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Total body propofol clearance (TBPC) after living-donor liver transplantation (LDLT) surgery is decreased in patients with a long warm ischemic time

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Abstract
Metabolic capacity after liver transplant surgery may be affected by the graft size and by hepatic injury during the surgery. This study was carried out to investigate the postoperative total body propofol clearance (TBPC) in living-donor liver transplantation (LDLT) patients and to investigate the major factors that contribute to decreased postoperative TBPC in LDLT patients. Fourteen patients scheduled for LDLT were included in this study. Propofol was administered at a rate of 2.0 mg·kg^{-1}·h^{-1} as a sedative in the intensive care unit (ICU) setting. To calculate TBPC, propofol arterial blood concentration was measured by HPLC. Five variables were selected as factors affecting postoperative TBPC; bleeding volume (BLD), warm ischemic time (WIT), cold ischemic time (CIT), graft weight/standard liver volume ratio (GW/SLV), and portal blood flow after surgery (PBF). After factor analysis of six variables, including TBPC, varimax rotation was carried out, and this yielded three interpretable factors that accounted for 75.5% of the total variance in the data set. TBPC, WIT, CIT, and BLD were loaded on the first factor, PBF on the second factor, and GW/SLV on the third factor. The adjusted correlation coefficient between TBPC and WIT showed the highest value (r = –0.61) in the first factor. The LDLT patients were divided into two groups according to WIT; group A (WIT > 100 min) and group B (WIT < 100 min). Mean TBPC values in group A and group B were 14.6 ± 2.1 and 28.5 ± 4.1 ml·kg^{-1}·min^{-1}, respectively (P < 0.0001). These data suggest that LDLT patients with a long WIT have a risk of deteriorated drug metabolism.

Key words Living-donor liver transplantation · Propofol · Clearance · Ischemia · Portal blood flow · Factor analysis

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Propofol is a widely used agent for anesthesia during surgery and for sedation in the intensive care unit (ICU). The pharmacokinetics of propofol have been studied in surgical patients without liver dysfunction [1–3] and in those with moderate liver cirrhosis [3]. These studies indicated that total body propofol clearance (TBPC) was similar in nonhepatic surgery patients and in surgical patients with moderate liver cirrhosis, indicating that TBPC did not decrease even in cirrhotic patients. During the past decade, the number of living-donor liver transplantations (LDLTs) has increased due to the shortage of cadaver donor organs. LDLT has several advantages over cadaveric liver transplantation; families have strong emotional reasons for donating, both recipient and donor have time to control their physical status, and donor organs are in better condition upon grafting. However, graft size is usually limited, for the donor's safety, and ischemic hepatic injury during surgery still remains a clinically significant problem for the recipient. Drug clearance may be compromised when the graft size is small or when graft function is impaired during surgery.

The aim of this study was to investigate the postoperative TBPC in LDLT patients and to determine the factors that affected postoperative TPBC after LDLT surgery, using a factor analysis method.

Fourteen patients scheduled for LDLT were included in this study. The study was approved by the Institutional Review Board of Gunma University Hospital, and written informed consent was obtained from all patients.

Anesthesia was induced with vecuronium (0.1 mg·kg^{-1}) and propofol (2 mg·kg^{-1}) and then maintained with vecuronium (4.4 ± 0.9 mg·h^{-1}) and isoflurane (1.1% ± 0.46%). Fentanyl was given as needed. The propofol infusion (1.0–2.5 mg·kg^{-1}·h^{-1}) was started at the

Table 1. Patients' characteristics and propofol kinetics data in the ICU

Case no.	Age (years)	Wt (kg)	Sex	BLD (ml)	GW/SLV (%)	CIT (min)	WIT (min)	PF conc. ($\mu g \cdot ml^{-1}$)	TBPC ($ml \cdot kg^{-1} \cdot min^{-1}$)	PBF ($l \cdot min^{-1}$)	ICU stay (days)
1	60	62.5	M	27974	43.7	127	147	2.8	12.1	ND	9
2	19	66.5	M	4382	40.3	128	130	2	17.1	0.34	2
3	55	56	M	10416	37.1	260	230	2.2	15.3	0.42	6
4	13	44.7	M	22676	48.4	119	276	2.4	13.9	0.83	7
5	51	72.4	M	15580	46	97	20	1.14	29	1.02	8
6	58	58	F	4850	43	68	24	1.3	27	1.6	12
7	61	55	M	9938	71	144	34	1	33	1.66	9
8	55	56	M	12275	41.4	73	63	1.1	31.2	1.23	3
9	48	80	M	1445	50.3	43	51	1.4	30	1.37	6
10	53	73.3	F	1365	57.7	59	34	0.5	32	1.25	3
11	61	49.2	M	4411	50.8	39	39	1	33	1.51	3
12	56	62.5	M	3881	40.5	70	30	1.02	24	0.94	9
13	12	40	F	11300	46.7	60	32	1.5	21.1	1.44	3
14	14	42	M	706	61.5	52	60	1.4	25	0.96	30

TBPC, total body propofol clearance; BLD, bleeding volume; WIT, warm ischemic time; CIT, cold ischemic time; GW/SLV, graft weight/standard liver volume ratio; PBF, portal blood flow after surgery; ND, not detected

time of reperfusion. The propofol infusion rate was kept constant ($2.0 mg \cdot kg^{-1} \cdot h^{-1}$) for 2 h in the ICU. Then 5 ml of blood was sampled into heparinized syringes from an arterial line and stored at 4°C for later analysis. Within 24 h, propofol concentrations in whole blood were measured by high performance liquid chromatography (HPLC), as reported previously [4,5]. It has been reported that, 2 h after the start of constant infusion, the propofol concentration reached more than 85% of the final steady-state value [6]; therefore, the level of propofol 2 h after the start of constant infusion was regarded as a pseudo-steady state.

TBPC was calculated using the following equation:

$$TBPC = \text{infusion rate}/Css$$

where Css was regarded as the propofol concentration in the steady state.

Portal blood flow was measured immediately after admission to the ICU, using Doppler ultrasonography (Nemio-30; Toshiba, Tokyo, Japan).

Factor analysis was used to determine the dimensions underlying the pattern of inter-relationships and to reduce or rearrange the variable set to smaller factor sets of related variables. Extracted factors were rotated to obtain the simplest and most interpretable factors and to preserve independence among the factors. Correlations among the variables in the first factor were evaluated using Pearson's correlation coefficient (r). The unpaired t-test was used to compare the TBPC in patients with a long warm ischemic time (WIT) with that in patients with a short WIT. Origin 7.0 software (Origin Lab Cooperative, Northampton, MA, USA) was used for statistical analysis. Data values are presented as means ± SD, and P values of less than 0.05 were considered statistically significant.

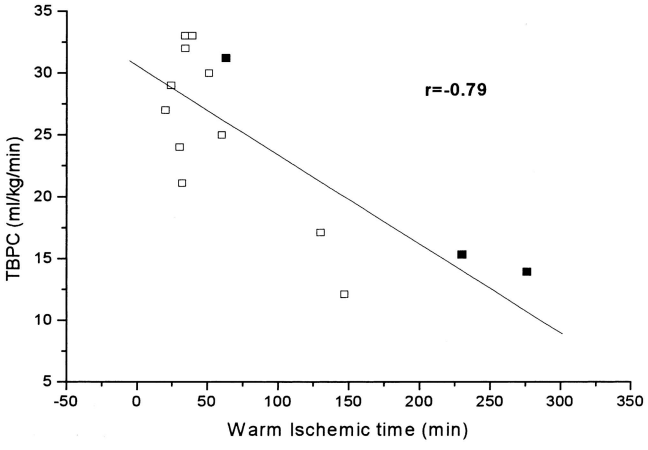

Fig. 1. Correlation between total body propofol clearance (*TBPC*) and warm ischemic time. *Black squares* show patients who did not survive. *Open squares*, patients who survived

The patients' characteristics on ICU admission are shown in Table 1. After factor analysis for six variables, including TBPC, varimax rotation was carried out, and this yielded three interpretable factors that accounted for 75.5% of the total variance in the data set. TBPC, WIT, cold ischemic time (CIT), and bleeding volume (BLD) were loaded on the first factor, graft weight/standard liver volume ratio (PBF) on the second factor, and portal blood flow after surgery (GW/SLV) on the third factor (Table 2). The adjusted correlation coefficient between TBPC and WIT showed the highest value ($r = -0.61$) in the first factor (which was –0.79 before adjustment; see Fig. 1). The LDLT patients were further divided into two groups according to WIT; group A (WIT > 100 min) and group B (WIT < 100 min).

Table 2. Varimax rotated factor matrix

	Factor 1	Factor 2	Factor 3
WIT	**0.843**	–0.397	0.151
BLD	**0.767**	0.312	0.205
TBPC	**–0.726**	0.226	–0.461
CIT	**0.614**	–0.379	0.089
PBF	–0.140	**0.945**	–0.294
GW/SLV	–0.178	0.185	**–0.726**

The analysis included the warm ischemic time (WIT), bleeding during operation (BLD), total body propofol clearance (TBPC), cold ischemia time (CIT), portal blood flow (PBF), and graft weight/standard liver volume ratio (GW/SLV), in patients receiving LDLT
Significant variables are indicated in bold for clarification

Mean TBPC values in group A and group B were 14.6 ± 2.1 and $28.5 \pm 4.1\,ml \cdot kg^{-1} \cdot min^{-1}$, respectively ($P < 0.0001$).

Three of the 14 patients died after the surgery. In group A, 2 patients died of multiple organ failure (MOF), due to abdominal infection and methicillin-resistant *Staphylococcus aureus* sepsis, on postoperative day (POD) 133 and POD 123. One patient in group B died of pulmonary aspergillosis, on POD 44.

TBPC in surgical patients without liver dysfunction and in those with moderate liver cirrhosis has been reported previously [1–3]. Earlier reports showed no significant differences in TBPC among these patient groups, even in patients undergoing cardiac surgery with cardiopulmonary bypass [4] or in patients who received propofol sedation in the ICU for prolonged periods [7]. However, in patients undergoing LDLT, postoperative metabolic function may be impaired by limited graft size, ischemic hepatic injury during surgery, and impaired hepatic blood flow after the surgery.

We selected five variables which could affect postoperative TBPC. However, because these variables were correlated with each other, showing multicollinearity, we first carried out factor analysis to rearrange our data set.

As shown in our factor analysis, WIT had the highest loading among the variables in the first factor, and the adjusted correlation coefficient between TBPC and WIT showed the highest value among the variables in the first factor ($r = –0.61$). In addition, mean TBPC was extremely low in the long-WIT group. It could be considered that WIT was the most significant contributor to the postoperative TBPC decrease.

The effect of ischemic damage on liver metabolic enzyme activity has been reported by several investigators [8–10]. Izuishi et al. [11] reported deterioration of liver drug-metabolizing enzyme activity lasting for up to 10 days after warm ischemia. Our data are consistent with those of Nowak et al. [12], who reported that warm ischemia was more injurious than cold ischemia, in an in vitro study. Propofol is hydroxylated and then glucuronized by liver cytochrome P450 (CYP) (phase 1) [13], and it is also directly glucuronized to a water-soluble conjugate by uridine diphospho-glucuronosyltransferase (UGT) (phase 2) [14] in the endoplasmic membrane [15]. We did not investigate these liver drug-metabolizing enzyme activities, but the decrease in TBPC may be due to a decrease in phase-1 and/or phase-2 enzymatic metabolism.

The clearance of flow-limited drugs such as propofol may decrease under conditions of low hepatic blood flow [16,17]. We could not estimate total hepatic blood flow because of inability to measure hepatic arterial blood flow by the doppler ultrasonography, but PBF has been shown to be dominant after liver transplant surgery, because hepatic arterial blood flow is usually limited after the vascular anastomosis [18,19]. In our data set, PBF was shown as the second factor, and the adjusted correlation coefficient between TBPC and PBF had a low value ($r = 0.15$). Our data suggest that PBF was not a major contributor to the postoperative TBPC decrease in our patient group. However, we cannot rule out the effect of hepatic arterial blood flow in this study.

It has been shown that the dose of an immunosuppressive drug required to reach a therapeutic target level is significantly correlated with GW/SLV [20,21], indicating limited drug metabolism in LDLT patients. In our data set, GW/SLV was shown as the third factor, and the adjusted correlation coefficient between TBPC and GW/SLV had a low value ($r = 0.35$). In this study, the GW/SLV was greater than 40%, which is not small-for-size. The low correlation may have been due to the population of our patient group.

Our findings showed the significant effect of WIT on the postoperative TBPC decrease, using factor analysis, a correlation matrix, and unpaired *t*-test. The patient numbers were limited, but this study suggests that drug clearance is decreased in LDLT patients with extended WIT.

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