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Influence of insulin on glucose metabolism and energy expenditure in septic patientsZdenek Rusavy¹, Vladimir Sramek², Silvie Lacigova³, Ivan Novak⁴, Pavel Tesinsky⁵ and Ian A Macdonald⁶¹Head, Metabolic Group in Plzen, Department of Medicine I, Charles University Hospital, Plzen, Czech Republic²Doctor, Intensive Care Medicine in Brno, Department of Anesthesiology and Intensive Care, University Hospital, Brno, Czech Republic³Doctor, Diabetology and Nutrition Unit in Plzen, Department of Medicine I, Charles University Hospital, Plzen, Czech Republic⁴Head, Intensive Care Unit in Plzen, Department of Medicine I, Charles University Hospital, Plzen, Czech Republic⁵Doctor, Nutrition Unit, Department of Medicine I, Charles University Hospital, Plzen, Czech Republic⁶Professor and Dean of Medical School, Department of Physiology and Pharmacology, QMC Nottingham, UKCorresponding author: Zdenek Rusavy, rusavy@fnplzen.cz

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Critical Care 2004, **8**:R213-R220 (DOI 10.1186/cc2868)This article is online at: <http://ccforum.com/content/8/4/R213>© 2004 Rusavy *et al.*; licensee BioMed Central Ltd. This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL.**Abstract****Introduction** It is recognized that administration of insulin with glucose decreases catabolic response in sepsis. The aim of the present study was to compare the effects of two levels of insulinaemia on glucose metabolism and energy expenditure in septic patients and volunteers.**Methods** Glucose uptake, oxidation and storage, and energy expenditure were measured, using indirect calorimetry, in 20 stable septic patients and 10 volunteers in a two-step hyperinsulinaemic (serum insulin levels 250 and 1250 mIU/l), euglycaemic (blood glucose concentration 5 mmol/l) clamp. Differences between steps of the clamp (from serum insulin 1250 to 250 mIU/l) for all parameters were calculated for each individual, and compared between septic patients and volunteers using the Wilcoxon nonpaired test.**Results** Differences in glucose uptake and storage were significantly less in septic patients. The differences in glucose oxidation between the groups were not statistically significant. Baseline energy expenditure was significantly higher in septic patients, and there was no significant increase in either step of the clamp in this group; when comparing the two groups, the differences between steps were significantly greater in volunteers.**Conclusion** A hyperdynamic state of sepsis leads to a decrease in glucose uptake and storage in comparison with healthy volunteers. An increase in insulinaemia leads to an increase in all parameters of glucose metabolism, but the increases in glucose uptake and storage are significantly lower in septic patients. A high level of insulinaemia in sepsis increases glucose uptake and oxidation significantly, but not energy expenditure, in comparison with volunteers.**Keywords:** energy expenditure, euglycaemic clamp, glucose uptake, insulin, sepsis**Introduction**

Many of the host responses to sepsis are similar to those seen after major injury, with increased energy expenditure (EE), enhanced protein catabolism [1-3], increased use of lipids as oxidative fuel, and impaired glucose metabolism [4]. Septic patients are insulin resistant; they have increased hepatic glu-

cose production, reduced peripheral glucose utilization and increased lipolysis [5].

The causes of the metabolic changes that accompany sepsis are not clear. It seems that neither stress hormones (glucagon, catecholamines, corticosteroids, growth hormone) nor high

levels of gluconeogenic precursors (lactate, alanine, glycerol) are the main cause of this syndrome [6,7]. Endotoxin or the cytokines tumour necrosis factor- α and interleukin-1 can induce a state of insulin resistance when they are infused continuously. It is possible that, because of this insulin resistance, the cytokines may redistribute glucose away from skeletal muscle to ensure adequate nutrient supply to inflammatory cells [7-9].

The postinjury metabolic changes characterized by insulin resistance are severe but fully reversible, and high doses of insulin together with glucose can have an important protein sparing effect in critically ill patients [10-12]. After surgery dogs have elevated hepatic glucose production, which can be suppressed by exogenous insulin. By contrast, postoperative sepsis in dogs is associated with more marked elevation in gluconeogenesis, with low response to exogenous insulin [13]. Dahn and coworkers [14] found that patients with a combination of trauma and sepsis had a hepatic glucose production almost six times higher (with absolute values of 16.6 $\mu\text{mol/kg per min}$) than that in patients with comparable trauma alone. In these traumatized septic patients, gluconeogenesis was responsible for 93% of hepatic glucose production, as compared with 87% in the injured patients and 46% in healthy individuals. In septic cancer bearing patients, resistance to insulin's effect on plasma free fatty acid turnover (an index of lipolysis) is more pronounced than resistance to its inhibiting effect on endogenous glucose production or its stimulating effect on tissue glucose uptake [15]. The extent of injury suffered by patients based on the injury severity score correlated only with their EE, but not with hepatic glucose production, glycaemia, glucose oxidation, glucose turnover, or nonoxidative glucose utilization [12]. Shaw and Wolfe [2] also found no correlation between injury severity score and glucose production in 33 critically ill patients suffering from blunt trauma.

Thus, sepsis combined with trauma is associated with more marked insulin resistance and disturbance of glucose metabolism than is trauma alone [13,14]. It is unclear whether this is a simple additive effect on glucose metabolism or whether there is some interaction, with trauma enhancing the effect of sepsis. Thus, it would be worthwhile to study septic patients who do not have associated trauma. We therefore conducted the present study to evaluate the action of insulin on glucose metabolism and associated thermogenesis in sepsis uncomplicated by trauma. Specifically, we studied the effect of two levels of insulinaemia (250 mIU/l in step 1 and 1250 mIU/l in step 2) in the presence of a euglycaemic clamp on glucose metabolism (glucose uptake, oxidation, storage) and EE in septic patients.

Methods

Twenty septic nondiabetic patients were studied over a 2.5-year period (Table 1). The patients were in a hyperdynamic state of sepsis 3–7 days following admission to the intensive

Table 1

Characteristics of the septic patients

Characteristic	Details
Number of patients	20
Gram-positive/Gram-negative sepsis	16/4
Duration from admission to start of study (days)	3.8 (2.5–5.4)
APACHE II score	20.2 (18.3–22.4)
Parenteral nutrition (kcal/kg per 24 hours)	20.2 (16.3–24.2)
Enteral nutrition (kcal/kg per 24 hours)	6.3 (3.2–10.1)
Insulin requirement/24 hours (IU/24 hours)	56 (48–74)

Values are expressed as number or as median (interquartile range). APACHE, Acute Physiology and Chronic Health Evaluation.

care unit, after their acute state had been stabilized and vasoactive drugs stopped. All of the patients underwent mechanical ventilation and required parenteral nutrition (all-in-one system), together with low doses of enteral nutrition. All required a continuous intravenous infusion of insulin to maintain their blood glucose concentration below 10 mmol/l.

Severity of illness was assessed in each patient immediately before the study using the Acute Physiology and Chronic Health Evaluation II scoring system [16,17], and empirical criteria for the diagnosis of sepsis [18-20] were used. For inclusion in the study, each patient was required to satisfy at least four of the criteria presented in Table 2, together with a suspicion of infection. The causes of sepsis at admission were bronchopneumonia ($n = 5$), cholangitis ($n = 2$), urosepsis ($n = 3$), catheter-related sepsis ($n = 3$), and sepsis as a complication of treatment for acute haemoblastosis, mostly after bone marrow transplantation and without a clear focus ($n = 7$). These criteria were applied because the method used in the study to measure glucose parameters and EE (indirect calorimetry) requires patients in a hyperdynamic phase of sepsis to be relatively stable, both haemodynamically and in terms of respiratory status, and not receiving vasoactive treatment. Stability during the study was defined as not requiring a change in ventilatory setting, no need for large volumes of fluids and/or vasoactive drug treatment, and no change of body temperature ($\pm 1^\circ\text{C}$). The main reasons for excluding a patient from the study were haemodynamic instability and changes in pH, which can invalidate the indirect calorimetry method. Inclusion and exclusion criteria for the patients are summarized in Table 2. Also included was a control group of healthy volunteers, who were not obese and had no family history of diabetes.

The study was conducted in the medical intensive care unit at Charles University Hospital, Plzen, Czech Republic. The study protocol was approved by the local university ethical committee, and written informed consent was obtained from volunteers and the patient's family before they were entered into the study. All investigations were conducted between 07:00 and

Table 2**Inclusion and exclusion criteria**

Inclusion criteria		Exclusion criteria	
Temperature (°C)	>38.5 or <36	FiO ₂	>0.7
White cell count (×10 ⁹ /l)	>12 or <3.5	Mean blood pressure (mmHg)	<75
Mean CI (l/min per m ²) and SVR (dynes/s·m ⁻⁵)	CI > 4.5, SVR (dynes/s·m ⁻⁵) <800	Mean CI (l/min per m ²)	<3
Platelets count (×10 ⁹ /l)	<100	Changes in serum buffer base	> 10% in the past 12 hours
Blood cultures	Positive	Increasing trend in serum lactate level	in the past 12 hours
Clinical evidence of sepsis	Positive	Haemofiltration or haemodialysis	

CI, cardiac index; FiO₂ = partial oxygen pressure in inspired air; SVR, systemic vascular resistance.

13:00 hours. Patients did not receive any nutritional support or intravenous insulin for at least 9 hours before the study. Crystalloids were infused as indicated clinically, together with established drug treatments. A multilumen central venous catheter and arterial catheter, already positioned in the patients, were used for infusion of all test substances and blood sampling, respectively. Each patient's height was measured using a tape measure with the patient in the supine position. Weight was measured using a bed weighing system (Datex II; Datex-Ohmeda Division Instrumentarium Corp., Helsinki, Finland) and body mass index was calculated.

Volunteers were recruited from among the hospital staff and their relatives. They were advised to consume a weight-maintaining diet containing at least 200 g/day of carbohydrates for 3 days before the study. None was receiving any medication. Arterialized venous blood was sampled using a cannula inserted retrogradely into a dorsal hand vein, with the hand resting in a warm air box (55–60°C) to 'arterialize' the blood [21,22]. A second cannula was placed in an antecubital vein for infusion of all test substances.

The clamp technique was as follows. A two-step insulin clamp, each step being 120 min in duration, was performed using a primed continuous insulin infusion (Humulin R; Ely Lilly, Pennsylvania, Penn. USA). In step 1 insulin was infused, using a syringe pump (Braun, Melsungen AG, Melsungen, Germany), to achieve a steady serum insulin level (IRI) of 250 mIU/l. In the second step insulin was infused at a fivefold higher rate to achieve an IRI of 1250 mIU/l. During both steps, 20% glucose (Infusia Horastev, Horastev, Czech Republic) was infused at a variable rate using an infusion pump (Braun) to maintain the arterial blood glucose concentration at 5 mmol/l (i.e. a glucose clamp) [23]. During the clamp, blood glucose concentration was measured every 5 min (HemoCue glucose analyser; HemoCue Ltd, Ängelholm, Sweden) and the rate of glucose infusion adjusted to maintain the blood glucose concentration at 5 mmol/l. During the steady state periods of each step in the clamp, the blood glucose concentration was maintained within 5% of the target value (i.e. 5 mmol/l), which ensured the pres-

ence of glycaemic stability during periods when insulin sensitivity was being assessed.

Throughout the baseline period and for the last 40 min of each step of the clamp (i.e. steady state periods), oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured using indirect calorimetry (Deltatrac II; Datex-Ohmeda Division Instrumentarium Corp., Helsinki Finland), in canopy mode for healthy volunteers and in respiratory mode for mechanically ventilated patients. EE and respiratory quotient (RQ) were calculated (RQ = VCO₂/VO₂). Protein oxidation was calculated from urinary urea excretion rate corrected for changes in the body urea pool using standard formula. Amounts of VCO₂ and VO₂ involved in protein oxidation (VCO₂prot and VO₂prot) were then subtracted from the total values measured using indirect calorimetry to yield the nonprotein RQ (i.e. nonprotein VCO₂/nonprotein VO₂). Peripheral glucose utilization (mg/kg per min) was calculated as a rate of exogenous glucose infused in each steady state period of the clamp, and the mean for each step was calculated [23]. Whole body glucose oxidation (mg/kg per min) was calculated from the nonprotein RQ. Nonoxidative glucose disposal, which equals glucose storage in healthy individuals, was calculated as the difference between glucose utilization and oxidation.

Blood samples for substances other than glucose were taken at the end of the baseline period and twice (at 5 and 15 min) in each steady state period, and means were calculated. C-peptide and 'free' serum insulin (IRI) were determined by radioimmunoassay (Serono Diagnostics, Milan, Italy), triglycerides and lactate using the enzymatic method (analyzer Hitachi 717; ROCH Diagnostics, Mannheim, Germany), free fatty acids using the photometry method (Hitachi 717), and alanine by the ion exchange chromatography method using an analyser (Mikrotechna, Praha, Czech Republic). Blood gases were measured using a blood gas analyzer (ABL 520™ Radiometer, Copenhagen, Denmark), urea in urine by an enzymatic method using an analyzer (Hitachi 717), serum potassium using a flame photometer (Corning, London, UK) and osmolality using an osmometer (Knauer, Berlin, Germany).

Statistical analysis

Data are expressed as mean \pm standard deviation. Statistical analyses were conducted to determine whether distributions were normal, and paired t-tests were used for within-group and Wilcoxon's test was used for between-group comparisons. Because of the relatively small numbers of measurements, in which the type of distribution cannot be determined with full certainty, we opted not to assume normality of the distributions. Therefore, nonparametric tests were used for the evaluation (Wilcoxon's test: paired for within groups and non-paired for between groups). The distribution of values is described by medians and interquartile ranges. For easier interpretation of the comparison of the effects of insulin in septic patients and volunteers, for each parameter we opted to calculate the differences between steps 2 and 1, and between step 1 and baseline for each individual, and we tested the differences in these calculated values between the groups.

Results

All patients and volunteers remained stable and completed the study. A comparison of septic patients and volunteers at baseline, before the clamp protocol, is provided in Table 3. Measured insulin concentrations in plasma (IRI) were significantly higher in septic patients than in volunteers at baseline. In step 1 of the clamp the measured IRI (median [interquartile range]) was 197.5 (184.6–225.8) mIU/l in septic patients and in volunteers it was 212.4 (182.3–226.2) mIU/l. In step 2 of the clamp the measured IRI in septic patients was 1941.4 (1894.7–2356.8) mIU/l and in volunteers it was 2200.2 (1886.3–2451.6) mIU/l. The difference between groups in measured IRI was not statistically significant at either step.

Findings regarding glucose metabolism in septic patients and volunteers are shown in Tables 4,5,6. Glucose uptake (Table 4) increased significantly within both groups; however, in the comparison of differences (step 1 minus step 2) between septic patients and volunteers it increased significantly more in volunteers. Similar results were obtained for glucose storage (Table 6). Glucose oxidation increased within both groups, but comparison of differences between groups was not statistically significant. The EE findings in septic patients and volunteers are shown in Table 7. In septic patients the differences between baseline, step 1 and step 2 were not statistically significant. In volunteers there was a significant increase in EE between baseline and step 1, and between step 1 and step 2. EE at baseline was significantly greater in septic patients than in volunteers. The differences between septic patients and volunteers in step 1 minus baseline, and step 2 minus step 1 were also statistically significant; specifically, the increase in EE was lower in septic patients in step 1 and in step 2. The RQ findings are presented in Table 8. RQ increased in both groups, and the increases were statistically significant, but findings in the comparison between groups were not significant.

At step 1 plasma alanine did not change in comparison with baseline in septic patients (411.2 [320.3–511.6] and 398.3 [352.4–489.5] μ mol/l, respectively), but at step 2 it decreased significantly (252.4 [186.7–276.7] μ mol/l; $P < 0.01$). For the statistical evaluation the Wilcoxon paired test was used. There was a decreasing trend in free fatty acids in septic patients during the study (0.37 [0.22–0.57] μ mol/l at baseline, 0.26 [0.19–0.44] μ mol/l at step 1, and 0.24 [0.18–0.38] μ mol/l at

Table 3

Comparison of septic patients and volunteers at baseline

Parameter	Septic patients	Volunteers	Wilcoxon test
Number of patients	20	10	-
BMI (kg/m ²)	26 (24.6–27.8)	22 (21–26.6)	NS
Age (years)	65 (52–68)	39 (22–61)	$P < 0.05$
Energy expenditure (kcal/24 hours)	2116 (1880–2455)	1657 (1513–1826)	$P < 0.01$
Respiratory quotient	0.79 (0.77–0.85)	0.83 (0.82–0.86)	NS
Glycaemia (mmol/l)	6.2 (5.25–8.21)	4.6 (4.4–5.2)	$P < 0.001$
Insulinaemia (mIU/l)	37.2 (28.3–75.1)	12.7 (9.3–28.4)	$P < 0.05$
HbA _{1c} (%)	4.9 (4.5–5.1)	4.8 (4.6–5.2)	NS
Lactate (mmol/l)	1.1 (1.0–1.3)	0.9 (0.8–1.2)	NS
Buffer base (mmol/l)	23.6 (22.7–24.1)	24.1 (22.1–24.2)	NS
Potassium (mmol/l)	4.3 (4.1–4.6)	3.9 (3.8–4.3)	NS
Triglycerides (mmol/l)	2.15 (2.00–2.73)	1.91 (1.82–2.54)	NS
C-peptide (nmol/l)	0.9 (0.6–1.4)	1.1 (0.7–1.9)	NS

Values are expressed as number or as median (interquartile range). BMI, body mass index; NS, not significant.

Table 4**Glucose uptake in septic patients and volunteers**

Parameter	Septic patients	Volunteers	Significance (between groups) ¹
Glucose uptake in step 1	3.61 (2.31–5.58)	11.0 (9.74–12.85)	-
Glucose uptake in step 2	6.4 (5.25–8.21)	17.2 (14.05–19.20)	-
Significance (within groups) ² : step 1 versus step 2	$P < 0.001$	$P < 0.01$	-
Difference between step 2 and step 1	2.5 (0.93, 4.47)	5.3 (4.14, 6.40)	$P < 0.01$

Values are expressed as median (interquartile range). ¹By Wilcoxon's nonpaired test. ²By Wilcoxon's paired test.

Table 5**Glucose oxidation in septic patients and volunteers**

Parameter	Septic patients	Volunteers	Significance (between groups) ¹
Glucose oxidation in step 1	2.82 (1.66–4.02)	3.4 (3.00–4.00)	-
Glucose oxidation in step 2	3.73 (2.73–4.97)	4.5 (4.30–5.65)	-
Significance (within groups) ² : step 1 versus step 2	$P < 0.01$	$P < 0.01$	-
Difference between step 2 and step 1	0.71 (-0.26–0.72)	1.22 (0.30–1.75)	NS

Values are expressed as median (interquartile range). ¹By Wilcoxon's nonpaired test. ²By Wilcoxon's paired test.

Table 6**Glucose storage in septic patients and volunteers**

Parameter	Septic patients	Volunteers	Significance (between groups) ¹
Glucose storage in step 1	0.4 (-0.4 to +3.19)	7.6 (5.80–9.50)	-
Glucose storage in step 2	2.3 (0.92–4.16)	11.6 (9.70–13.60)	-
Significance (within groups) ² : step 1 versus step 2	$P < 0.01$	$P < 0.01$	-
Difference between step 2 and step 1	1.51 (0.24–2.69)	4.0 (2.95–5.30)	$P < 0.01$

Values are expressed as median (interquartile range). ¹By Wilcoxon's nonpaired test. ²By Wilcoxon's paired test.

Table 7**Energy expenditure in septic patients and volunteers**

Parameter	Septic patients	Volunteers	Significance (between groups) ¹
EE at baseline	2116 (1880–2455)	1657 (1513–1826)	++
EE in step 1	2213 (1914–2475)	1850 (1731–2079)	-
Significance (within groups) ² : baseline versus step 1	NS	$P < 0.01$	-
Difference between step 1 and baseline	35.00 (-110 to +260)	217.75 (101.58–309.08)	+
EE in step 2	2179 (1911–2179)	2019 (1907–2230)	-
Significance (within groups) ² : step 1 versus step 2	NS	$P < 0.05$	-
Difference between step 2 and step 1	-12 (-61 to +153)	154 (-21 to +288)	-

Values are expressed as median (interquartile range). ¹By Wilcoxon's nonpaired test. ²By Wilcoxon's paired test. EE, energy expenditure; NS, not significant; ++, $p < 0.05$; +, $p < 0.01$.

Table 8**Respiratory quotient in septic patients and volunteers**

Parameter	Septic patients	Volunteers	Significance (between groups) ¹
RQ at baseline	0.79 (0.77–0.85)	0.83 (0.82–0.86)	NS
RQ in step 1	0.91 (0.85–0.97)	0.90 (0.85–0.96)	-
Significance (within groups) ² : baseline versus step 1	$P < 0.01$	$P < 0.01$	-
Difference between step 1 and baseline	0.08 (0.04–0.17)	0.09 (0.05–0.11)	NS
RQ in step 2	0.97 (0.89–1.01)	0.97 (0.96–0.98)	
Significance (within groups) ² : step 1 versus step 2	$P < 0.05$	$P < 0.01$	
Difference between step 2 and step 1	0.03 (0.00–0.08)	0.03 (0.02–0.08)	NS

Values are expressed as median (interquartile range). ¹By Wilcoxon's nonpaired test. ²By Wilcoxon's paired test. RQ, respiratory quotient; NS, not significant.

step 2), although the differences were not statistically significant.

In comparison with findings at baseline, potassium, lactate, urea, base excess and osmolality in both steps of the clamp were not statistically different. In volunteers all results were normal; only free fatty acids exhibited a trend similar to that in septic patients, but this was not statistically significant.

Discussion

Many trials have attempted to manipulate the metabolic response to critical illness. Van den Berghe and coworkers [24] normalized the blood glucose level (4.4–6.1 mmol/l) in intensive care patients by using insulin and glucose. In comparison with conventionally treated septic patients, this method decreased mortality (4.6% versus 8.0%), decreased the incidence of multiple organ failure with a proven septic focus, and decreased renal dysfunction and need for red cell transfusion. In another study of diabetic patients who had suffered a myocardial infarction [25], intensive insulin treatment was performed to achieve a blood glucose concentration below 11 mmol/l. This resulted in a significant improvement in patient outcomes, including later mortality. These studies were limited to patients undergoing cardiac surgery or who had suffered acute myocardial infarction, and therefore the results cannot be extrapolated without further study to patients with other types of critical illness. It is impossible to differentiate between the direct effects of infused insulin and the effects of preventing hyperglycaemia. Insulin might play a role that is independent of its effect on glycaemia. Insulin has been shown to inhibit tumour necrosis factor- α [26], increase glucose uptake, and produce a significant protein anabolic effect [27].

Glucose uptake

In healthy people, during the steady state period of a hyperinsulinaemic glucose clamp, the rate of exogenous infusion of glucose (corrected for changes in body extracellular glucose

space and urinary glucose excretion) is equal to the rate of glucose utilization because endogenous glucose production is suppressed by hyperinsulinaemia [23]. The suppressive effects of both insulin and glucose on endogenous glucose production are altered in critically ill patients. This would lead to an underestimation of the rate of total glucose utilization of up to 3 mg/kg per min [28,29]. Another study conducted in septic patients [30] indicated that hepatic glucose production would be suppressed completely at a serum insulin of 240 mIU/l. Nevertheless, because the glucose uptake was markedly lower in septic patients than in volunteers in the present study, it is clear that the insulin resistance of sepsis hindered glucose utilization. The increased glucose uptake in extreme nonphysiological levels of insulinaemia in our study suggests that insulin resistance may be overcome, at least partially, in sepsis. We can conclude that an increase in insulinaemia in sepsis further increases glucose utilization.

Glucose oxidation and storage

In some human studies glucose oxidation was unaffected by sepsis [15] and in others it was decreased [2]. In our study glucose oxidation decreased by a smaller extent than glucose utilization in septic patients in comparison with volunteers, but this was not statistically significant. If glucose oxidation is presented as a percentage of glucose uptake, then in the present study it was 74% at step 1 and 57% at step 2 in septic patients, and in volunteers it was only 32% and 29%, respectively. There is no marked deficiency in the ability to oxidize glucose during critical illness [31], but glucose storage is markedly limited in sepsis [32]. We found that there was limited glucose storage at both steps of the clamp in septic patients in comparison with volunteers, which indicates that insulin resistance in sepsis affects glucose storage to a greater degree than it affects glucose oxidation. Similar results were also presented by Saeed and coworkers [32]. We can conclude that glucose oxidation, and to some extent glucose storage, can be increased in septic patients by increasing the

insulin dosage, but it appears that the deficiency in glucose storage cannot be attenuated to any significant degree by a high insulin dosage.

Energy expenditure

The indirect calorimetry measurements not only provide information on substrate oxidation but also allow whole body EE to be estimated. In multiple organ failure there is no relationship between severity of illness and EE, and so EE cannot reliably be predicted and must be measured using indirect calorimetry [33]. Measurement of EE in ventilated patients with multiple organ failure have consistently yielded a wide range of values (50–200% of the estimated value, calculated on the basis of age, sex, height and weight) [33]. In the present study the baseline EE of the volunteers and septic patients were measured and are shown in Tables 3 and 5. It is clear that the septic patients had elevated baseline values, along with greater variation between individual patients, than did the volunteers. During the clamp, EE increased only marginally in septic patients by 4.6% in step 1 and by 6.3% in step 2, as compared with EE at baseline. This contrasted with a significant increase in EE in volunteers by 13.7% in step 1 and by 23.8% in step 2, as compared with EE at baseline. In volunteers insulin stimulation of glucose metabolism is accompanied by an increase in EE (thermogenic effect of glucose). In patients with multiple organ failure, such an increase in EE does not occur [3]. Brandi reported similar results from patients after major uncomplicated surgery and severely ill patients suffering from blunt trauma [1]. In the present study relatively stable EE was maintained in septic patients despite increased glucose utilization and oxidation. It is possible that the increased energy costs associated with increased glucose utilization were offset by the simultaneous decrease in other energy consuming metabolic processes (e.g. gluconeogenesis, protein catabolism).

Other metabolites

The decreasing levels of alanine during step 2 of the clamp in septic patients suggest a possible decrease in protein catabolism. However, there was no significant decrease in free fatty acids in septic patients, indicating an inability of these insulin concentrations to overcome the insulin resistance in adipose tissue [5].

Limitations of the study

The volunteers were younger, and had lower fasting glycaemia and EE. Increased age decreases insulin sensitivity, and the older age of the septic patients could have influenced our findings to some extent. Measured insulin concentrations in plasma were significantly higher in septic patients than in volunteers at baseline (Table 2). In both steps of the clamp, the measured insulinaemia was lower in septic patients but the difference was not statistically significant. These differences between insulinaemias were small and could be due to laboratory errors that may occur when measuring extreme insulin concentrations, and probably do not influence the results. Esti-

mation of substrate metabolism from urine sampling and indirect calorimetry has its limitations [34]. We assumed that any error is the same for septic patients as for volunteers, because the former were stable with regard to acid-base balance and were receiving nutritional support. Despite the fact that the Deltatrac monitor has been validated for indirect calorimetry measurements in intensive care units, calculation of carbohydrate and fat utilization on the basis of nonprotein RQ (i.e. without the use of isotopes) can lead to errors if the rates of gluconeogenesis and ketogenesis are changing [34].

Conclusion

The hyperdynamic state of sepsis, in comparison with healthy volunteers, leads to decreases in glucose uptake, oxidation and storage. During the hyperinsulinaemic, euglycaemic clamp experiments, an increase in insulinaemia significantly increased glucose uptake, oxidation and storage in both groups. The lower glucose uptake in septic patients was mainly due to an impairment in glucose storage. Increasing levels of insulinaemia in patients with sepsis increased glucose uptake significantly, but not EE, in comparison with volunteers. Further studies are needed to establish whether insulin may have a positive effect in sepsis by increasing the rate of glucose oxidation with simultaneous reduction in protein catabolism [35].

Key messages

The lower glucose uptake in septic patients is mainly due to impairment in glucose storage. The increasing level of insulin in euglycaemic clamp leads to an increase in glucose uptake mainly due to the oxidation of glucose.

The increase of glucose uptake and oxidation of glucose at the increasing insulinaemia doesn't lead to any statistically significant increase of the energy expenditure in septic patients

Competing interests

None declared.

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