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Alteration of redox state of human serum albumin in patients under anesthesia and invasive surgery

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Abstract

Human serum albumin is a mixture of mercapt- (HMA, reduced form) and nonmercaptalbumin (HNA, oxidized form). We studied the mercapt↔nonmercapt conversion of human serum albumin, which reflects the redox state of the extracellular fluids, in cardiac and other common surgical patients using high-performance liquid chromatography. Mean values of [(HMA)/(HMA+HNA)]±standard deviation, [$f_{HMA} \pm \sigma$], for patients who received common surgery (group 1) and cardiac surgery (group 2) at the start of anesthesia were 0.636±0.050 ($n=83$) and 0.615±0.062 ($n=14$), respectively. f_{HMA} values were markedly lower than those for healthy male adults of 0.750±0.028 ($n=28$). f_{HMA} values increased at 24 h after the start of anesthesia and decreased on the 4th postoperative day in most of the patients. These postoperative changes were prominent in cardiac surgical patients. Although f_{HMA} values after the 7th postoperative day recovered to those at the start of anesthesia in almost all of common surgical patients, those in cardiac surgical patients never recovered even on the 21st postoperative day. © 1997 Elsevier Science B.V.

Keywords: Human serum albumin; Mercaptalbumin; Nonmercaptalbumin

1. Introduction

Serum albumin is a mixture of mercapt- and nonmercaptalbumin, i.e. a protein redox couple in plasma. Although much is known about effects of anesthesia and surgical operation on redox couples, such as reduced-oxidized glutathione (GSH–GSSG) [1–6], lactate–pyruvate (L–P), β-hydroxybutylate–acetoacetate (BOHB–AcAc) [7–10] etc., little is known about alterations of the redox state of human serum albumin (HSA) under anesthesia and surgery. It was reported by Sogami et al. [11–13], Era et al. [14,15], King [16] and Andersson [17] that nonmercaptalbumin (oxidized form) is composed of two kinds of mixed disulfide compounds, i.e., mixed disulfide with cysteine or glutathione. It was also reported by several groups [14,18–22] that the sulfhydryl group of mercaptalbumin is oxidized to form oxidation products higher than mixed disulfide, such as sulfenic, sulfinic and sulfonic states. It was reported by Sogami et al. [11–13] and Era et al. [14,15] that high-performance liquid chromatographic (HPLC) analysis of HSA on Asahipak GS-520H columns at neutral pH (eluent buffer, 0.03 *M* sodium

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phosphate buffer, 0.15 M Na_2SO_4, pH 6.87) showed two peaks, the principal component corresponding to human mercaptalbumin (HMA) and the secondary one to nonmercaptalbumin (HNA) having mixed disulfide with cysteine or glutathione. The fraction of HMA (f_{HMA}=(HMA)/[(HMA)+(HNA)]) might reflect the participation of HSA in maintaining a constant redox potential in the extracellular fluids [14,15]. Therefore, we studied the redox state of HSA in patients receiving anesthesia and invasive surgery, using f_{HMA} values.

2. Experimental

2.1. Samples

Serial changes of f_{HMA} values for patients who received elective surgery (group 1, n=83) and cardiac surgery (group 2, n=14) were studied pre- and postoperatively. Patients in both groups had neither hepatic nor renal dysfunctions. Profiles of the two groups are shown in Table 1. The patients in group 1 were in ASA (American Society of Anesthesiologists) physical status class 1 or 2, and patients in group 2 had no systematic diseases other than heart disease. Sera were obtained from these patients according to the following schedule: start and end of anesthesia, 24 h after the start of anesthesia, and on the 4th, 7th, 14th and 21st postoperative days. Sera were stored at −80°C until HPLC analysis to suppress the HMA→HNA conversion of HSA [15].

The value of f_{HMA} was calculated by dividing the area under the peak corresponding to HMA by the sum of areas under the peaks corresponding to HMA and HNA, respectively. To obtain these respective areas, a graphical method of symmetrical resolution was employed, as previously reported [11–15].

The plasma concentrations of L, P, BOHB and AcAc were measured spectrophotometrically as an enzyme-dependent change in NADH concentrations (L and P by the method of Marbach and Well [23], and BOHB and AcAc by the method of Williamson et al. [24]).

2.2. Apparatus and chromatographic conditions

HPLC analysis of 5-μl serum samples was carried out with a Plasmagraph (Asahi Medical, Tokyo, Japan), assembled as follows: a Model ERC-3110 degasser (Erma Optical Works, Tokyo, Japan); a Jasco twincle pump (Japan Spectroscopic, Tokyo, Japan); two Asahipak GS-520H columns (Asahi Chemical Industry, Kawasaki, Japan) (25×0.75 cm I.D.; maintained at 32±1°C); a Jasco Uvidec 100 IV UV monitor; an autosampler (a Tosoh Model AS-48, Tosoh, Tokyo, Japan or a Hitachi Model 638-08,

Table 1
Profiles of the patients (data expressed as mean±σ)

	Group 1 (without complications)	Group 2 (cardiac surgery)	P
No. of cases	83	14	—
Sex (male:female)	37:46	8:6	—
Age (years)	48±11	46±15	N.S.
Aorta clamp time (min)	—	68±34	—
ECC time (min)	—	131±57	—
Operation time (min)	228±148	427±142	***
Anesthesia time (min)	314±161	532±146	***
Blood transfusion (ml)	896±674 (23)	2200±1020 (10)	**
Albumin transfusion (ml)	—	1758±1076 (13)	—
Glucose infusion (g/kg/h)	0.176±0.089 (82)	—	—

ECC, extracorporeal circulation. Numbers in parentheses show patients transfused or infused. 'Albumin' shows commercial albumin preparation (4.4% Plasma Protein Fraction®·Baxter or 4.4% Plasmanate®·Cutter).

All patients were under 70 years of age in both groups.

In group 1, halothane anesthesia in 23, enflurane anesthesia in 23, neuroleptanesthesia (NLA) in 18, combination of enflurane with NLA in 13, thiopental anesthesia in two, epidural and/or spinal anesthesia in four patients, were used, respectively. In group 2, fentanyl anesthesia and diazepam, if necessary, were used. Nitrous oxide was supplemented in all patients.

**P<0.01; ***P<0.001; N.S., not significant (unpaired Student's t-test).

Table 2
$\bar{f}_{HMA}$ values for group 1

	Start of anesthesia ($n=83$)	End of anesthesia ($n=83$)	24 h ($n=83$)	4th day ($n=83$)	7th day ($n=83$)	14th day ($n=83$)	21st day ($n=55$)
$\bar{f}_{HMA}$	0.636	0.648	0.667	0.614	0.622	0.632	(0.639)
σ	0.050	0.054	0.067	0.061	0.058	0.051	(0.061)
	——**——						
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	———N.S.———						

*$P<0.05$; **$P<0.01$; ***$P<0.001$; N.S., not significant (paired Student's t-test).

Table 3
$\bar{f}_{HMA}$ values for group 2

	Start of anesthesia ($n=14$)	End of anesthesia ($n=14$)	24 h ($n=14$)	4th day ($n=14$)	7th day ($n=14$)	14th day ($n=14$)	21st day ($n=14$)
$\bar{f}_{HMA}$	0.615	0.606	0.691	0.547	0.563	0.573	0.569
σ	0.062	0.066	0.043	0.058	0.048	0.048	0.058
	——NS——						
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*$P<0.05$; **$P<0.01$; ***$P<0.001$; N.S., not significant (paired Student's t-test).

Hitachi, Tokyo, Japan). Eluent buffer solution was 0.03 *M* sodium phosphate buffer, 0.30 *M* trisodium citrate, pH 6.80 (citrate buffer), and was filtered through a Millipore Sterivex-GS filter unit (0.22 μm), or a Triton X-100-free Millipore membrane (0.45 μm) (Millipore, Bedford, MA, USA). The flow-rate of the citrate buffer was 0.80 ml/min.

2.3. Data analyses

Data were analyzed for statistical significance using paired Student's t-test for within-group analysis, and unpaired Student's t-test for between-group analysis.

3. Results and discussion

$\bar{f}_{HMA}$ values for groups 1 ($n=83$) and 2 ($n=14$) at the start of anesthesia were 0.636±0.050 and 0.615±0.062, respectively (Tables 2 and 3). It was reported by Sogami et al. [12,13] that $\bar{f}_{HMA}$ values for patients of hepatic and/or renal dysfunctions are significantly lower than those for normal healthy adults. Although patients in groups 1 and 2 had neither hepatic nor renal dysfunctions, $\bar{f}_{HMA}$ values at the start of anesthesia were markedly lower than those for healthy male adults of 0.750±0.028 [12–14]. Low $\bar{f}_{HMA}$ values of both groups at the start of anesthesia might be due to drug administration, invasive examinations stress and/or fasting before the surgical operation.

Time-dependent alteration of $\bar{f}_{HMA}$ values for pre- and postoperative stages in group 1 is shown in Table 2. $\bar{f}_{HMA}$ values showed a significant increase 24 h after the start of anesthesia ($P<0.001$), and a significant decrease on the 4th postoperative day ($P<0.001$). Then, $\bar{f}_{HMA}$ gradually increased and recovered to a value similar to that at the start of anesthesia on the 14th postoperative day, as shown in Table 2. Although the number of patients in group 2 (cardiac surgery) was only 14, $\bar{f}_{HMA}$ values also

showed a significant increase 24 h after the start of anesthesia ($P<0.001$), and a significant decrease on the 4th postoperative day ($P<0.001$), as shown in Table 3. Furthermore, recoveries of f_{HMA} values for group 2 were incomplete even on the 14th ($P<0.05$) and 21st postoperative days ($P<0.05$). Examples of HPLC profiles of HSA and f_{HMA} values for patients of groups 1 and 2 are shown in Figs. 1 and 2, respectively. Since the GS-520H column is primarily a size-exclusion column, retention times for HMA and HNA were far different from those for other serum proteins such as immunoglobulin and transferrin [15]. The last sharp peak immediately after the HNA fraction, is the peak for uric acid [15]. It is known that acute-phase proteins, such as C-reactive protein (M_r, 105 000), α_1-acid glycoprotein (37 000), serum amyloid A (12 000), α_2-macroglobulin (720 000), etc., increase in concentration in response to acute inflammation or tissue damage, such as surgical operations [25,26]. However, no detectable changes in serum concentrations of these proteins were observed perioperatively, as judged by this HPLC analysis.

The above results for groups 1 and 2 clearly indicate the following interesting findings concerning f_{HMA} values: first, changes in redox state of HSA toward reduced state 24 h after the start of anesthesia

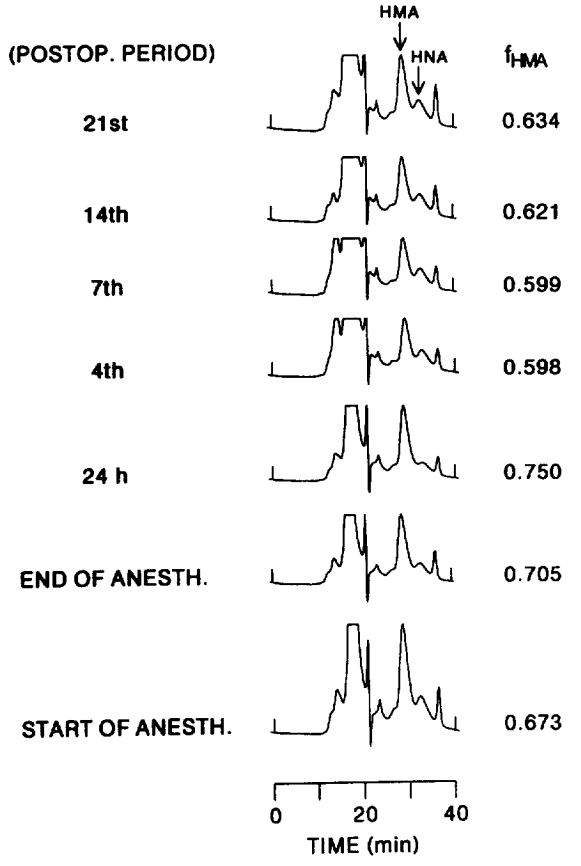

Fig. 1. Time-course of mercapt–nonmercapt conversion of HSA (HPLC profiles) in a patient from group 1 (without complications). Eluent, citrate buffer; column temperature, 32±1°C; sample size, 5 μl; flow-rate, 0.80 ml/min. HMA and HNA indicate human mercaptalbumin and nonmercaptalbumin, respectively.

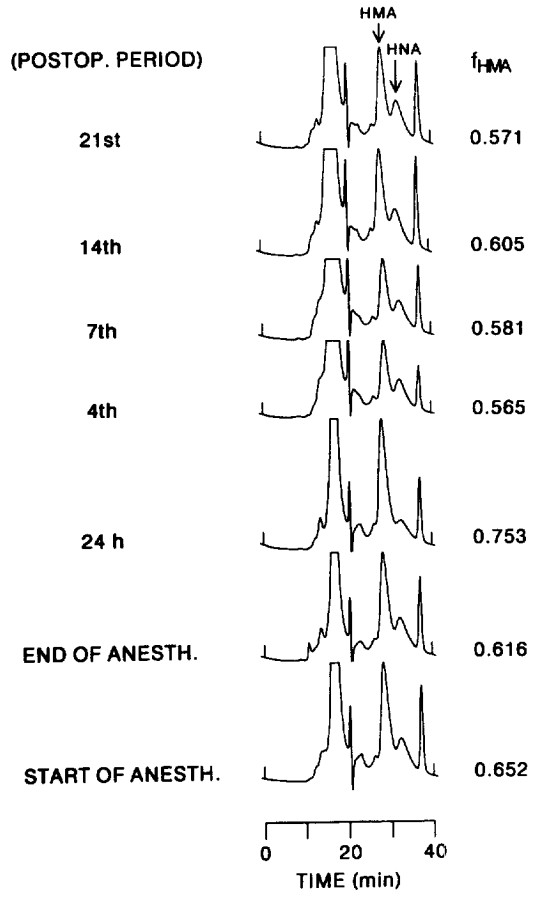

Fig. 2. Time-course of mercapt–nonmercapt conversion of HSA (HPLC profiles) in a patient from group 2 (cardiac surgery). Eluent, citrate buffer; column temperature, 32±1°C; sample size, 5 μl; flow-rate, 0.80 ml/min. HMA and HNA indicate human mercaptalbumin and nonmercaptalbumin, respectively.

(HNA→HMA conversion of HSA); second, changes toward oxidized state on the 4th postoperative day (HMA→HNA conversion of HSA). Therefore, we attempted to analyze statistically the effects of various clinical factors, such as blood or albumin transfusions, glucose infusion, methods of anesthesia and operation, etc., on the HMA↔HNA conversion of HSA in groups 1 and 2.

Intraoperative blood or albumin transfusions and glucose infusion might have effects on $\bar{f}_{HMA}$ values at the end of anesthesia and after anesthesia, respectively. $\bar{f}_{HMA}$ values for banked whole blood ($n=19$; preservation period = 14.6±3.1 days), packed cells ($n=12$; 11.6±4.4 days) and fresh whole blood ($n=4$; less than 3 days) were 0.678±0.044, 0.716±0.027 and 0.710±0.011, respectively. $\bar{f}_{HMA}$ values of these blood preparations were higher than those for patients in both groups at the start of anesthesia. However, the transfused blood in group 1 (Table 1) was too small to affect $\bar{f}_{HMA}$ values at the end of anesthesia. $\bar{f}_{HMA}$ values of commercial albumin preparations for clinical use were found to be 0.2–0.5 by Sogami et al. [12]. Although doses of blood and albumin preparations, transfused in group 2, were very large, blood and albumin preparations with high and low $\bar{f}_{HMA}$ values, respectively, might have opposite actions on $\bar{f}_{HMA}$ value at the end of anesthesia, resulting in no change in $\bar{f}_{HMA}$ values. Since small amounts of these preparations were transfused postoperatively to patients in both groups, HNA→HMA and HMA→HNA conversions of HSA 24 h after the start of anesthesia and on the 4th postoperative day, respectively, were not affected by these transfusions. However, it is worth noting that occurrence of hemolysis was often severe using a bypass pump during extracorporeal circulation (ECC) in group 2, resulting in the release of GSH from red blood cells into blood. Released GSH may facilitate the HNA→HMA conversion of HSA.

Although glucose, in general, acts as a reducing agent in the living system, an intraoperative infusion rate of glucose in group 1 was small enough to prevent hyperglycemia higher than 200 mg/dl and no glucose was infused in group 2, as shown in Table 1. We found, incidentally, no correlation between intraoperative glucose doses (g/kg/h) and post-$\bar{f}_{HMA}$/pre-$\bar{f}_{HMA}$ ratios, where pre-$\bar{f}_{HMA}$ and post-$\bar{f}_{HMA}$ are $\bar{f}_{HMA}$ values at the start of anesthesia and 24 h after the start of anesthesia, respectively, in group 1 ($n=49$, without blood transfusion; $r=-0.196$, not significant). However, it may be expected that intraoperative glucose infusion affects the increase in $\bar{f}_{HMA}$ value 24 h after the start of anesthesia to varying degrees in individual patients of the group 1. On the other hand, it was reported that blood glucose level increased often markedly above 350–400 mg/dl during and immediately after cardiopulmonary bypass (CPB), despite priming and administering glucose-free solution [27–32]. In these situations, elevation of blood glucose may increase $\bar{f}_{HMA}$ values 24 h after the start of anesthesia in group 2.

In our study, the inhalation and intravenous anesthetics described in the legend of Table 1 were used. Almost all of these drugs are known to bind to HSA [33]. Two distinct drug-binding sites are commonly called the warfarin- and the diazepam-binding sites [34,35]. More recently, X-ray crystallographic studies of serum albumin have revealed that the diazepam-binding site is located far from the position of the reactive sulfhydryl (Cys-34) which plays a role in HMA↔HNA conversion of HSA [36]. Moreover, diazepam/HSA mole ratios in groups 1 and 2 were 0.014 and 0.033, respectively. Therefore, diazepam administered in this study might have no effect on HMA↔HNA conversion of HSA. Both inhalation anesthetics, such as halothane, enflurane, and intravenous anesthetics, such as thiopental and fentanyl, are thought to bind to the individual hydrophobic areas on the HSA molecule. Although pharmacokinetic interactions between an inhalation anesthetic and another drug in regard to its binding to HSA have been demonstrated in vitro [37–39], at present there is no report on the involvement of HMA↔HNA conversion of HSA in anesthetic drug–HSA interactions. However, effects of inhalation anesthetics and surgical operations on redox couples such as GSH–GSSG [1–6], L-P, BOHB–AcAc [7–10] in tissues and blood, were reported by several groups.

GSH depletions in various tissues, such as liver, blood, etc., following inhalation anesthetics and surgery in experimental animals and humans, were studied by many groups [1–6]. In animal experiments, anesthesia had no significant effect on concentration of GSH in tissues except when anesthetics, such as fluroxene, were used. GSH is translo-

cated from the liver, and probably other tissues, to plasma, and such GSH constitutes the major source of plasma thiol [40,41] (see also Refs. in [40]). Intravascular GSH metabolism seems to involve reduction of disulfide bonds of plasma constituents, such as proteins, low-molecular-mass disulfide compounds, etc [40]. On the other hand, one potential function of a basal lateral membrane-bound enzyme with thiol-oxidizing activity, which is found in several tissues such as rat kidney, rat small intestine etc., is to catalyze the plasma thiol to disulfides (see Ref. [41] and Refs. therein). Therefore, the redox state of GSH/GSSG may be maintained by transport of GSH out of cells and extracellular oxidation of GSH to GSSG [41]. Hahn et al. [42] also reported that the half-life of GSH in rat blood plasma is a few minutes. Therefore, the redox state of GSH/GSSG, which might be fluctuating rapidly, might be maintained by transport of GSH out of hepatic cells, extracellular oxidation of GSH to GSSG and renal excretion [40,41]. Anderson and Meister [40] reported that when plasma is allowed to stand at 23°C for short periods, GSH level decreases rapidly. Therefore, we did not analyze low-molecular-mass thiol compounds such as GSH, cysteine, etc. Since f_{HMA} values of HSA in sera did not decrease rapidly even at 25°C [15], HMA/HNA might be slowly affected by the redox state of blood plasma compared with GSH/GSSG. As already stated, substantial amounts of GSH are translocated from hepatic cells to blood plasma [40]. f_{HMA} values 24 h after the start of anesthesia in patients with hepatic dysfunction in another group ($n=26$; mean age, 53±11 years; f_{HMA} at the start of anesthesia, 0.575±0.052; profile of this group not shown in Table 1) showed a slight increase ($P<0.05$) compared with significant increases in f_{HMA} values in groups 1 and 2 (Tables 2 and 3, $P<0.001$), indicating that GSH translocation from liver is important for the HNA→HMA conversion of HSA 24 h after the start of anesthesia.

Two redox couples, L–P and BOHB–AcAc are normally found in plasma. The L–P and BOHB–AcAc couples are most active metabolically in cytosol and mitochondria, respectively [7]. Thus, these redox couples might reflect compartmental redox state in cells [7]. It has been reported that L/P and BOHB/AcAc ratios increase in patients undergoing cardiac surgery due to impaired tissue oxygenation and/or electron transport systems [8–10]. Therefore, we tried to find out whether SH/S-S redox state monitored by f_{HMA} values of HSA, reflects the tissue redox state, monitored by L/P and BOHB/AcAc ratios in plasma in patients in group 2 after anesthesia and cardiac surgery with CPB. Arterial blood samples were obtained from patients in group 2 according to the following schedule: the start of anesthesia (A), 0, 1, 2 h after the start of CPB (C_0, C_1, C_2), 0, 1, 2, 4, 8, 24 h after the end of CPB (P_0, P_1, P_2, P_4, P_8, P_{24}), and the time between P_8 and P_{24}. f_{HMA} values showed significant increases at P_8 ($P<0.01$), 24 h after the start of anesthesia ($P<0.001$) and P_{24} ($P<0.05$) (Fig. 3). L/P and BOHB/AcAc ratios showed significant decreases at the following times: L/P ratio, P_4 ($P<0.05$), P_8 ($P<0.01$) and P_{24} ($P<0.01$); BOHB/AcAc ratio, C_0, P_0, P_1, P_2 and P_{24} ($P<0.05$), as shown in Fig. 3. It is worth noting that, as described above, the profile of the time-course of f_{HMA} values seems to be the mirror image of that for the L/P ratio. However, the detailed mechanism of this phenomenon necessitates more information on the relation between intracellu-

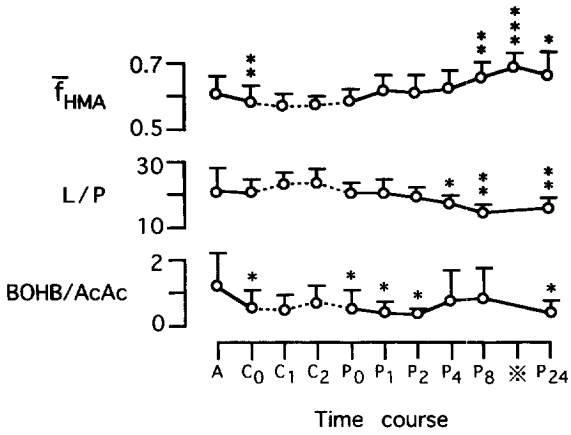

Fig. 3. $\bar{f}_{HMA}$ values, L/P and BOHB/AcAc ratios of arterial blood samples during and after cardiopulmonary bypass (CPB) in group 2 ($n=14$ except for C_1 and C_2). A, C_0, C_1, C_2 indicate the start of anesthesia, 0, 1, 2 h after the start of CPB, and P_0, P_1, P_2, P_4, P_8, P_{24} indicate 0, 1, 2, 4, 8, 24 h after the end of CPB, respectively. The symbol between P_8 and P_{24} corresponds to 24 h after the start of anesthesia as shown in Table 3 (the time between P_8 and P_{24}). As numbers of cases in C_1 and C_2 were less than 10, statistical analysis was not performed in C_1 and C_2. *, ** and *** indicate significances of $P<0.05$, $P<0.01$ and $P<0.001$ vs. A, respectively (paired Student's t-test).

lar redox couples, such as L–P, BOHB–AcAc and HMA–HNA, in extracellular fluids.

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