Epidural blockade improves substrate utilization after surgery

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Epidural blockade improves substrate utilization after surgery. Am J Physiol Endocrinol Metab 279: E646–E653, 2000.—The purpose of this study was to test the hypothesis that epidural blockade with local anesthetic improves the anticyanotic effects of glucose after colorectal surgery. Sixteen patients were randomly assigned to undergo a 6-h stable isotope infusion study (3 h fasted, 3 h glucose infusion at 4 mg · kg⁻¹ · min⁻¹) on the second postoperative day with or without perioperative epidural blockade. Protein synthesis, breakdown and oxidation, and glucose production and clearance were assessed by L-[1-¹⁴C]leucine and [6,6-²H₆]glucose. Epidural blockade did not affect protein and glucose metabolism in the fasted state. Glucose infusion increased glucose clearance (P < 0.05), accompanied by an increase in the respiratory quotient (P < 0.05) and a decrease in leucine oxidation (P < 0.05) only in the presence of epidural blockade. An inverse correlation (r = 0.74, P < 0.05) between changes in glucose clearance and leucine oxidation was observed. In conclusion, epidural blockade facilitates whole body glucose uptake and inhibits endogenous protein oxidation after abdominal surgery, indicating a shift from a protein to a more glucose-dominated substrate utilization.

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Glucose administration at a higher rate fails to further inhibit glucose production in surgical patients but results in an increase in glucose oxidation and a more pronounced decrease of urea synthesis, an indirect parameter of protein catabolism (31). It has therefore been postulated that once enough glucose is given to achieve the maximal inhibition of gluconeogenesis the justification of administering higher doses resides in the ability of the body to oxidize the infused glucose. Hence, provision of energy and thereby minimizing the amount of amino acids oxidized for energy production has been regarded as a second mechanism responsible for the protein-preserving effect of glucose in critically ill patients.

Although provision of adequate quantities of glucose, either alone or as part of total parenteral nutrition, attenuates the protein losses via an increase in whole body protein synthesis, the elevated rate of protein catabolism continues unaltered (32). This limited effectiveness of nutritional support has been attributed to the nonsuppressibility of gluconeogenesis by glucose administration and to the impaired capacity of stressed patients to oxidize glucose, which is given in excess of the amount required for most efficient suppression of gluconeogenesis. Only one-half of the glucose infused at 4 mg · kg⁻¹ · min⁻¹ is directly oxidized after surgical or accidental trauma, and this percentage even fell when glucose was administered in higher doses (32, 36).

The fact that even vigorous nutritional support fails to entirely curtail protein catabolism after trauma and during sepsis has led to the investigation of various pharmacological approaches. Infusion of insulin, the body’s key endocrine regulatory factor to promote protein anabolism, ameliorates protein losses in critically ill patients (2, 26). To overcome perioperative insulin resistance, however, insulin has to be administered in high doses (26). At the same time, provision of excessive amounts of glucose is required to maintain normoglycemia. This issue raises potential metabolic concerns because high carbohydrate intake causes fatty infiltration of the liver (12) and stimulates carbon dioxide production (1).
Because pain has been regarded as a potent trigger for the catabolic response to surgery, manipulation of the stress response by different analgesic techniques represents a more direct pharmacological approach to modify protein catabolism. It is well established that blockade of nociceptive and nonnociceptive pathways, such as the sympathetic nervous system, by epidural local anesthetics improves nitrogen balance (34), attenuates the rise in whole body protein breakdown (7), and prevents the decrease of muscle protein synthesis after surgery (4). These results, however, were exclusively obtained in patients receiving perioperative parenteral feeding with impact on all aspects of protein and glucose economy.

The aim of this project was to test the hypothesis that the anticonatal effects of parenteral administration of glucose can be enhanced by epidural blockade with local anesthetics, initiated before and maintained after colorectal surgery. To gain an integrated insight into protein and glucose metabolism, dynamic changes in protein breakdown, amino acid oxidation, protein synthesis, glucose production, and glucose clearance were assessed by using stable isotope tracer kinetics in the fasted and fed state.

**METHODS**

**Patients**

The study was approved by the Ethics Committee of the hospital, and informed consent was obtained from all patients. Sixteen patients with localized nonmetastatic adenocarcinoma of the rectosigmoid colon scheduled for elective colorectal surgery were admitted to the study (Table 1). 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 <35 g/L. The patients were allocated according to a computer-generated randomization schedule to an epidural group (EDA group) receiving perioperative epidural blockade with bupivacaine and fentanyl (n = 8) or a control group receiving postoperative patient-controlled analgesia (PCA) with intravenous morphine (n = 8).

**Table 1. Biometric and clinical data of patients**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>4/4</td>
<td>3/5</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57 ± 22</td>
<td>53 ± 15</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 ± 9</td>
<td>168 ± 10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 14</td>
<td>66 ± 13</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>2/6</td>
<td>1/7</td>
</tr>
<tr>
<td>Preoperative fasting, min</td>
<td>2,299 ± 82</td>
<td>2,318 ± 81</td>
</tr>
<tr>
<td>Surgery (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colectomy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Transverse colon resection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low anterior resection</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>198 ± 78</td>
<td>214 ± 82</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of patients. ASA; American Society of Anesthesiology.

**Anesthesia and Surgical Care**

At arrival in the anesthetic room, the patients in the EDA group assumed a sitting position, and an epidural catheter was inserted at one of the thoracic vertebral levels between T10 and T12. Neural blockade was initiated with 0.5% bupivacaine to achieve a bilateral sensory block to ice and pin prick from thoracic dermatome level four (T4) to sacral dermatome level five (S5). The block was maintained during the operation with boluses of 0.25% bupivacaine. General anesthesia in both groups was induced with intravenous thiopentone and was maintained with 35% nitrous oxide in oxygen and isoflurane. Fentanyl (3 μg/kg) was administered in the control group before surgical incision. All operations were carried out by the same surgeon and at the same time of the day (from 1100 to 1400). Patients in both groups received hypocaloric nutritional supplementation with glucose from 0800 to 2000 on the first postoperative day (100 ml/h 5% glucose equivalent to ~250 kcal) followed by infusion of 0.9% NaCl (100 ml/h) until the study period.

Sensory blockade from T4 to L3 covering the 10- to 15-cm paramedian subumbilical incision was postoperatively maintained in the EDA group by continuous epidural infusion of 0.1% bupivacaine supplemented with 2 μg/ml fentanyl. In the control group, pain relief was achieved by PCA with intravenous morphine. The incremental dose of morphine was 1–2 mg, lockout was 8 min, and dose duration was 30 s. Postoperative pain intensity was estimated using a 10-cm visual analog scale (VAS from 0 = no pain to 10 = worst pain imaginable). Pain treatment in both groups was adjusted to obtain a VAS score at rest below four. Patients in both groups were asked by the ward nurse to rise in bed, sit on the bed, and stretch the lower limbs.

**Glucose Infusion**

After a 3-h period of fasting, a solution of crystallized beet sugar (10% dextrose anhydrous; Avebe, Foxhol, Holland) was infused at 4 mg · kg⁻¹ · min⁻¹ for 3 h. The solution was prepared by the local pharmacy under sterile conditions and was tested for sterility, stability, and absence of pyrogens before intravenous infusion. The beet dextrose solution was chosen because of its low ¹³C content and therefore the lack of significant perturbation of ¹³CO₂ enrichment in expired air (6).

**Experimental Protocol**

Plasma kinetics of leucine and glucose were determined by a primed constant infusion of tracer quantities of L-[¹-¹³C]leucine (99% ¹³C) and [6,6-²H₂]glucose (99% ²H) obtained from Cambridge Isotope Laboratories (Cambridge, MA). Before each infusion study, sterile solutions of isotopes were prepared in the hospital pharmacy and were kept at 4°C until administration.

All tests were performed in the fasted state beginning at 0800 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 · kg⁻¹ · h⁻¹ saline. A second superficial 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 NaH¹³CO₃, 4 μmol/kg L-[¹-¹³C]leucine, and 22 μmol/kg [6,6-²H₂]glucose were administered and followed immediately by continuous infusions of 0.06 μmol · kg⁻¹ · min⁻¹ L-[¹-
Fig. 1. Time course of the infusion of isotopes and collection of plasma and expired air samples (○), indirect calorimetry (open rectangles), and collection of plasma for the determination of metabolic substrates and hormones (x) in the fasted state and during the infusion of glucose.

$^{13}$Cleucine lasting 6 h. [6,6-$^{2}$H$_{2}$]glucose was infused at a rate of 0.22 µmol · kg$^{-1}$ · min$^{-1}$ during the first 3 h (fasted period) and then was changed to 0.44 µmol · kg$^{-1}$ · min$^{-1}$ during the 3 h of 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 immediately 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 Fig. 1.

**Gaseous Exchange**

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted and fed state. The subjects were lying in a semirecumbent position (20°), breathing room air in the ventilated hood, for 20 min on each occasion. Oxygen consumption ($V_{O_{2}}$) and carbon dioxide production ($V_{CO_{2}}$) were measured, and the respiratory quotient (RQ) was calculated. An average value of $V_{O_{2}}$, $V_{CO_{2}}$, and RQ was taken, with a coefficient of variation <10%.

**Analytical Methods**

Isotopic enrichments. Plasma α-[1-13C]ketoisocaproate (α-KIC) enrichment was determined by electron-impact-select-ed-ion monitoring gas chromatography-mass spectrometry using the method previously described by Mamer and Montgomery (21), except that t-butyldimethylsilyl rather than trimethylsilyl derivatives were prepared. Expired 13CO$_{2}$ enrichment was determined by isotope ratio-mass spectrometry (Analytical Precision AP2003, Manchester, UK; see Ref. 28). Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-$^{2}$H$_{2}$]glucose enrichment was determined by gas chromatography-mass spectrometry using electron-impact ionization (27). 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 cortisol, insulin, and glucagon were measured by sensitive and specific double-antibody RIAs (Amershams International, Amersham, Bucks, UK).

**Calculations**

When a physiological and isotopic steady state exists, the rate of appearance ($R_{a}$) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (APE or atom percentage excess) calculated by

$$R_{a} = (APE_{pl}/APE_{inf} - 1) \times F \tag{1}$$

where F is the infusion rate of the labeled tracer (µmol · kg$^{-1}$ · min$^{-1}$), APE$_{inf}$ is the tracer enrichment in the infusion, and APE$_{pl}$ is the tracer enrichment in plasma. The APE used in this calculation was the mean of the four APE determined during steady-state conditions obtained at each phase of the studies. 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 <5% was used as a confirmation of a valid plateau.

Under steady-state conditions, leucine flux ($Q$) is defined by the formula

$$Q = S + O = B + I \tag{2}$$

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. In the postabsorptive state, the sole source of the essential amino acid leucine for protein synthesis and oxidation is that derived from the breakdown of endogenous proteins. Inspection of Eq. 2 indicates that, when studies are conducted after absorption, leucine flux is equal to leucine breakdown (22). Plasma enrichment of α-[1-13C]KIC during infusion of [6,6-$^{2}$H$_{2}$]leucine has been used as the basis for calculating both flux and oxidation of leucine (29). This steady-state reciprocal-pool model is considered to provide a more precise representation of intracellular precursor pool enrichment than leucine itself (29). In the calculation of oxidation, factors of 0.76 for the fasting state and 0.81 for the fed state were applied to account for the fraction of 13CO$_{2}$ released from leucine but retained within slow turnover rate pools of the body (22).

In the fasted state, the glucose $R_{s}$ 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 glucose $R_{s}$. In the physiological steady state, whole body glucose uptake equals the rate of endogenous glucose production. Because glucose uptake increases proportionally as blood glucose concentrations rise, changes in whole body glucose uptake do not necessarily reflect corresponding changes in the tissue’s ability to take up glucose. This may be because most glucose uptake occurs in non-insulin-sensitive tissues, and the rate of uptake 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 glucose $R_{c}$ divided by the corresponding plasma glucose concentration.

**Statistics**

All data are presented as means ± SD. Comparisons for each dependent variable were performed using two-factorial ANOVA with the factors epidural blockade and glucose infusion. ANOVA for repeated measurements was applied to...
analyze any significant change in the plasma concentrations of metabolic substrates (glucose, lactate) and hormones (cortisol, insulin, glucagon) during glucose administration. If no significant change was detected between the two measurements obtained in the fasted state and after 120 and 180 min of glucose infusion, the two average values were compared.

The relationships between leucine Ra and glucose Ra in the postabsorptive state and between changes in glucose clearance and leucine oxidation during glucose administrations were evaluated by the correlation coefficient. Statistical significance was accepted at \( P < 0.05 \).

**RESULTS**

**Patients**

There were no differences between the two groups regarding sex, age, height, and weight of patients. Preoperative fasting time and duration of surgery were also similar in both groups. Estimated blood loss never exceeded 400 ml, and no patient received blood transfusion. The average VAS at rest obtained 12 and 24 h after surgery and at the beginning of the infusion study on the second postoperative day was similar in the two groups (PCA group: 1.4 ± 0.8 cm; EDA group: 1.1 ± 0.6 cm). On the first postoperative day, patients in both groups were able to sit on the bed, but none of the patients could leave the bed for a walk.

**Stable Isotope Kinetics**

In all experiments, a plateau in the enrichments of plasma \( \alpha_{-13C} \)KIC, \( [6,6-2H_2] \)glucose, and expired \( ^{13} \)CO\(_2\) was achieved in the fasted and fed state (coefficient of variation <5%), permitting the use of the steady-state equation.

Epidural blockade had no significant effect on whole body protein synthesis, breakdown, leucine oxidation, glucose production, and glucose clearance in the fasted state (Table 2). A weak but significant correlation between leucine Ra and glucose Ra could be observed \( (r = 0.59, P < 0.05) \); Fig. 2).

Administration of glucose suppressed endogenous glucose production to a similar extent in both groups \( (P < 0.001) \) but did not significantly affect leucine Ra or protein synthesis. Glucose infusion decreased leucine oxidation in the EDA group \( (P < 0.05) \) without significant influence in the control patients. Glucose clearance did not change significantly in the control group but increased in patients with epidural blockade \( (P < 0.05) \), indicating improved insulin sensitivity. There was a significant inverse correlation between the changes in leucine oxidation and glucose clearance \( (r = -0.74, P < 0.05) \); Fig. 3).

**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 glucose infusion were not significantly different. Glucose administration increased the plasma glucose and insulin concentration \( (P < 0.001) \), whereas plasma concentrations of lactate, glucagon, and cortisol remained unchanged.

**Gaseous Exchange**

\( V_{O2}, V_{CO2}, \) and RQ were not significantly affected by epidural blockade in the fasted state (Table 4). Glucose infusion increased the RQ in the EDA group \( (P < 0.05) \) without exerting any significant effect on \( V_{O2}, V_{CO2}, V_{O2}, V_{CO2}, \) and RQ did not change significantly in the control group.

**DISCUSSION**

The results of the present study indicate that epidural blockade with local anesthetics facilitates whole

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Table 2. Kinetics of leucine and glucose metabolism in the fasted state and fed state

<table>
<thead>
<tr>
<th></th>
<th>Control Fasted</th>
<th>Control Fed</th>
<th>Epidural Fasted</th>
<th>Epidural Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine Ra, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
<td>120.6 ± 28.1</td>
<td>113.9 ± 29.2</td>
<td>117.9 ± 27.2</td>
<td>113.4 ± 27.9</td>
</tr>
<tr>
<td>Leucine oxidation, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
<td>17.2 ± 3.6</td>
<td>19.9 ± 4.1</td>
<td>20.5 ± 3.7</td>
<td>17.7 ± 4.8</td>
</tr>
<tr>
<td>Protein synthesis, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
<td>103.5 ± 27.1</td>
<td>94.0 ± 26.8</td>
<td>97.4 ± 24.7</td>
<td>95.7 ± 25.4</td>
</tr>
<tr>
<td>Glucose Ra, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>11.35 ± 1.36</td>
<td>23.06 ± 1.53</td>
<td>10.69 ± 3.04</td>
<td>23.91 ± 3.25</td>
</tr>
<tr>
<td>Endogenous glucose Ra, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>11.35 ± 1.36</td>
<td>1.15 ± 2.25</td>
<td>10.69 ± 3.04</td>
<td>2.20 ± 2.43</td>
</tr>
<tr>
<td>Glucose clearance, ml ( \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>2.20 ± 0.44</td>
<td>2.94 ± 0.38</td>
<td>2.06 ± 0.38</td>
<td>2.47 ± 0.50</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. Ra, rate of appearance. Endogenous glucose Ra was calculated by subtracting the rate of exogenous glucose infusion from total glucose Ra. *\( P < 0.05 \) and †\( P < 0.001 \) compared with fasted state.
Glucose, mmol/l 5.2
metabolites and hormones in the fasted and fed state
Table 3.
ing and feeding (33). Therefore, the impact of surgery
hormonal and metabolic changes associated with fast-
trogenous parenteral nutrition, did not consider the
conducted in patients receiving isocaloric and isoni-
production in patients after various surgical proce-
dominal surgery (7). In addition, epidural local anes-
body protein breakdown and oxidation after lower ab-
thetic rate (4), and attenuation of the rise in whole
body glucose uptake and decreases endogenous protein
oxidation during glucose infusion [change in glucose clearance = 3.08 – (1.135 × change in leucine oxidation), r = −0.74, P < 0.05].
●, Control group; ○, epidural group.
body glucose uptake and decreases endogenous protein
oxidation after abdominal surgery, indicating a shift
from a protein to a more glucose-dominated substrate
utilization. Epidural blockade, however, does not signi-
ificantly alter endogenous glucose production and
whole body protein catabolism in the fasted state. This
finding appears to be in contrast to the widely held
notion of beneficial effects of noiceptive blockade with
local anesthetics upon postoperative protein and glu-
cose metabolism such as improvement of nitrogen bal-
ance (34), blunting the fall in muscle fractional syn-
thetic rate (4), and attenuation of the rise in whole
body protein breakdown and oxidation after lower ab-
dominal surgery (7). In addition, epidural local anes-
thesia have been shown to decrease glucose and urea
production in patients after various surgical proce-
dures (30). These studies, however, being exclusively
conducted in patients receiving isocaloric and iso-
rogenous parenteral nutrition, did not consider the
hormonal and metabolic changes associated with fast-
ing and feeding (33). Therefore, the impact of surgery
and neural blockade might have been masked by
greater changes resulting from nutritional factors. In
an attempt to control for the potential metabolic im-
 pact of the patients’ nutritional status, the present
study was undertaken in both postabsorptive and fed
states. This study design also has been chosen because
it has been demonstrated that epidural blockade does
not influence protein economy after surgery when peri-
operative calorie intake is low (14) or absent (3). Thus
the failure of epidural blockade to affect protein catab-
olism in the current study may well be explained by the
minimal amount of calories administered on the first
postoperative day and the absence of nitrogen in the
diet, lending further support to the contention that the
protein-sparing effect of epidural blockade requires
adequate energy and nitrogen supply.
It has to be noted that mean postoperative leucine
Rn, glucose Rn, and leucine oxidation rate in the fasted
state were not elevated compared with values obtained
in healthy volunteers after an overnight fast (28). This
lack of difference can also be explained by the different
nutritional status of postabsorptive subjects and fast-
ing surgical patients. Patients who participated in the
present study fasted for ~38 h before surgery (due to
bowel preparation) and received only minimal amounts
of glucose on the first postoperative day. It is well
recognized that starvation causes a progressive fall in
urinary nitrogen excretion accompanied by a decrease
in the release of amino acids from the muscle and a
decrease in whole body glucose production (19). Pa-
tients undergoing colorectal surgery, who were contin-
uously fed starting 6 days before the operation until 4
days after surgery, showed higher rates of leucine
breakdown and oxidation than patients in the present
protocol (5). In contrast, protein kinetics in patients
after abdominal surgery receiving perioperative hypo-
caloric nutrition were similar to those observed in
this study (6).
A weak but significant correlation between leucine
Rn and glucose Rn was observed in the fasted state,
suggesting a direct relationship between whole body
protein breakdown and glucose production. This
assumption is supported by investigations in healthy
volunteers (16) and surgical patients (30) reporting
parallel changes in urea production, an indirect
marker of protein catabolism, and whole body glucose
production. Based on the results of these studies, it has
been concluded that muscle protein is broken down to

Table 4. Gaseous exchange in patients with and without epidural blockade in the fasted and fed state

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Epidural</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>VO₂, ml/min</td>
<td>243 ± 59</td>
<td>245 ± 81</td>
<td>216 ± 53</td>
<td>206 ± 50</td>
</tr>
<tr>
<td>VCO₂, ml/min</td>
<td>180 ± 40</td>
<td>191 ± 55</td>
<td>159 ± 32</td>
<td>164 ± 41</td>
</tr>
<tr>
<td>RQ</td>
<td>0.75 ± 0.02</td>
<td>0.78 ± 0.07</td>
<td>0.75 ± 0.04</td>
<td>0.80 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. VO₂, whole body oxygen consumption; VCO₂, whole body carbon dioxide production; RQ, respiratory quotient. *P < 0.05 compared with fasted state.

Table 3. Plasma concentrations of circulating metabolites and hormones in the fasted and fed state

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Epidural</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.2 ± 0.7</td>
<td>10.1 ± 1.9*</td>
<td>5.2 ± 0.5</td>
<td>9.8 ± 0.9*</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.6</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Cortisol, pg/ml</td>
<td>254 ± 80</td>
<td>295 ± 81</td>
<td>282 ± 149</td>
<td>328 ± 186</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>115 ± 60</td>
<td>392 ± 185*</td>
<td>99 ± 18</td>
<td>268 ± 133*</td>
</tr>
<tr>
<td>Glucagon, pmol/l</td>
<td>25 ± 9</td>
<td>19 ± 16</td>
<td>27 ± 6</td>
<td>17 ± 5</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. *P < 0.001 compared with fasted state.
provide gluconeogenic amino acids for de novo gluco-
neogenesis in the liver (35). Whole body glucose pro-
duction is, depending on the metabolic state, composed
(to a varying extent) of glycogenolysis and gluconeo-
genesis. The use of [6,6-\textsuperscript{2}H\textsubscript{2}]glucose does not allow
differentiation between the two metabolic pathways.
Considering the long preoperative fasting period of
the patients entering this study protocol and the fact that
only little glucose was administered after surgery, it
seems likely that the patient’s glycogen stores were
depleted. The results of a recent study show that glu-
coneogenesis accounts for almost all of the glucose
produced after 42 h of fasting (9). Thus the rate of
glucose production measured on the second day after
colorectal surgery presumably was equivalent to glu-
coneogenesis.

The nitrogen-sparing effect of glucose is well docu-
mented in surgical patients and has been primarily
ascribed to a decrease in urea production (32). Urea is
synthesized in the liver when amino acids are deami-
nated, leaving the carbon skeleton for glucose produc-
tion. It has been proposed that hepatic ureagenesis is
inhibited either via suppression of gluconeogenesis or
via reduction in the release of amino acids from periph-
ery. It has been proposed that hepatic ureagenesis is
inhibited either via suppression of gluconeogenesis or
via reduction in the release of amino acids from periph-
eral tissues, resulting in a decrease in ureagenic
amino-nitrogen supply to the liver (16, 23). Admin-
istration of glucose in the present study at 4 mg · kg\textsuperscript{-1} ·
min\textsuperscript{-1} almost completely suppressed glucose produc-
tion in all patients but did not affect protein break-
down, as reflected by the unchanged leucine R\textsubscript{\alpha}.
This finding is consistent with previous observations in
normal subjects and surgical patients that low-dose glu-
cose administration causing a doubling of insulin con-
centration (similar to the insulin response in the
present study) does not influence the degradation of
peripheral protein (13, 20, 28). This does not, however,
rule out the possibility that decreased mobilization of
amino acids may be a major component of the nitrogen-
sparing effect elicited by massive infusions of glucose
and insulin. Infusion of exogenous insulin, which in-
creases plasma insulin concentrations >150 μU/ml,
blocks the release of muscle amino nitrogen (25),
whereas insulin clamped at a plasma level of 80 μU/ml
induces a marked decrease in whole body leucine
breakdown (10).

Providing energy and thereby minimizing the need of
amino acid oxidation for energy coverage has been
regarded as a second mechanism responsible for the
protein-preserving effect of glucose during catabolic
illness. It has been suggested that, once maximal inhi-
bition of gluconeogenesis has been achieved, infused
glucose will be oxidized to a greater extent (35). The
validity of this hypothesis is further confirmed by the
present results demonstrating a significant inverse
correlation between changes in whole body glucose
clearance and endogenous leucine oxidation. The sig-
nificant increase in glucose clearance in patients with
epidural blockade is accompanied by a decrease in
leucine oxidation, although both parameters do not
significantly change in the control group. This observ-
ation is in line with the previous notion that neural
blockade with local anesthetics is able to normalize
impaired glucose tolerance and insulin sensitivity dur-
ing surgical stress (15, 17). Because no direct relation-
ship exists between the ability of tissues to clear glu-
cose from the blood and subsequent glucose oxidation
(35) and absolute values of glucose oxidation were not
obtained in the present study, the exact amount of
glucose oxidation is not known. However, the calor-
metric data in patients with epidural blockade reveal-
ing a significant increase in the RQ during glucose
infusion give indirect evidence that glucose oxidation
increased.

It can therefore be concluded that the improvement
of uptake and oxidative utilization of glucose by epi-
dural blockade results in the inhibition of endogenous
amino acid oxidation, leading to a better preservation
of whole body nitrogen.

From the present study, it is difficult to ascertain the
mechanisms involved in the modifying effects of epi-
dural blockade upon glucose and protein metabolism in
the fed state. The fact that glucose clearance was
higher in the EDA group during glucose administra-
tion while the insulin response was unaffected indi-
cates a greater insulin sensitivity. It remains question-
able, however, if improved insulin sensitivity also was
responsible for the suppression of leucine oxidation.
Regarding the impact of insulin on endogenous protein
oxidation, conflicting results have been provided in the
literature reporting stimulatory (8), inhibitory (24), or
no effects (11). Furthermore, a direct influence of in-
creased glucose availability cannot be separated from
the insulin response that is induced by hyperglycemia
because the observed changes in protein and glucose
metabolism during glucose administration can occur
independently of the action of insulin. Urea produc-
tion is suppressed to the same degree when insulin secre-
tion is blocked by somatostatin as when insulin plasma
concentration increases after 2 h of glucose infusion at
4 mg · kg\textsuperscript{-1} · min\textsuperscript{-1} (37). Whole body glucose clearance
and oxidation also rise regardless of whether insulin is
held at the basal level or is allowed to change sponta-
nanously (37).

Because our study protocol was not designed to dis-
sect the biochemical factors responsible for the changes
in postoperative substrate utilization in the EDA
group, we can only speculate on the underlying endo-
crine mechanisms. Epidural blockade with local anesthe-
thetics has been frequently shown to suppress the
cortisol and sympathoadrenergic response to abdomi-
nal surgery, thereby facilitating the anticatabolic ac-
tion of insulin (18). Thus the improvement of insulin
sensitivity observed in the EDA group might have
resulted from the inhibitory effect of epidural local
anesthetics on the perioperative increase in the circu-
lating levels of cortisol, epinephrine, and norepineph-
rine. Plasma catecholamine concentrations were not
measured in the present study, and there was no sig-
nificant difference in the plasma cortisol concentra-
tions between the two groups, neither in the fasted nor
in the fed state. It cannot be ruled out, however, that
more frequent intra- and postoperative cortisol measurements could have revealed such a difference.

To optimize postoperative analgesia in the EDA group, a combined infusion of bupivacaine and fentanyl was administered in the present investigation. The effects of epidural opioids on the metabolic endocrine changes induced by surgical trauma have been demonstrated to be less pronounced compared with local anesthetics in spite of equivalent satisfactory pain relief (18). According to the results of several studies, epidural opioids in contrast to epidural local anesthetics failed to attenuate the hyperglycemic, sympathoadrenergic, and catabolic response to surgery (14, 18). Although a potential metabolic impact of epidural fentanyl cannot be entirely excluded in the current study, this effect was probably small.

In conclusion, epidural blockade established before and continued after abdominal surgery does not influence protein catabolism and glucose metabolism in the fasted state. Intravenous administration of glucose improves glucose uptake and spares body protein, as reflected by a decrease in endogenous protein oxidation only in the presence of epidural blockade.

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