# Simulated Postaggression Metabolism in Healthy Subjects: Metabolic Changes and Insulin Resistance

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**Postaggression metabolism (PAM) is difficult to study in critically ill patients. The objective of this study was to simulate PAM in healthy subjects to quantify insulin sensitivity under these conditions. Six healthy men (age, 24 ± 1 years; body mass index, 22.0 ± 0.7 kg/m$^2$ [mean ± SE]) received an intravenous (IV) infusion of insulin-counteracting hormones (epinephrine 100 ng/kg/min, glucagon 16 ng/kg/min, hydrocortisone 5 µg/kg/min, and growth hormone [GH]-releasing hormone 50 µg/h) for 4 hours in addition to glucose (270 mg/kg/h). Control experiments used glucose only. In additional experiments, insulin sensitivity was measured by a two-step hyperinsulinemic glucose clamp with and without concomitant hormone infusion (insulin infusion rate, 2.5 and 5.0 mU/kg/min for hormone infusion or 1.0 and 2.5 mU/kg/min for control experiments). Plasma stress hormones reached levels comparable to severe PAM (epinephrine, 1,085 ± 89 pg/mL; glucagon, 1,100 ± 114 pg/mL; cortisone, 1,004 ± 32 ng/mL; and GH, 20.6 ± 6.1 pg/mL) in the hormone infusion experiment. This resulted in hyperglycemia and hyperinsulinemia (steady-state blood glucose, 19.7 ± 0.4 mmol/L; serum insulin, 352 ±8 pmol/L) in comparison to the control experiments with glucose infusion only (maximal blood glucose 7.2 ± 0.8 mmol/L; serum insulin, 110 ± 16 pmol/L). The insulin sensitivity index ($S_I$) was 88% ± 6% lower during hormone infusion (0.6 ± 0.4 mL/min/m$^2$/µU/min) compared with the control experiments (4.5 ± 1.3 mL/min/m$^2$/µU/min). Infusion of insulin-counteracting hormones at high doses allows simulation of the changes in carbohydrate metabolism observed in PAM in healthy subjects. The observed profound decrease in insulin sensitivity explains the hyperglycemia observed in nondiabetic critically ill patients. With this experimental setup, standardized investigations of therapeutic interventions in PAM should be possible.**

PATIENTS WITH SEVERE TRAUMA, burns, or septicemia show an adaptation of their metabolism to severe stress. This so-called postaggression metabolism (PAM) involves considerable changes in carbohydrate metabolism, mainly due to the counter-insulin effect of high levels of stress hormones. In critically ill patients in intensive care settings, blood glucose concentrations can increase to over 17 mmol/L,[1-3] and even high-dose insulin infusions might not be effective to decrease blood glucose in the acute phase of the disease. It has not been clarified as to whether this hyperglycemia is mainly due to a decrease in insulin sensitivity in these patients or, at least partly, to the infusion of glucose under conditions of parenteral nutrition.

There are only a few data on the etiology, pathogenesis, and optimal interventions for postaggression hyperglycemia, mainly because studies in critically ill patients are difficult to perform and might be ethically dubious. Therefore, simulation of acute phases of PAM has been tried in healthy subjects or in experimental animal models by infusing insulin-counteracting hormones.[4-10] However, the validity of these studies is limited, since in most studies only one insulin-counteracting hormone was infused and/or the hormone dose was too small to achieve the serum hormone concentrations observed in PAM in clinical settings. It is well known that the combined blood glucose-increasing effect of simultaneous infusion of several insulin-counteracting hormones is much more pronounced than the effects of single insulin-counteracting hormones.[10]

The goal of our study was (1) to create an experimental setup to simulate PAM in healthy subjects and (2) to quantify changes in insulin sensitivity under these conditions. Therefore, we simulated PAM in healthy subjects by simultaneously infusing four insulin-counteracting hormones (epinephrine, glucagon, hydrocortisone, and growth hormone [GH]). Additionally, glucose was infused to simulate a type of parental nutrition. In further experiments, we quantified the changes in insulin sensitivity by performing euglycemio-hyperinsulinemic glucose clamps with and without concomitant hormone infusion.

## SUBJECTS AND METHODS

Six healthy men (age, 24 ± 1 years; body mass index, 22.0 ± 0.7 kg/m$^2$ [mean ± SE]) participated in the study after a detailed explanation of the study procedure and provision of informed consent. Physical examination of the subjects and other appropriate measures were used to exclude cardiac or any other relevant disease. The study was approved by the local ethics committee.

On 4 different study days, the following protocols were performed: (1) simulation of PAM by intravenous (IV) infusion of stress hormones (Table 1) plus IV glucose to simulate parenteral nutrition, (2) control experiment with IV infusion of glucose only, (3) measurement of insulin sensitivity ($S_I$) using a two-step euglycemic-hyperinsulinemic glucose clamp with IV hormone infusion, and (4) measurement of $S_I$ without hormone infusion.

The experiments began at 8:30 AM after an overnight fast. In protocol 1, a venous cannula was inserted for blood sampling in the left cubital vein, and two more venous lines were inserted in the other arm for infusion of stress hormones and glucose. The hormone infusion consisted of a solution of 2.5 mg epinephrine, 200 mg hydrocortisone, and 0.4 mg glucagon diluted in 50 mL physiologic saline (Table 1). Two milliliters of human albumin (20%) was added to prevent adsorption of the peptides to the surface of the plastic tubing. GH secretion was stimulated by infusion of GH-releasing hormone (200 µg somatoliberin in 20 mL NaCl). After a basal phase of 30 minutes, IV infusion of the stress hormones was started. Sixty minutes later, glucose (270 mg/kg/h; 20% solution) was infused IV to simulate a type of parenteral nutrition. Stress hormones and glucose were infused for 4 hours, respectively, so that the hormone infusion was stopped 1 hour before the glucose. Blood samples for estimation of hormones (serum insulin and infused hormones) and metabolites (ketone bodies, pyruvate, lactate, free fatty

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**Table 1. Composition of the Hormone Infusion and Respective Infusion Rates**

| Hormone | Trade Name | Infusion Rate |
|---|---|---|
| Adrenaline | Suprarenin 1 mg/mL* | 100 ng/(kg · min) |
| Glucagon | Glucagon 1 mg† | 16 ng/(kg · min) |
| Hydrocortisone | Hydrocortison 100‡ | 5 μg/(kg · min) |
| Somatoliberin | Somatobiss (bissendorf peptide)§ | 50 μg/h |

*Hoechst, Frankfurt, Germany.
†Novo-Nordisk, Copenhagen, Denmark.
‡Upjohn, Kalamazoo, MI.
§Bissendorf, Hamburg, Germany.

acids [FFAs], and urea) were drawn at 30-minute intervals, and for estimation of plasma glucose at 15-minute intervals.

To distinguish the metabolic effect of the infused stress hormones from that of the infused glucose, a control experiment (protocol 2) was performed with only glucose infusion at the same dose as in protocol 1 over 4 hours. The study procedure was otherwise identical.

To quantify changes in insulin sensitivity induced by the simulated PAM, euglycemic-hyperinsulinemic glucose clamps were performed. The subjects were connected to a Biostator (Life Science Instruments, Elkhart, IN) by means of three venous cannulas. For continuous measurement of blood glucose, one cannula was inserted into a vein of the left hand. Blood was withdrawn continuously by means of a double-lumen catheter and transferred to the glucose sensor of the Biostator. To establish arterialization of the venous blood, the hand was kept in a heated box with a constant air temperature of 55°C. Glucose, insulin, and the stress hormones were infused into a vein of the contralateral right forearm. After a baseline phase of 30 minutes, the insulin solution (Actrapid; Novo Nordisk, Bagsvaerd, Denmark; 40 U/mL and 5 mL human albumin per 100 mL physiologic saline) was infused at a rate of 2.5 mU/kg/min for 120 minutes, and afterward at 5.0 mU/kg/min for a further 120 minutes. During the experiments, the glucose infusion rate (GIR) necessary to neutralize the blood glucose-lowering effect of the insulin was registered. Blood glucose was kept constant at 5.0 mmol/L. The dosing and composition of the stress hormone infusion were identical to protocol 1. Blood samples for estimation of hormone concentrations and plasma glucose were drawn at 30-minute intervals from the third cannula in the cubital vein of the left arm. During the last 30 minutes of both insulin infusion phases (steady-state phase I and II), blood samples were drawn at 10-minute intervals. To estimate the influence of the stress hormones on insulin sensitivity, no hormones were infused during protocol 4 (insulin infusion rate, 1.0 and 2.5 mU/kg/min).

For calculation of the insulin sensitivity index ($S_I$), the difference in the GIR during the two steady-state phases (delta-GIR, corrected for body surface) was divided by the difference in the established insulinemia (delta-Ins) at the established glycemia (BG):

$$S_I = \frac{\text{delta-GIR}}{\text{delta-Ins} \times \text{BG}} \text{ (mL/min/m}^2\text{/μU/mL)}.$$

### *Laboratory Methods*

Plasma glucose concentrations were determined by a kinetic glucose oxidase method (Beckman Glucose Analyser II; Beckman Instruments, Munich, Germany). Serum insulin (Phadebas; Pharmacia, Uppsala, Sweden) and plasma glucagon (antibody 04A; generous gift from Professor R.H. Unger, Dallas, TX) were determined by radioimmunoassay. The serum cortisol level was measured radioimmunologically by a competitive protein-binding method.[11] GH was determined by radioimmunoassay by a double-antibody method.[12] Plasma catecholamine levels were measured radioenzymatically.[13] Plasma concentrations of β-hydroxybutyrate and acetoacetate, pyruvate, and lactate were determined by enzymatic methods.[14,15] FFAs were determined by gas chromatography.[16] Urea content was measured by the urease reaction (Reflotron; Boehringer, Mannheim, Germany).

### *Statistical Methods*

Results are presented as the mean ± SE. For statistical analysis, the paired *t* test was used. To compare non–normally distributed variables, a nonparametric test (Wilcoxon matched-pair signed-rank test) was used. A $P$ value less than .5 was considered a statistically significant difference (two-sided test).

## RESULTS

Infusion of the hormone mixture (protocol 1) led to a severalfold increase of serum hormone concentrations above the basal values (glucagon, fivefold; epinephrine, 18-fold; and cortisone, fivefold) and GH increased from basal values less than the detection level to greater than 20 μg/mL (Fig 1). During stress hormone infusion, these levels remained fairly constant. Within 30 minutes after the end of infusion, epinephrine, glucagon, and GH nearly reached basal values again. Due to the lower plasma clearance rate of cortisol, concentrations decreased considerably but did not return to basal levels again. We defined the last 30 minutes of hormone infusion (150 to 180 minutes after the start of glucose infusion) as the steady-state period. Hormone concentrations achieved during this period were used for comparison to the level seen during PAM in clinical situations (Table 2).

In the control experiments (protocol 2) with glucose infusion only, hormone levels decreased to less than basal values during the experiments (Fig 1). Thus, significantly higher hormone concentrations were reached during the steady-state phase on the study day with stress hormone infusion versus the control experiment ($P < .01$ for epinephrine, glucagon, and cortisone; $P < .05$ for GH).

Hormone infusion led to an immediate increase in blood glucose above baseline (5.2 mmol/L). The combined effects of the hormone and glucose infusion led to a maximal glycemia of 20.2 ± 1.0 mmol/L 180 minutes after start of glucose infusion (Fig 2; steady-state phase, 19.7 ± 0.4 mmol/L). After termination of the stress hormone infusion but with ongoing glucose infusion, blood glucose decreased to 14.6 ± 1.1 mmol/L at the end of the experiments. During the control experiments, a minor increase in blood glucose to maximal values of 7.2 ± 0.8 mmol/L was observed 75 minutes after the start of glucose infusion (Fig 2).

During the first 60 minutes with infusion of stress hormones, serum insulin remained at basal values despite increasing glycemia. Serum insulin concentrations started to increase just with the beginning of glucose infusion (Fig 2). Maximal insulinemia (542 ± 79 pmol/L) was reached 210 minutes after the start of glucose infusion; thereafter, insulin levels slowly decreased despite ongoing glucose infusion. In the control experiments, maximal insulinemia was considerably lower (110 ± 16 pmol/L, $P < .05$; Fig 2 and Table 2).

Infusion of stress hormones led to a change in lactate and pyruvate levels parallel to that of blood glucose, ie, there was an increase until the end of hormone infusion, followed by a decrease until the end of the experiment (Fig 2). Lactate

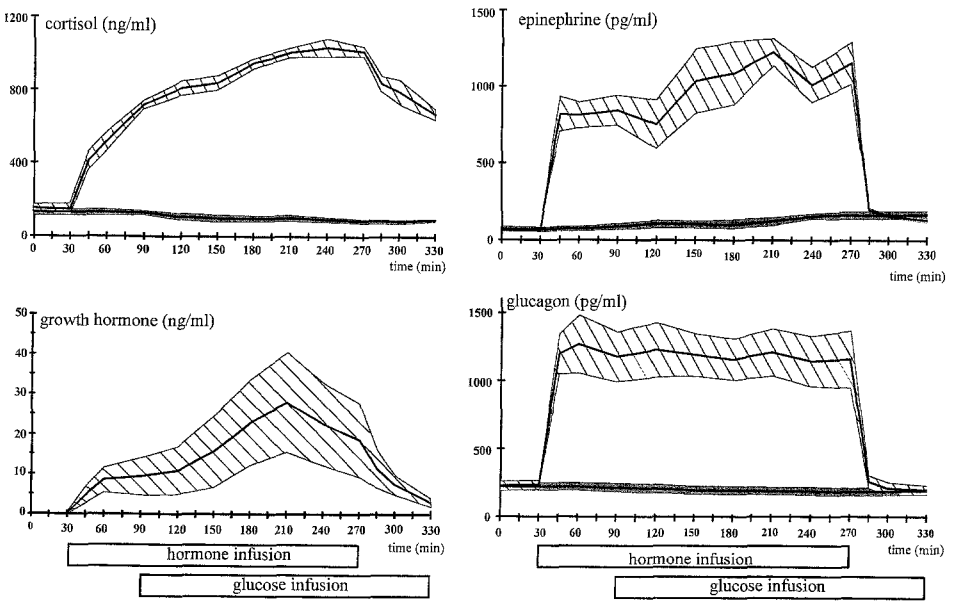


**Fig 1. Established hormone concentrations during simulated PAM (lines with hatched overlay, ±1 SE - range) in comparison to the control experiment without the hormone mixture infusion (lines with gray overlay, SE - range). GH concentrations were below the detection limit during the control experiment without hormone infusion, and therefore these data are not shown.**

increased more than pyruvate in the first 60 minutes of hormone infusion, resulting in a decrease of the pyruvate to lactate ratio. In the control experiments with glucose infusion only, lactate and pyruvate levels did not change significantly. β-Hydroxybutyrate and FFA concentrations increased immediately after the start of hormone infusion (Fig 2; basal, 36 ± 3 mmol/L; maximal, 143 ± 50 mmol/L). After beginning of the glucose infusion, these decreased to concentrations of 20 ± 4 mmol/L at the end of the experiment, ie, below basal values. Glucose infusion alone (protocol 2) did not result in a significant change of β-hydroxybutyrate concentrations, but, in a continuous decrease of FFA concentrations, which were 50% less than basal values at the end of the experiment (Fig 2). Serum urea concentrations remained nearly constant in all of the protocols. Infusion of the four insulin-counteracting hormones resulted in a decrease of the $S_I$ of 88% (4.5 ± 1.3 mL/min/m²/μU/mL for control experiments and 0.6 ± 0.4 mL/min/m²/μU/mL for hormone infusion, $P < .001$; Table 3). During the euglycemic-hyperinsulinemic glucose clamp with hormone infusion, serum insulin concentrations of 125 ± 24 μU/mL (insulin infusion at 2.5 mU/kg/min) and 364 ± 128 μU/mL (insulin infusion at 5.0 mU/kg/min) were achieved. In the control experiments without hormone infusion (and with lower insulin infusion rates, 1.0 and 2.5 mU/kg/min), serum insulin concentrations were 50 ± 10 and 131 ± 26 μU/mL.

## DISCUSSION

The aim of this study was to investigate changes in carbohydrate metabolism under conditions of a simulated acute-phase PAM, established by simultaneous infusion of four insulin-counteracting hormones. Blood glucose concentrations of greater than 19.5 mmol/L reached here in the steady-state phase by combined hormone and glucose infusion are comparable to those observed under clinical conditions.[1,2] In intensive care units, blood glucose concentrations in critically ill patients between 10 and 17 mmol/L were regarded as acceptable, even in view of the osmotic problems induced by glucosuria.[3] The insulinemia observed in our study was also comparable to that observed in patients in PAM who receive parental nutrition.[17-19] Further evidence that simulation of PAM is feasible by a combined infusion of stress hormones is the similarity between the delayed increase of insulinemia after glucose infusion shown in our experiments (60 to 120 minutes) and that observed in patients after surgery or after acute myocardial infarction

**Table 2. Metabolic Changes Induced by Infusion of Four Insulin-Counteracting Hormones to Simulate PAM and Concomitant Glucose Infusion (protocol 1) and During the Control Experiment With Glucose Infusion Only (mean ± SE)**

| | Simulated PAM | | | Control | | |
|---|---|---|---|---|---|---|
| Parameter | Basal Phase | Steady State | End of Experiment | Basal Phase | Steady State | End of Experiment |
| Blood glucose (mmol/L) | 5.2 ± 0.2 | 19.7 ± 0.4 | 14.6 ± 1.1 | 4.8 ± 0.1 | 6.1 ± 0.2 | 6.2 ± 0.3 |
| Insulin (pmol/L) | 41 ± 4 | 352 ± 48 | 449 ± 53 | 36 ± 3 | 98 ± 10 | 95 ± 25 |
| Epinephrine (pg/mL) | 61 ± 1.7 | 1,085 ± 89 | 133 ± 15 | 60 ± 2.2 | 68 ± 1.6 | 75 ± 1.7 |
| Cortisol (ng/mL) | 136 ± 17.5 | 1,004 ± 32 | 598 ± 78 | 130 ± 37 | 89 ± 9 | 91 ± 8 |
| Glucagon (pg/mL) | 238 ± 19.8 | 1,100 ± 114 | 207 ± 29 | 221 ± 21 | 190 ± 20 | 199 ± 29 |
| Growth Hormone (ng/mL) | 0.2 ± 0.1 | 20.6 ± 6.1 | 3.1 ± 0.9 | 0.8 ± 0.05 | 0.2 ± 0.00 | 0.8 ± 0.03 |
| Pyruvate (μmol/L) | 86 ± 7 | 188 ± 20.2 | 166 ± 17 | 75.4 ± 5.6 | 72.4 ± 4.3 | 66.6 ± 7.7 |
| Lactate (mmol/L) | 1.4 ± 0.1 | 5.5 ± 0.3 | 3.0 ± 0.2 | 1.23 ± 0.09 | 1.27 ± 0.08 | 1.18 ± 0.08 |
| FFA (μmol/L) | 374 ± 39 | 440 ± 54 | 149 ± 23 | 583 ± 41 | 265 ± 14 | 294 ± 72 |
| β-Hydroxybutyrate (μmol/L) | 35.7 ± 2.5 | 29.5 ± 0.5 | 19.7 ± 3.6 | 35.6 ± 4.1 | 30.6 ± 1.1 | 29.5 ± 2.0 |
| Urea (mg/dL) | 32.5 ± 1.3 | 29.5 ± 0.5 | 19.7 ± 3.6 | 33.8 ± 1.1 | 30.6 ± 1.1 | 29.5 ± 2.0 |

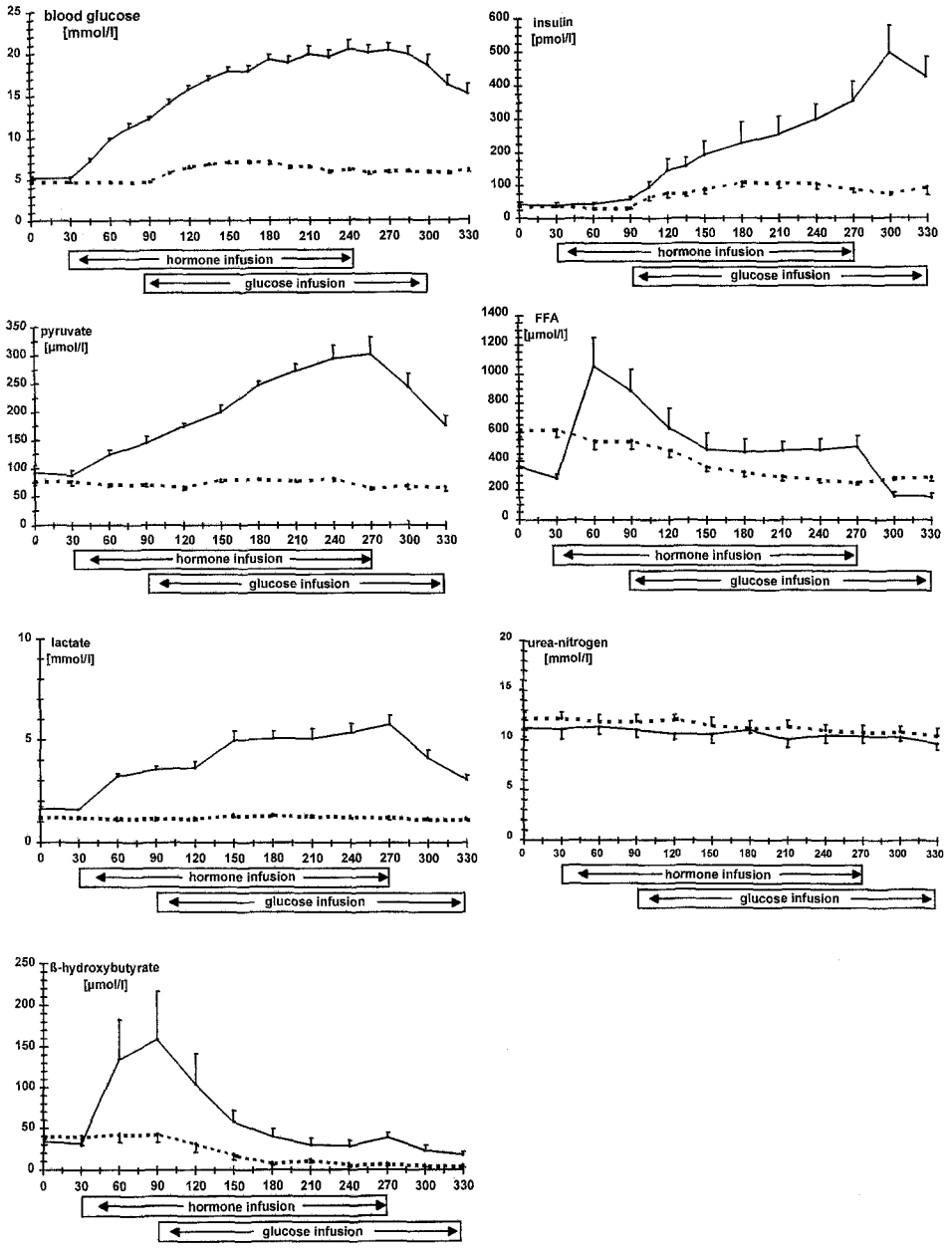


**Fig 2. Changes in metabolic parameters (mean ± SE) during experiments with simulated PAM in comparison to the control experiments.**

following IV glucose infusion.[20] This phenomenon, which is even observed with extreme blood glucose concentrations as associated with open-heart surgery and hemodilution, is probably caused by a profound adrenergic suppression of endogenous insulin secretion.[5,21,22] Within the concept of the protein-sparing effect of IV glucose infusion in PAM, the addition of pharmacological doses of insulin seems useful, since endogenous insulin secretion is still not pronounced because of adrenergic suppression (despite the profound stimulation of glucagon on insulin secretion).

The suppression of insulin secretion during the first few hours after a severe trauma is associated with an increase in FFAs and blood glucose.[23] Only after several hours, the massive hyperglycemia results in an increase of insulin secretion.[23] Accordingly, in our experiments hormone infusion by itself did not result in an immediate increase of insulin secretion. Only after the infusion of glucose was started and after prolonged and pronounced hyperglycemia did insulin levels increase. The increase of lactate and pyruvate levels—as a sign of unsuppressed glycolysis (as well as epinephrine-stimulated muscle glycogenolysis)—is also indicative of a relative insulin deficiency. The initial decrease of the pyruvate to lactate ratio points to a predominance of anaerobic glycolysis in the acute phases of PAM. The latter in association with the observed increase of FFAs and β-hydroxybutyrate is also a well-known sequelae of relative insulin deficiency.[24,25] The increase in the pyruvate to lactate ratio can also be explained by a preferentially more rapid uptake of pyruvate versus lactate by the liver, which would be responding to the gluconeogenic stimulus of epinephrine (and later, cortisol and GH). Nevertheless, taking the marked decrease in insulin sensitivity into account, it seems plausible that these metabolic changes are at least partly due to relative insulin deficiency.

The concentrations of FFA, urea, pyruvate, lactate, and

**Table 3. $S_I$ in the Six Healthy Men With and Without IV Infusion of Hormones**

| Patient No. | Without Hormone Infusion | With Hormone Infusion | Reduction (%) |
|---|---|---|---|
| 1 | 3.67 | 0.41 | 89 |
| 2 | 3.61 | 0.26 | 93 |
| 3 | 6.98 | 1.07 | 85 |
| 4 | 4.26 | 0.89 | 79 |
| 5 | 5.06 | 0.67 | 87 |
| 6 | 3.34 | 0.21 | 94 |
| Mean | 4.49 | 0.59 | 88 |

β-hydroxybutyrate in our simulated PAM model were similar to values reported in the literature for critically ill patients.[17,26-29] However, it should be pointed out that the data in the literature are scanty and somewhat conflicting, which might be due to the wide variability of medical conditions and clinical interventions associated with PAM.[30] The fact that in our experiments blood glucose levels after stress hormone infusion increased before the glucose infusion was started indicates that predominantly stress hormones (rather than the IV glucose given to patients for purposes of parental nutrition) are of major importance for the hyperglycemia observed in critically patients. This is indicated as well by the much higher glucose concentrations achieved with hormone infusion in comparison to the control experiments with glucose infusion only. It has been propagated especially in patients with respiratory insufficiency to replace parenteral glucose solutions with solutions of amino acids, lipids, or glucose substitutes in order to keep the respiratory quotient low.[31] However, no data have been published as to whether avoidance of IV glucose will indeed reduce hyperglycemia associated with PAM. Future studies are required to critically evaluate the impact of glucose infusion on hyperglycemia. Our model offers the opportunity to perform those studies as well in healthy subjects.

The observed dramatic deterioration of insulin sensitivity in the simulated PAM experiments is in accordance with a causal role of insulin resistance in the development of hyperglycemia in clinical settings, explaining that even massive doses of insulin are often not effective to decrease hyperglycemia in critically ill patients. We did not determine whether the combined hormone infusion caused the typical changes in electrolytes and intravascular volume associated with PAM (eg, increased potassium excretion, intravascular volume contraction, etc.). However, the presence of these effects, which all contribute to insulin resistance, is highly probable since they are typical effects of the high doses of epinephrine used here.

The aim of our study was to simulate the acute effect of PAM on carbohydrate metabolism. It must be noted that this experimental model with an infusion protocol of only 6 hours is not designed to simulate long-term changes or to increase protein catabolism to the degree observed in bona fide PAM. Protein catabolism seems to be (at least partly) mediated by other hormones, particularly cytokines,[32-35] which are not included in the model. However, for ethical reasons, it seems impossible to extend the simulation of PAM in healthy subjects to a high degree of protein catabolism.

In summary, simulation of the acute derangements in carbohydrate metabolism observed in critically ill patients by high-dose combined infusion of the insulin-counteracting hormones glucagon, cortisol, GH, and epinephrine in healthy subjects is possible. The experimental model presented here can be used to simulate different degrees of severity of PAM in healthy subjects and to study the effects of medical interventions, eg, various modes of parental nutrition (eg, addition or substitution of glucose with amino acids, triglycerides, or glucose substitutes such as Xylit), under standardized conditions.

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