An Assessment of the Role of Exhaled Carbon Monoxide in Acute Asthmatic Exacerbations in Hospitalised Patients

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ABSTRACT

Exhaled carbon monoxide is a useful marker of airway inflammation in untreated asthma. Whether exhaled CO is clinically useful in steroid treated patients in a hospital setting is uncertain. We therefore studied exhaled CO as a marker of asthma severity in clinical practice.

Non-smoking "acute" asthmatics (hospitalised; n=33), "stable" asthmatics (n=35), and healthy controls (n=22) were recruited. Exhaled CO, peak expiratory flow (PEF) and FEV_1 were measured daily (hospitalised cases) or once only (stable outpatients). Inpatients were managed without knowledge of the results.

Exhaled CO levels in acute asthmatics (initial levels), stable asthmatics and controls were similar (median=2.0 ppm, h=5.05, p=0.08). In *acute asthmatics*, initial exhaled CO did not correlate with duration of hospitalisation, doses of intravenous corticosteroids, doses of nebulised salbutamol, PEF (% predicted) or FEV_1 (% predicted). In *stable asthmatics*, exhaled CO did not correlate with corticosteroid dosage, PEF (% predicted) or FEV_1 (% predicted).

In the setting of acute hospitalised asthma patients, exhaled CO may not add any further to clinical management. This may in part be due to prior treatment with corticosteroids.

Keywords: carbon monoxide, asthma, clinical practice

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INTRODUCTION

Asthma is a disorder of the airways characterised by intermittent reversible airway obstruction, nonspecific bronchial hyperresponsiveness and chronic airway inflammation. Bronchial mucosal biopsies[1,2] and bronchoalveolar lavage[2] obtained by fibreoptic bronchoscopy are the current "gold standards" for assessment of airway inflammation. Less invasive methods of assessing airway inflammation include the measurement of nitric oxide (NO) in exhaled breath[3,4] and eosinophils in induced sputum[5]. However, these tests cannot be easily done nor are they readily available. It is thus not surprising that clinical guidelines for asthma severity and treatment are still based on assessment of symptoms, signs, functional status, and objective measurement of airway function[6,7].

Recently, Zayasu et al[8] and Horvath et al[9] found that exhaled carbon monoxide (CO) may reflect inflammation in the asthmatic lung. Exhaled CO levels were higher in untreated asthmatics than in non-smoking healthy controls[8,9], and together with sputum eosinophil counts decreased significantly after four weeks of inhaled corticosteroid therapy[8]. Exhaled CO levels have also been shown to increase during an asthmatic exacerbation[10]. Therefore, measurement of exhaled CO may be a simple method of detecting and assessing airway inflammation, and assessing anti-inflammatory treatment in asthma. They also found that treated asthmatics already on inhaled corticosteroids and stable for two weeks and non-smoking healthy controls had similar exhaled CO levels[8,9]. However, in both these studies, steroids were started only after CO measurements were started.

In the hospital setting, many patients who present with acute asthma would already be on steroid therapy (at least inhaled) prior to presentation. If exhaled CO levels in this setting predict the subsequent course or severity of the episode, it could help guide the attending physician in management decisions. We therefore studied exhaled CO levels in both stable and acute hospitalised asthmatics to see if they correlated with the severity of an exacerbation. This simple non-invasive marker of the severity of an exacerbation would add to the clinical assessment of these patients.

METHODS

Patients

We prospectively recruited consecutive "acute" and "stable" asthmatics between January and July 1998.

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Table I. Physical characteristics and pulmonary function.

	Subjects (n)	Age (year)	Sex	PEF (% pred)	FEV_1 (% pred)
Controls	22	39 ± 14	11M/11F	NA	NA
Acute asthmatics	33	43 ± 17	11M/22F	54.6 ± 22.1*	51.8 ± 24.9*
Stable asthmatics	35	41 ± 14	18M/17F	89.3 ± 19.7	75.8 ± 21.4

* Initial values on the morning after admission
* Values are mean ± SD

They were lifelong non-smokers, diagnosed to have asthma based on established criteria[6] and had no other pulmonary diseases. Their physical characteristics and pulmonary function are shown in Table I.

The acute asthmatics (n=33) were patients who were admitted for asthma in the hospital's Department of Respiratory Medicine and were recruited on the first morning after admission. Only those able to hold their breath at vital capacity for 20 seconds and perform spirometric measurements were included for analysis. Twenty (61%) were on long term inhaled steroids. The mean dose was 1615 µg/day (standard deviation 1697 µg/day). All were managed by respiratory physicians without knowledge of the exhaled CO levels. All were given intravenous corticosteroids at the Emergency Department and these continued until withdrawn by the physician in charge. Nebulised salbutamol was also given according to symptoms.

The stable asthmatics (n=35) were ambulatory outpatients whose asthma had been stable with no upper respiratory tract infections (URTIs) or exacerbations in the preceding six weeks and whose inhaled corticosteroid dosage remained unchanged for at least one month. Baseline asthma severity was classified according to published guidelines[6].

A control group of 22 healthy non-smoking subjects who had no URTI in the preceding six weeks were also recruited.

Measurements

Exhaled CO was measured with a commercially available portable electrochemical analyser (Bedfont EC-50, Bedfont Scientific Ltd, Kent, England) which was calibrated just prior to the start of the study with a mixture of 50 ppm CO in air. The instrument was zeroed daily before use and the background CO reading (0-1 ppm) was subtracted from the values obtained from the patient. Measurement was made using the method described by Jarvis et al[11], in which subjects are asked to exhale fully, inhale deeply, and hold their breath for 20 seconds before exhaling rapidly into a disposable mouthpiece. This procedure was repeated three times, with one minute of normal breathing between each repetition. The mean of three exhaled CO readings was used for analysis.

Spirometry was measured by the bedside with a portable spirometer (Autospiro AS-600, Minato, Japan) according to standard techniques[12]. The best of three technically acceptable forced expiratory volume in one second (FEV_1) and the best peak expiratory flow (PEF) were used for analyses. All PEF and FEV_1 data were expressed as a percentage of the predicted value rather than as absolute values. Hospitalised patients had the first CO reading taken the morning after admission and readings were taken again in the evenings. The exhaled CO levels were measured twice a day, at approximately the same time, until discharge. Spirometry was measured daily in the morning together with exhaled CO until discharge.

Exhaled CO, PEF and FEV_1 were measured once in stable asthmatics. Only exhaled CO was measured in non-smoking healthy control subjects on one occasion.

Statistical Analysis

All results were expressed as median (25^{th} - 75^{th} percentile) unless otherwise stated. In acute asthmatics, the initial exhaled CO recorded on the morning after admission and the maximum exhaled CO recorded during hospitalisation were used for analysis. For PEF and FEV_1, the initial and worst results during hospitalisation were used for analysis. Kruskal Wallis ANOVA on rank test and Spearman rank correlation test were used for data analyses. Rank sum test (initial exhaled CO) and Student's t test (maximum exhaled CO) were used for comparison between those who were treated and those who were untreated prior to hospitalisation. A p value less than or equal to 0.05 was taken to be significant.

RESULTS

Exhaled CO was reproducible in all subjects and the subject readings on the EC50 analyser were similar among three sequential manoeuvres in non-smoking control subjects [2.0 (1.0-2.0) ppm versus 2.0 (2.0-2.0) ppm versus 2.0 (2.0-2.0) ppm; p=0.756], acute asthmatics [2.0 (1.0-2.3) ppm versus 2.0 (1.0-2.0)

Table II. Exhaled CO in the different study populations.

	Exhaled CO levels
Acute Asthmatics - Initial[a]	2.0 (1.2 - 2.2)
Acute Asthmatics - Maximal[b]	
Stable Asthmatics	2.0 (2.0 - 3.0)
Normals	2.0 (1.7 - 2.0)

• Values used are the median. The 25th to 75th percentile are in brackets.
[a] Initial exhaled CO on admission.
[b] Maximal exhaled CO value obtained during hospital stay.

ppm versus 2.0 (1.0-2.0) ppm; p=0.795), and stable asthmatics [2.0 (2.0-3.0) ppm in all; p=0.956].

Initial exhaled CO in hospitalised acute asthmatics [2.0 (1.2-2.2) ppm] did not differ significantly from exhaled CO in stable asthmatics [2.0 (2.0-3.0) ppm] and healthy control subjects [2.0 (1.7-2.0) ppm; p=0.008] (Table II). Similarly, maximum exhaled CO recorded during hospitalisation [2.7 (1.7-3.0) ppm] in acute asthmatics did not differ significantly from exhaled CO in stable asthmatics and healthy controls (p=0.15).

In *acute asthmatics*, there were no differences in morning exhaled CO levels during the first three days of hospitalisation (median=2.0, 2.0, 1.65 ppm; p=0.771). Similarly, there were no differences in the evening exhaled CO levels from the first to third day (median=1.7, 1.7, 2.35 ppm; p=0.334).

There was no correlation between initial exhaled CO with duration of hospitalisation (r=0.06, p=0.749), doses of intravenous corticosteroid after one outlier with 14 doses of intravenous corticosteroids was excluded (r=0.328, p=0.0667), doses of nebulised salbutamol (r= 0.29, p=0.107), initial percent predicted PEF (r=-0.05, p=0.770), worst percent predicted PEF, initial percent predicted FEV_1 (r=0.02, p=0.917) or worst percent predicted FEV_1. Similarly, there was no correlation between maximum exhaled CO with duration of hospitalisation (r=0.31, p=0.078), doses of intravenous corticosteroids (r=0.385, p=0.029 after excluding one outlier), initial percent predicted PEF (r=-0.04, p=0.833), worst percent predicted PEF (r=-0.0007, p=0.996), initial percent predicted FEV_1 (r=-0.07, p=0.737) or worst percent predicted FEV_1 (r=-0.08, p=0.722).

The initial exhaled CO in those who were on oral or inhaled corticosteroids prior to hospitalisation (n=20, median=1.85 ppm) and those who were untreated (n=13, median=2.00 ppm) did not differ significantly (p=0.883). The maximum exhaled CO in those who were treated (mean=2.4, SD=0.7 ppm) and those who were untreated (mean=2.6, SD=0.9 ppm) prior to hospitalisation did not differ significantly (p=0.355).

In *stable asthmatics*, exhaled CO levels did not correlate with corticosteroid dosage (r=-0.03, p=0.85), percent predicted PEF (r=-0.01, p=0.95) and percent predicted FEV_1 (r=-0.04, p=0.83). There was no difference in exhaled CO levels among mild intermittent (n=14), moderate persistent (n=12) and severe persistent (n=8) asthmatics (median=2.0 ppm, p=0.90). There was only one mild persistent asthmatic.

DISCUSSION

Oxidative stress and reactive oxygen species have been implicated in the pathogenesis of asthma[13] and chronic obstructive lung disease[14]. One of the mechanisms protecting against an oxidative stress is the induction of a stress response protein, heme oxgyenase-1 (HO-1)[15-18]. Increased HO-1 protein expression may be due to the induction of enzyme by inflammatory cytokines and oxidants such as interleukins, tumour necrosis factor-α (TNF-α), interferon-γ, and H_2O_2, which are capable of inducing HO-1 expression in cell line and tissues[16,18]. In the respiratory tract, HO-1 is induced in epithelial cells and infiltrating inflammatory cells[15]. Induced HO-1 catalyses the degradation of heme to bilirubin, an antioxidant that can scavenge hydroxyl radicals in vitro as efficiently as α-tocopherol[18]. The by-products of HO-1 activity are free iron and CO[18]. Therefore, measurement of exhaled CO, a putative index of HO-1 activity, may be a simple method for detecting and monitoring cytokine mediated inflammation and oxidative stress in the respiratory tract and of assessing inflammatory treatment.

Such bench to bedside possibilities for respiratory diseases were heightened with three recent publications which found increased exhaled CO in patients with untreated asthma[8], upper respiratory tract infection (URTI)[19] and bronchiectasis[20]. It is interesting that exhaled CO levels remained high in bronchiectasis treated with inhaled corticosteroids when compared with healthy controls, and that exhaled CO levels were similar in both treated and untreated bronchiectasis. This may be due to the modest response to treatment[21] and the neutrophil dominant airway inflammation in bronchiectasis[22].

We found that treated stable asthmatics and healthy control subjects had similar exhaled CO levels, which is consistent with previous findings[8,9]. In addition, we found that even in asthmatics with acute exacerbation requiring hospitalisation, measured exhaled CO levels were no different from those measured in stable asthmatics and healthy controls. This may be due to the effect

of inhaled corticosteroids, which is known to decrease exhaled CO levels in previously untreated asthmatics[8,9]. The mechanism for this is probably downregulatation of HO-1 production by glucocorticoids[22]. The majority (61%) of the asthmatics with acute exacerbation were treated with inhaled corticosteroids prior to hospitalisation. However, there were no significant differences in exhaled CO levels between treated (n=20) and untreated (n=13) asthmatics with acute exacerbation.

Yamara et al[10] recently found that exhaled CO increased during an asthmatic exacerbation and is seemingly in conflict with our findings. However, our patients who were on inhaled steroids were on much higher doses. Even those not on long term inhaled steroids may have been recently given oral steroids by their primary physicians before admission as their symptoms were likely to be severe prior to admission. All patients were also given intravenous steroids prior to transfer to the wards. As exhaled CO was only measured a few hours later, this may have confounded the outcome.

Furthermore, the "initial" exhaled CO and the maximum exhaled CO recorded during hospitalisation ("maximum" CO) did not always coincide. This was not unexpected as the time course of maximum airway inflammation, and hence HO-1 induction and CO production, depends on the balance of mediators, cytokines and chemokines in the airway[23]. The "initial" exhaled CO during an acute exacerbation may not be at the time of maximum airway inflammation, and this further limits its usefulness as a marker of asthma severity in the clinical setting.

In conclusion, exhaled CO measurement is simple, reproducible and non-invasive. It has been shown to correlate with asthmatic exacerbations. However, prior treatment with oral, inhaled and intravenous steroids may confound the readings. In the setting of an acute hospitalisation where patients are seen with no prior notice and may not be followed up after, exhaled CO as a marker of the severity of an exacerbation in such a setting needs further evaluation as to its clinical utility.

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