Rapid Infusion of Hydroxyethyl Starch 70/0.5 but not Acetate Ringer's Solution Decreases the Plasma Concentration of Propofol during Target-controlled Infusion

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ABSTRACT

Background: Rapid fluid infusion resulting in increased hepatic blood flow may decrease the propofol plasma concentration (Cp) because propofol is a high hepatic extraction drug. The authors investigated the effects of rapid colloid and crystalloid infusions on the propofol Cp during target-controlled infusion.

Methods: Thirty-six patients were randomly assigned to 1 of 3 interventions (12 patients per group). At least 30 min after the start of propofol infusion, patients received either a 6% hydroxyethyl starch (HES) solution at 24 $ml \cdot kg^{-1} \cdot h^{-1}$ or acetated Ringer's solution at 24 or 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the first 20 min. In all groups, acetated Ringer's solution was infused at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the next 20 min. The propofol Cp was measured every 2.5 min as the primary outcome. Cardiac output, blood volume, and indocyanine green disappearance rate were determined using a pulse dye densitogram analyzer before and after the start of fluid administration. Effective hepatic blood flow was calculated as the blood volume multiplied by the indocyanine green disappearance rate.

Results: The rapid HES infusion significantly decreased the propofol Cp by 22 to 37%, compared to the Cp at 0 min, whereas the rapid or maintenance infusion of acetate Ringer's solution did not decrease the propofol Cp. Rapid HES infusion, but not acetate Ringer's solution infusion, increased the effective hepatic blood flow.

Conclusions: Rapid HES infusion increased the effective hepatic blood flow, resulting in a decreased propofol Cp during target-controlled infusion. Rapid HES infusion should be used cautiously as it may decrease the depth of anesthesia.
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PROPOFOL is a common anesthetic drug infused continuously for the induction and maintenance of anesthesia. When propofol is administered using target-controlled infusion (TCI) to maintain the predicted concentration calculated by a pharmacokinetic model,[1–6] the measured concentration can be kept within the clinically acceptable range under stable conditions.[7–9] However, various factors, including cardiac output (CO)[10] and uncompensated bleeding,[11] can influence the difference between the measured and predicted concentrations.

Rapid fluid infusion is a common clinical practice for preventing or treating hypovolemia during anesthesia. The rapid fluid infusion appears to reduce the plasma concentration (Cp) of propofol due to hemodilution. However, volume loading itself has little impact on the reduction of the concentration because propofol is rapidly distributed to the extravascular space, which has a large volume of distribution.[12–14]

Propofol is a high hepatic extraction drug.[15] Therefore, the time course of the propofol Cp is likely affected by changes in the hepatic blood flow (HBF) due to alterations in its clearance.[16,17] As rapid colloid infusion may increase the HBF,[18] the measured Cp of propofol may decrease during and after rapid colloid infusion when the predicted Cp is maintained at a constant value using TCI.

What We Already Know about This Topic

- Propofol is often administered by target-controlled infusion to rapidly achieve and maintain a desired plasma concentration
- Because propofol has a high hepatic extraction ratio, changes in hepatic blood flow can increase its elimination clearance and, as a result, decrease the plasma concentrations produced by a target-controlled infusion
- Rapid colloid infusion may increase hepatic blood flow

What This Article Tells Us That Is New

- Rapid infusion of 8 ml/kg 6% hydroxyethyl starch 70/0.5 over 20 min increased hepatic blood flow by approximately 25% and decreased the targeted plasma propofol concentration by up to 37%
- Rapid infusion of 8 ml/kg acetated Ringer's solution over 20 min did not affect either hepatic blood flow or the targeted plasma propofol concentration

The aim of the current study was to investigate the influence of rapid colloid and crystalloid infusions on the time course of the propofol Cp during TCI. We also assessed the

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influence of the rapid fluid infusions on hemodynamic variables, including the HBF using pulse dye densitometry. To focus on the changes in the variables, including the propofol Cp and hemodynamic variables, we calculated the ratio of the current measurement to the baseline measurement for each variable, because the baseline values differ between patients. Details of the ratio calculation are described in Statistical Analysis. To avoid the influence of surgical stimulation on the hemodynamic parameters, we performed all study procedures before surgery began. We hypothesized that rapid colloid infusion but not rapid crystalloid infusion would decrease the Cp of propofol during TCI.

Materials and Methods

Clinical Protocol

The study was approved by the Committee on Medical Ethics at the National Defense Medical College Hospital, Saitama, Japan, and was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000004358, Dr. Masui, October 7, 2010, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000005209&language=E). After written informed consent was obtained, we enrolled 24 male and 13 female patients aged 43 to 76 yr who had an American Society of Anesthesiologists physical status classification of I or II and were scheduled for gastroenterological surgery between June 30, 2009, and July 27, 2009. Exclusion criteria included a body mass index of more than 30 kg/m^2; neurologic disorders; recent use of psychoactive medicines; significant cardiovascular, pulmonary, hepatic, or renal dysfunction; or an allergic reaction to soybeans or eggs.

No premedication was given to any of the patients. After arriving in the operating room, all patients underwent routine monitoring including electrocardiography, noninvasive blood pressure, pulse oximetry, and electroencephalography. An epidural catheter was inserted if necessary, without any epidural infusion of local anesthetics or opioids until the end of the blood sampling period for the study. After oxygenation, anesthesia was induced and maintained by plasma-targeted TCI of propofol using a TCI pump (TE-371, Terumo Corporation, Japan) with the Diprifusor® TCI system (AstraZeneca K.K., Japan) incorporating the Marsh pharmacokinetic model (fig. 1).[13] Propofol was infused directly into an intravenous catheter at a forearm vein without any other simultaneous fluids to prevent the propofol infusion from becoming unstable. If a patient respond to verbal commands at the point when the effect-site concentration equaled the targeted Cp minus one, *e.g.*, the effect-site concentration was 2 μg/ml when the targeted Cp was 3 μg/ml, then we increased the targeted concentration by 0.5 μg/ml. Once the patient stopped responding, the targeted Cp of propofol was fixed until the end of the study, and 0.8 mg/kg rocuronium was given. Endotracheal 4% lidocaine (2 ml) was administered before tracheal intubation to reduce the hemodynamic response. After the trachea was intubated, mechanical ventilation commenced to maintain the end-tidal carbon dioxide between 30 and 35 mmHg with 45% O_2 in the air at a fresh gas flow rate of 6 l/min. For blood sampling, a 22-gauge catheter was inserted in the radial artery contralateral to the venous catheter for propofol infusion. For the administration of the study fluids, an 18-gauge catheter was placed in an instep peripheral vein. We began administering the study fluids at least 30 min after the start of the propofol infusion.

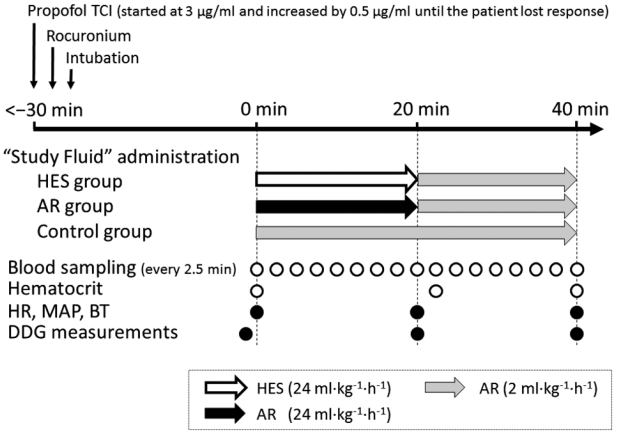

Fig. 1. Study protocol. Propofol was administered using plasma-targeted target-controlled infusion (TCI) on the Marsh pharmacokinetic model.[13] When a patient responded to verbal commands at the effect-site concentration being the targeted plasma concentration minus one, *e.g.*, the effect-site concentration was 2 μg/ml when the targeted plasma concentration was 3 μg/ml, the targeted concentration was increased by 0.5 μg/ml. In the 6% hydroxyethyl starch (HES) and acetated Ringer's (AR) solution groups, HES and AR solution was infused at 24 $ml \cdot kg^{-1} \cdot h^{-1}$ during the first 20 min, respectively, followed by infusion of AR at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the next 20 min. In the control group, AR was infused at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the 40 min. Blood samples to determine the plasma concentration of propofol were taken every 2.5 min. Hematocrit, heart rate (HR), mean arterial pressure (MAP), body temperature (BT), and pulse dye densitogram (DDG) measurements including cardiac output, blood volume, and indocyanine green disappearance rate were assessed three times.

Study Fluid Administration

The patients were randomly allocated to one of three groups: the hydroxyethyl starch (HES) solution group, the acetated Ringer's (AR) solution group, and the control group, in a patient-blinded fashion using a permuted block design with a block size of three. All patients were administered the following study fluids for 40 min (fig. 1). In the HES group, 8 ml/kg of 6% HES 70/0.5 solution (SALINHES fluid solution 6%®, Fresenius Kabi Japan, Japan) was infused at 24 $ml \cdot kg^{-1} \cdot h^{-1}$ during the first 20 min. In the AR group, 8 ml/kg of AR solution (Veen-F Injection®, Kowa Pharmaceuticals, Japan) was infused at 24 $ml \cdot kg^{-1} \cdot h^{-1}$ during the first 20 min. In both the HES and AR groups, AR solution was infused at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the last 20 min. In the control

group, AR solution was infused at 2 ml·kg^{-1}·h^{-1} for the full 40 min. An infusion pump (TE-171, Terumo Corporation, Japan) was used to administer the study fluids. No other fluid was administered from the onset of propofol administration to the end of the study fluid administration period.

Sample Acquisition and Handling

Arterial blood samples were taken every 2.5 min during the study fluid administration period (fig. 1). All of the samples were used to measure the Cp of propofol, and three samples that were taken at 0, 22.5, and 40 min after the start of the study fluid administration were used to measure the hematocrit. The samples for the Cp measurements were centrifuged. The plasma was transferred to polyethylene tubes and stored at −20°C until assayed. The hematocrit was determined using Stat Profile M® (Nova Biomedical, Japan).

Measurements during Fluid Administration

The mean arterial pressure, heart rate, and body temperature were recorded at 0, 20, and 40 min after the start of the study fluid administration (fig. 1). The CO, blood volume, and indocyanine green disappearance rate were determined using a pulse dye densitogram (DDG) analyzer with an earlobe or finger sensor (DDG-3300, Nihon Kohden, Japan). The accuracy of the CO measurement has been confirmed using the thermodilution method, and the percentage difference in the mean CO measured by DDG and the thermodilution method was 4.5 ± 19.6% (mean ± SD).[19] The accuracy of the other DDG measures, *i.e.*, the blood volume and indocyanine green disappearance rate, has also been confirmed using the standard radioisotope method[20] and measured indocyanine green concentrations,[21] respectively. For the DDG measurements, 10 mg indocyanine green (Diagnogreen, Daiichi Pharmaceutical, Japan) was administered followed by a 20-ml saline flush *via* the instep peripheral vein before and 20 and 40 min after the start of study fluid administration (fig. 1). The first DDG measurement was completed immediately before the start of fluid administration. The effective HBF was calculated as the blood volume multiplied by the indocyanine green disappearance rate.[20]

Drug Assay

The total Cp of propofol was determined using high-performance liquid chromatography (RF-550, CTO-10AS, LC-10AD, SIL-10AD, SCL-10A, and DGU-14A; Shimadzu, Japan) with fluorescence detection at an emission wavelength of 310 nm after an excitation wavelength of 276 nm.[22] To each 200-μl sample, 500 μl of precipitating solution (acetonitrile) and 1 μg thymol (internal standard) were added. The samples, which were mixed with a vortex mixer, were centrifuged for 10 min. Then, 50 μl of the supernatant of the mixed samples was injected into a 25 cm × 4.6-mm ID Inertsil ODS-3 high-performance liquid chromatography column (GL Science, Japan). The detection limit of this apparatus is 10 ng/ml, and we confirmed the linearity of the signal concentration ratio from 50 ng/ml to 50 μg/ml (r^2 = 0.9998).

Statistical Analysis

The sample size was determined using the following conditions: to detect a 0.3 difference in the "Cp ratio," which was the primary outcome measure and was defined as the measured Cp divided by the measured Cp at 0 min in an individual, between the HES and control groups; an assumption that the variance of the Cp ratio was 0.2 in all groups based on previous data[9]; and to have a power of 0.80 and an α of 0.05. Thus, the required sample size was determined to be 11 for each group.

The ratios of Cp, mean arterial pressure, heart rate, hematocrit, CO, blood volume, and effective HBF were calculated as the estimate divided by the baseline estimate at 0 min or before the start of the study fluid administration. Time courses of the Cp ratios are described with the Friedman supersmoother, which is a nonparametric regression estimate.[23] Numerical data are expressed as the mean ± SD or mean ± SD (range). Repeated measures two-way analysis of variance was used, with the group as one factor and time as the repeated measures factor. The main effect of time or group is presented as the F [dfn, dfd], where dfn represents the degrees of freedom of the numerator and dfd the degrees of freedom of the denominator. For each analysis of variance, patients with missing values were excluded. The Sidak test was applied for the *post hoc* analysis after the two-way analyses for multiple comparisons between the groups at each time point or between the first and later measurements within a group. A multiplicity adjusted *P* value (referred to simply as *P* value) of less than 0.05 was regarded as significant. Statistical analyses were performed using Prism 6.07 (GraphPad Software, USA) and R version 3.2.2 (http://www.R-project.org; accessed September 18, 2015).

Results

Thirty-six patients (12 patients in each group) completed the current study (fig. 2). One patient was excluded because a vasopressor had to be administered to treat hypotension. No other patients experienced hemodynamic instability during the study. Six patients were excluded due to technical problems with the DDG measurement (insufficient sensor fitting): two patients (one in each of the AR and control groups) had insufficient CO measurements and five patients (four in the AR group and one in the HES group) had insufficient blood volume and indocyanine green disappearance

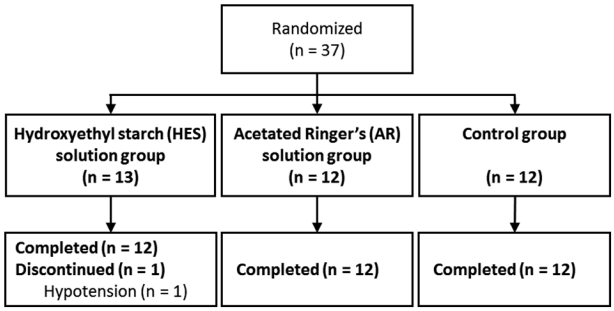

Fig. 2. Flow diagram. AR = acetated Ringer's solution; HES = 6% hydroxyethyl starch.

Table 1. Patient Characteristics

	HES Group (n = 12)	AR Group (n = 12)	Control Group (n = 12)
Male/female	8/4	9/3	7/5
Age (yr)	63 ± 8	64 ± 8	62 ± 11
Height (cm)	164 ± 9	163 ± 8	163 ± 8
Weight (kg)	60 ± 10	58 ± 12	57 ± 9

AR = acetated Ringer's (solution); HES = hydroxyethyl starch (solution).

rate measurements. The patient characteristics are shown in table 1. All data from these patients were used for the analyses. The hemodynamic variables, body temperature, and DDG measurements are shown in table 2. All patients lost their response to verbal commands at the target Cp of propofol, up to 4.5 μg/ml. The targeted Cp during study fluid administration was 3 or 3.5 μg/ml for all patients, with the exception of two patients in the AR group who required a target Cp of 4.0 or 4.5 μg/ml. The time courses of the measured Cp are shown in figure 3. There were no differences in the measured concentrations at 0 min across the groups (5.5 ± 1.9 [2.5–9.0] μg/ml in the HES group; 4.9 ± 1.8 [1.7–7.5] μg/ml in the AR group, $P = 0.834$ *vs.* HES group; 5.7 ± 1.9 [3.3–9.0] in the control group, $P = 0.992$ *vs.* HES group and $P = 0.682$ *vs.* AR group). There were no episodes of anesthetic awareness in any patients.

The time courses and values for the Cp ratios are shown in figure 3 and table 3. Two-way analysis of variance revealed significant main effects of group (F [2, 33] = 14.14, $P < 0.001$) and time (F [16, 528] = 10.37, $P < 0.001$) and a significant interaction between group and time (F [32, 528] = 2.82, $P < 0.001$). The rapid infusion of HES significantly decreased the propofol Cp at 10 to 40 min, compared with the Cp at 0 min, by 22 to 37% (P values are shown in table 3), whereas no significant reductions in the propofol Cp were observed during the rapid or slow infusion of AR solution (AR or control groups, respectively) over the 40-min period. When comparing the Cp ratios among the groups, the Cp ratio in the HES group was significantly lower than the Cp ratio in the AR group, by 17 to 34% between 5 and 40 min, and significantly lower than the ratio in the control group, by 18 to 35% between 10 and 40 min (P values are shown in table 3).

The ratios of the mean arterial pressure, heart rate, hematocrit, CO, blood volume, and effective HBF are shown in figure 4. No significant differences in the mean arterial pressure were observed within or among the groups (fig. 4A; main effect of group: F [2, 33] = 0.48, $P = 0.624$; main effect of time: F [2, 66] = 0.31, $P = 0.732$; interaction between group and time: F [4, 66] = 1.85, $P = 0.130$). The heart rate at 20 and 40 min was lower than that at 0 min by 14 and 19% in the HES group, 12 and 12% in the AR group, and 9 and 10% in the control group, respectively ($P < 0.001$ for all comparisons, fig. 4B; main effect of group: F [2, 33] = 3.53, $P = 0.041$; main effect of time: F [2, 66] = 86.2, $P < 0.001$; interaction: F [4, 66] = 2.87, $P = 0.030$). The heart rate at 40 min in the HES group was significantly lower than the heart rates in the AR group by 6% ($P = 0.021$) and in the control group by 9% ($P = 0.001$, fig. 4B). Both rapid

Table 2. Hemodynamic Variables, Body Temperature, and Pulse Dye Densitogram Measurements

	Group	Before/0 min	20/22.5 min	40 min
Mean arterial pressure (mmHg)	HES (n = 12)	68 ± 18	69 ± 10	71 ± 11
	AR (n = 12)	69 ± 15	72 ± 15	66 ± 12
	Control (n = 12)	67 ± 9	65 ± 8	67 ± 6
Heart rate (/min)	HES (n = 12)	69 ± 9	59 ± 7	55 ± 6
	AR (n = 12)	73 ± 14	64 ± 12	64 ± 12
	Control (n = 12)	69 ± 15	63 ± 14	61 ± 12
Hematocrit (%)	HES (n = 12)	36 ± 3	31 ± 3	32 ± 3
	AR (n = 12)	36 ± 3	32 ± 4	33 ± 4
	Control (n = 12)	35 ± 5	35 ± 5	35 ± 5
Body temperature (°C)	HES (n = 12)	36.0 ± 0.5	35.7 ± 0.6	35.7 ± 0.6
	AR (n = 12)	36.2 ± 0.4	36.0 ± 0.5	36.0 ± 0.5
	Control (n = 12)	36.3 ± 0.4	36.1 ± 0.5	36.0 ± 0.5
Cardiac output (l/min)	HES (n = 12)	4.6 ± 1.6	4.2 ± 1.0	4.0 ± 1.0
	AR (n = 11)	4.0 ± 1.3	3.8 ± 1.4	3.8 ± 1.3
	Control (n = 11)	4.0 ± 1.2	3.2 ± 0.7	3.3 ± 0.6
Blood volume (l)	HES (n = 11)	5.2 ± 1.4	5.1 ± 1.0	5.1 ± 1.0
	AR (n = 8)	4.5 ± 1.2	4.4 ± 0.9	4.4 ± 0.9
	Control (n = 12)	4.4 ± 1.1	4.2 ± 0.9	4.1 ± 0.7
Indocyanine green disappearance rate (/min)	HES (n = 11)	0.180 ± 0.043	0.223 ± 0.039	0.221 ± 0.033
	AR (n = 8)	0.188 ± 0.029	0.202 ± 0.025	0.198 ± 0.025
	Control (n = 12)	0.190 ± 0.062	0.174 ± 0.037	0.197 ± 0.038

Hematocrit was assessed at 0, 22.5, and 40 min; heart rate, mean arterial pressure, and body temperature were assessed at 0, 20, and 40 min; the other variables were assessed before and 20 and 40 min after the start of the study fluid administration. Cardiac output, blood volume, and indocyanine green disappearance rate were assessed using a pulse dye densitogram analyzer.

AR = acetated Ringer's (solution); HES = hydroxyethyl starch (solution).

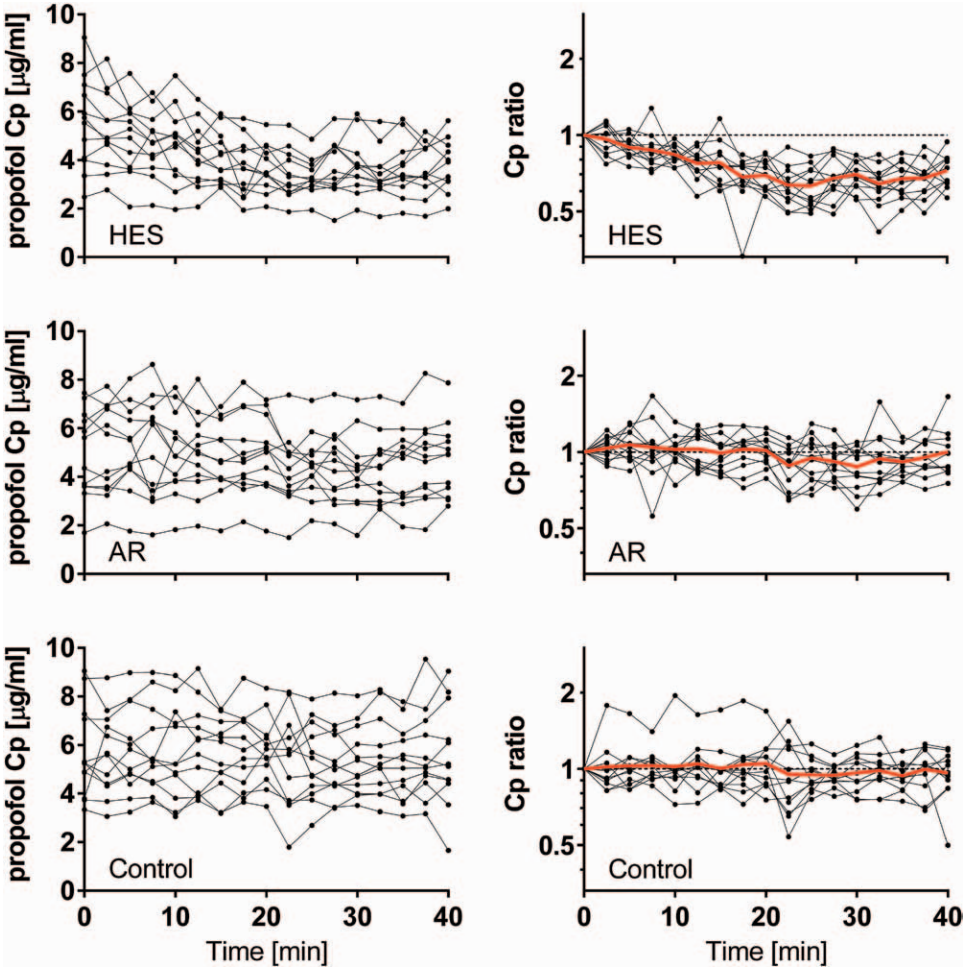

Fig. 3. Time courses of measured plasma concentration (Cp) and Cp ratio of propofol. Each *black circle* indicates each measured Cp or Cp ratio. All measures in an individual are connected with *lines*. The Cp ratio was defined as the Cp divided by the Cp at 0 min. *Red line* indicates the Friedman supersmoother, which is a nonparametric regression estimate.[23] AR = acetated Ringer's solution; HES = 6% hydroxyethyl starch solution.

infusions significantly decreased the hematocrit by 13% at 22.5 min and 12% at 40 min in the HES group, and by 10% at 22.5 min and 8% at 40 min in the AR group ($P < 0.001$ for all, fig. 4C; main effect of group: F [2, 33] = 13.68, $P < 0.001$; main effect of time: F [2, 66] = 47.62, $P < 0.001$; interaction: F [4, 66] = 10.04, $P < 0.001$). The CO in the control group significantly decreased by 18% at 20 min ($P = 0.001$) and by 15% at 40 min ($P = 0.009$, fig. 4D; main effect of group: F [2, 31] = 1.71, $P = 0.197$; main effect of time: F [2, 62] = 6.03, $P = 0.004$; interaction: F [4, 62] = 1.68, $P = 0.167$) compared to the CO at 0 min. In the other groups, the COs were similar over the 40-min period. No significant differences in the estimated blood volume were observed over time (fig. 4E; main effect of group: F [2, 28] = 0.93, $P = 0.406$; main effect of time: F [2, 56] = 0.18, $P = 0.834$; interaction: F [4, 56] = 0.89, $P = 0.475$). The rapid infusion of HES for 20 min significantly increased the effective HBF by 27% at 20 min ($P < 0.001$) and by 26% at 40 min ($P < 0.001$, fig. 4F; main effect of group: F [2, 28] = 3.68, $P = 0.038$; main effect of time: F [2, 56] = 5.37, $P = 0.007$; interaction: F [4, 56] = 3.67, $P = 0.010$) compared to the effective HBF at 0 min. In the other groups, no significant changes in the effective HBF were noted during the study fluid administration period.

Discussion

We found that the rapid infusion of 6% HES 70/0.5, but not AR solution (8 ml/kg), over a 20-min period decreased the propofol Cp to 63% of the baseline Cp during TCI at a fixed targeted Cp (fig. 3 and table 3). Moreover, the rapid infusion of HES significantly increased the HBF by approximately 25% (fig. 4). Under the settings of the current study, the decreased CO had little influence on the propofol Cp.

The increase in the effective HBF was the only significant reason for the decrease in the measured Cp of propofol during TCI in the current study. When comparing the findings between the HES and AR groups, the propofol Cp decreased and the effective HBF increased during the rapid infusion of HES, whereas neither the propofol Cp nor the effective HBF changed during the rapid infusion of AR solution

Table 3. Plasma Concentration Ratio of Propofol

	HES Group		AR Group		Control Group		*P* Value between Groups		
Time (min)	Cp Ratio	*P* Value *vs.* 0 min	Cp Ratio	*P* Value *vs.* 0 min	Cp Ratio	*P* Value *vs.* 0 min	HES *vs.* AR	HES *vs.* Control	AR *vs.* Control
0	1	–	1	–	1	–	–	–	–
2.5	0.96 ± 0.12	> 0.999	1.04 ± 0.11	> 0.999	1.02 ± 0.26	> 0.999	0.640	0.801	0.992
5.0	0.90 ± 0.09	0.399	1.07 ± 0.15	0.942	1.03 ± 0.22	> 0.999	0.037	0.160	0.911
7.5	0.87 ± 0.15	0.126	1.04 ± 0.27	0.999	1.03 ± 0.14	> 0.999	0.038	0.067	0.995
10.0	0.84 ± 0.07	0.014	1.02 ± 0.14	> 0.999	1.02 ± 0.30	> 0.999	0.022	0.026	> 0.999
12.5	0.77 ± 0.10	< 0.001	1.03 ± 0.18	> 0.999	1.05 ± 0.23	0.999	< 0.001	< 0.001	0.992
15.0	0.78 ± 0.16	< 0.001	0.99 ± 0.15	> 0.999	1.00 ± 0.24	> 0.999	0.006	0.003	0.997
17.5	0.68 ± 0.13	< 0.001	1.03 ± 0.17	> 0.999	1.04 ± 0.28	> 0.999	< 0.001	< 0.001	0.997
20.0	0.69 ± 0.10	< 0.001	1.01 ± 0.13	> 0.999	1.05 ± 0.25	0.997	< 0.001	< 0.001	0.937
22.5	0.63 ± 0.12	< 0.001	0.88 ± 0.16	0.224	0.95 ± 0.30	0.986	0.001	< 0.001	0.768
25.0	0.63 ± 0.11	< 0.001	0.95 ± 0.20	0.995	0.95 ± 0.15	0.993	< 0.001	< 0.001	> 0.999
27.5	0.67 ± 0.13	< 0.001	0.92 ± 0.15	0.766	0.94 ± 0.10	0.986	0.001	0.000	0.976
30.0	0.70 ± 0.10	< 0.001	0.87 ± 0.16	0.138	0.96 ± 0.16	> 0.999	0.033	0.000	0.474
32.5	0.64 ± 0.11	< 0.001	0.94 ± 0.25	0.981	0.98 ± 0.16	> 0.999	< 0.001	< 0.001	0.901
35.0	0.67 ± 0.11	< 0.001	0.91 ± 0.12	0.700	0.94 ± 0.12	0.967	0.002	< 0.001	0.980
37.5	0.68 ± 0.11	< 0.001	0.95 ± 0.15	0.998	1.00 ± 0.18	> 0.999	< 0.001	< 0.001	0.892
40.0	0.72 ± 0.11	< 0.001	1.00 ± 0.24	> 0.999	0.96 ± 0.19	> 0.999	< 0.001	0.002	0.915

AR = acetated Ringer's (solution); Cp = plasma concentration; HES = hydroxyethyl starch (solution).

(figs. 3 and 4 and table 3). In both groups, the hematocrit decreased and the COs were similar during the fluid infusion (fig. 4). According to the traditional pharmacokinetic theory, the clearance of high hepatic extraction drugs will be affected by changes in HBF.[17] As the hepatic extraction ratio of propofol was reported to be high, at 0.87,[15] the increased HBF caused by the rapid infusion of HES likely increased the hepatic metabolic clearance of propofol. A previous study showed that goal-directed colloid, but not crystalloid, administration increased the microcirculatory blood flow in the small intestine.[24] Another study revealed that HES improved rheology after acute normovolemic hemodilution.[25] The principal determinants of HBF are the vascular resistance across the intestine, the hepatic arterial resistance, and hydrodynamic interactions.[26] Rheologic change may be a reason for the HBF increment in the HES group. Additionally, propofol itself might enhance the HBF increase in the HES group. HBF increased by approximately 25% in the current study, while a rapid infusion of 500 ml of 6% HES (130/0.4) within 10 min increased the HBF by 11% before the induction of general anesthesia.[18] The decrement of propofol Cp (fig. 3) suggests that more propofol may flow into the liver. In an animal study, propofol increased the total HBF in a dose-dependent fashion.[27] Otsuki *et al.*[28] reported that, against blood withdrawn to a hematocrit at 15% over 30 min, a 1:1 fluid replacement with 6% HES 200/0.5 reduced the systemic vascular resistance index to 47%, whereas a 3:1 fluid replacement with lactated Ringer's solution (1 ml bleeding was replaced with 3 ml of solution) reduced it to 61%. Additional crystalloid infusions might increase the HBF, although we did not infuse the crystalloid more than the colloid to avoid fluid overload.

The COs at 20 and 40 min in the control group were approximately 20% less than the COs in the AR group (fig. 4). However, the time course of the Cp did not change in both groups (fig. 3). These results indicated that the CO had little influence on the propofol Cp in the current study. The reduction in CO in the control group may be caused not by propofol but by a decrease in sympathetic nervous system activity after tracheal intubation. It was reported that propofol reduced systemic vascular resistance but not CO after a 2 mg/kg bolus followed by 6 mg kg^{-1} h^{-1} over 60 min without tracheal intubation.[29] It might be expected that the propofol Cp would increase in the control group due to significant CO reduction. Kurita *et al.*[10] reported that the propranolol-induced CO reduction decreased the propofol Cp, which contrasts our result. This discrepancy might be caused by propranolol, which leads to a greater decrease in the splanchnic blood flow than what occurs after a reduction in CO alone in patients with liver function impairment.[30] When considering the first-pass and recirculated Cps[31] of propofol (the sum of these is total propofol Cp) in the control group, first-pass Cp may increase because of CO reduction. As propofol Cp did not change over time, recirculated Cp might decrease due to an increase in distribution clearance but not due to an increase in metabolic clearance because of HBF reduction (although insignificant; fig. 4). In the control group, the following factors might increase the amount of intravascular propofol transferring to the extravascular space, which results in an increase in distribution clearance: velocity of drug transportation in a peripheral vein decreases with CO reduction; peripheral perfusion improves with a decrease in systemic vascular resistance by propofol regardless of the change in CO.[32]

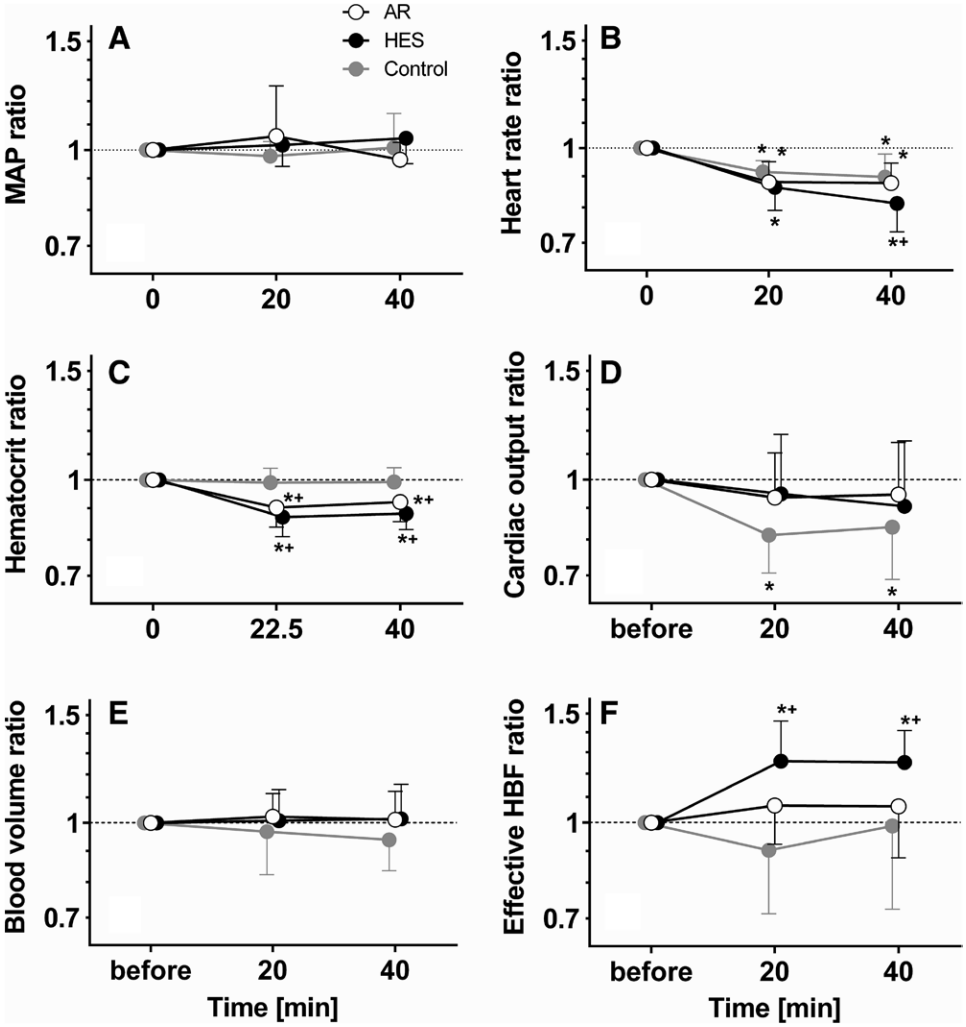

Fig. 4. The changes of mean arterial pressure (MAP), heart rate, hematocrit, cardiac output, blood volume, and effective hepatic blood flow (HBF). The ratios were defined as the estimate of MAP, heart rate, hematocrit, cardiac output, blood volume, or effective HBF divided by the baseline estimate assessed before or at the start of propofol administration. The cardiac output, blood volume, and indocyanine green disappearance rate were determined using pulse dye densitogram. The effective hepatic blood flow was calculated as the blood volume multiplied by the indocyanine green disappearance rate. Each *circle* and *whisker* indicate the mean and SD of the variable. *Significant difference within the same group *versus* the baseline estimate (in *B*: $P < 0.001$ at 20 and 40 min for all groups; in *C*: $P < 0.001$ at 22.5 and 40 min for the hydroxyethyl starch [HES] solution and acetated Ringer's [AR] solution groups; in *D*: $P = 0.001$ at 20 min and 0.009 at 40 min for the control group; in *F*: $P < 0.001$ at 20 and 40 min for the HES group). +Significant difference at the same time point *versus* the control group (in *B*: $P = 0.001$ at 40 min in the HES group; in *C*: $P < 0.001$ at 22.5 and 40 min in the HES group and at 22.5 min in the AR group, $P = 0.001$ at 40 min in the AR group; in *F*: $P < 0.001$ at 20 min and = 0.042 at 40 min in the HES group), or *versus* the AR group (in *B*: $P = 0.021$ at 40 min in the HES group).

Hemodilution did not influence the propofol concentration. Although the hematocrit decreased in the AR group but not in the control group (fig. 4), the time course of the propofol Cp was similar in both groups (fig. 3). This was expected because intravenous propofol is rapidly distributed to the extravascular space, which is much larger than the intravascular space.[12–14] Massey *et al.*[12] reported that the propofol concentration obtained from the radial artery during continuous infusion was not altered by the onset of cardiopulmonary bypass with an extra 2.2 l of crystalloid.

The mean arterial pressure was stable during the study fluid administration period, while the heart rate decreased from 0 to 20 min after the study fluid administration was initiated (fig. 4). The change in the heart rate did not influence the measured propofol Cp, as the propofol Cp did not change over the 40-min period in the control group (fig. 3). Because the CO also decreased between 0 and 20 min after initiating the study fluid administration (fig. 4), approximately 50 min would be necessary to achieve a stable hemodynamic state after starting propofol TCI.

The assessed blood volumes in the HES and AR groups were not significantly different from the blood volume in the control group, although 8 ml/kg of fluid was infused during general anesthesia. Similarly, Simon *et al.*[18] reported that the blood volume assessed with a DDG analyzer did not increase after a 500-ml colloid infusion in orthopedic, urologic, gynecologic, or abdominal surgery patients before anesthesia induction. In contrast, Ueyama *et al.*[33] reported that the assessed blood volume significantly increased after a 500-ml colloid infusion in full-term pregnant patients before anesthesia induction. Patient characteristics such as age and pregnancy might influence the blood volume assessments. The time courses of the blood volume and hematocrit were similar between the HES and AR groups, although the HES group is expected to have a greater blood volume. As propofol reduces systemic vascular resistance,[32] the clearance of crystalloid from the circulation to the extravascular space might be slower due to lower peripheral vascular pressure.[34]

Possible causes of decreasing propofol Cp in the HES group remain unclear but include an increase in the distribution clearance or free propofol fraction. The distribution clearance might increase due to an improvement in the microcirculation, which may increase the amount of intravascular propofol transferring to the extravascular space, after HES administration.[24] The free propofol fraction might also be increased by HES administration because propofol is highly bound to serum proteins.[35] However, as the hepatic extraction ratio of propofol is high (0.87),[15] a change in the free fraction of propofol would have only a small influence on its hepatic clearance.

To compensate for the altered propofol clearance in patients receiving HES solutions rapidly, the infusion rate of propofol could be changed. Using similar conditions in the HES group (an 8 ml/kg HES infusion over 20 min is performed 30 min after the start of propofol TCI at 3 μg/ml with the Marsh model[13]), the following dosing theoretically maintains the propofol Cp at approximately constant in an average patient: target concentration increased up to 1.6 times (reciprocal of 0.63, which is the minimum Cp ratio in the HES group) or infusion rates increased to 1.2, 1.4, 1.5, 1.7, 1.9, 1.7, 1.6, and 1.3 times every 5 min over 40 min.

One limitation of the current study was that we took blood samples during the 20-min period after the end of the rapid fluid infusion because of the limited amount of time available before the start of surgery. Thus, the duration of the effects of rapid HES infusion on the measured propofol Cp and effective HBF remains unknown. Another limitation was that the infusion volume, infusion speed, or type of fluid may have influenced the measured propofol Cp. The distribution of the measured propofol Cp might limit its clinical relevance, because the measured Cp at 0 min was less than 3 μg/ml in only one patient in each of the HES and AR groups. Although the current study covers a range of 3 to 5 μg/ml, the reported therapeutic range of propofol is 2 to 5 μg/ml.[36] Further investigation is required to address these limitations.

In conclusion, the rapid infusion of 6% HES, but not AR solution (8 ml/kg), for 20 min decreased the propofol Cp during plasma-targeted TCI at a fixed target concentration. As the decrement of propofol Cp may decrease the depth of anesthesia and might result in anesthetic awareness, the targeted Cp or infusion rate of propofol may have to be increased up to 1.6 or 2 times, respectively, during and shortly after the rapid infusion of HES to maintain the desired Cp in our population. It should be noted that appropriate increment of dosage may differ depending on age, which can influence the pharmacokinetics and pharmacodynamics of propofol.[14,37] The increase in the effective HBF that was induced by the HES infusion was found to be the cause of the reduction in the measured propofol Cp. The concentrations of other drugs with high liver extraction ratios may also be decreased by the rapid infusion of HES. In the experimental setting of the current study, the hemodynamic changes, including the changes in the CO and heart rate, did not influence the propofol Cp. Further study is required to examine the pharmacodynamic changes during rapid HES infusion.

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Competing Interests

The authors declare no competing interests.

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Full protocol available at: kenichi@masuinet.com. Raw data available at: kenichi@masuinet.com.

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