Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1508 – 1513
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Perioperative amino acid supplementation of hypocaloric glucose does not impair glucose metabolism after surgery

Thomas Schricker[a,*], Linda Wykes[b], George Carvalho[a], Louise Mazza[a], Leopold Eberhart[c], Franco Carli[a], Sarkis Meterissian[d]

[a]*Department of Anesthesia, McGill University Montreal, Royal Victoria Hospital, Montreal, Quebec, Canada H3A 1A1*
[b]*School of Dietetics and Human Nutrition, McGill University Montreal, Royal Victoria Hospital, Montreal, Quebec, Canada H3A 1A1*
[c]*Department of Anesthesia and Intensive Care Medicine, Philipps University Marburg, D 35037 Marburg, Germany*
[d]*Department of Surgery, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada H3A 1A1*

Received 14 November 2006; accepted 25 June 2007

Abstract

We tested the hypothesis that perioperative amino acid supplementation of hypocaloric dextrose would attenuate the inhibitory effect of glucose on endogenous glucose production after surgery. Sixteen patients undergoing colorectal cancer surgery were randomly assigned to receive intravenous glucose either with or without amino acids. Nutrition was administered over 48 hours from surgical skin incision until the second postoperative day. Glucose provided 50% and amino acids 20% of the patient's measured resting energy expenditure. Glucose rate of appearance was assessed by [6,6-$^2H_2$]glucose before and after surgery. Circulating concentrations of glucose, lactate, insulin, and glucagon were also determined. Hypocaloric glucose suppressed postoperative endogenous glucose production to a similar degree in both groups. The circulating concentrations of glucose increased to the same extent, whereas there was no significant change in plasma concentrations of lactate, glucagon, and cortisol. Postoperative plasma levels of insulin were significantly higher in patients receiving amino acids ($P = .009$). Perioperative amino acid administration does not mitigate the inhibitory effect of glucose on glucose production or aggravate hyperglycemia after colorectal surgery.

1. Introduction

The maintenance of nitrogen equilibrium after surgery depends on levels of both energy and protein intake [1]. By current theory, the improvement of nitrogen balance caused by increased energy intake can be abolished if the provision of amino acids is inadequate. Conversely, beneficial effects of increased protein intake are blunted in the presence of inadequate energy supply. These assumptions are based on the fact that there is a biochemical link between protein and glucose metabolism. As a consequence of decreased insulin sensitivity (due to counterregulatory endocrine responses) and the depletion of glycogen stores (due to preoperative fasting), gluconeogenesis increases postoperatively [2]. Because amino acids serve as precursors for de novo glucose synthesis in the liver, the efficiency with which amino acids are directed toward anabolic pathways is related to the reduction of gluconeogenesis by exogenous glucose [3,4].

Recent evidence in healthy volunteers indicates that amino acids have a significant impact on glucose metabolism [5]. The infusion of amino acids has been demonstrated to directly stimulate gluconeogenesis sufficiently to induce hyperglycemia [5-7]. Furthermore, increased circulating plasma concentrations of amino acids inhibited glucose transport/phosphorylation into skeletal muscle [8] leading to impaired muscle glycogen synthesis and reduced whole-body glucose disposal [9]. Considering the detrimental effects of even moderate hyperglycemia on surgical outcome, any disturbance of perioperative glucose homeostasis by nutritional interventions assumes clinical importance [10-13].

The present study investigated the effects of perioperative amino acid supplementation of hypocaloric glucose on glucose metabolism, the hypothesis being that the

* Corresponding author. Tel.: +1 514 9341934x34883; fax: +1 514 8431698.
E-mail address: thomas.schricker@mcgill.ca (T. Schricker).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.06.017

administration of amino acids would attenuate the inhibitory influence of glucose on endogenous glucose production after major abdominal surgery.

2. Materials and methods

2.1. Patients and ethics

We approached patients undergoing elective resection for colonic cancer at the Royal Victoria Hospital, Montreal, Canada. Patients who had evidence of distant metastatic disease, weight loss of more than 10% over the preceding 3 months, congestive heart failure, hepatic disease, diabetes, and those receiving drugs known to have metabolic effects such as corticosteroids or β-blockers were excluded. The study was approved by the ethics committee of the Royal Victoria Hospital, Montreal, Canada, and carried out in accordance with the Declaration of Helsinki. Written consent was obtained from each patient before enrollment.

2.2. Protocol

The principal investigator (TS) approached and enrolled patients. Randomization was performed by computer-generated random allocation. Patients were randomly allocated to one group of patients receiving glucose only (glucose) and a second group of patients receiving glucose and amino acids (glucose/amino acids). The surgeon, patient, and biochemist responsible for sample workup and data analysis were not aware of the group assignment.

Feeding started on the day of surgery at skin incision and continued until noon on the second day after surgery. The feeding solutions were administered through an 18G intravenous cannula inserted into a forearm vein. In both groups, the rate of glucose infusion (dextrose 10%) was adjusted to provide 50% of the patient's resting energy expenditure (REE) as determined by indirect calorimetry 1 hour before surgery and at noon on the first postoperative day. Amino acids (Travasol, Baxter, Montreal, Canada) were infused at a rate to provide 20% of the patient's REE. The composition of the Travasol solution (in micromoles per milliliter), which was verified before each administration, was as follows: proline 35, threonine 34, glycine 217, alanine 207, valine 36, methionine 37, isoleucine 34, leucine 45, tyrosine 2, phenylalanine 35, tryptophan 9, lysine 38, histidine 26, arginine 57.

No premedication was given. All operations were carried out by the same surgeon (SM). General anesthesia included propofol, fentanyl, rocuronium, nitrous oxide, and isoflurane and was performed by the same anesthesiologist (TS). Patients were covered with a warming blanket to maintain intraoperative normothermia. Epidural catheters were inserted between T9 and T12 before induction of general anesthesia. Bupivacaine 0.5% (15-20 mL) was injected to produce a confirmed bilateral segmental sensory block to pin prick from T4 to S1. Additional 0.25% bupivacaine (5-10 mL) was injected 1 to 2 hours later. At the end of surgery, epidural bupivacaine 0.1% supplemented with 2 μg/mL fentanyl was administered continuously at a rate of 10 to 15 mL/h and maintained for at least 48 hours. The infusion was adjusted to maintain a bilateral sensory block between T7 and L1 and to provide a pain score (numerical scale from 0 = no pain to 10 = worst pain imaginable) at rest of less than 4.

2.3. Measurements

Before the operation, we recorded the sex, age, weight, and height of the patients. Glucose kinetics were measured from 6:00 to 9:00 AM, after overnight fasting, on the day of surgery, and from 09:00 AM to noon on the second postoperative day. Plasma kinetics of glucose were determined by a primed constant infusion of tracer quantities of [6,6-$^2H_2$]glucose. Blood was collected before the infusion to determine baseline enrichments. A priming dose of 22μmol/kg [6,6-$^2H_2$]glucose was administered followed by an infusion of 0.22μmol/kg per minute of [6,6-$^2H_2$]glucose. Four blood samples after 150, 160, 170, and 180 minutes of isotope infusion were collected to determine plasma glucose kinetics, that is, the rate of glucose appearance. Circulating concentrations of amino acids, glucose, lactate, insulin, glucagon, and cortisol were determined at 180 minutes of the pre- and postoperative isotope infusion periods.

The patient's REE was measured by indirect calorimetry (Datex Instrumentarium Deltatrac, Helsinki, Finland). The subject was lying in a semi-recumbent position (20°) and breathing room air in the ventilated hood for 30 minutes on each occasion. Oxygen consumption and carbon dioxide production were measured. Energy expenditure and respiratory quotient were calculated. Average values were taken, with a coefficient of variation (CV) of less than 10%.

2.4. Analytical methods

Each blood sample was transferred immediately to a heparinized tube and centrifuged at 4°C. The plasma obtained was stored at −70°C until analysis. Plasma glucose was derivatized to its pentaacetate compound and analyzed by electron impact ionization gas chromatography-mass spectrometry, as previously described [14]. Isotopic enrichment of [6,6-$^2H_2$]glucose was calculated as molecules percent excess (MPE) on duplicate injections of 4 samples at isotopic steady state and 1 baseline sample. After deproteinization with sulfosalicylic acid, the plasma amino acid concentrations were determined by the amino acid analyzer Biochrom 30 (Biochrom, Cambridge, UK). Plasma glucose concentrations were determined by a glucose oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate concentrations were measured by an assay based on lactate oxidase using the Synchron CX System (Beckman Instruments, Fullerton, CA). Serum concentrations of insulin, and plasma

Table 1
Characteristics of the patients

Characteristic	Glucose	Glucose and amino acids
Age (y)	61 ± 11	63 ± 15
Sex (male/female)	4/3	3/4
Weight at admission (kg)	74 ± 9	74 ± 12
Height (cm)	172 ± 10	171 ± 7
Type of surgery		
Right hemicolectomy	1	2
Left hemicolectomy	1	1
Sigmoid colectomy	5	4
Duration of surgery (min)	185 ± 61	188 ± 74
Estimated blood loss (mL)	307 ± 137	257 ± 117

Values are expressed as means ± SD.

concentrations of glucagon and cortisol were determined by radioimmunoassays (Amersham International, Amersham, Bucks, UK).

2.5. Calculations

Whole-body glucose kinetics were calculated by conventional isotope dilution practice using a 2-pool stochastic model during steady-state conditions. At isotopic steady state, the R_a of unlabeled substrate can be derived from the plasma enrichment (MPE) calculated by $R_a = (MPE_{inf}/MPE_{pl} - 1) \times F$, where F is the infusion rate of the labeled tracer (μmol/kg per minute), MPE_{inf} is the tracer enrichment in the infusate, and MPE_{pl} is the tracer enrichment in plasma at steady state. The MPE value used in this calculation represents the mean of the MPE values determined during each isotopic plateau. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of the MPE values around their mean, expressed as the CV. A CV of less than 5% was used as a confirmation of a valid plateau.

In the fasted state or when glucose intake is zero, R_a glucose equals the rate of endogenous glucose production. The exogenous glucose infusion rate was subtracted from the total R_a glucose to determine endogenous glucose production during the infusion of glucose.

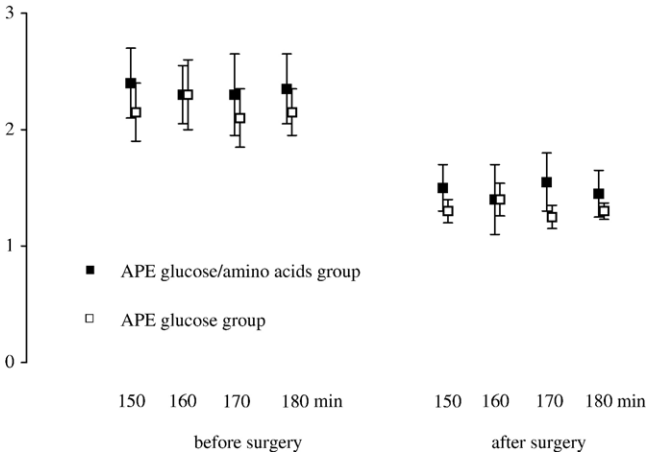

Fig. 1. Isotopic enrichments (MPE) ± SD of [6,6-$^2H_2$]glucose before and after surgery.

Table 2
Glucose kinetics, metabolic substrates, and hormones

Variable	Glucose		Glucose and amino acids		P
	Before surgery	2 d after surgery	Before surgery	2 d after surgery	
Glucose rate of appearance (μmol kg^{-1} min^{-1})	10.3 ± 0.4	16.8 ± 2.2	9.7 ± 1.5	14.7 ± 2.1	.145
Endogenous glucose rate of appearance (μmol kg^{-1} min^{-1})	10.3 ± 0.4	6.5 ± 1.6	9.7 ± 1.5	5.6 ± 2.6	.818
Glucose (mmol/L)	5.3 ± 0.4	7.4 ± 0.9	4.9 ± 0.4	6.3 ± 0.7	.228
Lactate (mmol/L)	0.8 ± 0.1	1.1 ± 0.3	1.1 ± 0.4	1.2 ± 0.5	.558
Insulin (pmol/L)	53 ± 13	91 ± 22	36 ± 28	126 ± 47	.009
Glucagon (pmol/L)	16 ± 3	17 ± 10	20 ± 4	22 ± 5	.770
Insulin/glucagon	3.3 ± 0.9	6.5 ± 2.9	2.0 ± 1.7	6.0 ± 2.3	.673
Cortisol (nmol/L)	288 ± 98	382 ± 111	282 ± 122	241 ± 85	.050

Values are expressed as means ± SD. P values indicate the probability that the changes from pre- to postoperative values were modulated by the type of feeding (t test).

2.6. Statistical methods

The primary end point was glucose production on the second postoperative day. A prospective power analysis revealed that 7 patients per group provided a power of 98% to detect a difference between the 2 treatment groups with a type I error of 5% that is twice the expected SD of each group. Results are expressed as mean ± SD. Statistical analysis of changes from pre- to postoperative values was performed using the t test. Differences were judged significant if P was .05 or less.

3. Results

Table 1 shows the demographic profile of the patients studied. No relevant differences were observed between the 2 groups. There was no clinical evidence of thrombophlebitis at the infusion site in either group, and the perioperative course was uneventful.

An isotopic plateau of [6,6-$^2H_2$]glucose was achieved in all patients (CV <5%) permitting the use of the steady-state equation (Fig. 1). Hypocaloric glucose suppressed postoperative endogenous glucose production to a similar degree in both groups (Table 2). Glucose clearance and the circulating concentrations of glucose postoperatively increased to the same extent, whereas there was no significant change in plasma concentrations of lactate, glucagon, and cortisol (Table 2).

Supplementation of amino acids resulted in a greater stimulation of the plasma levels of insulin after surgery (P = .009). Whole-body oxygen consumption and carbon dioxide production remained unchanged 2 days after

Table 3
Gaseous exchange

Variable	Glucose		Glucose and amino acids		*P*
	Before surgery	2 d after surgery	Before surgery	2 d after surgery	
Oxygen consumption (mL/min)	234 ± 14	231 ± 20	235 ± 56	234 ± 52	.943
Carbon dioxide production (mL/min)	180 ± 7	195 ± 23	181 ± 40	191 ± 44	.845
Respiratory quotient	0.77 ± 0.03	0.84 ± 0.03	0.77 ± 0.03	0.82 ± 0.02	.159

Values are expressed as means ± SD. *P* values indicate the probability that the changes from pre- to postoperative values were modulated by the type of feeding (*t* test).

surgery (Table 3). The respiratory quotient postoperatively increased whether or not amino acids were administered (Table 3). The circulating concentrations of most amino acids in the glucose group decreased, in particular the branched-chain amino acids and glutamine, which also decreased in the amino acid group (Table 4). In patients receiving amino acids, the plasma concentrations of the amino acids that were provided by Travasol increased after surgery (Table 4).

4. Discussion

The results of this study demonstrate that the infusion of amino acids neither affects the inhibitory effect of glucose on endogenous glucose production nor worsens hyperglycemia 2 days after colorectal surgery. The greater postoperative augmentation of plasma insulin in patients receiving amino acids may have indirectly blunted the stimulatory effects of gluconeogenic amino acids on glucose production.

Because nitrogen equilibrium after surgery is affected by both substrate and energy intake, the interaction between glucose and protein metabolism gains clinical relevance [1]. Positive correlations between glucose production and protein breakdown have been observed in fasting surgical patients, indicating that muscle protein is broken down to supply amino acids as gluconeogenic substrates for hepatic glucose synthesis [14,15]. Because of the occurrence of insulin resistance and the fasting-induced depletion of glycogen stores, typical features of the catabolic response to surgery, gluconeogenesis increases postoperatively [2]. If the rate of gluconeogenesis from amino acids can be suppressed by exogenous glucose, that amount of nitrogen will be available for re-incorporation into protein rather than for excretion as urea. Therefore, the protein-sparing effects of perioperative nutritional support depend, in part, on the reduction of endogenous glucose production.

Although the relationship between amino acid and glucose metabolism has been well described in healthy volunteers, little is known about the impact of amino acid administration on glucose metabolism in the context of surgical tissue trauma. In a healthy individual, infusion of branched-chain amino acids, which are predominantly metabolized in skeletal muscle, inhibited insulin-mediated glucose uptake in the forearm bed [8,9]. Short-term supplementation of hypocaloric glucose with a large

Table 4
Amino acids

Amino acid (μmol/L)	Glucose			Glucose and amino acids		
	Before surgery	2 d after surgery	Change	Before surgery	2 d after surgery	Change
Aspartate	3 ± 1	3 ± 1	−1 ± 1	4 ± 1	4 ± 1	0 ± 2
Asparagine	68 ± 14	61 ± 18	−8 ± 17	52 ± 25	26 ± 19	−26 ± 23
Threonine	81 ± 19	75 ± 12	−6 ± 27	86 ± 17	124 ± 27	37 ± 23
Serine	80 ± 14	63 ± 12	−18 ± 19	87 ± 16	91 ± 27	4 ± 25
Glutamate	74 ± 9	64 ± 15	−10 ± 16	85 ± 21	92 ± 34	8 ± 28
Glutamine	438 ± 81	340 ± 70	−98 ± 57	465 ± 71	350 ± 119	−114 ± 104
Glycine	216 ± 98	163 ± 59	−53 ± 44	230 ± 98	416 ± 148	186 ± 136
Alanine	232 ± 72	206 ± 46	−26 ± 78	226 ± 41	313 ± 77	87 ± 59
Valine	178 ± 44	138 ± 20	−40 ± 37	172 ± 25	235 ± 43	63 ± 57
Leucine	118 ± 22	96 ± 15	−23 ± 27	109 ± 22	148 ± 26	39 ± 29
Isoleucine	52 ± 16	41 ± 5	−12 ± 18	53 ± 9	86 ± 16	32 ± 13
Cysteine	3 ± 2	2 ± 1	−1 ± 2	2 ± 2	1 ± 0	−1 ± 2
Methionine	15 ± 6	18 ± 5	3 ± 7	16 ± 5	43 ± 15	27 ± 12
Tyrosine	46 ± 11	47 ± 12	1 ± 15	48 ± 15	59 ± 13	11 ± 21
Phenylalanine	51 ± 7	65 ± 9	14 ± 11	51 ± 10	107 ± 23	56 ± 19
Lysine	157 ± 34	141 ± 31	−16 ± 34	149 ± 29	172 ± 31	23 ± 42
Histidine	76 ± 11	64 ± 12	−12 ± 10	81 ± 14	112 ± 19	32 ± 17
Arginine	61 ± 8	47 ± 8	−14 ± 14	63 ± 8	102 ± 31	39 ± 31
Proline	128 ± 31	98 ± 23	−31 ± 22	141 ± 21	173 ± 25	32 ± 20
Tryptophan	11 ± 8	7 ± 2	−4 ± 7	8 ± 5	16 ± 2	−1 ± 8

Values are expressed as means ± SD.

amount of amino acids (3.33 mg/kg per minute) increased endogenous glucose production by 84% and gluconeogenesis by 235%, respectively [6]. This substantial augmentation of glucose production, which occurred despite hyperinsulinemia, was a result of the increased availability of gluconeogenic amino acids and elevated plasma concentrations of glucagon, a strong stimulator of gluconeogenesis [16]. Pancreatic clamp studies designed to exclude indirect effects resulting from amino acid–induced secretion of glucoregulatory hormones concluded that, with insulin and glucagon concentrations clamped at baseline levels, amino acids directly stimulate gluconeogenesis and induce hyperglycemia as reflected by blood glucose levels greater than 7 mmol/L [5]. Evidence has mounted suggesting that even moderate increases in blood glucose are associated with poor outcome, particularly in the surgical patient population. Patients with fasting glucose levels of greater than 7 mmol/L or random blood glucose levels of greater than 11.1mmol/L on general surgical wards had an 18-fold increased in-hospital mortality, a longer length of stay, and a greater risk of infection [10]. In a heterogenous group of critically ill patients, mortality was directly correlated with increasing glucose levels of greater than 5 mmol/L [17]. On the other hand, strict maintenance of normoglycemia significantly reduced mortality and morbidity in the surgical intensive care unit [18].

The conditions of the present protocol differ from those applied in former studies in healthy volunteers, making direct comparison difficult. The present investigation was performed in surgical patients with cancer using a 48-hour infusion of hypocaloric glucose together with amino acids at a rate equivalent to 20% of the patient's measured REE, that is, close to 1 g/kg per day. This rate was chosen because it provides approximately the same amount of protein that is being oxidized after colorectal surgery and, thus, is isonitrogenous [15]. All patients received epidural anesthesia during surgery followed by continuous postoperative epidural analgesia with potential impact on glucose homeostasis. Effective segmental blockade of efferent and afferent fibers by epidural local anesthetic has been shown to attenuate the hyperglycemic response to abdominal surgery by improving glucose utilization and preventing the increase in glucose production [15,19,20].

As opposed to previous pancreatic clamp studies, no methodological attempts were made in the present protocol that would allow to distinguish between direct and indirect hormone-mediated effects of amino acids on glucose metabolism.

Combined amino acid–glucose administration stimulated insulin secretion to a greater extent than glucose administration alone, most likely a consequence of the insulinotropic effects of certain amino acids that were provided, in particular arginine, leucine, and phenylalanine [21]. Thus, it cannot be excluded that hyperinsulinemia counteracted to some extent the stimulatory effect of gluconeogenic amino acids on glucose production. Despite the greater insulin response in patients receiving amino acids, endogenous glucose production similarly decreased in both groups and was 40% lower than before surgery. Postoperative glucose production rates were also lower than values previously reported in patients who were studied on the second day after colorectal surgery under fasting conditions [15]. This finding agrees with previous observations in trauma patients showing no increase in glucose production in the presence of amino acids infused at a rate similar to that used in the present protocol [22]. In fact, most recent evidence indicates that the short-term infusion of a relatively large amount of amino acids 2 days after colorectal surgery slightly decreases endogenous glucose production mediated through an increase in the circulating concentration of insulin [23].

Postabsorptive glycogenolysis constitutes approximately 75% of total glucose output, the remaining 25% being derived from gluconeogenesis [24]. Although gluconeogenesis is expected to increase after surgery, the present study cannot quantify the gluconeogenic contribution to total glucose production because the tracer kinetics used do not allow the identification of the specific biochemical pathway. This is a limitation of the study.

In summary, under the conditions of the present study, perioperative provision of an isonitrogenous amount of amino acids in patients receiving hypocaloric glucose does not impair glucose metabolism after colorectal cancer surgery. In contrast to observations made in healthy volunteers, amino acid administration does not mitigate the inhibitory effect of glucose on postoperative glucose production and, more important, does not aggravate hyperglycemia. Whether these metabolic findings are relevant for fit patients undergoing elective abdominal procedures remains questionable. However, recent evidence demonstrates that hypocaloric nutrition together with optimal pain control by epidural analgesia is a key component of strategies designed to improve recovery after colorectal surgery [25].

Acknowledgments

The study was supported by the Canadian Institutes of Health Research (Ottawa, Canada, to TS) and by Fonds de la recherche en sante Quebec (to TS). The supporting organizations had no role in study design, data collection, data analysis, data interpretation, or in the writing of the manuscript. We gratefully acknowledge the help of the nurses on the surgical floors at the Royal Victoria Hospital, Montreal, and Ann Wright for reviewing the manuscript.

References

[1] Munro H. Energy and protein intakes as determinants of nitrogen balance. Kidney Int 1978;14:313-6.
[2] Gump F, Long C, Geiger J, Kinney J. The significance of altered gluconeogenesis in surgical catabolism. J Trauma 1975;15:704-13.

[3] Shaw J, Klein S, Wolfe R. Assessment of alanine, urea and glucose interrelationships in normal subjects and in patients with sepsis with stable isotopic tracers. Surgery 1985;97:557-67.
[4] Felig P. Amino acid metabolism in man. Annu Rev Biochem 1975;44:933-55.
[5] Krebs M, Brehm A, Krssak M, et al. Direct and indirect effects of amino acids on hepatic glucose metabolism in humans. Diabetologia 2003;46:917-25.
[6] Tappy L, Acheson K, Normand S, et al. Effects of infused amino acids on glucose production and utilization in healthy human subjects. Am J Physiol 1992;262:E826-33.
[7] Boden G, Tappy L. Effects of amino acids on glucose disposal. Diabetes 1990;39:1079-84.
[8] Schwenk WF, Haymond MW. Decreased uptake of glucose by human forearm during infusion of leucine, isoleucine, or threonine. Diabetes 1987;36:199-204.
[9] Krebs M, Krssak M, Bernroider E, et al. Mechanism of amino acid acid-induced skeletal muscle insulin resistance in humans. Diabetes 2002;51:599-605.
[10] Umpierrez GE, Isaacs SD, Bazargan H, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978-82.
[11] Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc 2005;80:862-6.
[12] Anderson RE, Klerdal K, Ivert T, Hammar N, Barr G, Öwall A. Are even impaired fasting glucose levels preoperatively associated with increased mortality after CABG surgery. Eur Heart J 2005;26:1513-8.
[13] Doenst T, Wijeysundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2005;130:1144e1-8.
[14] Schricker T, Lattermann R, Fiset P, Wykes L, Carli F. Integrated analysis of protein and glucose metabolism during surgery: effects of anesthesia. J Appl Physiol 2001;91:2523-30.
[15] Schricker T, Wykes L, Carli F. Epidural blockade improves substrate utilization after surgery. Am J Physiol 2000;279:E646-53.
[16] Boden G, Tappy L, Jadali F, Hoeldtke D, Rezvani I, Owen OE. Role of glucagon in disposal of an amino acid load. Am J Physiol 1990;259: E225-32.
[17] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogenous population of critically ill patients. Mayo Clin Proc 2003;78:1471-8.
[18] van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359-67.
[19] Lattermann R, Wykes L, Carli F, Schricker T. Epidural analgesia modifies perioperative glucose production without affecting protein catabolism. Anesthesiology 2002;97:374-81.
[20] Uchida I, Asoh T, Shirasaka C, Tsuji H. Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique. Br J Surg 1988;75:557-62.
[21] Floyd Jr JC, Fajans SS, Conn JW, Knopf RF, Rull J. Stimulation of insulin secretion by amino acids. J Clin Invest 1966;45:1487-502.
[22] Long CL, Nelson KM, Geiger JW, et al. Effect of amino acid infusion on glucose production in trauma patients. J Trauma 1996;40:335-41.
[23] Donatelli F, Schricker T, Mistraletti G, et al. Postoperative infusion of amino acids induces a positive protein balance independently of the type of analgesia used. Anesthesiology 2006;105:253-9.
[24] Landau BR, Wahren J, Chandramouli V, Shumann WC, Ekberg K, Kalhan SC. Contribution of gluconeogenesis to glucose production in the fasted state. J Clin Invest 1996;98:378-85.
[25] Carli F, Mayo N, Klubien K, Schricker T, Beliveau P, Trudel J. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery. Results of a randomized trial. Anesthesiology 2002;97:540-9.