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ORIGINAL ARTICLE

Protein sparing during general anesthesia with a propofol solution containing medium-chain triglycerides for gastrectomy: comparison with sevoflurane anesthesia

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Abstract
Purpose Despite the importance of the inhibition of catabolic response to surgery, the effects of different anesthetic techniques on the catabolic response in surgical patients are controversial. This study compared the endocrine-metabolic responses and protein catabolism during gastrectomy in patients who received either sevoflurane or propofol anesthesia with remifentanil.
Methods Thirty-seven patients (American Society of Anesthesiologists status I–III) aged 20–79 years undergoing elective gastrectomy were randomly assigned to receive sevoflurane anesthesia with remifentanil ($n = 19$) or intravenous propofol anesthesia (Propofol-Lipuro® 1 %; B. Braun, Melshungen AG, Germany) with remifentanil ($n = 18$). Urine samples were collected every 1 h after skin incision (0 h) and the urinary 3-methylhistidine:creatinine ratio (3-MH/Cr ratio) was used as a marker of protein catabolism. Respiratory quotient was measured during a 1 h period following skin incision.
Results The 3-MH/Cr ratio significantly increased at 1–2 and 2–3 h compared to 0 and 0–1 h in both groups, but the propofol group exhibited a lower 3-MH/Cr ratio (nmol/μmol) than the sevoflurane group at 1–2 h (15.7 vs. 18.2, $P = 0.012$) and 2–3 h (15.9 vs. 18.1, $P = 0.025$). A difference was observed in the respiratory quotient between the sevoflurane and propofol groups (0.726 vs. 0.707, $P = 0.003$).
Conclusion A lower 3-MH/Cr ratio and a lower respiratory quotient during propofol anesthesia, compared to those exhibited during sevoflurane anesthesia, suggest that protein sparing probably occurs through the utilization of medium-chain triglycerides contained in the fat emulsion of propofol solution as a fuel source.

Keywords Fat emulsion · Free fatty acid · 3-Methylhistidine · Protein metabolism

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Introduction

Despite the consensus that intraoperative protein sparing may improve postoperative recovery [1, 2], the effects of different anesthetic techniques on the immediate catabolic response in surgical patients are controversial [3–6]. A previous study in patients undergoing abdominal hysterectomy showed that propofol anesthesia combined with sufentanil attenuated the hyperglycemic response during surgery compared to enflurane anesthesia combined with fentanyl [4]. However, another study by the same group demonstrated that whole body protein breakdown and glucose metabolism were reduced during surgery, regardless of the anesthesia method. That is, metabolic changes analyzed by isotope dilution during colorectal surgery were comparable for propofol and for desflurane anesthesia supplemented with remifentanil [5]. These controversial findings suggest that metabolic and endocrine responses to surgical stress under different anesthetic methods are greatly affected by the type of surgery. Therefore, the findings in patients undergoing lower abdominal surgery cannot be extrapolated to upper abdominal surgery, with its increased surgical stress.

Another key point to consider when comparing metabolic changes under propofol and inhalational anesthesia is

the considerable amount of fat being supplied as an emulsion during propofol anesthesia. Given that preoperative fasting reduces insulin sensitivity and increases lipolysis [7], it is possible that fat contained in the propofol solution could be used as an energy source to an extent that affects metabolism during surgery.

In this context, this study compared endocrine-metabolic responses and protein catabolism during gastrectomy in patients who received general anesthesia with sevoflurane or propofol combined with remifentanil. The primary outcome measure was the time course of urinary excretion of 3-methylhistidine, which is known to be a noninvasive marker of protein catabolism [8, 9], and the secondary outcome measure was the respiratory quotient (RQ) during surgery. The aim of this study was to determine whether general anesthesia with propofol had a different effect on endocrine-metabolic responses and thus protein catabolism during gastrectomy compared to general anesthesia with sevoflurane.

Materials and methods

Patients

The study was approved by the Institutional Review Board of Hyogo College of Medicine (no. 578; May 14, 2008), and informed consent was obtained from all patients. Forty consecutive patients (American Society of Anesthesiologists physical status I–III) aged 20–79 years who underwent elective gastrectomy between June 2008 and October 2009 were included. Patients with cardiac, hepatic, renal, or metabolic disorders or those receiving any medication known to affect metabolism were excluded.

Procedure

All patients fasted from midnight before the surgery. Patients were randomly assigned by a computerized random number generator to receive inhalational anesthesia with a combination of sevoflurane and remifentanil (Sevo group, $n = 20$) or intravenous anesthesia with a combination of propofol (Propofol-Lipuro® 1 %; B. Braun, Melshungen AG, Germany) and remifentanil (Prop group, $n = 20$). Propofol-Lipuro® 1 % is an oil-in-water emulsion containing 1 % propofol in a 1:1 mixture of 5 % medium- and 5 % long-chain triglycerides (MCT/LCT). Anesthesia in both groups was induced with propofol 2 mg/kg and remifentanil. Tracheal intubation was facilitated by 0.1 mg/kg vecuronium, and the lungs were ventilated to normocapnia (35–40 mmHg) with oxygen-enriched air (inspired O_2 fraction = 0.4). Anesthesia in the Prop group was maintained by continuous infusion of propofol at a rate of 10 mg/kg/h, and reduced to 6 mg/kg/h after 10 min, according to the previous study [2]. In the Sevo group, anesthesia was maintained with sevoflurane at end-tidal concentrations of 1–2 %. End-tidal sevoflurane concentrations during surgery and the infusion rate of remifentanil in both groups were adjusted to maintain a bispectral index of 40–60, and to keep heart rate and mean arterial blood pressure within 30 % of the preoperative values. An epidural catheter was indwelled before the induction of anesthesia and used only for postoperative pain relief. Acetated Ringer's solution (10 ml/kg) was administered during the period from induction of anesthesia to skin incision to compensate for fasting-induced fluid depletion, and at an infusion rate of 6–12 ml/kg/h during surgery. Packed red blood cells were transfused when the blood hemoglobin concentration was <8–9 g/dl. A rewarming cover blanket system and fluid warmers were used to maintain the body temperature of patients above 36 °C during surgery.

Blood and urine sampling

A radial artery was cannulated to provide access for blood sampling. Serum samples for the analysis of serum concentrations of metabolic substrates (glucose, ketone bodies, free fatty acids, triglycerides) and hormones (insulin, cortisol) were drawn immediately before skin incision (i.e., 0 h) and at 2 and 4 h after skin incision. Each blood sample was immediately transferred to a tube and centrifuged at 4 °C. The serum obtained was stored at −70 °C. Serum concentrations of glucose, ketone bodies, free fatty acids, and triglycerides were measured by enzymatic methods. Insulin and cortisol were analyzed with chemiluminescent enzyme immunoassay and radioimmunoassay, respectively.

Urine samples were collected every hour following skin incision, and the concentrations of 3-methylhistidine (nmol/l) and creatinine (μmol/l) in the collected urine samples were measured by high-performance liquid chromatography and an enzymatic method, respectively. The urinary 3-methylhistidine:creatinine ratio (3-MH/Cr ratio, nmol/μmol) was used as a marker of protein catabolism.

Metabolic measurements

Measurements of oxygen consumption per unit time (VO_2, l/h) and carbon dioxide production (VCO_2, l/h) were carried out every 5 min during surgery using a noninvasive modular metabolic monitor (M-COVX; GE Healthcare, St. Giles, UK). RQ was calculated as VCO_2/VO_2, and the averaged RQ value during each 1 h period following skin incision was used for the analysis.

Statistics

Data are expressed as the mean (SD) or median (interquartile range), depending on the distribution. Patient characteristics were compared between the groups, and the Student's t test or the rank-sum test was used to test for significance. The χ^2 test was used to analyze categorical variables such as gender and American Society of Anesthesiologists physical status.

Differences between and within groups for repeated measurements during surgery (i.e., 3-MH/Cr ratio, serum concentrations of metabolic substrates and hormones, RQ) were analyzed by two-way repeated analysis of variance, with the group as the factor and time points as repeated factors. The Student–Newman–Keuls test was used as a post hoc test for comparison.

Based on a preliminary study, we estimated the 3-MH/Cr ratios as 15–20 for each group with a standard deviation of 2.0. Given that a reduction in the 3-MH/Cr ratio of 2.0 (approximately 10 %) is clinically meaningful, a sample of 17 patients in each group was needed to detect a difference of 2.0 in the means of the 3-MH/Cr ratio with a power of 80 % and a significance level of 0.05. Three additional patients per group were enrolled to compensate for possible dropouts. The SigmaPlot 12 (Systat Software Inc., Chicago, IL, USA) software package was used for statistical analyses and sample size calculation. Statistical significance was accepted at $P < 0.05$.

Results

One patient in the Sevo group and two patients in the Prop group were excluded from the analysis because of conversion to a palliative surgery resulting in short-duration surgery (<3 h) (Fig. 1). Patient characteristics were comparable between the two groups, except for a case with a relatively low age (25 years) in the Prop group (Table 1). The mean infusion rate of remifentanil in the Prop group was high compared to that in the Sevo group [0.31 (0.11) μg/kg/min vs. 0.24 (0.05) μg/kg/min, $P = 0.017$]. Five patients in the Sevo group were transfused packed red blood cells, while no patients in the Prop group were transfused.

Serum concentrations of glucose and ketone bodies significantly increased at 2 and 4 h compared to 0 h in both groups, but there were no differences in these concentrations between the groups (Table 2). The serum concentration of free fatty acids in the Prop group at 0 h was almost double that of the Sevo group ($P < 0.001$), and the Prop group showed a higher level of free fatty acids compared to the Sevo group at 2 h ($P = 0.008$). While no significant changes in free fatty acid concentration with time were found for the Sevo group, the concentration decreased at 2 h and 4 h compared to 0 h for the Prop group ($P < 0.001$). At 2 and 4 h after incision, the serum concentration of triglycerides in the Prop group was almost double that of the Sevo group ($P < 0.001$, $P = 0.002$, respectively). The serum concentration of insulin increased

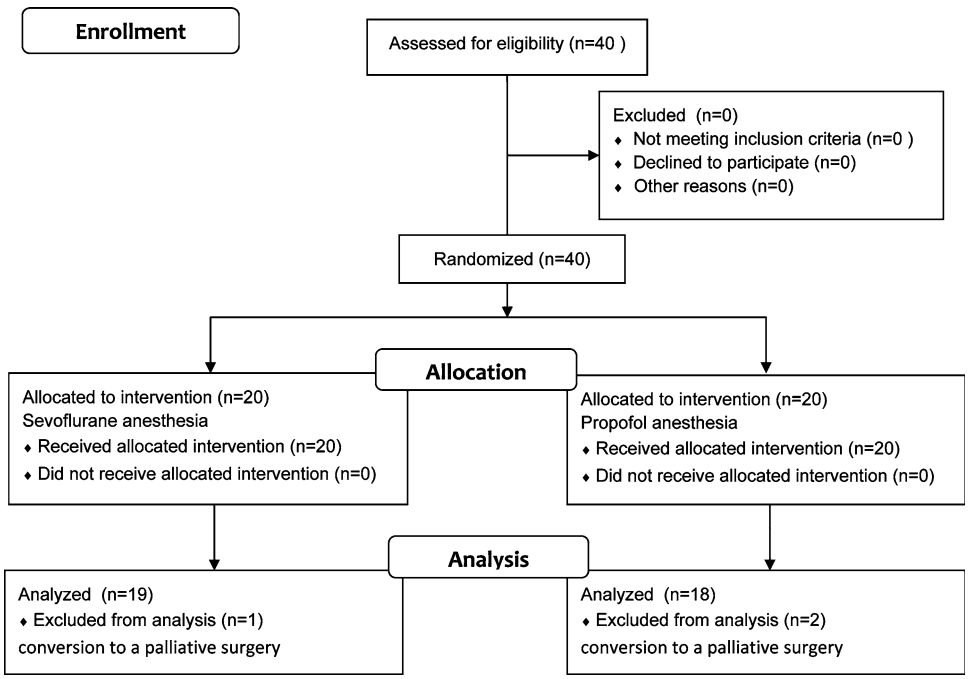

Fig. 1 CONSORT flow diagram

Table 1 Demographic and intraoperative data for the sevoflurane and propofol groups

	Sevoflurane ($n = 19$)	Propofol ($n = 18$)	P value
Gender (male/female)	12/7	13/5	0.33
Age (years)	68 (9)	60 (14)	0.043
Weight (kg)	55.7 (10.6)	58.1 (14.2)	0.58
BMI (kg/m^2)	21.5 (18.7–23.4)	20.5 (18.5–23.7)	0.87
ASA status (I/II/III)	6/10/3	4/13/1	0.76
Duration of fasting (h)	9.0 (9.0–12.0)	9.0 (9.0–13.4)	0.52
Duration of surgery (h)	4.1 (4.0–5.1)	4.1 (4.0–4.6)	0.73
Fluid infusion (ml/kg)	68.5 (61.3–80.0)	64.8 (52.6–93.3)	0.46
Transfusion (ml/kg)	0.0 (0.0–4.7)	0.0 (0.0–0.0)	0.023
Blood loss (ml/kg)	9.3 (5.6–17.2)	7.9 (4.7–11.8)	0.29
Urine (ml/kg)	6.4 (5.3–11.5)	9.2 (3.5–18.8)	0.84

Data are expressed as the mean (SD), median (interquartile range), or number

ASA American Society of Anesthesiologists

Table 2 Serum concentrations of metabolites and hormones in the sevoflurane ($n = 19$) and propofol ($n = 18$) groups

	Time after incision (h)		
	0	2	4
Glucose (mg/dl)			
Sevoflurane	94 (15)	109 (21)*	112 (22)*
Propofol	96 (10)	109 (19)*	109 (20)*
Ketone bodies (mmol/l)			
Sevoflurane	0.71 (0.48)	1.07 (0.58)*	1.11 (0.61)*
Propofol	0.71 (0.55)	0.94 (0.63)$^{\$}$	0.94 (0.73)$^{\$}$
Free fatty acids (mEq/l)			
Sevoflurane	0.98 (0.25)	0.88 (0.23)	0.93 (0.28)
Propofol	2.09 (1.09)¶	1.36 (0.44)*,†	1.23 (0.39)*
Triglycerides (mg/dl)			
Sevoflurane	97.5 (48.8)	78.3 (43.5)$^{\$}$	59.7 (31.6)$^{*,\&}$
Propofol	119.1 (48.6)	146.7 (72.1)*,¶	120.3 (70.0)§,†
Insulin (μIU/ml)			
Sevoflurane	1.84 (1.40)	2.76 (2.36)	2.18 (1.45)
Propofol	2.96 (1.45)	4.07 (2.55)$^{\#,\ddagger}$	2.53 (1.61)$^{\&}$
Cortisol (μg/dl)			
Sevoflurane	8.36 (3.19)	10.8 (7.1)	9.58 (7.34)
Propofol	8.14 (2.58)	10.4 (7.3)	7.85 (6.20)

Data are expressed as mean (SD)

* $P < 0.001$; $^{\$}$ $P < 0.01$; $^{\#}$ $P < 0.05$ (all relative to 0 h)

§ $P < 0.001$

$^{\&}$ $P < 0.01$ (both relative to 2 h)

¶ $P < 0.001$; † $P < 0.01$

‡ $P < 0.05$ (all relative to the sevoflurane group)

at 2 h in the Prop group compared to 0 h ($P = 0.011$), and was higher than that of the Sevo group ($P = 0.036$). As for the serum concentration of cortisol, there were no differences between the groups or time points.

The 3-MH/Cr ratio increased at 1–2, 2–3, and 3–4 h compared to 0 h ($P < 0.001$, $P < 0.001$, $P = 0.013$, respectively) and 0–1 h ($P < 0.001$, $P < 0.001$, $P = 0.002$, respectively) in the Sevo group, and at 1–2 and 2–3 h compared to 0–1 h ($P = 0.011$, $P = 0.010$, respectively) in the Prop group (Fig. 2). The Prop group exhibited a lower 3-MH/Cr ratio (nmol/μmol) than the Sevo group at 1–2 h (15.7 vs. 18.2) and 2–3 h (15.9 vs. 18.1).

The RQs of the two groups (i.e., sevoflurane vs. propofol) exhibited a difference (0.726 vs. 0.707, $P = 0.003$), with a significant difference between the groups at 0–1 h (Table 3).

Discussion

The major finding of the present study was that the Prop group exhibited low urinary excretion of 3-methylhistidine at 1–2 and 2–3 h during surgery and low RQ throughout the surgery compared to the Sevo group. Given that urinary excretion of 3-methylhistidine increases with accelerated protein catabolism [8, 9], this finding suggests that propofol anesthesia may attenuate the time-dependent increase in protein catabolism compared to sevoflurane anesthesia.

The inhibition of protein catabolism during propofol anesthesia suggests a protein-sparing effect of propofol anesthesia. Contrary to the previous findings that insulin level was not affected during surgery under propofol anesthesia [4, 5], the Prop group exhibited an increase in serum insulin level from 0 to 2 h, whereas no changes over time were observed in the Sevo group (Table 2). Protein sparing by exogenous glucose accompanied by an increased insulin level has been observed during colorectal surgery [2]. However, this is likely not the case with the Prop group because no glucose was infused, and the RQ (1.0 for glucose; 0.802 for protein; 0.718 for fat) [10] for propofol anesthesia was significantly lower than that for sevoflurane anesthesia (0.708 vs. 0.734 at 0–1 h). A previous study on patients undergoing colorectal surgery showed that propofol infusion itself decreased plasma cortisol concentration and whole body protein breakdown before skin incision [11]. However, this scenario may not be applicable to our study because we assessed metabolic changes during surgery, and the serum

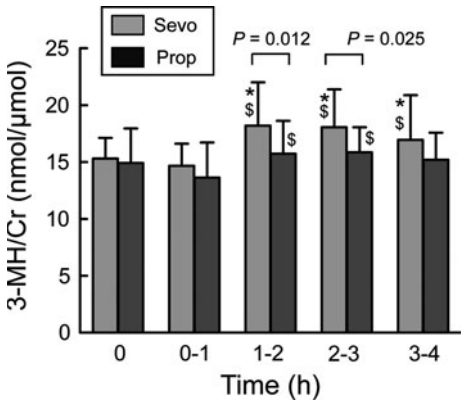

Fig. 2 Comparison of the urinary 3-methylhistidine:creatinine ratio (3-MH/Cr ratio) between the sevoflurane (Sevo, $n = 19$) and propofol (Prop, $n = 18$) groups. Values are presented as the mean (SD). *Different from 0 h; $^{\$}$different from 0–1 h

cortisol concentration did not significantly change throughout surgery (Table 2).

A more probable mechanism of protein sparing in the Prop group is the acceleration of fat utilization during propofol anesthesia. Indeed, a comparable increase in serum ketone bodies in both groups during surgery (Table 2) suggests the utilization of endogenous fat in both groups. However, the low RQ for propofol anesthesia compared to sevoflurane anesthesia indicates accelerated use of fat during propofol anesthesia. Furthermore, given that the mobilization of endogenous fat is stimulated by a decrease in serum glucose level accompanied by low insulin levels [12], the metabolic response of the high serum insulin levels in the Prop group suggests that endogenous fat is unlikely to be responsible for the accelerated utilization. On the other hand, the Prop group received fat (MCT:LCT = 1:1) in the form of fat emulsion contained in the propofol solution. The protein-sparing effect of exogenous MCT has been demonstrated in surgical patients [13] and critically ill patients [14–16]. MCT, compared to LCT, is rapidly hydrolyzed and oxidized to fatty acids and ketones [16]. This scenario is supported by significant increases in the serum concentrations of free fatty acids at 0 h and 2 h in the Prop group compared to the Sevo group. Given that surgery was started 40 min on average after the induction of anesthesia, it is assumed that, at 0 h, a 60 kg patient in the Prop group was given 2 g of MCT (approximate molecular weight 700) and thus 8.6 mEq of fatty acid in the form of triglyceride, while a patient in the Sevo group was given 0.6 g of MCT (only at the induction of anesthesia) and thus 2.6 mEq of fatty acid. Consequently, this difference in the amount of fatty acid (6.0 mEq) is enough to explain the difference in the plasma concentration of free fatty acid at 0 h (i.e., 1 mEq/l, Table 2). Because fatty acid signaling stimulates insulin secretion by β-cells [17], the observed increase in serum insulin in the Prop group may be due to an increase in the serum levels of free fatty acids.

Jiang et al. [13] compared the metabolic effects of MCT and LCT emulsions in perioperative patients receiving total parenteral nutrition and found that MCT was more efficiently cleared by peripheral muscle tissue and improved nitrogen retention. This phenomenon may be associated with increasing plasma levels of ketone and insulin, as observed in the Prop group in the present study. Indeed, the Prop group received 6 mg/kg/h of propofol solution, and this infusion rate corresponds to a fat infusion rate of 0.06 g/kg/h, which is comparable to the infusion of fat emulsion in 10 % Lipofundin (MCT:LCT = 1:1) (0.065 g/kg/h) [13]. Thus, it is conceivable that MCT present in the fat emulsion of the propofol solution can be used as a fuel, thereby limiting protein breakdown. The decreases in the 3-MH/Cr ratio for the Prop group in comparison with the ratio for the Sevo group were 14 % at 1–2 h and 12 % at 2–3 h (Fig. 2), consistent with the previous finding for septic patients: that total parenteral nutrition containing MCT/LCT decreased 3-MH/Cr (nmol/μmol) by 15 % compared with that containing LCT (42.6 vs. 49.9) [14].

The validity of the 3-MH/Cr ratio as a noninvasive marker of protein catabolism during surgery is not fully established. The value of the 3-MH/Cr ratio (nmol/μmol) at 0 h in the present study (i.e., 15) was comparable to that seen for normal subjects [16.4 (0.6), mean (SD), $n = 18$] [18]. Previous studies showed that the intraoperative administration of acetated Ringer's solution containing 1 % glucose, compared to that without the glucose, inhibited the increase in the urinary 3-MH/Cr ratio during

Table 3 Respiratory quotients for the sevoflurane ($n = 19$) and propofol ($n = 18$) groups

	Time (h)			
	0–1	1–2	2–3	3–4
Sevoflurane	0.734 (0.049)	0.723 (0.040)	0.722 (0.042)	0.724 (0.045)
Propofol*	0.708 (0.037)$^{\$}$	0.702 (0.030)	0.710 (0.038)	0.706 (0.027)

Data are expressed as mean (SD)

* Difference for the comparison between the sevoflurane and propofol groups ($P = 0.003$)

$^{\$}$ Difference versus the sevoflurane group ($P = 0.050$)

gastrointestinal surgery [19] and decreased the plasma concentration of 3-methylhistidine at the end of minor otorhinolaryngeal surgeries under general anesthesia [20]. Those patients received glucose corresponding to energies of 0.32–0.4 kcal/kg/h [19] and 0.24 kcal/kg/h [20], which are identical to the energy from MCT (8 kcal/g) in the Prop group, who received MCT at a rate of 0.03 g/kg/h (i.e., 0.24 kcal/kg/h). Given that the plasma concentration of 3-methylhistidine was correlated with the urinary excretion of 3-methylhistidine [21], it is not unreasonable to assume that the 3-MH/Cr ratio may reflect protein catabolism during surgery, although changes in the ratio may be delayed compared to changes in the plasma concentration of 3-methylhistidine.

One limitation of the present study is that the kinetics of metabolic substrates were not examined. Accordingly, it was difficult to determine the tissue availability of these substrates from their circulating concentrations and thus clearly identify which substrates were used for protein sparing. Moreover, the present study cannot exclude direct effects of propofol and sevoflurane on different metabolic patterns between the groups. Second, we cannot completely deny the possibility that different patient characteristics between the groups, such as age, severity of illness, depth of anesthesia, and cytokines might have contributed to the metabolic differences during general anesthesia. While the sevoflurane concentration could be varied, the propofol infusion rate was fixed, thereby leading to an increased remifentanil infusion rate. However, the difference in remifentanil infusion rate between the groups is unlikely to be responsible for the metabolic difference given the minor metabolic effects of the opioid itself [5]. Moreover, transfusion of packed red blood cells in the Sevo group is unlikely to significantly affect metabolism at 1–2 h (i.e., a high urinary 3-MH/Cr ratio), given that transfusion was started at 2 h on average. As serum cortisol concentrations and serum glucose concentrations did not differ between the groups (Table 2), severity of surgical stress was unlikely to be responsible for the metabolic response differences. Finally, the present study cannot discriminate the metabolic effect of fat emulsion from that of propofol itself; therefore, to validate our conclusion, further investigation is required in order to compare metabolic responses between general anesthesia with propofol containing medium-chain triglycerides and that with propofol containing only long-chain triglycerides.

In conclusion, general anesthesia with a solution of propofol and medium-chain triglycerides attenuated protein catabolism during gastrectomy compared to sevoflurane anesthesia. This beneficial effect may be attributed to medium-chain triglycerides in the propofol solution acting as a fuel source. However, it remains to be investigated whether the difference in protein catabolism between propofol and sevoflurane anesthesia seen in the present study persists postoperatively and affects postoperative recovery.

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Conflict of interest The authors have no conflicts of interest.

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