

Effects of Glucose Load on Catabolism during Propofol-Based Anesthesia with Remifentanyl in Patients with Diabetes Mellitus: A Prospective Randomized Trial

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Abstract

Background: Perioperative exacerbation of hyperglycemia and insulin resistance is associated with increased complications in patients with diabetes mellitus. We recently reported that glucose load during anesthesia with sevoflurane suppressed lipid catabolism in diabetic patients. In contrast to inhaled anesthetics, propofol solution contains triglycerides, which can be an energy source during surgery. However, the clinical relevance of glucose load under propofol-based anesthesia in diabetic patients is unknown. Therefore, we investigated the effect of intraoperative glucose load on catabolism during propofol-based anesthesia in patients with diabetes mellitus. **Methods:** Twenty-three patients with diabetes mellitus undergoing elective surgery with propofol-remifentanyl-based anesthesia were randomly assigned to receive a glucose load (1.5 mg/kg/min) or not. Plasma levels of glucose, insulin, cortisol, catecholamines, acetoacetic acid, free fatty acids, ketone bodies, 3-hydroxybutyric acid, and 3-methylhistidine/creatinine, used as a marker for protein catabolism, were measured at the start of surgery and 3 h later. **Results:** Glucose and insulin levels were significantly higher in patients who received a glucose load than in those who did not. Nonetheless, the levels of cortisol and catecholamines were unchanged during surgery. Similarly, the difference in the levels of markers for lipid as well as protein catabolism was not significant between the groups at 3 h after the start of surgery. **Conclusions:** Changes in lipid as well as protein catabolism were not altered by glucose load in diabetic patients under propo-

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fol-based anesthesia with remifentanyl. Our study suggested that continuous infusion of propofol at a clinical dose is sufficient to reduce the requirement for glucose infusion during surgery in patients with diabetes.

Keywords

Diabetes, Propofol, Glucose Infusion, Catabolism

1. Introduction

Impairment of glucose tolerance during anesthesia is induced by stress response to surgery and increases the release of catecholamines and stress hormones such as cortisol, leading to hyperglycemia. A sustained hyperglycemic state may lead to postoperative complications including the attenuation of the immune response to infection, delayed wound healing, and increased mortality in patients with diabetes mellitus [1].

A recent study showed that the infusion of low-dose glucose attenuated fat catabolism without inducing hyperglycemia in non-diabetic patients under remifentanyl-based anesthesia with sevoflurane [2]. We recently reported that glucose load during surgery under remifentanyl-based anesthesia with sevoflurane decreased fatcatabolism in diabetic patients, without changing protein sparing and the secretion of stress hormones regulating glucose homeostasis [3]. The increase in fat catabolism can cause ketoacidosis and elevation of plasma free fatty acids; both of which are linked to sudden death due to increased myocardial oxygen consumption and induction of arrhythmia [4]. Therefore, intraoperative glucose infusion might be beneficial during surgery in patients with diabetes. It is reported that propofol-based anesthesia with sufentanyl prevents elevation of blood glucose, cortisol, and catecholamine concentrations and attenuates the hyperglycemic response, compared with enflurane-based anesthesia in patients undergoing lower abdominal surgery [5]. Taken together with the previous report that preoperative fasting increases lipid catabolism [6], it is likely that the lipid component (*i.e.*, triglycerides) in the propofol solution can be used as an energy source against surgical stress, leading to the prevention of hyperglycemia and catabolism, and reduce the requirement for glucose load, compared with sevoflurane-based anesthesia. Therefore, we investigated the impact of glucose load on fat and protein catabolism in diabetic patients undergoing propofol-based anesthesia with remifentanyl during surgery.

2. Materials and Methods

2.1. Patients

We enrolled 29 ASA II patients undergoing elective surgery from August 2013 to July 2014, who were previously diagnosed with diabetes according to the guidelines of the Japan Diabetes Society (fasting plasma glucose level >126 mg/dL and 75 g oral glucose tolerance test >200 mg/dL, or glycosylated hemoglobin [National Glycohemoglobin Standardization Program] >6.5%, or casual plasma glucose level >200 mg/dL) were enrolled. The patients were randomly assigned to receive a glucose load G(+) or a non-glucose load G(-) (**Figure 1**). The fasting time of all patients was 8 h before entry to the operating room. Patients receiving preoperative glucose infusion, or perioperative corticosteroids, catecholamines, and blood transfusion were excluded from the study.

2.2. Ethics

The study was approved by the Ethics Committee of Kagoshima University Hospital (No. 25-18) on May 31 2013, and registered with the University Hospital Medical Information Network Center (ID: UMIN000010914). Informed consent was obtained from all patients enrolled in this study.

2.3. Anesthesia

After arrival in the operating room, a 20 G catheter was inserted into the patient's forearm and bicarbonate Ringer's solution was infused. Patients in the G(+) group were administered a 10% glucose solution with glucose-free bicarbonate Ringer's solution at a rate of 1.5 mg/kg/min. General anesthesia was induced by targeted

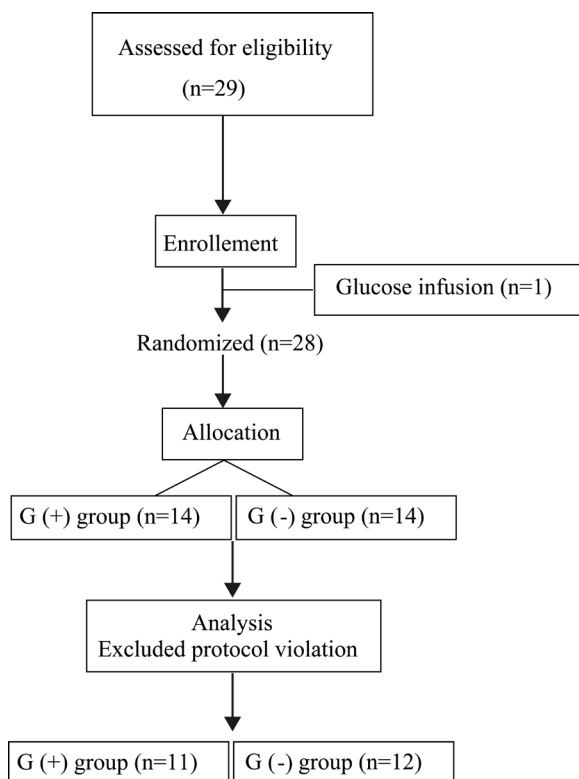


Figure 1. Patient distribution. One of the 29 patients eligible for the study was excluded because of glucose infusion before operation. The remaining 28 patients were randomized to the glucose load G(+) or the non-glucose load G(-) group. After the analysis, 5 patients were excluded because of protocol violation, blood transfusion, or the administration of catecholamines or corticosteroids during surgery.

controlled infusion of propofol (3.0 - 4.0 $\mu\text{g}/\text{mL}$), remifentanyl (0.3 - 0.5 $\mu\text{g}/\text{kg}/\text{min}$), and rocuronium bromide (0.6 mg/kg), and maintained with propofol (2.0 - 3.0 $\mu\text{g}/\text{mL}$) and remifentanyl (0.1 - 0.5 $\mu\text{g}/\text{kg}/\text{min}$) in order that bispectral index was maintained between 40 and 60. Rocuronium bromide was given intermittently based on train-of-four monitoring. Changes in the infusion rate of a glucose-free plasma substitute within 5 - 10 mL/kg/min were allowed, depending on bleeding volume and hemodynamic changes. Plasma concentration of glucose was measured hourly. Insulin was intravenously administered if the plasma concentration of glucose exceeded 200 mg/dL. The tidal volume was set at 8 mL/kg, the respiratory rate at 10 - 12/min, and the O_2/air mixture at FiO_2 0.4 - 0.5 to maintain an end-tidal CO_2 of 35 - 40 mmHg. Patients receiving glucose infusion before operation, corticosteroids, catecholamines, and blood transfusion in the perioperative periods were excluded from the study.

2.4. Measurements

Blood samples were obtained at the start of surgery and 3 h later. Blood samples were centrifuged at 150 g at 4°C for 10 min, and plasma and serum samples were stored at -20°C until analysis. Plasma glucose was measured by the hexokinase UV method, dopamine, adrenaline, and noradrenaline by catecholamine tests, and urine 3-methylhistidine (3-MH) by high-performance liquid chromatography. Serum levels of free fatty acids, ketone bodies, acetoacetic acid, 3-hydroxybutyric acid and creatinine (Cr) were measured enzymatically; serum insulin by a chemiluminescent enzyme immunoassay; and serum cortisol by radioimmunoassay. The assays were performed by SRL Inc (Tokyo, Japan).

2.5. Statistical Analysis

The primary end point was determined based on the previous studies [2] [7]. The minimum number of patients

in each group was 11, with an α value of 0.05 and a power of 80%. Demographic data were analyzed using an unpaired *t* test and χ^2 test. The difference between the groups was evaluated using two-way analysis of variance followed by the Bonferroni test. Data are presented as mean \pm standard deviation. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with Prism 5 (Graph Pad Software, San Diego, CA, USA).

3. Results

One patient was excluded because of preoperative glucose infusion before operation. Three patients from the G(+) group and two from the G(-) were excluded because of protocol violation, blood transfusion, or intraoperative administration of catecholamines or corticosteroids (Figure 1). The characteristics of patients (Table 1) and types of surgical procedures (Table 2) were similar between the two groups.

The plasma glucose level at 3 h after the start of surgery was significantly higher than that at the start of surgery in patients receiving glucose infusion (G(+): 176.5 ± 20.2 vs. 148.4 ± 18.5 mg/dL, respectively; $P = 0.0028$), whereas the glucose level at 3 h was significantly lower than that at the start of surgery in the G(-) group (103.9 ± 10.0 vs. 114.6 ± 12.3 mg/dL, respectively; $P = 0.0294$) (Figure 2). The glucose level at 3 h was significantly higher in the G(+) compared with G(-) group. No patients received perioperative intravenous insulin. Similarly, the serum level of insulin at 3 h was significantly higher than at the start of surgery in the G(+) group (14.8 ± 14.2 vs. 6.2 ± 6.5 μ IU/mL, respectively; $P = 0.0383$), whereas the serum level of insulin was unchanged (4.8 ± 4.9 vs. 4.7 ± 4.7 μ IU/mL, respectively; $P = 0.99$). Serum levels of insulin at 3 h were significantly higher in the G(+) group than in the G(-) group (14.82 ± 14.18 vs. 4.73 ± 4.68 μ IU/ml, respectively; $P = 0.012$). The data of the two groups did not differ significantly with respect to the levels of cortisol, dopamine, adrenaline, and noradrenaline

Table 1. Patient characteristics.

	G(+) (n = 11)	G(-) (n = 12)	<i>P</i> values
Male/female	7/4	6/6	$P = 0.51$
Age (year)	68.1 ± 8.6	67.1 ± 12.3	$P = 0.96$
BMI (kg/m ²)	24.8 ± 3.4	24.8 ± 3.6	$P = 0.95$
Operation time (min)	260 ± 143	212 ± 53	$P = 0.39$
Anesthetic time (min)	406 ± 177	332 ± 49	$P = 0.34$
Blood loss (ml)	121 ± 116	46 ± 55	$P = 0.24$
Transfusion volume (ml)	2566 ± 1182	2130 ± 462	$P = 0.40$

BMI: body mass index; Data are expressed as mean \pm SD.

Table 2. Type of surgical procedure performed.

	G(+) (n = 11)	G(-) (n = 12)
VATS	3	7
Lap-colectomy ESS	1	1
	1	0
Lap-gynecological	0	1
Thyroidectomy	1	0
Tympanoplasty	0	1
Thymectomy	2	0
Laminectomy	1	1
Nephrectomy	1	0
Soft tissue tumor resection	1	1

Lap: laparoscopic, VATS: video-assisted thoracic surgery, ESS: endoscopic sinus surgery.

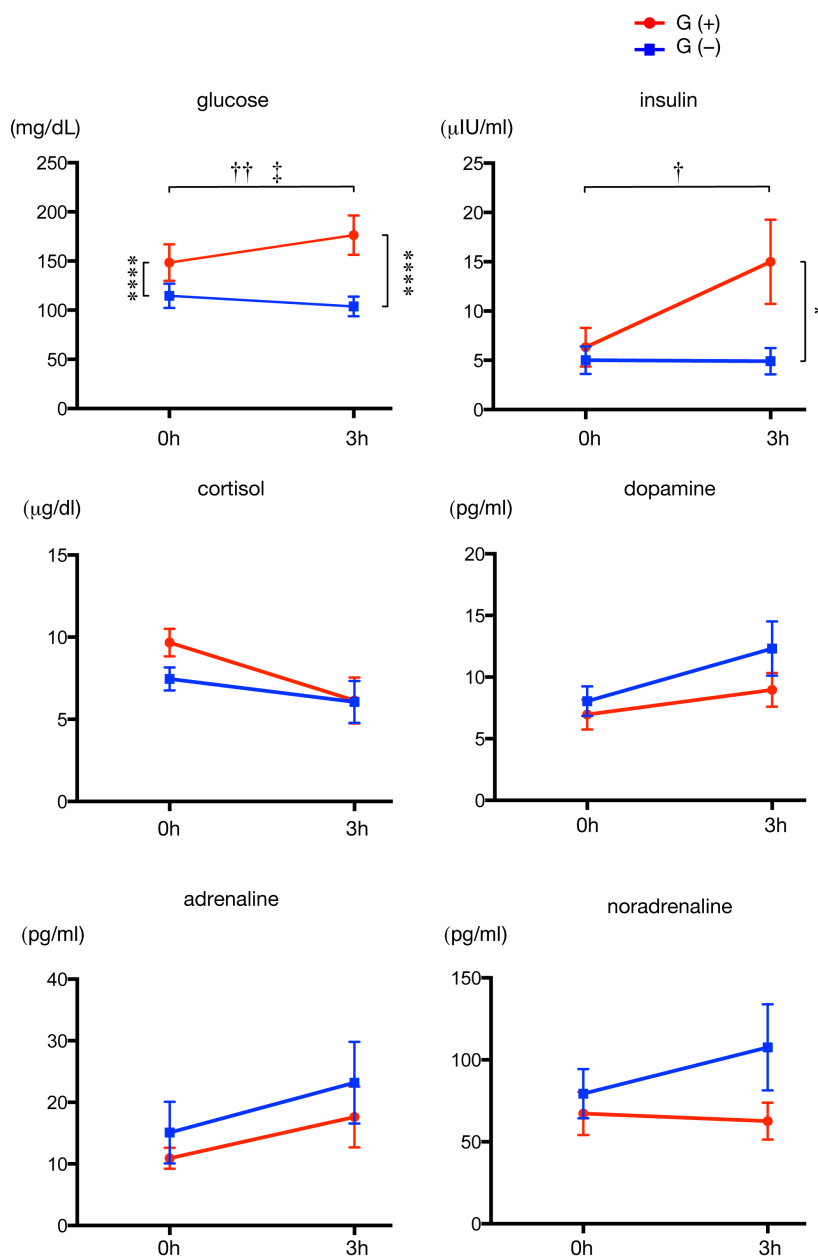


Figure 2. Plasma glucose, serum insulin, and plasma cortisol, dopamine, adrenaline, and noradrenaline levels at the start of surgery (0 h) and 3 h later (3 h) in G(+) and G(-) patients. A two-way analysis of variance was performed followed by Bonferroni's post-hoc comparison. * $P < 0.05$, **** $P < 0.0001$ compared with the G(-) group. † $P < 0.05$, †† $P < 0.01$ compared with 0 h in the G(+) group. ‡ $P < 0.05$ compared with 0 h in the G(-) group.

at any time point. The serum levels of acetoacetic acid, total ketone body, 3-hydroxybutyric acid, and free fatty acids did not differ between the G(+) and G(-) groups at any time point. However, in the G(+) group, the levels of acetoacetic acid (0 h vs. 3 h: 130.0 ± 58.7 vs. 63.1 ± 57.7 $\mu\text{mol/L}$, $P = 0.0139$), total ketone bodies (0 h vs. 3 h: 433.3 ± 260.1 vs. 179.5 ± 210.3 $\mu\text{mol/L}$, $P = 0.0205$), and 3-hydroxybutyric acid (0 h vs. 3 h: 303.3 ± 207.0 vs. 116.4 ± 154.4 $\mu\text{mol/L}$, $P = 0.0262$) were significantly decreased at 3 h compared with those values at the start of surgery (Figure 3). The changes in the levels of 3-MH/Cre during surgery were slight in both the G(+) (0 h vs. 3 h: 1.43 ± 0.67 vs. 1.42 ± 0.50 , $P = 0.99$) and G(-) (0 h vs. 3 h: 1.80 ± 0.46 vs. 1.61 ± 0.54 $\mu\text{mol/L}$, $P = 0.65$) groups.

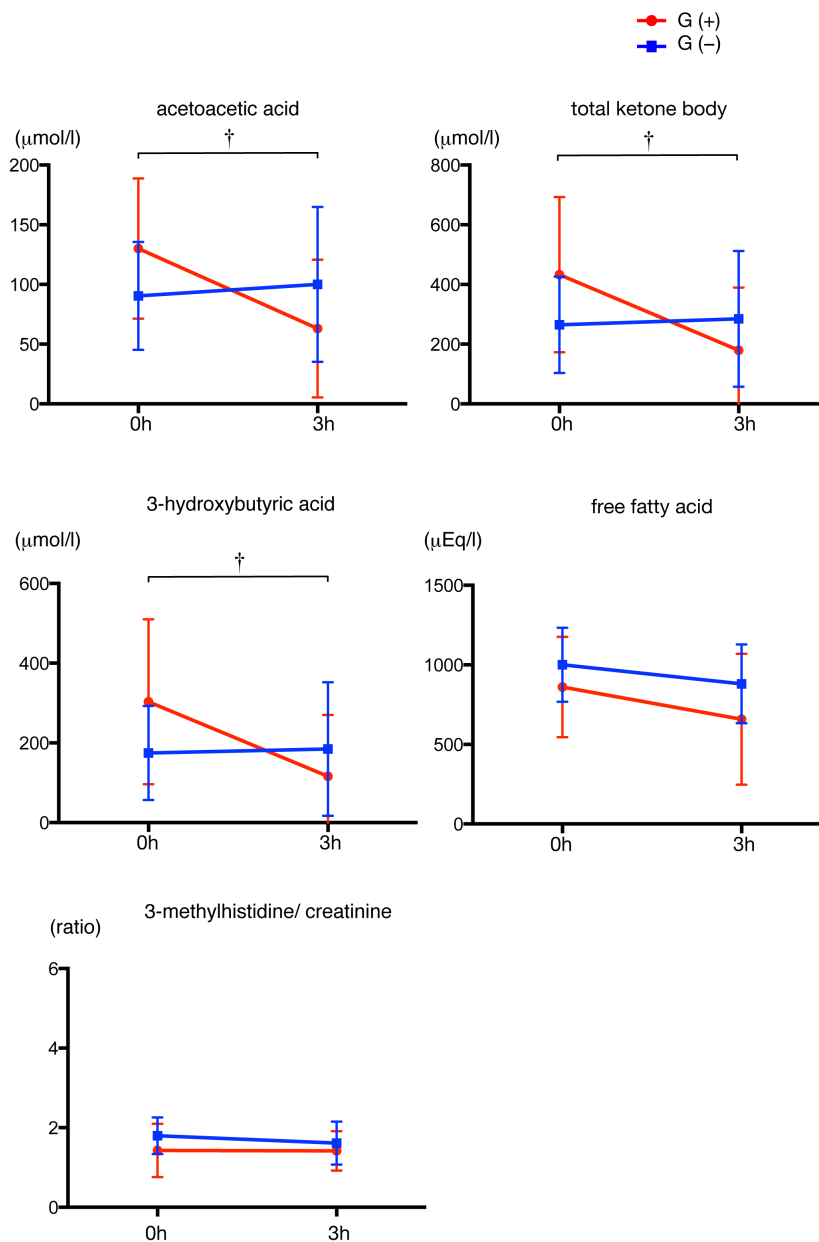


Figure 3. Plasma levels of acetoacetic acid, total ketone bodies, 3-hydroxybutyric acid, free fatty acids, and 3-MH/Cr at the start of surgery (0 h) and 3 h later (3 h) in G(+) and G(-) patients. A two-way analysis of variance was performed followed by Bonferroni's post-hoc comparisons. †*P* < 0.05 compared with 0 h in the G(+) group.

4. Discussion

Surgical stress induces insulin resistance by increasing the release of stress hormones that antagonize insulin action, such as cortisol, adrenaline, and noradrenaline, leading to the impaired glucose tolerance, cellular starvation, protein catabolism, and hyperglycemic ketogenesis. It is reported that blood glucose increases during maintenance of anesthesia with isoflurane compared with propofol during abdominal hysterectomy in patients with diabetes [8], suggesting that the lipid supply of propofol infusion inhibits hyperglycemia due to surgical stress. In our previous study, the levels of acetoacetic acid and total ketone bodies were decreased in diabetic patients receiving a glucose load under sevoflurane-based anesthesia with remifentanyl. In contrast, in the present study, glucose load under propofol-based anesthesia with remifentanyl did not alter the levels of stress hormones

and markers of fat catabolism at 3 h after the start of surgery although the levels of glucose and insulin were significantly elevated by glucose load.

In this study, we used Diprivan (Astrazeneca Pharmaceuticals LP, Wilmington, DE, USA) as the propofol solution, which formulates propofol with long-chain triglycerides. In contrast, the formulation of Propofol-Lipuro® (B. Braun, melshungen AG, Germany) formulates propofol in a mixture of medium- and long-chain triglycerides. Although pharmacodynamics and pharmacokinetics assessed by time to induction of loss of consciousness and time to awaking does not differ between the two formulations [9], medium-chain triglycerides forming the lipid emulsion of Propofol-Lipuro are more rapidly metabolized, accelerating the production of ketone bodies such as acetoacetate and β -hydroxybutyrate [10]. Nagao *et al.* reported that the 3-MH/Cr ratio significantly increased after the start of surgery in non-diabetic patients receiving sevoflurane-based compared with propofol-based anesthesia [11]. The serum concentration of free fatty acids and triglycerides in the propofol group was significantly increased compared with those in the sevoflurane group, whereas the difference in the serum concentration of ketone bodies was not significant. Propofol-Lipuro 1%, which was an oil-in-water emulsion containing 1% propofol in a 1:1 mixture of 5% medium- and 5% long-chain triglycerides, was administered in the propofol group. Therefore, the difference in lipid and protein catabolism between sevoflurane and propofol-based anesthesia in their study might have been owing to the presence of medium-chain triglycerides in the propofol solution. In addition, we cannot distinguish the effects of propofol itself from those of fat emulsion. Therefore, the impacts of the different lipid additives of the propofol solution on metabolism in patients with diabetes must be elucidated by comparing metabolic changes during anesthesia with propofol containing medium- and long-chain triglycerides.

Previous studies have shown that the serum level of insulin is significantly lower during surgery under isoflurane-based anesthesia with remifentanyl compared with propofol-based anesthesia with remifentanyl with no changes in cortisol levels in patients undergoing craniotomy [12]. This suggests that anesthetics might influence insulin secretion or resistance. Taken together with our previous study, the levels of glucose and insulin were increased by glucose infusion similarly during surgery under propofol- and sevoflurane-based anesthesia in diabetic patients receiving glucose load [3]. This suggests that insulin secretion and its effect against glucose elevation is similar regardless of the anesthetics used in diabetic patients. In addition, the difference in anesthetics might be less significant under combination with remifentanyl. Continuous infusion of high-dose remifentanyl during elective gastrectomy reduces postoperative insulin resistance compared with the use of low-dose remifentanyl, while postoperative muscle protein catabolism is unchanged [13]. Therefore, remifentanyl might have an inhibitory effect on insulin responsiveness regardless of combined anesthetics.

We cannot deny the possibility that the type of surgical procedure, the composition of transfusion, and consumption of remifentanyl and propofol affected the production of metabolites measured in this study. The baseline levels of acetoacetic acid, total ketone bodies, and 3-hydroxybutyric acid in patients receiving glucose load were elevated although the difference was not significant (Figure 3). The glucose infusion was started before the induction of anesthesia, therefore, glucose load to patients undergoing 8-h fasting might increase lipid catabolism until the start of surgery. In addition, the measurements were performed only at the start of surgery and 3 h later. Because these markers for fat catabolism were significantly decreased at 3 h compared with at the start of surgery in patients receiving glucose load, glucose infusion under propofol anesthesia with remifentanyl might suppress lipid catabolism. Small sample size of the study is associated with a decrease in statistical power. Further investigation is required to evaluate long-term effects of glucose infusion on catabolism in prolonged operations.

5. Conclusion

Our study revealed that, in diabetic patients undergoing surgery with propofol-based anesthesia with remifentanyl, administration of an intraoperative glucose load did not alter the production of stress hormones, or fat or protein catabolism despite the increased levels of glucose and insulin. These results suggest that, in contrast to sevoflurane-based anesthesia, propofol might inhibit fat catabolism in diabetic patients in the absence of glucose infusion.

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No one other than the authors contributed substantially to the performance of this study or to the drafting of the

manuscript.

Competing Interest

The authors have no conflicts of interest to declare, financial or otherwise.

Authors' Contribution

T.Y., M.H.-M., and M.N. participated in study design. T.Y. performed the preparation of the blood samples for measurement. T.Y. and M.N. performed statistical analysis. M.H.-M., A.M. and Y.K. drafted the manuscript. All authors read and approved the final manuscript.

Trial Registration

The University Hospital Medical Information Network identifier: UMIN000010914.

References

- [1] Pomposelli, J.J., Baxter 3rd, J.K., Babineau, T.J., Pomfret, E.A., Driscoll, D.F., Forse, R.A. and Bistran, B.R. (1998) Early Postoperative Glucose Control Predicts Nosocomial Infection Rate in Diabetic Patients. *JPEN Journal of Parenteral and Enteral Nutrition*, **22**, 77-81. <http://dx.doi.org/10.1177/014860719802200277>
- [2] Kambe, N., Tanaka, K., Kakuta, N., Kawanishi, R. and Tsutsumi, Y.M. (2014) The Influence of Glucose Load on Metabolism during Minor Surgery Using Remifentanyl-Induced Anesthesia. *Acta Anaesthesiol Scand*, **58**, 948-954. <http://dx.doi.org/10.1111/aas.12335>
- [3] Hasegawa-Moriyama, M., Nakahara, M., Saito, T., Yamada, T., Mukaiharu, K., Masuda, M., Matsunaga, A. and Kanmura, Y. (2015) The Effects of Glucose Load on Catabolism during Remifentanyl-Based Anesthesia in Patients with Diabetes Mellitus: A Prospective Randomized Trial. *Open Journal of Anesthesiology*, **5**, 155-162.
- [4] Oliver, M.F. (2006) Sudden Cardiac Death: The Lost Fatty acid Hypothesis. *QJM*, **99**, 701-709. <http://dx.doi.org/10.1093/qjmed/hcl084>
- [5] Schricker, T., Carli, F., Schreiber, M., Wachter, U., Geisser, W., Lattermann, R. and Georgieff, M. (2000) Propofol/Sufentanyl Anesthesia Suppresses the Metabolic and Endocrine Response during, Not after, Lower Abdominal Surgery. *Anesthesia and Analgesia*, **90**, 450-455.
- [6] Nygren, J. (2006) The Metabolic Effects of Fasting and Surgery. *Best Practice & Research Clinical Anaesthesiology*, **20**, 429-438. <http://dx.doi.org/10.1016/j.bpa.2006.02.004>
- [7] Yamasaki, K., Inagaki, Y., Mochida, S., Funaki, K., Takahashi, S. and Sakamoto, S. (2010) Effect of Intraoperative Acetated Ringer's Solution with 1% Glucose on Glucose and Protein Metabolism. *Journal of Anesthesia*, **24**, 426-431. <http://dx.doi.org/10.1007/s00540-010-0926-1>
- [8] Behdad, S., Mortazavizadeh, A., Ayatollahi, V., Khadiv, Z. and Khalilzadeh, S. (2014) The Effects of Propofol and Isoflurane on Blood Glucose during Abdominal Hysterectomy in Diabetic Patients. *Diabetes & Metabolism Journal*, **38**, 311-316. <http://dx.doi.org/10.4093/dmj.2014.38.4.311>
- [9] Ward, D.S., Norton, J.R., Guivarc'h, P.H., Litman, R.S. and Bailey, P.L. (2002) Pharmacodynamics and Pharmacokinetics of Propofol in a Medium-Chain Triglyceride Emulsion. *Anesthesiology*, **97**, 1401-1408.
- [10] Johnson, R.C.C.R. (1986) Metabolism of Medium-Chain Triglyceride Lipid Emulsion. *Nutrition International*, **2**, 150-158.
- [11] Nagao, Y., Tataru, T., Fujita, K., Sugi, T., Kotani, J. and Hirose, M. (2013) Protein Sparing during General Anesthesia with a Propofol Solution Containing Medium-Chain Triglycerides for Gastrectomy: Comparison with Sevoflurane Anesthesia. *Journal of Anesthesia*, **27**, 359-365. <http://dx.doi.org/10.1007/s00540-012-1546-8>
- [12] Cok, O.Y., Ozkose, Z., Pasaoglu, H. and Yardim, S. (2011) Glucose Response during Craniotomy: Propofol-Remifentanyl versus Isoflurane-Remifentanyl. *Minerva Anesthesiologica*, **77**, 1141-1148.
- [13] Taniguchi, H., Sasaki, T., Fujita, H., Takano, O., Hayashi, T., Cho, H., Yoshikawa, T. and Tsuburaya, A. (2013) The Effect of Intraoperative Use of High-Dose Remifentanyl on Postoperative Insulin Resistance and Muscle Protein Catabolism: A Randomized Controlled Study. *International Journal of Medical Sciences*, **10**, 1099-1107. <http://dx.doi.org/10.7150/ijms.5924>

List of Abbreviations

3-MH: 3-methyl histidine

Cr: creatinine