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Severity of insulin resistance in critically ill medical patients

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Abstract

Critical illness is characterized by a hypermetabolic state associated with increased mortality, which is partly ascribed to the occurrence of hyperglycemia caused by enhanced endogenous glucose production and insulin resistance (IR). Insulin resistance is well described in patients after surgery and trauma. However, it is less clearly quantified in critically ill medical patients. In this clinical cohort study, IR (M value) was quantified in 40 critically ill medical patients and 25 matched, healthy controls by isoglycemic hyperinsulinemic clamps after an overnight fast on the day after admission to a medical intensive care unit. Energy and substrate metabolism were measured by using indirect calorimetry in the patients before and during the clamp. The severity of illness was assessed by the acute physiology and chronic health evaluation (APACHE) III score. M values of critically ill medical patients were significantly lower compared with healthy controls (2.29 ± 1.0 and 7.6 ± 2.9 mg/kg per minute, respectively; $P < .001$) and were closely related to APACHE III scores ($r = -0.43$, $P < .01$), body mass index ($r = -0.41$, $P < .01$), and resting energy expenditure ($r = 0.40$, $P < .05$). The M value was not associated with age, basal glucose concentrations, and respiratory quotient, and it did not differ among patients with various admission diagnoses. In conclusion, insulin sensitivity was found to be reduced by 70% in critically ill medical patients. The severity of IR was associated with the severity of illness, body mass index, and resting energy expenditure, but not with substrate oxidation rates. In addition, the severity of IR did not vary among patients with different admission diagnoses.

1. Introduction

Insulin resistance (IR) is a clinical state characterized by impaired glucose disposal in the presence of either normal or elevated serum insulin concentrations [1,2]. This phenomenon, which can be quantified by the isoglycemic hyperinsulinemic clamp technique [3], is regarded partly as a natural response to assure the availability of limited carbohydrate stores for glucose-dependent and insulin-independent vital organ systems [4]. Insulin-sensitive tissues concurrently use fat instead of glucose to meet energy requirements [4,5]. Nonetheless, development of hyperglycemia has been shown to be associated with increased morbidity and mortality [6-10]. An achievement of normoglycemia in critically ill patients after surgery resulted in a 43% reduced mortality rate compared with patients treated with standard care [8]. However, a less clear benefit of metabolic control has been found for critically ill medical patients [10].

Glucose abnormalities associated with IR have been described in septic as well as in critically ill patients after surgery and trauma [11-16]. Black et al have shown a 51% increase in IR by using a 1 mU/kg per minute clamp in 6 patients after injury [12]. Such an increase in IR has also been found in postsurgical patients with abdominal or pelvic sepsis after the need for prolonged hospital treatment [13]. The severity of IR depended on the magnitude of the operation in postsurgical patients, and it has been shown that the severity of illness was the dominant factor associated with glucose intolerance in the perioperative period [14,15]. For septic patients after severe burn injury, Shangraw and colleagues [16] showed that insulin-mediated maximum glucose uptake was markedly impaired, whereas

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IR of burn patients without sepsis was comparable to that in bed-rest controls. Thus, most of the studies were focused on critically ill patients after surgery and injury. Data on critically ill medical patients during the early course of their illness are scarce.

We have, therefore, performed the present study to quantify the severity of IR on the day after the admission to a medical intensive care unit (ICU) and to identify possible determinants affecting IR in critically ill medical patients. In addition, the influence of IR on energy and substrate metabolism of the patients was evaluated.

2. Materials and methods

Forty critically ill medical patients subsequently admitted to our medical ICU and 25 healthy controls matched for age, sex, and body mass index (BMI), were included into this clinical cohort study (Table 1). For the patients, ICU admission diagnoses were documented (Table 2). The severity of their illness was assessed by the acute physiology and chronic health evaluation (APACHE) III score [17]. Patients aged younger than 18 years, patients with HIV infection and preexisting diabetes mellitus, and patients who had recent surgical procedures, thermal injury, and trauma before ICU admission were excluded from the study. Furthermore, critically ill medical patients artificially ventilated with an inspired oxygen fraction greater than 60% on the study day were excluded because performance of indirect calorimetry is not valuable in such patients [18].

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki of 1975 as revised in 1983, and it was approved by the Institutional Review Board of the University of Vienna. Patients' consent was obtained according to the demand of the Institutional Review Board.

2.1. Clamp study

In both critically ill patients and healthy controls, IR was quantified by a 1 mU/kg per minute isoglycemic hyperinsulinemic clamp technique [3]. Therefore, an insulin infusate (Insulin Novo Nordisk Actrapid HM, NovoNordisk, Denmark) was prepared in isotonic saline, to which 2 mL of the patient's blood per 50 mL infusate was added to prevent absorption of insulin by plastic surfaces [3].

Table 1
Characteristics of critically ill medical patients and healthy controls

	Patients	Controls
Sex, F/M, n	12/28	7/18
Age (y)	56 ± 14	52 ± 6
BMI (kg/m^2)	26.9 ± 6.2	26.0 ± 4.0
Fasting BG (mg/dL)	114 ± 26**	89 ± 8
Clamp BG (mg/dL)	114 ± 28**	89 ± 8
Fasting insulin (μU/mL)	18.8 ± 18.6*	6.8 ± 3.2
Ss-insulin (μU/mL)	63.6 ± 32*	72.7 ± 15.8
M value (mg/kg per minute)	2.29 ± 1.0**	7.6 ± 2.9
MCR (mL/m^2 per minute)	1465 ± 1923**	635 ± 135
M/I	4.59 ± 4.5**	11.0 ± 4.3

BG indicates blood glucose concentration; Ss-insulin, serum insulin concentrations during steady state of the clamp.

* $P < .05$ compared with healthy controls.

** $P < .001$ compared with healthy controls.

Table 2
Admission diagnoses of critically ill medical patients, n (%)

Respiratory insufficiency	10 (25)
CPR	9 (23)
Sepsis	6 (15)
Neurologic disorders	5 (13)
Cardiogenic shock	5 (13)
Primary MOF	5 (13)

CPR indicates cardiopulmonary resuscitation; MOF, multiple organ failure.

All clamp studies started at 0800 hours after an overnight fast on the day after admission to the medical ICU. After a baseline period of 30 minutes, during which basal blood glucose concentrations were determined, insulin infusion was started in a primed continuous manner to raise and maintain plasma insulin concentrations to a new plateau level. Therefore, a 10-minute priming infusion was followed by a constant infusion for 110 minutes as described previously [3]. During insulin administration, blood glucose concentration was maintained at its basal concentration by variable rates of a glucose infusion (Glucose 20%, Fresenius Kabi Pharma, Graz, Austria). Blood glucose concentrations were monitored at bedside by using the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Anaheim, CA). Blood samples for insulin were drawn at baseline as well as 60, 90, and 120 minutes thereafter. These samples were centrifuged, and the supernatant was frozen at −80 °C until analyzed doubly using a liquid radioimmunoassay (Pharmacia-Upjohn, Uppsala, Sweden).

IR (M value) was expressed as milligrams per kilogram per minute and was calculated by using the glucose infusion rate, the space correction, and eventual urinary glucose losses according to DeFronzo et al [3]. In addition, the metabolic clearance rate (MCR) of insulin and the index of tissue sensitivity to insulin (M/I) were calculated as previously described [3]. The MCR of insulin was expressed as milliliters per meter squared per minute, and it was calculated by using the insulin infusion rate (microunits per meter squared per minute) and the increase in plasma insulin concentrations above basal (microunits per milliliter) [3]. Body surface area was assessed by using the formula of DuBois and DuBois [19]. The M/I ratio was multiplied by 100 for convenience of data expression.

2.2. Indirect calorimetry

Resting energy expenditure (REE) and substrate oxidation rates were measured during the baseline period by indirect calorimetry after an overnight fast as described previously [20]. A second measurement was done during the last 30 minutes of the isoglycemic hyperinsulinemic clamp.

REE as well as fat and carbohydrate oxidation rates were calculated according to Ferrannini [21] and Frayn [22]. Protein oxidation was estimated from the urea nitrogen appearance rate, which was calculated from the urine urea

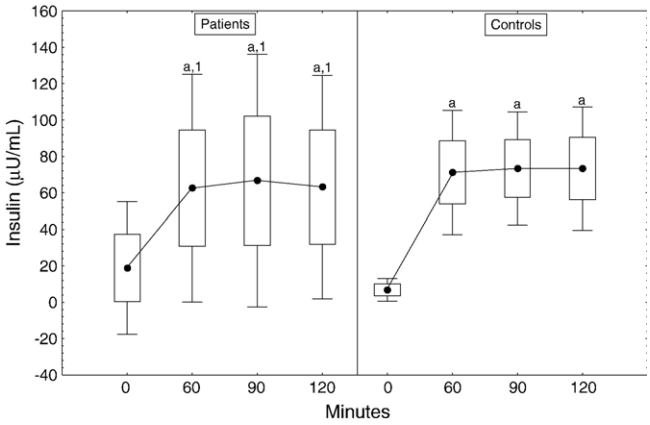

Fig. 1. Box-and-whisker plot of serum insulin concentrations (microunits per milliliter) of critically ill medical patients and healthy controls at baseline (0) as well as during the isoglycemic hyperinsulinemic clamp (60, 90, and 120 minutes). Box indicates SD; whiskers, 95% confidence interval. [a]$P < .05$ compared with baseline values, [1]$P < .001$ compared with corresponding insulin values of healthy controls.

nitrogen concentration and the urine volume per day as described elsewhere [23]. REE was expressed as kilojoules per kilogram of body weight.

2.3. Statistical analysis

Results are presented as mean ± SD. A P value less than .05 was considered as significant. Comparison of data between groups was performed by using the Mann-Whitney U test. Differences in gender distribution were assessed by the χ^2 test. To evaluate differences of variables before and during the clamp procedure, a Wilcoxon test of paired data was used. Correlation between variables was calculated using the Spearman correlation coefficient (r). To show differences of M values between patients with different admission diagnoses as well as of serum insulin and glucose concentrations across time, a repeated-measures analysis of variance (ANOVA) was used. If the results were found to be statistically significant, a Scheffe test was used for post hoc testing. STATISTICA for WINDOWS (StatSoft, Tulsa, OK) was used for statistical analysis.

Table 3
Metabolic studies of the critically ill medical patients at baseline and during the clamp

	Baseline	Clamp
VO_2 (mL/min)	266 ± 64	263 ± 70
VCO_2 (mL/min)	204 ± 47	218 ± 55*
RQ	0.77 ± 0.06	0.83 ± 0.06*
NPRQ	0.76 ± 0.09	0.86 ± 0.14*
REE (kJ/kg)	94.9 ± 18.0	96.5 ± 21.9
UNP (g/d)	11.0 ± 6.4	9.8 ± 10.8
GOX (mg/kg per minute)	0.61 ± 0.9	1.58 ± 0.9*
FOX (mg/kg per minute)	1.16 ± 0.5	0.85 ± 0.5*
POX (mg/kg per minute)	0.60 ± 0.4	0.51 ± 0.4

UNP indicates urea nitrogen appearance rate; GOX, glucose oxidation rate; FOX, fat oxidation rate; POX, protein oxidation rate.

* $P < .01$ compared with baseline.

3. Results

Critically ill medical patients (n = 40) and healthy controls (n = 25) did not differ in sex distribution, age, and BMI (Table 1). ICU admission diagnoses of the patients are shown in Table 2. The severity of illness assessed by the APACHE III score was 77 ± 23.

Blood glucose and insulin concentrations at baseline as well as during steady state of the clamp procedure for both patients and healthy controls are presented in Table 1. The isoglycemic hyperinsulinemic clamp caused a significant increase of the serum insulin concentrations in patients and healthy controls (Table 1, Fig. 1). The clamp procedure revealed severe IR as indicated by a significantly decreased M value in our patients compared with healthy controls. The MCR of insulin was found to be higher and the M/I ratio was lower in patients than in healthy controls (Table 1).

Baseline metabolic characteristics of the patients in the postabsorptive state are shown in Table 3. Respiratory quotient (RQ) and nonprotein RQ (NPRQ) were found to be low (ie, <0.8) in our patients. During the period of hyperinsulinemia, oxygen consumption (VO_2), REE, and urea nitrogen appearance rate did not change. Carbon dioxide production (VCO_2), RQ, and NPRQ and, therefore, glucose and fat oxidation changed significantly compared with baseline values. Protein oxidation remained unchanged during the clamp compared with baseline values (Table 3, Fig. 2). Twelve (30%) patients showed negative glucose oxidation rates before and none of the patients during the clamp procedure.

There was a negative correlation between M values and APACHE III scores in critically ill patients ($r = -0.43$, $P < .01$). M values were associated with REE before ($r = 0.40$, $P < .05$) and during the clamp procedure ($r = 0.36$, $P < .05$). In addition, M values correlated with the BMI of our patients ($r = -0.41$, $P < .01$). The M values were not associated with age and basal blood glucose concentrations

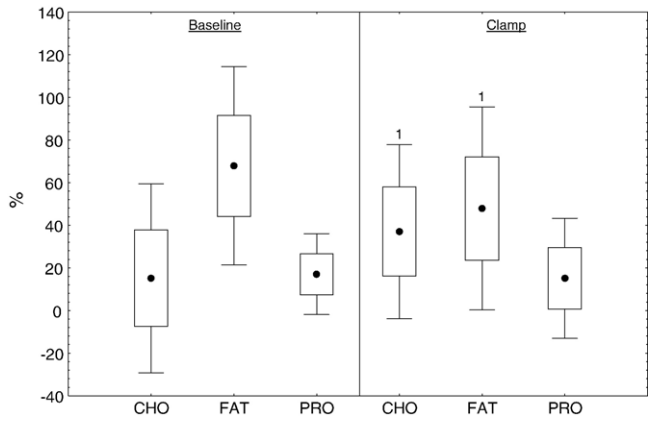

Fig. 2. Substrate oxidation rates for carbohydrates (CHO), fat (FAT), and protein (PRO) expressed as a percentage of REE of critically ill medical patients at baseline and during the clamp procedure. Data are expressed as box-and-whisker plots. Box indicates SD; whiskers, 95% confidence interval. [1]$P < .001$ compared with corresponding values at baseline.

as well as with V_{O_2}, V_{CO_2}, RQ, NPRQ, urea nitrogen appearance rate, and substrate oxidation rates obtained before and during the isoglycemic hyperinsulinemic clamp. In addition, no difference was found for the M values of our patients with different ICU admission diagnoses.

4. Discussion

This clinical cohort study revealed severe IR in critically ill medical patients on the day after ICU admission. IR was associated with severity of illness, BMI, and REE of the patients. No association was found between IR and basal glucose concentrations as well as substrate oxidation rates. In addition, IR did not differ between patients with different ICU admission diagnoses.

IR is defined as unresponsiveness of anabolic processes to the normal effects of insulin, and it has been postulated that many metabolic abnormalities associated with critical illness are related to a loss of tissue sensitivity to insulin [1,2]. In critically ill surgical patients, insulin sensitivity has been shown to be decreased by 50% compared with healthy controls [12,13]. In our critically ill medical patients, insulin sensitivity was found to be reduced by 70% compared with healthy controls, indicating severe impairment of insulin-mediated glucose uptake by all body tissues. The impairment of insulin sensitivity was not related to the underlying causes for ICU admission but to the severity of illness as assessed by the APACHE III classification system, an objective scoring measure of the severity of disease widely used in intensive care [17]. Thus, the development of IR was no disease-specific reaction but a prevailing response to critical illness. This relationship between severity of IR and severity of illness could be explained by an increased production of serum cytokines because it has been shown that cytokine concentrations increased along with the severity of illness, and it has been suggested that these key components of the systemic inflammatory and stress response induce IR [2,24]. Moreover, serum cytokines increase serum concentrations of counterregulatory hormones during critical illness. It has been suggested that IR arises secondarily to the counter-regulatory hormone response [25].

IR impairs the major glucoregulatory functions of insulin including stimulation of glucose transport, inhibition of gluconeogenesis, and stimulation of net glycogen synthesis as well as glucose oxidation [26]. Consequently, glucose oxidation was decreased in our patients as reflected by a low RQ, although serum insulin concentrations were increased. Such decreased glucose oxidation rates are in accordance with other studies performed in critically ill patients [16,18]. Administration of insulin accompanied by supplementary glucose infusion during the clamp caused an increase of the calculated glucose oxidation rates. However, the observed increase of glucose oxidation could also be an expression of diminished gluconeogenesis. The rates of glucose oxidation assessed by indirect calorimetry are the algebraic sum of glucose oxidation and glucose synthesis, and it has been shown that a 1 mU/kg per minute clamp was able to completely suppress endogenous glucose production [21,27]. In addition, the severity of IR did not correlate with the calculated glucose oxidation rates. Thus, IR has a minor impact on glucose oxidation per se, but it could impair glycogen synthesis, the major pathway of glucose disappearance. This assumption is in accordance with the findings of Thorell et al [11], who showed that insulin administration during total parenteral nutrition in trauma patients resulted in reduced endogenous glucose production, whereas whole-body glucose disposal remained unchanged.

Insulin administration during the clamp induced an increase of serum insulin concentrations in our patients and healthy controls. Nonetheless, serum insulin concentrations were lower in patients compared with healthy controls. This difference was ascribed to the increased MCR of insulin found in our critically ill medical patients. This increased MCR of insulin is in contrast to studies undertaken previously in noncritically ill patients, in which MCR of insulin was *slower* when IR was increased [28,29]. This discrepancy could be explained by alterations of blood flow in the splanchnic region. Insulin uptake and insulin degradation occur in all insulin-sensitive tissues; however, the liver is the primary site of insulin clearance [30]. Liver tissue extracts approximately 50% of the plasma insulin flowing through the organ [31]. Because hepatic blood flow has been shown to be increased in critically ill patients [32], the increased MCR of insulin found in our critically ill medical patients could therefore reflect an adaptation of hepatic function to critical illness.

Along with alterations in glucose metabolism, fat was the major oxidative fuel at baseline, as shown previously for critically ill patients [23,33]. This finding revealed an increased reliance on lipid as an oxidative substrate during the postabsorptive state. Increased fat oxidation indicated an apparent resistance to the antilipolytic effect of insulin already at baseline. During the clamp procedure fat oxidation decreased; nonetheless, fat remained the major oxidative fuel to meet energy requirements. Thus, the impairment of the antilipolytic effect of insulin in adipose tissue could be more pronounced than the effect of IR on endogenous glucose production. This assumption is in accordance with the findings of Chambrier et al [27], who showed that plasma fatty acids were not totally suppressed during pharmacological insulin stimulation in septic patients.

REE remained unchanged during isoglycemic hyperinsulinemia, indicating that the combined administration of glucose and insulin did not induce nutrient-mediated thermogenesis. REE was influenced by the severity of IR before as well as during the clamp procedure. REE decreased if IR deteriorated. The association between REE and the severity of IR could be explained by the impaired glucose storage because glucose storage is an energy-consuming process [34].

In the general population, IR is associated with distinct disorders such as obesity, which can be quantified by the

increase of the BMI [35,36]. For obese subjects a linear relationship between IR and BMI has been established [37]. BMI was also related to the severity of IR in our critically ill medical patients; thus, IR was more pronounced in patients with higher BMI values. Hence, body mass remained a relevant cause for IR during critical illness.

Because we measured IR in the early course of critical illness, it can be assumed that IR occurred very rapidly in critically ill medical patients. This finding corresponds to experimental studies in human volunteers in which IR developed within a few hours after an administration of gram-negative bacterial lipopolysaccharide [25].

In conclusion, IR was found to be severe in critically ill medical patients. The occurrence of IR was independent of the underlying cause for ICU admission, and it was detected early during the course of critical illness. IR was associated with the severity of illness, BMI, and REE of the patients, but it did not affect substrate oxidation rates.

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