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LETTER TO THE EDITOR

Dear Editor

A Surrogate Marker of Airway Hyperresponsiveness in Patients with Bronchial Asthma

Airway hyperresponsiveness (AHR) is a characteristic functional abnormality of asthma. In general, the severity of the AHR correlates with the severity of asthma.[1] Therefore, the evaluation of AHR has been reported to be useful for the diagnosis and management of asthma.[2-4] To evaluate the degree of AHR, an inhalation challenge test (ICT) with a bronchoconstrictor is usually performed. However, the ICT can cause bronchospasm, and the method is complicated for general practitioners. An alternative method to evaluate the AHR more safely and easily is needed for general practitioners.

The precise mechanism responsible for AHR has not been clarified. However, factors altering the airway structure appear to be most closely related to AHR.[4] In this context, the baseline lung function is known to be associated with AHR.[5,6] However, there have been no reports of using spirometry to predict the degree of AHR. We investigated surrogate markers for AHR, and found that spirometry can predict the degree of AHR, and might therefore be useful for the management of asthma.

This study was a retrospective study. Asthmatic patients who underwent an ICT between January 2010 and September 2012 in The Fraternity Memorial Hospital, Tokyo, Japan were continuously enrolled in this study. Patients who had absolute contraindications for the ICT based on the American Thoracic Society (ATS) guidelines were not present in the population.[7] The diagnoses were made based on the Global Initiative for Asthma (GINA) guidelines.[2] This study was approved by the ethics committee of The Fraternity Memorial Hospital.

Prior to ICT, the baseline lung function was measured with a spirometer (Auto Spiro AS-500; Minato, Osaka, Japan). ICT was performed by modifying the method according to the ATS guidelines.[7] Histamine dihydrochloride (Nacali Tesque, Kyoto, Japan) was administered using a nebulizer, in doubling dose from 0.039 to 20 mg/ml. The cut-off level of PC_{20} was defined as 4 mg/ml.

The correlation coefficients were obtained by a Spearman's rank correlation test. The diagnostic performance was expressed as the sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve. The optimal cut-off levels were determined by the ROC curves.

The study subjects included 215 adult patients with asthma, 112 males and 103 females, 25 of whom were current smokers, 72 were ex-smokers and 118 were nonsmokers. Eighty-four patients were newly diagnosed with asthma, and the other patients had received treatment classified from Step 2 to Step 5 according to the GINA guideline.[2] The mean age of the patients was 47.7 ± 16.2 years. The mean value of the FEV_1/FVC was 84.3 ± 7.2%. The mean value of the FEV_1 %predicted was 85.3 ± 14.5%.

Table 1 The relationship between PC_{20} and the variables obtained by spirometry

	R	*p* value	
FEV1	0.1412	0.0639	ns
FEV_1/FVC	0.2370	0.0017	**
FEV_1 %pred.	0.4618	<0.0001	***
PEF	0.1803	0.0176	*
PEF %pred.	0.3988	<0.0001	***
FEF_{50}	0.2940	<0.0001	***
FEF_{50} %pred.	0.4769	<0.0001	***
FEF_{75}	0.1620	0.0332	*
FEF_{75} %pred.	0.4207	<0.0001	***
FEF_{25}	0.2997	<0.0001	***
FEF_{25-75}	0.2665	<0.0004	***
FEF_{25-75} %pred.	0.4982	<0.0001	***
FEF_{75}/Ht	0.1713	0.0242	*
FEF_{75}/Ht %pred.	0.3391	<0.0001	***

***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

The correlation analysis between PC_{20} and the variables obtained by spirometry was performed in 173 patients whose PC_{20} was no more than 20 mg/ml. Almost all variables obtained by the flow volume curves were correlated with the value of PC_{20} (Table 1). Among those, the Forced expiratory flow at 25-75% of FVC (FEF_{25-75}) %predicted showed the highest correlation with PC_{20} ($r = 0.4982$, $p < 0.0001$), followed by the FEF_{50} %predicted ($r = 0.4769$, $p < 0.0001$) and FEV_1 %predicted ($r = 0.4618$, $p < 0.0001$).

We selected the top three variables based on the correlation analysis, the FEF_{25-75} %predicted, FEF_{50} %predicted and FEV_1 %predicted, as candidates to predict the asthmatics who would have a high degree of AHR. When 4 mg/dl was employed as a cut-off level for PC_{20}, the areas under the ROC curves of the FEF_{25-75} %predicted, FEF_{50} %predicted and FEV_1 %predicted were 0.75, 0.75 and 0.76, respectively. According to the ROC analysis, the optimal cut-off levels of the FEF_{25-75} %predicted, FEF_{50} %predicted and FEV_1 %predicted were 73.5%, 77.5% and 84.5%, respectively. When these cut-off levels were applied, the FEF_{50} %predicted showed the highest sensitivity and specificity, which were 70.4% and 74.0%, respectively. The optimal cut-off levels, sensitivities and the specificities obtained by the ROC analysis are shown in Table 2.

Our results show that spirometry has the new po-

Table 2 Diagnostic performance of FEF_{25-75} %predicted, FEF_{50} %predicted and FEV_1 %predicted obtained by ROC analysis

	Cut-off	Sensitivity (%)	Specificity (%)
FEF_{25-75} %predicted	73.5	70.4	71.0
FEF_{50} %predicted	77.5	70.4	74.0
FEV_1 %predicted	84.5	64.4	72.0

tential to predict the degree of AHR. Spirometry is a safe and easy examination, which does not require specialized personnel or laboratories. Our findings are thought to be especially useful for general practitioners. Among the variables obtained by spirometry, we recommend that the FEF_{50} %predicted is the best value to predict asthmatics with PC_{20} <4 mg/ml, because of its higher sensitivity and specificity. The FEF_{25-75} %predicted and FEV_1 %predicted also might be good surrogate markers, but their sensitivity and specificity were lower than those of the FEF_{50} %predicted.

We believe that 4 mg/ml is appropriate as a cut-off level for confirming the presence of AHR, because a PC_{20} value of 4-16 mg/ml is borderline AHR.[7] In fact, the target PC_{20} was 4 mg/ml in a recent report which suggested the usefulness of a strategy to reduce the AHR.[3] Therefore, we employed 4 mg/ml as a cut-off level for PC_{20} in the present study. Considering our results, a FEF_{50} %predicted >77.5% might be useful as a target value in the hospital, where the ICT cannot be performed. Even when the cut-off levels of PC_{20} are set at different values other than 4 mg/ml, FEF_{50} %predicted maintains relatively fair sensitivities and specificities. However, the higher PC_{20} is, the lower the sensitivities and specificities tend to become (data not shown).

The association between AHR and the baseline lung function has long been recognized.[5] The precise mechanism underlying this relationship is still poorly understood. However, as mentioned above, the structural changes in the airway are thought to have a close association with the AHR.[8] The inner airway wall thickening amplifies airway smooth muscle (ASM) shortening,[9] and the hypertrophy and hyperplasia of the ASM increases the smooth muscle strength.[10] The adventitial thickening then uncouples the airway from the surrounding parenchyma, resulting in a reduction of the tethering forces to oppose the airway narrowing.[8] These structural changes are thought to influence the baseline lung function. Given that we showed that almost all of the variables obtained by the flow volume curve were correlated with the PC_{20}, these structural changes might be involved in the development of AHR in the central airway, as well as in the peripheral airway. Moreover, we showed that the highest correlation was between the PC_{20} and FEF_{25-75} %predicted, suggesting importance of the small airway in the development of AHR as previously reported.[11]

We believe that the application of spirometry can have a great impact on clinical practice, especially for general practitioners. Moreover, the higher correlation between the PC_{20} and variables responsible for the peripheral airway status implies the importance of the small airway in the development of AHR.

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