POSTOPERATIVE PROTEIN METABOLISM: EFFECT OF NURSING ELDERLY PATIENTS FOR 24 H AFTER ABDOMINAL SURGERY IN A THERMONEUTRAL ENVIRONMENT

F. CARLI, J. WEBSTER, M. PEARSON, J. FORREST, S. VENKATESAN, D. WENHAM AND D. HALLIDAY

SUMMARY

We have studied the effect of intraoperative body heat conservation and 24-h thermoneutrality on postoperative whole body protein turnover using stable isotope methodology in a group of elderly patients undergoing colorectal surgery for recto-sigmoid adenocarcinoma. Two groups of eight patients were studied. One group (control, or cold) received routine intraoperative and postoperative care. All patients in the second group (warmed) were maintained at normothermia during anaesthesia and surgery; these patients were nursed after surgery in a warm room (ambient temperature 28–30 °C) for a period of 24 h. General anaesthesia, surgical care and nutritional support were similar in both groups. A constant nutritional intake, based on nitrogen 0.1 g kg⁻¹ day⁻¹ and energy 20 kcal kg⁻¹ day⁻¹, was provided orally for 7 days before surgery and i.v. after operation for 4 consecutive days. Whole body protein breakdown and synthesis, as assessed by stable isotope methodology, increased significantly 2 and 4 days after surgery in both groups (P < 0.01), but the increase in protein breakdown in the warmed group on day 2 was significantly less than that in the cold group (P < 0.05). The increase in leucine oxidation in the warmed group on the 2nd day after surgery was not significant, and was less than the increase observed in the cold group (P < 0.05). However, by the 4th day, leucine oxidation was enhanced significantly in both groups (P < 0.01). The cumulative urinary nitrogen excretion over 4 days and the loss of fat-free mass, as measured by total body potassium 7 days after surgery, were significantly less in the warmed group compared with the cold group (P < 0.05). Urinary excretion of adrenaline and cortisol after surgery was significantly less in the warmed group compared with the cold group (P < 0.05). Thus the attenuated whole body protein breakdown and amino acid oxidation observed in the warmed group after surgery might be explained, to some extent, by the specific hormonal suppression achieved with thermoneutrality.

KEY WORDS

Metabolism: protein. Temperature: cooling, metabolism.

Surgery is associated with changes in plasma and muscle contents of amino acids, resulting in loss of nitrogen from the body [1]. The conventional use of nitrogen balance as a criterion for assessing postoperative protein metabolism has a major limitation in that it provides no insight into the mechanisms of the processes involved [2]. Negative nitrogen balance might be the result of a decrease in protein synthesis while protein breakdown is unaffected, augmented proteolysis while synthesis remains unchanged, or intermediate permutations of these processes. In addition, nitrogen equilibrium does not necessarily reflect an adequate state of organ protein metabolism or of nutritional status, as it does not reveal possible alterations in the intensity, quality or distribution of tissue and organ protein metabolism [3].

F. CARLI, F.C.A.N.A.E.S., J. WEBSTER, PH.D., J. FORREST, S.R.N. (Department of Anaesthetics); M. PEARSON, B.S.C., S.R.D. (Department of Dietetics); S. VENKATESAN, PH.D., D. WENHAM, D. HALLIDAY, PH.D. (Nutrition Research Group); Northwick Park Hospital and MRC Clinical Research Centre, Harrow, Middlesex. Accepted for Publication: October 19, 1990.

Correspondence to F.C.
Recent advances in stable isotope methodology have now made it possible to provide a more direct determination of whole body protein turnover after surgery by measuring breakdown, oxidation and synthesis of body proteins [4].

The effect of maintenance of normothermia during and immediately after surgery on postoperative nitrogen economy and energy expenditure has been investigated in previous studies [5, 6] and shown to be beneficial in attenuating protein loss. Moreover, nursing patients with burns and major fractures at a thermoneutral temperature may attenuate post-injury increase in metabolic rate and urinary nitrogen excretion [7].

The present study was designed to evaluate the changes in whole body protein turnover, fat-free mass and catabolic hormones occurring during the first 4 days after colorectal surgery in patients maintained normothermic during anaesthesia and surgery, and nursed in a thermoneutral environment during the first 24 h after operation.

PATIENTS AND METHODS

We studied 16 patients suffering from well differentiated recto-sigmoid adenocarcinoma undergoing either anterior or abdomino-perineal resection. In all subjects, the tumour was localized and no metastatic dissemination was found by either ultrasound of the liver or by the surgeon. None of the patients suffered from malnutrition or metabolic disorders and all gave informed consent to participate in this investigation, which was approved by the local Ethics Committee.

A daily controlled oral diet containing nitrogen 0.1 g/kg body weight and 1200-1600 calories (5021-6698 kJ) (1.1 times the resting metabolic rate), as estimated from the equations of Harris and Benedict [8], was commenced 7 days before surgery under direct supervision of a dietician. The same amount of nitrogen and calories was administered i.v. after surgery, starting 6 h from the end of surgery when cardiorespiratory conditions were stable, and maintained for 4 days. This nutritional regimen, based on a mixture of glucose, lipids and amino acids (KabiVitrum, Stockholm) was administered via a peripheral cannula at a constant rate by means of a volumetric infusion pump (IMED 928, IMED, Milton). The caloric contribution was as follows: carbohydrate 35%, fat 60% and protein 5%. On the day before surgery, skinfold thicknesses (biceps, triceps, subscapular and iliac crest) and mid-arm circumference were measured and the percentage body fat calculated [9]. In addition, total body potassium (TBK) was measured using a whole body counter and fat-free mass calculated [10].

Anaesthesia, surgery and postoperative care

Premedication comprised papaveretum 15-20 mg and hyoscine 0.2-0.4 mg i.m. 60-90 min before surgery. General anaesthesia was induced with thiopentone and neuromuscular block obtained with pancuronium. The lungs were ventilated to normocapnia with a mixture of 70% nitrous oxide and enflurane in oxygen. Patients were allocated randomly to two groups (cold or warmed). The cold group (n = 8) served as controls, and these patients received routine anaesthetic and surgical care. At the end of surgery, they were kept in the recovery room for a period of 1–2 h before leaving for the ward, where they were nursed routinely. The ambient temperature in the wards varied between 19 and 23 °C during the period of investigation. In contrast, in the patients in the warmed group, core temperature was maintained during surgery at preoperative values by active warming of the inspired gases, i.v. fluids and skin surface. At the end of surgery all patients in this group were transferred for a period of 24 h to a thermostatically controlled room adjacent to the recovery area where the ambient temperature was maintained between 28 and 30 °C and relative humidity was between 30 and 40%.

During surgery all patients in the two groups received an i.v. infusion of Hartmann’s solution 6 ml kg⁻¹ h⁻¹. Whole blood was administered when blood loss exceeded 20% of the patient’s circulating volume.

Anaesthesia and surgery occurred mid-morning and the operations were performed by the same surgical team. Pain relief after surgery consisted of a continuous subcutaneous infusion of papaveretum 3–7 mg h⁻¹ for 72 h.

Before induction of anaesthesia, a thermocouple probe was inserted under direct vision in the aural canal and secured with cotton wool to avoid draughts. Aural canal temperature (an indication of core temperature) was measured before and at the end of surgery, and hourly for the first 24 h after surgery.

Ambient temperature in the thermostatically controlled room and the wards was measured in the proximity of the patient with a thermocouple probe. All the probes and the thermometer had
TABLE I. Patient characteristics in the two groups studied (mean (SD or range)). BMI = Body mass index; FFM = fat-free mass

<table>
<thead>
<tr>
<th></th>
<th>Cold group (n = 8)</th>
<th>Warmed group (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>4:4</td>
<td>5:3</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70 (58-78)</td>
<td>73 (63-78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 (17)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>23 (2)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>28 (5)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>43 (9)</td>
<td>49 (6)</td>
</tr>
<tr>
<td>Serum albumin (g litre(^{-1}))</td>
<td>43.2 (2.4)</td>
<td>41.5 (7.1)</td>
</tr>
</tbody>
</table>

TABLE II. Clinical data of the two groups studied (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Cold group (n = 8)</th>
<th>Warmed group (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postabsorptive period before surgery (h)</td>
<td>15 (3)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>191 (22)</td>
<td>182 (17)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>875 (125)</td>
<td>927 (178)</td>
</tr>
<tr>
<td>Total amount of s.c. papaveretum administered over 24 h (mg)</td>
<td>127 (27)</td>
<td>108 (18)</td>
</tr>
</tbody>
</table>

been calibrated previously and found to be accurate to ±0.1 °C over the temperature range studied.

Experimental procedure

Oral and i.v. nutritional intakes were withheld from midnight before the morning of the studies, which were conducted between 08:00 and 12:00. The tracer infusions were carried out in all patients the day before surgery and on days 2 and 4 after surgery. A superficial vein in the dorsum of the hand was cannulated to provide access for infusion of L-[\(\text{\text{-13}}\)]\text{C\}leucine. Blood was sampled from a cannula placed in the contralateral hand vein. L-[\(\text{\text{-13}}\)]\text{C\}leucine (99% \(^{13}\text{C}\)) and 99% \(^{13}\text{C\}-\text{sodium bicarbonate (NaH}^{13}\text{CO}_3\) were purchased from Cambridge Isotope Laboratories (Cambridge, MA, U.S.A.).

Blood and air samples were collected before the infusion to measure basal carbon-13 enrichment, after which prime doses of NaH\(^{13}\text{CO}_3\) 0.08 mg kg\(^{-1}\) and L-[\(\text{\text{-13}}\)]\text{C\}leucine 0.5 mg kg\(^{-1}\) were administered. The continuous infusion of labelled leucine was started immediately and continued for a period of 4 h. Two hours after the start of the isotope infusion, when the tracer was assumed from previous studies to have reached an isotope steady state, venous blood and expired air samples were collected every 15 min for the remainder of the study. All blood samples were centrifuged immediately at 4 °C and the plasma was stored at −70 °C until required for analysis.

Plasma α-[\(\text{\text{-13}}\)]\text{C\}ketoisocaproate (α-KIC) enrichment was determined by chemical ionization selected-ion monitoring mass spectrometry using n-ketovaleric acid as an internal standard [11]. Carbon-13 labelled carbon dioxide (\(^{13}\text{CO}_2\)) enrichment in expired breath was determined on the day of the study by means of isotope ratio mass spectrometry using an established technique [12]. Plateau enrichment for both plasma α-KIC and expired carbon dioxide was considered to have been established provided the coefficient of variation was less than 5% at 2–4 h of the infusion.

Whole body leucine kinetics were calculated using a two-pool stochastic model applied during the steady state conditions obtained during the final 2 h of each study [13]. Plasma enrichment of α-[\(\text{\text{-13}}\)]\text{C\}KIC was used as the basis for calculating both flux and oxidation of leucine [14]. In the calculation of oxidation, a factor of 0.81 was used to account for the fraction of \(^{13}\text{CO}_2\) released from leucine but retained in the bicarbonate pool of the body.

Indirect calorimetry was performed over a 1-h period during the 2-h isotope plateau on each day of the study, and oxygen consumption (\(\text{\(V\text{O}_2\)}\)) and carbon dioxide production (\(\text{\(V\text{CO}_2\)}\)) were measured (Datex, Deltatrac, Finland).

TBK was measured non-invasively on the day before and 7 days after surgery in a whole body counter with a precision of 3% and accuracy of 4% [10]. The method relies on the measurement of gamma emissions from naturally radioactive potassium (potassium-40) present in the body as 0.012% of the naturally occurring isotopes of potassium. As 98% of potassium is located in the lean tissue, this measurement represents an index of fat-free mass. The degree of preoperative depletion, an indicator of nutritional assessment, was calculated from the ratio between the predicted and measured preoperative values, while the change in TBK occurring with surgery was obtained from the difference between the preoperative and postoperative measured TBK concentrations.

Twenty-four hour urine collections were obtained on two consecutive days before surgery and four consecutive days after surgery and analysed for total nitrogen, creatinine, noradrenaline, ad-
renaline and cortisol concentrations. Total nitrogen was measured by the automated method of chemiluminescence [15] and creatinine determined by the SMAC automated procedure. Urinary catecholamine concentrations were measured by reversed-phase ion-paired high pressure liquid chromatography with electrochemical detection [16], and urinary cortisol was measured by a fluorimetric method [17].

Statistical analysis

Results are expressed as mean (1 SD). Paired and unpaired Student’s t test were used when appropriate, and differences for all tests were considered significant at $P < 0.05$.

RESULTS

There were no significant differences between the two groups in patient characteristics, duration of surgery or blood loss (tables I, II). Aural canal temperature in the cold group decreased significantly ($P < 0.01$) during surgery and returned towards preoperative values during the first 8 h of recovery (fig. 1). The peak temperature was recorded in both groups 16 h from the end of surgery. Shivering was recorded only during the first 2 h after operation in four of eight patients in the cold group.

Urinary total nitrogen and creatinine

Preoperative mean (SD) values of urinary total nitrogen were similar for both groups: nitrogen 1.01 (0.02) mmol kg$^{-1}$ day$^{-1}$ per mmol of creatinine for the cold group and 0.97 (0.02) mmol kg$^{-1}$ day$^{-1}$ for the warmed group. Cumulative excretion of nitrogen during the first 4 days after operation was significantly greater in the cold group compared with the warmed group: nitrogen 5.5 (1.0) mmol kg$^{-1}$ day$^{-1}$ per mmol of creatinine for the cold group and 4.1 (1.2) mmol kg$^{-1}$ day$^{-1}$ for the warmed group ($P < 0.05$). Creatinine excretion increased significantly from 6.6 (3.1) mmol day$^{-1}$ in the cold group and 5.9 (2.7) mmol day$^{-1}$ in the warmed group before surgery to 13.8 (5.7) mmol day$^{-1}$ and 14.6 (6.3) mmol day$^{-1}$, respectively, on day 1 after surgery. Thereafter, the values decreased in both groups, but remained greater than preoperative values during the study period. No difference was observed between the two groups.

Whole body protein turnover

The sequential changes in whole body leucine kinetics following surgery in the two groups are presented in figure 2. In the fasted state, flux was equal to breakdown, there being no contribution from exogenous sources of leucine. Carbon-13 enrichments for plasma oc-KIC and expired carbon dioxide had an average coefficient of variation of 4.37% and 0.92%, respectively.

Leucine flux/breakdown increased significantly in both groups, 2 and 4 days after surgery; however, the greatest increase occurred in the cold group (28%) on day 2, and this was significantly different from that occurring in the warmed group (18%) ($P < 0.04$). On the fourth day after surgery there was no significant difference between the two groups. In the cold group, leucine oxidation increased significantly by 24% ($P < 0.001$) on day 2 and remained increased on day 4 ($P < 0.001$). In contrast, no significant increase occurred on day 2 in the warmed group, but on day 4 leucine oxidation was significantly increased compared with preoperative values ($P < 0.01$). Incorporation of leucine into protein (protein synthetic rate) increased significantly in both groups on both days 2 and 4 ($P < 0.01$), and no difference was observed between the two groups at any time.

Total body potassium

The mean (SD) preoperative percentage ratio of observed over expected value of TBK was similar in both groups of patients studied: 0.97 (0.1) in the cold group and 0.98 (0.07) in the warmed group. The mean (SD) decrease in TBK 7 days
after surgery was 342 (162) mmol in the cold group and 183 (95) mmol in the warmed group ($P = 0.03$).

**Urinary adrenaline, noradrenaline and cortisol**

The changes in urinary excretion of adrenaline and cortisol are presented in Table III. Adrenaline excretion was similar in both groups before surgery and increased significantly after surgery in both groups ($P < 0.05$). Adrenaline concentration, however, was significantly greater in the cold group compared with the warmed group on day 1 ($P < 0.05$). Thereafter, the excretion in the warmed group remained lower, but it was not significantly different from the cold group. Urinary excretion of cortisol increased significantly after surgery in both groups, but this was significantly less in the warmed group compared with the cold group on days 1, 2 and 3 ($P < 0.05$). Urinary noradrenaline increased significantly after surgery in both groups and there was no significant difference between them.

**Gas exchange**

$\dot{V}O_2$ and $\dot{V}CO_2$ increased in both groups on days 2 and 4 after surgery by approximately 7–10%. No significant difference was observed between the two groups at any time.
TEMPERATURE AND POSTOPERATIVE PROTEIN METABOLISM

DISCUSSION

This study has shown that conservation of body heat during surgery and preservation of thermoneutrality extended for 24 h after surgery caused a significantly smaller increase in whole body protein breakdown and amino acid oxidation during the postoperative period. This resulted in attenuated excretion of body nitrogen and loss of fat-free mass.

We have reported that attempts to prevent loss of body heat during surgery resulted in attenuation of protein breakdown as measured by urinary total nitrogen and 3-methylhistidine excretion [18]. However, as we highlighted previously, control of dietary intake during metabolic studies is essential for interpretation of changes in protein metabolism with surgery [19]. Nutrient withdrawal reduces protein synthesis by up to 40% [20], while refeeding a malnourished patient causes stimulation of synthesis [21]. In the present study we have approached this problem by standardizing the nutritional intake before and after surgery; thus the nitrogen intake was moderate and the calories were based on the patients' resting energy expenditure. This strict dietary control allowed us to separate the effect of trauma from that of starvation in the interpretation of the changes in protein turnover [19].

None of the patients was nutritionally depleted before surgery, as indicated both by physical characteristics and plasma concentrations of albumin.

The particular surgical procedure was chosen as it represents a reproducible model of major intensity of trauma which elicits neuroendocrine responses and substrate changes in the postoperative period. Attempts to quantitate the possible effects of a malignant tumour on protein metabolism of the host have produced conflicting results. Thus the first such study in humans reported enhanced protein turnover in patients with colorectal neoplasm which was approximately proportional to the estimated tumour burden [22]. Similar results have been obtained in patients with various tumours [23–25] in adults with non-oat cell carcinoma of the lung [26] and in children with leukaemia and lymphoma [27]. In sharp contrast to these observations, resection of colonic tumours failed to show any effect on protein metabolism [28]. Similarly, no effect of a tumour on host protein metabolism could be demonstrated in cachectic patients with lung tumours [29], germ cell tumours [30] or in patients with malignant tumours of the large bowel, with or without metastatic disease [31]. That the apparent discrepancies outlined above may result from differences in experimental design, patients, feeding regimens or methods of data presentation have been examined in detail [31].

As observed in this study, whole body protein breakdown (measured by leucine kinetics) increased significantly in both groups, 2 and 4 days after surgery. However, the breakdown was significantly less enhanced in the warmed group on day 2 compared with the cold group. This result was supported by the fact that the rate of oxidation of leucine on day 2, in those patients maintained at thermoneutrality for the first 24 h after surgery, did not change significantly from preoperative values. Rates of protein breakdown and oxidation between the two groups were not statistically different by day 4.

Whole body protein synthetic rate increased significantly in both groups after surgery by approximately the same amount, indicating similar availability of amino acids for the formation of new proteins in the body. This was associated with an increase in postoperative oxygen consumption on days 2 and 4 in the same direction, reflecting the energy-requiring nature of the processes most likely to be involved: protein synthesis and gluconeogenesis.

It is of interest that the attenuation in whole body protein breakdown and oxidation in the warmed group was limited to the 2nd day after operation, which coincided with the provision of thermoneutrality during the first 24 h after surgery. These results are in agreement with previous work on the effect of high ambient temperature on postoperative protein breakdown in surgical patients [32]. It is at this same period that the excretion of urinary adrenaline and cortisol was significantly less in the warmed group compared with the cold group. A role for these counter-regulatory hormones in modulating protein metabolism has been proposed previously [33]. However, other mediators of proteolysis occurring in plasma after trauma might be involved [34].

This is the first evidence we have that hormonal modulation might be a mechanism for reduced protein breakdown and oxidation in association with maintenance of thermoneutrality. From the present results, one could speculate that provision of thermoneutrality extended for a longer period of time might spare some postoperative protein
breakdown and amino acid oxidation throughout the catabolic phase. In contrast, whole body protein synthesis was not enhanced by preservation of body heat.

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