Exhaled carbon monoxide in lung disease

To the Editor:

We read with interest the paper by ZETTERQUIST *et al.* [1] in which the levels of exhaled nitric oxide (NO) and carbon monoxide (CO) were measured in a group of asthmatic and cystic fibrosis (CF) patients using two different methods. A new fast-response nondisperse infrared (NDIR) CO analyser was used alongside the old electrochemical method and the results obtained with the two methods were compared.

Surprisingly, contrary to what has previously been shown by our own and other groups [2–6], as shown by both methods, the levels of exhaled CO were found to be similar in a group of asthmatic patients and patients with CF compared with normal subjects. The authors conclude that exhaled CO is not a marker of airway inflammation and may derive predominantly from the alveoli, as its exhaled concentrations are not flow-dependent and increase after a breath-hold.

Even though we previously acknowledged that the measurement of exhaled CO may be of more interest in patients with severe asthma compared to those with the mild form of the disease [7, 8], we feel that the measurement of exhaled CO maybe useful in CF patients [5, 6, 8]. We suggest that the discrepancies found may be mainly attributed to different techniques and, ultimately, different methods.

First, ZETTERQUIST *et al.* [1] used the basic Bedfont analyser for the measurement of CO. However, in our previously published studies by us a modified version of the Bedfont analyser was used. In this altered version, the exhalation flow rate was standardised and controlled, and a resistance was added to the exhalation flow to produce enough mouth pressure to close the soft palate allowing the separation of nasal air from exhaled air. Besides controlling these parameters, contrary to what is stated in this paper, we did connect the analyser to a computer and the exhaled CO traces could be studied point by point and in relation to exhaled volumes.

Secondly, in our studies, the exhalation manoeuvre was different from that used in the paper by ZETTERQUIST *et al* [1]. We used a single-breath technique without breath-hold. We agree with the authors that breath-hold increases exhaled CO levels, but in addition, this may also eliminate the bronchial contribution to the total production of CO, which would be biased towards the alveolar component because of alveolar CO diffusion in the bronchial space during the time of breath-hold. This may explain the similar levels of exhaled CO in the studied groups compared to normal subjects.

Thirdly, in this paper, the contamination of exhaled CO with ambient CO was taken into account only in the NDIR method, in which the patients were asked to breathe CO (and NO)-free air. We have previously shown that exhaled CO may be affected by ambient CO and that this influence may be reduced by subtracting ambient CO from exhaled CO [6]. Unfortunately, in this study, this was not considered when analysing the levels of CO obtained with the Bedfont analyser.

In conclusion, the authors of the paper compared the results obtained with two different methods and exhalation techniques. The effect of ambient contamination and breath-hold were not taken into account. Both these variables and the use of different exhalation techniques may explain the discrepancy in the data obtained by ZETTERQUIST *et al.* [1] and the other investigators in this area. Using fast analysers like the nondisperse infrared analyser may not be beneficial by itself if the exhalation technique is not standardised. Furthermore, comparisons of the data obtained by other numerous groups may only be possible if the same technique and methods are used.

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References

1. Zetterquist W, Marteus H, Johannesson M, *et al.* Exhaled carbon monoxide is not elevated in patients with asthma or cystic fibrosis. *Eur Respir J* 2002; 20: 92–99.
2. Zayasu K, Sekizawa K, Okinaga S, Yamaya M, Ohrui T, Sasaki H. Increased carbon monoxide in exhaled air of asthmatic patients. *Am J Respir Crit Care Med* 1997; 156: 1140–1143.
3. Horvath I, Donnelly LE, Kiss A, Paredi P, Kharitonov SA, Barnes PJ. Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. *Thorax* 1998; 53: 668–672.
4. Yamara M, Sekizawa K, Ishizuka S, Monma M, Sasaki H. Exhaled carbon monoxide levels during treatment of acute asthma. *Eur Respir J* 1999; 13: 757–760.
5. Paredi P, Shah PL, Montuschi P, *et al.* Increased carbon monoxide in exhaled air of patients with cystic fibrosis. *Thorax* 1999; 54: 917–920.
6. Antuni JD, Kharitonov SA, Hughes D, Hodson ME, Barnes PJ. Increase in exhaled carbon monoxide during exacerbations of cystic fibrosis. *Thorax* 2000; 55: 138–142.
7. Stirling RG, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Exhaled breath carbon monoxide (CO) is minimally elevated in severe but not mild atopic asthma. *Am J Respir Crit Care Med* 2000; 161: A922.
8. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1693–1722.

From the authors:

We appreciate the interest P. Paredi and colleagues have shown in our article. In their letter, they describe

some differences in the methodologies used and suggest that these differences may explain why our results on exhaled carbon monoxide (CO) in asthma and cystic fibrosis [1] contrast with their previous findings. We agree that it is preferable to use standardised methods, but there is as yet no consensus on standardised methods for exhaled CO measurements.

With regard to possible contamination with nasal CO, we did have our patients exhale against a resistance using one of the two methods. However, in another study, we had not been able to detect any nasal CO formation whatsoever [2], so this may be a minor problem.

Although we used a 15-s breath-hold time before exhalation and they did not, the methods are more or less equivalent in that the patients in their studies exhaled for ~25 s in contrast to 10 s in our study, resulting in the same time for CO diffusion in the alveoli when recording end-tidal CO values. Furthermore, other researchers have used a 20-s breath-hold and still reported elevated CO levels in various respiratory conditions [3–5].

We used CO-free air for inhalation in one of the set-ups because we do not believe that subtraction of inhaled (ambient) CO is a correct procedure. The inhaled CO concentration will affect the concentration gradient for CO over the alveolar membranes (and possibly in the airways), and should not be compensated for by direct subtraction.

Our data primarily indicate an alveolar origin of exhaled CO. For many years now, exhaled CO has been used to detect smoking behaviour, for which this method is sometimes superior, even to urinary cotinine measurements [6]. Exhaled CO is also used to detect haemolysis in the newborn with high sensitivity [7]. In both these cases, the increase in exhaled CO is due to increased levels of carboxyhaemoglobin. Interestingly, it was recently suggested that the increase in exhaled CO in respiratory diseases like asthma is also due to increased carboxyhaemoglobin [8], again indicating an alveolar origin of exhaled CO. The cause of the increased carboxyhaemoglobin levels in respiratory conditions, increased haem breakdown or increased uptake/reduced elimination of inhaled CO, remains to be clarified. However, the latter is indicated by several studies [9–11], and it is well known that exposure to ambient CO (passive smoking, car exhaust) is sufficient to increase exhaled CO [12–13].

In conclusion, we do not agree that the contrasting results in our study depend on the suggested methodological differences. The reason for the disparate findings should be studied further. In any case, we believe that the profound alveolar contribution of CO derived from carboxyhaemoglobin, will make it difficult to use exhaled CO as a marker of airway inflammation.

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References

1. Zetterquist W, Marteus H, Johannesson M, *et al.* Exhaled carbon monoxide is not elevated in patients with asthma or cystic fibrosis. *Eur Respir J* 2002; 20: 92–99.
2. Lundberg JON, Palm J, Alving K. Nitric oxide but not carbon monoxide is continuously released in the human nasal airways. *Eur Respir J* 2002; 20: 100–103.
3. Zayasu K, Sekizawa K, Okinaga S, Yamaya M, Ohrui T, Sasaki H. Increased carbon monoxide in exhaled air of asthmatic patients. *Am J Respir Crit Care Med* 1997; 156: 1140–1143.
4. Yamaya M, Sekizawa K, Ishizuka S, Monma M, Mizuta K, Sasaki H. Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. *Am J Respir Crit Care Med* 1998; 158: 311–314.
5. Monma M, Yamaya M, Sekizawa K, *et al.* Increased carbon monoxide in exhaled air of patients with seasonal allergic rhinitis. *Clin Exp Allergy* 1999; 29: 1537–1541.
6. Secker-Walker RH, Vacek PM, Flynn BS, Mead PB. Exhaled carbon monoxide and urinary cotinine as measures of smoking in pregnancy. *Addict Behav* 1997; 22: 671–684.
7. Stevenson DK, Vreman HJ. Carbon monoxide and bilirubin production in neonates. *Pediatrics* 1997; 100: 252–254.
8. Yasuda H, Yamaya M, Nakayama K, *et al.* Increased blood carboxyhemoglobin concentration in the inflammatory pulmonary diseases. *Am J Respir Crit Care Med* 2001; 163: A50.
9. Togores B, Bosch M, Agusti AG. The measurement of exhaled carbon monoxide is influenced by airflow obstruction. *Eur Respir J* 2000; 15: 177–180.
10. Antuni JD, Ward S, Cramer D, Kharitonov SA, Barnes PJ. Uptake and elimination of exhaled carbon monoxide in patients with interstitial lung disease is related to the degree of impairment of carbon monoxide diffusion capacity. *Am J Respir Crit Care Med* 1999; 159: A220.
11. Graham BL, Mink JT, Cotton DJ. Overestimation of the single-breath carbon monoxide diffusing capacity in patients with air-flow obstruction. *Am Rev Respir Dis* 1984; 129: 403–408.
12. Gourgoulianis KI, Gogou E, Hamos V, Molyvdas PA. Indoor maternal smoking doubles adolescents′ exhaled carbon monoxide. *Acta Paediatr* 2002; 91: 712–713.
13. Cunnington AJ, Hormbrey P. Breath analysis to detect recent exposure to carbon monoxide. *Postgrad Med J* 2002; 78: 233–237.