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Carboxyhemoglobin and postsurgical hyperbilirubinemia in patients undergoing esophagectomy

Ryohei Serita, Hiroshi Morisaki, Tomoyuki Satoh, Yasushi Innami, Shizuko Kosugi, Shin-ichi Yamamoto, Yoshihisa Morita, Yoshifumi Kotake, and Junzo Takeda

Department of Anesthesiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

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Introduction

Recent evidence has demonstrated that carbon monoxide (CO), a product of heme degradation, is a potent endogenous modulator of various physiological events such as platelet aggregation, activation of guanylate cyclase, and microvascular regulation [1,2]. Since bilirubin is produced concurrently with equimolar CO via heme oxygenase, the measurement of endogenous CO as exhaled CO or carboxyhemoglobin (HbCO) has been regarded as a useful indicator of heme oxygenase activity and/or the bilirubin production rate in neonates [3,4]. In postsurgical hyperbilirubinemia, however, the clinical implications of HbCO level, deriving from both endogenous and exogenous sources, remain to be determined. Endogenous CO is mainly produced by heme metabolism associated with the destruction of erythrocytes, as well as nonhemoglobin-derived pathways such as myoglobin, heme-containing enzymes, or others [1]. Given the rationale that surgical impacts followed by hypercytokinemia could induce heme oxygenase-1 (HO-1) [1,3], it is plausible to postulate that postsurgical hyperbilirubinemia is caused not only by several major mechanisms, including blood transfusion, liver injury, or infection, but also by increased bilirubin production associated with HO-1 activity. Although hyperbilirubinemia is a typical sequela of major surgery such as esophagectomy, the clinical markers to differentiate such a pathological process to the development of postsurgical hyperbilirubinemia are limited [5,6]. We therefore examined the arterial HbCO levels in patients receiving esophagectomy and reconstruction surgery to clarify the factors contributing to postsurgical hyperbilirubinemia.

Address correspondence to: H. Morisaki
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Materials and methods

Before starting the study, informed consent and institutional approval were obtained. Fifty-nine patients (60 ± 8 years of age) who were to receive esophagectomy and reconstruction surgery, accompanied by both thoracotomy and laparotomy, were examined independently from two previous investigations. No patient had major complications in their cardiopulmonary system or a recent smoking habit 2 weeks preoperatively. The excretion rates of indocyanine green (25 mg) at 15 min were all less than 10% preoperatively. In this study, hyperbilirubinemia was defined as a total bilirubin over 1.4 mg·dl^{-1}. The arterial HbCO and HbCO content, defined as HbCO × Hb, were followed up for 2 weeks after surgery. In this study we introduced the concept of bilirubin index (BI), i.e., total bilirubin/HbCO content, as a marker of bilirubin metabolism in relation to its production rate. Thus, the higher the BI, the more profoundly the bilirubin metabolism is depressed compared with its production rate.

The Hb, HbCO, and methemoglobin were measured by using a cooximeter (OSM3, Radiometer, Copenhagen, Denmark), and other biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total protein were measured by routine hospital laboratory analysis. Both intra- and interassays of covariates for the cooximeter were less than 0.2%. Data are presented as mean ± SD unless otherwise specified. One-way analysis of variance followed by Scheffe's post hoc test was applied to detect statistical differences where appropriate. A P value of less than 0.05 was considered to be significant.

Table 1. Characteristics and laboratory data for 59 patients following esophagectomy

	Normobilirubinemia group ($n = 28$)	Early hyperbilirubinemia group ($n = 15$)	Late hyperbilirubinemia group ($n = 16$)
Age (years)	57 ± 8	60 ± 7	60 ± 6
Males/females	26/2	12/3	16/0
Total bilirubin ($mg \cdot dl^{-1}$)	0.88 ± 0.22	1.67 ± 0.21*	3.09 ± 1.33**
Total protein ($g \cdot dl^{-1}$)	5.6 ± 0.4	5.5 ± 0.4	5.4 ± 0.4
Prothrombin time (%)	61 ± 15	54 ± 12	57 ± 12
AST ($IU \cdot l^{-1}$)	67 ± 22	80 ± 44	69 ± 28
ALT ($IU \cdot l^{-1}$)	36 ± 14	39 ± 21	38 ± 21
C-reactive protein ($mg \cdot dl^{-1}$)	9.1 ± 5.1	8.1 ± 4.3	7.6 ± 1.9
WBC counts (mm^{-3})	7400 ± 2200	7120 ± 2660	7450 ± 2600
Transfusion volume (ml)	360 ± 720	660 ± 500	740 ± 600
Number of patients receiving transfusion	15/28	8/15	8/16
PEEP (mmHg)	3 ± 1	3 ± 1	4 ± 1
PaO_2/FiO_2	343 ± 65	337 ± 109	300 ± 88
Hb ($g \cdot dl^{-1}$)	11.1 ± 1.1	11.4 ± 0.8	10.7 ± 1.7
Methemoglobin (%)	0.68 ± 0.19	0.78 ± 0.25	0.72 ± 0.18
HbCO (%)	0.91 ± 0.18	1.22 ± 0.17*	1.12 ± 0.13
HbCO content ($\times 10^{-2} g \cdot dl^{-1}$)	10.1 ± 2.2	13.6 ± 1.8*	11.9 ± 3.5

Data were the maximum values of total bilirubin obtained
AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cells; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspiratory oxygen; Hb, hemoglobin; HbCO, carboxyhemoglobin; HbCO content, HbCO × Hb
* $P < 0.05$, ** $P < 0.01$ *vs* normobilirubinemia group

Results

In a preparatory series of data collection from postsurgical patients without hyperbilirubinemia, we found that arterial HbCO and HbCO content both had a positive correlation with the mixed venous content, and that the standard ranges of arterial HbCO and HbCO content were 0.96 ± 0.30% and 11.2 ± 3.9 × $10^{-2} g \cdot dl^{-1}$, respectively.

Thirty-one of 59 postesophagectomy patients (53%) showed an elevation of serum bilirubin within a 2-week postsurgical period. The peak values of total bilirubin among the patients with hyperbilirubinemia showed a biphasic pattern: the early phase of hyperbilirubinemia was observed on postoperative days 1–3 ($n = 15$; 1.67 ± 0.21 $mg \cdot dl^{-1}$), and the late phase on postoperative days 5–11 ($n = 16$; 3.09 ± 1.33 $mg \cdot dl^{-1}$). No patient showing hyperbilirubinemia in the early phase was allocated into the late-phase group. Table 1 gives the patients characteristics and the laboratory data for the normobilirubinemia, early hyperbilirubinemia, and late hyperbilirubinemia groups. Except for bilirubin level, there were no significant differences in the laboratory data in relation to hepatic dysfunction or inflammatory responses between the three groups. In addition, respiratory parameters such as positive end-expiratory pressure (PEEP) level and PaO_2/fraction of inspiratory oxygen (FiO_2) ratio showed that the facility for gas exchange was not severely damaged in any group. Among the parameters listed in Table 1, only the volume of the blood transfusion positively correlated with arterial HbCO ($y = 0.87 + 1.94 \times 10^{-2}$, $r = 0.51$). Despite there being no differences in the transfusion volume between the groups, it should be noted that the data were not normally distributed, and approximately half of the patients in each group received no transfusion during the perioperative period (Table 1). Although most (except one) patients in the early hyperbilirubinemia group showed a HbCO and HbCO content within the standard range, the averages of the two variables were significantly elevated compared with the normobilirubinemia group ($P < 0.05$). On the other hand, the BI in the late hyperbilirubinemia group was significantly higher than that in the normobilirubinemia and early hyperbilirubinemia groups ($P < 0.01$). The BI of the latter group was significantly higher than that in the normobilirubinemia group ($P < 0.05$) (Fig. 1).

Discussion

The current study suggests that arterial HbCO level could be a clinical marker to diagnose postsurgical hyperbilirubinemia in patients following esophagectomy: the early elevation of bilirubin is caused to some extent by production excess, whereas late hyperbilirubinemia, which is more profound than the former, is mainly due to its metabolism or excretion retardation. In other words, increased bilirubin production, possibly via the induction of heme oxygenase, is likely to play a consequential role in the early phase of hyperbilirubinemia. On the other hand, the late phase is mainly caused by

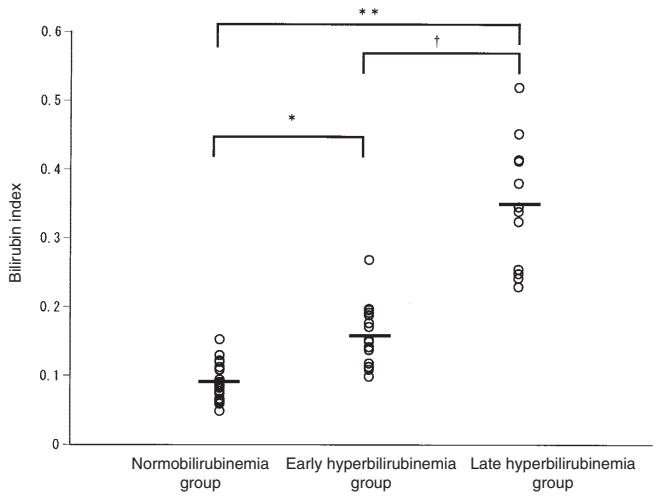

Fig. 1. Bilirubin index [BI = total bilirubin/(carboxyhemoglobin × hemoglobin)] in 59 patients following esophagectomy. $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* normobilirubinemia group; $^{\dagger}P < 0.01$ *vs* early hyperbilirubinemia group

other compromised factors such as drug-induced or infection-related hepatocellular dysfunction.

Postsurgical hyperbilirubinemia is caused by several factors: (i) excess production of bilirubin, (ii) decreased uptake of bilirubin into hepatic cells, (iii) disturbed intracellular protein binding or conjugation, (iv) disturbed secretion of conjugated bilirubin into bile canaliculi, or (v) intrahepatic or extrahepatic bile-duct obstruction [7,8]. Compared with neonatal hyperbilirubinemia, which is mainly caused by production excess, most postsurgical hyperbilirubinemia is a result of hepatocellular injury and/or increased bilirubin load [2,7]. Blood transfusion is a key factor in the development of postsurgical hyperbilirubinemia because it provides not only heme per se, but also HbCO from the banked blood [9]. However, it should be noted that half of the postsurgical hyperbilirubinemia cases could not be accounted for by blood transfusions, and that total amounts of transfusion were not different between the groups. In addition, several times the amount of bilirubin loading caused by hemolysis or blood transfusion can be excreted without increasing serum bilirubin under normal liver function [7]. Also, the findings that serum transaminases and other related factors such as total protein and prothrombin time were not different indicated that there must be other factors contributing to the development of postsurgical hyperbilirubinemia due to production excess. Although it could be argued that only one patient showed excessive production of bilirubin beyond the standard range, as measured by arterial HbCO and HbCO content, the bilirubin production rate in the early hyperbilirubinemia group was significantly higher than in the normobilirubinemia or late hyperbilirubinemia groups.

There are some limitations on how these data can be interpreted. First, cardiopulmonary function, which was fairly well preserved within the normal range under inotropic support and mechanical ventilation, might have modified the level of arterial HbCO. Ostrander et al. [10] showed a poor correlation between HbCO and heme catabolic rate in neonatal patients with respiratory dysfunction. In addition, FiO_2, which was generally maintained between 0.4 and 0.6 in this study, could affect arterial HbCO level. Conversely, it should be noted that gaseous sources of exogenous CO such as tobacco or air pollution could be excluded in this study setting. Second, since this study was aimed at clarifying the role of arterial HbCO in patients who were at risk of postsurgical hyperbilirubinemia, we defined hyperbilirubinemia as total bilirubin over $1.4\,mg{\cdot}dl^{-1}$, i.e., beyond the normal range. In a clinical situation, however, mild hyperbilirubinemia, i.e., total bilirubin less than $2\,mg{\cdot}dl^{-1}$ may not be significant during the postsurgical period [7]. Third, it could be argued that the absolute value of BI per se is not conclusive; BI is modulated by several factors such as total bilirubin, Hb, and exogenous and endogenous HbCO. In addition, the total volume of the blood transfusion, the major source of exogenous CO during the perioperative periods, varied among patients. In our study population, however, the HbCO content was almost within the standard ranges for postsurgical patients, suggesting that the BI could directly mirror the intensity of bilirubin metabolism retardation.

In summary, although further studies are obviously required, the present results using arterial HbCO level suggest that the early elevation of bilirubin is caused to some extent by production excess, whereas late hyperbilirubinemia is mainly due to its metabolism or excretion retardation in patients undergoing esophagectomy and reconstruction surgery.

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