
CHANGES IN ARTERIAL OXYGEN TENSION CORRELATE WITH CHANGES IN END-EXPIRATORY CARBON MONOXIDE LEVEL

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Schober P, Kalmanowicz M, Schwarte LA, Weimann J, Loer SA. Changes in arterial oxygen tension correlate with changes in end-expiratory carbon monoxide level.

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ABSTRACT. Objective. Carbon monoxide (CO) and oxygen compete for haemoglobin binding sites. While the effects of increased inspiratory oxygen fractions on exhaled carbon monoxide concentrations have been studied previously, the relationships between intravascular oxygen tension, blood carboxyhaemoglobin levels and expiratory CO concentrations remain unclear. We therefore studied the effects of increases in arterial oxygen tension as crucial determinant for the displacement of carbon monoxide from its haemoglobin bond during lung passage. **Methods.** Measurements of end-expiratory CO concentrations (eCO), arterial oxygen tensions and carboxyhaemoglobin concentrations were performed in 19 patients while breathing air and oxygen. **Results.** With increasing PaO₂ (from 11.5 ± 1.9 to 35.2 ± 10.3 kPa) end-expiratory CO concentrations increased from 8.6 ± 4.9 to 16.7 ± 9.4 ppm, $p < 0.001$, with a mean increase of 0.36 ppm CO per kPa increase in PaO₂ (ΔeCO [ppm] = 0.36 * ΔPaO_2 [kPa]). Increases of arterial oxygen tension correlated with increases of end-expiratory CO concentration ($r^2 = 0.33$). Arterial carboxyhaemoglobin concentrations decreased from 1.06 ± 0.37 during air breathing to 0.92 ± 0.35 % after 5 minutes of oxygen inhalation ($p < 0.001$). **Conclusions.** Oxygen-induced increases in exhaled CO correlate with increases in arterial oxygen tensions. Furthermore, oxygen inhalation reduces carboxyhaemoglobin levels, supporting the concept of accelerated CO elimination by oxygen via the lungs.

KEY WORDS. Carbon monoxide, oxygen, haemoglobin.

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INTRODUCTION

In recent years, endogenous carbon monoxide (CO) production has been shown to play a critical role during inflammatory processes [1–4]. In line with this, exhaled CO has been found to be increased in critically ill patients [5–7], and thus may be used as a diagnostic or monitoring tool. We and others have previously shown that high inspired oxygen concentrations, that are often used during mechanical ventilation in these patients, increase exhaled CO concentrations [8, 9] and may therefore interfere with exhaled CO measurements. Since oxygen and CO compete for identical haemoglobin binding sites [10] and this competition occurs in the vascular rather than the alveolar compartment, we hypothesize that the oxygen-induced displacement of CO from haemoglobin largely depends

on pulmonary capillary rather than alveolar oxygen tension. Pulmonary capillary oxygen tension is inaccessible to clinical measurements and arterial oxygen tension (PaO₂) is often used as a surrogate. However, especially in the critically ill, PaO₂ may not be predicted from FiO₂ due to altered gas diffusion through the alveolo-capillary membrane and widely scattered ventilation-perfusion ratios as part of inflammatory pulmonary diseases. Therefore, this study in 19 patients scheduled for cardiac surgery was based on the hypothesis that PaO₂ rather than the FiO₂ may correlate with exhaled CO levels.

METHODS AND MATERIALS

After approval by the Institutional Review Board and informed consent, patients scheduled for cardiac surgery ($n = 19$, Table 1) were routinely instrumented preoperatively with arterial lines. Among the patients were two current smokers who were abstinent for more than 12 hours prior to surgery.

Measurements

End-expiratory CO (eCO in parts per million, ppm) concentrations were measured with an electrochemical analyzer (microPac, Dräger, Lübeck, Germany) with a sampling rate of 0.5 Hz. According to the manufacturer's specifications CO is measured in a range from 0 to 400 ppm with a reproducibility of (3%). In order to obtain samples of end-expiratory gas at room air patients were asked to exhale slowly from total lung capacity to expiratory reserve volume over a period of approximately 20 seconds into a disposable mouthpiece connected to the analyzer via a 30 cm hose. At the end of expiration gas flow ceased and the end-expiratory gas remaining in the hose (volume 5.9 ml) served as the sample for determination of alveolar CO concentrations. Technical aspects of the measurements including time-course and reproducibility have been described in detail previously and we

Table 1. Demographic data (mean \pm SD).

Gender (female/male)	3 female/16 male
Age (years)	69.9 \pm 7.5
Height (cm)	171.5 \pm 8.5
Weight (kg)	83.3 \pm 12.7
Baseline haemoglobin (g dl ⁻¹)	12.1 \pm 1.3
Baseline arterial P _a O ₂ (kPa)	11.5 \pm 1.9
Baseline arterial P _a CO ₂ (kPa)	5.1 \pm 0.5

have shown that a stable alveolar plateau is reached during expiration [8]. This plateau value was defined as end-expiratory carbon monoxide concentration.

All measurements were performed in a non-smoking area (operating theatre). Before each measurement, ambient CO levels as well as CO concentrations within the oxygen reservoir were measured to exclude exogenous CO sources.

Arterial oxygen tension (PaO₂) and arterial carboxyhaemoglobin levels (CO-Hb) were measured using a standard clinical blood gas analyzer (ABL 725, Radiometer, Copenhagen, Denmark).

Study protocol

Baseline measurements of eCO, PaO₂, CO-Hb were performed after patients have been rested for 10 minutes in a supine position. Subsequently, patients breathed oxygen via a tightly fitting face mask for 5 minutes until expiratory oxygen fraction was above 0.9 in all patients excluding dilution of alveolar gas by residual nitrogen. Then, all measurements were repeated as described above.

Statistics

Data are presented as mean \pm standard deviation. Differences between values obtained during air and oxygen breathing were analyzed by two-tailed, paired *t*-test (Prism 4.0 statistical package, GraphPad Software, San Diego, CA, USA). Correlations were calculated using Pearson's correlation coefficient (r^2). A $p < 0.05$ was considered statistically significant.

RESULTS

Oxygen inhalation resulted in an increase in PaO₂ from 11.5 \pm 1.9 to 35.2 \pm 10.3 kPa ($p < 0.001$, Figure 1a), as well as an increase in eCO levels from 8.6 \pm 4.9 to 16.7 \pm 9.4 ppm ($p < 0.001$, Figure 1b). As shown in Figure 2 the increase in PaO₂ was associated with an increase in eCO in all patients with exception of one patient in which eCO levels remained constant. The mean increase in eCO per increase in PaO₂ ($\Delta eCO/\Delta PaO_2$) was 0.36 \pm 0.28 ppm/kPa with a significant correlation between these two parameters ($r^2 = 0.33$, $p < 0.01$). Moreover, while eCO increased, arterial carboxyhaemoglobin concentrations decreased from baseline values of 1.06 \pm 0.37 during air breathing to 0.92 \pm 0.35 % while inhalation of oxygen ($p < 0.001$, Figure 3). ECO concentrations did not correlate with arterial carboxyhaemoglobin concentrations ($P = 0.83$).

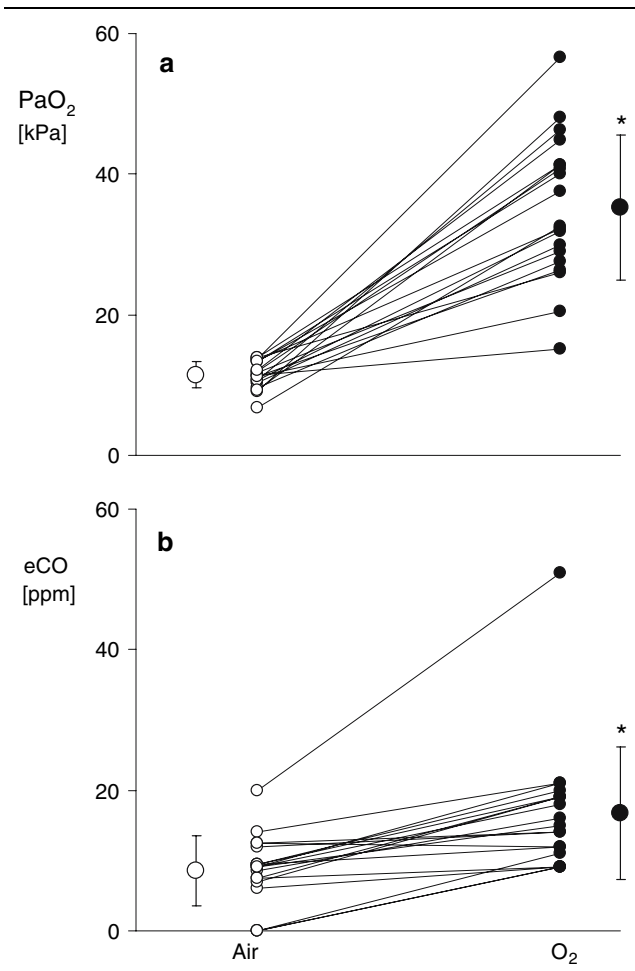


Fig. 1. Arterial oxygen tensions (PaO_2 , Figure 1a) and end-expiratory carbon monoxide concentrations (eCO , Figure 1b) of patients ($n = 19$, individual values and mean \pm SD, $\star < 0.001$) while breathing air (open circles) and oxygen (closed circles). Open and closed circles representing the same patient are connected by a line.

DISCUSSION

Exhaled carbon monoxide originates from exogenous (ambient CO) and endogenous sources. Endogenous CO production is mainly due to degradation of haeme and the first and rate-limiting step of this metabolic pathway is catalyzed by microsomal haeme oxygenase [1–3, 11]. Of the three known isoforms, haeme oxygenase-1 is inducible by oxidative stress and, therefore, elevated exhaled carbon monoxide levels were suggested to be a non-invasive marker of local airway and systemic inflammation [5–7, 12–15]. Moreover, elevated expiratory CO concentrations may be of diagnostic value in patients with suspected carbon monoxide intoxication [16]. Since critically ill patients as well as patients with inflammation or intoxication are often treated with oxygen, awareness

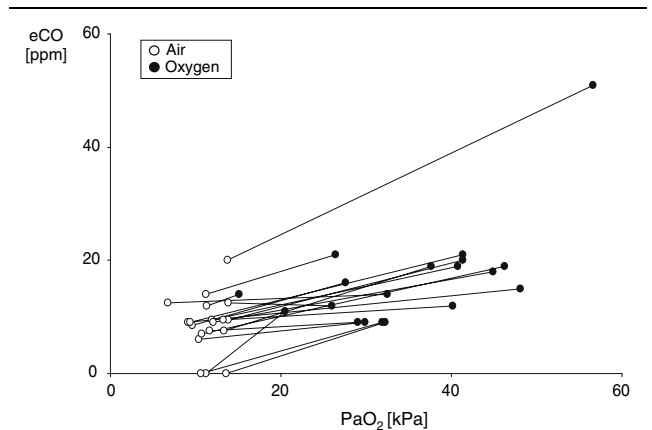


Fig. 2. Arterial oxygen tension (PaO_2) and corresponding end-expiratory carbon monoxide concentration (eCO) of patients ($n = 19$) while breathing air (open circles) and oxygen (closed circles). Open and closed circles representing the same patient are connected by a line. The mean slope corresponding to the mean increase in end-expiratory CO concentration per kPa increase in PaO_2 ($\Delta eCO/\Delta PaO_2$) is 0.36.

of effects of oxygen inhalation on expiratory and blood CO concentrations may be helpful in the interpretation of the obtained measurements.

We measured exhaled carbon monoxide concentrations in patients in supine position breathing room air or oxygen. CO concentrations were quantified with an electrochemical analyzer as described previously [8]. The last portions of the exhaled gas represented samples of alveolar air and were defined as endexpiratory CO concentrations. All measurements were performed in a non-smoking area. In addition, we determined CO concentrations in the ambient air to ensure that all measured CO represented endogenous carbon monoxide of the patients. During inhalation of oxygen, we measured

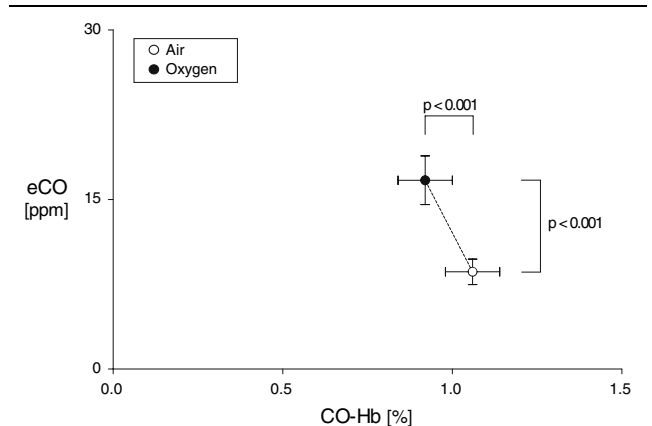


Fig. 3. Arterial carboxyhaemoglobin ($CO-Hb$) and end-expiratory carbon monoxide concentration (eCO) of patients ($n = 19$, mean \pm SEM) while breathing air (open circles) and oxygen (closed circles).

in- as well as expiratory oxygen concentrations to exclude that the alveolar gas was diluted by residual or co-inspired nitrogen. Endexpiratory oxygen fractions corresponding to alveolar fractions were above 0.9 in all patients.

It is well established that oxygen competes with CO for the same haemoglobin binding sites, which is the basis for treating CO intoxications by inhalation of high oxygen concentrations. Indeed, we and others have recently demonstrated that increases in inspiratory oxygen fractions are associated with an increase in exhaled CO levels [8, 9]. However, this may only be valid for lung regions with a normal pulmonary gas exchange through the alveolar-capillary membrane, i.e. a ventilation-to-perfusion ratio close to 1. Accordingly, ventilation-perfusion mismatch, as it occurs during lung diseases such as COPD (increased dead-space ventilation) or the acute respiratory distress syndrome (increased intrapulmonary shunting), may result in both impaired oxygen uptake and CO excretion through the lungs. Therefore, we hypothesized that increases in exhaled CO levels may correlate with increases in arterial oxygen tensions (PaO_2). Indeed, breathing oxygen through a tightly fitted face mask caused an increase in PaO_2 in all patients. On the basis of a wide range of oxygen-induced changes in PaO_2 (3.7 to 42.8 kPa) in our patients, we found that increases in PaO_2 significantly correlated with increases in eCO. Moreover, we demonstrated oxygen inhalation to reduce CO-Hb levels, supporting the concept of accelerated CO elimination by oxygen via the lungs. In accordance to our findings, Weaver et al. observed in a retrospective analysis in patients an inverse correlation between arterial oxygen tension and carboxyhaemoglobin half-life and thus increased elimination [17]. However, Weaver et al. studied changes in blood CO levels during continuous O_2 breathing, not during acute PaO_2 changes. Our study aimed to investigate the relationship between acute changes in PaO_2 and changes in endexpiratory CO concentration. To the best of our knowledge, the data show for the first time prospectively a correlation between ΔeCO and ΔPaO_2 . While our data suggest that eCO levels obtained in acutely ill patients receiving oxygen therapy may be erroneously high because of a high PaO_2 it must be emphasized that these data only apply to acute changes of PaO_2 . However, patients may be treated with higher inspiratory oxygen concentrations for a longer period of time and it seems unlikely that acute eCO changes in this study can reliably represent stable eCO levels during hours of oxygen therapy. Thus our data may only serve as a qualitative advisory but do not allow estimations of PaO_2 -adjusted eCO concentrations. Moreover, we did not find a correlation between eCO concentrations and arterial CO-Hb levels, so that CO-Hb concentrations may not be estimated from eCO

concentrations. Further work is needed to determine the value of measuring eCO in acutely ill patients, and/or CO intoxicated patients, and the best procedures for these clinical scenarios.

In summary, our study demonstrates that oxygen-induced increases in exhaled CO correlate with increases in arterial oxygen tensions. This is likely explained by an accelerated carbon monoxide elimination during lung passage.

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