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The Anabolic Effect of Epidural Blockade Requires Energy and Substrate Supply

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Background: **The authors examined the hypothesis that continuous thoracic epidural blockade with local anesthetic and opioid, in contrast to patient-controlled intravenous analgesia with morphine, stimulates postoperative whole body protein synthesis during combined provision of energy (4 mg · kg^{-1} · min^{-1} glucose) and amino acids (0.02 ml · kg^{-1} · min^{-1} Travasol™ 10%, equivalent to approximately 2.9 g · kg^{-1} · day^{-1}).**

Methods: **Sixteen patients were randomly assigned to undergo a 6-h stable isotope infusion study (3 h fasted, 3 h feeding) on the second day after colorectal surgery performed with or without perioperative epidural blockade. Protein synthesis, breakdown and oxidation, glucose production, and clearance were measured by L-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose.**

Results: **Epidural blockade did not affect protein and glucose metabolism in the fasted state. Parenteral alimentation decreased endogenous protein breakdown and glucose production to the same extent in both groups. Administration of glucose and amino acids was associated with an increase in whole body protein synthesis that was modified by the type of analgesia, *i.e.*, protein synthesis increased by 13% in the epidural group (from 93.3 ± 16.6 to 104.5 ± 11.1 μmol · kg^{-1} · h^{-1}) and by 4% in the patient-controlled analgesia group (from 90.0 ± 27.1 to 92.9 ± 14.8 μmol · kg^{-1} · h^{-1}; $P = 0.054$).**

Conclusions: **Epidural blockade accentuates the stimulating effect of parenteral alimentation on whole body protein synthesis.**

NET loss of body protein is a prominent feature of the catabolic response to surgical tissue trauma.[1] Because protein represents both structural and functional components, perioperative erosion of lean body mass contributes to immunosuppression, delayed wound healing, decreased muscle strength, and fatigue, which may result in prolonged convalescence and increased morbidity.[2] Although several protein-sparing strategies have been developed to minimize protein wasting following surgery, nitrogen losses can neither be completely suppressed nor organ function promptly restored.[3]

The pivotal role of the peripheral and central nervous system in triggering the catabolic responses to surgery has been demonstrated indirectly in patients undergoing surgery with regional anesthesia.[3] It can be shown that neuraxial block of efferent and afferent signals with local anesthetics, *i.e.*, epidural blockade, produces excellent functional pain relief, accelerates recovery, and reduces mortality after major surgery.[4–6] Parts of these clinical effects of epidural blockade were attributed to its protein-preserving properties[3]; in fact, epidural blockade, established before and maintained after abdominal procedures, has been shown to attenuate postoperative nitrogen excretion,[7–9] to blunt the increase in whole body protein breakdown and amino acid oxidation,[10,11] and to arrest the decrease in muscle protein synthesis.[12] The results of these studies, however, were exclusively obtained in patients receiving continuous parenteral nutrition. Therefore, the metabolic effects of analgesia and surgery could have been masked by greater changes evoked by nutritional factors.

In an attempt to control for the patient's feeding status, we recently investigated the impact of epidural blockade on protein catabolism in the fasted state and during short-term infusion of glucose.[13] Consistent with the previous observation that epidural blockade fails to influence protein catabolism when energy intake is low,[14] administration of epidural local anesthetic in the latter study did not affect whole body protein breakdown and oxidation in the fasted state. Epidural blockade, in contrast to patient-controlled analgesia (PCA) using intravenous morphine, increased whole body glucose uptake, which was accompanied by a decrease in endogenous amino acid oxidation. Whole body protein synthesis, however, was not altered by the infusion of glucose, whether patients received epidural blockade or not. We concluded that the protein-sparing action of epidural blockade requires adequate energy supply and that energy provision alone does not stimulate whole body protein synthesis after surgery. We also speculated that the failure of epidural blockade to promote protein synthesis in this protocol resulted from the lack of provision of anabolic substrates, *i.e.*, amino acids.

Thus, the purpose of the current protocol was to test the hypothesis that epidural blockade with local anesthetic, in contrast to PCA using intravenous morphine, increases whole body protein synthesis after abdominal surgery if amino acids are administered together with glucose.

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Methods

Patients

The study was approved by the Ethics Committee of the Royal Victoria Hospital. Informed consent was obtained from sixteen patients with localized colorectal carcinoma scheduled for elective colorectal surgery. None of the patients suffered from cardiac, hepatic, renal, or metabolic disease. No subject had developed recent weight loss or had a plasma albumin concentration less than 35 g/l. The patients were allocated according to a computer-generated randomization schedule into an epidural group receiving epidural blockade with bupivacaine and fentanyl (n = 8) or a control group receiving postoperative PCA with intravenous morphine (n = 8).

Anesthesia and Surgical Care

At arrival in the anesthetic room, patients in the epidural group received an epidural catheter inserted at one of the thoracic vertebral levels between T10 and T12. Bilateral sensory block to ice and pin prick from thoracic dermatome level four (T4) to sacral dermatome level five (S5) blockade was achieved with 0.5% bupivacaine and maintained during the operation with boluses of 0.25% bupivacaine (approximately 10 ml/h). General anesthesia in both groups was induced by thiopentone and continued with 35% nitrous oxide in oxygen and isoflurane. Fentanyl (3 μg/kg) was administered intravenously in the control group prior to surgical incision. General anesthesia in the control group was maintained with isoflurane. In the epidural group, isoflurane was administered at end-tidal concentrations of approximately 0.4 vol% to achieve tolerance of the endotracheal tube and to prevent awareness. All operations were conducted by the same surgeon and at the same time of the day (from 11 AM to 2 PM). All patients received a bolus of 10 ml/kg normal saline before induction followed by 10–15 $ml \cdot kg^{-1} \cdot h^{-1}$ during surgery. Blood losses were replaced with normal saline at a ratio of 3 to 1. Patients in both groups received hypocaloric nutritional supplementation with glucose from 8 AM to 8 PM on the first postoperative day (100 ml/h glucose 5%, equivalent to approximately 250 kcal) followed by infusion of NaCl 0.9% (100 ml/h) until the study period.

Sensory blockade from T8 to L3 was postoperatively maintained in the epidural group by continuous epidural infusion of 0.1% bupivacaine supplemented with 2 μg/ml fentanyl administered at a rate between 14 and 16 ml/h. An additional bolus of 5 ml bupivacaine 0.25% was given, if needed, to maintain the spread of the block. In the control group, pain relief was achieved by PCA with intravenous morphine. The incremental dose of morphine was 1 to 2 mg, lockout was 8 min, and dose duration was 30 s. Pain treatment in both groups was adjusted to obtain a visual analog scale score less than 4 at rest (scale from 0 = no pain to 10 = worst pain imaginable). Patients in both groups were asked by the ward nurse to rise in bed, sit on the bed, and stretch the lower limbs.

Parenteral Nutrition

Following a 3-h period of fasting, a solution of crystallized beet sugar (10% Dextrose anhydrous; Avebe, Foxhol, Holland) was infused at 4 $mg \cdot kg^{-1} \cdot min^{-1}$ with a 10% amino acid solution without electrolytes (Travasol™; Baxter, Montreal, Canada) for 3 h. The dextrose solution was prepared by the local pharmacy under sterile conditions and tested for sterility, stability, and absence of pyrogens prior to intravenous infusion. The composition of the Travasol™ solution, which was verified before each administration, was as follows: 35 μmol/ml proline, 34 μmol/ml threonine, 217 μmol/ml glycine, 207 μmol/ml alanine, 36 μmol/ml valine, 37 μmol/ml methionine, 34 μmol/ml isoleucine, 45 μmol/ml leucine, 2 μmol/ml tyrosine, 35 μmol/ml phenylalanine, 9 μmol/ml tryptophan, 38 μmol/ml lysine, 26 μmol/ml histidine, and 57 μmol/ml arginine. Based on the results of a previous study by Castellino et al.,[15] the rate of amino acid infusion was set at 0.02 $ml \cdot kg^{-1} \cdot min^{-1}$ (equivalent to approximately 2.9 $g \cdot kg^{-1} \cdot day^{-1}$) to achieve plasma amino acid concentrations at least twofold above basal. The beet dextrose solution was chosen because of its low ^{13}C content and therefore the lack of significant perturbation of $^{13}CO_2$ enrichment in expired air.[16] Previous studies further showed that the infusion of a solution containing dextrose and amino acids does not perturb baseline $^{13}CO_2$ enrichment in humans.[17]

Experimental Protocol

Plasma kinetics of leucine and glucose were determined by a primed constant infusion of tracer quantities of L-[1-^{13}C]leucine (99% ^{13}C) and [6,6-$^2H_2$]glucose (99% ^2H; Cambridge Isotope Laboratories, Cambridge, MA). Sterile solutions of labeled isotopes were prepared in the hospital pharmacy and kept at 4°C until administration.

All tests were performed in the fasted state beginning at 8 AM on the second postoperative day. The patients were studied in a temperature- and humidity-controlled environment (24°C, 35–42% relative humidity). A superficial vein in the dorsum of the hand was cannulated, and the cannula was kept patent with 2 $ml \cdot kg^{-1} \cdot h^{-1}$ saline. A second vein in the contralateral arm was cannulated to provide access for the infusion of the stable isotopes. Blood and expired air samples were collected before the infusion to determine baseline enrichments. Priming doses of 1 μmol/kg $NaH^{13}CO_3$, 4 μmol/kg L-[1-^{13}C]leucine, and 22 μmol/kg [6,6-$^2H_2$]glucose were administered and followed immediately by continuous infusions of 0.06 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ L-[1-^{13}C]leucine lasting 6 h. [6,6-$^2H_2$]glucose was infused a rate of 0.22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during the first 3 h (fasted

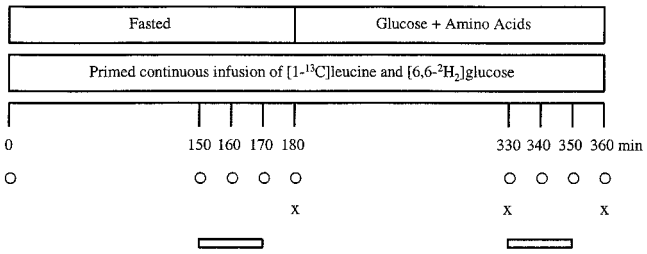

Fig. 1. Time course of the infusion of isotopes and collection of plasma and expired air samples (white circles), collection of plasma for the determination of metabolic substrates (glucose, lactate, nonesterified fatty acids, amino acids) and hormones (cortisol, insulin, glucagon) (x), and indirect calorimetry (open rectangles) in the fasted state and during feeding.

period) and then changed to 0.44 μmol · kg^{-1} · min^{-1} during unlabeled glucose administration. Toward the end of each 3-h study period, four blood and expired breath samples were collected at 10-min intervals. Each blood sample was transferred to a heparinized tube, centrifuged at 4°C (3,000*g*, 15 min) and stored at −70°C. Breath samples were collected in a 2-l latex bag and transferred immediately to 20-ml vacutainers. A schematic representation of the protocol is shown in figure 1.

Gaseous Exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted and fed states. The subjects were lying in a semirecumbent position, 20°, breathing room air in the ventilated hood, for 20 min on each occasion. Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured, and the respiratory quotient was calculated. An average value of $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory quotient was taken, with a coefficient of variation less than 10%.

Analytical Methods

Isotopic Enrichments. Plasma [1-^{13}C]α-ketoisocaproate enrichment was determined by electron impact selected-ion monitoring gas chromatography–mass spectrometry using the method previously described by Mamer and Montgomery,[18] except that the t-butylmethylsilyl rather than trimethylsilyl derivatives were prepared. Expired ^{13}C-carbon dioxide enrichment was determined by isotope ratio mass spectrometry (Analytical Precision AP2003, Manchester, United Kingdom).[19] Plasma glucose was derivatized to its pentaacetate compound and the [6,6-$^2H_2$]glucose enrichment determined by gas chromatography–mass spectrometry using electron impact ionization.[20] In each analysis run, duplicate injections were always performed, and their means were taken to represent enrichment.

Plasma Metabolites and Hormones. Plasma glucose was measured by a glucose-oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate assay was based on lactate oxidase and was performed using the synchron CX 7 system (Beckman Instruments). Circulating concentrations of nonesterified fatty acids were measured by an enzymatic assay (Boehringer Mannheim, Laval, Quebec, Canada). Amino acid concentrations in the plasma and the infusate acids were analyzed by high-performance liquid chromatography as described previously.[20] Circulating concentrations of plasma cortisol, insulin, and glucagon were measured by sensitive and specific double antibody radioimmunoassays (Amersham International, Amersham, Bucks, United Kingdom).

Calculations. During isotopic steady state conditions, the rate of appearance (R_a) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (atom percentage excess [APE]) calculated by:

$$R_a = (APE_{inf}/APE_{pl} - 1) \cdot F$$

where F is the infusion rate of the labeled tracer (in micromoles per kilogram per minute), APE_{inf} is the tracer enrichment in the infusate, and APE_{pl} is the tracer enrichment in plasma, respectively. The APE used in this calculation are the mean of the four APE values determined at each steady state. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of values above their mean, expressed as coefficient of variation. A coefficient of variation less than 5% was used as a confirmation of a valid plateau.

During 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 and diet. When the subjects are in the postabsorptive state, the leucine intake equals zero and B = Q. When amino acids are being infused intravenously, the rate of leucine infusion (I) must be subtracted from the total leucine flux to calculate the rate of endogenous leucine release. The rate of exogenous leucine infusion was calculated as the product of the infusate leucine concentration in micromoles per milliliter and the infusion rate in milliliters per minute. Plasma enrichment of [1-^{13}C]α-ketoisocaproate during infusion of L-[1-^{13}C]leucine has been used as the basis for calculating both flux and oxidation of leucine.[21] This steady state reciprocal pool model is considered to represent the intracellular precursor pool enrichment more precisely than leucine itself.[21] In the calculation of oxidation, a factor of 0.76 was applied in the fasted state to account for the fraction of ^{13}C-carbon dioxide released from leucine but retained within slow turnover rate pools of the body.[19] During feeding, the fraction of recovery is higher, with reported retention

factors of 0.90 or greater.[22] Consistent with the previous work of our group on leucine kinetics in patients receiving parenteral nutrition with amino acids and dextrose, a factor of 0.92 was used in the current study.[17]

In the fasted state, the R_a glucose was equal to the endogenous production of glucose. During glucose infusion, endogenous glucose production was calculated by subtracting the glucose infusion rate from the total R_a glucose. In the physiologic steady state, whole body glucose uptake equals the rate of endogenous glucose production. Because glucose uptake increases proportionally as blood glucose concentrations increase, changes in whole body glucose uptake do not necessarily reflect corresponding changes in the tissues' ability to take up glucose. This may be because most glucose after surgery is taken up by the wound and the cells of the immune system, and the rate of uptake by these non–insulin-sensitive tissues is to a large extent determined by the diffusion gradient for glucose. Thus, the rate of glucose uptake has to be corrected for the prevailing plasma glucose concentration. The resulting value, the glucose clearance rate, represents an index of the ability of tissues to take up glucose. The plasma clearance rate of glucose was calculated as R_a glucose divided by the corresponding plasma glucose concentration.

Statistics

All data are presented as mean ± SD. Based on an expected difference in protein synthesis of 10 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ between the two groups (SD 5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$; power 80%; $P = 0.05$) a total number of 14 patients was calculated to be sufficient. Analyses of dependent variables were performed using two-factorial analysis of variance for repeated measures. Significant effects induced by parenteral nutrition were assumed when P values for time dependency were less than 0.05. Influences by the analgetic regimen were accepted as significant when the interaction term of the analysis of variance was less than 0.05. All analyses were performed using the General Linear Model in SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

Results

Patients

One patient in the PCA group had to be excluded from further analysis because he inadvertently did not receive amino acids (because of an error made by pharmacy preparing the feeding solutions). There were no differences between the two groups regarding sex, age, height, and weight of patients as well as duration of surgery (table 1). Estimated blood loss never exceeded 400 ml, and no patient received blood transfusion. The visual analog scale values obtained at rest 12 and 24 h after surgery and at the beginning of the study were comparable in the two groups (PCA group, 12 h: 1.8 ± 1.0, 24 h: 1.9 ± 0.9, study: 1.6 ± 0.8; epidural group, 12 h: 1.2 ± 1.0, 24 h: 1.4 ± 1.1, study: 1.3 ± 0.7). On the first postoperative day, patients in both groups were able to sit on the bed, but none of the patients ambulated.

Table 1. Biometric and Clinical Data of Patients

	Control	Epidural
Sex (F:M)	4:3	5:3
Age (yr)	61 ± 12	56 ± 22
Height (cm)	168 ± 7	163 ± 10
Weight (kg)	70 ± 7	62 ± 11
Surgery (n)		
Colectomy	1	3
Left hemicolectomy	1	1
Sigmoid resection	1	1
Low anterior resection	4	3
Duration of surgery (min)	209 ± 43	200 ± 96
Estimated blood loss (ml)	264 ± 103	175 ± 93

Values are presented as mean ± SD.

Glucose and Protein Kinetics

In all experiments, a plateau in the enrichments of plasma [1-^{13}C]α-ketoisocaproate, [6,6-$^2H_2$]glucose, and expired ^{13}C-carbon dioxide was achieved in the fasted and fed states (coefficient of variation < 5%), permitting the use of the steady state equation (fig. 2).

Whole body protein synthesis, breakdown and leucine oxidation, glucose production, and clearance in the fasted state were similar in the two groups (table 2). Administration of glucose and amino acids suppressed the endogenous R_a glucose and R_a leucine to the same extent in both groups, while leucine oxidation and glucose clearance increased, with glucose clearance being greater in patients with epidural blockade (table 2). Parenteral alimentation was associated with an increase in whole body protein synthesis (table 2), which was modified by the type of analgesia, *i.e.*, protein synthesis increased by 13% in the epidural group and by 4% in the PCA group. This stimulating effect of epidural blockade just failed to reach statistical significance ($P = 0.054$).

Metabolites and Hormones

Epidural blockade had no significant influence on circulating concentrations of metabolic substrates and hormones in the fasted state (table 3). Plasma concentrations of metabolites and hormones obtained after 150 and 180 min of feeding also were not different. Combined glucose and amino acid administration increased the plasma glucose and insulin concentration, while plasma concentrations of lactate, glucagon, and cortisol remained unchanged. Plasma concentrations of nonesterified fatty acids decreased to a comparable degree in both groups with parenteral feeding. Amino acid plasma concentrations during fasting conditions were comparable in the two groups and increased to a similar extent during feeding (table 4).

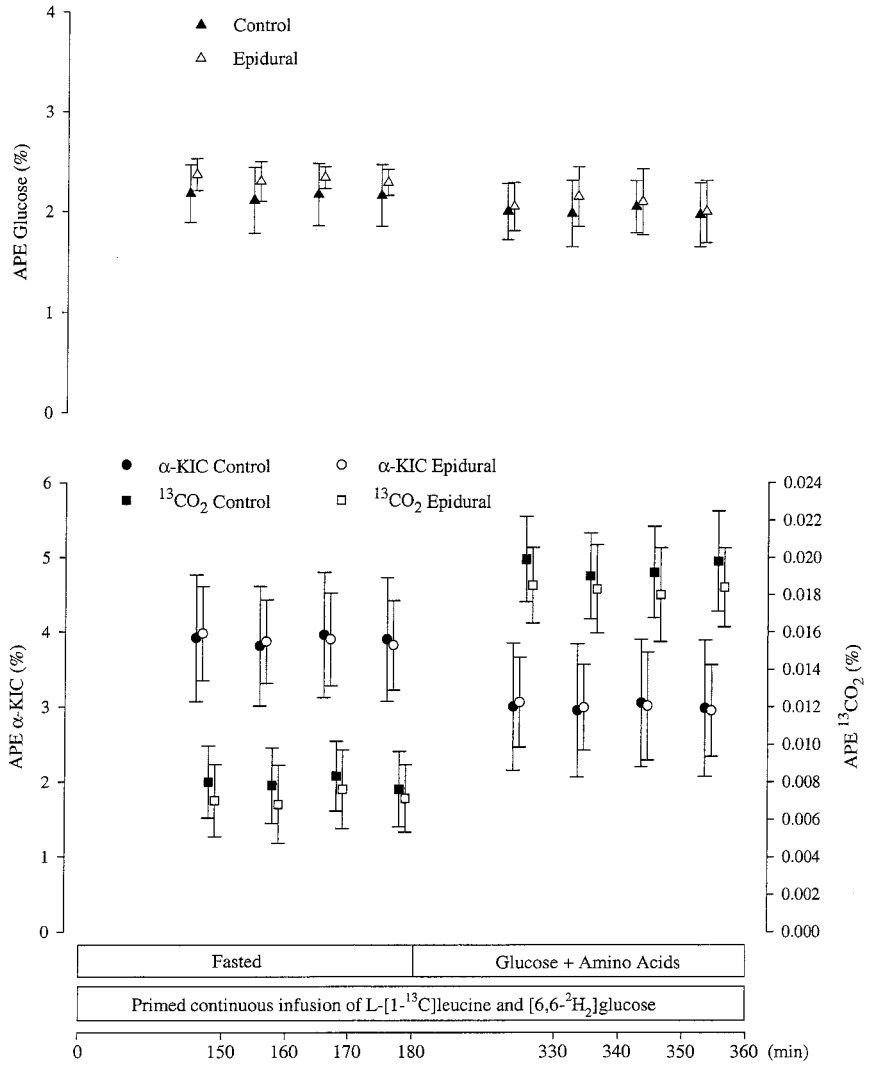

Fig. 2. Plateau enrichments, expressed in atom percent excess (APE), of [1-^{13}C]α-ketoisocaproate (KIC), ^{13}C-carbon dioxide, and [6,6-$^{2}H_2$]glucose.

Gaseous Exchange

$\dot{V}O_2$, $\dot{V}CO_2$, and respiratory quotient were not significantly affected by epidural blockade in the fasted state (table 5). Combined glucose and amino acid infusion stimulated $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory quotient in both groups, with $\dot{V}O_2$ and $\dot{V}CO_2$ increasing to a greater extent in patients receiving PCA.

Discussion

Although total parenteral nutrition has been shown to attenuate protein losses during catabolic surgical illness, only subjects with starvation and malnourished patients with cancer can be rendered anabolic.[23–25] In contrast, unselected isocaloric or hypercaloric nutritional support

Table 2. Kinetics of Leucine and Glucose Metabolism in the Fasted State and Fed State

	Control		Epidural		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
R_a leucine (μmol · kg^{-1} · h^{-1})	110.8 ± 15.2	139.1 ± 11.4	111.2 ± 19.8	145.3 ± 20.3	<0.0001	0.711	0.276
Endogenous R_a leucine (μmol · kg^{-1} · h^{-1})	110.8 ± 15.2	88.3 ± 10.0	111.2 ± 19.8	95.8 ± 17.3	<0.0001	0.632	0.167
Leucine oxidation (μmol · kg^{-1} · h^{-1})	20.8 ± 7.2	46.5 ± 12.1	17.9 ± 9.0	40.8 ± 12.7	<0.0001	0.387	0.597
Protein synthesis (μmol · kg^{-1} · h^{-1})	90.0 ± 27.1	92.9 ± 14.8	93.3 ± 16.6	104.5 ± 11.1	0.0022	0.342	0.054
R_a glucose (μmol · kg^{-1} · min^{-1})	10.0 ± 1.7	26.5 ± 5.2	11.0 ± 2.1	27.6 ± 3.0	<0.0001	0.446	0.943
Endogenous R_a glucose (μmol · kg^{-1} · min^{-1})	10.0 ± 1.7	3.8 ± 4.5	11.0 ± 2.1	4.5 ± 3.7	<0.0001	0.543	0.901
Glucose clearance (ml · kg^{-1} · min^{-1})	2.0 ± 0.3	2.3 ± 0.4	2.3 ± 0.6	2.9 ± 0.6	0.0046	0.047	0.713

Values are presented as mean ± SD. The endogenous glucose and leucine rates of appearance (R_a) were calculated by subtracting the rates of exogenous glucose and leucine infusion from the total glucose and leucine R_a, respectively.

* Probability that values are influenced by parenteral alimentation. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

Table 3. Plasma Concentrations of Circulating Metabolites and Hormones in the Fasted and Fed State

	Control		Epidural		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
Glucose (mM)	5.3 ± 0.9	11.4 ± 1.2	4.8 ± 0.7	9.8 ± 1.9	<0.0001	0.116	0.309
Lactate (mM)	0.6 ± 0.1	1.1 ± 0.3	0.8 ± 0.4	1.0 ± 0.5	<0.0001	0.757	0.093
NEFA (μM)	467 ± 109	126 ± 79	428 ± 110	119 ± 63	<0.0001	0.598	0.494
Cortisol (nM)	387 ± 55	413 ± 128	266 ± 129	331 ± 160	0.125	0.106	0.512
Insulin (pM)	63 ± 25	836 ± 384	55 ± 14	684 ± 406	<0.0001	0.464	0.479
Glucagon (pM)	26 ± 11	36 ± 24	19 ± 5	19 ± 5	0.114	0.066	0.110

Values are presented as mean ± SD.

* Probability that values are influenced by parenteral alimentation. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

NEFA = nonesterified fatty acids.

in well-nourished surgical patients is not only ineffective to induce anabolism,[26–28] but is also associated with increased morbidity.[29] Despite the fact that the peripheral and central nervous system represents a common pathway initiating the catabolic responses to surgery, none of the studies investigating the protein-preserving effects of various feeding strategies was controlled for the type of pain treatment used perioperatively. The results of the current study demonstrate that epidural blockade accentuates the increase in whole body protein synthesis during parenteral alimentation when compared with PCA with intravenous morphine, further emphasizing the central role of analgesia in modifying the catabolic response to surgical stress.

Net balance of body protein can be calculated from the difference between total nitrogen intake and nitrogen loss. The obvious shortcoming of nitrogen balance or body composition measurements is that the contributions from dynamic changes in protein synthesis and degradation cannot be separated. The absolute rates of protein synthesis, oxidation, and breakdown can be directly measured *in vivo* by use of isotopically labeled amino acids such as L-[1-^{13}C]leucine. It has to be noted that changes detected by isotope infusion studies performed over a few hours after surgery, in contrast to continuous nitrogen balance measurements, are not necessarily representative of the metabolic alterations occurring during the whole postoperative period.

Studies applying isotope tracer technology showed that the principal biochemical mechanisms responsible for enhanced protein wasting after surgery are increased proteolysis[30,31] and amino acid oxidation,[11,32] along with an insufficient augmentation or decrease in protein synthesis.[33–35] Accordingly, in our subjects the rates of protein breakdown and amino acid oxidation on the second postoperative day were approximately 15% higher than in patients with gastrointestinal cancer studied immediately prior to colorectal surgery.[36] The type of pain treatment did not specifically influence the kinetics of protein catabolism in the fasted state, support-

Table 4. Circulating Plasma Concentrations of Amino Acids (μM) in the Fasted and Fed State

	Control		Epidural	
	Fasted	Fed	Fasted	Fed
Aspartate	7 ± 4	9 ± 4	5 ± 4	7 ± 5
Threonine	80 ± 26	190 ± 30	87 ± 15	191 ± 40
Serine	68 ± 18	108 ± 17	77 ± 19	112 ± 21
Glutamate	44 ± 21	45 ± 12	34 ± 11	45 ± 20
Glutamine	421 ± 77	482 ± 64	436 ± 52	458 ± 61
Glycine	165 ± 56	914 ± 75	181 ± 78	898 ± 193
Alanine	127 ± 42	679 ± 121	155 ± 48	662 ± 202
Valine	187 ± 77	371 ± 90	205 ± 76	338 ± 66
Leucine	132 ± 52	229 ± 95	155 ± 51	271 ± 53
Isoleucine	62 ± 28	173 ± 48	84 ± 37	175 ± 34
Cysteine	14 ± 12	13 ± 6	17 ± 11	19 ± 9
Methionine	17 ± 4	136 ± 18	18 ± 3	126 ± 26
Tyrosine	47 ± 6	70 ± 48	53 ± 14	67 ± 19
Phenylalanine	58 ± 12	180 ± 35	50 ± 7	159 ± 23
Lysine	117 ± 35	250 ± 55	128 ± 31	239 ± 44
Histidine	49 ± 16	117 ± 26	55 ± 17	131 ± 25
Arginine	39 ± 16	207 ± 35	49 ± 12	194 ± 48
Proline	110 ± 41	258 ± 37	125 ± 25	250 ± 43
Total amino acids	1,959 ± 108	4,416 ± 656	1,790 ± 409	4,588 ± 542

Values are presented as mean ± SD.

Table 5. Gaseous Exchange in the Fasted and Fed State

	Control		Epidural		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
$\dot{V}O_2$ (ml/min)	240 ± 42	268 ± 50	234 ± 51	238 ± 51	0.004	0.486	0.016
$\dot{V}CO_2$ (ml/min)	176 ± 25	217 ± 38	173 ± 35	185 ± 32	<0.0001	0.311	0.005
RQ	0.74 ± 0.04	0.81 ± 0.02	0.74 ± 0.02	0.78 ± 0.05	<0.0001	0.428	0.125

Values are presented as mean ± SD.

* Probability that values are influenced by parenteral alimentation. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

$\dot{V}O_2$ = whole body oxygen consumption; $\dot{V}CO_2$ = whole body carbon dioxide production; RQ = respiratory quotient.

ing the previously held contention that the anabolic effect of epidural blockade requires adequate energy and substrate supply.[13,37]

The nitrogen-sparing effect of parenteral nutrition after surgical trauma and during sepsis is well documented. However, even vigorous forms of artificial nutrition usually fail to produce positive nitrogen balance, *i.e.*, anabolism. It has been suggested that the resistance to establishing positive nitrogen balance in critically ill patients is primarily a problem of returning the synthesis rate of protein to normal rather than stemming an accelerated breakdown of body protein.[38] This assumption is based on results obtained in burn and trauma patients, in whom total parenteral nutrition was capable of increasing whole body protein synthesis, whereas the elevated rate of protein breakdown continued unaltered.[39] Only few studies addressed the mechanisms by which parenteral feeding modifies the catabolic responses to elective abdominal surgery. Early studies using urinary nitrogen and 3-methyl histidine excretion measurements indicated that isocaloric or hypercaloric total parenteral nutrition promotes nitrogen retention, and the underlying mechanism is *via* an increase in protein synthesis.[40] Isocaloric isonitrogenous nutrition after uncomplicated surgery was associated with an increase in protein synthesis, while protein breakdown remained elevated.[31] In contrast, intravenous nutrition following major abdominal procedures suppressed leucine flux as assessed by [1-^{14}C] leucine kinetics,[41] but did not impede the postoperative decrease in muscle protein synthesis.[34] In the current protocol, short-term administration of glucose together with amino acids 2 days after elective colorectal surgery decreased endogenous protein breakdown in all patients. The reduction of the R_a leucine by 20% was similar to the decrease previously demonstrated after abdominal surgery,[41] but less pronounced than in healthy volunteers, who showed a 70% decrease in protein breakdown during similar conditions (plasma insulin concentrations clamped at 650 pM accompanied by elevated plasma amino acid concentrations twofold to threefold above basal).[15] Amino acid oxidation increased after 3 h of feeding, most likely a result from a mass action effect caused by increased oxidizable substrate availability. Contrary to patients in the PCA group, who showed only a 3% increase, whole body protein synthesis increased by 14% in patients receiving epidural blockade. This increase is less than the 30% enhancement reported in normal (nonsurgical) subjects, who were studied during similar metabolic and endocrine circumstances.[15,42] The stimulation of protein synthesis in patients with epidural blockade was accompanied by a greater glucose clearance, indicating improved whole body glucose uptake. This result is in line with the previous notion that epidural blockade with local anesthetic is able to stimulate postoperative glucose utilization and to normalize impaired glucose tolerance during surgery.[43,44] Because muscle protein is broken down to provide gluconeogenic amino acids for *de novo* glucose synthesis, gluconeogenesis occupies a central position in catabolic pathways. There is recent evidence of this interdependence of protein and glucose metabolism in surgical patients as reflected by the significant correlation between endogenous protein breakdown and glucose production during and after surgery.[13,36] Hence, the inhibitory effect of exogenous glucose on glucose production has been considered an important factor contributing to the nitrogen-sparing action of energy supply. Independent of the type of analgesia, parenteral nutrition in the current study inhibited the glucose rate of appearance by 60%, which is less than the complete suppression of endogenous glucose production that was achieved in normal postabsorptive subjects by the same glucose infusion rate ($4\ mg \cdot kg^{-1} \cdot min^{-1}$).[45]

It was not the intention of this protocol to dissect the factors responsible for the anabolic action of epidural blockade and nutrition in the current study. We therefore can only speculate about the underlying hormonal mechanisms. Insulin and glucagon represent both key endocrine regulators of protein metabolism.[22] While glucagon plasma concentrations remained unchanged throughout the study period, combined glucose and amino acid administration led to a 10- to 12-fold increase in the plasma insulin concentration. Although the insulin response to parenteral nutrition was not affected by epidural blockade, the higher glucose clearance indicates a greater insulin sensitivity during epidural blockade, which in turn affects protein homeostasis. This assumption is further supported by the results of a re-

cent study showing that epidural blockade ameliorates insulin sensitivity after upper abdominal surgery.[46]

It is well recognized that perioperative insulin resistance resulting from increased plasma concentrations of counterregulatory hormones (cortisol, glucagon, catecholamines) is crucial in mediating protein losses after surgery.[47,48] Epidural blockade with local anesthetic has been frequently shown to suppress the cortisol, glucagon, and sympathoadrenergic responses to abdominal surgery, thereby facilitating the anticatabolic action of insulin.[49,50] Thus, the improvement of insulin sensitivity in the epidural group might have been a consequence of the inhibitory effect of epidural local anesthetics on the endocrine stress responses. Plasma catecholamine concentrations were not measured in the current study, and there was no significant difference in the plasma cortisol and glucagon concentrations between the two groups, neither in the fasted nor in the fed state. It cannot be ruled out, however, that more frequent intraoperative and postoperative hormone measurements could have revealed such a difference.

In summary, the current finding of an accentuating effect of epidural blockade on whole body protein synthesis in presence of parenteral alimentation further underscores the essential role of analgesia in modulating nutrient utilization and the catabolic responses to surgery.

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