 (47%)

Wilcoxon Mann-Whitney test was used for data analysis. COR is expressed as absolute (cmH2O·s·L-1) and pMV (%). SDbv=between-visit standard deviation; COV=the coefficient of variation; ICC=intraclass correlation coefficient; COR=the coefficient of repeatability. [a]$p < 0.05$ COPD versus asthma.

Compare the long-term variability of IOS parameters in degree of airway obstruction of stable COPD.

Long-term variability of PFT and IOS parameters in COPD severity are shown in Table 3. Between-visit variability (SDbv) of R5 was statistically different in GOLD1-2, GOLD3 and GOLD4 patients (H=8.85, P=0.012). Between-visit variability relative to the mean (COV) for FEV1, R5 and R5-R20 were statistically different in GOLD1-2, GOLD3 and GOLD4 patients (H=19.03, P<0.0001; H=6.38, P=0.041; H=13.98, P=0.001), difference between GOLD1-2 and GOLD3 groups for FEV1 (P=0.001), and between GOLD1-2 and GOLD4 groups (P<0.0001), however, between GOLD3 and GOLD4 was not (P>0.05); R5 was statistical

difference between GOLD3 and GOLD4 groups (P=0.042), between GOLD1-2 and GOLD3 was not (P>0.05), and between GOLD1-2 and GOLD4 was not (P>0.05);

R5-R20 was statistical difference between GOLD1-2 and GOLD4 groups (P=0.001), between GOLD3 and GOLD4 groups (P=0.048), however, between GOLD1-2 and GOLD3 was not (P>0.05). Moreover, the relative between-visit variability (SDbv) and COV for IOS parameters were higher than for spirometry in different stages of COPD.

It was exciting that the higher the COPD stage, the lower ICC valve of spirometry parameters, nevertheless, the ICC value of IOS parameters were relatively stable and high, which were higher than the ICC value for spirometry parameters in GOLD3 and GOLD4 stage. Similarly, the higher the COPD stage, the higher COR value of spirometry parameters, but the COR value of IOS parameters were relatively stable and lower than the COR value of spirometry parameters in GOLD3 and GOLD4 stage.

Table 3

long-term variability of spirometry and IOS parameters in degree of airway obstruction of stable COPD.

	COPD-All (N=73)	COPD-GOLD1-2 (N=23)	COPD-GOLD3 (N=31)	COPD-GOLD4 (N=19)
SDbv				
FEV1, L	0.15 (0.09-0.22)	0.12 (0.06-0.17)	0.17 (0.11-0.23)	0.14 (0.10-0.20)
MEF 50, L	0.10 (0.06-0.19)	0.15 (0.07-0.22)	0.11 (0.05-0.19)	0.09 (0.05-0.13)
MEF 25, L	0.04 (0.02-0.08)	0.05 (0.03-0.08)	0.04 (0.02-0.05)	0.04 (0.02-0.06)
MMEF 75/25, L	0.08 (0.05-0.13)	0.11 (0.07-0.13)	0.07 (0.04-0.13)	0.07 (0.05-0.10)
R5, $cmH2O \cdot s \cdot L^{-1}$	0.86 (0.52-1.23)	0.66 (0.45-1.12)	1.09 (0.86-1.36)	0.59 (0.99-2.27) [d]
R20, $cmH2O \cdot s \cdot L^{-1}$	0.40 (0.29-0.61)	0.39 (0.27-0.62)	0.49 (0.37-0.82)	0.33 (0.30-0.48)
R5-R20, $cmH2O \cdot s \cdot L^{-1}$	0.71 (0.45-1.16)	0.58 (0.42-0.92)	0.95 (0.57-1.27)	0.51 (0.42-1.00)
COV				
FEV1, L	15% (8%-20%)	7% (3%-15%)	17% (10%-23) [a]	17% (12%-26%) [b]
MEF 50, L	20% (10%-31%)	17% (8%-22%)	24% (11%-38%)	24% (16%-35%)
MEF 25, L	18% (11%-28%)	16% (10%-30%)	16% (12%-27%)	23% (12%-29%)
MMEF 75/25, L	17% (12%-25%)	17% (12%-19%)	21% (11%-32%)	20% (16%-34%)
R5, $cmH2O \cdot s \cdot L^{-1}$	15% (10%-21%)	17% (10%-21%)	17% (12%-25%)	10% (3%-18%) [c]
R20, $cmH2O \cdot s \cdot L^{-1}$	13% (10%-19%)	12% (10%-17%)	16% (11%-22%)	13% (9%-16%)
R5-R20, $cmH2O \cdot s \cdot L^{-1}$	29% (20%-45%)	45% (26%-59%)	32% (22%-43%)	21% (9%-29%) [b c]
ICC				
FEV1, L	0.94	0.96	0.79	0.68
MEF 50, L	0.94	0.93	0.76	0.66
MEF 25, L	0.84	0.88	0.34	0.37
MMEF 75/25, L	0.94	0.95	0.75	0.67

R5, $cmH2O{\cdot}s{\cdot}L^{-1}$	0.90	0.85	0.90	0.90
R20, $cmH2O{\cdot}s{\cdot}L^{-1}$	0.84	0.79	0.83	0.85
R5-R20, $cmH2O{\cdot}s{\cdot}L^{-1}$	0.84	0.77	0.80	0.84
COR				
FEV1, L	0.45 (23%)	0.44 (21%)	0.49 (43%)	0.38 (49%)
MEF 50, L	0.40 (26%)	0.50 (29%)	0.39 (49%)	0.27 (54%)
MEF 25, L	0.18 (45%)	0.20 (39%)	0.18 (83%)	0.15 (83%)
MMEF 75/25, L	0.31 (28%)	0.37 (29%)	0.31 (51%)	0.21 (58%)
R5, $cmH2O{\cdot}s{\cdot}L^{-1}$	2.73 (35%)	2.42 (44%)	3.21 (36%)	2.17 (34%)
R20, $cmH2O{\cdot}s{\cdot}L^{-1}$	1.62 (47%)	1.38 (50%)	1.97 (50%)	1.13 (42%)
R5-R20, $cmH2O{\cdot}s{\cdot}L^{-1}$	2.54 (46%)	2.33 (60%)	2.92 (51%)	2.17 (47%)

[a] $p < 0.05$ COPD-GOLD1-2 versus COPD-GOLD3; [b] $p < 0.05$ COPD-GOLD1-2 versus COPD-GOLD4; [c] $p < 0.05$ COPD-GOLD3 versus COPD-GOLD4; [d] $p < 0.05$ COPD-GOLD3 versus COPD-GOLD4. See Table 2 legend for expansion of abbreviations.

Associations between long-term variability and degree of airway obstruction of stable COPD.

The relationships between spirometry and FOT parameters in the three subject groups are shown in Fig 2. Since there is only one case of GOLD1 and its value is large, this case is not analyzed. R5 correlated with FEV1 in GOLD2 and GOLD3 (r_s=-0.51, p<0.05; r_s =-0.60, p<0.05) (Fig 2.A); R20 correlated with FEV1 in GOLD3 (r_s =-0.60, p<0.05) (Fig 2.C); R5-R20 correlated with FEV1 in GOLD2 and GOLD3 (r_s =-0.59, p<0.05; r_s =-0.49, p<0.05) (Fig 2.E);

SDbv of R5 correlated with FEV1% predicted in GOLD3 (r_s=0.36, p<0.05) (Fig 2.B); SDbv of R5-R20 correlated with FEV1% predicted in GOLD3 (r_s=0.40, p<0.05) (Fig 2.F).

The predictors of long-term variability of the IOS parameters were determined by multiple regression analysis (Table 4). Potential predictors include FEV1%, mean IOS parameter, Age and BMI. FEV1% was potential predictor for long-term variability of R5 and R5-R20 (t=2.90, P=0.005; t=2.44, P=0.017), the mean value was potential predictor for long-term variability of R5, R20 and R5-R20(P<0.05). Age and BMI were not potential predictors for long-term variability of IOS parameters.

Table 4

Results of the multiple regression analyses to determine the relationship between long-term variability and airflow obstruction.

	B	SE	β-Coefficient	t	p-Value
Predictors of long-term variability of log R5					
FEV1%	0.007	0.003	0.347	2.899	0.005
Mean R5	0.059	0.020	0.344	2.914	0.005
Age	-0.003	0.004	-0.075	-0.650	0.518
BMI	-0.005	0.010	-0.056	-0.498	0.620
Predictors of long-term variability of log R20					
FEV1%	0.000	0.002	-0.006	-0.051	0.959
Mean R20	0.118	0.037	0.357	3.158	0.002
Age	0.001	0.003	0.053	0.478	0.634
BMI	0.012	0.008	0.168	1.476	0.144
Predictors of long-term variability of log R5-R20					
FEV1%	0.007	0.003	0.303	2.441	0.017
Mean R5-20	0.108	0.031	0.437	3.509	0.001
Age	0.002	0.004	0.057	0.500	0.618
BMI	-0.013	0.010	-0.144	-1.304	0.196

Discussion

In this study, we measured long-term variability of IOS parameters in stable COPD and asthma. There was chronic airway obstruction in COPD and asthma, IOS is a novel method to detect airway obstruction. Although COPD patients are older than asthma (P<0.0001), only R20 was not statistically different between COPD and asthma (P=0.778) according to baseline characteristics and lung function, it demonstrated that COPD and asthma may have similar degree of central airway obstruction, and COPD has a higher degree of small airway obstruction than asthma (R5-R20:P<0.0001). Perhaps as airway obstruction increases with disease progression and airway modification, characteristic changes in resistance and reactance are more pronounced. Particularly, reactance becoming more more negative thereby causing resonant frequency to increase further. At the same time overall resistance increases but more so at low frequencies than at high frequencies. Thus, when we compared the long-term variability of spirometry and IOS parameters in COPD and Asthma, we found that SDbv of FEV1, MEF 50, MEF 25, R5

and R5-R20 were statistically different in COPD and asthma, SDbv of FEV1, MEF 50, MEF 25 were lower than R5, R20 and R5-R20. COV for R5-R20 was statistically different between COPD and asthma, however, R5 and R20 were not. In COPD it is well established that the changes in R5, R20 correlate well with GOLD1 to GOLD 4 severity and our results tend to corroborate this.

Besides, COR in R5 up to 35% in COPD and 36% asthma, while in R20 up to 47% in COPD and 46% asthma can be present, and R5-R20 up to 46% in COPD and 47% asthma. Meanwhile, the relative CORs for IOS were more variable than for spirometry. However, the repeatability of IOS parameters were high (>0.80) ICC values in COPD and asthma, ICC values of IOS parameters were higher than for spirometry. We are not sure if this has any relationship to the pliability of distal airway differences in the two conditions. These results suggested that while there was higher long-term variability in IOS measurements than spirometry, it was still highly repeatable and stable. The high variability may be due to different baseline characteristics, the airway caliber and elastic characteristics of respiratory system, which fluctuated with time [15, 16].

The current gold standard to assess airway limitations is spirometry. However, performing an optimal spirometry always requires good patient cooperation. Additionally, because repeated forced breathing causes changes in bronchial motor tension, false positive results occur often. Studies on the quality of spirometry in elderly patients have shown that only 30% of patients are able to perform a spirometry that meets the fulfilled quality standards of the European Respiratory Society/American Thoracic Society[17, 18]. Furthermore, FEV1 cannot fully assess small airway abnormalities. Thus, MMEF parameter has been studied as another marker of small airway function, but is highly variable due to atmospheric airway obstruction[19], similar to our conclusions. We found that between-visit variability (SDbv) of R5 was statistical difference between GOLD1-2, GOLD3 and GOLD4 groups (P=0.012),. Between-visit variability relative to the mean (COV) for FEV1, R5 and R5-R20 were statistically different in GOLD1-2, GOLD3 and GOLD4 patients. Moreover, the value of SDbv and COV for IOS parameters were higher than for spirometry in different stages of COPD. The higher the COPD stage, the lower ICC value of spirometry parameters (FEV1, MEF50, MEF25 and MEF75/25), ICC values are less than 0.8 in GOLD3 and GOLD4. The lower ICC value of FEV1 perhaps is because COPD patients with poorer lung function are less able to cooperate. Nevertheless, the ICC value (>0.8) of IOS parameters were relatively stable and high. Similarly, the higher the COPD stage, the higher COR value of spirometry parameters, but the COR value of IOS parameters were relatively stable. The results show that long-term variability of spirometry parameters (FEV1, MEF50, MEF25 and MEF75/25) is higher, repeatability was lower than IOS parameters in different GOLD stage, and the higher the stage, the worse the repeatability. Further explanation, IOS parameters can maintain relative stability and repeatability over time, and can be used as a routine adjunct test for lung function.

The short-term variability in IOS parameters is known, particularly within-day, day-to-day or week-to-week repeatability of resistance (Rrs) and reactance (Xrs) with high ICC values (>0.80) [8, 9, 20] . It is the first study to relate measurement of long-term variability to airflow obstruction. Previous studies have largely assessed the within session repeatability and variability of resistance[21-23]. However, these studies may not be applicable to clinical settings, where stable patients are often assessed several months apart. In

this study, repeatability of IOS measurements between clinical visits was a representation of the real-world behavior of these parameters. The median (IQR) time between first and third visit was 6.1(3.4-16.6) months in COPD and 4.9(4.0-12.6) months in asthma (Table 1). Only one study conducted a long-term variability analysis of IOS parameters in stable COPD and asthma[10]. They only performed a long-term variability analysis at consecutive three follow-ups. Based on what is already known, with this study our research reveals: 1. Our sample size is much larger; 2. It is the first study to compared long-term variability between IOS parameters and spirometry in COPD, COPD-GOLD stages, and asthma; 3. It is also the first study to determine the relationship between long-term variability and airflow obstruction in COPD.

A study reported significant correlations at baseline between FEV1 and R5 ($p<0.05$), but not with R20. At 1-year follow up, there was no significant change in FEV1and R5, but R20 significantly is increased. Moreover, the changes in R5 and R20 did not significantly correlate with the changes in FEV1. They revealed that R20 was unrelated to the severity of airflow obstruction in patients with COPD[24]. Another study considered that the greater day-to-day variability of Rrs and Xrs seen in COPD is related to airflow obstruction, the 5 FOT parameters are highly repeatable in healthy normal, asthmatic and COPD subjects[8].These conclusions are somewhat similar to our study, but their study had only a short-term follow-up period. We found that at first three visits, R5 correlated with FEV1 in GOLD2 and GOLD3 (r_s=-0.51, $p<0.05$; r_s =-0.60, $p<0.05$); R20 correlated with FEV1 in GOLD3 (r_s =-0.60, $p<0.05$); R5-R20 correlated with FEV1 in GOLD2 and GOLD3 (r_s =-0.59, $p<0.05$; r_s =-0.49, $p<0.05$), in addition, the results of the multiple regression analyses indicated that FEV1% was potential predictor for long-term variability of R5 and R5-R20 (t=2.90,P=0.005; t=2.44, P=0.017), the mean value was potential predictor for long-term variability of R5, R20 and R5-R20 ($P<0.05$), Age and BMI were not related to long-term variability of IOS parameters. These results showed that the severity of airflow obstruction was correlated with long-term variability of R5 and R5-R20, not with long-term variability of R20, there was a small contribution from the mean value for long-term variability of R5, R20 and R5-R20.

One potential limitation of this study is that the groups were not matched by sex and age in different diseases and COPD-GOLD stages. There was one female in GOLD1, 20 men and 2 women in GOLD2, 25 men and 6 women in GOLD3, 18 men and 1 female in GOLD4, 58 men and 61 women in asthma. However, both studies were associated with standard deviation between visits and were unlikely to affect results, and COPD patients are mainly elderly men, which is more consistent with the real clinical environment, consistent with other studies [10, 22].

Conclusion

In summary, this study suggests that IOS parameters have high long-term repeatability as shown by high ICC values ($P>0.80$) in asthma and COPD, associated with a wide numerical range of values across obstructive airway diseases, the lower ICC valve of spirometry parameters in different GOLD stages, especially ICC values are less than 0.8 in GOLD3 and GOLD4, but also that variability (SDbv) differs between diseases and GOLD stages, probably because of differences in baseline values, the airway

caliber and elastic characteristics of respiratory system, in addition, the greater long-term variability seen in COPD is connected with airflow obstruction. These findings also help determine thresholds for MCIDs, what's more, IOS can be used as a routine auxiliary test of lung function to monitor disease progression, disease activity, disease progression or positive treatment response over a long period of time. IOS will not replace spirometry anytime soon as the two tests measure very different things. However, if IOS is used as a complimentary test to spirometry for long term follow up, it proves to be clinically very useful.

Abbreviations

COPD: chronic obstructive pulmonary disease; IOS: impulse oscillometry; SDbv: the standard deviation; COV: the coefficient of variation; ICC: intraclass correlation coefficient; COR: the coefficient of repeatability; FOT: forced oscillation technique;R5: R at 5 Hz; R20: R at 20 Hz; FEV1: forced expiratory volume in 1 s; MCID: the minimal clinically important difference; PFT: Pulmonary Function Tests; GOLD: the Global Initiative for Chronic Obstructive Lung Disease; FVC: forced vital capacity; pMV: percentage of close to maximal variation;BMI: body mass index; MEF: maximal expiratory flow; MMEF: maximum mid expiratory flow; Rrs: resistance; Xrs: reactance; IQR, the median

Declarations

Ethics approval and consent to participate

All patients in this study were informed at admission that their medical records were likely to be used for clinical studies. Ethical approval by the medical ethics committee of Shanghai pulmonary hospital was obtained.

Consent for publication

Not applicable.

Availability of data and materials

All the related data are presented in the manuscript.

Competing interests

The authors confirm that there are no conflicts of interest

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Contributorship statement

Conceived and designed the experiments: JHX JG.

Performed the experiments: XXS YC WLY .

Analyzed the data: JHX XXS JG.

Contributed reagents/materials/analysis tools: JHX HQZ JML.

Wrote the paper: JHX BP JG.

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Figures

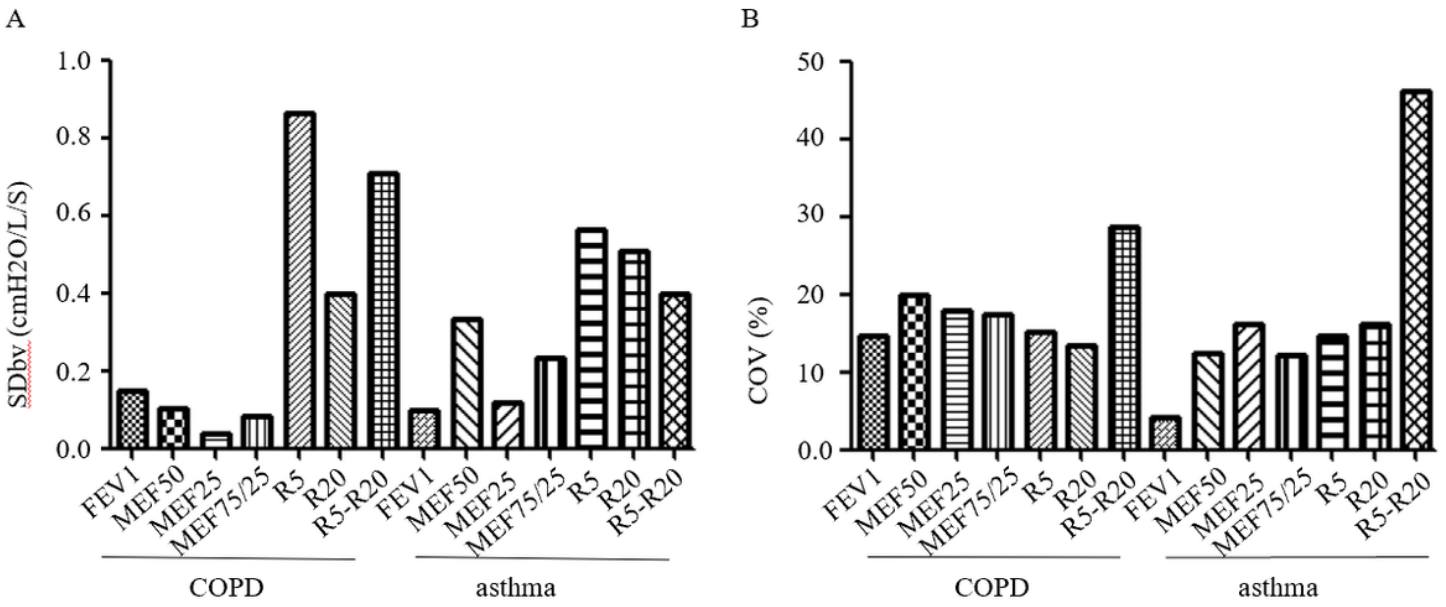

Figure 1

Long-term variability of lung function and IOS parameters in stable COPD and asthma: SDbv (A) and COV (B) using GraphPad Prism 5 (Graphing replicates or error bars plot: Median). See Table 2 legend for expansion of abbreviations.

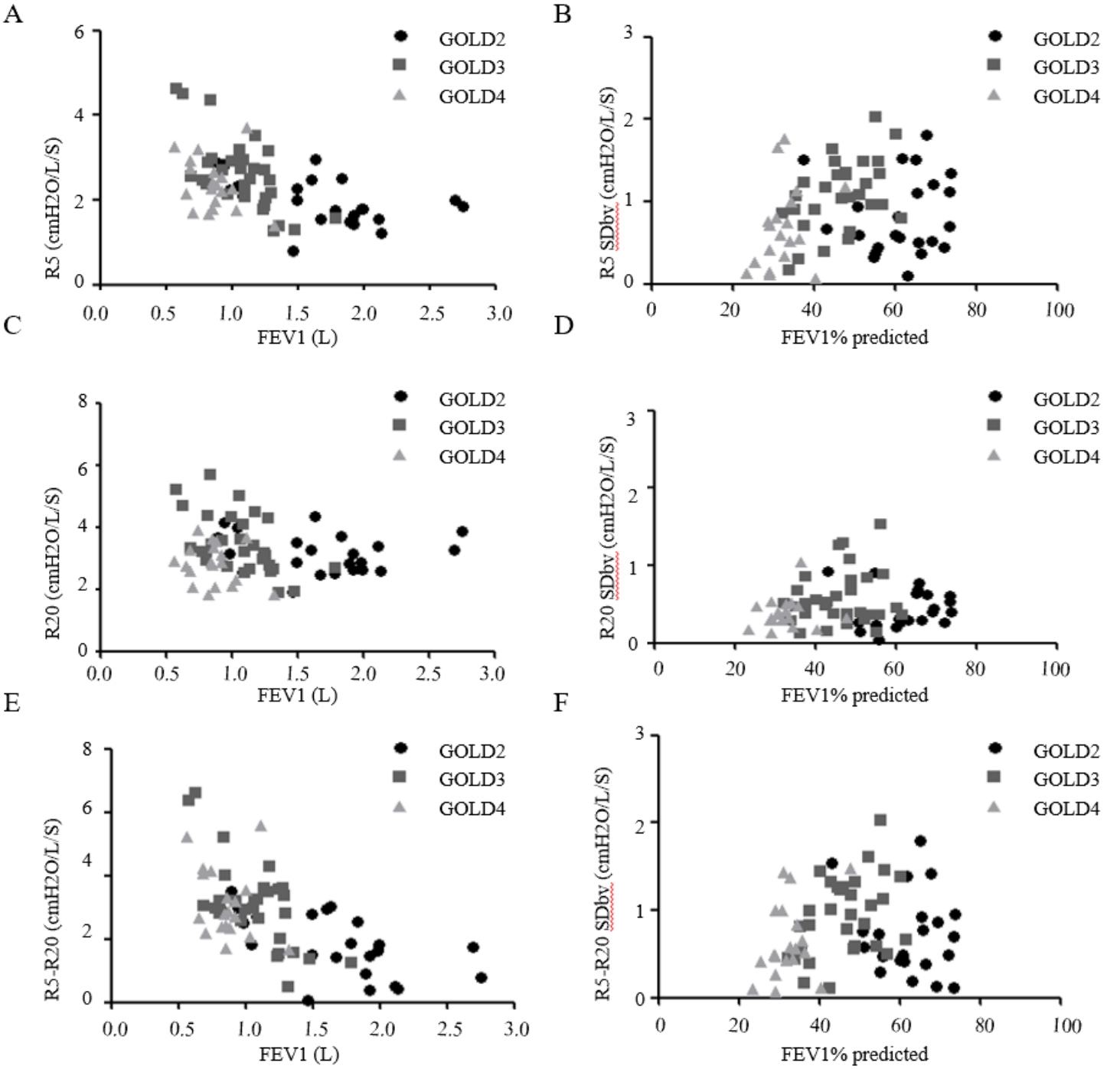

Figure 2

Relationships between spirometry and FOT parameters in the three subject groups: (A) mean FEV1 and mean R5 (GOLD2 r_s=-0.51, p<0.05; GOLD3 r_s =-0.60, p<0.05; GOLD4 r_s=-0.24, p>0.05), (B) FEV1% predicted and R5 SDbv (GOLD2 r_s =0.29, p>0.05; GOLD3 r_s=0.36, p<0.05; GOLD4 r_s =0.27, p>0.05), (C) mean FEV1 and mean R20 (GOLD2 r_s =-0.16, p>0.05; GOLD3 r_s =-0.60, p<0.05; GOLD4 r_s =-0.06, p>0.05), (D) FEV1% predicted and R20 SDbv (GOLD2 r_s =0.25, p>0.05; GOLD3 r_s=0.04, p>0.05; GOLD4 r_s =-0.07, p>0.05), (E) mean FEV1 and mean R5-R20 (GOLD2 r_s =-0.59, p<0.05; GOLD3 r_s =-0.49, p<0.05; GOLD4 r_s =-0.27,

p>0.05), (F) FEV1% predicted and R5-R20 SDbv (GOLD2 r_s =-0.07, p>0.05; GOLD3 r_s=0.40, p<0.05; GOLD4 r_s =0.43, p>0.05).