

Review Series: Non-Invasive Monitoring of Airway Inflammation in Asthma

Impulse Oscillometry; Therapeutic Impacts of Transdermal Long-Acting Beta-2 Agonist Patch in Elderly Asthma with Inhaled Corticosteroid Alone

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ABSTRACT

Growing interest had been focused on the involvement of the small airways in asthma, and impulse oscillometry (IOS) has been utilized as pulmonary functions for detecting large and small airways diseases separately. IOS can measure respiratory resistance and reactance at multiple frequencies, not available by spirometry or body plethysmography, is non-invasive techniques and convenient for elderly patients with a low dependency on cooperation during tidal breathing. IOS indices were well correlated with not only predicted FEV1 but also FEF25-75, residual volume/total lung capacity, delta N2 of a single nitrogen washout test which representing air trapping and inhomogeneous ventilation in the distal lung. These parameters and QOL scores were improved by additional transdermal long-acting beta-2 agonist patch even in well-controlled elderly asthma treating with inhaled corticosteroids alone. IOS may have a complementary role of spirometry in detecting subtle airways changes in general practice. However, systemic studies are required to investigate the clinical implication of each IOS index.

KEY WORDS

elderly asthma, impulse oscillometry, inhaled corticosteroid, long-acting beta-2 agonist patch, small airway

ABBREVIATIONS

IOS, impulse oscillometry; COPD, chronic obstructive pulmonary disease; FOT, forced oscillation technique; R, resistance; X, reactance; Fres, resonant frequency at reactance zero; FEF25-75, forced expiratory flow at 25% to 75% of forced vital capacity; VC, vital capacity; FEV1, forced expiratory volume in one second; RV, residual volume; TLC, total lung capacity; ICS, inhaled corticosteroid; SBNW, a single-breath nitrogen washout; ACT, asthma control test; LABA, long-acting beta-2 agonist; QOL, quality of life.

INTRODUCTION

Impulse oscillometry (IOS) is a type of forced oscillation technique (FOT), which can evaluate respiratory resistance (R) and reactance (X) at various oscillatory frequencies, which cannot be measured by spirometry

and body plethysmography. In recent years, IOS is increasingly used in many clinical researches as pulmonary function parameters in asthma and chronic obstructive pulmonary disease (COPD).¹⁻⁸ IOS is convenient for elderly patients and children with a low dependency on cooperation during tidal

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breathing. And changes in R measured by IOS during methacholine challenge correlated better with asthma symptoms than traditional spirometric measures, implying a higher sensitive index.³ IOS parameters correlated better with clinical symptoms and asthma control than spirometry indices.⁹ However, clinical implication of each IOS index remains under discussion.

Elderly asthma is critical and over 85% of asthma death appears in over 65 year-old people in Japan. Pathophysiological and clinical characteristics of elderly asthma are 1) prominent small airways impairment comparing with young adults, 2) non-allergic type, 3) high rate co-morbidity of COPD, heart diseases, gastroesophageal reflex, 4) poor inhalation technique and poor adherence. Recent recommendation on the appropriate use of long-acting beta-2 agonist (LABA) by U.S. FDA (June 2, 2010) said LABA should be used only in asthmatic patients with inadequate control although inhaled corticosteroid (ICS) use.

In this review, we describe follows 1) assessment of small airways disease using traditional pulmonary function tests, 2) advantage and demerit of IOS, 3) correlation between IOS and traditional pulmonary function tests, 4) add-on effects of transdermal LABA patch on small airways impairment in elderly asthma who receiving ICS assessed by IOS.

ASSESSMENT OF SMALL AIRWAYS FUNCTION IN TRADITIONAL PULMONARY FUNCTION TESTS

Increasing evidences demonstrate that small airways function is associated with asthma control,^{9,13} and small airways disease is critical therapeutic target. Extensive pulmonary obstructive disease can be present in the small airways with little abnormality in traditional pulmonary function tests, therefore the small airways are sometimes referred to as the 'silent zone'. In general practice, conventional spirometry has a limited capacity to distinguish the small and large airways. Peak expiratory flow (PEF) and forced expiratory volume in one second (FEV1) mainly reflect the large airways function, on the other hand FEF25-75 is believed to represent small airways function,¹⁴ but it suffers from poor reproducibility.¹⁵ Residual volume (RV) divided by total lung capacity (TLC) measured using body plethysmography is one of the index of air-trapping due to small airways narrowing. Another examination assessing heterogeneity of peripheral lung ventilation is delta N2; gradient of the slope of the nitrogen alveolar plateau at phase III in a single-breath nitrogen washout (SBNW) test.¹⁵ In recent years, non-invasive physiological parameters of alveolar nitric oxide, multiple-breath nitrogen washout test, and FOT including IOS can identify airways response from large and small airways.¹⁷

IOS

IOS uses flow oscillations generated by a loud speaker that are superimposed on tidal breathing. The resulting pressure and low changes are assessed by Fourier analysis to determine respiratory impedance; resistance and reactance, at multiple frequencies. A commercially available IOS machine (Master Screen-IOS; CareFusion, Germany) fulfils the standard recommendation,^{18,19} therefore in this review we describe about this machine. Rectangular mechanical impulses containing a continuous power spectrum of 0-100 Hz are generated by a simple on/off control switch on a loudspeaker through a mouthpiece during tidal breathing. The impulse is having the interval of 0.2 second, and impulse duration is about 45 milli second. The patients support their cheeks and mouth floor to reduce upper airway shunting while tests are performed. Impedance measurements including R and X from 5 to 20 Hz (R5, R20, and X5) and resonant frequency reactance (Fres), which represents the Hz at which the negative reactance reaches zero (Fig. 1). Integrated area of low-frequency reactance (AX) is also calculated as shown in Figure 1. We implicated R5 as a index of total airway resistance, R5-R20 (the fall in resistance from 5 to 20 Hz), X5, AX, and Fres as indices for small airway disease, and R20 for a value of large airways.^{4,5,20-23} Reliability of IOS indices were evaluated within- and between-day, and coefficient of variation were under 10%.^{24,25}

Dellaca *et al.*²⁶⁻²⁸ indicated that respiratory system reactance measured by FOT changed to be more negative value during flow-limited expiration in patients with COPD. When airflow limitation is present, oscillometry signal cannot pass through the choke points to reach the alveoli,²⁹ resulting in a marked reduction apparent compliance and thus the value of X5 change to be more negative physiologically.³⁰ The with-in breath changes in X5 have been suggested to reflect the number of choke points present and overall distribution within the bronchial tree, and to represent the overall distribution of expiratory flow limitation during tidal breathing.²⁶⁻²⁸ In COPD, as airflow obstruction worsens, expiratory flow limitation appears as much lower flow for a given lung volume and becomes present at rest or at least early during exercise.³¹ There is evidence that IOS and plethysmography are more sensitive than spirometry for detecting bronchodilator effects in patients with asthma and COPD.^{2,32} And airway resistance measured by IOS during methacholine challenge correlated better with asthma symptoms than traditional spirometric measures implying a higher sensitive index.³ Recently, Takeda *et al.*⁹ reported that IOS parameters correlated better with clinical symptoms and asthma control than spirometry indices in asthmatic patients.

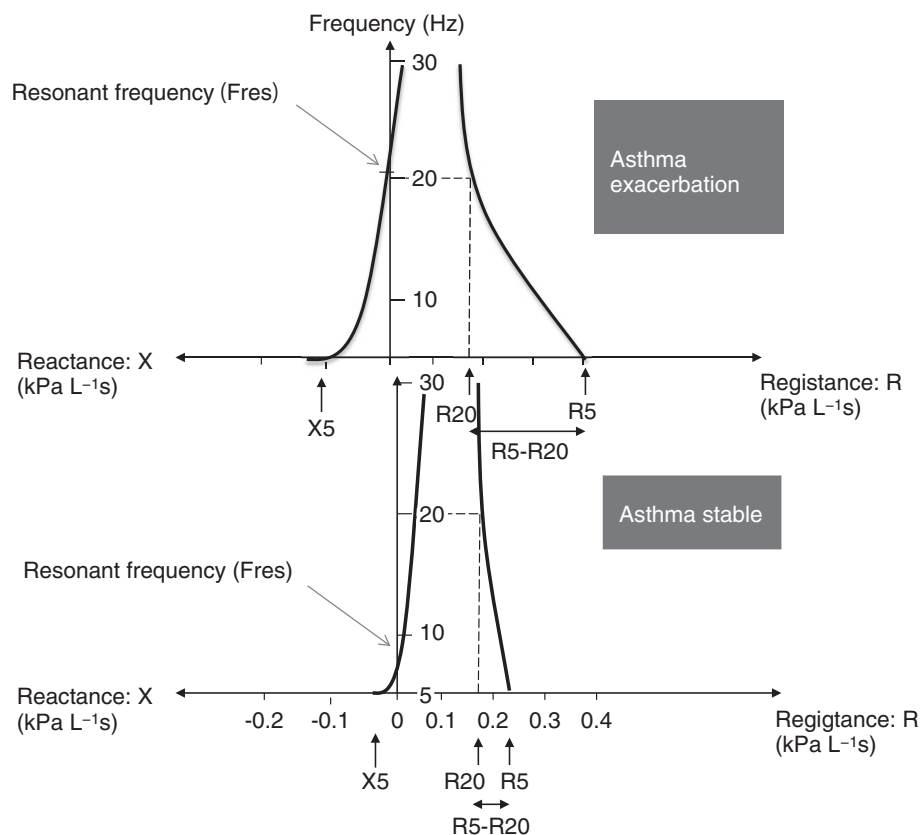


Fig. 1 Schematic illustration of impulse oscillometry indices over oscillation frequency, including R5, R20, R5-R20, Fres, X5, and AX. Upper represents the pattern during exacerbation of asthma and lower demonstrates stable period.

CORRELATIONS BETWEEN IOS AND TRADITIONAL PULMONARY FUNCTION TESTS

We reported that relationship between IOS indices and traditional pulmonary function tests were performed in 80 stable elderly asthmatic patients (>65 years) treating with inhaled corticosteroids.³³ This study approved by the Ethic Committee at Sapporo Medical University, and written informed consent was obtained from all patients. Spirometry and body phrenisomography using CHESTAC-8800 (Chest, Tokyo, Japan) were done after IOS examination. TLC and RV were determined by the helium gas dilution. The best of three consecutive examinations was recorded. Finally, SBNW test assessing heterogeneity of small airway obstruction using CHESTAC-8800 filled with 100% oxygen and equipped with a nitrogen meter connected to the mouthpiece, allowing continuous sampling.¹⁶ The expiratory nitrogen concentration (%N₂) was plotted against lung volume (between TLC and RV), producing the expiratory nitrogen washout curve. The slope of the nitrogen alveolar plateau (delta N₂, phase III) was calculated by drawing the best-fit line through phase III of the expiratory volume-concentration curve.

Results are shown in Table 1. Total respiratory resistance of R5 was best correlated with PEF. Fres and R5-R20 evaluated by IOS were good correlated with traditional lung function tests of small airways obstruction and heterogeneity lung ventilation of predicted FEV₁, FEF₂₅₋₇₅, RV/TLC, and delta N₂ in elderly asthma. Therefore R5-R20 and Fres may be new indices for small airways disease, with little intension of patients.

Previously, Yamaguchi *et al.*⁵ reported that IOS parameter of R5-R20 had a good correlation with FEF₂₅₋₇₅ or RV/TLC, therefore R5-R20 seems to be a good maker for detection for small airways disease. On the other hand Tsuburai *et al.*³⁴ recently described Fres was best correlated to predicted FEV₁ and predicted FEF₂₅₋₇₅ using a Mostgraph (Chest, Tokyo, Japan) machine which is another type of FOT available in Japan. These results suggested that IOS indices of R5-R20 and Fres seems to be small airways dysfunction presenting heterogeneity of small airways narrowing consequently uneven ventilation of the lung. In contrary, R5 may indicate total airway narrowing.

Table 1 Correlation between traditional pulmonary function tests and impulse oscillometry in elderly asthma ($n = 80$) using simple linear regression analysis

IOS indices		PF (L/sec)	pFEV1 (%)	FEF25-75 (L/sec)	RV/TLC (%)	Delta N2 (%)
Resistance	R5	-0.61**	-0.64**	-0.56**	0.40**	0.27**
	R20	-0.57**	-0.50**	-0.46**	0.24*	ns
	R5-R20	-0.46**	-0.61**	-0.49**	0.46*	0.32**
Reactance	X5	0.45**	0.53**	0.41**	-0.37**	ns
	Ax	-0.44**	-0.58**	-0.44**	0.43**	0.24*
Resonant frequency	Fres	-0.56**	-0.66**	-0.60**	0.49**	0.43**

FEV1, forced expiratory volume in one second; FEF25-75, mid-forced expiratory flow; RV, residual volume; TLC, total lung capacity; VC, vital capacity; Delta N2, slope of phase III at the single-breath N2 washout; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; X5, reactance at 5 Hz; AX, integrated of negative value of reactance from 5 Hz to zero; Fres, frequency at which reactance is zero; ns, not significant.

** $p < 0.05$, * $p < 0.01$.

Table 2 Baseline characteristics of the two groups in elderly asthma ($n = 33$)

		LABA add on	Control	p
Patients (n)		16	17	-
Age (years)		70.2 $\pm$ 7.17	70.3 $\pm$ 6.45	0.9644* ¹
Sex (%)	Male	7 (43.8)	6 (35.3)	0.7283* ²
	Female	9 (56.3)	11 (64.7)	
Severity by JPGL (%)	Mild	4 (25.0)	8 (47.1)	0.1948* ³
	Moderate	12 (75.0)	9 (52.9)	
	Severe	0	0	
ICS (%)	FP	6 (37.5)	7 (41.2)	0.8919* ²
	BDP	4 (25.0)	3 (17.6)	
	BUD	4 (25.0)	3 (17.6)	
	CIC	2 (12.5)	4 (23.5)	
Tobacco (%)	Non-Smokers	10 (62.5)	13 (76.5)	0.4646* ²
	Ex-Smokers	6 (37.5)	4 (23.5)	
ACT (score)		21.9 $\pm$ 1.69	22.5 $\pm$ 1.50	0.4162* ³

*¹ t-test, *² Fisher's Exact test, *³ Wilcoxon rank sum test.

JPGL, Asthma Prevention and Management Guideline 2009, Japan (in Japanese).

TRANSDERMAL LABA FOR ELDERLY ASTHMATICS

Transdermal LABA patch of tulobuterol, sustains a release of effective blood concentration for 24 hours,^{35,36} which has been developed in Japan. Its adhesive layer is stable when attached to a mildly fat-soluble, and serves as a drug container because its reservoir system retains tulobuterol as crystal. This unique transdermal LABA is applied to mild to severe persistent asthmatic patients in Japanese Guideline for the Diagnosis and Treatment of Allergic Diseases 2010 (in Japanese). This patch has two advantages; 1) available for elderly people who has poor inhalation technique, 2) available when strong cough persists during asthma exacerbation, on the other hand, one

disadvantage is dermatitis but its frequency is a few.

We assessed the additional effects of this transdermal LABA on small airways disease using IOS in elderly asthmatics. This study is multi-center, open-labeled, age-matched, and 4-week treatment of 2 mg of tulobuterol patch, approved by the Ethic Committee at our hospital and clinic, and written informed consent was obtained from all patients. Patients with chronic obstructive pulmonary disease and heat diseases were excluded. A total of 33 stable elderly asthmatics treating with inhaled corticosteroid (ICS) monotherapy divided into two groups; treatment ($n = 16$, Group T) and control ($n = 17$, group C) (Table 2). We measured IOS indices and asthma control test (ACTTM)³⁷ before and after the therapy. GlaxoSmith Kline (Tokyo, Japan), the developer of the ACTTM,

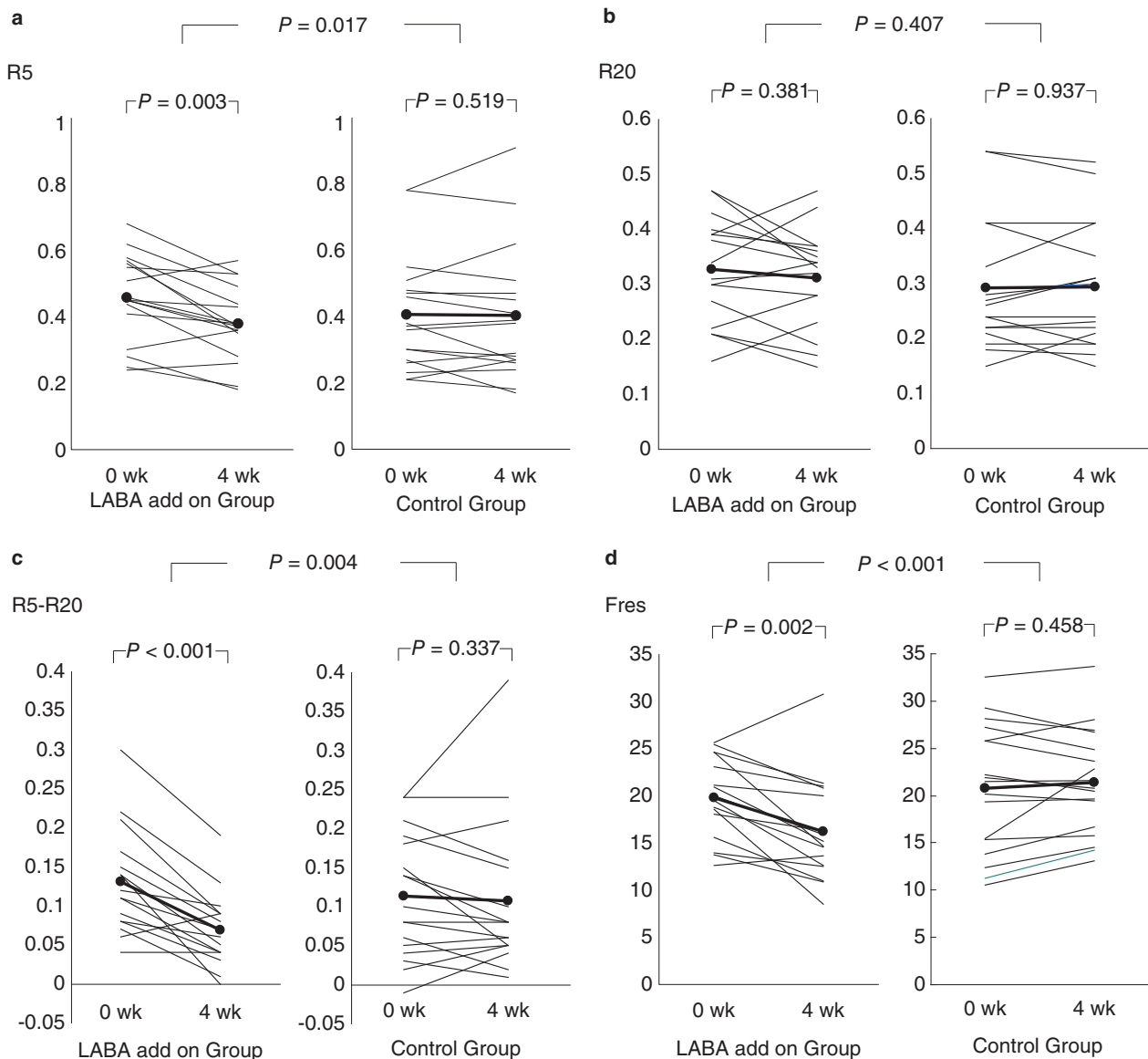


Fig. 2 Therapeutic changes in IOS indices before and after 4-week treatment in LABA add on group and control group. **a**, R5; **b**, R20; **c**, R5-R20; and **d**, Fres. All paired within-subject data were evaluated using the Wilcoxon signed rank test, and paired within-group data were assessed by the Wilcoxon rank sum test.

provides written permission for its use. In addition, we evaluate within-breath change of each IOS index; R5 (e-i), R20 (e-i), R5-20 (e-i), X5 (e-i), and AX (e-i). This parameter is calculated as follows; mean value of expiratory phase minus that of inspiratory phase, demonstrating the collapse or narrowing of small and large airways within tidal breathing.⁶ Recently, Ohishi *et al.*³⁸ reported a new approach for assessing within-breath behavior of oscillatory mechanics for evaluating the severity of COPD. There were no significant differences between group C and T in baseline patients characteristics, IOS indices and ACTTM score (Table 2).

All parameters except R20 were significantly im-

proved in group T and no change disclosed in group C (Fig. 2, Table 3). ACTTM score was significantly improved from 21.94 ± 1.7 to 23.3 ± 1.6 after treatment with tulobuterol in group T ($p < 0.01$) (Table 3). In group T, R5-R20 (e-i) significantly ($0.042 \text{ kPaSL}^{-1} \pm 0.03$ vs $0.013 \text{ kPaSL}^{-1} \pm 0.03$; $p < 0.05$) improved (Fig. 3), but R5 (e-i), R20 (e-i), X5 (e-i), and AX (e-i) were not improved (data not shown). Fres was also significantly improved in group T and not for group C (Fig. 3).

Next we calculate the change of each parameter before and 4 weeks after this trial in both group T and group C. Best correlation showed between the change in ACTTM score and the change in Fres, sug-

Table 3 Effect of 4 week-treatment of transdermal long-acting beta-2 agonist on IOS and ACT score in elderly asthmatic patients treating with inhaled corticosteroid monotherapy

	LABA add-on Group			Control Group			<i>p</i> between [‡]
	Baseline	4 weeks	<i>P</i> [†]	Baseline	4 weeks	<i>P</i> [†]	
R5	0.46 ± 0.14	0.38 ± 0.12	0.0034	0.41 ± 0.18	0.40 ± 0.20	0.5194	0.0191
R20	0.33 ± 0.10	0.31 ± 0.09	0.3957	0.29 ± 0.12	0.30 ± 0.11	0.9377	0.4065
R5-R20	0.13 ± 0.07	0.07 ± 0.05	0.0003	0.11 ± 0.08	0.11 ± 0.10	0.3375	0.0042
R5-R20/R5	27.81 ± 9.03	17.7 ± 9.47	0.0034	26.02 ± 13.34	23.22 ± 9.60	0.3060	0.0267
X5	-0.19 ± 0.09	-0.13 ± 0.06	0.0007	-0.19 ± 0.13	-0.17 ± 0.14	0.0917	0.1489
Fres	19.78 ± 4.27	16.24 ± 5.49	0.0027	20.75 ± 6.77	21.35 ± 5.59	0.4586	0.0007
AX	1.17 ± 0.79	0.63 ± 0.50	<0.0001	1.28 ± 1.11	1.16 ± 1.31	0.1426	0.0201
eR5	0.63 ± 0.50	0.40 ± 0.13	0.0457	0.45 ± 0.20	0.45 ± 0.25	0.4250	0.1824
eR20	0.34 ± 0.11	0.32 ± 0.09	0.3555	0.31 ± 0.12	0.32 ± 0.12	0.9613	0.2875
eR5-R20	0.15 ± 0.09	0.07 ± 0.06	0.0001	0.14 ± 0.11	0.13 ± 0.15	0.2579	0.0291
eX5	-0.19 ± 0.14	-0.12 ± 0.07	0.0005	-0.20 ± 0.16	-0.19 ± 0.21	0.2819	0.0550
eAX	1.36 ± 1.16	0.65 ± 0.64	<0.0001	1.62 ± 1.58	1.51 ± 2.03	0.1928	0.0367
iR5	0.41 ± 0.12	0.36 ± 0.11	0.0161	0.35 ± 0.14	0.34 ± 0.15	0.6799	0.0605
iR20	0.30 ± 0.09	0.29 ± 0.09	0.6277	0.27 ± 0.10	0.26 ± 0.10	0.5520	0.8145
iR5-R20	0.11 ± 0.05	0.06 ± 0.03	0.0005	0.08 ± 0.05	0.08 ± 0.05	0.8149	0.0032
iX5	-0.19 ± 0.07	-0.15 ± 0.06	0.0049	-0.17 ± 0.09	-0.15 ± 0.09	0.0095	0.4359
iAX	1.03 ± 0.57	0.62 ± 0.35	<0.0001	0.92 ± 0.61	0.79 ± 0.59	0.0479	0.0033
ACT	21.94 ± 1.69	23.25 ± 1.61	0.0010	22.47 ± 1.50	22.35 ± 1.66	0.8359	0.0032

[†] Wilcoxon signed rank test, [‡] Wilcoxon rank sum test.

All values presented as mean (SD). Comparison between groups were made with Mann-Whitney U-test. All paired within-subject data were evaluated using the Wilcoxon signed rank test, and paired within-group data were assessed by the Wilcoxon rank sum test.

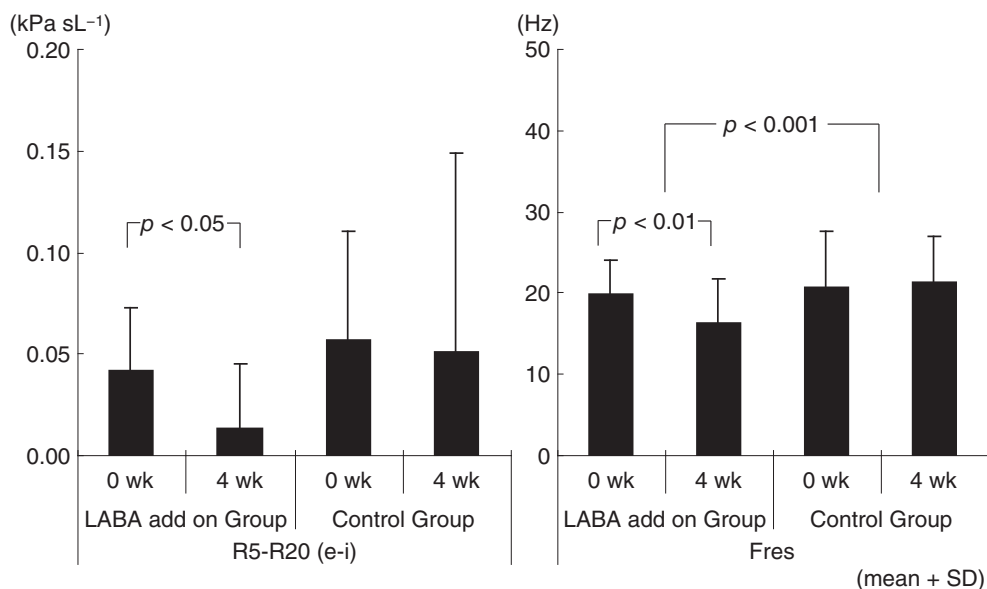


Fig. 3 Therapeutic effects in IOS parameters pre and post 4-week treatment in LABA add on group and control group using R5-R20 (e-i): mean value of R5-R20 in expiratory phase minus in inspiratory phase and Fres. All paired within-subject data were using the Wilcoxon signed rank test. Comparisons between groups were made with the Wilcoxon rank sum test.

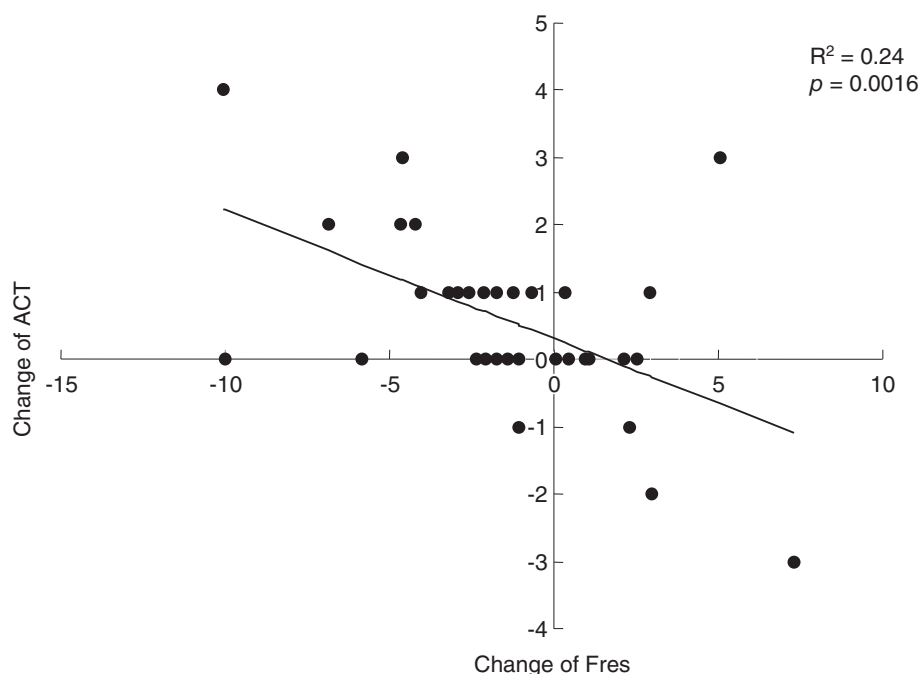


Fig. 4 Relationship between change in asthma symptom score (ACT™) and change in IOS index (Fres) between before and after 4-week treatment in elderly asthmatic patients ($n = 33$), using simple linear regression analysis.

gesting that change of Fres might reflect asthma symptoms in elderly asthmatic patients (Fig. 4). Takeda *et al.*⁹ recently described that IOS parameters correlated better with clinical symptoms and asthma control than spirometry indices in asthmatic patients. It was suggested that IOS indices was one of the good marker to reflect real life asthmatic symptoms in well-controlled elderly asthma.

Tamura *et al.* reported that this tulobuterol patch exerts dose-related add-on effects in patients receiving ICSs.³⁹ Hozawa *et al.*⁷ reported that tulobuterol patch could be used as a long-term add-on controller for asthmatic patients receiving ICS. Hoshino⁴ described that IOS indices of R5-R20, X5, and AX, and late-phase induced sputum allowed detection of changes in the small airways that could not be detected by spirometry. Although our study was open trial, tulobuterol patch might have additional effects of improving small airways impairment in elderly asthmatic patients who had treated with ICS alone. The particles of ICS might insufficiently reach to complicated destructing and narrowing small airways by aging, therefore transdermal delivery of LABA may reach to small airways. IOS may be a useful tool for detecting subtle airway changes, especially small airways disease, without any intention.

CONCLUDING REMARKS

This review article mentioned about the usefulness of IOS, a type of FOT, which is non-invasive and conven-

ient for elderly patients with a low dependency on cooperation during tidal breathing. National Health Insurance of Japan covers this examination from April 2012. IOS may have a complementary role to spirometry or body plethysmography. However, clinical implication of each IOS index remains under discussion, therefore further investigation should be needed in both basic and clinical area.

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