Integrated analysis of protein and glucose metabolism during surgery: effects of anesthesia

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Schricker, Thomas, Ralph Lattermann, Pierre Fiset, Linda Wykes, and Franco Carli. Integrated analysis of protein and glucose metabolism during surgery: effects of anesthesia. J Appl Physiol 91: 2523–2530, 2001.—The aim of this study was to assess dynamic changes in protein and glucose metabolism during surgery. Twelve patients undergoing colorectal surgery received either intravenous propofol anesthesia (n = 6) or inhalational anesthesia with desflurane (n = 6). Pre- and intraoperative protein and glucose kinetics were analyzed by an isotope dilution technique using L-[1-13C]leucine and [6,6-2H2]glucose. Plasma concentrations of glucose, lactate, free fatty acids, insulin, glucagon, and cortisol were measured before and after 2 h of surgery. The rates of appearance of leucine and glucose, leucine oxidation, protein synthesis, and glucose clearance decreased during surgery, independent of the type of anesthesia (P < 0.05). A correlation between the rate of appearance of leucine and glucose was observed (r = 0.755, P < 0.001). Intraoperative plasma cortisol and glucose concentrations increased (P < 0.05), whereas plasma concentrations of lactate, free fatty acids, insulin, and glucagon did not change. Surgery causes a depression of whole body protein and glucose metabolism, independent of the anesthetic technique. There is a correlation between perioperative glucose production and protein breakdown.

LOSS OF BODY PROTEIN REPRESENTS a typical feature of the catabolic response to surgery. Cumulative urinary nitrogen excretion, a traditional measure to quantify oxidative protein losses, has been shown to range between 40 and 80 g after uncomplicated abdominal procedures (24). Because 1 g of nitrogen is the equivalent of 30 g of hydrated lean tissue, a total loss of 50 g of nitrogen would be the equivalent of 1,500 g of lean tissue. The latter point is of utmost clinical relevance, because the length of time for return of normal physiological function after discharge from the hospital is related to the extent of loss of lean body mass during hospitalization (9).

Nitrogen balance studies reflect only net gain or loss of protein from the body. Nitrogen equilibrium, however, is maintained by careful balance between rates of protein synthesis and degradation. Negative nitrogen balance, therefore, can occur if the protein breakdown and amino acid oxidation increase and synthesis remains the same or if breakdown and oxidation rates remain unchanged and the rate of protein synthesis decreases. The use of isotopically labeled, nonradioactive amino acids allows for quantification of the kinetics in protein breakdown, protein synthesis, and amino acid oxidation. Studies employing this methodology in humans already improved our understanding of altered protein homeostasis after surgery (7, 19) and trauma (4, 10) by demonstrating increased rates of proteolysis and amino acid oxidation, along with an insufficient increase in protein synthesis.

There is also evidence of a significant interdependence between perioperative protein and glucose metabolism (38). As a result of increased concentrations of counterregulatory hormones and the depletion of glycogen stores, gluconeogenesis is stimulated under postoperative conditions (17). Muscle protein becomes the major source of gluconeogenic precursors via the gluconeogenic amino acids released during proteolysis. Thus gluconeogenesis has been proposed to occupy a central position in catabolic pathways, causing much of the postoperative protein losses (40).

Although a large amount of information has been accumulated on the metabolic alterations occurring the days after surgery, the effects of surgical tissue trauma and anesthesia on the immediate catabolic response have not been studied so far in humans. Hence, the aim of the present study was to provide an integrated analysis of the dynamic changes in protein and glucose metabolism during abdominal surgery. Whole body protein breakdown, amino acid oxidation, protein synthesis, as well as glucose production and clearance were determined by an isotope dilution technique using L-[1-13C]leucine and [6,6-2H2]glucose in patients undergoing colorectal surgery. To investigate whether the choice of anesthetic agent exerts a specific influence on protein and glucose kinetics, patients were allocated to receive either inhalation anesthesia with...
desflurane or an intravenous technique using continuous infusion of propofol.

**METHODS**

The study was approved by the Ethics Committee of the Royal Victoria Hospital, and informed consent was obtained from 12 patients undergoing elective colorectal surgery (Table 1). None of the patients was suffering from cardiac, hepatic, renal, or metabolic disorders or receiving any medication known to affect protein and glucose metabolism. No subject had developed recent weight loss or had a plasma albumin concentration < 40 g/l.

Patients were randomly assigned to receive either total intravenous anesthesia with propofol and remifentanil (propofol group, n = 6) or inhalation anesthesia using desflurane combined with remifentanil (desflurane group, n = 6). Anesthesia in both groups was induced with 1 μg/kg remifentanil given over 60 s followed by propofol administered at a rate of 1 mg/s until loss of response to verbal command. Tracheal intubation was facilitated by 0.6 mg/kg rocuronium, and the lungs were ventilated to normocapnia (35–40 mmHg) with oxygen-enriched air (inspired O2 fraction = 0.35). Nitrous oxide was not used in the study, as it has the same molecular weight as CO2 and thus interferes with the isotope ratio measurement of expired-air 13CO2.

Anesthesia in the propofol group was maintained by continuous infusion of propofol at a rate of 10 mg·kg⁻¹·h⁻¹ reduced to 6 mg·kg⁻¹·h⁻¹ after 10 min. Anesthesia in the desflurane group was maintained with desflurane at end-tidal concentrations between 4 and 5%. Propofol infusion rates and end-tidal desflurane concentration during surgery were adjusted to keep the heart rate and mean arterial pressure within 20% of the preoperative values. Remifentanil was administered at a constant rate of 0.125 μg·kg⁻¹·min⁻¹ in both groups. The degree of muscle relaxation was monitored using the train-of-four ratio, and supplemental doses of rocuronium were given to achieve complete muscle relaxation throughout the intraoperative period. Hemodynamic monitoring was performed by invasive arterial blood pressure measurement, a three-lead electrocardiogram monitor, and finger pulse oximetry. Normal saline (0.9%) was infused at a rate of 2 ml·kg⁻¹·h⁻¹ before, and between 6 and 10 ml·kg⁻¹·h⁻¹ during, the operation. A bolus of 10 ml/kg was given before the surgery to compensate for fasting-induced fluid depletion. The patients were covered with a warming blanket to maintain normothermia. Body temperature was measured with a thermocouple probe inserted in the nasopharynx, as this site is in close proximity of the hypothalamus.

The kinetics of whole body leucine and glucose metabolism, i.e., rates of appearance (Ra) of leucine and glucose, and leucine oxidation were measured by an isotope dilution technique using the stable isotope tracers L-[1-13C]leucine, NaH13CO3, and [6,6-2H2]glucose (Cambridge Isotope Laboratories, Cambridge, MA). All isotope solutions were prepared under sterile conditions in the hospital pharmacy. An aliquot of tracer was dissolved in a known volume of sterile water. The solution was passed through a 0.22-μm filter into injection bottles. The bottles were sealed off, heat sterilized at 121°C for 15 min, and kept at 4°C until administration. Each set of solutions was confirmed to be free of pyrogens.

All patients were studied on the day of surgery between 7:00 and 8:00 AM after fasting for ~32 h. Only clear fluids were allowed until midnight the day preceding the operation because of bowel preparation as required for colorectal surgery. No premedication was given. A superficial vein in the dorsum of the hand was cannulated, and the cannula was kept patent with heparinized saline. A second superficial vein in the contralateral arm was cannulated to provide access for the infusion of the isotopes. Blood and expired air samples were collected before the isotope infusion to determine baseline isotope enrichments. Primed 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-[1-13C]leucine and 0.22 μmol·kg⁻¹·min⁻¹ [6,6-2H2]glucose.

Four arterialized blood and expired-air samples were collected after 150, 160, 170, and 180 min of preoperative isotope infusion, when the tracer was assumed to have reached an isotopic steady state. Thereafter, anesthesia was induced, and surgery was performed. Five blood and expired-air samples were taken after 80, 90, 100, 110, and 120 min into surgery. Plasma samples for the analysis of the plasma concentrations of metabolic substrates (glucose, lactate) and hormones (insulin, glucagon, cortisol) were drawn before surgery and after 80 and 120 min of surgery. Plasma concentrations of free fatty acids (FFA) were determined before and after 120 min of surgery. Each blood sample was transferred immediately to a heparinized tube and centrifuged at 4°C. The plasma obtained was stored at ~7°C until isotope enrichments were measured. Expired-air samples were collected through a mouthpiece in a 2-liter latex bag and transferred immediately to 20-ml vacutainers to await 13CO2 isotope enrichment analysis. During artificial ventilation, expired gases were collected by means of a one-way valve into a 5-liter bag. Production of CO2 was measured by indirect calorimetry (Datex Deltatrac, Helsinki, Finland) over a 20-min period during plasma L-[1-13C]leucine and [6,6-2H2]glucose steady state before and during surgery. A graphic illustration of the study protocol is presented in Fig. 1.

Whole body glucose and leucine kinetics were calculated by conventional isotope dilution practice using a two-pool stochastic model during steady-state conditions, obtained at each phase of the studies, before and during surgery. When an isotopic steady state exists, the Ra of unlabeled substrate in plasma can be derived from the plasma enrichment (APE) calculated by Ra = (APEout/APEpl − 1)·F, where F is the infusion rate of the labeled tracer (μmol·kg⁻¹·min⁻¹), APEout is the tracer enrichment in the infusionate, and APEpl is the tracer enrichment in plasma at steady state. The APE value used in this calculation represents the mean of the APE values determined during each isotopic plateau. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of the APE values above their mean, expressed as a coefficient of variation (CV). A CV < 5% was used as a confirmation of a valid plateau.

Table 1. Biometric and clinical data of patients

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Desflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>54 ± 19</td>
<td>50 ± 20</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162 ± 9</td>
<td>167 ± 10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63 ± 7</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>2/4</td>
<td>3/3</td>
</tr>
<tr>
<td>Surgery (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colectomy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hemicolecotomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Blood loss, ml</td>
<td>280 ± 160</td>
<td>250 ± 80</td>
</tr>
<tr>
<td>Normal saline, ml</td>
<td>2,892 ± 358</td>
<td>2,966 ± 216</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of patients. Estimated blood loss and normal saline infused until the end of the study period are given.
Under steady-state conditions, leucine flux (Q) is defined by the equation $Q = S + O = B + I$, where $S$ is the rate at which leucine is incorporated into body protein, $O$ is the rate of leucine oxidation, $B$ is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and $I$ is the rate of dietary intake or the rate of infusion of L-[1-13C]leucine ( $\mu$mol·kg$^{-1}$·h$^{-1}$) or both. Inspection of that formula indicates that, when studies are conducted in the postabsorptive state, flux is equal to break- 

down. Enrichment of plasma lactate assay was based on lactate method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate enrichment more precisely than leucine itself indicates that, when studies are conducted in the postabsorptive state, flux is equal to breakdown. Enrichment of plasma $\alpha$-ketoisocaproate ( $\alpha$-KIC) during infusion of L-[1-13C]leucine has been used to determine whole body leucine kinetics. This steady-state reciprocal pool model is considered to represent the intracellular precursor pool enrichment more precisely than leucine itself (30).

The clearance rate of glucose was calculated as the $K_c$ of glucose divided by the corresponding plasma glucose concentration. Plasma $\alpha$-KIC enrichment was determined by positive chemical ionization gas chromatography-mass spectrometry, as previously described (38). Expired $^{13}$CO$_2$ enrichment was analyzed by means of isotope ratio mass spectrometry and chemical ionization gas chromatography-mass spectrometry, using electron impact ionization (38). In each analysis run, duplicate injections were always performed, and their means were taken to represent the intracellular precursor pool enrichment more precisely than leucine itself (30).

The clearance rate of glucose was calculated as the $K_c$ of glucose divided by the corresponding plasma glucose concentration. Plasma $\alpha$-KIC enrichment was determined by positive chemical ionization gas chromatography-mass spectrometry, as previously described (38). Expired $^{13}$CO$_2$ enrichment was analyzed by means of isotope ratio mass spectrometry and used to calculate leucine oxidation. A factor of 0.81 was applied to account for the fraction of $^{13}$CO$_2$ released by [13C]leucine oxidation but retained within slow turnover rate pools of the body (38). Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-2H$_2$]glucose enrichment was determined by gas chromatography-mass spectrometry using electron capture detection (38). In each analysis run, duplicate injections were always performed, and their means were taken to represent the intracellular precursor pool enrichment. Plasma concentration of glucose was measured by a glucose oxidase and was performed using the synchronous CX 7 system (Beckman Instruments). Plasma concentrations of FFA were analyzed by using the Boehringer Mannheim enzymatic colorimetric kit (Laval, Quebec). Circulating concentrations of insulin and glucagon were measured by sensitive and specific double-antibody radioimmunoassays (Amersham International, Bucks, UK). Cortisol plasma concentration was measured using the Ciba Corning ACS 180 automated immunoassay (Ciba Corning Diagnostic, East Walpole, MA).

Data are presented as means ± SD. Differences between and within groups for repeated measurements during surgery (hemodynamics, oxygen saturation, plasma concentrations of metabolic substrates and hormones) were analyzed by analysis of variance. If no significant change was detected between the intraoperative measurements, the average value was compared with the value obtained before surgery. Changes in whole body protein and glucose kinetics within and between the two groups were determined using the Student’s t-test. The relationship between $R_a$ leucine and $R_a$ glucose was evaluated by the correlation coefficient. Statistical significance was accepted at $P < 0.05$.

**RESULTS**

There were no differences between the two groups regarding age, height, weight, and gender (Table 1). The mean total amount of remifentanil administered in both groups was similar (propofol group: 1,011 ± 44 μg, desflurane group: 1,147 ± 70 μg). Patients in the propofol group received a total amount of 1,065 ± 53 mg propofol. The mean end-tidal desflurane concentration in the desflurane group was 4.6 ± 1.6% volume.

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### Table 2. Hemodynamic variables and oxygen saturation

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>80 min</th>
<th>90 min</th>
<th>100 min</th>
<th>110 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>100 ± 8</td>
<td>89 ± 13</td>
<td>88 ± 8</td>
<td>90 ± 6</td>
<td>86 ± 13</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>Desflurane</td>
<td>96 ± 8</td>
<td>86 ± 8</td>
<td>86 ± 8</td>
<td>81 ± 13</td>
<td>89 ± 12</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>79 ± 12</td>
<td>68 ± 15</td>
<td>68 ± 16</td>
<td>69 ± 15</td>
<td>69 ± 13</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Desflurane</td>
<td>74 ± 10</td>
<td>72 ± 14</td>
<td>69 ± 12</td>
<td>69 ± 13</td>
<td>68 ± 12</td>
<td>70 ± 15</td>
</tr>
<tr>
<td>Transcutaneous O$_2$ saturation, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>98 ± 1</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>Desflurane</td>
<td>98 ± 2</td>
<td>99 ± 1</td>
<td>100 ± 1</td>
<td>100 ± 1</td>
<td>100 ± 1</td>
<td>99 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SD.

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after 80 min and 4.4 ± 1.3% volume after 120 min of surgery, respectively. Estimated blood loss never exceeded 400 ml, and no patient received blood transfusion. The hematocrit (propofol group: 38 ± 8%, desflurane group: 40 ± 5% before surgery) decreased to 32 ± 5% in the propofol group (P < 0.05) and to 32 ± 3% in the desflurane group (P < 0.05) after 120 min of surgery. Heart rate and mean arterial pressure did not change throughout the study period without showing any differences between the two groups (Table 2).

Plateau enrichments for plasma α-[1-13C]KIC, [6,6-2H2]glucose, and expired 13CO2 were achieved in all infusions before and during surgery (coefficient of variation < 4% for all isotopes; Fig. 2). In both groups, a decrease in CO2 production was observed (propofol group from 155 ± 23 to 135 ± 15 ml/min, desflurane group from 182 ± 48 to 148 ± 45 ml/min; P < 0.05). Whole body protein breakdown (Rα leucine), leucine oxidation, and protein synthesis decreased during surgery (P < 0.05) without showing any differences between the two groups (Table 3). Endogenous glucose production and glucose clearance also decreased in both groups during the operation (P < 0.05). There was a significant correlation between the Rα glucose and Rα leucine obtained before and during surgery (r = 0.755, P < 0.001; Fig. 3).

Intraoperative plasma concentrations of glucose and cortisol increased to a comparable extent in both groups (P < 0.05), whereas lactate, insulin, and glucagon plasma concentrations remained unaltered (Table 4). Similarly, preoperative plasma concentrations of FFA, 878 ± 158 μmol/l in the desflurane group and...
894 ± 226 μmol/l in the propofol group, did not change after 120 min of surgery (desflurane group: 832 ± 203 μmol/l, propofol group: 1,041 ± 213 μmol/l).

DISCUSSION

Although valuable information on the regulation and alteration of perioperative body protein economy has been obtained by nitrogen balance measurements, this technique fails to provide insight into the different dynamic and adaptive mechanisms that might result in balance. Recent studies applying stable isotope tracer kinetics in surgical patients showed that protein losses after abdominal surgery are the consequence of dynamic and adaptive mechanisms that might result in balance. Recent studies applying stable isotope tracer kinetics in surgical patients showed that protein losses after abdominal surgery are the consequence of adaptive and dynamic mechanisms that might result in balance.

Alterations in protein metabolism in the present study are the consequence of adaptive and dynamic mechanisms that might result in balance. Although valuable information on the regulation and alteration of perioperative body protein economy has been obtained by nitrogen balance measurements, this technique fails to provide insight into the different dynamic and adaptive mechanisms that might result in balance.

Table 3. Glucose and leucine kinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol Before surgery</th>
<th>Propofol During surgery</th>
<th>Desflurane Before surgery</th>
<th>Desflurane During surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_a leucine, μmol·kg⁻¹·h⁻¹</td>
<td>100.9 ± 19.9</td>
<td>84.3 ± 15.1*</td>
<td>98.1 ± 15.1</td>
<td>80.6 ± 9.6*</td>
</tr>
<tr>
<td>Leucine oxidation, μmol·kg⁻¹·h⁻¹</td>
<td>16.4 ± 3.8</td>
<td>11.3 ± 3.7*</td>
<td>18.6 ± 6.0</td>
<td>14.7 ± 5.6*</td>
</tr>
<tr>
<td>Protein synthesis, μmol·kg⁻¹·h⁻¹</td>
<td>84.5 ± 17.0</td>
<td>72.9 ± 15.1*</td>
<td>79.5 ± 10.2</td>
<td>64.2 ± 6.4*</td>
</tr>
<tr>
<td>R_a glucose, μmol·kg⁻¹·min⁻¹</td>
<td>10.1 ± 1.4</td>
<td>9.3 ± 1.2*</td>
<td>9.7 ± 0.6</td>
<td>9.0 ± 0.7*</td>
</tr>
<tr>
<td>Glucose clearance, ml·kg⁻¹·min⁻¹</td>
<td>2.0 ± 0.4</td>
<td>1.5 ± 0.2*</td>
<td>2.0 ± 0.3</td>
<td>1.5 ± 0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SD. R_a, rate of appearance. *P < 0.05 vs. before surgery.

Table 4. Plasma concentrations of metabolic substrates and hormones

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Surgery</th>
<th>80 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>Propofol 5.0 ± 0.7</td>
<td>6.4 ± 0.5*</td>
<td>6.4 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>Desflurane 4.5 ± 1.4</td>
<td>5.7 ± 0.8*</td>
<td>6.1 ± 0.5*</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>Propofol 1.0 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Desflurane 1.3 ± 0.4</td>
<td>1.0 ± 0.5</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>Propofol 85 ± 16</td>
<td>93 ± 31</td>
<td>89 ± 13</td>
</tr>
<tr>
<td></td>
<td>Desflurane 98 ± 27</td>
<td>79 ± 35</td>
<td>80 ± 30</td>
</tr>
<tr>
<td>Glucagon, pmol/l</td>
<td>Propofol 18 ± 2</td>
<td>20 ± 6</td>
<td>20 ± 5</td>
</tr>
<tr>
<td></td>
<td>Desflurane 20 ± 8</td>
<td>15 ± 5</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>Cortisol, mmol/l</td>
<td>Propofol 348 ± 178</td>
<td>767 ± 133*</td>
<td>804 ± 124*</td>
</tr>
<tr>
<td></td>
<td>Desflurane 446 ± 128</td>
<td>935 ± 242*</td>
<td>808 ± 274*</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 vs. before surgery.
cannot be attributed to the action of the anesthetic agents themselves, because the influence of inhalation agents (6) and propofol (37) on leucine kinetics, in the absence of surgery, has been shown to be small. It also seems possible to dismiss these changes as being the result of a contraction in the distribution space of infused leucine as a consequence of anesthesia and/or surgery-induced peripheral vasoconstriction, because surgical blood loss was minimal, patients were hemodynamically stable and well hydrated, and hypothermia as well as systemic hypoxemia were avoided throughout the study period. Because both ischemia and hypoxia have been shown to exert suppressory effects on muscle protein metabolism in animals, it is, however, a possibility that any decrease in peripheral muscle perfusion and subsequent regional depression of protein metabolism contributed to the overall effect in the whole body (29). However, a marked release of free amino acids from the leg was observed in patients undergoing cholecystectomy (28), which further emphasizes the notion that whole body protein turnover values obtained by tracer kinetics give only averages over the summation of all individual processes involved. As a result, protein metabolic processes in specific tissues, such as muscle or liver, remain unknown.

The present finding of depressed whole body protein metabolism during colorectal surgery is in agreement with the results of two observational reports demonstrating similar changes during pelvic (6) and cardiac procedures (34) performed under inhalational anesthesia. Our results also are in line with the previous finding of a significant decrease in muscle protein synthesis obtained immediately after cholecystectomy by using the L-[1-13C]leucine flooding method (14) and the more recent observation of a rapid inhibition of liver protein synthesis during laparoscopic surgery (2).

Our study protocol was not designed to dissect the biochemical factors responsible for the changes in intraoperative protein metabolism. Hence, we can only speculate on underlying mechanisms.

Increasing FFA availability in vivo and in vitro leads to a decrease in leucine oxidation and/or turnover (1, 5). Some evidence also suggests that hyperketonemia associated with starvation has a direct protein-sparing effect on skeletal muscle (33). Plasma concentrations of FFA in the present study did not change during the operation, whereas circulating ketone body concentrations were not measured. According to the results of recent studies, hyperketonemia during the first 2 h of abdominal surgery is mild, with plasma ketone body concentrations remaining <0.5 mmol/l (35, 23). Because fasting-induced ketosis has been defined as being present when blood acetoacetate has risen to 1.0 mmol/l and hydroxybutyrate to 2–3 mmol/l, antica
tabolic effects of intraoperative hyperketonemia are unlikely (22).

Based on the results from combined hormone infusion studies, it has been postulated that impairment of insulin sensitivity resulting from the perioperative increase in the plasma levels of the counterregulatory hormones cortisol and glucagon plays a key role in mediating protein losses after surgery (18, 20). As plasma concentrations of insulin and glucagon did not significantly change in the present study, alterations in the glucagon/insulin system seem an unlikely cause for the observed intraoperative decrease in protein catabolism. It is interesting to note that hyperglycemia, as seen during surgery, exerts an inhibiting influence on protein metabolism, even without concomitant changes in insulin. Urea production, an indirect index of protein breakdown, has been suppressed to the same degree when insulin secretion was blocked by somatostatin as when insulin plasma concentration increased after 2 h of glucose infusion (41).

Considering the well-known catabolic action of cortisol, decreased rates of protein breakdown and oxidation observed after 120 min of surgery in the presence of increased intraoperative cortisol plasma concentration appear to be paradoxical. It has to be noted, however, that the catabolic effects of corticosteroids, which act either directly or indirectly by permissively enhancing the action of glucagon and epinephrine, are unlikely to take effect within 2 h. Cortisol infusion has been shown to have only little impact on nitrogen losses, leucine flux, and amino acid oxidation during the first 24 h in healthy subjects (15).

Patients participating in the present protocol fasted for ∼30 h before surgery (due to bowel preparation), with potential impact on whole body protein metabolism. Previous studies suggest that, in the first 1–3 days of fasting, the release of amino acids from whole body proteins and protein oxidation increase compared with postabsorptive values (39). By 7–10 days (late fasting), this early increase in protein turnover is superseded by a reduction of proteolysis even further below the prefasting values (21). Because patients in the present protocol were studied under the conditions of early fasting, fasting per se presumably does not account for the significant inhibition of protein metabolism during surgery.

Similar to our recent observation in patients 2 days after abdominal surgery, a significant correlation between the Ra leucine and Ra glucose was detected, indicating a direct relationship between whole body protein breakdown and glucose production in surgical patients (38). These results fit well with the conclusion that muscle protein is broken down to provide gluconeogenic amino acids for de novo gluconeogenesis in the liver (40). Under postabsorptive conditions, glyco
genesis constitutes ∼50% of whole body glucose production, with the remainder being derived from gluconeogenesis (25). In the present study, the entire contribution of gluconeogenesis could not be quantified, because the use of [6,6-2H2]glucose does not allow differentiation between the two metabolic pathways. Gluconeogenesis progressively increases with the duration of fasting, contributing to >90% of glucose production after 42 h of fasting (8). Taking into account the subjects’ long fasting period before the operation, it seems likely that the majority of glucose in our patients was produced through gluconeogenesis.
Glucose production in the present study decreased during surgery, whereas plasma glucose concentrations increased, indicating diminished whole body glucose clearance. These findings are in accordance with the results of a previous study demonstrating decreases in glucose production and glucose utilization in patients undergoing hip surgery (32). Thus we conclude that the hyperglycemic response to surgical trauma is caused by impaired glucose utilization and not by stimulated gluconeogenesis, as previously proposed in patients who were studied several days after surgery and major injury (27). Because a primary effect of cortisol in humans is to impair insulin function and diminish glucose utilization by decreasing the rate at which insulin activates the glucose uptake system, the increase in cortisol plasma concentrations conceivably contributed to reduced glucose clearance in our patients (3).

Although we did not measure catecholamine plasma concentrations, we have to assume that both anesthetic techniques administered (desflurane and propofol combined with low-dose remifentanil infusion) did not completely block the sympathoadrenergic responses to surgery in our patients (36). As reduced glucose clearance has been identified as the primary mechanism whereby catecholamines induce hyperglycemia, increases in the plasma concentrations of epinephrine and norepinephrine most likely also were responsible for the hyperglycemic response observed during surgery (13).

The metabolic endocrine responses to colorectal surgery were not influenced by the type of anesthesia employed in the present protocol. Neither propofol nor desflurane anesthesia prevented the increases in plasma glucose and cortisol concentrations during surgery. This finding is in contrast to the previously held contention that propofol is capable of attenuating the surgical stress responses as reflected in lower cortisol, catecholamines, and glucose plasma concentrations compared with inhalational anesthesia (11, 12, 31). Because propofol anesthesia was supplemented with large doses of morphine, fentanyl, or alfentanil, which per se own significant anticytotoxic properties (16), the metabolic effects of propofol, however, could not be separated in the latter studies. In order not to mask the metabolic influence of propofol and desflurane anesthesia, we administered the opioid remifentanil at low doses with presumably little impact on the catabolic response to surgery. The metabolic effects of remifentanil have not been investigated so far in surgical patients. Previous studies, however, using identical amounts of fentanyl, a synthetic opioid with similar potency as remifentanil, demonstrated that low-dose opioid anesthesia does not modify the metabolic and endocrine alterations during surgery (16, 26).

In conclusion, we have utilized L-[1-13C]leucine and [6,6-2H2]glucose infusions to characterize the kinetics in protein and glucose metabolism during abdominal surgery. We observed during surgery a depression of whole body protein and glucose metabolism with the hyperglycemic response being caused by a decreased whole body glucose clearance and with a significant relationship between glucose production and protein breakdown. All metabolic changes occur independent of the anesthetics used, i.e., propofol and desflurane.

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