ISSN 2466-488X (Online) doi:10.5937/sjait1702007T

Original article

CARBOXYHEMOGLOBIN CHANGES IN RELATION TO INSPIRED OXYGEN FRACTION DURING GENERAL ANESTHESIA

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Abstract

Introduction: Measurement of carboxyhemoglobin could be a new method for evaluation of the severity of inflammatory airway disease, acute organ dysfunction, or stress by surgery and anesthesia. To use this measurement during mechanical ventilation, it is important to clarify the effects of factors that interfere with carboxyhemoglobin levels. The aim of our study was to investigate the perioperative changes of carboxyhemoglobin to inspired oxygen fraction during general anesthesia and mechanical ventilation. Our second aim was to evaluate the effect of preoxygenation on the level of carboxyhemoglobin.

Methods: The study included 30 patients scheduled for urologic surgery under general endotracheal anesthesia, aged 18–60 years, divided into two groups. The study group comprised patients who were smoking cigarettes or tobacco pipe, while the control group included non-smokers. In both groups carboxyhemoglobin levels were determined preoperatively, after preoxygenation, and one hour after induction in anesthesia.

Results: carboxyhemoglobin levels were decreased after preoxygenation in both groups. One hour after induction in anesthesia under mechanical ventilation with inhaled fraction of a mixture of O2 (50%) and air (50%) the average values of carboxyhemoglobin between the two groups were different. The average values of carboxyhemoglobin between the two groups in all three time points were statistically significantly different (p=0.00).

Conclusion: Changes in carboxyhemoglobin concentrations in arterial blood occur during general anesthesia and mechanical ventilation, although these amplitudes are small when compared to carbon monoxide intoxication. It is likely that organ perfusion and functions are affected by these monoxide gas mediators during surgery.

***Key words**: carboxyhemoglobin, inspired oxygen fraction, general anesthesia*

INTRODUCTION

Heme oxygenase (HO) produces carbon monoxide (CO) during the breakdown of heme molecules (1). Synthesized CO diffuses out of cells, enters the blood to form carboxyhemoglobin (COHb) and is transported to the lungs, where it is excreted in the ambient air (2). Thus, COHb levels could reflect the induction of HO-1. The inhalation of tobacco smoke containing up to 5% carbon monoxide can substantially raise the level of COHb in the blood, thus tobacco smoke is the major source of exogenous CO (3). COHb levels have been reported to increase in inflammatory airway disease (4,5), severe sepsis (6), and in critically ill patients (7). Exhaled CO and arterial COHb increase after surgery under both general and spinal anesthesia, which may be due to oxidative stress caused by anesthesia or surgery (8). Endogenous CO production calculated by COHb levels, correlates with the severity of acute illness and might reflect the severity of acute organ dysfunction (9). Thus, measurement of COHb during mechanical ventilation could be a new method for evaluating the severity

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of inflammatory airway disease, acute organ dysfunction, or stress by surgery and anesthesia. To use this measurement during mechanical ventilation, it is important to clarify the effects of factors that interfere with COHb levels. High fractions of inspired oxygen (FiO_2) and mechanical ventilation are often used in critically ill patients or during general anesthesia. High FiO_2 is generally used to treat patients with CO poisoning, as it increases elimination of CO and increases exhaled CO. It is important to understand the effects of the FiO_2 on CO elimination when monitoring exhaled CO, apart from the setting of CO poisoning, in mechanically ventilated patients. To our knowledge, very little has been published regarding the effects of changes of FiO_2 on COHb levels in mechanically ventilated patients. One study we were able to find in the literature demonstrated that pulmonary elimination of CO increased markedly, but transiently, with inspiration of FiO_2 1.0 (10). Since it is difficult to metabolize CO *in vivo*, and CO binds with high affinity to hemoglobin, it is easy to measure the endogenous production of CO as COHb using spectrophotometry (6). To determine the precise effects of changes of FiO_2 on COHb, we initially investigated the effects of changes of FiO_2 on COHb levels in mechanically ventilated patients during general anesthesia. Second, to determine the time course of the changes of COHb levels by FiO_2, we investigated the effects of preoxygenation with inhalation of FiO_2 1.0 for three minutes on arterial COHb concentrations.

METHODS

Subjects

This prospective clinical study was performed as a pilot study at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation and Intensive Care in Skopje. The study was conducted after the approval by the Ethics Committee at the Medical Faculty (nº: 03-4407/8) and the obtained signed informed consent by every patient. We enrolled 30 consecutive patients scheduled for elective urologic surgery under general endotracheal anesthesia, aged 18–60 years, under physiological score for preoperative assessment of health – ASA (American Society of Anesthesiologists) 1 and 2. The study excluded all patients having surgery under local or regional anesthesia, patients with any history of respiratory disease, pregnant patients, and transplant patients. The patients were assigned into two groups: Group 1 (n=15) smokers (smoking ≥10 cigarettes or 30 grams of pipe tobacco per week) and Group 2 (n=15) never-smokers (those who had never smoked cigarettes or pipe tobacco) (11).

Study design

All patients underwent standard preoperative protocol for nothing per mouth (for 6 hours), were normothermic and premedicated with oral Diazepam 5 mg 90 min before surgery. The standardized anesthesia protocol was applied in all patients. After preoxygenation with 100% O_2/ 6L/min, for 3 minutes, the induction was started with midazolam 1-2 mg fentanyl (2-10 μg/kg) and propofol (1-2 mg/kg). The intubation was facilitated with rocuronium bromide 0.6 mg/kg. Following induction of anesthesia all patients were manually ventilated for 2 min. After two minutes the patients were intubated and mechanically ventilated with inhaled fraction of a mixture of O_2 (50%) and air (50%). Mechanical ventilation was pressure controlled/volume guarantied I:E/1:2, PEEP 5 cmH_2O. Tidal volume was 6-8 ml/kg, respiratory rate was 12. The anesthesia was maintained with continuous infusion of propofol 0.1 – 0.2 mg/kg/min, fentanyl 1-2 mcg/kg and rocuronium bromide 0.3 mg/kg.

Measurements

Arterial blood gas analysis was performed at three time points: T_0 - before surgery under respiration with room air (baseline value); T_1 - after preoxygenation with 100% O_2 for 3 minutes with 6L/min flow, and T_2 - one hour after induction in anesthesia under mechanical ventilation with inhaled fraction of a mixture of O_2 (50%) and air (50%). Level of COHb was determined using a heparinized blood sample that was collected by puncture from peripheral artery. COHb, total Hb, and partial pressure of carbon dioxide (PCO_2 mmHg) and oxygen (PO_2 mmHg) in arterial blood samples were performed by blood gas analyzer (SIEMENS RAPID Point 500 Systems). COHb was analyzed spectrophotometrically using its specific absorption and reference wavelengths. The analyzer runs a zero

calibration of the optical system against a colorless calibration fluid at least every 4 hours to guarantee accuracy. Other biochemical measurements and electrolyte levels were determined by standard laboratory methods.

Statistical analysis

Continuous variables are reported as medians and ranges, and categorical variables are expressed as percentages. Statistical analysis was performed by analysis of variance and difference test. P value less than 0.5 was considered statistically significant. All analyses were performed with the SPSS statistical software.

RESULTS

The pilot study enrolled 30 patients in both groups from the period of January 2017 till April 2017. Between both groups of patients, the baseline demographic characteristics were similar with respect to sex, age, weight, height BMI and ASA. The baseline demographics and clinical characteristics of patients are shown in Table 1.

Table 2 presents the characteristics of the surgery and in table 3 are presented the hemodynamic data of the patients. In both, non-smoking and smoking groups, 30% of the interventions were laparoscopic. The average duration of all of the surgeries was 185.667 ± 15.667 min. Fluid therapy for the first perioperative hour was similar in both groups 1120 ± 211.11 for the smoking group and 1100 ± 207.01 for the non-smoking group. In five cases of Group 1 and in eight cases of Group 2 blood transfusion was performed after completion of the measurements of COHb concentration in arterial blood samples. Oxygen saturation was stable and no significant morbid events occurred during surgeries. Effects of changes of FiO_2 on COHb levels are presented in Table 4.

In the smoking group, COHb was significantly higher at all three time points than in the non-smoking group, and decreased after preoxygenation. After the increase of FiO_2 on 100% for three minutes during the period of preoxygenation COHb levels decreased rapidly. After the decrease of FiO_2 with mixture of O_2 (50%) and air (50%) levels of COHb increased gradually over one hour.

The values of COHb were statistically significantly different in the smoking compared to non-smoking group (from 2.1 ± 1.02 vs. 1.92 ± 0.97 vs. 2.0 ± 1.05) for smoking group and (from 0.47 ± 0.27 vs. 0.47 ± 0.39) for non-smoking group. The

Table 1. Demographic and clinical characteristics (Mean ± SD)

Parameters	Group Smokers n=15	Group Non-smokers n= 15	P
Sex M/F	11/4	10/5	NS
Age	50.2 ± 12.84	49.93 ± 13.99	NS
ASA I/II	0/15	2/13	NS
BMI (m^2)	25.84 ± 3.5	25.92 ± 2.76	NS

Abbreviations: F - female; M – male; ASA- American Society of Anesthesiologist, BMI-Body Mass Index; NS-Not significant ($p > 0.05$)

Table 2. Characteristics of the surgery (Mean ± SD)

Groups	Surgery Open/Laparoscopic	Anesthesia time (min)	Operation time (min)	Blood transfusion (no/yes)	Transfusion unit
Smokers n=15	11/4	143.3 ± 62.38	174.66 ± 68.2	10/5	1
Non-smokers n=15	11/4	159.33 ± 64.65	196.6 ± 67.65	7/8	1.4
Operation smokers / non-smokers	Nephrectomy (7/6) Varicocele repair (2/2) Radical prostatectomy (3/4) Radical cystectomy (3/3)				

Table 3. Hemodynamic data of the patients

		Smokers (n=15)	Non-smokers (n=15)
HR - T_0		82.26 ± 12.62	81.73 ± 8.09
HR – T_1		71.93 ± 12.04	64.26 ± 7.55
HR – T_2		74.13 ± 11.75	74.13 ± 11.75
BP - T_0		147.2/ 85.4 ± 20.53/18.57	152.133/84.66 ± 19.6/10.01
BP – T_1		120/67.26 ± 13.2/7.44	114.73/70.4 ± 8.36/9.98
BP – T_2		123.6672.6 ± 19.88/6.73	123.4/75.2 ± 8.95/8.1
Fluids infusion	≤ 6 (ml kg^{-1} h^{-1})	n=1	n=1
	6 to 9 (ml kg^{-1} h^{-1})	n=1	n=2
	9 to 13 (ml kg^{-1} h^{-1})	n=13	n=12

Values are expressed as mean ± standard error of the mean.
T_0 - preoperative; T_1 - after preoxygenation; T_2 - one hour after induction in anesthesia; HR - heart rat; BP – blood pressure.

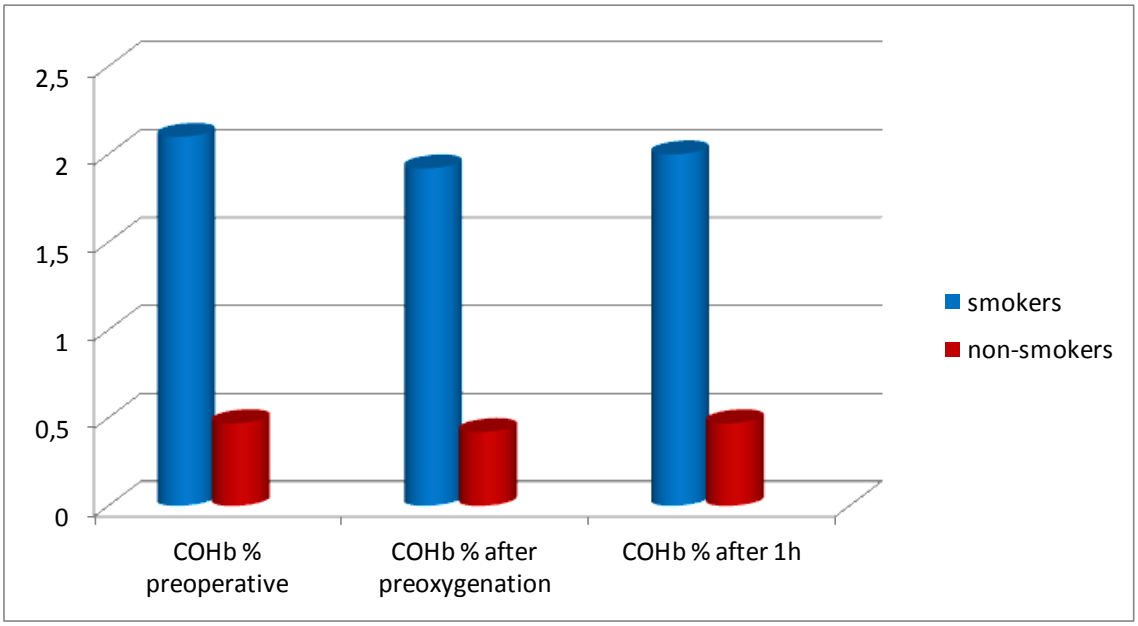
Table 4 . Perioperative changes in carboxyhemoglobin in the Smoking and Non-smoking Group with different FiO_2

	T_0 – Room air	T_1 – FiO_2 100%	T_2 - FiO_2 50%
Group Smokers n=15			
COHb %	2.1 ± 1.02	1.92 ± 0.97	2.0 ± 1.05 %
Total Hb g/L	137.73 ± 24.3	121.13 ± 30.18	115.4 ± 18.76
FO_2Hb %	93.7 ± 2.46	96.17 ± 2.34	92.5 ± 2.42
PCO_2 mmhg	38.07 ± 6.16	45.62 ± 10.31	44.54 ± 7.91
PO_2 mmHg	78.96 ± 10.81	166.67 ± 128.2	85.12 ± 19.57
Group Non-smokers n=15			
COHb %	0.47 ± 0.27	0.42 ± 0.34	0.47 ± 0.39
Total Hb g/L	139.46 ± 22.9	131.2 ± 22.54	114.26 ± 18.22
FO_2Hb %	96.52 ± 1.66	98.08 ± 0.78	95.35 ± 2.37
PCO_2 mmHg	38.61 ± 5.07	39.3 ± 8.62	40.11 ± 6.35
PO_2 mmHg	83.94 ± 8.95	157.25 ± 56.85	93.21 ± 12.78

Values are expressed as mean ± standard error of the mean.
T_0 - preoperative; T_1 - after preoxygenation; T_2 - one hour after induction in anesthesia;
COHb - carboxyhemoglobin; Hb - hemoglobin; FO_2Hb – fractional oxyhemoglobin; PCO_2 - partial pressure of carbon dioxide; PO_2 - partial pressure of oxygen, FiO_2 - inhaled fraction of oxygen .

average values of COHb between the two groups were statistically significantly different. At baseline preoperative value T_0, p=0.000, at the second time point T_1 after preoxygenation p value was p=0.000 and at the third time point T_2, p=0.000.

Graph 1. Changes of the average values of COHb in the groups



DISCUSSION

The analysis indicated that smoking increases COHb and that the effect of smoking remains even after mechanical ventilation. We demonstrated that COHb levels change rapidly in response to changes of FiO_2 (100% – 50%) in mechanically ventilated patients during general anesthesia. We have also shown that FiO_2 of 100% accelerated the elimination of CO from the body, decreased the blood COHb concentration, and FiO_2 50% for 1 h increased the levels of COHb to basal levels in non-smokers; but this change was not observed in smokers.

It has been reported that CO is produced by the interaction of volatile anesthetics, including sevoflurane (12,13). We eliminated the influence of CO production through this interaction in our study, as we used intravenous anesthesia. Levy et al. in their study observed a significant increase of CO, during general anesthesia in infants and children and Tang *et al.* (15) observed identical findings in adults when low flow anesthesia was used. In our study normal flow anesthesia was used in all patients.

Pneumoperitoneum with CO_2 is created during laparoscopic surgery, but there is not a pathway which converts CO_2 to CO, thus the blood gas analysis does not indicate retention of CO_2 at several hours after extubation. Due to the incomplete combustion of the tissue it has been proposed that laparoscopic surgery with electric cautery is likely to generate CO (16). We compared laparoscopic (n=4) and open surgery (n=11) and we did not found any significant differences in COHb.

The principal physiological variables that determine blood concentrations of COHb, and therefore exhaled CO concentrations are: 1) rate of CO production, 2) alveolar ventilation, 3) diffusing capacity of the lung, 4) mean oxygen tension in the pulmonary capillaries, and 5) concentration of CO in the inspired air (2). According to the study of Hayashi *et al.* systemic inflammation caused by surgery and/or anesthesia and artificial ventilation elicits oxidative stress, which induces systemic HO-1 induction and leads to the production of endogenous CO. Synthesized CO forms carboxyhemoglobin, which is transported to the lung, from which it is excreted (8). In this study, we measured COHb levels in mechanically ventilated patients during general anesthesia. Patients' lungs were ventilated with a fixed tidal volume and respiration rate, and thus, alveolar ventilation was kept constant. No blood transfusion was performed during the measurement. There was some degree of hemodynamic fluctuation in response to changing anesthetic depth and the degree of surgical stimulation, which could change pulmonary blood flow during measurements. However, these effects on COHb levels might be smaller than the effects of change of FiO_2 and could be cancelled out in statistical analysis with repeated measurements. Oxygen tension in

all three arterial blood samples remains stable after the changes in FiO_2, and no obvious events such as pulmonary edema occurred, suggesting that the diffusing capacity of the lung was constant. Mean oxygen tension in the pulmonary capillaries and blood COHb concentrations are, thus, major determinants of the observed changes of COHb levels. The initial changes of COHb levels may be due to the change of mean oxygen tension in the pulmonary capillaries. CO and oxygen bind to the same site on hemoglobin and therefore compete against each other. The higher FiO_2 induces an increase in the mean oxygen tension in pulmonary capillaries, to increase the affinity of hemoglobin to oxygen, resulting in increased elimination of CO from the blood through expiration. The lower FiO_2 induces a lower mean oxygen tension in the pulmonary capillaries, to decrease the binding of hemoglobin to oxygen, resulting in less elimination of CO from the blood through expiration. We demonstrated that the decrease of COHb at least 3 min after the increase of FiO_2 may be due to the elimination of CO from the body, by increased elimination of CO from the lung.

The alveolar oxygen tension determines the exchange rate between oxygen and CO, and most endogenous generated CO is thus exhaled into the airway (17). Zegdi *et al.* (10) demonstrated that pulmonary elimination of CO was markedly, but transiently, dependent on FiO_2, and suggested that pulmonary elimination of CO returned to a baseline value after several hours of high FiO_2. This study demonstrated that the return of COHb levels to baseline after 1h of FiO_2 50%, reflects the decrease of blood COHb concentrations. In support of this hypothesis, when the FiO_2 was returned to 50% after inhalation of high FiO_2, COHb levels were lower than the basal level in Group 1, and similar to basal values in Group 2.

This study demonstrated that we should address the effects of the concentration of inspired oxygen and its time course on COHb levels in mechanically ventilated patients. It is possible to misinterpret high levels of COHb induced by inspiration of high FiO_2 as a reflection of the severity of inflammatory airway disease, acute organ dysfunction, or stress from surgery and anesthesia. It is a standard procedure to deliver high concentrations of oxygen to such patients. However, other factors that might influence COHb, such as blood transfusion, should be investigated in future studies.

Our study has limitations. The preliminary observations of our study require further validation in larger prospective populations in order to clarify the underlying mechanisms since a major limitation of this study is the relatively small sample size in both subgroups that makes statistical analysis difficult. Thus, our results should be interpreted with caution. Another limitation was that the measurements were made without blinding of the researcher to the experimental group.

CONCLUSION

We have demonstrated that CO is eliminated more rapidly when patients are ventilated with 100% O_2. However, this effect is not sustained as COHb quickly returns to baseline when FiO_2 is reduced to 50%. When COHb levels are determined in mechanically ventilated patients, the consequences of changes of FiO_2 and its duration must be considered when interpreting these measurements.

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