EFFECT OF HEAT CONSERVATION DURING AND AFTER MAJOR ABDOMINAL SURGERY ON MUSCLE PROTEIN BREAKDOWN IN ELDERLY PATIENTS

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The accelerated rate of nitrogen loss from the body after major surgical operations remains a matter of concern, especially when patients are elderly and unable to eat for prolonged periods of time. Several attempts to minimize these metabolic effects have been suggested: for example, high-dose opiate anaesthesia (Hall, 1980), extradural analgesia (Brandt et al., 1978), parenteral nutrition (Blackburn and Bistrian, 1977; Freund et al., 1979), the infusion of sodium-β-hydroxybutyrate (Sherwin, Hendler and Felig, 1975) and the administration of insulin (Woolfson, Heatley and Allison, 1979) —but with little success.

In a previous study (Carli, Clark and Woollen, 1982) it was attempted to decrease protein catabolism by introducing a warm environment during and immediately after surgery, and observed that those patients whose body temperature was kept within normal limits during the period of surgery excreted less urea nitrogen. Since our previous investigation was poorly controlled in some respects (type of surgery, preoperative protein intake, absence of preoperative values), the present study was undertaken to examine more critically the effects of maintenance of normothermia on the loss of muscle protein, the excretion of the amino acid 3-methylhistidine (3-MeH), an indicator of muscle protein breakdown, and urea nitrogen loss were measured in the urine collected the day before, and on the 2nd and 4th postoperative days. Prevention of heat loss during and after surgery caused a significant decrease in muscle protein degradation and nitrogen loss.

PATIENTS AND METHODS
Sixteen patients aged more than 60 yr, classified as ASA 2 or 3 were studied. Patients with metabolic disorders and with a significant degree of weight loss were excluded. All patients underwent elective surgery for large bowel tumours: seven sigmoid colectomies and nine hemicolecctomies distributed equally in each group (vide infra). All operations were undertaken by the same surgeon.

The patients were randomly allocated to two groups: cold (C) and warmed (W). Group C served as the control while in group W (test group) efforts were made to minimize heat loss during surgery.

The patients were on a meat-free diet for a period of 48 h preceding surgery and a laxative was used to empty the bowels. All were premedicated...
with pethidine 1 mg kg\(^{-1}\) and promethazine 0.4 mg kg\(^{-1}\) i.m.

Anaesthesia was induced with thiopentone, the trachea intubated with the aid of pancuronium 0.1 mg kg\(^{-1}\) and the lungs ventilated with a mixture of nitrous oxide in oxygen at a minute volume of 100 ml kg\(^{-1}\). Anaesthesia was maintained with increments of fentanyl 50 \(\mu\)g and droperidol 0.15 mg kg\(^{-1}\) as indicated clinically. Normocapnia was ensured by monitoring the end-tidal carbon dioxide concentration.

In group W, inspired gases were warmed and humidified using a cascade humidifier (Bennet) set to deliver gases at 36 °C at mouth level.

Hartmann's solution was infused i.v. at 4 ml kg\(^{-1}\) h\(^{-1}\) and blood was given to five patients in each group. Those in group W received all fluids warmed to 37 °C using a blood warmer (Fenwal).

In group W all the exposed parts of the body, except the abdomen, were covered with warmed cotton padding and warmed fluids were used for irrigation, and to wash the bowels and peritoneum. At the end of surgery, a metallized plastic sheet was placed over these patients to minimize heat loss in the recovery area.

Ambient temperature and relative humidity in the operating room were kept constant at 21 °C and 60%, respectively. The recovery room temperature varied between 25 °C and 27 °C.

Postoperative i.v. fluids consisted of a mixture of 4% dextrose and 0.18% sodium chloride at a rate of 40 ml kg\(^{-1}\) day\(^{-1}\) for 3 days followed by fluids by mouth. Four skin surface and auditory meatus temperatures were measured before induction, every 30 min during surgery and every 1 h for 6 h in the recovery room by means of an electrical thermometer (Yellow-Springs) which was calibrated against a mercury glass thermometer. Mean skin temperatures (°C) were calculated using the four-points formula proposed by Ramanathan (1964):

\[
\text{Mean skin } t^o = 0.3 \left( \text{t}_{\text{chest}} + \text{t}_{\text{arm}} \right) + 0.2 \left( \text{t}_{\text{thigh}} + \text{t}_{\text{calf}} \right)
\]

Mean body temperature was calculated by averaging the mean skin and auditory meatus temperatures according to the equation (Colin et al., 1971):

\[
\text{Mean } t_{\text{body}} = 0.66 \times t_{\text{ear canal}} + 0.34 \times \text{mean } t_{\text{skin}}
\]

Blood samples were collected on the day before surgery and on the 2nd and 4th days after surgery, and the concentrations of urea, creatinine, cortisol and ketone bodies (β-hydroxybutyrate and acetoacetate) measured. Blood samples for the measurement of cortisol concentration were drawn at 08.00 h to minimize the influence of diurnal variation.

Urine was collected for 24 h before, and on the 2nd and 4th days after surgery for the measurement of the urinary concentrations of urea, creatinine and 3-methylhistidine.

**Assay methods**

**Ketone bodies.** β-Hydroxybutyrate and acetoacetate were assayed by the enzymic procedure. Heparinized blood samples were taken on ice and centrifuged without delay (3000 \(g\) for 10 min at 4 °C). The plasma samples were frozen (−18 °C) and usually assayed within 24 h.

**Acetoacetate** was assayed using the modifications by Price, Lloyd and Alberti (1977) of the procedure of Williamson, Mellanby and Krebs (1962).

**β-Hydroxybutyrate** was assayed by the method of Williamson, Mellanby and Krebs (1962) as modified by Moore, Marcus and Sax (1982).

**Cortisol concentration** was determined by the Gamma-Coat (\(^{125}\)I)-RIA procedure based on the competitive binding principles of radioimmunoassay. Samples and standards were incubated with \(^{125}\)I-cortisol tracer in antibody-coated tubes (Yalow and Berson, 1971; Rodbard and Hutt, 1974).

**3-Methylhistidine** concentration was measured automatically on a Beckman 120-C Amino Acid Analyzer using the short column of the physiological system (citrate buffer 0.38 mol litre\(^{-1}\), pH 4.26 from 0 to 185 min and citrate buffer 0.35 mol litre\(^{-1}\), pH 5.28 from 185 to 345 min) (Williamson et al., 1977; Marliss, Wei and Dietrich, 1979).

**Urea nitrogen** was determined by the SMAC automated procedure using diacetyl monoxide and thiosemicarbazide and ferric ions for colour intensification—modifications of the methods of Coulombe and Favreau (1963).

**Creatinine concentration** was estimated by the automated SMAC procedure based on the original Jaffe reaction with saturated picric acid in an alkaline medium by Chasson, Grady and Stanley (1961).
Table I. Patient data and change in body temperature during operation (mean±SEM). Statistically significant difference between values for groups C and W: * P = 0.001

<table>
<thead>
<tr>
<th></th>
<th>Cold group (C)</th>
<th>Warmed group (W)</th>
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<tr>
<td><strong>M/F</strong></td>
<td>3/5</td>
<td>4/4</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>68.4±3.0</td>
<td>70.4±1.7</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>64.6±2.3</td>
<td>63.4±3.4</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.71±0.03</td>
<td>1.64±0.03</td>
</tr>
<tr>
<td><strong>Duration of op. (min)</strong></td>
<td>234±19</td>
<td>225±19</td>
</tr>
<tr>
<td>**Mean body temp. (<strong>C)</strong></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td><strong>Before</strong></td>
<td>35.8±0.1</td>
<td>35.2±0.1</td>
</tr>
<tr>
<td><strong>After</strong></td>
<td>33.6±0.3*</td>
<td>35.4±0.1</td>
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Statistical analyses of the data were performed using Student’s paired and unpaired t tests. Results are presented as mean±(SEM) and a statistically significant change was considered to have occurred when P values were 0.05 or less.

**RESULTS**

The physical characteristics of the patients, the duration of surgery and the total body temperatures at the beginning and at the end of surgery are shown in table I. The mean ages, weights, heights and durations of surgery were comparable in the two groups.

The mean body temperature in group C at the end of surgery was decreased by 2.2 °C, while in group W it was increased by 0.2 °C.

Serum concentration of the ketone bodies, plasma cortisol concentration and 24-h urine volumes showed no differences between the two groups after operation (table II). In the warmed group, the excretion of urea nitrogen, expressed as urinary urea:creatinine ratio, was significantly decreased on the 2nd and 4th days after operation, compared with the preoperative value (fig. 1). In contrast, in group C, the urea nitrogen excretion was increased on the 2nd day after surgery. A significant difference between the two groups was present on the second day: urea nitrogen excretion was 6.5 mg g⁻¹ in the cold group, while in the warmed group it was 3.9 mg g⁻¹.

The excretion of 3-MeH, expressed as urinary 3-MeH:creatinine ratio showed an increase in both groups after surgery, with a significantly greater increase in group C (fig. 2). As predicted, the urea:creatinine ratio was positively correlated with the methylhistidine:creatinine ratio (t = 0.59, P < 0.05). A significant positive correlation was found between the postoperative increase in

Table II. Concentrations of serum ketone bodies and plasma cortisol, and urine volume measured the day before surgery, and on the 2nd and 4th postoperative days. No statistical differences were found within groups, or between groups

<table>
<thead>
<tr>
<th></th>
<th>Cold group (C) (mean±SEM)</th>
<th>Warmed group (W) (mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketone bodies (mmol ml⁻¹)</strong></td>
<td>7 0.17±0.04 0.19±0.11 0.12±0.04</td>
<td>7 0.05±0.01 0.12±0.04 0.10±0.04</td>
</tr>
<tr>
<td><strong>Cortisol (mmol litre⁻¹)</strong></td>
<td>7 463±69 474±38 425±58</td>
<td>6 491±38 532±96 502±27</td>
</tr>
<tr>
<td><strong>Urine volume (litre/24 h)</strong></td>
<td>8 1.0±0.2 1.8±0.3 2.0±0.4</td>
<td>8 1.6±0.3 2.0±0.3 1.9±0.2</td>
</tr>
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3-methylhistidine: creatinine ratio and the negative change in concentrations of plasma ketone bodies (fig. 3).

No difference in creatinine clearance was found between the two groups, even though in group W there was a significant increase on the 2nd day compared with the preoperative value (49 ml min\(^{-1}\) to 79 ml min\(^{-1}\)).

DISCUSSION

The present study shows that an attempt to conserve body heat during prolonged abdominal surgery resulted in a substantial decrease in the urinary excretion of urea nitrogen and 3-methylhistidine. The decrease in the excretion of urea nitrogen in the warmed group is in accord with a previous study which attempted to establish a relationship between heat loss and nitrogen excretion (Carli, Clark and Woollen, 1982).

Urea nitrogen excretion and nitrogen balance have been used as criteria for assessing protein metabolism (Benotti and Blackburn, 1979) and the value of different nutritional techniques. However, these measurements present a number of problems: it is possible to be in nitrogen balance and yet have a subnormal synthesis of a range of physiologically important proteins (James, Sender and Waterlow, 1976). In addition, a common clinical error in the determination of nitrogen balance is the unmeasured non-urinary protein loss which occurs with nasogastric suction, biliary, cutaneous or enterocutaneous fistula, severe diarrhoea or haemorrhage (Phinney, 1981). Therefore, we decided to examine one method of measuring the absolute rate of muscle protein breakdown. This was achieved by identifying an amino-acid which is not re-utilized. The amino acid 3-methylhistidine is formed in the muscle by methylation of histidine residues after the synthesis of actin and myosin peptide chains (Long et al., 1975). When liberated during the breakdown of muscle protein, 3-MeH is not re-utilized for synthesis and is excreted unchanged in the urine. Therefore, the excretion of the amino acid 3-MeH has been taken as an estimate of muscle protein breakdown (Elia et al., 1981).

There are conflicting views about the wasting of skeletal muscle following surgery or malnutrition and whether this is caused primarily by alterations in the rate of protein synthesis or by an increase in protein breakdown. Rennie and Millward (1983) presented strong evidence in favour of a decrease in protein synthesis following studies on protein turnover, and on the release of 3-MeH from human and animal legs (Lundholm et al., 1982). In contrast, Baracos and colleagues (1983) and Clowes and co-workers (1983) supported the contention that it is protein breakdown which is increased primarily following injury.

The validity of the urinary excretion of 3-MeH as a marker of the breakdown of skeletal muscle...
protein has been questioned by Rennie and Millward (1983), who suggested that urinary 3-MeH comes in large part from the breakdown of visceral protein in organs such as skin and gut. However, Ballard and Thomas (1983) have challenged this hypothesis and pointed out that urinary 3-MeH correlates well with amino acid flux across muscles and that, therefore, it can be considered as a valid marker of muscle protein breakdown.

The output of 3-MeH has been expressed as a ratio of urinary 3-MeH to urinary creatinine, since the loss of muscle mass during ageing can be correlated with a change in the rate of degradation of myofibrillar protein. Our preoperative values for 3-MeH were smaller than those reported by Young and Munro (1978) in elderly patients. However, it is likely that these patients, with large bowel tumours, had an altered protein turnover and that the 48-h fast which preceded surgery decreased muscle protein breakdown.

Plasma cortisol concentrations did not show any change 48 h after surgery, in either group. Serum ketone body concentrations were measured and no difference was found between the two groups after surgery. However, it is interesting to note that patients in both groups were normoketonaemic (defined as a concentration of β-hydroxybutyrate plus acetoacetate less than 0.2 mmol) and the preoperative value of group W was lower than that in group C. When the negative change in serum ketone bodies was compared with the increase in 3-MeH:creatinine ratio, a significant correlation was found (fig. 3). This is in accordance with several authors (Smith et al., 1975; Wedge et al., 1976; Rich and Wright, 1979) who showed that patients with hypoketonaemia excreted greater amounts of nitrogen and 3-methylhistidine than hyperketonaemic patients who lost less body protein. Pawan and Semple (1983) found that an infusion of DL 3-hydroxybutyrate to obese subjects decreased the net body protein loss.

On the contrary, Miles and colleagues (1983) found no effect of ketone body infusion on 3-methylhistidine excretion, and they suggested a direct effect of alkalinization on either proteolysis from skeletal muscle or renal excretion of this compound. The question arises as to whether hyperketonaemia is itself of key importance in modulating the outflow of nitrogen from muscle, or merely an index of a common mechanism affecting both ketogenesis and muscle protein breakdown. The overall mechanisms responsible for the beneficial effects of a thermoneutral environment during and after surgery are far from being elucidated, and this field needs further study.

Creatinine clearance significantly improved in the postoperative period in the warmed group, and this might support the concept that the excretion of 3-MeH is not affected by renal function.

From these findings, we conclude that the net loss of muscle protein caused by large bowel surgery in the elderly can be minimized, in part, by ensuring a thermoneutral environment during surgery.

REFERENCES


HEAT CONSERVATION AND MUSCLE PROTEIN BREAKDOWN


