

Increased carbon monoxide in exhaled air of patients with seasonal allergic rhinitis

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Summary

Background Carbon monoxide (CO) can be detected in exhaled air and is increased in asthmatic patients. However, it is uncertain whether exhaled CO is increased in patients with allergic rhinitis.

Objective and methods To study whether exhaled CO is increased in patients with allergic rhinitis, exhaled CO concentrations were measured on a CO monitor by vital capacity manoeuvre in 86 patients with seasonal allergic rhinitis during and out of the cedar pollen season.

Results During the season, exhaled CO concentrations were 3.6 ± 0.3 p.p.m. and decreased to 1.2 ± 0.1 p.p.m. out of the season. The values of exhaled CO out of the season were similar to those in age-matched non-smoking healthy control subjects (1.2 ± 0.1 p.p.m.). Exhaled CO concentrations were significantly higher in patients with symptoms than in those without symptoms ($P < 0.01$). Exhaled CO concentrations in patients did not differ significantly among oral and nasal exhalation, and oral exhalation with an expiratory resistance ($P > 0.20$).

Conclusion These findings suggest that allergic rhinitis increases the concentration of CO in exhaled air and increases in exhaled CO may be derived from lower airways.

Keywords: airway inflammation, alveolar macrophages, asthma, carbon monoxide, haem oxygenase, nitric oxide

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Introduction

Haem oxygenase (HO) generates the gas carbon monoxide (CO) as a product of haem degradation [1]. Measurements of CO in exhaled air have identified elevated levels in asthma, and it has been proposed that this may serve as an indirect marker of airway inflammation [2]. Consistent with this, inhaled corticosteroid therapy, which has been shown to reduce airway inflammation, is associated with a reduction in exhaled levels of CO in asthma [2]. The infiltration of T lymphocytes, eosinophils and mucosal-type mast cells is observed in the nasal specimens obtained from symptomatic seasonal allergic rhinitis [3]. Likewise, a number of pro-inflammatory cytokines and chemokines such as interleukin

(IL)-1, IL-5 and IL-6 have been identified as possible mediators in rhinitis [4–6]. However, no measures of CO in nasal exhaled air have been made in rhinitis, in which there is a common form of inflammation similar to that described in asthma in the lower airways.

Thus to determine whether levels of CO are increased in patients with seasonal allergic rhinitis, measurements of CO in exhaled air were made during nasal and oral exhalation in patients with seasonal allergic rhinitis, and the results were compared with the same measurements made in nonatopic volunteers.

Materials and methods

Subjects

We studied 30 normal non-smoking control subjects and 86

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patients with seasonal cedar pollen-sensitive rhinitis who did not have asthma. In the 30 control subjects there was no history of respiratory or cardiovascular disease. None of these 30 control subjects were receiving long-term medication. All patients had a history of seasonal allergic rhinitis for at least 2 years, with upper airway but not lower airway symptoms. None of the patients with seasonal rhinitis had perennial rhinitis, nasal polyposis, sinus disease, chronic nasal obstruction, or other serious illness. A positive cutaneous response (skin prick test that produced a 3-mm weal) to cedar pollen was identified in all patients but none of the controls had positive skin test responses to a battery of standard antigens including cedar pollen.

Study protocol

The study was performed in February during the cedar pollen season in Japan. To assess the clinical symptoms, subjects were instructed to record their clinical symptoms every day over 1 week before the study. The presence of symptoms (nasal obstruction, rhinorrhea and sneezing) were recorded and the intensity of each symptom was evaluated every day. The intensity of symptoms were scored according to a 4-point scale: 0, no symptoms; 1, mild symptoms (present but not troublesome); 2, moderate symptoms (frequently troublesome but not sufficient to interfere with normal daily activity or night-time sleep); and 3, severe symptoms (sufficiently troublesome to interfere with normal daily activity or night-time sleep) [7]. Mean value of the daily total symptom score of the three symptoms over 1 week before the study was used to define two subgroups: patients with a mean value of a daily total symptom score below 1 (called without symptoms) and patients with a mean value of a daily total symptom score above 2 (called with symptoms) [8]. None of the patients were receiving topical or oral corticosteroids or topical cromoglycate preparations at least 3 weeks before the study. However, patients with symptoms were treated with topical cromoglycate or topical corticosteroid after CO measurement. All patients with seasonal allergic rhinitis were also studied in May, out of the cedar pollen season, at a time when they were free of symptoms. Physical characteristics, pulmonary function test results, and Brinkman's index (number of

cigarettes/day $\times$ year) are shown in Table 1. The study was approved by the Tohoku University Ethics Committee, and subjects gave informed consent.

Measurement of exhaled CO

Exhaled CO was measured on a portable Bedfont EC50 analyser (Bedfont Technical Instruments Ltd, Sittingbourne, UK) using the method described by Jarvis and colleagues [9] in which subjects are asked to exhale fully, inhale deeply, and hold their breath for 20 s before exhaling rapidly. Inhalation and exhalation were performed both orally and nasally. For oral exhalation a mouthpiece was used and a nose clip fitted, whereas for nasal measurements subjects exhaled through a tight-fitting nasal mask (Nasal Continuous Positive Pressure [CPAP] mask; Respironics, Monroeville, PA, USA) [10]. This procedure was repeated three times, with 1 min of normal breathing between each repetition, and the mean value was used for analysis [2]. Background CO values (0–1 p.p.m.) were obtained prior to the subject readings. To avoid analysis with a value of exhaled CO concentration below 1.0 p.p.m., the background level was subtracted from the average value obtained from three sequential manoeuvres in each patient. The exhaled CO concentrations were always values above 1.0 p.p.m. before subtracting the background level throughout the experiments.

To examine the contribution of the upper airway to the level of exhaled CO, an external resistance was added to maintain a mouth pressure greater than 20 mmHg during oral exhalation. A continuous pressure in the mouth greater than 20 mmHg is reported to close the velum during expiration to exclude nasal CO that may leak throughout expiration in the presence of an open velum [11]. Mouth pressure was measured by a differential pressure transducer (Model MP45; Validyne, Northridge, CA, USA) and displayed on an oscilloscope (Tektronix 5103 N; Tektronix Corp., Beaverton, OR, USA).

Prior to the start of the study, the analyser was calibrated with a mixture of 50 p.p.m. CO in air [9]. Exhaled CO concentration measured by the Bedfont EC50 analyser is reported to correlate closely with blood carboxyhaemoglobin concentration over the range of values encountered in smokers and non-smokers [12,13].

Table 1. Physical characteristics and pulmonary function test results

Subjects	Age (years)*	Sex (M/F)*	FEV (% pred.)*	FEV ₁ (% pred.)*	Brinkman's index
Control (<i>n</i> = 30)	37 $\pm$ 3	12/18	101 $\pm$ 5	96 $\pm$ 4	0
Allergic rhinitis (<i>n</i> = 86)	39 $\pm$ 2	32/54	98 $\pm$ 5	94 $\pm$ 5	0

* Values presented as means $\pm$ SE.

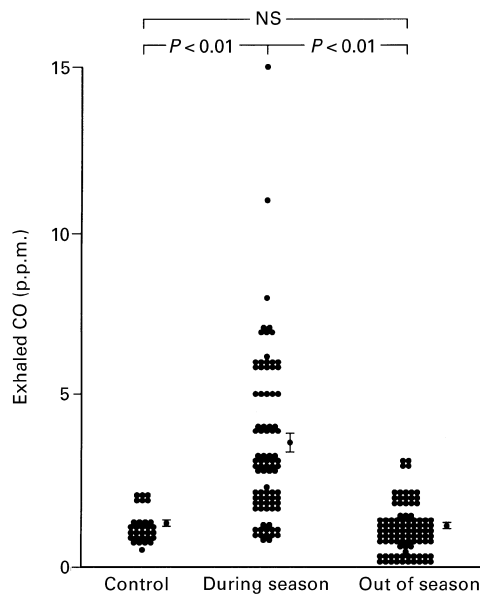


Fig. 1. CO concentrations in exhaled air in control subjects ($n=30$) and patients with allergic rhinitis ($n=86$) during and out of the cedar pollen season. Mean values $\pm$ SE are indicated by closed circles with error bars

Statistical analysis

Results are reported as mean $\pm$ SE. Statistical analysis was made with the Wilcoxon rank test. Significance was accepted at $P < 0.05$.

Results

Mean CO concentration exhaled orally was 1.2 ± 0.1 p.p.m. in healthy control subjects. In patients with allergic rhinitis, the exhaled CO was significantly higher during the cedar pollen season than that in control subjects (Fig. 1). However, the exhaled CO values out of the season in patients with allergic rhinitis did not differ significantly from those in control subjects ($P > 0.20$) (Fig. 1). Orally exhaled CO values during the cedar pollen season were significantly higher in patients with symptoms than in those without symptoms (Table 2).

However, exhaled CO values did not differ significantly

among oral and nasal exhalation, and oral exhalation with an expiratory resistance in both control subjects and patients with allergic rhinitis ($P > 0.20$) (Table 3).

Discussion

We have shown that seasonal cedar pollen-sensitive rhinitis is associated with an increase in exhaled CO in patients during the cedar pollen season, and that levels of exhaled CO are higher in patients with symptoms than in those without symptoms. Furthermore, there is a reduction in exhaled CO out of the cedar pollen season to values that are similar to those in nonatopic control subjects. This suggests that allergic rhinitis increases the production of CO in the respiratory tract.

The exhaled CO concentration was similar between oral and nasal exhalation in both control subjects and patients with allergic rhinitis, suggesting that the increase in CO may be derived from the lower respiratory tract. This is consistent with the results that the exhaled CO concentration did not differ between oral exhalation with and without an expiratory resistance. The resistance closes the velum during expiration and excludes nasal CO that may leak throughout expiration in the presence of an open velum [11].

In contrast with symptomatic rhinitis, lower airway symptoms were not present in any patients, even in the absence of asthmatic symptoms. However, sub-clinical inflammation has been reported in patients with allergic rhinitis with evidence of eosinophil accumulation [14,15] and enhanced collagen deposition in the lower airways [15]. It is therefore possible that in patients with seasonal allergic rhinitis, inflammatory cell accumulation occurs within the lower airways but does not reach a sufficient threshold to induce symptoms. The identification of enhanced CO levels in such patients suggests that CO measurement is a sensitive method of monitoring airway inflammation.

Increased levels of nasal nitric oxide (NO) have been reported in patients with allergic rhinitis [8,16,17]. Since patients with rhinitis show expression of inducible NO synthase in nasal epithelial cells [18], it is suggested that the increased levels of NO in nasal air of patients with rhinitis may be derived from inducible NO synthase expression in nasal mucosa [17]. However, the present study

Table 2. Mean total symptom score and exhaled CO in patients with and without symptoms. Values presented as mean $\pm$ SE

	Age (years)	Sex (M/F)	Mean total symptom score	Exhaled CO (p.p.m.)
Allergic rhinitis				
With symptoms ($n=60$)	40 ± 3	22/38	$4.2 \pm 0.5^*$	$4.0 \pm 0.3^*$
Without symptoms ($n=26$)	37 ± 5	10/16	0.3 ± 0.1	2.5 ± 0.3

* $P < 0.01$ from without symptoms

Subjects	Exhaled CO (p.p.m.)		
	Oral exhalation	Nasal exhalation	Expiratory resistance
Control (<i>n</i> = 30)	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
Allergic rhinitis (<i>n</i> = 86)	3.6 ± 0.3	3.8 ± 0.4	3.5 ± 0.3

Table 3. Exhaled CO concentration in oral and nasal exhalation, and oral exhalation with an expiratory resistance. Values presented as mean ± SE

suggests that the contribution of nasal mucosa to increased CO production in exhaled air of patients with allergic rhinitis may be minimal. This is consistent with results from a recent report that upper airways do not influence exhaled CO levels in healthy subjects [19]. The source of increased levels of exhaled CO in patients with allergic rhinitis is uncertain. However, alveolar macrophages have been shown to express HO-1, an inducible form of HO [20], and elevated levels of exhaled CO are reported to be associated with an increased expression of HO-1 in airway macrophages in asthmatic patients [21]. These data suggest that the increased levels of exhaled CO in patients with allergic rhinitis may also be derived from HO-1 expression in alveolar macrophages.

Although we have shown an elevation of exhaled CO in patients with allergic rhinitis during the cedar pollen season that decreases out of season, it is uncertain whether the level of CO in exhaled air is merely an indicator of lower airway inflammation or causative link in the biology of allergic rhinitis. However, the demonstration that allergic rhinitis is associated with a high level of exhaled CO suggests a potential role for this mode of measurement to monitor disease activity and airway inflammation in patients with allergic rhinitis.

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