Glucose and insulin administration while maintaining normoglycemia inhibits whole body protein breakdown and synthesis after cardiac surgery

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The body’s metabolic response to surgical tissue trauma is characterized by hyperglycemia, enhanced proteolysis, and amino acid (AA) oxidation, resulting in nitrogen loss and negative protein balance (33). This response to stress was first described almost 80 years ago in four patients with lower limb injuries (7). Since then the stress response to trauma and surgery has been the focus of much attention in the medical literature. The metabolic response to stress is mediated through neural pathways and the neuroendocrine axis. Various hormones (catecholamines, cortisol) and cytokines [IL-1, IL-6, and tumor necrosis factor (TNF)] are involved in the catabolic response to the surgical tissue trauma. The main goal of this response is restoration of adequate tissue perfusion, oxygenation, and release of substrates for the vital organs (8, 30). Over the last few decades attempts have been made to find different ways to modulate this exaggerated neurohormonal stress response to improve delivery and utilization of substrates. Some strategies include changing surgical techniques, enhancing anesthetic strategies (neuraxial blockade), and introducing nutritional/metabolic modalities, for instance the hyperinsulinemic-normoglycemic clamp (HNC) technique (5, 21).

Stress hyperglycemia is the result of increased hepatic gluconeogenesis, glycogenolysis, and peripheral insulin resistance (8). This rise in blood glucose levels is directly related to the severity of the surgical stress. In patients undergoing cardiac surgery, blood glucose concentrations can increase up to 10–12 mmol/l for 24 h. The initial rise in blood glucose during the surgical procedure is due to breakdown of hepatic glycogen. As the surgical stress continues and glycogen stores in the liver get consumed and depleted, hepatic gluconeogenesis becomes a significant contributor to glucose blood. AAs derived from muscle protein breakdown are one of the essential substrates in hepatic gluconeogenesis along with lactate, pyruvate, and glycerol. As such, muscle proteolysis, the hallmark of the catabolic response to surgical tissue trauma, is directly related to glucose production (23). Because even moderately increased blood glucose concentrations are associated with poor clinical outcome after open heart surgery, insulin is being used frequently to maintain normoglycemia (9, 12). Although the pivotal role of insulin in the regulation of glucose homeostasis is well known, its effect on protein catabolism in this patient population is not (28).

We recently demonstrated that insulin administered as part of a hyperinsulinemic-normoglycemic clamp during open heart surgery caused significant hypoaminoacidemia (15). Branched-chain amino acids decreased by almost 70%, while AAs linked with the malate-aspartate cycle were reduced by 30%. As the measurement of static plasma concentrations does not allow any conclusion with regard to underlying dynamic metabolic changes, it remained unclear whether hypoaminoacidemia was a consequence of reduced proteolysis or increased incorporation of AA into newly synthesized proteins.

The purpose of the present study was to investigate the effect of insulin on whole body protein kinetics in patients undergoing cardiac surgery. Our hypothesis was that hypoaminoacidemia in the presence of hyperinsulinemia and normoglycemia...
is the result of suppressed protein breakdown rather than stimulated protein synthesis.

**METHODS**

**Study Population**

With the approval of the Research Ethics Board of the McGill University Health Center we obtained written informed consent from patients scheduled for elective coronary artery bypass grafting (CABG) requiring cardiopulmonary bypass (CPB).

Exclusion criteria included severe malnutrition (weight loss >20% in the preceding 3 mo, albumin level <35 g/l, and body mass index <20 kg/m²), morbid obesity (body mass index > 35 kg/m²), chronic liver disease, severe left ventricular dysfunction (left ventricular ejection fraction <20%), cancer, and dialysis.

Using a computer program (Plan procedure; SAS software, Cary, NC), consenting patients were randomly allocated to receive insulin or standard metabolic care. The surgeon, nurses, and personnel performing the laboratory analyses were blinded to the patients’ group assignment.

**Perioperative Care**

All patients received standard surgical and anesthetic care as established by the Departments of Anaesthesia and Cardiac Surgery at the Royal Victoria Hospital, McGill University Health Centre. All patients were operated on by the same surgeon (DST). General anesthesia was induced with intravenous midazolam (0.1 mg/kg) and suxentanil (0.5 µg·kg⁻¹·h⁻¹), and midazolam (40 µg·kg⁻¹·h⁻¹). Hemodynamic monitoring was performed with catheters placed in the right radial artery, the superior vena cava, and the pulmonary artery. Tranexamic acid (2 g bolus followed by continuous infusion of 5 mg·kg⁻¹·h⁻¹) was used as the antifibrinolytic agent during surgery.

Prior to CPB heparin 400 U/kg was given intravenously to obtain an activated clotting time >500 s. The ascending aorta and the right atrium were cannulated, the aorta was cross-clamped, and cardioplegia administered. Once coronary anastomoses were sutured and the aortic cross-clamp removed, the patient was separated from CPB. Intravenous dobutamine (2.5 µg·kg⁻¹·min⁻¹) was started if the cardiac index remained <2.2 l·min⁻¹·m⁻² despite adequate fluid resuscitation. Intravenous norepinephrine (1–10 µg/min) was used if systolic blood pressure remained consistently <100 mmHg.

After the administration of protamine (1 mg/100 U heparin) aortic and venous cannulas were removed, homeostasis established, and the pericardium and sternum closed. Patients were transferred to the Intensive Care Unit (ICU) and ventilated to normocapnia. Sedation was maintained using continuous infusions of propofol (10–25 µg·kg⁻¹·min⁻¹) until the end of the study. All subjects were maintained normothermic during the study period.

**Study Protocol**

**Control group.** Arterial blood glucose measurements were performed every 30 min using the Accu-chek glucose monitor (Roche Diagnostics). If the blood glucose was ≥10.0 mmol/l, an insulin (Humulin R regular insulin, Eli Lilly, Indianapolis, IN) bolus of 2 U was given followed by the infusion of 2 U/h. The rate of insulin infusion was adjusted according to the following sliding scale: 1) <4.1 mmol/l, stop insulin infusion and administer 25 ml dextrose 50%; 2) 4.1–6.0 mmol/l, stop insulin infusion; 3) 6.1–10.0 mmol/l, maintain current infusion rate; and 4) >10.0 mmol/l, increase infusion by 2 U/h.

**Insulin group.** After obtaining a baseline blood glucose value, a 2 U priming bolus of insulin was given followed by an insulin infusion of 5 mU·kg⁻¹·min⁻¹. Additional boluses of insulin were given if the blood glucose remained ≥6.0 mmol/l with incremental 2 U of insulin for each 2 mmol/l increase in blood glucose. Ten minutes after commencing the insulin infusion, and when the blood glucose was ≤6.0 mmol/l, a variable continuous infusion of glucose (dextrose 20%) supplemented with potassium (40 meq/l) and phosphate (30 mmol/l) was administered to maintain the blood glucose between 4.0 and 6.0 mmol/l. Insulin infusions were continued until the end of the study period. Arterial blood glucose was measured every 15–20 min.

**Leucine Kinetics, Metabolic Substrates, and Hormones**

Whole body leucine and glucose metabolism measurements were made under postabsorptive conditions on the day before surgery and, postoperatively, in the ICU (Fig. 1). Plasma kinetics of glucose and leucine, i.e., the glucose and leucine rate of appearance (Ra), leucine oxidation, and nonoxidative leucine disposal, were determined by a primed constant infusion of tracer quantities of L-[1-¹³C]leucine and [6,6-²H₂]glucose. Blood and expired air samples were collected, before the infusion, to analyze baseline enrichments. Priming doses of NaH¹³CO₃ (1 µmol/kg po), L-[¹³C]leucine (4 µmol/kg iv), and [6,6-²H₂]glucose (22 µmol/kg iv) were administered followed by the infusion of L-[1-¹³C]leucine (0.06 µmol·kg⁻¹·min⁻¹) and [6,6-²H₂]glucose in plasma and expired ¹³CO₂.
CA) (18).
Pentafluorobenzyl ester (Hewlett-Packard 5988A GC/MS, Palo Alto, was analyzed by electron-impact selected-ion monitoring gas chro-
tron-impact ionization.

During the postoperative period, while the patients’ lungs
were ventilated, breath samples were collected through a mouthpiece in a
centrifuged at 4°C, and the resulting plasma was stored at
180 min of the pre- and
isotope infusion period. In addition four blood
isotope enrichments four expired breath samples were taken after 150,
and mobile phase B was acetonitrile:methanol:
water (45:45:10). Initial gradient was 2% B for 0.5 min, then 2% to
57% B in 20 min followed by 5 min reequilibration before the next
Primary and secondary AAs were measured by fluorescence
with excitation and emission wavelengths of 230 nm and 450 nm,
respectively. Data from standards and samples were analyzed using
MassHunter B.05 software.

### Table 1. Patient and surgical characteristics

<table>
<thead>
<tr>
<th></th>
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<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
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<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
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<td>65.9 ± 7.2</td>
</tr>
<tr>
<td>Sex, M/F</td>
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<td>8/1</td>
</tr>
<tr>
<td>Weight, kg</td>
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<td>79.2 ± 15.4</td>
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<tr>
<td>Height, m</td>
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<td>1.7 ± 0.1</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>25.8 ± 4.1</td>
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<td>DM</td>
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<td>1</td>
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<tr>
<td>Oral agents</td>
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<td>1</td>
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<tr>
<td>Insulin</td>
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<td>0</td>
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<tr>
<td>HbA1c, %</td>
<td>6.2 ± 0.7</td>
<td>6.0 ± 0.3</td>
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<td>LVEF, %</td>
<td>43.3 ± 13.5</td>
<td>50.6 ± 12.6</td>
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<tr>
<td>BMI</td>
<td>28.9 ± 4.1</td>
<td>25.8 ± 4.1</td>
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<td>Insulin</td>
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<td>50.6 ± 12.6</td>
</tr>
</tbody>
</table>

Values are means ± SD or no. of patients. M, male; F, female; BMI, body
mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LVEF, left
ventricular ejection fraction; CPB, cardiopulmonary bypass; EBL, estimated
blood loss; PRBC, packed red blood cells. P values were determined by
unpaired t-test, χ² test, and Fisher’s exact test where appropriate.

3H2glucose (0.44 μmol·kg⁻¹·min⁻¹). For the determination of 13CO2
isotope enrichments four expired breath samples were taken after 150,
160, 170, and 180 min of isotope infusion. In addition four blood
samples were collected to determine whole body leucine and glucose
kinetics. Plasma concentrations of lactate, amino acids, insulin, and cortisol were determined at 180 min of the pre- and
postoperative isotope infusion period.

Blood samples were immediately transferred to a heparinized tube,
centrifuged at 4°C, and the resulting plasma was stored at
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postoperative isotope infusion period.

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postoperative isotope infusion period.

Whole body leucine and glucose kinetics were calculated by the
conventional isotope dilution technique using a two-pool random
model during steady-state conditions (19, 29). At isotopic steady state
the Ra of unlabeled substrate in plasma is derived from the plasma
isotope enrichment, expressed as MPE, according to the following
equation: \( R_a = I(MPE_{inf}/MPE_{pl} - 1) \), where \( I \) is the infusion rate of the tracer, \( MPE_{inf} \) is the enrichment of the tracer in the infusate, and
\( MPE_{pl} \) is the tracer enrichment in plasma. The final MPE values
represent the mean of all the MPE measurements during each isotopic
plateau. Isotopic steady-state conditions were regarded as valid when the CV of the MPE values at isotopic plateau was <5%.

At isotopic steady state, leucine flux (Q) is quantified by the following formula: \( Q = S + O = B + I \), where \( S \) is the rate of synthesis of protein from leucine, \( O \) is the rate of oxidation, \( B \) is

### Gaseous Exchange

Oxygen consumption and carbon dioxide production were measured
by indirect calorimetry (Datex Instrumentation Deltatrac, Helsinki,
Finland) over a period of 20 min toward the end of each isotope
infusion study. Average values were taken, with a coefficient of variation (CV) <10%.

### Calculations

Calculations

Whole body leucine and glucose kinetics were calculated by the
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the Ra of unlabeled substrate in plasma is derived from the plasma
isotope enrichment, expressed as MPE, according to the following
equation: \( R_a = I(MPE_{inf}/MPE_{pl} - 1) \), where \( I \) is the infusion rate of the tracer, \( MPE_{inf} \) is the enrichment of the tracer in the infusate, and
\( MPE_{pl} \) is the tracer enrichment in plasma. The final MPE values
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At isotopic steady state, leucine flux (Q) is quantified by the following formula: \( Q = S + O = B + I \), where \( S \) is the rate of synthesis of protein from leucine, \( O \) is the rate of oxidation, \( B \) is
protein breakdown, and I is the dietary intake. Furthermore Q is equal
to Ra (Ra /I and the rate of disappearance (Rd; Rd)
When tracer studies are done in fasting states, leucine flux equals B.
The rate of protein synthesis is calculated by subtracting leucine
oxidation from leucine flux (S /O). Protein balance is calcu-
lated as protein synthesis minus leucine Ra with positive values
indicating anabolism and negative values catabolism. Plasma[1-13C]KIC is used to calculate the flux and oxidation of leucine. The
[1-13C]-KIC is formed intracellularly from leucine and is released into the
systemic circulation. It reflects the intracellular precursor pool enrich-
ment more accurately than plasma leucine itself (20). In the calcula-
tion of leucine oxidation, a correction factor of 0.76 was used in the
fasted state to account for the fraction of 13CO2 released from leucine
but retained within slow turnover rate pools of the body (19).
Under postabsorptive conditions the Ra of glucose represents en-
dogenous production of glucose. During glucose infusion, endoge-
nous Ra of glucose was calculated by subtracting the glucose infusion
rate from the total Ra of glucose.
In the calculation of leucine oxidation in patients receiving the
hyperinsulinemic-normoglycemic clamp, correction was made for the
dilution effect of 13CO2 due to the low 13C content of the glucose
infusion. The correctional factor obtained in two additional clamp
studies without L-[1-13C]leucine was 10%.

Statistical Analysis
The primary end point of the study was the Ra of leucine on the first
postoperative day. Based on previously observed differences in
branched-chain amino acids, we expected a difference of at least 40%
between the two groups. To detect this difference with a type I error
of 5% and a power of at least 90%, nine patients in each group were
required.
Patients’ characteristics and perioperative data were compared
using the unpaired Student’s t-test, chi-square test, and Fisher’s exact
test where appropriate. Blood glucose levels at different time points
between the two groups were compared using linear mixed models.
Unpaired Student’s t-test was used to compare AA concentrations
between the two groups. Paired Student’s test was used to assess the
differences in the AA levels within the same group. The difference in
whole body leucine kinetics, gaseous exchange, and plasma concen-
trations of hormones and substrates between the two groups was
analyzed by using ANOVA for repeated measurements (before and
after surgery). The relationship between Ra leucine and endogenous
Ra glucose was evaluated by the correlation coefficient. All data are
presented as means ± SD unless otherwise specified. Statistical
significance was set as P < 0.05. All P values presented are two-
tailed. All statistical analyses were performed using SAS 9.2 (SAS
Institute).

RESULTS
We enrolled and studied 18 patients with 9 in the control
group and 9 in the insulin group. Baseline characteristics and
surgical data were similar in the two groups (Table 1).
Blood glucose concentrations progressively rose in the control
group without exceeding 10 mmol/l (Fig. 2). Hence no
insulin was required. In the insulin group blood glucose levels were kept in the normoglycemic range between 4.0 and 6.0 mmol/l (Fig. 2). No episode of hypoglycemia (blood glucose < 3.5 mmol/l) was observed.

Isotopic plateaus of plasma $\alpha$-[1-$^{13}$C]KIC, [6,6-$^{2}$H$_2$]glucose, and expired $^{13}$CO$_2$ were obtained in all patients (Figs. 3, 4, and 5). There was no difference in preoperative leucine and glucose kinetics between groups. Postoperative Ra leucine and protein synthesis significantly decreased in patients receiving insulin and glucose, while protein kinetics did not change in the control group (Table 2). There was a nonsignificant decrease in leucine oxidation and balance after surgery in the insulin group. Endogenous glucose production postoperatively decreased in the insulin group and remained unchanged in the control group (Table 2). A positive correlation between endogenous Ra glucose and Ra leucine was observed in patients receiving insulin ($r^2 = 0.385$).

Whole body O$_2$ consumption remained unchanged postoperatively in both groups. Whole body CO$_2$ production and respiratory quotient increased after surgery in the insulin group indicating stimulated glucose oxidation (Table 3). Lactate concentrations increased in both groups to a similar extent after surgery (control group preoperatively 0.9 ± 0.2, postoperatively 1.6 ± 0.8 mmol/l; insulin group preoperatively 0.7 ± 0.3, postoperatively 1.3 ± 0.3 mmol/l). Preoperative plasma insulin (control group 51 ± 24 pmol/l, insulin group 45 ± 17 pmol/l) and cortisol (control group 173 ± 74 nmol/l, insulin group 158 ± 84 nmol/l) were measured.

Table 2. Whole body leucine and glucose kinetics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Insulin</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra leucine, mmol·kg$^{-1}$·h$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>95.0 ± 15.1</td>
<td>105.3 ± 9.8</td>
<td>0.0011</td>
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<tr>
<td>After surgery</td>
<td>97.5 ± 12.9</td>
<td>85.2 ± 9.2</td>
<td>0.0005</td>
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<tr>
<td>Leucine oxidation, mmol·kg$^{-1}$·h$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>16.3 ± 3.2</td>
<td>16.6 ± 3.3</td>
<td>0.0656</td>
</tr>
<tr>
<td>After surgery</td>
<td>16.6 ± 3.2</td>
<td>12.8 ± 4.1</td>
<td>0.0811</td>
</tr>
<tr>
<td>Protein synthesis, mmol·kg$^{-1}$·h$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>78.6 ± 12.3</td>
<td>88.7 ± 8.7</td>
<td>0.0015</td>
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<tr>
<td>After surgery</td>
<td>80.9 ± 10.3</td>
<td>72.4 ± 8.4</td>
<td>0.0005</td>
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<tr>
<td>Leucine balance, mmol·kg$^{-1}$·h$^{-1}$</td>
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<td></td>
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</tr>
<tr>
<td>Before surgery</td>
<td>−16.3 ± 3.2</td>
<td>−16.6 ± 3.3</td>
<td>0.0656</td>
</tr>
<tr>
<td>After surgery</td>
<td>−16.3 ± 3.2</td>
<td>−12.8 ± 4.1</td>
<td>0.0811</td>
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<tr>
<td>Endogenous Ra glucose, µmol·kg$^{-1}$·min$^{-1}$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>9.3 ± 1.2</td>
<td>10.0 ± 1.6</td>
<td>0.0045</td>
</tr>
<tr>
<td>After surgery</td>
<td>12.7 ± 1.2</td>
<td>3.7 ± 2.5</td>
<td>&lt;0.0001</td>
</tr>
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</table>

Values are means ± SD. Ra, rate of appearance. $P$ value was determined by ANOVA for repeated measures. *Probability that values change after surgery. †Probability that values are different between the two groups. ‡Probability that postoperative changes are different between the two groups.
insulin group 131 ± 57 nmol/l) concentrations were similar in the two groups. In the insulin group plasma insulin levels were significantly elevated compared with patients in the control group (3,647 ± 532 pmol/l vs. 52 ± 35 pmol/l, P < 0.001). Plasma cortisol levels increased postoperatively without showing any difference between the two groups (control group 13 of 20 essential (EAA) and nonessential AA (NEAA) decreased to a significantly greater extent than in the control group (Table 4).

Table 4. Plasma AA concentrations

<table>
<thead>
<tr>
<th>Control</th>
<th>Insulin</th>
<th>P Value for Differences</th>
</tr>
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<tbody>
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<td></td>
<td></td>
<td>Between groups at BL*</td>
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<tr>
<td></td>
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<tr>
<td>Histoamine</td>
<td>67 ± 6</td>
<td>58 ± 10</td>
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<tr>
<td>Threonine</td>
<td>122 ± 40</td>
<td>75 ± 26</td>
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<tr>
<td>Valine</td>
<td>237 ± 30</td>
<td>230 ± 42</td>
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<tr>
<td>Methionine</td>
<td>19 ± 5</td>
<td>8 ± 4</td>
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<tr>
<td>Tryptophan</td>
<td>48 ± 7</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>82 ± 10</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>73 ± 9</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>Leucine</td>
<td>143 ± 15</td>
<td>116 ± 27</td>
</tr>
<tr>
<td>Lysine</td>
<td>168 ± 19</td>
<td>120 ± 18</td>
</tr>
</tbody>
</table>

Plasma NEAA concentrations, nmol/l

| Glutamate | 100 ± 69  | 111 ± 50   | −10     | 71 ± 29 | 75 ± 29 | −6 | 0.2562 | 0.0846 | 0.4775 | 0.6074 |
| Asparagine | 38 ± 7    | 20 ± 6    | 48     | 38 ± 14 | 12 ± 8  | 67 | 0.9942 | 0.0289 | <0.0001 | <0.0001 |
| Serine   | 85 ± 16   | 52 ± 8    | 39    | 102 ± 18 | 37 ± 8  | 64 | 0.0500 | 0.0018 | 0.0009 | <0.0001 |
| Glutamine | 627 ± 93  | 420 ± 80  | 33     | 736 ± 122 | 382 ± 107 | 48 | 0.0500 | 0.4195 | <0.0001 | <0.0001 |
| Glycine  | 168 ± 51  | 118 ± 16  | 30     | 187 ± 45 | 119 ± 32 | 36 | 0.4085 | 0.9241 | 0.0151 | <0.0001 |
| Citrulline | 34 ± 10   | 22 ± 3    | 35    | 45 ± 16 | 18 ± 7   | 61 | 0.0994 | 0.1164 | 0.0106 | <0.0001 |
| Arginine | 75 ± 21   | 44 ± 9    | 42    | 67 ± 9  | 30 ± 8   | 55 | 0.3159 | 0.0055 | 0.0032 | <0.0001 |
| Alanine  | 368 ± 91  | 250 ± 84  | 32     | 310 ± 50 | 169 ± 22 | 45 | 0.1125 | 0.0318 | <0.0001 | <0.0001 |
| Tyrosine | 68 ± 14   | 57 ± 17   | 16    | 63 ± 11 | 38 ± 10  | 40 | 0.4058 | 0.0093 | 0.0268 | <0.0001 |
| Ornithine | 74 ± 20   | 42 ± 7    | 44    | 75 ± 24 | 27 ± 10  | 65 | 0.8977 | 0.0034 | <0.0001 | 0.0001 |
| Proline  | 306 ± 140 | 176 ± 87  | 43    | 197 ± 45 | 79 ± 28  | 60 | 0.0689 | 0.0254 | 0.0046 | <0.0001 |

Values are means ± SD. EAA, essential amino acids; NEAA, nonessential amino acids; BL, baseline. %Decrease are calculated from the mean values (% of ICU values decrease from BL). *Unpaired t-test; †paired t-test.

DISCUSSION

The results of the present study demonstrate that insulin, administered at 5 mU·kg⁻¹·min⁻¹ as part of a normoglycemic clamp, reduces whole body protein breakdown by 20% and synthesis by 19% after open heart surgery. This decrease in proteolysis in the presence of supraphysiological hyperinsulinemia (plasma insulin at 3,600 pmol/l) was less pronounced than that previously reported in healthy subjects. Fukagawa et al. (11) showed a 25% lower leucine rate of appearance during the infusion of 30 mU·m⁻²·min⁻¹ insulin and a plasma insulin level at 520 pmol/l, and a 30% inhibition of protein breakdown with the infusion of 400 mU·m⁻²·min⁻¹ insulin and a plasma insulin concentration of 16,600 pmol/l. Tessari et al. (27)
demonstrated comparable suppression of protein breakdown with the administration of insulin at 500 mU·m⁻²·min⁻¹ in normal subjects after overnight fasting.

Similar to the observed change in protein breakdown, whole body protein synthesis decreased in patients receiving insulin, most likely a consequence of reduced substrate supply, i.e., hypoaminoacidemia. As demonstrated in a previous study in cardiac surgery insulin administration led to a 30–60% decrease in the circulating concentrations of most AAs (15). By contrast, patients with lung cancer and healthy young subjects showed increased protein synthesis and positive protein balance if hypoaminoacidemia was avoided by exogenous provision of amino acids (6, 32) suggesting that the anabolic action of insulin requires adequate substrate supply (1, 4). This assumption is supported by studies in burn patients showing anabolic effects of insulin on muscle protein synthesis when iso- or hyperaminoacidemia was maintained (14).

Surgical stress induces transient insulin resistance, which leads to an increase in hyperglycemia and an inability of insulin to inhibit protein synthesis via the phosphatidylinositol-3-kinase (PI3K)/Akt pathway that activates two important ubiquitin protein ligases: Atrogen-1/MAFbx and MURF-1 (26, 28, 31). High-dose insulin, through its membrane receptors, overcomes insulin resistance and thereby decreases whole body protein wasting and lowers plasma AA levels. The lack of circulating AAs is one of the main reasons why protein synthesis is inhibited in the presence of insulin. However, this can be overcome by the simultaneous provision of AAs (2, 6, 14).

Although the present study was not designed to dissect the mechanisms responsible for the metabolic effects of insulin, two additional factors may have contributed to the metabolic effects of HNC: administration of glucose as part of the normoglycemic clamp and strict maintenance of normoglycemia. Patients in the hyperinsulinemic-normoglycemic clamp group received glucose at an average dose of 3.6 ± 0.7 mg·kg⁻¹·min⁻¹. The administration of that amount of glucose inhibits gluconeogenesis and, thus, lowers the need for glucoplastic AAs. In fact, similar to previous reports in surgical patients a positive correlation between protein breakdown and endogenous glucose production was observed in our patients receiving insulin and glucose (24).

Hyperglycemia, per se, has been shown to exacerbate protein catabolism during critical illness and may blunt the anabolic response to feeding. In burn patients the extent of net muscle protein catabolism increased proportionally with the level of blood glucose (13). In contrast active glycemic control was associated with less nitrogen loss in the critically ill (16).

After major cancer surgery, hyperglycemia induced by paren-teral nutrition was accompanied by muscle protein catabolism, while maintenance of normoglycemia restored a neutral protein balance in these patients (3). The mechanism underlying the antitumorative influence of normoglycemia can be attributed to the stimulation of skeletal muscle protein synthesis and the decrease in extramuscular tissue proteolysis (3, 10). Hyperglycemia has been shown to be associated with a 50% greater skeletal leucine oxidation rate when compared with normoglycemia (10). Moreover, hyperglycemia prompts the activation of the enzyme branched-chain α-ketoacid dehydrogenase, which catalyzes the initial irreversible step in the leucine oxidation pathway (25). A greater intracellular leucine avail-

ability caused by the inhibition of leucine oxidation could, therefore, directly stimulate protein synthesis (17).

In summary, we observed that achieving supraphysiological levels of exogenous insulin while maintaining normoglycemia after CABG surgery decreased whole body protein breakdown and synthesis. However, net protein balance remained negative. It remains to be investigated whether anabolism can be achieved in this patient population by the avoidance of hypoaminoacidemia, by simultaneous infusion of amino acids.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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