# Epidural Ropivacaine versus Epidural Morphine and the Catabolic Response to Colonic Surgery

Stable Isotope Kinetic Studies in the Fasted State and during Infusion of Glucose

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Background: The authors examined the hypothesis that epidural administration of local anesthetic, in contrast to epidural analgesia with morphine, inhibits postoperative protein oxidation during administration of glucose.

*Methods:* Fourteen patients were randomly assigned to undergo a 6-h stable isotope infusion study (3 h fasted, 3 h feeding with 4 mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> glucose) on the second day after colorectal surgery using epidural analgesia with either continuous ropivacaine or intermittent morphine. Protein synthesis, breakdown and oxidation, and glucose production were measured by L·[1- $^{13}$ C]leucine and [6,6- $^{2}$ H<sub>2</sub>]glucose. Substrate oxidation rates were determined by indirect calorimetry. Plasma concentrations of metabolic substrates and hormones were also measured.

Results: Whole body protein breakdown, oxidation, synthesis, and glucose production in the fasted state were similar between the two groups. Glucose administration decreased protein breakdown (P=0.01), protein synthesis (P=0.001), and glucose production (P=0.001) to the same extent in both groups, whereas protein oxidation was not significantly affected. The type of epidural analgesia did not significantly influence the circulating concentrations of metabolic substrates and hormones in the fasted or in the fed state. Carbohydrate oxidation rate in the ropivacaine group was greater than in patients receiving morphine (P=0.04), regardless of whether glucose was infused.

Conclusion: Epidural analgesia achieved with ropivacaine or morphine does not suppress the catabolic response to surgery, either under fasting conditions or in the presence of an energy supply.

NEGATIVE nitrogen balance is a characteristic feature of the catabolic response to surgical tissue trauma. As protein breakdown and oxidation increase, urinary nitrogen excretion exceeds nitrogen intake, resulting in a net loss of body protein. Perioperative erosion of lean body mass has been associated with immunosuppression and muscle weakness, leading to prolonged convalescence and morbidity. Several protein-sparing strategies have

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been developed to minimize protein wasting after surgery, including neuraxial blockade and nutrition.

It can be shown that effective segmental pain relief with epidural analgesia reduces urinary nitrogen excretion, 4-6 blunts whole body protein oxidation, 7,8 and minimizes the decrease in muscle protein synthesis.9 Most of these studies were conducted in patients receiving continuous parenteral alimentation, making it difficult to distinguish between the effects of analgesia and those produced by nutritional therapy. In an attempt to control for the patient's feeding status after surgery, we recently investigated the impact of epidural analgesia on protein catabolism in the fasted state and during infusion of glucose. 10 Consistent with more recent findings, 11 epidural analgesia did not affect protein breakdown and oxidation in the absence of energy supply but, in contrast to intravenous analgesia, facilitated the oxidative utilization of glucose and decreased amino acid oxidation.<sup>11</sup> Because epidural analgesia in the latter study was achieved by the combined administration of bupivacaine and fentanyl, the metabolic effects of the local anesthetic and the opiate could not be separated. It is commonly believed that, despite provision of equivalent satisfactory pain relief, epidural analgesia with opiates is not as effective in obtunding the catabolic responses as epidural local anesthetic, 12 indicating that pain relief per se does not ameliorate the metabolic and endocrine alterations induced by surgery. 13 However, studies reporting that better pain relief achieved with epidural morphine compared with intravenous analgesia attenuates the perioperative increase in plasma cortisol and glucose suggest that pain could be a modifying factor. 14

In light of this controversy, it is necessary to determine what link exists among the type of epidural analgesia, the catabolic response, and the utilization of nutrients after abdominal surgery. Therefore, we examined the effects of continuously maintained epidural analgesia with ropivacaine *versus* intermittent epidural analgesia with morphine on postoperative protein and glucose metabolism in the fasted state and during infusion of 4 mg · kg<sup>-1</sup> · min<sup>-1</sup> glucose, the hypothesis being that glucose administration inhibits amino acid oxidation better in presence of epidural local anesthetic. Protein and glucose kinetics in this protocol were assessed using a stable isotope tracer technique (I-[1-<sup>13</sup>C]leucine, [6,6-<sup>2</sup>H<sub>2</sub>]glucose).

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Received from the Department of Anesthesia and the School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada, and the Department of Anesthesia and Intensive Care Medicine, Philipps-University Marburg, Germany. Submitted for publication August 5, 2003. Accepted for publication November 19, 2003. Supported by the 2000 Carl Koller Memorial Research Grant from the American Society of Regional Anesthesia and Pain Medicine, Richmond, Virginia (to Dr. Schricker), and by funds from the Research Institute of the Royal Victoria Hospital, Montreal, Quebec, Canada (to Dr. Schricker).

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# **Materials and Methods**

#### **Patients**

The study was approved by the Research Ethics Board of the Royal Victoria Hospital (Montreal, Quebec, Canada). Informed consent was obtained from 14 patients with localized colonic carcinoma scheduled to undergo elective colorectal surgery. None of the patients had cardiac, hepatic, renal, or metabolic disease. No subject had experienced recent weight loss or had a plasma albumin concentration below 35 g/l. The patients were randomly allocated to a group receiving continuous epidural blockade with local anesthetic (ropivacaine group, n=7) or a group receiving intermittent epidural opiate (morphine group, n=7).

# Anesthesia and Surgical Care

At the time of arrival in the operating room, patients received an epidural catheter inserted at one of the thoracic vertebral levels between T10 and T12. In the ropivacaine group, bilateral sensory block to ice and pin prick from thoracic dermatome level four (T4) to sacral dermatome level five (S5) blockade was achieved by 0.75% ropivacaine and maintained during the operation with constant infusion of 0.2% ropivacaine (10 ml/h). In the morphine group, a bolus of 100  $\mu$ g/kg morphine was given immediately after insertion of the epidural catheter. General anesthesia was induced with 1.5 µg/kg fentanyl in the ropivacaine group and 5.0 μg/kg fentanyl in the morphine group followed by 3-5 mg/kg thiopentone. Tracheal intubation was facilitated with 0.6 mg/kg rocuronium, and patients' lungs were ventilated with 35% oxygen in nitrous oxide to maintain normocapnia. Supplemental doses of rocuronium were given for complete surgical muscle relaxation. In the ropivacaine group, isoflurane was administered at end-tidal concentrations between 0.3 and 0.4 vol% to achieve tolerance of the endotracheal tube and to prevent awareness. General anesthesia in the morphine group was continued with isoflurane at end-tidal concentrations as required to keep heart rate and mean arterial pressure within 20% of preoperative values. All patients received a bolus of 10 ml/kg normal saline before induction of anesthesia, followed by  $6-8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  during surgery. Decreases in mean arterial blood pressure (< 60 mmHg) were treated with fluid administration (normal saline) and increments of phenylephrine (0.1 mg). All operations were performed by the same surgeon and at the same time of the day (from 11:00 to 14:00 h). Patients in both groups received hypocaloric nutritional supplementation with glucose from 08:00 to 20:00 h on the first postoperative day (100 ml/h glucose, 5%; equivalent to approximately 250 kcal/day) followed by infusion of 0.9% NaCl (100 ml/h) until the study period.

Bilateral sensory blockade from T8 to L3 was postoperatively maintained in the ropivacaine group by continuous epidural infusion of 0.2% ropivacaine. In the morphine group, pain relief was achieved by intermittent administration of morphine  $(30-60 \mu g/kg)$  every 8 h after surgery. Pain treatment was adjusted in both groups to achieve a visual analog scale score of less than four at rest (scale from 0 [no pain] to 10 [worst pain]). Pain scores at rest and on movement (visual analog scores) were obtained 12 and 24 h after surgery and on the morning of the second postoperative day.

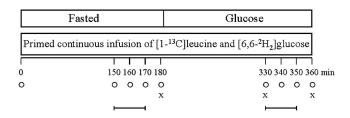
#### Parenteral Nutrition

On the second postoperative day, after a 3-h period of fasting (from 08:00 to 11:00 h), a solution of crystallized beet glucose (10% dextrose anhydrous; Avebe, Foxhol, The Netherlands) was infused at 4 mg  $\cdot$  kg $^{-1} \cdot$  min $^{-1}$  for 3 h. The dextrose solution was prepared by the local pharmacy under sterile conditions and tested for sterility, stability, and absence of pyrogens before intravenous infusion. The beet dextrose solution was chosen because of its low  $^{13}$ C content and therefore the lack of significant perturbation of  $^{13}$ CO<sub>2</sub> enrichment in expired air.  $^{15}$ 

## Experimental Protocol

Plasma kinetics of leucine and glucose were determined by a primed constant infusion of L-[1-<sup>13</sup>C]leucine (99% <sup>13</sup>C) and [6,6-<sup>2</sup>H<sub>2</sub>]glucose (99% <sup>2</sup>H; Cambridge Isotope Laboratories, Cambridge, MA). Sterile solutions of isotopes were prepared in the hospital pharmacy and kept at 4°C until administration.

All tests were performed in the fasted state, beginning at 08:00 h on the second postoperative day. The patients were observed 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 kept patent with 2 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> saline. A second vein in the contralateral arm was cannulated to provide access for infusion of the stable isotopes. Blood and expired air samples were collected before infusion to determine baseline enrichments. Priming doses of 1 \(\mu\text{mol/kg NaH\$^{13}CO}\_3\), 4 \(\mu\text{mol/kg I-[1- $^{13}$ C]leucine, and 22  $\mu$ mol/kg [6,6- $^{2}$ H<sub>2</sub>]glucose were administered and followed immediately by continuous infusions of L-[1- $^{13}$ C]leucine 0.06  $\mu$ mol  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ lasting 6 h. [6,6-2H2]glucose was infused at a rate of  $0.22~\mu mol \cdot kg^{-1} \cdot min^{-1}$  during the first 3 h (fasted period) and was then changed to  $0.44 \mu \text{mol} \cdot \text{kg}^{-1}$ . min<sup>-1</sup> 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 (3,000g, 15 min), and stored at -70°C. Breath samples were collected in a 2-1 latex bag and transferred immediately to 20-ml Vacutainers (Becton, Dickinson, Franklin Lakes, NJ). A schematic representation of the protocol is shown in figure 1.



- isotope enrichments
- x plasma concentrations of metabolic substrates and hormones
- indirect calorimetry

Fig. 1. Time course of infusion of isotopes, collection of plasma and expired air samples, and indirect calorimetry in the fasted state and during feeding.

## 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 and carbon dioxide production were measured, and the respiratory quotient was calculated. Average values were taken, with a coefficient of variation of less than 10%. Carbohydrate and lipid oxidation rates were calculated using standard formulas. Protein oxidation was calculated using the measured rate of leucine oxidation and assuming that leucine represents 8% of the total body protein. 17

# Analytical Methods

**Isotopic Enrichments.** Plasma [1-<sup>13</sup>C]α-ketoisocaproate enrichment was determined by electron impact selected-ion monitoring gas chromatography-mass spectrometry using methods previously described. Expired <sup>13</sup>C-carbon dioxide enrichment was determined by isotope ratio mass spectrometry (Analytical Precision AP2003, Manchester, United Kingdom). Plasma glucose was derivatized to its pentaacetate compound, and the [6,6-<sup>2</sup>H<sub>2</sub>]glucose enrichment was determined by gas chromatography-mass spectrometry using electron impact ionization. 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 plasma cortisol, insulin, and glucagon were measured by sensitive and specific double-antibody radioimmunoassays (Amersham International, Amersham, Bucks, United Kingdom).

### Calculations

Under isotopic steady state conditions, the rate of appearance of unlabeled substrate in plasma can be

calculated by the formula: rate of appearance = (atom percent excess in the infusate/atom percent excess in plasma -1)  $\times$  infusion rate of the labeled tracer. The atom percent excess used in this calculation is the mean of the four 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 the coefficient of variation. A coefficient of variation less than 5% was used as a confirmation of a valid plateau.

Under steady state conditions, leucine flux is defined by the formula: leucine flux = rate at which leucine is incorporated into body protein + rate of oxidation of leucine = rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown + rate of leucine intake in tracer and diet. When subjects are in the postabsorptive state, the leucine intake by food equals zero, and thus, the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown equals leucine flux. Plasma enrichment of  $[1^{-13}C]\alpha$ -ketoisocaproate during infusion of L-[1-13C] leucine has been used as the basis for calculating both flux and oxidation of leucine. 19 This steady state reciprocal pool model represents the intracellular precursor pool enrichment more precisely than leucine itself. 19 In the calculation of oxidation, factors of 0.75 for the fasting state and 0.81 for the fed state were applied to account for the fraction of 13C-carbon dioxide released from leucine but retained within slow turnover rate pools of the body.<sup>20</sup>

In the fasted state, the rate of appearance of 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 rate of appearance of glucose.

#### Statistics

The primary endpoint of the study was whole body leucine oxidation in the fed state. Secondary endpoints included the leucine rate of appearance and protein synthesis. On the basis of our previous studies, a difference of mean leucine oxidation of at least 4  $\mu$ mol · kg<sup>-1</sup> · min<sup>-1</sup> between the two analgetic regimes (between-group effect) and between the fasted and the fed state (withingroup effect) was defined as metabolically relevant. Assuming an SD as achieved previously, 10 a repeated measure design with 2  $\times$  7 patients achieves a power 70% to detect a between-group effect size of 0.72 and a power of 99% to detect the within-group effect size of 0.88 with a type I error of 5%. This prospective power analysis was performed with PASS 2002 (Number Cruncher Statistical Systems, Kaysville, UT).

Analyses of dependent variables were performed using two-factorial analysis of variance for repeated measures. Significant effects induced by feeding were assumed when P values for time dependency were below 0.05.

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Table 1. Biometric and Clinical Data of Patients

	Epidural Morphine	Epidural Ropivacaine		
Sex (Female:Male)	3:4	4:3		
Age, yr	$57 \pm 20$	$49 \pm 17$		
Height, cm	168 ± 8	$170 \pm 13$		
Weight, kg	$70 \pm 16$	$72 \pm 16$		
Surgery, n				
Hemicolectomy	4	3		
Sigmoid resection	3	4		
Duration of surgery, min	$186 \pm 58$	$214 \pm 95$		
Estimated blood loss, ml	$343\pm124$	$371\pm287$		

Values are presented as mean  $\pm$  SD.

Influences by the analysis regimen were accepted as significant when the interaction term of the analysis of variance was below 0.05. All analyses were performed using the general linear model in SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

#### **Results**

#### **Patients**

There were no differences between the two groups regarding sex, age, height, or weight of patients or 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 (ropivacaine group, 12 h:  $1.6 \pm 1.0$ , 24 h:  $1.7 \pm 1.1$ , study:  $1.5 \pm 0.7$ ; morphine group, 12 h:  $1.9 \pm 1.0$ , 24 h:  $1.8 \pm 0.9$ , study:  $1.6 \pm 0.8$ ). Throughout the study period, pain scores on movement were smaller in the ropivacaine group than in the morphine group (ropivacaine group, 12 h:  $3.0 \pm 1.0$ , 24 h:  $3.2 \pm 1.0$ , study:  $3.0 \pm 0.7$ ; morphine group, 12 h:  $4.5 \pm 0.9$ , 24 h:  $4.4 \pm 0.9$ , study:  $4.3 \pm 0.9$ ).

#### Glucose and Protein Kinetics

In all experiments, 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 in the fasted and fed state (coefficient of variation < 5%), permitting

use of the steady state equation. Whole body rates of appearance of leucine, leucine oxidation, protein synthesis, and glucose production in the fasted state were similar between the two groups (table 2). Glucose administration significantly decreased the rate of appearance of leucine, protein synthesis, and the rate of appearance of glucose to the same extent in both groups, whereas leucine oxidation was not significantly affected.

#### Metabolites and Hormones

The type of epidural analgesia did not significantly influence the 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 were not significantly different. Glucose administration significantly increased the plasma concentrations of glucose and insulin, whereas the concentration of glucagon significantly decreased. The plasma concentrations of lactate and cortisol remained unchanged.

## Gaseous Exchange

Whole body oxygen consumption, carbon dioxide production, and respiratory quotient were not significantly affected by the type of epidural analgesia in the fasted state (table 4). Glucose infusion significantly increased the respiratory quotient in the ropivacaine group only. Carbohydrate oxidation rates in patients receiving epidural ropivacaine were significantly greater than in patients receiving morphine, regardless of whether glucose was infused. Feeding significantly increased carbohydrate oxidation and decreased lipid oxidation in both groups.

## Discussion

Epidural opiates are routinely used for pain relief after major abdominal procedures. They confer advantage over local anesthetics in the sense that they provide good quality of analgesia without causing sympathetic and motor blockade. There is evidence, however, that epidural opiates do not suppress the catabolic responses to surgery as pro-

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

	Epidural Morphine		Epidural Ropivacaine		P Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
$R_a$ leucine, $\mu$ mol·kg <sup>-1</sup> ·h <sup>-1</sup>	126 ± 31	114 ± 27	138 ± 20	124 ± 32	0.01	0.47	0.79
Leucine oxidation, $\mu$ mol · kg <sup>-1</sup> · h <sup>-1</sup>	$29 \pm 11$	$33 \pm 13$	$32 \pm 10$	$35 \pm 12$	0.09	0.68	0.91
Protein synthesis, $\mu$ mol · kg <sup>-1</sup> · h <sup>-1</sup>	$98 \pm 37$	$81 \pm 27$	$106 \pm 12$	$88 \pm 28$	0.001	0.56	0.87
$R_a$ glucose, $\mu$ mol · kg <sup>-1</sup> · min <sup>-1</sup>	$11.7 \pm 2.3$	$25.9 \pm 2.6$	$12.9 \pm 2.0$	$27.2 \pm 1.8$	< 0.001	0.24	0.84
Endogenous $R_a$ glucose, $\mu$ mol $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>	$11.8\pm2.3$	$2.3\pm2.1$	$12.9\pm2.0$	$3.9\pm2.0$	< 0.001	0.18	0.73

Values are presented as mean ± SD.

<sup>\*</sup> Probability that values are influenced by parenteral alimentation. † Probability that values are influenced by the type of analgesia, regardless of whether nutrition was administered. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

 $R_a$  = rate of appearance, endogenous glucose  $R_a$  was calculated by subtracting the rates of exogenous glucose infusion from the total glucose  $R_a$ .

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

	Epidural Morphine		Epidural F	Epidural Ropivacaine		P Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡	
Glucose, mм	4.9 ± 1.1	10.3 ± 1.5	5.6 ± 0.8	10.4 ± 1.5	< 0.001	0.43	0.50	
Lactate, mm	$0.6 \pm 0.1$	$0.7 \pm 0.2$	$0.9 \pm 0.2$	$1.1 \pm 0.5$	0.06	0.05	0.50	
Cortisol, nm	$373 \pm 145$	$404 \pm 280$	$406 \pm 207$	$365 \pm 152$	0.91	0.98	0.39	
Insulin, pM	$97 \pm 27$	$382 \pm 225$	$103 \pm 42$	$388 \pm 189$	< 0.001	0.92	0.99	
Glucagon, рм	19 ± 6	8 ± 2	$22 \pm 10$	10 ± 4	< 0.001	0.46	0.64	

Values are presented as mean  $\pm$  SD.

foundly as local anesthetics because those responses are thought to be predominantly mediated by neurogenic rather than opioid receptor-dependent pathways.<sup>12</sup>

In the current study, protein catabolism as assessed under fasting conditions on the second day after surgery was not modified by the type of epidural analgesia. The whole body leucine oxidation rate was twice the value previously reported in patients before colonic cancer surgery, indicating that neither epidural regimen was able to inhibit oxidative protein wasting postoperatively. 21,22 This result seems to contrast with the wide belief that segmental blockade of nociceptive signals at the spinal cord level by local anesthetic attenuates the surgical stress response more effectively than the epidural administration of opiates. 12 Nine hours after abdominal hysterectomy, patients who had received two boluses of epidural morphine showed greater plasma cortisol and glucose concentrations than patients who had received epidural bupivacaine continuously. 14 Single doses of epidural morphine<sup>23</sup> or diamorphine<sup>24</sup> failed to blunt the immediate metabolic response to upper abdominal surgery, but plasma cortisol subsequently decreased secondary to improved pain control when compared with intravenous opiate-based analgesia. 24 In abdominal aorta surgery, one epidural bolus of morphine resulted in a marked reduction in plasma norepinephrine concentrations.<sup>25</sup> Two studies compared the metabolic end endocrine effects of epidural opiates and local anesthetics in the postoperative period. 26,27 Intermittent epidural morphine was unable to prevent the increase in the urinary excretion of cortisol, epinephrine, norepinephrine, and nitrogen, both on separate days and on cumulative measurements over 4 days after colorectal procedures. <sup>26</sup> Epidural morphine administered every 12 h after gastrectomy reduced urinary excretion of cortisol and catecholamines, although less than epidural local anesthetics. <sup>27</sup>

The heterogeneity of findings with regard to the anticatabolic effects of epidural opiates can be partly explained by the fact that none of the previous studies were controlled for the patients' feeding status. For example, patients in the study of Hjortso *et al.*<sup>26</sup> were parenterally fed an isonitrogenous hypocaloric diet with 70 g protein and 200 g dextrose daily throughout the 4-day study period. In the study by Tsuji *et al.*,<sup>27</sup> substrates were infused over the first 72 postoperative hours at 15 kcal  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>, with 80% as glucose and 20% as lipid. Hence, the impact of surgery and analgesia on the catabolic responses was masked by metabolic changes resulting from nutritional factors.

In light of the most recent demonstrations that the protein-preserving influence of epidural analgesia requires an energy supply,  $^{10,11}$  our patients were exposed to fasted and fed states. The infusion of glucose at 4 mg  $\cdot$  kg  $^{-1}$  · min  $^{-1}$  did not significantly reduce whole body protein oxidation, regardless of whether epidural ropivacaine was administered. This contrasts with our previous observation of anticatabolic effects of epidural anesthesia using an identical study paradigm, except that in the

Table 4. Gaseous Exchange and Substrate Oxidation Rates in the Fasted and Fed States

	Epidural Morphine		Epidural Ropivacaine		P Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
Vo₂, ml/min	235 ± 52	236 ± 34	247 ± 54	244 ± 54	0.66	0.59	0.96
Vco <sub>2</sub> , ml/min	$182 \pm 33$	$189 \pm 25$	$202 \pm 51$	$214 \pm 44$	0.30	0.07	0.59
RQ	$0.80 \pm 0.04$	$0.80 \pm 0.03$	$0.81 \pm 0.05$	$0.86 \pm 0.06$	0.01	0.10	0.047
Protein oxidation, g/d	$82 \pm 44$	$93 \pm 50$	$94 \pm 49$	$106 \pm 54$	0.09	0.70	0.91
Carbohydrate oxidation, g/d	$79 \pm 53$	$104 \pm 43$	$136 \pm 89$	$201 \pm 75$	0.002	0.04	0.13
Lipid oxidation, g/d	$97\pm44$	$84 \pm 28$	$80\pm30$	$53\pm36$	0.01	0.19	0.32

Values are presented as mean  $\pm$  SD. Protein oxidation was calculated using the leucine oxidation rate and assuming that leucine represents 8% of total body protein.

<sup>\*</sup> Probability that values are influenced by parenteral alimentation. † Probability that values are influenced by the type of analgesia, regardless of whether nutrition was administered. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

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 $RQ = respiratory quotient; Vco_2 = whole body carbon dioxide production; Vo_2 = whole body oxygen consumption.$ 

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former study, epidural bupivacaine was supplemented with fentanyl. The current failure of ropivacaine alone to significantly affect protein catabolism may lend support to the hypothesis that local anesthetic and opioid must be administered concomitantly to achieve protein sparing after surgery. 10,11,18 This assumption is further underscored by the fact that several variables in the ropivacaine group were increased when compared with corresponding values obtained in patients receiving epidural bupivacaine-fentanyl, i.e., fasting leucine oxidation was increased by 50%, endogenous glucose production was increased by 20%, and plasma cortisol concentration was increased by 50%. 10,18 The lack of anticatabolic action of epidural ropivacaine in the current protocol, despite superior dynamic pain control, further indicates that the quality of pain relief does not determine the extent of catabolism after abdominal surgery.<sup>13</sup>

Notwithstanding its failure to modify protein catabolism, epidural administration of ropivacaine was associated with augmented carbohydrate oxidation in the fasted state and during dextrose infusion. This is in accord with our recent demonstration that epidural bupivacaine-fentanyl facilitates oxidative glucose utilization after colorectal surgery when compared with intravenous analgesia. 10 Improved carbohydrate oxidation by epidural local anesthetic has been previously attributed to the attenuation of postoperative insulin resistance. 10,28 In addition, neuraxial blockade has been shown to normalize intravenous glucose tolerance in patients undergoing lower abdominal surgery. <sup>29,30</sup> In the current investigation, tissue insulin sensitivity was not determined, and plasma concentrations of insulin and counterregulatory hormones (glucagon, cortisol) were not different between the two groups. Therefore, we can only speculate that improved insulin sensitivity was responsible for the increased carbohydrate oxidation in the ropivacaine group.

In conclusion, perioperative epidural analgesia achieved by either intermittent boluses of morphine or continuous ropivacaine was not able to suppress the catabolic response to colonic surgery. Independent of the type of epidural analgesia, short-term administration of glucose did not affect the increased oxidative protein loss 2 days after surgery.

The authors thank Paul Beliveau, M.D. (Assistant Professor, Department of Surgery, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada), for permission to study his patients.

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