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Increased Carbon Monoxide in Exhaled Air of Critically Ill Patients

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Heme oxygenase produces carbon monoxide (CO) during breakdown of heme molecules primarily in liver and spleen. Recent data suggest that CO is also produced in the lungs. CO is excreted by exhalation via the lungs. A number of inflammatory agents induce the expression of heme oxygenase, possibly leading to increased CO production. To investigate whether critical illness results in increased CO production we measured the CO concentration in exhaled air in 30 critically ill patients and in healthy controls (n = 6). Critically ill patients showed a significantly higher CO concentration in exhaled air (median 2.4 ppm, 95% CI 1.0–7.0 ppm vs median 1.55 ppm, 95% CI 1.2–1.7 ppm, P = 0.01) as well as total CO production (median 20 ml/min, 95% CI 8 to 90 ml/min vs median 13.5 ml/min, 95% CI 11 to 19 ml/min, P = 0.026) compared to healthy controls. No correlation was found between CO concentration in exhaled air and carboxyhemoglobin concentration in arterial and central venous blood (P > 0.05). The increase of CO concentration in exhaled air in critical illness suggests an induction of inducible heme oxygenase (HO-1) and might reflect the severity of illness.

Key Words: **carbon monoxide; heme oxygenase; human; critical illness.**

Heme oxygenase (HO) is the rate limiting enzyme in the degradation of heme, producing biliverdin, iron and carbon monoxide (CO) (1). Three genetic isoforms of the enzyme have been identified: the inducible form HO-1 (also called heat shock protein 32) and the constitutive forms HO-2 and HO-3 (1–3). The constitutive forms are distributed throughout the body with high activities in the brain (1). HO-1, inducible by its substrate heme, is predominantly expressed in liver and spleen. Beside of heme HO-1 is highly inducible by a number of oxidative agents (1, 2) and is ubiquitously expressed and active, especially in lung tissue (4). Inflammatory airway diseases are associated with increased CO in exhaled air, suggesting an induction of HO-1 in the respiratory tract (5–7).

Apart from its role in heme catabolism HO and its product CO is hypothesized to have multiple functions in the organism. CO, similarly to the gaseous molecule nitric oxide, mediates neural transmission and regulates the vascular tone via activation of the soluble guanylate cyclase. Its role in the regulation of hepatic vascular resistance has been demonstrated (8). Heme oxygenase and its products mediate protection in atherogenesis and hypoxia (9). There is increasing evidence that HO-1 has antioxidative properties (2, 10). As oxidative stress induces HO-1 and results in increased activity of HO-1 (1, 2), oxidative stress possibly results in an increase in endogenous CO-production (9). According to current knowledge, CO generated in the tissues is bound to hemoglobin (carboxyhemoglobin) and exhaled via the lungs. Recently it has been shown that in critically ill patients the level of carboxyhemoglobin is higher compared to healthy controls (9, 11, 12). In this study we investigated whether the concentration of CO in exhaled air of critically ill patients is increased compared to healthy subjects.

METHODS

The local ethics committee waived the need for informed consent, since the measurement of CO concentration in exhaled air is noninvasive and blood gas analysis was routinely performed for medical care. We measured exhaled CO concentrations on a CO monitor (Draeger-Werke, Luebeck, Germany) in critically ill patients (n = 30) and in healthy non-smoking controls (n = 6). CO production was calculated by CO concentration in exhaled air multiplied by minute volume. The 6 healthy controls with a mean age of 27 ± 3.1 years were free of respiratory infections for at least 4 weeks prior to the study and did not receive any regular medication. They breathed spontaneously via a mouthpiece connected to a ventilator (EVITA 4, Draeger-Werke, Luebeck, Germany). The critically ill patients (mean age ± SEM, 66 ± 2.9 years) had been mechanically ventilated (EVITA 4, Draeger-Werke, Luebeck, Germany) for 5 ± 1 days prior to measurement. Carboxyhemoglobin was measured in arterial (COHba) and central venous (COHbv) blood in critically ill patients and the difference was calculated (COHba-v). Arterial and central venous blood was sampled

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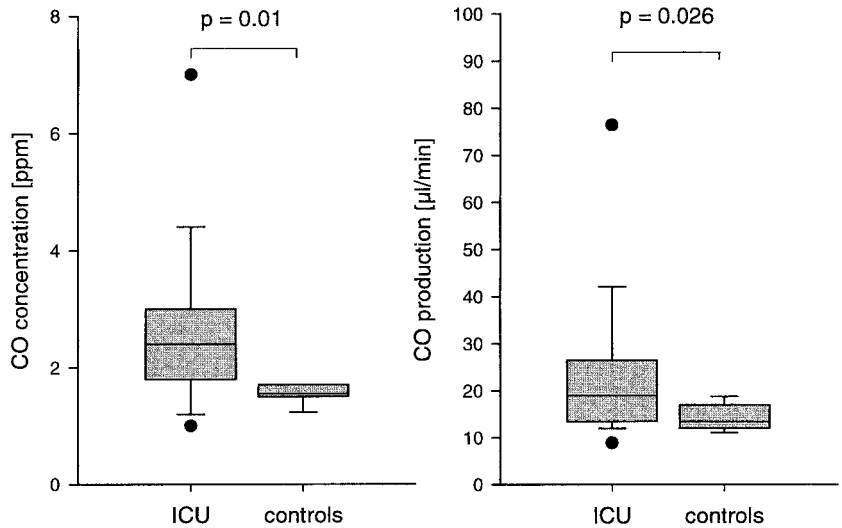

FIG. 1. CO concentration in exhaled air and CO production in critically ill patients (ICU) and healthy controls (control). Boxes, 25th to 75th percentiles, with centerline as median; SE bars, 10th to 90th percentiles; dots, 5th and 95th percentiles; $P = 0.01$: significantly higher CO concentration in exhaled air in critically ill patients compared to healthy controls by Mann–Whitney Rank Sum test. $P = 0.026$: significantly higher CO production in critically ill patients compared to healthy controls by Mann–Whitney Rank Sum test.

anaerobically in heparinized tubes (Sarstedt, Nümbrecht, Germany). The samples were immediately analyzed by a blood gas analyzer/oxymeter (ABL 620; Radiometer AB, Copenhagen, Denmark). The results are expressed as median, 95% confidence interval (CI). The data were analyzed using Mann–Whitney Rank Sum test. Correlation analysis was performed with the Pearson Product Moment Correlation. Significance was accepted at $P < 0.05$.

RESULTS

Critically ill patients showed significantly higher CO concentrations in exhaled air compared to healthy controls (median 2.4 ppm, 95% CI 1.0 to 7.0 ppm vs median 1.55, 95% CI 1.2 to 1.7, $P = 0.01$) (Fig. 1). CO production, calculated by CO concentration in exhaled air and respiratory minute volume, was significantly higher in critically ill patients compared to controls (median 20 ml/min, 95% CI 8 to 90 ml/min vs median 13.5 ml/min, 95% CI 11 to 19 ml/min; $P = 0.026$) (Fig. 1). In critically ill patients, CO concentration in exhaled air and CO production, respectively, did not correlate with carboxyhemoglobin in arterial and central venous blood (Fig. 2), with COHba-v and with age.

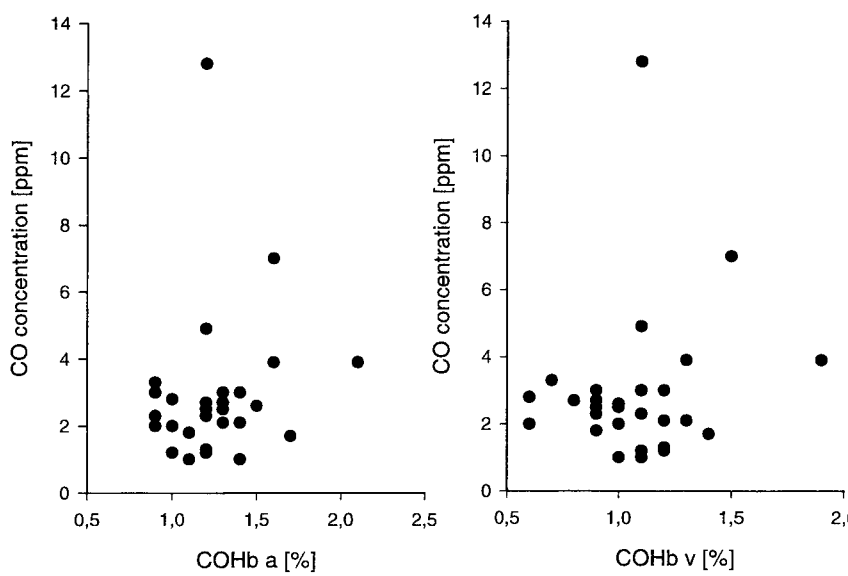

FIG. 2. Arterial carboxyhemoglobin (COHba) and central venous carboxyhemoglobin (COHbv) are plotted against the corresponding CO concentration in exhaled air of critically ill patients. No significant correlation by Pearson Product Moment Correlation ($P < 0.05$).

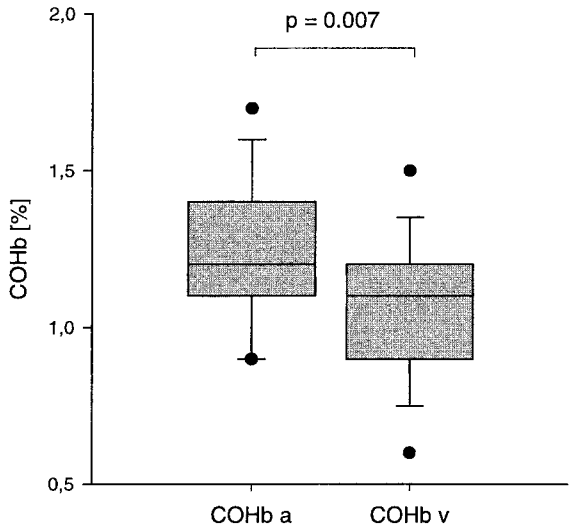

FIG. 3. Carboxyhemoglobin in arterial (COHba) and central venous blood (COHbv) in critically ill patients. Boxes, 25th to 75th percentiles, with centerline as median; SE bars, 10th to 90th percentiles; dots, 5th and 95th percentiles; $P = 0.007$: significant higher COHba vs COHbv levels in critically ill patients by Mann–Whitney Rank Sum test.

COHba was significantly higher compared to COHbv ($P = 0.007$) (Fig. 3). Data are shown as boxes (25th to 75th percentiles) with centerline as median, SE bars (10th to 90th percentiles), and dots (5th and 95th percentiles).

DISCUSSION

The major finding of the presented study is the significantly higher CO concentration in exhaled air in critically ill patients compared to healthy controls. There was no correlation between CO concentration in exhaled air and carboxyhemoglobin. Similar to previous findings (11) we observed a significantly higher concentration of carboxyhemoglobin in arterial compared to central venous blood.

Oxidative stress can provoke induction of HO-1. HO-1 has been shown to play an important role in adaptation and defense against oxidative stress (2, 4, 10, 13, 14). In contrast to these findings recent studies could also demonstrate that the suppression of HO-1 can lead to cell protection (15, 16). Depending on the experimental setting, HO-1 function can result in both cell protection and cell injury (17). Little is known about the mechanism by which HO-1 might provide benefit in oxidative stress: HO may protect cells against oxidative injury by degrading the pro-oxidant heme and producing the antioxidant bilirubin (18). Also, evidence suggests, that the product CO mediates cell protection (19). The observed increase in CO concentration in exhaled air in critically ill patients suggests an increase in HO-1 activity, possibly due to an induction of HO-1 in critically illness. As CO concentration in exhaled air, similar to CO_2 concentration, might vary, depending on the rate and volume of ventilation, we calculated the CO production as a parameter, which might be less dependent on the ventilatory rate and volume. The CO production, similar to the CO concentration, was significantly higher in the critically ill. The higher levels of carboxyhemoglobin in critically ill patients compared to healthy controls (11) support the hypothesis that critically illness results in increased expression and activity of HO-1. Although CO production and CO concentration in exhaled air and carboxyhemoglobin were increased in critically ill patients, similar to recent studies (20) no correlation could be found between CO concentration in exhaled air and carboxyhemoglobin. This observation might be due to the nonlinear behavior of the binding of CO to hemoglobin (21).

The higher concentration of carboxyhemoglobin in arterial compared to central venous blood support the hypothesis of pulmonary CO production. It might be argued that this difference is due to a CO production in the heart. A CO production in the myocardium would result in increased levels of carboxyhemoglobin in the coronary sinus which is drained into the right artrium and can therefore not contribute to higher COHb levels in the arterial system. A possible CO production in the endocard of the left ventricle resulting in increasing arterial COHb concentrations could be excluded because COHb measured in canine pulmonary artery was significantly lower than COHb measured in the left artrium (Weber, T., 1999, personal communication).

As CO concentration in exhaled air and CO production are increased in critically ill patients CO concentration in exhaled air might reflect the severity of illness. With regard to antioxidant properties of HO-1/CO the activity of HO-1 and therefore the CO concentration in exhaled air may also indicate the ability of the organism to protect itself against oxidative stress. Outcome studies should investigate this question.

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