Insulin Resistance and Hyperinsulinemia in Patients With Chronic Congestive Heart Failure

Giuseppe Paolisso, Stefano De Riu, Giuseppe Marrazzo, Mario Verza, Michele Varricchio, and Felice D’Onofrio

Congestive heart failure is a condition associated with increased plasma norepinephrine levels. Moreover, norepinephrine has been recently demonstrated to affect glucose homeostasis by decreasing insulin sensitivity. In the present study, eight patients suffering from chronic congestive heart failure and 10 healthy age- and body mass index-matched subjects were submitted to both an oral glucose tolerance test (OGTT, 75 g) and a euglycemic hyperinsulinemic glucose clamp. During the 360 minutes of the glucose clamp, insulin was infused at three different rates (25, 50, and 100 mU/kg/h), while D-1H glucose infusion allowed determination of glucose turnover. In basal conditions, patients versus controls had similar plasma glucose (5.2 ± 0.1 vs 4.9 ± 0.2 mmol/L; P = NS), but higher plasma insulin (125.7 ± 9.2 vs 25.7 ± 3.3 pmol/L; P < .01), norepinephrine (5.39 ± 0.13 vs 1.47 ± 0.22 nmol/L; P < .001), and free fatty acid (FFA) (927 ± 79 vs 792 ± 88 pmol/L; P < .05) levels. In patients, basal plasma norepinephrine correlated with FFA levels (r = .65, P < .025). After loading glucose, plasma glucose and insulin levels were still significantly higher in patients than controls. Euglycemic hyperinsulinemic glucose clamp produced a lower insulin-mediated inhibition of endogenous (hepatic) glucose production (HGP) and a greater increase in both glucose disappearance rate (Rd) and glucose metabolic clearance rate (gMCR) in patients than in controls during the first two insulin infusion rates (25 and 50 mU/kg/h). By contrast, these differences disappeared during the highest insulin infusion rate (100 mU/kg/h). Insulin-mediated decrease in plasma FFA levels was also lower in patients than controls. In conclusion, our study shows that in patients suffering from chronic congestive heart failure, an insulin-resistant state seems to occur as a consequence of a contemporary increase in plasma norepinephrine levels.

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Previous reports have shown that plasma norepinephrine levels are increased in patients with heart failure, and that basal plasma norepinephrine levels are considerably higher in patients with severe symptoms than in those with mild ones. In addition, norepinephrine levels may be looked at as a guide to the prognosis in those patients. In regard to glucose homeostasis and its regulation by counterregulatory hormones, epinephrine and glucagon, rather than norepinephrine, have always been considered to play a major role.

Nevertheless, Marangou et al have recently demonstrated that moderate elevation in plasma norepinephrine levels reduces glucose tolerance and insulin sensitivity, while it significantly increases lipolysis and free fatty acid (FFA) levels.

In light of this knowledge, the present study aimed to investigate the possible existence of an insulin-resistant state in patients suffering from congestive heart failure in whom a significant increase in plasma norepinephrine level was found.

MATERIALS AND METHODS

Subjects

Eight patients suffering from congestive chronic heart failure were studied. All patients were in a stabilized clinical phase of the disease, not receiving treatment during the 5-day period before study, and hospitalized to monitor cardiac functions and to prevent an acute reappraisal of the disease. Diagnosis of chronic congestive heart failure was made after complete clinical examination and confirmed by instrumental analyses according to Jafri et al.

All patients had been previously treated by digitalis and nonthiazidic diuretics and had hepatic and renal functions in the upper limit of the normal range (as documented by routine laboratory tests) and nonsignificantly different from those detected in control subjects. Ten healthy age- and body mass index-matched volunteers chosen among subjects concurring sedentary life served as a control group. None of the subjects (patients and controls) had any family history of diabetes and all were on diets containing 250 g of carbohydrates per day. After a complete explanation of the potential risks, all subjects gave informed consent to participate to the study, which was approved by the ethical committee of our institution. More detailed data concerning the subjects are summarized in Table 1.

Experimental Design

The subjects were studied in the morning, starting at 8:00 to 9:00 AM after a 12-hour overnight fast. They were placed on bed rest and kept supine throughout the experiment. On day 1, basal samples for plasma counterregulatory hormone levels determination was drawn, and an oral glucose tolerance test (OGTT, 75 g) was performed. On day 2, a euglycemic hyperinsulinemic glucose clamp was performed. In the latter test, 18-gauge polyethylene catheters were inserted into the antecubital vein of each arm: one was used for infusions and the other permitted insertion of a double-lumen catheter for continuous blood withdrawal using the BioStator (Life Science Instruments, Miles Laboratories, Elkart, IN). A superficial dorsal hand vein was cannulated in anterograde fashion with a 19-gauge butterfly needle and kept patent by a slow infusion of saline solution. The hand was kept warm by an electric lamp for intermittent sampling of arterialized venous blood. During the 360 minutes of the test, insulin (Actrapid HM, Novo, Copenhagen, Denmark) was infused at three different rates (25, 50, and 100 mU/kg/h), each lasting 120 minutes, while glucagon (Novo) was infused at the fixed rate of 67 ng/min. To inhibit endogenous pancreas secretion, cyclic somatostatin (Stilamin, Serono, Italy; 4.5 μg/min) was infused from 0 to 360 minutes. All three hormones—insulin, glucagon, and somatostatin—were dissolved in saline containing 0.3 g/100 mL human serum albumin (Human Albumin, ISI, Milan, Italy). Along with insulin infusion, variable amounts of...
glucose were infused according to the principles of the euglycemic glucose clamp described by De Fronzo et al. Glucose was infused as a 30% solution to which 0.26 mEq KCl was added to prevent hypokalemia. To quantify the rate of endogenous (hepatic) glucose production (HGP) and the rate of overall glucose disappearance (Rd) in the basal state and during glucose clamp, a primed (20 μCi), continuous (0.2 μCi/min) infusion of d-3H-glucose (New England Nuclear, Boston, MA; specific activity, 115 Ci/mmol) dissolved in saline was used. At least 2 hours were allowed for isotopic equilibration, during which the Biostator was calibrated between basal values and those calculated in the last 60 minutes of each insulin infusion rate (50 mU/kg/h). Percent of inhibition of endogenous (hepatic) glucose production (HGP) was calculated as the difference between glucose appearance and GIR. Changes in HGP and Rd were calculated as the difference between basal values and those calculated in the last 60 minutes of the second insulin infusion rate (50 mU/kg/h). Percent of inhibition in endogenous (hepatic) glucose production (HGP) and FFA levels, as well as of increase in Rd, were calculated by taking the basal values equal to 100% and the mean value during the last 60 minutes of each insulin infusion rate of each parameter. Glucose and insulin area under the curve were calculated as increment above baseline by trapezoidal method using an Apple II desk computer.

All statistical comparisons between patients and controls were performed by two-tailed t test for unpaired data and confirmed by nonparametric test (Wilcoxon test, sum of the rank). Correlation coefficients were calculated using the coefficient r of Pearson. A value of P < .05 was chosen as level of significance. All results are means ± SEM.

**RESULTS**

**Fasting Metabolic and Hormonal Parameters**

In the fasting, postabsorptive state, plasma glucose levels (5.2 ± 0.1 v 4.9 ± 0.2 mmol/L, P = NS) were similar in both groups of subjects, despite the fact that patients had higher plasma insulin levels (125.7 ± 9.2 v 35.7 ± 3.3 pmol/L, P < .01) (Table 1). Plasma counterregulatory hormone levels (Table 2) demonstrated that only plasma norepinephrine levels were significantly higher in patients than controls.
Table 2. Basal Plasma Counterregulatory Hormone Levels in Controls and Patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 10)</th>
<th>Patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon (ng/L)</td>
<td>121 ± 18</td>
<td>133 ± 34</td>
</tr>
<tr>
<td>Growth hormone (µg/L)</td>
<td>3.7 ± 0.2</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>333 ± 10</td>
<td>349.7 ± 41.5</td>
</tr>
<tr>
<td>Adrenaline (pmol/L)</td>
<td>356.6 ± 55.1</td>
<td>361.8 ± 44.4</td>
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<tr>
<td>Norepinephrine (nmol/L)</td>
<td>1.47 ± 0.22</td>
<td>5.39 ± 0.13</td>
</tr>
</tbody>
</table>

NOTE. All results are means ± SE. All determinations were performed after overnight fast (12-hour).

Oral Glucose Tolerance Test

After loading with 75 g of glucose (Fig 1), plasma glucose and plasma insulin levels were still significantly higher in the patients than in controls throughout the study. In particular, after 2 hours, plasma glucose (9.0 ± 0.5 v 6.9 ± 0.3 mmol/L, P < .01) and insulin (279 ± 27 v 213 ± 30 pmol/L, P < .02) levels achieved higher values in patients than controls, respectively. Plasma glucose (419 ± 58 v 311 ± 65 mmol/L x 180 min, P < .01) and insulin (22.9 ± 1.5 v 19.2 ± 1.1 nmol/L x 180 min, P < .05) area under the curves were also significantly higher in patients than controls.

Euglycemic Hyperinsulinemic Glucose Clamp

Before the euglycemic hyperinsulinemic glucose clamp, basal plasma glucose and insulin levels were not greatly different from those previously reported. After starting the infusions, plasma glucose (Fig 2) was kept close to basal values and within narrow ranges (coefficient of variations 3.3% ± 0.5% v 3.7% ± 0.3%, P = NS), without significant differences between both groups of subjects throughout the study. Plasma insulin levels reached a stable plateau at roughly 213,355 and 710 pmol/L when insulin infusion rates were 25, 50, and 100 mU/kg/h, respectively. No significant differences in plasma insulin levels were detected between patients and controls. Basal plasma C-peptide levels (1,118 ± 111 v 811 ± 97 pmol/L, P < .02 in patients and controls, respectively) were strongly and similarly inhibited by somatostatin infusion, reaching extremely low values at the end of the test in both patients and controls. Plasma glucagon levels were similarly replaced at basal levels in both groups of subjects without any significant difference between them.

GIR (Fig 3) increased more in controls than patients during the first two insulin infusion rates, while similar values were recorded in the last 120 minutes of the experiment.

Basal glucose turnover parameters (Fig 3) were slightly but not significantly different in patients and controls. Insulin delivery promptly decreased endogenous (hepatic)
GLUCOSE METABOLISM IN CONGESTIVE HEART FAILURE

GIR, HGP, Rd, and gMCR in control subjects (○) (n = 10) and in patients (●) (n = 8) during the euglycemic hyperinsulinemic glucose clamp. Statistically significant differences were *P < .05; **P < .01.

In our patients, a significant correlation (Fig 5) between basal plasma norepinephrine levels and A decrease in endogenous (hepatic) glucose production (HGP) or A increase in Rd was also found.

Changes in Plasma FFA Levels

In patients versus controls, plasma FFA levels were significantly higher in basal conditions (927 ± 79 versus 792 ± 88 μmol/L, P < .02) and less inhibited by insulin (Fig 6). In fact, at the end of the first two insulin infusion rates, percent of insulin-mediated decrease in plasma FFA levels achieved 15% ± 3% versus 31% ± 7% (P < .025) and 34% ± 8% versus 52% ± 9% (P < .012) in patients and controls, respectively. This difference disappeared at the end of the highest (100 mU/kg/h) insulin infusion rate. Furthermore, in our patients, basal plasma FFA levels were also significantly correlated (r = .65, P < .025) with basal plasma norepinephrine levels.

DISCUSSION

Heart failure is a well-known clinical syndrome in which an abnormal cardiac function is responsible for the inability...
of the heart to pump blood at a rate commensurate with tissue's requirements. Thus, in order to enhance heart rate in the failing myocardium, an increased norepinephrine secretion and an overdrive of adrenergic nervous system occur.\textsuperscript{1-4} Cohn et al\textsuperscript{1} have recently reported that, in heart failure, basal plasma norepinephrine levels are significantly raised, ranging between 400 and 1000 pg/mL, and are a guide to the prognosis. Furthermore, if in normal subjects no change or very little increase in norepinephrine levels occurs during moderate exercise, in patients suffering from heart failure, a greater increase exists.\textsuperscript{1-4} In those patients, a marked elevation of 24-hour urinary norepinephrine excretion also occurs.\textsuperscript{15} Notwithstanding, norepinephrine together with the well-known cardiovascular effects, may also exert a glucoregulatory action. In particular, it has been suggested that high pharmacological doses of norepinephrine transiently enhance hepatic glucose output,\textsuperscript{16} and can affect blood glucose and other metabolites, even in basal conditions, and at much lower levels of approximately 1.8 pg/mL.\textsuperscript{17} Sacca et al\textsuperscript{18} have also demonstrated that a small increase in plasma norepinephrine levels may slightly increase fasting blood glucose through a transient stimulation of basal hepatic glucose output without any change in basal glucose utilization or insulin or glucagon secretion. More recently, Marangou et al\textsuperscript{19} have shown that a mild elevation in plasma norepinephrine levels led to a 35% decrease in insulin sensitivity without any changes in glucose-mediated glucose disposal or pancreatic B-cell responsiveness.

In the present study, we confirm that patients suffering from congestive chronic heart failure have higher plasma norepinephrine levels; furthermore, we first show that in our patients this increase in plasma neurohormone levels may be responsible for an impaired glucose handling as demonstrated by OGTT and more clearly by glucose clamp. According to Kolterman et al,\textsuperscript{20} one can speculate that the insulin resistant state found in our patients might be due to a receptor defect (probably related to an antagonizing effect of norepinephrine on insulin target tissues); nevertheless, more appropriate in vitro studies will need to clarify this possibility.

In regard to the mechanism of action by which norepinephrine antagonizes the effect of insulin on target tissues, we hypothesize that FFA might have a major role. In fact, norepinephrine is known to produce a significant increase in plasma FFA levels.\textsuperscript{6,20-23} Elevated plasma FFA levels, by a mass-action mechanism, may increase their cellular uptake, thus stimulating lipid oxidation. In the muscle, the accelerated rate of fat oxidation can inhibit insulin-mediated glucose disposal, whereas, at liver site, it can stimulate gluconeogenesis and increase hepatic glucose output.\textsuperscript{20-23}

In addition, other factors than FFA may also play a role in the genesis of insulin resistance in our patients. Ketone
bodies may be among them. Although not measured in the present study, they are known to be elevated during norepinephrine infusions, thus contributing to impair glucose handling. A possible indirect inhibitory effect of norepinephrine on muscle glucose uptake through its β-adrenergic stimulatory properties should also not be excluded. Furthermore, norepinephrine is a mixed α- and β-agonist with limited β-adrenergic receptor activity, and, since glucose uptake is not significantly influenced by the α-adrenergic mechanism, it is unlikely that norepinephrine has a major direct role in glucose disposal inhibition.

The presence of an insulin-resistant state in patients suffering from chronic heart failure seems to us an interesting finding in light of the negative impact that such a metabolic abnormality may have on the already impaired heart function. Thus, those patients should be treated by a low carbohydrate diet in order to prevent or to control abnormal glucose handling.

In conclusion, we demonstrate that in chronic heart failure, the increase in plasma norepinephrine levels and the relative increase in FFA contribute to the development of an insulin-resistant state.

REFERENCES