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SHORT COMMUNICATION

Increased carboxyhemoglobin level during liver resection with inflow occlusion

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Abstract Controlling stress responses associated with ischemic changes due to bleeding and ischemia/reperfusion injury is essential for anesthetic management. Endogenous carboxyhemoglobin (COHb) is produced in the oxidative degradation of heme proteins by the stress-response enzyme heme oxygenase. Although the COHb level is elevated in critically ill patients, changes in endogenous COHb during anesthesia have not been well investigated. Therefore, we evaluated changes in endogenous COHb levels in patients undergoing liver resections with inflow occlusion. Levels of COHb were significantly increased after the Pringle maneuver. The inflow occlusion time in patients with increased COHb after the Pringle maneuver (ΔCOHb > 0.3 %) was significantly longer than in patients without increased COHb (ΔCOHb < 0.3 %) ($P = 0.01$). In addition, COHb changes were correlated with inflow occlusion time ($P = 0.005$, $R^2 = 0.21$). Neither total blood loss, transfusion volume of packed red blood cells, operation time, nor anesthetic time differed between patients with and without increased COHb. The results indicated that endogenous COHb levels were increased by inflow occlusion in patients undergoing liver resections, which suggests that changes in COHb may correlate with hepatic ischemia/reperfusion injury induced by inflow occlusion.

Keywords Endogenous COHb · Inflow occlusion · Liver resection

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Abbreviations

AST	Aspartate transaminase
ALT	Alanine transaminase
CO	Carbon monoxide
COHb	Carboxyhemoglobin
FiO_2	Fraction of inspired oxygen
Hb	Hemoglobin
PRBC	Packed red blood cells

Carbon monoxide (CO) is endogenously generated by the enzyme heme oxygenase in the context of oxidative stress responses induced by ischemia/reperfusion injury [1]. CO reacts with hemoglobin in the blood to form carboxyhemoglobin (COHb), which interferes with the oxygen-carrying capacity of the blood and can lead to hypoxia. Endogenous COHb increases in patients with liver cirrhosis [2], cancer and sepsis, and in those undergoing cardiopulmonary bypass and dialysis [3, 4]. Endogenous CO is reportedly protective against oxidative stress responses and exerts anti-apoptotic, anti-inflammatory effects at low concentration [5].

Inflow occlusion by clamping of the portal pedicle—the Pringle maneuver—is routinely used to prevent blood loss during liver resection [6]. However, the Pringle maneuver induces hepatic ischemia and reperfusion injury in the remnant liver, which is associated with increased postoperative morbidity and mortality [7]. Although postoperative arterial COHb concentrations tend to be significantly increased in patients undergoing surgery under general anesthesia [8], the factors that increase endogenous COHb production in the perioperative period are unclear. Therefore, we evaluated the intraoperative changes in COHb levels in patients undergoing liver resection with inflow

occlusion, and intraoperative events associated with the changes in COHb.

This study was approved by the ethics committee of Kagoshima University Hospital. Written informed consent was obtained from all participants. A total of 36 consecutive patients undergoing elective liver resection with inflow occlusion between December 2009 and July 2011 were enrolled in this study. Of the 36 patients, 2 had ASA physical status I, 33 had ASA status II, and 1 had ASA status III. Current smokers, patients treated with radiofrequency ablation or scheduled resections not requiring inflow occlusion, and patients under 18 years old were excluded. Epidural catheters were placed at T8/9 interspaces before anesthesia. General anesthesia was induced with propofol 1 mg/kg, remifentanil 0.3 μg/kg/min, and rocuronium 0.6 mg/kg. After tracheal intubation, anesthesia was maintained with 1–2 % sevoflurane, remifentanil 0.1–0.5 μg/kg/min, and rocuronium 10 mg with muscle relaxant monitoring. Ventilation was controlled with a fraction of inspired oxygen (FiO_2) of 0.35–0.5. Minute ventilation was maintained at 80–100 ml/kg (Aestiva5, Datex-Ohmeda). Surgical procedures were performed in a standardized manner under the supervision of two experienced hepatobiliary surgeons. After mobilization of the liver, inflow occlusion was achieved by the tourniquet technique around the portal triad. The length of time for continuous inflow occlusion was intermittent clamping with 15 min of ischemia and 5 min of reperfusion. Transfusion of packed red blood cells (PRBC) was performed to maintain hemoglobin (Hb) > 8.0 g/dL. Hb, COHb, and lactate were each measured using a blood gas analyzer (ABL700, Radiometer) at T_1, the start of operation; T_2, 5–10 min before clamping in the Pringle maneuver; T_3, 5–10 min after declamping; and T_4, the end of the operation. Exhaled carbon monoxide (CO) was measured by Carbolizer (mBA-2000, Taiyo). Differences among groups were analyzed using one-way ANOVA followed by Bonferroni tests or unpaired *t*-tests. Spearman correlation tests were used to explore correlations between changes in COHb and inflow occlusion times. All analyses were conducted using GraphPad Prism version 5 (GraphPad software, La Jolla). Results are expressed as the mean ± SD. $P < 0.05$ was considered statistically significant.

The mean COHb level was significantly increased at T_3, 5–10 min after declamping (T_1 1.27 ± 0.45, T_2 1.28 ± 0.49, T_3 1.52 ± 0.48, T_4 1.49 ± 0.54, $P < 0.04$), whereas the mean total Hb level was significantly decreased after declamping (T_1 11.0 ± 1.9, T_2 10.2 ± 1.6, T_3 9.1 ± 1.0, T_4 9.8 ± 1.2, $P < 0.0001$). Because the mean difference in COHb levels between T_2 and T_3 was 0.24 ± 0.44 %, the patients were divided into two groups; patients whose increased COHb between T_2 and T_3 was greater than 0.3 % (ΔCOHb > 0.3 %, $n = 14$), and those for whom it was less than 0.3 % (ΔCOHb < 0.3 %, $n = 22$). The inflow occlusion time in patients with an increase in COHb level between T_2 and T_3 (ΔCOHb > 0.3 %) was significantly longer than that in patients without an increased COHb level (ΔCOHb < 0.3 %) (Table 1). There was no difference in plasma lactate level, blood loss, changes in Hb level, transfusion volume of PRBC, anesthesia time, or operation time between the groups. In addition, changes in COHb level between T_2 and T_3 were significantly correlated with inflow occlusion time ($P = 0.005, R^2 = 0.21$) (Fig. 1).

In this study, endogenous COHb levels were significantly increased after inflow occlusion associated with the

Table 1 Intraoperative data

	ΔCOHb ($T_3 - T_2$) < 0.3 % ($n = 22$)	ΔCOHb ($T_3 - T_2$) > 0.3 % ($n = 14$)	*P*
Anesthesia time (min)	578 ± 110	627 ± 116	0.21
Operation time (min)	455 ± 111	498 ± 107	0.26
Inflow occlusion time (min)	67 ± 30	97 ± 34	0.01*
Blood loss (ml)	1905 ± 730	2303 ± 644	0.11
Transfusion volume (ml)	751 ± 549	720 ± 475	0.86
Mean BP (mmHg)	75 ± 6	73 ± 5	0.43
Mean HR (/min)	77 ± 11	75 ± 10	0.62
ΔLactate ($T_3 - T_2$) (mmol/L)	1.26 ± 1.03	2.00 ± 1.35	0.07

Data are the mean ± SD

BP blood pressure, *HR* heart rate, T_2 5–10 min before clamping in the Pringle maneuver, T_3 5–10 min after declamping

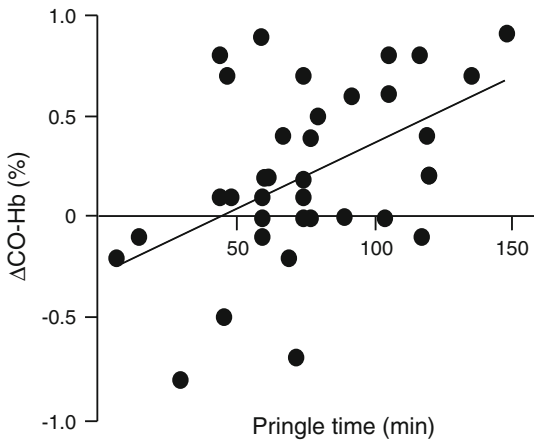

Fig. 1 Correlation between changes in carboxyhemoglobin levels and inflow occlusion time during liver resection (correlation between Pringle time and the change in carboxyhemoglobin (COHb) level between T_2 and T_3)

Pringle maneuver. Reportedly, this increased CO-Hb concentration was associated with altitude-induced hypoxia and shock [9], suggesting that intraoperative COHb is increased due to hypoxia-related events.

Although several cases with increased COHb levels due to high levels of contamination in PRBC administered during surgery have been reported previously [10, 11], PRBC transfusion volume did not differ between patients with and without increased COHb. Elimination of CO is also related to minute ventilation and FiO_2 [12]. The half-lives of COHb when a patient is breathing room air and 100 % oxygen are 4–6 h and 40–80 min, respectively [13]. In this study, FiO_2 was maintained at 0.5 during surgery and minute ventilation was kept at 80–100 ml/kg. Additionally, CO has been suggested to be produced by the breakdown of volatile anesthetics, including sevoflurane, due to reaction with desiccated absorbents [14, 15]. The temperature of the absorbent, soda lime, was kept at that of the ambient air (20–28 °C) at a flow of 3 L/min during surgery; the anesthesia time did not vary between groups (Table 1). Our study found a weak but significant correlation between plasma COHb levels and exhaled CO during surgery ($P = 0.0003$, $R^2 = 0.19$, data not shown). However, exhaled CO did not correlate with inflow occlusion time, suggesting that exhaled CO concentration may be influenced by multiple factors during surgery.

Here, arterial blood samples were used to measure plasma COHb. However, as venous COHb levels reportedly predict arterial levels quite accurately [16], samples obtained from central venous catheters might be used to evaluate the endogenous COHb level.

Although increased plasma COHb levels were significantly correlated with inflow occlusion time, there were no correlations between the intraoperative increase in COHb and the levels of aspartate transaminase (AST)/alanine transaminase (ALT) or prothrombin time measured on postoperative day 1, which are considered to be indicators of hepatic prognosis. Therefore, COHb could reflect intraoperative events associated with inflow occlusion during anesthesia; however, the clinical relevance of increased endogenous COHb during liver resection remains unclear.

In conclusion, we report that endogenous COHb levels increased after inflow occlusion in patients undergoing liver resection. Further clinical investigation is needed to evaluate the role of COHb in ischemia/reperfusion injury and the postoperative prognosis.

Conflict of interest None.

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