

Exhaled carbon monoxide in patients with lower respiratory tract infection

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Abstract The concentration of carbon monoxide (CO) in exhaled air is increased in patients with asthma, bronchiectasis and upper respiratory tract viral infections. However there is no information about the level of CO in patients with lower respiratory tract infection. We studied a group of 35 patients (22 males) aged 45 ± 3 (SEM) years with cough productive of purulent phlegm and pyrexia in a general practice setting. All were non-smokers or ex-smokers and none had a previous history of respiratory problems or diabetes. We measured CO level in exhaled air before and after a course of antibiotics. Therapy was deemed successful when patient no longer complained of cough productive of purulent phlegm. Twenty-eight of 35 patients had elevated CO level at their initial visit. Twenty-two out of 35 patients reported clinical improvement after antibiotic treatment and this was associated with a fall in exhaled CO level from 5.2 ± 0.5 ppm to 2.3 ± 0.3 ppm ($P < 0.0001$). We suggest that simple CO measurements in exhaled air can detect the inflammatory process within the airways caused by infection and that a repeat measurement can be used to assess the nature of inflammation. © 2001 Harcourt Publishers Ltd

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Keywords lower respiratory tract infection; inflammation; carbon monoxide.

INTRODUCTION

Carbon monoxide (CO) is produced in many tissues of the body by the enzyme heme oxygenase-1 (HO-1), which may be induced by inflammation and oxidative stress (1). Since HO-1 has been found in alveolar macrophages (2) and vascular endothelium (3) there have been suggestions that the level of exhaled CO may be a marker of inflammation and oxidative stress in airways. Inflammation and oxidative stress may induce HO-1 and the concentration of CO in exhaled air and therefore CO levels are increased in patients with asthma and other inflammatory lung diseases (4–8). Infection may increase HO-1 expression and a recent study showed increased CO levels in subjects with symptoms of upper respiratory tract viral infections (6). There is no information about the levels of CO levels in patients with symptoms of lower respiratory tract infections. Measurement of exhaled CO is simple and may provide a non-invasive means of monitoring respiratory infections in a general practice setting.

METHODS

The study population consisted of 35 patients (22 males) aged 45 ± 3 (SEM) years, attending a general practice clinic with symptoms of lower respiratory tract infection. All the subjects had a history of cough productive of purulent sputum and pyrexia for at least 3 days. Most of them were non-smokers and only five were ex-smokers, having smoked 5 ± 2 pack-years. None of them were passive smokers. They had no previous history of chest problems or diabetes and were not receiving any long-term medication. All subjects had their smoking status confirmed twice by urine dipstick testing for the presence of nicotine and/or its metabolites (NicCheck Test strips, Dynagen Inc, Cambridge, MA, U.S.A.). After physical examination and completing a medical questionnaire we measured peak expiratory flow (PEF) and CO in exhaled air. Ambient CO level was measured and was subtracted from the value obtained. However according to our previous study ambient air CO concentrations at levels 0–2 ppm do not affect exhaled CO.

Subsequently, all patients were given a course of a wide spectrum antibiotic (amoxicillin 500 mg tds or erythromycin 500 mg qds if they were allergic to penicillin) and asked to come back after 7 days for repetition of the tests. Therapy was deemed successful when the patient no longer complained of cough

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productive of sputum. Exhaled CO was measured by portable Bedfont E50 analyser (Bedfont Technical Instruments Ltd., Sittigbourne, Kent, U.K.) using a single slow exhalation (9).

The ethics committee approved the study.

Statistical analysis

Data are given as means \pm SEM. Comparison between groups was made by a Student's *t*-test. Significance was defined as $P < 0.05$.

RESULTS

Physical examination revealed pyrexia $> 38^{\circ}\text{C}$, but there was no other abnormalities detected. All patients had PEF $< 80\%$ of normal, which did not change after the treatment with antibiotic. During the first visit patients produced sputum samples, which confirmed purulent appearance.

Twenty-eight of 35 patients had elevated CO level at their initial visit compared to 37 normal non-smoking subjects (normal level 2.9 ± 0.2 ppm) (10). Twenty-nine patients were treated with amoxicillin and six with erythromycin.

Twenty-two out of 35 patients reported clinical improvement and this coincided with a fall of exhaled CO level from 5.2 ± 0.5 ppm to 2.3 ± 0.3 ppm [$P < 0.0001$; Fig. 1(a)]. In the remaining 13 patients who did not improve, there were no significant changes in exhaled CO levels, with CO level of 3.8 ± 1.5 ppm at the initial visit and 3.8 ± 1.4 ppm after treatment with antibiotic [$P > 0.05$; Fig. 1(b)]. Since there was a big

difference between the number of patients who were treated either with amoxicillin or erythromycin, it was not possible to make any comparison between exhaled CO level responses in each of the group. Seven patients had 'normal' exhaled CO levels (< 3 ppm) at initial visit. Three of those patients had clinical improvement after the treatment with antibiotic. However, in the other four patients there was no clinical improvement.

DISCUSSION

Our study showed that the majority of patients with clinical symptoms of lower respiratory tract infection had elevated exhaled CO levels. The clinical improvement after the treatment with antibiotics was associated with a reduction of exhaled CO. However, in 13 patients there was no clinical improvement after the treatment with antibiotic. In this group of patients the exhaled CO levels were lower, but statistically not significant, compared to the group who did respond. The reason for that could be that either they were treated with inappropriate antibiotic or they were suffering from a viral infection. In the other similar study there was a significant reduction in exhaled CO level after the upper respiratory tract infection, but the observation period was much longer than in our study (6). Seven patients had 'normal' initial measurement of exhaled CO level (below 3 ppm). However our 'normal' values differed from the other, similar study. If we accepted normal values our patients would have abnormal measurements. It is therefore necessary to establish and unify 'normal' values for the measurement of exhaled CO.

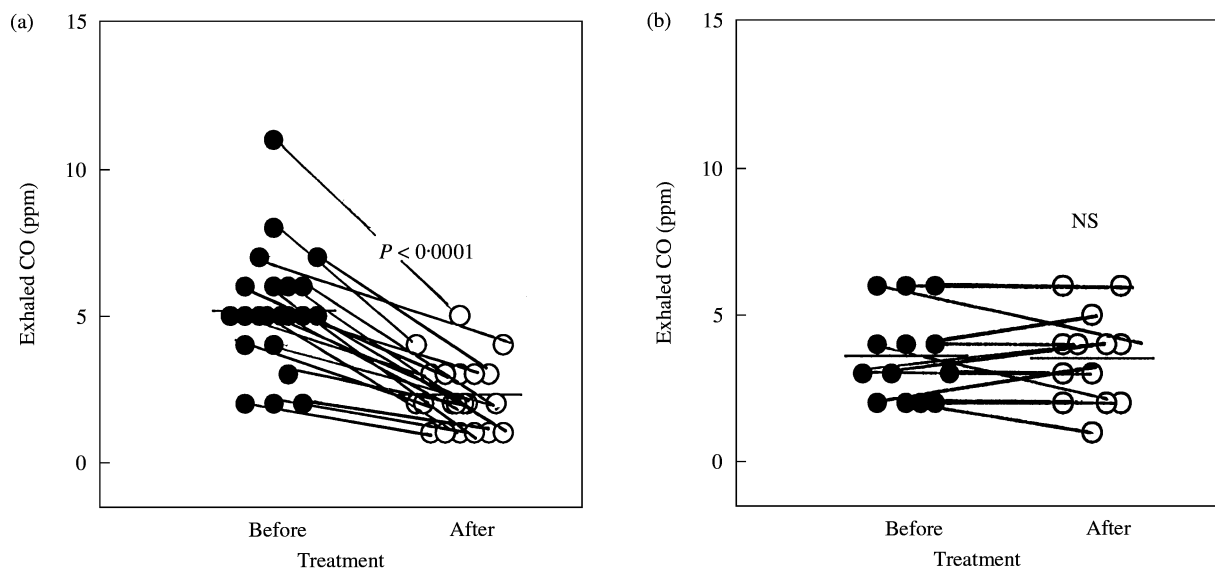


FIG. 1. Exhaled carbon monoxide (CO) before and after antibiotic treatment in two groups of patients with symptoms of lower respiratory tract infection. (a) Patients with clinical improvement; (b) patients without clinical improvement.

Although the exact cellular source of exhaled CO is not known, its elevation may reflect presence of inflammation and/or oxidative stress within airways (11). An elevation in exhaled CO has been reported in patients with mild and acute asthma with a subsequent fall after the treatment with inhaled corticosteroids (4). CO levels were elevated in patients with asthma following allergen challenge (12). More recently, an elevation of exhaled CO has been found in patients with upper respiratory tract infection, which subsequently fell after the recovery (6). Some of the patients in this study also had symptoms of lower respiratory tract infection.

Similarly, nitric oxide (NO), another marker of airways inflammation, has been found to be elevated in subjects with upper respiratory tract infection. NO level subsequently fell after the recovery period (13). Also, an elevated NO has been found in patients with asthma, which fell on treatment with inhaled steroids (14–16).

Our study showed an elevation of exhaled CO level in majority of patients with lower respiratory tract infection, which subsequently fell after the treatment with antibiotics. Bacterial infection may induce production of heme oxygenase, which has been shown to participate in resolution of inflammation in animals (17). Therefore, increased levels of exhaled CO in lower respiratory tract infection may reflect increased inflammation and oxidative stress in airways and could be a single, non-invasive tool for monitoring treatment with antibiotic. We have previously demonstrated an elevation of exhaled CO in patients with bronchiectasis (7) and cystic fibrosis (8), indicating that different types of inflammation may increase exhaled CO and that this measurement is not specific for any particular inflammatory disease of airways. Repeated measurements after treatment with either an inhaled corticosteroid (4,5) or an antibiotic provides information about the control of inflammation. Our study confirmed an elevation of exhaled CO in patients with symptoms of lower respiratory tract infection. The levels of CO subsequently fell after the treatment with antibiotic, which coincided with clinical improvement.

We suggest that simple CO measurement in exhaled air can detect increased inflammatory process within the airways, which has been caused by infection. The return of CO levels to normal after the treatment may be related to the reduction in inflammation. Elevated

exhaled CO levels may provide an early warning signal for an acute infection episode.

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