Relationship of the Arabic version of the asthma control test with ventilatory function tests and levels of exhaled nitric oxide in adult asthmatics

Syed S. Habib, MBBS, FCPS, *Mohammed A. Alzoghaibi,* BSc, PhD, *Abdullah A. Abba,* FRCP (Glas), FRCPI, *Mujtaba Hasan,* FCPS.

ABSTRACT

الأهداف: يهدف هذا المشروع إلى تحديد العلاقة بين اختبار التحكم بمرض الربو (اختبار الـ ACT)،باستخدام النسخة العربية،أكسيد النيتريك المزفر (FENO) ووظائف الرئة؛ وذلك للحصول على النقاط الفاصلة لهذا الاختبار ACT مع المستويات المعتمدة لدى جمعية الصدر الأمريكية للتحكم بالالتهابات.

الطريقة: قمنا بدراسة 59 مريض بالربو من البالغين بينهم 53 مريضاً أنهوا الدراسة بالكامل خلال الفترة من يوليو 2011 م إلى يونيو 2012م في جامعة الملك سعود، الرياض، المملكة العربية السعودية. وتم حساب مستويات الـ FENO بطريقة النايكس مينو (NIOX MINO®) وتم تسجيل وظائف التهوية بالطرق القياسية.

النتائج: كانت قيم الـFENO أعلى إحصائياً في مرضى الربو بدرجة20> طبقاً لـ ACT (35.4 ± 65.5) مقارنة بالمرضى ذوي الدرجة 20 ≥ طبقاً لـ ACT. (10.5± 27.4، p<0.001) من ضمن المشاركين الأصحاء طبقاً لـ ACT، 6 (25%) حالات كان لديها مستوى الـ FENOعالي، بينما مجموعة الأصحاء الأقل مستوى، 23 (79.3%) حاله كان لديها مستوى الـFENOعالي (نسبة فردية 11.5: p<0.0001 : الفترة الثابتة 3.16–41.72). هناك علاقة واضحة وأكيده بين FENOودرجة اختبار الـ ACT (r=–0.581، p<0.0001). عند النقطة الفاصلة العالمية 20 من الخصوصية والإحساسية. وضح ROC أن أعلى درجة للخصوصية والإحساسية تم تسجيلها في اختبار الـ ACT كانت عند 19 كنقطة فاصلة (90.5 و 81.2).

الخاتمة: تربط كلا من الـ FENO ودرجة اختبار الـ ACT علاقة سلبية، بينما تظهر علاقة غير هامة إحصائياً بين الـ FENO ووظائف الرئة. إن العلاقة الهامة والقوية بين مستوى الـFENO و درجة اختبار الـ ACT لهو مؤشر واضح على استمرارية الالتهاب في مرضى الربو ضعيفي التحكم.

Objectives: To determine the relationship between the asthma control test (ACT) score using the Arabic version, fractional exhaled nitric oxide (FENO), and lung functions, and to derive the cutoff points for the ACT score with the American Thoracic Society recommended FENO standard levels of inflammation control.

Methods: We recruited 59 adult asthmatics out of which 53 subjects completed the study between July 2011 and June 2012 at King Saud University, Riyadh, Saudi Arabia. The FENO levels were measured by NIOX MINO® (Aerocrine AB, Solna, Sweden), and ventilatory functions were recorded by standard techniques.

Results: The FENO values were significantly higher in patients with an ACT score <20 (65.5±35.4) compared with those patients with an ACT score ≥ 20 (27.4±10.5, $p<0.001$). Among the well-controlled group based on the ACT score criteria, 6 (25%) cases had high FENO levels, while among the poorly controlled group, 23 (79.3%) cases had high FENO levels (odds ratio: 11.5; $p<0.0001$; confidence interval: 3.16-41.72). There was a significant negative correlation between FENO and ACT score (r=-0.581, $p<0.0001$). At the international cutoff point of 20, the sensitivity was 95.2, and the specificity was 68.8. The receiver operating curve (ROC) showed that maximum sensitivity and specificity were observed at an ACT score cut off point of 19 (sensitivity: 90.5, and specificity: 81.2).

Conclusions: The FENO levels correlate negatively with ACT scores however, the relationship between FENO and lung function is not significant. A significant relationship between ACT score and FENO levels indicate that there is an ongoing inflammatory state in patients with poor asthma control.

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From the Departments of Physiology (Habib, Alzoghaibi), and Medicine (Abba, Hasan), College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Syed S. Habib, Professor & Consultant, Department of Physiology (29), College of Medicine, PO Box 2925, King Saud University, Riyadh 11461, Kingdom of Saudi Arabia. Tel. +966 (11) 4671604. Fax. +966 (11) 4672567. E-mail: shahidhabib44@hotmail.com

At present airflow obstruction in asthma is routinely monitored by history, physical examination, and spirometry. There is airway inflammation in asthma, which is central to its pathogenesis and there is recent evidence that its monitoring should be part of patient management.[1,2] Monitoring inflammation in asthmatic patients with fractional exhaled nitric oxide (FENO) is not yet included in current asthma guidelines, despite upcoming evidence that this may improve control.[3,4] It is well known that atopy is a significant factor associated with raised levels of FENO, in patients with or without asthma.[5,6] Research has suggested that the noninvasive FENO testing may be a useful tool in the diagnosis as well as in prognosis to indicate persistence of asthma and the severity of airway inflammation.[7,8] Recent reports also suggest that FENO can identify patients with difficult-to-treat asthma, and indicates the potential to respond to high doses of inhaled corticosteroids or systemic steroids.[9] The asthma control test (ACT) score was devised by Nathan et al in 2004,[10] and is recommended by the National Heart Lung and Blood Institute (NHLBI), and other organizations in the Asthma Guidelines 2007[11] as a validity tool to assess asthma control. The conventional measures of asthma severity include symptoms, amounts of β2-agonist used, and lung function. These measures do not assess airway inflammation. Therefore, they may not provide optimal assessment for guiding therapy, and are correlated poorly with eosinophilic inflammation on bronchial biopsies, or with FENO. Hence, FENO may be a quick and simple inflammatory marker to assess the impact of treatment changes on inflammation and to guide asthma therapy. Still, large long-term outcome trials are necessary to validate its usefulness. Although evaluation of asthma control using the ACT has been performed in the Saudi population in a previous study,[12] to investigate the prevalence of uncontrolled asthma, which was very high at 64%, still the relationship between the ACT score and FENO needs further elaboration, especially using the Arabic version of the ACT score questionnaire, since FENO is becoming a useful marker of airway inflammation. Therefore, this study aimed to determine the relationship between the scores computed from the ACT using the Arabic version, FENO targets according to the recent American Thoracic Society guidelines,[13] and ventilatory lung functions. Additionally, we tried to determine the best cutoff points for the ACT score with the recommended standard levels of inflammation control determined by measuring FENO levels.

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Methods.

This cross-sectional study was carried out at the Departments of Physiology and Medicine, College of Medicine and King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia between July 2011 and June 2012. The Research Ethics Committee of the College of Medicine Research Center approved the study protocol. The study was performed according to the principles of the Helsinki Declaration. All subjects studied were known asthmatic patients who had asthma for at least one year duration with mild to moderate symptoms. Patients with allergic rhinitis, chest cage, or spinal deformities, current smokers, chronic obstructive pulmonary disease, bronchiectasis, and emphysema interstitial lung diseases, or tumors were excluded. Asthmatic patients were recruited from the chest clinic in KKUH.

Measurements of fractional exhaled nitric oxide. The FENO measurements were performed according to the present recommendations of the American Thoracic Society using handheld NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). A FENO level of >47 ppb was used to indicate inflammation and uncontrolled asthma.[13]

Ventilatory function parameters. Spirometry was performed after recording FENO values and included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), percentage of forced expiratory volume in the first second (FEV1%), peak expiratory flow (PEF), and forced expiratory flow at 25 (FEF25), 50 (FEF50), and 75% (FEF75) of vital capacity. Ventilatory functions were measured using an electronic spirometer (Vitalograph Co, Clare, Ireland), which was calibrated daily.

Statistical analysis. Statistical analysis was performed using the Statistical Package for Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD for continuous variables. Categorical data were expressed as absolute numbers and percentages. The test applied for statistical analysis was Student's t-test and Pearson's correlation coefficient. Different groups were compared by chi-square test for categorical variables. The receiver operating curve (ROC) was used to detect control of inflammation in asthma by FENO and identify cutoff points with a higher sensitivity (true positive rate) and specificity (true negative rate). Positive

predictive values (PPV) and negative predictive values (NPV) were also calculated and compared for proposed and standard ACT score cutoff points. Spearman's correlation was calculated to determine the relation between age, height, weight, asthma duration, FENO, FVC, FEV1, and FEV1%. A $p \leq 0.05$ was considered statistically significant.

Results. We recruited 59 adult asthmatics out of which 53 participants completed the study. Clinical and demographic characteristics of all asthmatics are shown in **Table 1**. **Table 2** summarizes the history of medications in the patients. Mean FENO values were significantly higher in patients with an ACT score <20 (65.5 ± 35.4 ppb) compared with those patients with an ACT score ≥20 (27.4 ±10.5 ppb, $p<0.001$). Linear regression analysis revealed a significant negative correlation of FENO with ACT score (r=-0.581, $p<0.0001$) (**Figure 1**). There was no significant correlation of FENO with age, height, weight, asthma duration, and ventilatory function tests (**Table 3**). Twenty-four cases (45.3%) had an ACT score ≥20, and 29 cases (54.7%) had an ACT score <20. Among the well-controlled group, based on ACT score criteria, 18 (75%) cases had desirable FENO levels while 6 (25%) cases had high FENO levels. Among the poorly controlled group, 6 (20.7%) cases had desirable FENO levels while 23 (79.3%) cases had high FENO levels (odds ratio 11.5; 95% confidence interval [CI]: 3.16-41.72, $p<0.0001$). **Table 4** shows sensitivity, specificity, PPV, NPV for the different ACT cutoff points for uncontrolled asthma. The highest area under the curve (91%) corresponded to the ACT cutoff point of 19. We observed that the best pair of sensitivity and specificity was observed at the cutoff point of 19, at which sensitivity was 90.5% (95% CI: 76.2-100%) and specificity was 81.2% (95% CI: 65.6-93.7%). At the international cutoff point of 20, although sensitivity was high (95.23) the specificity was low (68.75). The total area under ROC curve was 91% with 95% CI: 83.5-98.5%, where the maximum sensitivity and specificity was observed at cutoff point of 19 as shown in **Figure 2**.

Table 1 - Clinical and demographic characteristics of all asthmatics included in a study at the Departments of Physiology and Medicine, College of Medicine and King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia (n=53).

Variables	n (%)
Gender	
Male	42
Female	11
Age, years	36.1 ± 14.3
Height, cm	167.3 ± 8.6
Weight, kg	80.3 ± 11.0
FEV1 L (% predicted)	3.2 ± 0.8 (84.4%)
FVC L (% predicted)	3.8 ± 0.7 (81.2%)
FEV1%	83.8 ± 7.7
ACT Score	17.6 ± 4.9
FENO, ppb	48.9 ± 33.3
Asthma duration, years	12.0 ± 10.3
Family history	32 (60.4)
Ex-smokers	23 (43.4)
Atopy	35 (64.8)
Allergic conjunctivitis	22 (41.5)
Eczema	15 (28.3)

FEV1 - forced expiratory volume in the first second, FVC - forced vital capacity, ACT - Asthma Control Test, FENO - fractional exhaled nitric oxide

Table 2 - History of medications in all patients included in a study at the Departments of Physiology and Medicine, College of Medicine and King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Variables	Frequency	Valid percent
None	8	15.1
Bronchodilators	21	39.6
Steroids	15	28.3
Leukotriene inhibitors	3	5.7
Mixed	6	11.3

Table 3 - Pearson's correlations coefficients age, height, weight, asthma duration, FENO, FVC, FEV1 and FEV1%.

Variables	Age	Height	Weight	Duration	FENO	FVC	FEV1	FEV1%
Age	1.0	-0.306*	-0.406†	-0.043	-0.157	-0.171	-0.185	-0.077
Height		1	0.670**	-0.153	0.071	0.310*	0.297*	0.185
Weight			1.0	-0.188	0.094	-0.001	-0.001	0.026
Duration				1.0	0.098	0.052	0.072	-0.031
FENO					1.0	0.041	0.033	-0.126

FEV1 - forced expiratory volume in first second, FVC - forced vital capacity, FEV1% - percentage of forced expiratory volume in the first second, *correlation is significant at the 0.05 level (2-tailed), †Correlation is significant at the 0.01 level (2-tailed)

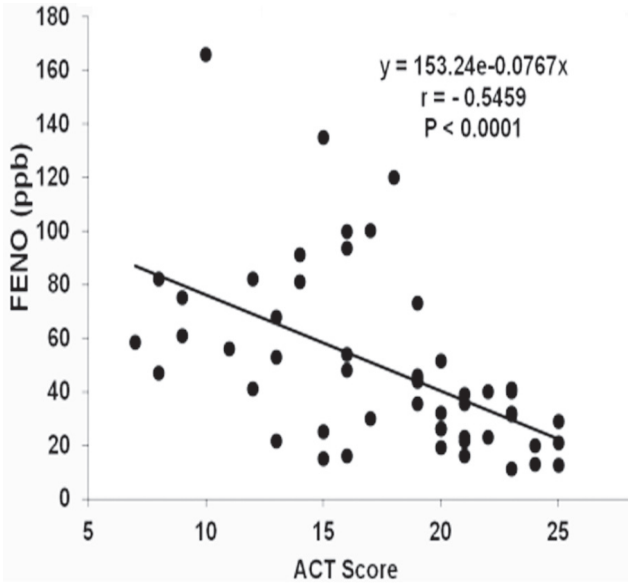

Figure 1 - Linear regression analysis between fractional exhaled nitric oxide (FENO) and asthma control test (ACT) Score.

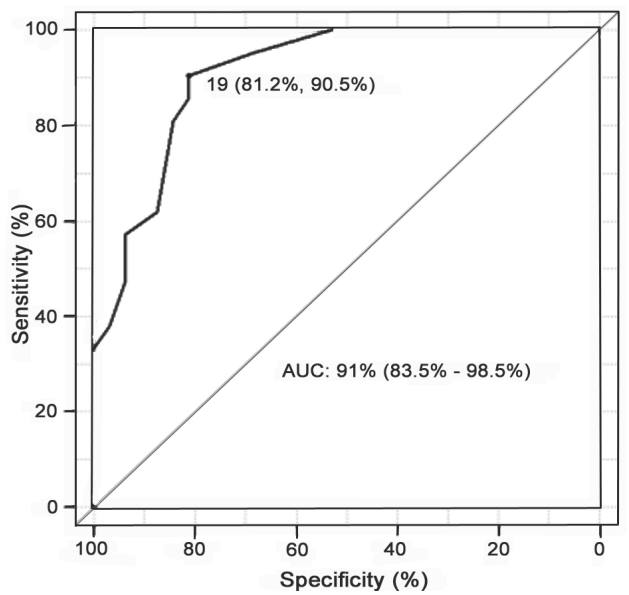

Figure 2 - A receiver operating curve (ROC) analysis showing the total area under ROC of approximately 91% with 95% confidence interval ([CI]: 83.5-98.5%). The maximum sensitivity and specificity was observed at cutoff point of 19. As shown in the figure sensitivity was 90.47% (CI: 76.2-100%), and specificity was 81.2% (CI: 65.6-93.7%).

Discussion. The present study shows the relationship of the ACT score with FENO and pulmonary functions. At present the conventional measures of asthma severity do not assess airways inflammation, and thus may not provide optimal assessment for guiding therapy. Moreover, they correlate poorly with eosinophilic inflammation on bronchial biopsies. The best paired sensitivity and specificity were observed at a cutoff point of 19 (90.5 and 81.2), with the highest area under the curve. Although the sensitivity was high (95.2) at a cutoff point of 20, yet the specificity was low (68.75). There was no significant correlation between FENO and ventilatory function tests

As an "inflammometer," FENO provides the clinician with severity of airway inflammation; thus, complementing conventional physiological testing. At present, measuring FENO in our clinical settings remains unpopular, although current studies are revealing that it runs in parallel to inflammation in a wide range of patients. The same methodology was used by Schatz et al[14] to test the reliability and validity of the ACT in a longitudinal study of asthmatic patients. They reported the same cutoff point of 19 to identify patients with poor asthma control. Similarly, a Spanish questionnaire validation study carried out by Vega et al[15] and also Thomas et al[16] showed the same results. However, they compared the ACT score with the levels of control according to GINA (Global Initiative for Asthma) to establish the best cutoff points for the ACT.

A similarly designed study by Alvarez-Gutiérrez et al[17] reported ACT cutoff points of ≥21 for controlled asthma, 19-20 for partially controlled asthma, and ≤18 for non-controlled asthma. They based their gold standard criteria on the Global Initiative for Asthma, which was not yet ratified. This may be the reason that our results differed from their observations. We used FENO cutoffs based on ATS recent guidelines.[17] They also observed significant but slight correlation between levels of FEV1, FENO, and ACT. They included smokers in their study, whereas, we excluded smokers as smoking is known to reduce FENO values.[18] However, there was no significant correlation between FENO and ventilatory function parameters in our study. There was a significant correlation between FENO and ACT score. The FENO was independently related to the ACT score and spirometric functions. In our report, the relationship of FENO with ventilatory functions was not significant.[19] In the Greek asthmatic population,[20] the ACT score was found to significantly reflect lung function and inflammation. In contrast to our study, Melosini et al[21] reported that ACT scores significantly correlated with symptoms, but not with ventilatory functions reversibility and FENO. In another study, the ACT score was correlated better with treatment decisions made by asthma specialists compared with

Table 4 - Asthma Control Test (ACT) score, and validity of different cut-off points for the classification of control of asthma.

Cut-off points	Sensitivity	Specificity	PPV	NPV
<25	100	9.4	42.0	100
<24	100	15.6	43.7	100
<23	100	31.2	48.8	100
<22	100	37.5	51.2	100
<21	100	53.5	58.3	100
<20	95.2	68.7	66.7	95.6
<19	90.5	81.2	76.0	92.8
<18	85.7	81.2	75.0	89.6
<17	80.9	84.4	77.3	87.1
<16	61.9	87.5	76.5	77.8
<15	57.1	93.7	85.7	76.9
<14	47.6	93.7	83.3	73.2
<13	38.1	96.9	88.9	70.4
<12	33.3	100	100	69.6
<11	28.6	100	100	68.1
<10	23.8	100	100	66.7
<9	14.3	100	100	64.0
<8	4.8	100	100	61.5

PPV - positive predictive values, NPV - negative predictive values

spirometry and FENO levels. An ACT score of ≤20 best correlated with uncontrolled asthma (sensitivity 70.5%, specificity 76.0%, PPV 76.2%, and NPV 70.2%) for predicting the plan for asthma therapy. In an ROC analysis, the ACT score had the highest prediction for changing asthma therapy when compared with FENO or ventilatory functions.[22] Shirai et al[23] also reported a significant relationship between levels of FEV1, FENO, and ACT scores.

The limitations of our study are its cross sectional design and small sample size. Further prospective follow up studies with a larger sample size are needed to elucidate proper monitoring of asthma control and management.

In conclusion, the FENO levels correlated negatively with the Arabic version of the ACT scores. Patients with low ACT scores had significantly higher levels of FENO compared with those with a higher ACT score. A significant strong relationship between ACT scores and FENO levels indicated that there was an ongoing inflammatory state in patients with poor asthma control.

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