 

# *Epidural Analgesia Enhances the Postoperative Anabolic Effect of Amino Acids in Diabetes Mellitus Type 2 Patients Undergoing Colon Surgery*

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***Background:*** **It has been suggested that diabetes mellitus type 2 amplifies the endocrine–metabolic stress response to surgery, and patients become more catabolic during the postoperative period. The aim of this study, conducted in patients with diabetes mellitus type 2 scheduled to undergo elective colorectal surgery, was to determine whether the anabolic effects of intravenous amino acids are more pronounced when receiving perioperative epidural analgesia compared with patient-controlled analgesia with intravenous morphine.**

***Methods:*** **Twelve patients were randomly assigned to receive either epidural analgesia or patient-controlled analgesia with intravenous morphine for perioperative pain control. Protein and glucose kinetics were measured before surgery and on the second postoperative day using L-[1-$^{13}$C]leucine and [6,6-$^{2}H_2$]glucose infusion during a fasted and a fed (amino acid infusion) state.**

***Results:*** **Preoperative parameters for glucose and protein kinetics were comparable in the fasted state for both groups. Postoperative amino acid infusion increased glucose concentration slightly ($P = 0.124$) and suppressed the endogenous rate of appearance of glucose ($P < 0.0001$) and glucose clearance ($P < 0.0001$) regardless of analgesia technique. The rate of appearance of leucine ($P = 0.002$), leucine oxidation ($P < 0.0001$), and protein synthesis ($P = 0.026$) increased, whereas net protein breakdown was decreased ($P = 0.002$), leading to a positive protein balance ($P < 0.0001$) in both groups. The increase in protein balance was greater in the epidural group compared with the patient-controlled analgesia group ($P = 0.027$).**

***Conclusion:*** **Diabetic patients receiving an amino acid infusion after surgery achieved a positive protein balance without hyperglycemia. This anabolic effect was greater in patients receiving epidural analgesia compared with patient-controlled analgesia with intravenous morphine.**

DIABETES mellitus is associated with high morbidity and mortality and is responsible for higher perioperative complication rates.[1] It has been hypothesized that diabetes mellitus type 2 (DM2) leads to pronounced muscle wasting and a catabolic state perioperatively due to the persistent metabolic derangements.[2] This loss of lean tissue promotes immunosuppression, delayed wound healing, and decreased muscle strength in nondiabetic patients.[3]

The catabolic stress response to surgery is characterized by typical metabolic and inflammatory changes as a result of mediators produced at the site of the surgical injury and afferent neural stimuli.[4,5] This endocrine–metabolic response leads to an increased secretion of catabolic stress hormones (most importantly cortisol, epinephrine, norepinephrine, and glucagon) and a state of insulin resistance.[6]

Continuous epidural analgesia has been shown to blunt the endocrine response, to reduce postoperative nitrogen excretion,[7] and to attenuate the increased amino acid oxidation[8] and whole body protein breakdown as well as the decrease in muscle protein synthesis.[9,10] These findings were reported in nondiabetic patients receiving continuous parenteral nutrition support, therefore suggesting that a protein-sparing effect of epidural blockade can only be achieved by providing adequate energy and nitrogenous substrate supply.[10,11]

Nevertheless, the attenuation of protein catabolism achieved with parenteral nutrition was accompanied by hyperglycemia with plasma glucose levels close to 10 mM, even when infused at a low dose.[10,11] Therefore, it has been suggested that refraining from infusing dextrose in nondiabetic and particularly in diabetic patients would prevent unnecessary hyperglycemia.[12]

The aim of this study was to compare the effect of perioperative epidural analgesia (EDA) *versus* patient-controlled analgesia (PCA) with intravenous morphine on postoperative protein and glucose metabolism in patients with DM2 after colorectal surgery in the fasted state and during intravenous administration of amino acids. It was hypothesized that amino acid infusion will increase protein synthesis and decrease protein breakdown resulting in a greater positive protein balance in those subjects receiving epidural analgesia.

## Materials and Methods

### *Patients*

Twelve patients with DM2 undergoing elective colorectal surgery were recruited between November 2004 and July 2006. The study protocol was approved by the research ethics board of the McGill University Health Centre, Montreal, Canada, and written informed consent

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was obtained from all patients. Inclusion criteria were age older than 18 yr, DM2 (controlled by diet, oral hypoglycemic medication, or insulin), and colorectal surgery for nonmetastatic disease (including right, transverse, left, sigmoid, subtotal, total, and hemicolectomy and low anterior resection). Exclusion criteria were severe cardiac, hepatic, renal, or metabolic disorders; diabetes mellitus type 1; plasma albumin concentration below 35 g/l; more than 10% weight loss over the preceding 3 months; anemia (hematocrit below 30%); use of steroids; previous spine surgery limiting the use of an epidural catheter; and pregnancy. No hemoglobin $A_{1c}$ levels were measured, but all patients in both groups had a preoperative fasting blood glucose less than 10 mM. The patients were randomly allocated by a computer-generated schedule into an epidural group (EDA group) receiving general anesthesia combined with perioperative EDA (n = 6) and a control group (PCA group) receiving general anesthesia combined with postoperative PCA with morphine (n = 6).

*Anesthesia and Perioperative Care*

Patients underwent bowel preparation on the day before surgery and were allowed to drink clear fluids until midnight. Patients were operated in the morning hours by two colorectal surgeons who collaborated as coinvestigators.

Oral hypoglycemic medications were discontinued on the day of surgery. Perioperative glycemic control was achieved by an insulin sliding scale aiming to maintain blood glucose levels between 5 and 10 mM. Plasma glucose was measured every 6 h.

In both groups, general anesthesia was induced by propofol, fentanyl, and rocuronium. General anesthesia was maintained using nitrous oxide in oxygen and desflurane. In the EDA group, an epidural catheter was inserted between thoracic vertebral levels T8 to T11 before the induction of general anesthesia. Neuraxial blockade was established with 0.5% bupivacaine to achieve a bilateral sensory block from T4 to S1 and maintained with a constant infusion of 0.25% bupivacaine during surgery. The sensory block was postoperatively maintained for at least 48 h by continuous epidural infusion of 0.1% bupivacaine supplemented with 3 $\mu$g/ml fentanyl. Pain levels were evaluated in all patients using an 11-point visual analog score (0 = no pain, 10 = excruciating pain) every 4 h after surgery. Pain treatment was adjusted to achieve a visual analog score level at rest below 3 and below 5 during mobilization or on coughing.

In the control group, patients received a PCA with intravenous morphine to control pain relief postoperatively. The incremental dose of morphine was 1–2 mg, lockout was 7 min, and dose duration was 30 s.

Patients received 0.9% normal saline, which was changed to 5% dextrose in ¼ normal saline after surgery, and were allowed to drink clear fluids postoperatively according to the state of bowel passage. At midnight of the first day after surgery, the infusion was changed to 0.9% normal saline and patients were only allowed to drink water.

*Experimental Protocol*

On the day before surgery, starting at 8:00 AM, patients underwent a 2-h tracer kinetic study to characterize baseline protein and glucose metabolism during a fasted state. Oral hypoglycemic medications were discontinued, and the patients fasting from midnight. The study was repeated starting at 8:00 AM on the second postoperative day with a 2-h fasted state followed by an additional 3-h fed state. Plasma kinetics of leucine and glucose were determined by primed constant infusions of the tracers L-[1-$^{13}$C] leucine (99% enriched) and [6,6-$^{2}H_2$]glucose (99% enriched) (Cambridge Isotope Laboratories, Cambridge, MA). Sterile solutions of tracers were prepared in the hospital pharmacy and kept at 4°C until administration.

Blood and expired air samples were collected to determine baseline enrichments. Each blood sample was transferred immediately to a heparinized tube, centrifuged at 4°C (2,400*g* × 10 min), and stored at −70°C. Breath samples were collected in a 2-l latex bag and transferred immediately to 10 ml vacutainers (BD Vacutainer; Becton Dickinson, Franklin Lakes, NJ).

The bicarbonate pool was primed with sodium bicarbonate ($NaH^{13}CO_3$, 0.08 mg/kg) administered orally at the start of the tracer infusion. Priming doses of L-[1-$^{13}$C]leucine (4 $\mu$mol/kg), and [6,6-$^{2}H_2$]glucose (22 $\mu$mol/kg) were injected and followed immediately by continuous infusions of 0.06 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ L-[1-$^{13}$C] leucine and 0.22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ [6,6-$^{2}H_2$]glucose over 2 h (fasted state). Blood and breath samples were collected at 90, 100, 110, and 120 min of the study period to determine the protein and glucose metabolism in the fasted state. On the second postoperative day, the tracer infusion study was repeated. After the 2-h fasting infusion, tracer infusions were continued over a subsequent 3-h period during which a 10% amino acid solution without electrolytes (Travasol®; Baxter, Montreal, Canada) was infused at a rate of 0.02 $ml \cdot kg^{-1} \cdot min^{-1}$ (equivalent to 2.9 $g \cdot kg^{-1} \cdot day^{-1}$) to achieve a plasma amino acid concentration at least twofold above the basal.[13] The composition of Travasol® was as previously described[14] and was verified before each administration. The L-[1-$^{13}$C] leucine tracer infusion rate was increased to 0.12 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ while [6,6-$^{2}H_2$]glucose maintained at 0.22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

Blood and breath samples were collected at 150, 160, 170, and 180 min to determine the protein and glucose kinetics in the fasted state. Blood samples were drawn during the last 10 min of the fasted and fed state periods for the analysis of glucose, glucagon, insulin, and cortisol.

Indirect calorimetry (Vmax 29N; SensorMedics, Yorba Linda, CA) was performed for 15 min in the last hour of the fasted and fed states during the preoperative and postoperative tracer kinetic study periods. Whole body

oxygen consumption and carbon dioxide production were determined.[6]

*Measurements*

**Isotopic Enrichments.** Plasma enrichment of [1-$^{13}$C]$\alpha$-ketoisocaproate, representing intracellular leucine, was used as the basis for calculating both flux and oxidation of leucine as described recently.[15,16] Plasma [1-$^{13}$C]$\alpha$-ketoisocaproate enrichment was analyzed by its pentafluorobenzylester derivative using methane negative chemical ionization gas chromatography–mass spectrometry. Plasma [6,6-$^{2}H_2$]glucose enrichment was determined from its pentaacetate derivative by gas chromatography–mass spectrometry analysis under electron impact conditions.[17] $^{13}$C-carbon dioxide enrichment in expired breath was determined by isotope ratio mass spectrometry (Analytical Precision AP2003; Manchester, United Kingdom).[15] Isotopic enrichment was calculated as atoms or molecules percent excess over baseline. Steady state conditions for [6,6-$^{2}H_2$]glucose, [1-$^{13}$C]$\alpha$-ketoisocaproate, and $^{13}$C-carbon dioxide were considered established provided that the coefficient of variation of the four samples in each study period was less than 5%.

**Plasma Metabolites and Hormones.** Plasma glucose was measured by an enzymatic colorimetric assay (GLU Glucose GOD-PAP; Roche Diagnostics, Indianapolis, IN) on automated clinical chemistry analyzers (Roche/Hitachi 904911: CAN 249 or Roche/Hitachi 912/917/MODULAR: CAN 525; Roche Diagnostics). Serum insulin was determined by a solid-phase, two-site chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000 Insulin; Diagnostic Products Corporation, Los Angeles, CA). Glucagon was determined by using a radioimmunoassay kit (Glucagon RIA KIT; Linco, St. Charles, MO). Plasma cortisol was measured by an immunoassay (Unicell DXI 800; Beckman Coulter, Brea, CA).

**Gaseous Exchange.** Average values of oxygen consumption and carbon dioxide production as well as the calculated respiratory quotient were determined by indirect calorimetry, accepting a coefficient of variation of less than 10% over 10 min.

**Calculation of Protein and Glucose Metabolism.** Whole body leucine and glucose kinetics were determined by conventional isotope dilution practice applying a two-pool stochastic model during steady state conditions of the fasted and fed states before and after surgery.[6]

The kinetics of the amino acid leucine, which makes up for 8% of whole body protein, represent the dynamics of protein metabolism in this study setting. Therefore, the terms *protein synthesis* and *protein balance* represent leucine kinetics and are used to present and discuss protein metabolism where not expressly labeled as *protein balance (whole body protein)*.

Under steady state conditions, leucine flux (Q) is defined by the formula Q = S + O = B + I, where S is the rate at which leucine is incorporated into body protein, O is the rate of oxidation of leucine, B is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of leucine intake including tracer (rate of infusion of L-[1-$^{13}$C]leucine [$\mu$mol $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$]) and diet. The calculation of the values for glucose and protein metabolism was performed as previously described.[14]

*Statistical Analysis*

The primary endpoint of the study was protein balance (represented by the values of leucine kinetics). On the basis of previous studies,[11] a difference in protein balance (leucine) of 7.5 $\mu$mol $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$ between the two groups was defined as metabolically relevant. Assuming a SD of 5 $\mu$mol $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$, a repeated-measures design with 2 times 7 patients achieves a power of 80% ($\alpha$ two-sided 0.05). The calculated power for 6 patients per group results in 73.8% ($\alpha$ two-sided 0.05).

Differences in preoperative values between treatment groups were assessed using a two-sided, two-sample Student *t* test. A repeated-measures two-way analysis of variance was used to examine differences between treatment groups across feeding states. An effect of treatment was assessed by significance of either the interaction term or the main effect of treatment. In the case of a significant interaction, differences between treatment groups were further explored through a two-sided, two-sample Student *t* test at each level of feeding. A significance level of 0.05 was used for all tests. Statistical analyses were conducted using Intercooled STATA 9.0 (1) (StataCorp, College Station, TX).

## Results

*Patients*

The two groups were similar regarding sex, age, height, weight, and duration of surgery (table 1). The pain scores measured by visual analog scale at rest, at 12 and 24 h after surgery, and during the study on the second postoperative day never exceeded the value of 4, and no patient reported severe pain in either group.

*Glucose and Protein Kinetics*

In all studies, a plateau in the enrichments of plasma [1-$^{13}$C]$\alpha$-ketoisocaproate, [6,6-$^{2}H_2$]glucose, and expired $^{13}$C-carbon dioxide was achieved (coefficient of variation $<$5%).

Preoperative glucose and protein kinetics (fig. 1) were comparable in both groups in the fasted state (table 2).

The postoperative administration of amino acids suppressed endogenous rate of appearance of glucose ($P <$ 0.0001) and glucose clearance ($P <$ 0.0001) regardless of

**Table 1. Biometric and Clinical Data of Patients**

| Variable | PCA | EDA |
|---|---|---|
| n | 6 | 6 |
| Age, yr | 68 ± 7 | 74 ± 9 |
| Weight, kg | 76 ± 16 | 87 ± 22 |
| BMI, kg/m$^2$ | 28.3 ± 4.5 | 28.9 ± 5.8 |
| Sex, M/F | 4/2 | 5/1 |
| ASA physical status, I/II/III | 0/3/3 | 0/3/3 |
| Type of surgery | | |
| Hemicolectomy/colectomy | 3 | 2 |
| Sigmoid resection | 0 | 1 |
| Anterior resection | 3 | 3 |
| Duration, min | 168 ± 78 | 167 ± 93 |
| Diabetes treatment, no/diet/OAD/insulin | 0/2/3/1 | 1/0/4/1 |

Values are mean ± SD.

ASA = American Society of Anesthesiologists; BMI = body mass index; EDA = epidural analgesia; OAD = oral antidiabetic drugs; PCA = patient-controlled analgesia.

the analgesia technique applied (table 3). The rate of appearance of leucine ($P = 0.002$), leucine oxidation ($P < 0.0001$), and protein synthesis ($P = 0.026$) increased with amino acid infusion, whereas net protein breakdown decreased ($P = 0.002$). These changes led to a positive protein balance ($P < 0.0001$; table 3). In the EDA group, amino acid feeding increased leucine oxidation and protein balance to a greater extent than in the PCA group ($P = 0.027$; table 3). Leucine oxidation and protein balance were higher in the EDA group compared with the PCA group in the fed state ($P = 0.023$) but were not different in the fasting state ($P = 0.726$; fig. 1). The postoperative net change of postoperative protein balance (leucine) was 37 $\mu mol \cdot h^{-1} \cdot kg^{-1}$ in the PCA groups and 45 $\mu mol \cdot h^{-1} \cdot kg^{-1}$ in the EDA group.

*Gaseous Exchange*

Preoperative oxygen consumption, carbon dioxide production, and respiratory quotient showed no significant difference in the fasted state for the two groups (table 2). During the postoperative administration of amino acids, carbon dioxide increased ($P = 0.041$). Patients with an epidural blockade showed a tendency toward a higher oxygen consumption ($P = 0.013$) and carbon dioxide production ($P = 0.035$) than patients of the PCA group postoperatively (table 4).

*Plasma Hormones and Metabolites*

Plasma glucose, insulin, cortisol, and glucagon concentrations were similar in both groups in the preoperative fasting study (table 2). In the postoperative period, amino acid feeding increased insulin ($P = 0.003$) and increased glucose concentration slightly ($P = 0.124$) regardless of analgesia technique (table 4). After surgery, glucagon, cortisol, and insulin/glucagon ratio were not affected by either feeding or analgesia technique (table 4).

## Discussion

This study shows that diabetic patients are in negative protein balance in the fasted state after colorectal surgery. Infusion of amino acids shifts protein balance to a positive state without causing hyperglycemia. This anabolic effect is more pronounced in patients receiving EDA compared with PCA (fig. 1).

The more positive protein balance in the EDA group was due to increased protein synthesis as well as decreased leucine oxidation and net protein breakdown, indicating that fewer amino acids were used as energy source and instead they were directed toward synthesis of new proteins. The difference of 10 $\mu mol \cdot kg^{-1} \cdot h^{-1}$ in protein balance (leucine) between the two study groups in the postoperative fed state represents 179 g of saved lean body mass in a 70-kg person per day. Although the impact of analgesia on these findings was not statistically significant, a trend toward a pronounced effect in the EDA group could be detected. It seems that exogenous amino acids have an influence on protein metabolism that is greater

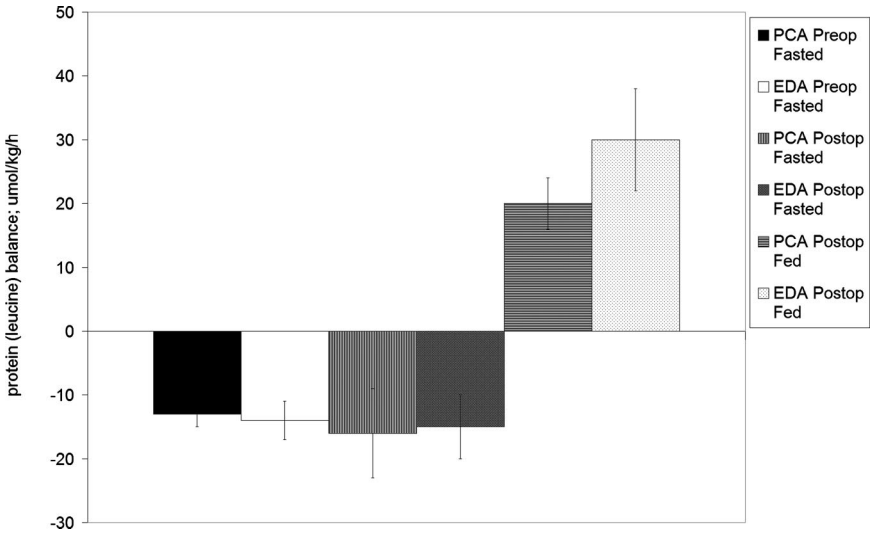


**Fig. 1. Preoperative and postoperative protein balance (leucine) of patients receiving epidural analgesia (EDA) or patient-controlled analgesia (PCA) in the fasted and fed states. Values are mean ± SD ($\mu mol \cdot kg^{-1} \cdot h^{-1}$); n = 6 per group.**

**Table 2. Preoperative Kinetics of Leucine and Glucose Metabolism, Hormones, and Metabolites and Gaseous Exchange of Patients Receiving EDA or PCA in the Fasted State**

| Variable | EDA | PCA | *P* Value |
|---|---|---|---|
| Endogenous rate of appearance of glucose, $\mu mol \cdot kg^{-1} \cdot min^{-1}$ | 13.56 ± 2.83 | 15.76 ± 3.37 | 0.2501 |
| Glucose clearance, $ml \cdot kg^{-1} \cdot min^{-1}$ | 1.85 ± 0.65 | 2.45 ± 0.81 | 0.1876 |
| Rate of appearance of leucine, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 107 ± 19 | 112 ± 9 | 0.5312 |
| Net protein breakdown, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 107 ± 19 | 112 ± 9 | 0.5312 |
| Leucine oxidation, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 14 ± 3 | 13 ± 2 | 0.3550 |
| Protein synthesis, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 92 ± 18 | 99 ± 7 | 0.4036 |
| Protein balance, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | −14 ± 3 | −13 ± 2 | 0.3550 |
| Glucose, mM | 7.9 ± 2.3 | 7.0 ± 2.3 | 0.4884 |
| Insulin, pM | 86 ± 61 | 83 ± 63 | 0.9456 |
| Glucagon, pM | 32 ± 7 | 28 ± 5 | 0.3289 |
| Cortisol, nM | 287 ± 67 | 308 ± 87 | 0.6628 |
| Insulin/glucagon ratio | 2.75 ± 1.74 | 2.84 ± 1.77 | 0.9250 |
| $V_{O_2}$, ml/min | 269 ± 81 | 200 ± 21 | 0.0744 |
| $V_{CO_2}$, ml/min | 187 ± 49 | 157 ± 15 | 0.1753 |
| RQ | 0.71 ± 0.12 | 0.78 ± 0.04 | 0.1753 |

Values are mean ± SD; n = 6 per group.

EDA = epidural blockade; PCA = patient-controlled analgesia; RQ = respiratory quotient; $V_{CO_2}$ = whole body carbon dioxide production; $V_{O_2}$ = whole body oxygen consumption.

than the type of analgesia. In fact, the infusion of amino acids postoperatively caused an average increase in protein balance of 40.5 $\mu mol \cdot kg^{-1} \cdot h^{-1}$, of which 10 $\mu mol \cdot kg^{-1} \cdot h^{-1}$ was due to type of analgesia. These findings are consistent with results from a previous trial in nondiabetics with the same postoperative setting (36.7 $\mu mol \cdot kg^{-1} \cdot h^{-1}$ and 7.3 $\mu mol \cdot kg^{-1} \cdot h^{-1}$, respectively),[14] indicating that the effect of amino acids on the protein balance was approximately five times greater than the type of analgesia. However, in diabetic patients, the interaction of feeding and analgesia technique was significantly higher for protein balance in the EDA group compared with PCA, whereas in nondiabetic patients, a higher effect in the PCA group was detectable.[14] This larger shift toward a positive protein balance (45 $\mu mol \cdot kg^{-1} \cdot h^{-1}$) in diabetic patients (nondiabetic patients, 33.2 $\mu mol \cdot kg^{-1} \cdot h^{-1}$)[14] with epidural analgesia occurs during the transition from the fasted to the fed state. However, it cannot be explained solely by a higher insulin sensitivity in the diabetic group, because glucose clearance (an index of insulin sensitivity) changed to a smaller extent in diabetic patients (·0.8 $ml \cdot kg^{-1} \cdot min^{-1}$) compared with nondiabetic patients (·1.2 $ml \cdot kg^{-1} \cdot min^{-1}$). It is rather possible that the epidural blockade in the diabetics contributed to a greater suppression of protein breakdown when compared with nondiabetics, therefore facilitating the incorporation of amino acids into newly made proteins.

**Table 3. Postoperative Glucose and Leucine Kinetics of Patients Receiving EDA or PCA in the Fasted and Fed States**

| | EDA | | PCA | | *P* Value | | |
|---|---|---|---|---|---|---|---|
| Variable | Fasted | Fed | Fasted | Fed | Feeding | Analgesia Technique | Interaction |
| Endogenous rate of appearance of glucose, $\mu mol \cdot kg^{-1} \cdot min^{-1}$ | 17.28 ± 3.30 | 12.17 ± 3.22 | 16.66 ± 2.50 | 13.66 ± 2.52 | **<0.0001** | 0.790 | 0.073 |
| Glucose clearance, $ml \cdot kg^{-1} \cdot min^{-1}$ | 2.43 ± 0.36 | 1.55 ± 0.31 | 2.26 ± 0.58 | 1.73 ± 0.32 | **<0.0001** | 0.994 | 0.097 |
| Rate of appearance of leucine, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 123 ± 19 | 141 ± 25 | 129 ± 11 | 165 ± 13 | **0.002** | 0.090 | 0.216 |
| Net protein breakdown, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 123 ± 19 | 88 ± 25 | 129 ± 11 | 111 ± 13 | **0.002** | 0.090 | 0.216 |
| Leucine oxidation, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 15 ± 5 | 24 ± 8 | 16 ± 7 | 33 ± 4 | **<0.0001** | 0.119 | **0.027** |
| Protein synthesis, $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | 108 ± 19 | 117 ± 21 | 113 ± 9 | 132 ± 13 | **0.026** | 0.217 | 0.435 |
| Protein balance (leucine), $\mu mol \cdot kg^{-1} \cdot h^{-1}$ | ·15 ± 5 | 30 ± 8 | ·16 ± 7 | 20 ± 4 | **<0.0001** | 0.1189 | **0.027** |
| Protein balance (whole body protein), $mg \cdot kg^{-1} \cdot h^{-1}$ | ·25 ± 8 | 49 ± 13 | ·26 ± 11 | 33 ± 7 | **<0.0001** | 0.1189 | **0.027** |

Values are mean ± SD; n = 6 per group. Statistically significant *P* value in bold.

EDA = epidural blockade; PCA = patient-controlled analgesia.

**Table 4. Postoperative Gaseous Exchange, Hormones, and Metabolites of Patients Receiving EDA or PCA in the Fasted and Fed States**

| | EDA | | PCA | | *P* Value | | |
|---|---|---|---|---|---|---|---|
| Variable | Fasted | Fed | Fasted | Fed | Feeding | Analgesia Technique | Interaction |
| $V_{O_2}$, ml/min | 262 ± 27 | 295 ± 78 | 200 ± 28 | 215 ± 41 | 0.137 | **0.013** | 0.570 |
| $V_{CO_2}$, ml/min | 194 ± 26 | 209 ± 50 | 150 ± 20 | 168 ± 25 | **0.041** | **0.035** | 0.822 |
| RQ | 0.74 ± 0.05 | 0.72 ± 0.11 | 0.75 ± 0.04 | 0.79 ± 0.04 | 0.856 | 0.182 | 0.286 |
| Glucose, mM | 7.2 ± 1.4 | 7.9 ± 1.7 | 7.8 ± 2.4 | 8.0 ± 1.3 | 0.124 | 0.732 | 0.327 |
| Insulin, pM | 57 ± 21 | 124 ± 61 | 78 ± 78 | 177 ± 148 | 0.003 | 0.456 | 0.462 |
| Glucagon, pM | 45 ± 25 | 66 ± 40 | 31 ± 17 | 67 ± 45 | 0.057 | 0.652 | 0.572 |
| Cortisol, nM | 511 ± 329 | 503 ± 432 | 435 ± 159 | 489 ± 204 | 0.549 | 0.795 | 0.430 |
| Insulin/glucagon ratio | 1.69 ± 1.06 | 2.48 ± 2.08 | 2.38 ± 1.52 | 2.74 ± 2.16 | 0.361 | 0.577 | 0.726 |

Values are mean ± SD; n = 6 per group. Statistically significant *P* value in bold.

EDA = epidural blockade; PCA = patient-controlled analgesia; RQ = respiratory quotient; $V_{CO_2}$ = whole body carbon dioxide production; $V_{O_2}$ = whole body oxygen consumption.

Suppression of gluconeogenesis has a protein-sparing effect, with a diminished need for gluconeogenic amino acids making this amount of nitrogen available for reincorporation into lean body mass instead of being used as an energy source and finally excreted as urea. The infusion of amino acids in the current study resulted in decreased endogenous glucose production by approximately 30%. This finding is consistent with a previous study for the same postoperative nutritional setting in nondiabetic patients.[14] In contrast, when amino acids were infused together with dextrose, endogenous glucose production was almost completely suppressed (80–90%).[10] Protein balance was higher in our study population and the nondiabetics fed with amino acids compared with nondiabetics receiving amino acids plus dextrose.

The infusion of dextrose even at low rates as performed in previous studies[10,11] caused hyperglycemia with plasma glucose levels up to 10 mM. In contrast, glucose levels in the current study did not exceed a mean of 8 mM, indicating that a positive protein balance can be achieved without hyperglycemia. There has been an increased awareness that elevated circulating concentrations of glucose are associated with immune suppression, leading to an increased risk of infection and postoperative complications after cardiac surgery.[12] Therefore, it has been emphasized that tight control of blood glucose levels must to be considered paramount in the perioperative management of patients at risk.[18]

Diabetes has been known to be responsible for muscle wasting and loss of lean body mass. However, the degree of protein breakdown depends on the extent of plasma glucose control. In fact, when compared with nondiabetics, patients with poorly controlled DM2 and obese DM2 patients had a higher rate of whole body protein breakdown.[19,20] In contrast, no alteration of leucine appearance or protein breakdown was found in DM2 patients who were under good or moderate glucose control.[21–25]

In opposition to previous studies our protocol included a preoperative assessment of the fasted state allowing to demonstrate that the baseline values of the two study groups for glucose and protein metabolism were comparable and, therefore, to better characterize the effect of the interventions.[10,11,14]

Although hemoglobin $A_{1c}$ was not measured in the current study, the levels of preoperative fasting plasma glucose concentrations indicated that the patients' diabetes was controlled adequately, and this was independent of the treatment used, which happened to be comparable between the two groups. Furthermore, it has been shown that the quality of treatment has only a small effect on protein metabolism in DM2 patients.[26]

One of the limitations of the current study is the small number of patients. However, even with this smaller sample size, the statistically significant difference in protein balance is clinically meaningful in terms of lean body mass. The result might be even more distinct for 7 patients per group achieving the initially aimed power of 0.8.

In summary, this study addresses the effects of epidural blockade on protein catabolism in diabetic patients after colorectal surgery. A short-term postoperative infusion of amino acids blunts protein breakdown and stimulates protein synthesis, resulting in a positive protein balance. This anabolic effect is greater in patients with epidural blockade than in those who received systemic analgesia.

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