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Arterio-Venous Carboxyhemoglobin Difference Suggests Carbonmonoxide Production by Human Lungs

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Carbon monoxide is hypothesized to be produced by the enzyme heme oxygenase predominantly in liver and spleen, bound to hemoglobin, and excreted by the lungs. Thus, venous carboxyhemoglobin is expected to be higher or equal to arterial carboxyhemoglobin. Unspecific inflammatory stimuli have been shown to induce heme oxygenase in lung tissue possibly leading to pulmonary carbon monoxide production. Arterial and central venous carboxyhemoglobin levels were measured in critically ill patients on the third day of ICU stay (n = 59) as well as in otherwise healthy humans prior to orthopedic surgery (n = 29). Arterial and central venous carboxyhemoglobin were higher in ICU patients than in healthy humans, respectively. In both groups, arterial carboxyhemoglobin was significantly higher than central venous carboxyhemoglobin. The arterio-venous carboxyhemoglobin differences were similar in both groups. The data suggest (a) increased CO-generation in critical illness and (b) pulmonary CO-production in healthy and critically ill humans. © 1998 Academic Press

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

Heme oxygenase (HO) is the rate limiting enzyme of endogenous carbon monoxide production. HO activity is high in systemic organs like liver, bone marrow and spleen (5). Recent experimental work emphasized that the inducible isoform heme oxygenase-1 (HO-1) may also be expressed in lung tissue in response to oxidant stress (2). The functional significance of HO/HO-1 and their product carbon monoxide in health and disease is not completely understood: It has been speculated that CO, similar to nitric oxide, may play a role in the regulation of cell function and communication (5).

According to current knowledge, CO generated in the tissues is bound to hemoglobin and to be exhaled *via* the lungs (3, 5). This implies a high CO content of the central venous blood as compared to the arterial blood. However a reciprocal relationship of arterial (aCOHb) and central venous (vCOHb) carboxyhemoglobin fraction was incidentally observed in blood of critically ill patients sampled for routine blood gas analysis performed by oximetry. In addition, carboxyhemoglobin fractions seemed to increased in critical illness. Therefore, we systematically studied arterial and central venous carboxyhemoglobin fractions in healthy subjects and critically ill patients. In case, critical illness is associated with systemic production of CO, the right atrial carboxyhemoglobin fraction (vCOHb) should be higher than or equal to the arterial carboxyhemoglobin fraction (aCOHb). In case HO-1 expressed in the lungs produces large amounts of CO, aCOHb may be higher than vCOHb.

METHODS

The local ethics committee waived the need for informed consent, since blood gas analysis was routinely performed for medical care. We measured aCOHb and vCOHb in critically ill patients (n = 59) on their third day in the intensive care unit (ICU). This time period was chosen to allow HO-1 to be expressed in response to the noxious stimuli responsible for the life threatening condition of the patients. Otherwise healthy humans (n = 29) prior to orthopedic surgery served as controls (CTRL). Arterial and right atrial blood was sampled anaerobically in heparinized tubes (Sarstedt, Nümbrecht, Germany). The samples were immediately analyzed by a blood gas analyzer/oximeter (ABL 620; Radiometer AB, Copenhagen, Denmark). The results are expressed as mean ± standard error of the mean. The data were analyzed using Student's t-test for unpaired data and paired data (between group comparison and within group comparison, respectively). Significance was accepted at $p < 0.05$.

RESULTS

In both groups, aCOHb was significantly higher than vCOHb suggesting pulmonary production of CO (Fig.

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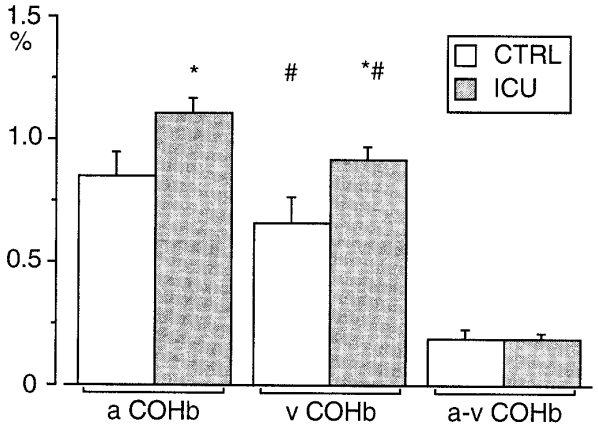

FIG. 1. a COHb, arterial carboxyhemoglobin; v COHb, central venous carboxyhemoglobin; a-v COHb, arterio-venous carboxyhemoglobin difference. ICU, critically ill patients; CTRL, healthy humans. *p < 0.05 ICU vs. CTRL, #p < 0.05 v COHb vs. a COHb.

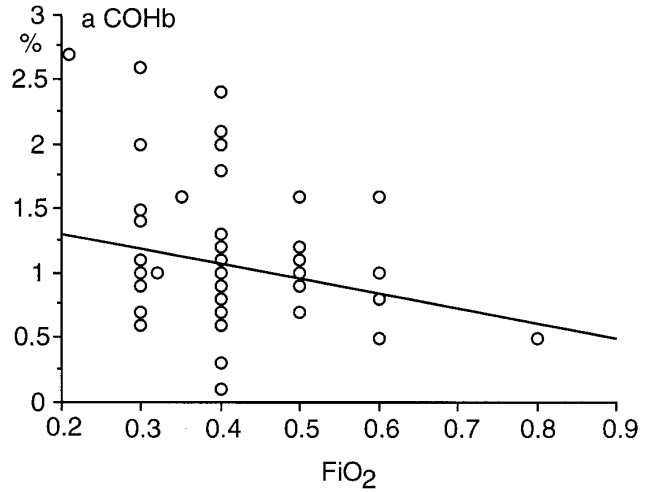

FIG. 3. The arterial carboxyhemoglobin fraction (a COHb) of the ICU patients is plotted against the corresponding inspiratory oxygen fraction (FiO_2). The variables are not significantly correlated ($p = 0.06$, $r^2 = 0.05$).

1). Both, aCOHb as well as vCOHb, were significantly higher in the ICU patients. However, the arterio-venous COHb difference was comparable between the groups (Fig. 1). The correlation between the arterio-venous oxyhemoglobin difference and the arterio-venous carboxyhemoglobin difference, although significant, was very weak ($r^2 = 0.08$, Fig. 2).

DISCUSSION

The present study has two major findings: First, carboxyhemoglobin levels were higher in critically ill patients as compared to healthy subjects. Second, in healthy humans as well as in critically ill patients, the carboxyhemoglobin fraction in the central venous blood is lower than in the arterial blood.

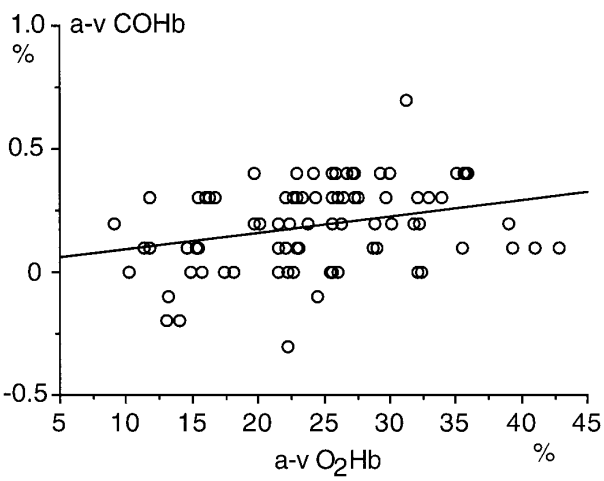

FIG. 2. The arterio-venous carboxyhemoglobin difference (a-v COHb) is plotted against the corresponding arteriovenous oxyhemoglobin difference (a-v O_2Hb). Despite statistical significance ($p < 0.05$) the correlation is very weak ($r^2 = 0.08$).

A positive arterio-venous carboxyhemoglobin difference was observed in both groups suggesting pulmonary production of carbon monoxide. The arterial-venous gradient of COHb necessitates loss of CO during passage through the systemic vascular bed. Spontaneous conversion of COHb to oxyhemoglobin has a slow reaction kinetic, and thus, can not be the cause of arterio-venous COHb difference. Due to systemic CO production, the arterio-venous gradient of COHb actually underestimates the amount of COHb which has to be metabolized or converted in the systemic circulation. We determined cardiac index and arterial and mixed venous COHb fraction in additional eight ICU patients with a pulmonary artery catheter in place. Minimal systemic consumption of CO was estimated to be 60 mL/h per m^2 body surface area, which is far more than the physiological production of 0.4 mL/h previously calculated (5). The site of COHb metabolism is unknown. The distribution of exogenous radioactive CO has suggested the transfer of CO to extravascular spaces, e.g. the liver, but failed to detect significant conversion of exogenous CO to CO_2 (6).

The conclusions are based on the assumption that COHb determined by oximetry reflects CO content of the blood. Since the arterio-venous COHb difference showed only a very weak correlation to the arterio-venous O_2Hb difference alteration of the COHb dissociation curve caused by changes in O_2Hb does not explain the observed arterio-venous COHb difference.

The results are further supported by a previous report of an arterio-venous difference of CO tension (0.07 mmHg and 0.03 mmHg in the arterial and venous

blood, respectively) (1). Likewise, in a heterogeneous population of patients with suspected CO poisoning, the mean arterio-venous COHb difference was 0.15 %, but did not reach statistical significance (7).

The data presented are not completely compatible with current knowledge. They suggest pulmonary production and systemic metabolism of CO. The amount of CO metabolized in this pathway is estimated to be about tenfold higher than previously assumed.

In ICU patients, the COHb fractions are elevated suggesting a physiologic role for HO-1 in critical illness. High inspiratory oxygen fractions have been shown to induce HO in rats (4). Although the ICU patients received elevated inspiratory oxygen fractions, it seems unlikely that oxygen-stress induced CO-production of HO-1 increased pulmonary CO release for the following reasons: First, there was no significant correlation between the inspiratory oxygen fraction and the arterial COHb fraction (Fig. 3). Second, the arterio-venous COHb difference was similar in healthy and in critically ill patients. Thus, the increased COHb fractions of the ICU patients are likely to be caused by systemic production.

The present study confirms the hypothesis, that increased CO production caused by HO-1 induction takes place in critical illness. The functional relevance of this pathway is not clear. Whether COHb may serve as a marker of severity of illness and whether manipulation of the HO-1/CO-pathway may offer any therapeutic option, has to be investigated in further studies.

REFERENCES

1. Bartlett, D. (1968) *Arch. Environ. Health* **16,** 719–727.
2. Choi, A. M., and Alam, J. (1996) *Am. J. Respir. Cell Mol. Biol.* **15,** 9–19.
3. Coburn, R. F., Blakemore, W. S., and Forster, R. E. (1963) *J. Clin. Invest.* **42,** 1172–1178.
4. Lee, P. J., Alam, J., Sylvester, S. L., Inamdar, N., Otterbein, L., and Choi, A. M. (1996) *Am. J. Respir. Cell Mol. Biol.* **14,** 556–568.
5. Marks, G. S., Brien, J. F., Nakatsu, K., and McLaughlin, B. E. (1991) *Trends Pharmacol. Sci.* **12,** 185–188.
6. Tobias, C. A., Lawrence, J. H., Roughton, F. J. W., Root, W. S., and Gregersen, M. I. (1945) *Am. J. Physiol.* **145,** 253.
7. Touger, M., Gallagher, E. J., and Tyrell, J. (1995) *Ann. Emerg. Med.* **25,** 481–483.