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Original Article

Exhaled carbon monoxide in children with asthma and allergic rhinitis

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Abstract

Background Exhaled carbon monoxide has been related to the degree of inflammation. An easy, inexpensive, and non-invasive test to measure exhaled CO levels (eCO) may help in supporting the diagnosis of asthma and allergic rhinitis (AR) in children.

Objective To compare the eCO levels in children with asthma, AR, or both asthma and AR, to children without asthma or AR.

Methods This was a cross-sectional study involving 450 children aged 13-14 years in Yogyakarta. Asthma and AR were determined according to the *International Study of Asthma and Allergies in Childhood* (ISAAC) study criteria, while eCO level was examined using a *Smokerlyzer®*. The levels of eCO between groups were analyzed using Kruskal-Wallis and Mann-Whitney tests.

Results Of 450 children, 48 (10.67%) had asthma only, 91 (20.22%) had AR only, 67 (14.89%) had both asthma and AR, and 244 (54.22%) had neither asthma nor AR. The eCO levels of children with asthma or AR were not significantly different compared to those without asthma and AR. However, children with both asthma and AR had significantly higher eCO level compared to children without asthma and AR.

Conclusion The levels of eCO in children with asthma only or AR only are similar to those without both diseases. Children with both asthma and AR have significant higher eCO compared to healthy children. **[Paediatr Indones. 2022;62:115-9 DOI: 10.14238/pi62.1.2022.115-9]**.

Keywords: *exhaled CO; asthma; allergic rhinitis; children*

The prevalence of allergic diseases in children and young adults is increasing, especially in low- and middle-income countries.[1-3] The prevalence of asthma in children aged 13-14 years from *Global Asthma Report* increase to 6-13% in Indonesia.[1,4] According to the *Riset Kesehatan Dasar/RISKESDAS* (Indonesia Basic Health Research) report, the prevalence of AR in Indonesia was 24.3% in 2017 and the prevalence of asthma was 2.4% in 2018.[5,6] The highest prevalence of asthma according to 2018 Indonesia Basic Health Research was found in Yogyakarta (4.5%).[6]

Although the mortality rate due to allergic diseases is not high, the increased prevalence, especially in asthma and AR, has become a global public health problem.[7] These diseases are often lifelong, decrease productivity, and increase the budget for health consumers. The socioeconomic impact has been classified into direct (frequent emergency room visits and higher health costs) and indirect (school and work absences). Both result decreased quality of life.[1,8]

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The diagnosis of asthma in children is mainly made based on symptoms and clinical findings. A bronchodilator test using spirometry is recommended to support the diagnosis, however, this requires special maneuvers, which young children may find difficult to perform. Even in older children, the ability to perform a spirometry exam is often challenging, resulting in inaccurate readings. In addition, spirometry for children is not widely available in health facilities in Indonesia. Similarly, the diagnosis of AR is also based on clinical symptoms and signs. Skin prick test may support the diagnosis, but it is not routinely performed in children. Several techniques have been developed to make a simple and non-invasive tool to assess the degree of airway inflammation, including examining levels of fractional exhaled nitric oxide (FeNO) and exhaled carbon monoxide (eCO).[9]

Carbon monoxide (CO) can be found in circulating erythrocytes (85%), myoglobin (15%), and very small amounts in body fluid. This CO is produced from heme degradation mediated by the heme oxygenation (HO) enzyme, which increases in inflammatory events.[9] Most CO from heme degradation is exhaled (about 80%) and called eCO. A study showed that eCO level was increased in children with asthma compared to children without asthma. As such, eCO can be used as a tool to monitor the degree of asthma control. However, the high level of eCO is not specific to asthma and can be found in acute respiratory viral infections.[10] The eCO level of AR patients was reportedly higher than in non-AR patients.[11]

A systematic review showed that the eCO level of asthmatics was higher than those without asthma, especially in persistent asthma; the level decreased with steroid therapy.[12] Another systematic review reported that eCO of asthmatics was higher than that of non-asthmatics, but eCO in AR was not different from in non-AR subjects.[13] The eCO looks promising as a non-invasive biomarker of respiratory tract inflammation and oxidative stress,[12] but pediatric studies of eCO levels in allergic diseases, especially asthma and AR, have been limited and inconclusive because partially reflect the disease severity, comorbidity, and control; while majority studies were in adult asthma. As such, we aimed to compare eCO levels in children with asthma, AR, or both asthma and AR, to children without asthma or AR.

Methods

This study was a part of a larger study on the prevalence of asthma among school-aged children in the Yogyakarta Province, held from June to December 2016. It was conducted in junior high schools in all districts of the province. Schools were selected by cluster random sampling. We recruited students aged 13-14 years who completed the questionnaires and provided written informed consent to undergo eCO examination. Active smokers (subject once or regularly smokes cigarette) were excluded from the study. The level of eCO was measured using *Smokerlyzer®*. Subjects inhaled and held their breath for 10-15 seconds, then blew into the disposable mouthpiece of the *Smokerlyzer®*. Subjects repeated the maneuver three times, and the average of three measurements was reported.

Diagnoses of asthma and AR were made based on ISAAC study criteria.[2,3] Asthma was defined as a 'yes' answer to any of the following questions: wheezing at any time (ever wheezed), wheezing in the last 12 months (current asthma), and previously diagnosed with asthma by a doctor (clinically-diagnosed asthma). For AR, the definition was as follows: AR symptoms (sneezing, congestion, or rhinorrhea) at any time when not having a common cold (previous rhinitis), AR symptoms in the last 12 months (current rhinitis), and previously diagnosed with AR by a doctor (clinically-diagnosed AR).

The severity of asthma was determined based on the frequency of attacks in the last 12 months as follows: no attack (no attack in the last 12 months), mild (1-3 attacks in the last 12 months), moderate (4-12 attacks in the last 12 months), or severe (more than 12 attacks in the last 12 months). The severity of AR was classified as no activity disturbance, mild (a little bit disturbing), moderate (quite disturbing), or severe (very disturbing).

We reported the results as mean or median and proportion, as appropiate. The eCO levels between healthy control children and children with asthma only, AR only, or both asthma and AR, were analyzed using ANOVA or Kruskal-Wallis and post-hoc non-parametric methods with Mann-Whitney, depending on the data distribution. This study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing; Universitas Gadjah Mada, Yogyakarta.

Results

A total of 450 children were enrolled in the study. The characteristics of subjects are presented in **Table 1**. The proportion of males and females was similar (54.9% *vs.* 45.1%, respectively) and the majority of the children had good nutritional status (68.5%).

One hundred fifteen children (25.56%) had asthma and 158 (35.11%) had AR. Of 115 children with asthma, 67 children (58.26% of asthma or 14.89% of all subjects) also had AR; of 158 children with AR, asthma occurred in 67 children (42.41% of AR). The detailed asthma and AR classification and severity of subjects are presented in **Tables 2** and **3**.

The median eCO level of children with asthma, AR, and healthy children was similar at 4 ppm (P=0.33 and P=0.19, respectively). However, children with both asthma and AR had the highest eCO level [median 5 ppm], which was significantly higher compared to the asthma only, AR only, and healthy control groups.

Discussion

The incidence of AR among children aged 13-14 years was 35.11%, which was more common than asthma (25.56%). These findings were higher than the Indonesia Basic Health Research, which reported 4.50% for asthma in 2018 and 24.30% for AR in 2017.[5,6] The different findings may be due to differing age groups of the population or differing method or questionnaires used to define asthma and AR. Asthma is more common in children arround aged 7 years compared to AR, but arround the age of 13 years, AR is more common than asthma.[14] The 3rd phase of the ISAAC study reported that the worldwide prevalence of asthma ranged from 2 to 37%.[2] The AR prevalence according to ARIA was 2-25%.[7]

Exhaled CO has been proposed as a test to support the diagnosis of asthma in children. However, previous studies in children and adults showed inconsistent results. We found that eCO in children with asthma only and children with AR only were not different from that of healthy children, However, eCO was higher in the asthma and AR group than the control group. Our finding was similar to two systematic reviews which reported that eCO level in children with intermittent

Table 1. Characteristics of subjects

Characteristics	Asthma only (n=48)	AR only (n=91)	Asthma and AR (n=67)	Control (n=244)	Total (n=450)
Gender, n (%)					
Male	29 (60.4)	53 (58.2)	33 (49.3)	132 (54.1)	247 (54.9)
Female	19 (39.6)	38 (41.8)	34 (50.7)	112 (45.9)	203 (45.1)
Nutritional status, n (%)					
Severely underweight	2 (4.2)	0	0	5 (2.0)	6 (1.3)
Underweight	1 (2.1)	2 (2.2)	6 (9.0)	13 (5.3)	23 (5.1)
Normal	31 (64.6)	61 (67)	41 (61.2)	175 (71.7)	308 (68.5)
Overweight	8 (16.6)	14 (15.4)	11 (16.4)	27 (11.2)	60 (13.3)
Obese	6 (12.5)	14 (15.4)	9 (13.4)	24 (9.8)	53 (11.8)

Table 2. Classification and severity of asthma

Parameters	Asthma only (n=48)	Asthma and AR (n=67)
Classification of asthma, n (%)		
Wheeze ever	14 (29.16)	13 (19.40)
Current asthma	6 (12.5)	5 (7.46)
Clinically-diagnosed asthma	28(14.58)	49 (4.48)
Severity of asthma, n (%)		
No asthma attack	32 (66.67)	33 (49.25)
Mild	16 (33.33)	22 (32.84)
Moderate	0	12 (17.91)
Severe	0	0

Table 3. Classification and severity of AR

Parameters	AR only (n=91)	Asthma and AR (n=67)
Classification of AR, n (%)		
Previous rhinitis	81 (89.0)	59 (88.1)
Current rhinitis	1 (1.1)	0
Clinically-diagnosed AR	9 (9.9)	8 (11.9)
Severity of AR, n (%)		
No activity disturbance	42 (46.2)	29 (43.3)
Mild (a little bit disturbing)	42 (46.2)	29 (43.3)
Moderate (quite disturbing)	7 (7.6)	8 (11.9)
Severe (very disturbing)	0	1 (1.5)

asthma and not in exacerbation was the same as healthy controls.[12,13] The systematic reviews also concluded that eCO level is influenced by asthma severity, in which chronic asthma patients had higher eCO than those with intermittent asthma.[12,13] Some cross-sectional studies also documented that children with persistent and severe asthma had higher eCO compared to healthy controls and children with episodic mild asthma.[10,15,16] Another study revealed that asthmatic children had increased eCO during exacerbation, but eCO returned to normal after beta-2-agonist and sodium cromoglicate therapy.[17]

The expression of heme oxygenase 1 (HO-1) enzyme is associated with the severity of inflammation and carboxyhaemoglobin (HbCO) levels, in which more severe exacerbation of asthma leads to more severe inflammatory processes.[18] Therefore, in severe inflammation the increased HbCO levels lead to increased eCO level. So, in children with mild asthma, and not in an exacerbation period as our subjects' expression of the HO-1 enzyme may be similar to children without asthma.[16]

Levels of eCO in AR have been inconsistent in previous studies. A systematic review reported that eCO in AR was not significantly different from that of healthy subjects.[13] Inflammation in AR is considered to be less than in asthma, so HO-1 enzyme expression in AR is lower than in asthma. Therefore, eCO level in AR is lower than in asthma. Other studies found that eCO levels were higher in subjects with AR and upper respiratory tract infection (URTI) group compared to healthy subjects, but the study had a very limited number of subjects.[11] In our study, the eCO level in AR subjects was not different from that of healthy controls either (P=0.19). Some possible causes of this result are as follows: 1) the majority of the children with AR had mild and not disturbing AR severity; 2) the study subjects were not in an exacerbated condition, so the degree of inflammation was mild and increased eCO level was not significant; 3) the possible use of intranasal corticosteroid inhalers or other medication which was not included in the questionnaire.

One of the strengths of our study was evaluating the eCO level in children with both asthma and AR, which is hardly ever reported. Allergic rhinitis is acknowledged to be a common comorbidity in children with asthma. Combined AR and asthma syndrome or the 'united airway disease' concept is based on the united location, manifestation, inflammation process, trigger of attack, epidemiologic connection, pathophysiology, and outcome.[19] The AR is a risk factor of asthma and vice versa, whereas 40% of AR patients are asthmatic, and 80% of asthmatic patients also have AR simptoms.[1,20]

In our study, we found that children with both asthma and AR had higher eCO level compared to healthy children. This observation may be due to the united airway disease phenomenon, in which inflammation in asthma conditions and AR occurs in one airway unit.[20,21] Chronic inflammation in asthma and AR is related to oxidative stress in the lungs and respiratory tract due to increased reactive oxygen species from inflammatory cells that play a role in the inflammatory process.[22] This is consistent with the results of a study stating that AR was a very important predictor in increasing eCO levels in asthmatic subjects compared to healthy individuals.16 In individuals with coexisting asthma and AR, exposure to allergens in the airways can cause wider inflammation, with more HO-1 enzyme expression,[16] and resulting in eCO levels which are higher than those in persons who have only asthma or AR, and healthy controls. As such, patients with coexisting asthma and AR need comprehensive management of both asthma and AR for better quality of life.

In conclusion, eCO level from *Smokerlyzer®* examination still can not be used to diagnose asthma nor AR, but might be useful for manage the asthma or AR control. Hence further study about eCO level of the various asthma and AR severity in children need to be done.

Conflict of interest

None declared.

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