

Exercise-Induced Airway Obstruction in Young Asthmatics Measured by Impulse Oscillometry

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■ Abstract

Background: Impulse oscillometry (IOS) is a good method for measuring airway resistance. It does not require special breathing skills and it can reflect different aspects of airway obstruction to those revealed by spirometry, which is an effort-dependent maneuver.

Objective: To evaluate the characteristics of airway obstruction in young asthmatics after an exercise bronchial provocation test (EBPT) using IOS.

Methods: Forty-seven young adults were enrolled in the study. All the participants underwent a methacholine bronchial provocation test (MBPT) and an EBPT for the evaluation of their asthma. IOS and spirometric parameters were collected at baseline and at 0, 5, 10, 20, and 30 minutes post-EBPT. The participants were divided into 2 groups according to MBPT positivity: an airway hyperresponsiveness (AHR) group and a no-AHR group.

Results: There were differences in the percent decrease in forced expiratory volume in the first second (FEV_1) between the 2 groups at 5, 10, and 20 minutes after exercise. Resistance at 5 Hz (R_5) increased in the AHR group but not in the no-AHR group at 5 and 10 minutes after exercise. Integration of reactance from 5 Hz to resonance frequency (area of reactance, AX) was also increased in the AHR group at only 5 and 10 minutes post-EBPT. ΔR_5 and ΔAX at 5 and 10 minutes post-exercise were well correlated with the percent decrease in FEV_1 .

Conclusions: IOS parameters, especially ΔR_5 and ΔAX , may be useful for performing objective evaluations and improving our understanding of exercise-induced airway obstruction in young asthmatics.

Key words: Impulse oscillometry. Exercise-induced bronchoconstriction. Asthma.

■ Resumen

Antecedentes: La oscilometría de impulsos (IOS) es un buen método para determinar la resistencia de las vías respiratorias. No requiere una técnica de respiración especial y puede reflejar aspectos de la obstrucción de las vías respiratorias distintos de los revelados por la espirometría, una maniobra dependiente del esfuerzo.

Objetivo: Evaluar las características de la obstrucción de las vías respiratorias en jóvenes asmáticos tras una prueba de provocación bronquial con ejercicio físico (PPBE) mediante IOS.

Métodos: En el estudio participaron cuarenta y siete adultos jóvenes. Todos los participantes se sometieron a una prueba de provocación bronquial con metacolina (PPBM) y a una PPBE para evaluar el asma. Se recopilaron los parámetros espirométricos y de la IOS al inicio del estudio y a los 0, 5, 10, 20 y 30 minutos tras la PPBE. Los participantes se dividieron en dos grupos según la positividad de la PPBM: un grupo con hiperreactividad de las vías respiratorias (HRVR) y un grupo sin HRVR.

Resultados: Se observaron diferencias en la disminución porcentual de volumen espiratorio máximo en el primer segundo (VEM_1) entre los dos grupos a los 5, 10 y 20 minutos tras el ejercicio físico. La resistencia a 5 Hz (R_5) aumentó en el grupo con HRVR pero no en el grupo sin HRVR a los 5 y 10 minutos tras el ejercicio físico. La integración de la reactancia desde 5 Hz hasta la frecuencia de resonancia (área de reactancia, AX) también aumentó en el grupo con HRVR a los 5 y 10 minutos después de la PPBE. Los parámetros ΔR_5 y ΔAX a los 5 y 10 minutos tras el ejercicio físico mostraron una buena correlación con la disminución porcentual de VEM_1 .

Conclusiones: Los parámetros de la IOS, especialmente ΔR_5 y ΔAX , pueden ser útiles para realizar evaluaciones subjetivas y mejorar el conocimiento de la obstrucción de las vías respiratorias inducida por el ejercicio físico en jóvenes asmáticos.

Palabras clave: Oscilometría de impulsos. Broncoconstricción inducida por el ejercicio físico. Asma.

Introduction

Exercise is an important exacerbating factor in bronchial asthma, especially in children and young adults because of their high level of physical activity [1]. The exercise bronchial provocation test (EBPT) has been used to confirm exercise-induced bronchoconstriction (EIB) [2]. In this test, serial spirometric data are collected after 5 to 10 minutes of exercise. A decrement in forced expiratory volume in the first second (FEV₁) from baseline is the most important diagnostic value, with a decrease of 10% or more indicating a diagnosis of EIB [3].

In allergic airway diseases such as asthma and allergic rhinitis, airway hyperresponsiveness (AHR) caused by nonspecific airway irritation is a characteristic finding [4]. However, there is controversy regarding whether or not exercise can induce or increase nonspecific AHR [5-7]. Although not all asthmatics present EIB, the EBPT is a necessary test, especially in pre-recruitment physical examinations for military conscription [8].

In many countries, including Korea, Turkey, and Switzerland, military reinforcement is supplied by obligatory recruitment [9], and the detection of draft evaders is important. In many other countries, however, such as the United States, England, and Japan, military forces are entirely made up of career soldiers [9]. In these countries, pre- and post-recruitment physical examinations are important when choosing suitable young men and women for the physically demanding tasks required in the military.

Spirometry is used to detect EIB [10] but because it is an effort-dependent forced maneuver, those undergoing this test can theoretically manipulate results [11]. Another technique known as the forced oscillation technique (FOT) offers a reliable means of measuring airway resistance. The FOT is useful for evaluating disease status or severity in chronic obstructive pulmonary disease and bronchial asthma [12] and is used with children and elderly patients unable to cooperate with forced expiration [13]. FOT measurements are taken during tidal breathing and therefore cannot be manipulated by those undergoing the test.

In this study, we evaluate exercise-induced airway characteristics measured by impulse oscillometry (IOS), a commercially-available FOT, in young asthmatics with nonspecific AHR.

Methods

Patients

Forty-seven individuals who visited the Allergy-Asthma Clinic at our institution between September 2006 and July 2008 were enrolled in the study. They were all male and wished to have their asthma status evaluated prior to mandatory military recruitment by the Korean Military Manpower Administration. The inclusion criterion was defined as the presence of intermittent asthma or mild persistent asthma as defined by the Global Initiative for Asthma guidelines [14]. Individuals on long-acting β_2 agonists and who had taken

rescue medication within 48 hours before the examination, or who had had an upper respiratory infection in the 4 previous weeks, were excluded. Those enrolled were divided into 2 groups according to their methacholine bronchial provocation test (MBPT) results: an AHR group (those with a PC₂₀ [amount of methacholine required to cause a 20% reduction in FEV₁ from baseline] of <25 mg/mL; n=35) and a no-AHR group (those with a PC₂₀ of \geq 25 mg/mL; n=12) (Table 1). The Institutional Review Board of Yonsei University approved the study (IRB protocol no. 4-2009-0241) and informed consent was obtained from all participants.

Exercise Bronchial Provocation Test

The exercise challenge was performed using a free-running test on a treadmill. The participants ran for 10 minutes or until 80% to 90% of their estimated maximum heart rate was achieved. Maximum heart rate was calculated using the equation $(205 - (1/2) \times \text{age})$ [15]. Heart rate was assessed using a heart rate monitor (VIASYS Healthcare, Höchberg, Germany). IOS and spirometry parameters were obtained at baseline and at 0, 5, 10, 20, and 30 minutes after the exercise challenge.

Impulse Oscillometry

IOS parameters were collected before conventional spirometry using the MasterLab IOS System (Erich Jaeger Co., Würzburg, Germany). Calibration was performed using a single volume of air (3 L) at different flow rates and a reference resistance device (0.2 kPa/L/s). The individuals wore a nose clip and a manufacturer-provided oval hard plastic mouthpiece to prevent expired air from escaping. They were also asked to support their cheeks with their hands to decrease shunt compliance. Artifacts caused by coughing, breath-holding, swallowing, and vocalization were not included. A single, experienced, respiratory technician performed all the IOS measurements. The parameters evaluated were resonance frequency (R_{freq}), resistance at 5 Hz (R_5), resistance at 10 Hz (R_{10}), resistance at 20 Hz (R_{20}), difference in resistance between 5 Hz and 20 Hz ($R_5 - R_{20}$), reactance at 5 Hz (X_5), and area of reactance (AX; area integrated from 5 Hz to R_{freq}). With the exception of R_{freq} , all of the above values were used to calculate differences from baseline.

Spirometry

Spirometric parameters were measured immediately after IOS measurements in all individuals. A pneumotachometer system with a Lilly head (MasterScreen system; Erich Jaeger Co.) was used to measure maximum expiratory flow volume. The spirometric flow-volume curve was obtained using international criteria [16]. All the individuals wore a nose clip and performed standard forced expiratory maneuvers. At least 3 acceptable attempts were included and the best was selected for the final analysis.

Methacholine Bronchial Provocation Test

The MBPT was also performed in all cases according to international guidelines [2]. Methacholine powder was distilled and diluted in isotonic saline and administered using a handheld

nebulizer (Devilbis 646; Devilbis Health Care Inc, Somerset, England) connected to a Rosental dosimeter (Devilbis Health Care Inc). For each dose, each individual inhaled 5 times from functional residual capacity without holding their breath after a full inspiration. The first concentration of administered methacholine was 0.075 mg/mL, and a dose-response curve was plotted by serial doubling in the concentration of methacholine up to 25 mg/mL. The PC₂₀ was calculated using linear interpolation between the last 2 points on the dose-response curve. When this value was lower than 25 mg/mL, AHR was considered to be present. The MBPT was conducted 2 weeks before the EBPT.

Statistical Analysis

Data were analyzed using version 12 of the SPSS statistical software (SPSS Inc, Chicago, Illinois, USA). Nonparametric statistical methods were used. The Mann-Whitney U test was used for comparing means and the Spearman rank correlation test was used for analyzing correlations. The discriminative properties of the different IOS parameters to identify AHR patients were evaluated using receiver operating characteristic (ROC) curves. To compare each variable, areas under the curve (AUC) with 95% confidence intervals (CIs) were determined. Significance was defined as $P < .05$. The data are shown as means \pm SEM. Logistic regression analysis was used to compare IOS parameters with FEV₁ values.

Results

Changes in Spirometry and Impulse Oscillometry Parameters After the Exercise Bronchial Provocation Test

There were no differences between the AHR group and the no-AHR group in terms of baseline spirometry results (forced vital capacity [FVC], FEV₁, or FEV₁/FVC), or IOS parameters. Baseline R_{freq} and AX values were slightly higher in the AHR group but the differences were not statistically significant (Table 1).

Significant differences were found between the groups in the EBPT, with considerable differences found for time-related patterns of spirometry and IOS parameters. In the AHR group, FEV₁ fell immediately after the exercise challenge with a maximum decrement of $-9.96 \pm 1.74\%$ ($0.11 \pm 0.97\%$ in the no-AHR group, $P < .001$) at 5 minutes and recovery of normal ranges at 10 to 30 minutes after the exercise challenge. There were no changes in FEV₁ in the no-AHR group (Figure 1A). R_{freq} was significantly higher in the AHR group than in the no-AHR group at 5 minutes (15.1 ± 0.6 Hz vs 12.8 ± 0.8 Hz, $P = .034$), 10 minutes (13.9 ± 0.7 Hz vs 10.7 ± 0.7 Hz, $P = .010$), 20 minutes (12.6 ± 0.6 Hz vs 9.5 ± 0.6 Hz, $P = .025$), and 30 minutes (12.2 ± 0.7 Hz vs 9.1 ± 0.5 Hz, $P = .033$) after exercise (Figure 1B). In addition, increments of resistance at 5 Hz (ΔR_5) were also much higher in the AHR than in the no-AHR group at 5 minutes

Table 1. Characteristics of Study Patients^a

	AHR (n=12)	No-AHR (n=35)	P Value
Age, y	20.7 (0.9)	20.3 (1.7)	.129
Sex (male:female)	12:0	33:0	
Height, cm	174.2 (6.1)	174.5 (5.3)	.625
Weight, kg	72.8 (11.5)	70.4 (10.7)	.575
Body mass index, kg/m ²	23.9 (3.3)	23.1 (3.1)	.584
FVC, L	4.68 (0.76)	4.53 (0.44)	.843
FEV ₁ , L	4.05 (0.72)	3.84 (0.42)	.337
FVC, % predicted	92.6 (9.4)	91.1 (7.9)	.843
FEV ₁ , % predicted	94.5 (13.5)	91.6 (10.0)	.342
FEV ₁ /FVC ratio, %	86.4 (7.2)	85.0 (7.5)	.433
R _{freq}	10.6 (3.5)	12.0 (3.3)	.143
R ₅	0.27 (0.05)	0.27 (0.08)	.723
R ₁₀	0.24 (0.05)	0.23 (0.06)	.669
R ₂₀	0.20 (0.05)	0.19 (0.05)	.462
R ₅ -R ₂₀	0.07 (0.03)	0.08 (0.06)	.722
X ₅	-0.08 (0.05)	-0.10 (0.06)	.704
AX	0.18 (0.14)	0.33 (0.41)	.209
PC ₂₀ , mg/mL ^b	>25.00	2.78 (2.72)	<.001

Abbreviations: AHR, airway hyperresponsiveness; AX, area of reactance (area integrated from 5 Hz to R_{freq}); FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; PC₂₀, amount of methacholine required to cause a 20% decrease in FEV₁ from baseline; R₅, resistance at 5 Hz; R_{freq}, resonance frequency; X₅, reactance at 5 Hz.

^aAll data are shown as means (SD).

^b $P < .01$.

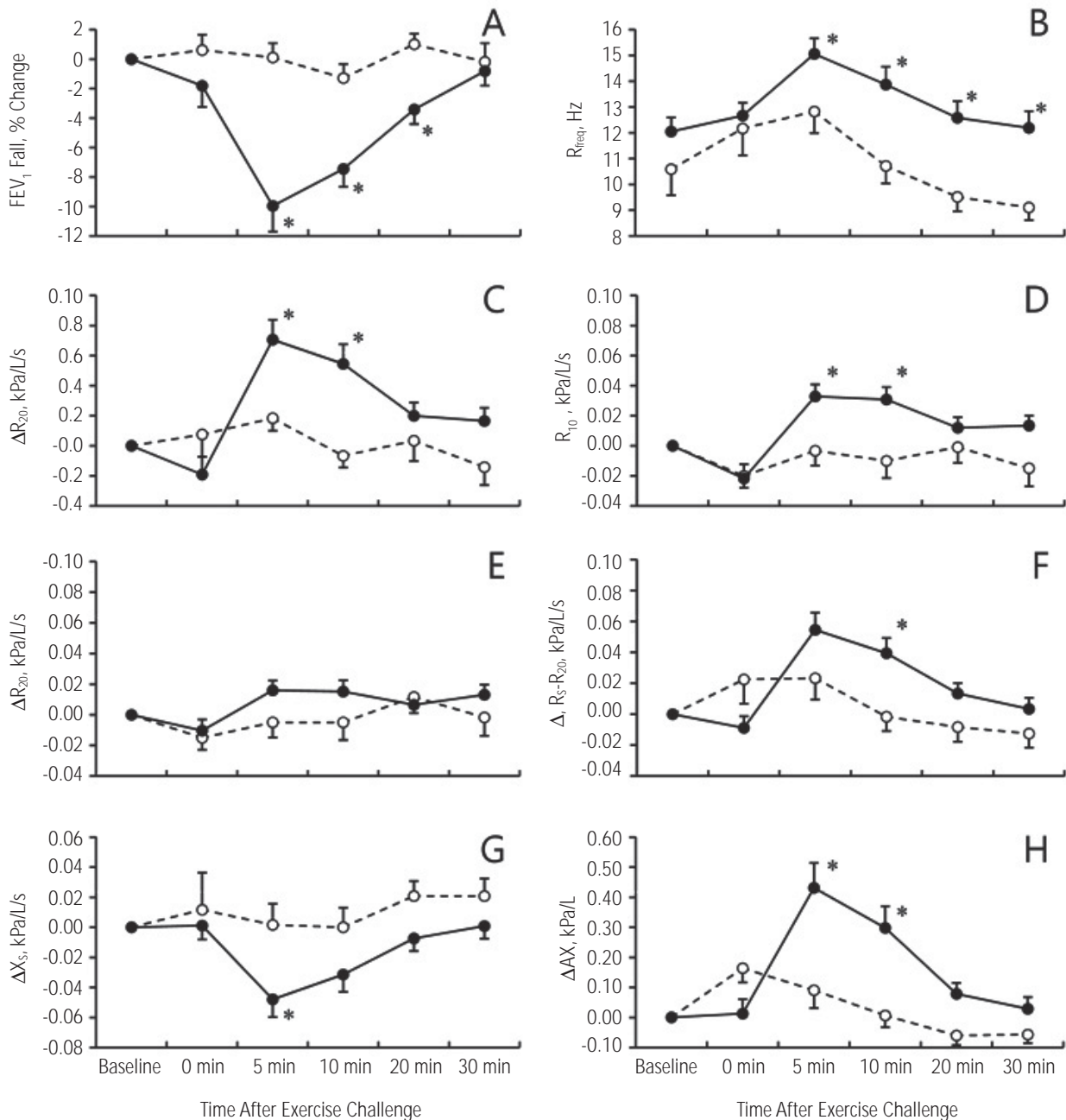


Figure 1. Serial changes in fall in forced expiratory volume in the first second (FEV₁) (A); R_{freq} (B); R₅ (C); R₁₀ (D); R₂₀ (E); (R₅-R₂₀) (F); X₅ (G); and AX (H) according to time after exercise bronchial provocation test. All data are shown as means±SEM. (*P*<.05). Open circles indicate the group without airway hyperresponsiveness (AHR) and closed circles, the group with AHR. AX indicates area of reactance (area integrated from 5 Hz to R_{freq}); R₅, resistance at 5 Hz; R_{freq}, resonance frequency; X₅, reactance at 5 Hz.

(0.071±0.013 kPa/L/s vs 0.018±0.008 kPa/L/s, *P*=.027) and 10 minutes (0.055±0.013 kPa/L/s vs -0.007±0.008 kPa/L/s, *P*<.001) post-challenge (Figure 1C). Increments of resistance at 10 Hz (ΔR₁₀) at both 5 minutes (0.033±0.008 kPa/L/s vs -0.003±0.010 kPa/L/s, *P*=.011) and 10 minutes (0.031±0.008 kPa/L/s vs -0.010±0.011 kPa/L/s, *P*=.005), in addition to Δ(R₅-

R₂₀) values (frequency dependency of airway resistance) at 10 minutes (0.039±0.010 kPa/L/s vs -0.002±0.009 kPa/L/s, *P*=.009) were also significantly higher in the AHR group than in the no-AHR group (Figures 1D, 1F). The decrease in reactance at 5 Hz (ΔX₅) at 5 minutes after the exercise challenge was greater in the AHR group than in the no-AHR

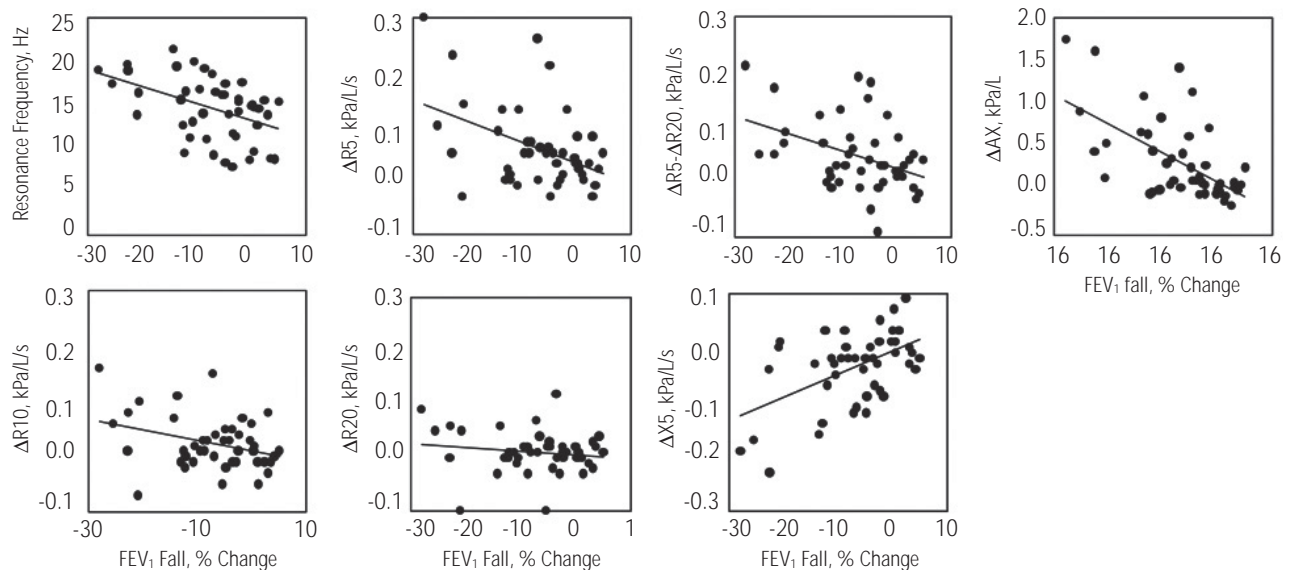


Figure 2. Correlations between fall in forced expiratory volume in the first second (FEV₁) vs. impulse oscillometry (IOS) parameters at 5 minutes after exercise challenges. R_{freq}, R₅, R₅-R₂₀, AX, and X₅ were all well correlated with FEV₁. The exceptions were R₁₀ and R₂₀. AX indicates area of reactance (area integrated from 5 Hz to R_{freq}); R₅, resistance at 5 Hz; R_{freq}, resonance frequency; X₅, reactance at 5 Hz.

Table 2. Correlation Coefficients (ρ) and P values of Fall in FEV₁ vs IOS Parameters

IOS Parameters	Time After Exercise Bronchial Provocation Test					
	0 min	5 min	10 min	20 min	30 min	
R _{freq}	ρ	0.040	-0.456 ^b	-0.412 ^b	-0.346 ^a	-0.159
	P	.791	.001	.004	.017	.287
ΔR5	ρ	0.156	-0.314 ^a	-0.367 ^a	-0.323 ^a	0.030
	P	.296	.032	.011	.027	.839
ΔR10	ρ	0.038	-0.278	-0.302 ^a	-0.296 ^a	-0.021
	P	.801	.059	.039	.043	.889
ΔR20	ρ	0.266	-0.104	-0.293 ^a	-0.145	0.064
	P	.071	.487	.046	.330	.669
Δ(R5-R20)	ρ	-0.097	-0.375 ^b	-0.328 ^a	-0.308 ^a	-0.136
	P	.517	.009	.024	.035	.363
ΔAX	ρ	-0.025	-0.545 ^b	-0.441 ^b	0.455 ^b	-0.229
	P	.867	<.001	.002	.001	.121
ΔX5	ρ	-0.171	0.396 ^b	0.190	0.138	0.084
	P	.249	.006	.201	.355	.577

Abbreviations: AX, area of reactance (area integrated from 5 Hz to R_{freq}); FEV₁, forced expiratory volume in the first second; IOS, impulse oscillometry; R₅, resistance at 5 Hz; R_{freq}, resonance frequency; X₅, reactance at 5 Hz.

^aP<.05.

^bP<.01.

group (-0.048±0.012 kPa/L/s vs 0.002±0.014 kPa/L/s, P=.040) (Figure 1G). Finally, AX values in the AHR group compared to the no-AHR group were also significantly increased at 5 minutes (0.431±0.083 kPa/L vs 0.091±0.060 kPa/L, P=.010) and 10 minutes (0.298±0.072 kPa/L vs 0.007±0.039 kPa/L, P=.031) after the exercise (Figure 1H).

Correlation Analysis of Spirometry and Impulse Oscillometry Parameters

The IOS parameters R_{freq}, ΔR₅, Δ(R₅-R₂₀), ΔAX, and ΔX₅ were all well correlated with the decrease in FEV₁ at 5 minutes after exercise (Figure 2). At 10 minutes, ΔR10 but not X5 was

correlated with this decrease. Specific correlation coefficients and *P* values are presented in Table 2. The correlations between the decrease in FEV₁ and R_{freq}, ΔR₅, Δ(R₅-R₂₀), and ΔAX were maintained from 5 minutes to 20 minutes after the exercise challenge.

Receiver Operating Characteristic Analysis

The ΔR₅ value at 10 minutes after exercising was the best parameter for distinguishing methacholine-induced AHR (AUC: 0.818, *P*=.001 with 95% CI 0.699-0.936) but ΔAX at 5 minutes also had distinguishing power (AUC, 0.746; *P*=.012; 95% CI, 0.595-0.898). A cutoff of 0.035 kPa/L/s for ΔR₅ at 5 minutes was capable of distinguishing between patients with AHR and those without with 63% sensitivity and 100% specificity. Furthermore, on analyzing maximum post-EBPT nominal changes, ΔR_{5max} was also useful for distinguishing between AHR and no-AHR (AUC, 0.755; *P*=.009; 95% CI, 0.612-0.898). A cutoff of 0.055 kPa/L/s for ΔR_{5max} had 71% sensitivity and 75% specificity.

Logistic Regression Analysis

Each sequential IOS parameter and decrease in FEV₁ was analyzed for the probability with which it could predict MBPT positivity. ΔR₅ (at 5 and 10 minutes), ΔAX (at 5, 10, and 20 minutes), and R_{freq} (at 10, 20 and 30 minutes) values proved to be capable of predicting MBPT positivity. These results support the ROC analysis explained above (data not shown).

Discussion

Many clinical studies have reported the usefulness of the FOT to evaluate airway obstruction in a variety of physiologic or pathologic conditions [15,17-21]. Although spirometry has reference values and high reproducibility, IOS can reflect other aspects of bronchial obstruction such as airway resistance and reactance. There are many reports of the FOT being used to describe airway characteristics in children and adults [15,18-20]. The technique has been used not only to assess the degree of airway obstruction, but also to evaluate bronchodilation or AHR induced by a nonspecific airway irritant such as methacholine. Song et al [18,19] reported that IOS parameters were significantly correlated with spirometry in asthmatic children, especially those with atopy. IOS could thus be a useful diagnostic tool in pediatric asthma and a helpful outcome measure for asthma treatment [18-19]. Mansur et al [20] suggested that IOS parameters during MBPT correlated better with asthma symptoms than spirometry parameters.

Some reports have suggested that the FOT is useful for evaluating exercise-induced bronchoconstriction or asthma [15,22]. Malmberg et al [15] reported that time-related patterns of exercise-induced changes in IOS parameters in children after a free running test. They also suggested that a 35% increase in R₅ might be an abnormal response. IOS parameters can detect airway obstruction not only after exercise, but also in eucapnic voluntary hyperventilation. In particular, R₅ has been found to be significantly correlated

with a decrease in FEV₁ [23]. In addition, Schweitzer et al [22] showed that deep inhalation measured by respiratory conductance could reverse EIB.

Our results support that IOS can measure exercise-induced airway characteristics in adults as well as spirometry, with exercise-induced airway resistance parameters measured by IOS correlating well with spirometry parameters. The most powerful marker for discriminating between patients with AHR and those without was ΔR₅ at 10 minutes after the exercise challenge, with a 0.035 kPa/L/s elevation from baseline. Also of value for this purpose were ΔAX at 5 minutes after exercise and maximum post-exercise changes in R₅ (ΔR_{5max}). These results support findings reported by Malmberg et al [15]. Yet our results are expressed as a numeric increment rather than a percent increment. ΔX₅ is well known as an IOS parameter that has large interindividual differences [15,21]. In our study, however, ΔX₅ did not show any statistical differences between individuals with AHR and those without, although resonance frequency did show meaningful differences after exercise. Because temperature increases during exercise may minimally affect IOS parameters after the EBPT [24], all the exercise challenges in the current study were performed in an air-conditioned room to minimize this effect.

IOS following an EBPT is a practical method for use in pre-recruitment physical examinations because it does not require forced maneuvers. This is important as individuals may attempt to manipulate spirometry results to their benefit in such tests. IOS, in contrast, is free from this risk. In Korea, all 18-year-old males must undergo a pre-recruitment physical examination at the Military Manpower Administration, even though they can be drafted at any age between 18 and 35 years. In addition, some young men attempt to evade their military service obligation.

The measurement of airway resistance by IOS does, however, have some limitations. The results, for instance, can be adversely affected by cheek movement, or by the use of vocal cords or the muscles of the pharyngeal wall [25]. Furthermore, in adults, the proportion of upper airway resistance in total airway resistance would be higher than that in children [26]. These technical limitations may result in considerable interobserver differences [27] and lower reproducibility compared with spirometry [28-29].

In conclusion, IOS revealed airway characteristics in individuals that performed an EBPT that were well correlated with those detected by spirometry. ΔR₅ and ΔAX were useful measurements for distinguishing between asthmatics presenting EIB and healthy individuals. The measurement of exercise-induced airway resistance using the IOS method would be useful to confirm exercise-induced airway obstruction in asthmatics without the need for effort-dependent forced expiration maneuvers.

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