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Impaired Insulin Sensitivity as an Independent Risk Factor for Mortality in Patients With Stable Chronic Heart Failure

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OBJECTIVES The aim of this study was to determine the significance of insulin resistance as an independent risk factor for impaired prognosis in patients with chronic heart failure (CHF).

BACKGROUND In CHF, impaired insulin sensitivity (S_I) indicates abnormal energy metabolism and is related to decreased exercise capacity and muscle fatigue. The relationship between insulin resistance (i.e., low S_I) and survival in patients with CHF has not been established.

METHODS We prospectively studied 105 male patients with CHF due to ischemic (63%) or non-ischemic (37%) etiology. All patients were in clinically stable condition (age 62 ± 1 year, New York Heart Association [NYHA] functional class 2.6 ± 0.1, left ventricular ejection fraction [LVEF] 28 ± 2%, peak oxygen uptake [V_{O_2}] 18.2 ± 0.7 ml/kg/min). Insulin sensitivity was assessed from glucose and insulin dynamic profiles during an intravenous glucose tolerance test using the minimal model technique.

RESULTS During a mean follow-up period of 44 ± 4 months, 53 patients (50%) died. Patients with S_I below the median value (median: 1.82 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$; n = 52) had worse survival (at two years 61% [range 47% to 74%]) than patients with S_I above the median value (n = 53; at two years 83% [range 73% to 93%]; risk ratio [RR] 0.38, 95% confidence interval [CI] 0.21 to 0.67; p = 0.001). Both patient groups were similar in terms of age, NYHA functional class, and body composition parameters (dual-energy X-ray absorptiometric scan; p > 0.2), but patients with a lower S_I had a lower LVEF (24 ± 2% vs. 33 ± 3%) and peak V_{O_2} (16.8 ± 1.0 ml/kg/min vs. 19.7 ± 1.0 ml/kg/min; both p < 0.05). On univariate Cox analysis, higher S_I predicted better survival (RR 0.56, 95% CI 0.35 to 0.89; p = 0.015). On stepwise multivariate analysis, S_I predicted mortality independently of other variables.

CONCLUSIONS In patients with CHF, lower S_I relates to higher mortality, independent of body composition and established prognosticators. Impaired S_I may have implications in the pathophysiology of CHF disease progression. Therapeutically targeting impaired insulin sensitivity may potentially be beneficial in patients with CHF. (J Am Coll Cardiol 2005;46:1019–26) © 2005 by the American College of Cardiology Foundation

Chronic heart failure (CHF) is a leading cause of both morbidity and mortality in Western society with increasing prevalence and health care costs. It has been shown that impaired whole-body insulin sensitivity (S_I) commonly occurs in CHF, independent of ischemic etiology (1). As part of the metabolic syndrome, insulin resistance is associated with arteriosclerotic cardiovascular disease, including ischemic CHF. It has been shown, however, that also patients with a *non-ischemic* etiology of CHF have impaired S_I (2,3) and the degree of insulin resistance correlates with the degree of heart failure (1). Increasing evidence suggests a relationship between impaired glucose metabolism and CHF. Diabetes mellitus has been shown to be a predisposing factor for development of CHF (4,5). In the Studies Of Left Ventricular Dysfunction (SOLVD), diabetes was an independent predictor of mortality and morbidity in CHF patients (6). In large heart failure trials, diabetes mellitus has a prevalence of 20% to 25% (7–10). The clinical significance of insulin resistance in CHF is not known. However, insulin resistance may occur prior to type 2 diabetes mellitus being diagnosed, so the prevalence of insulin resistance is likely much higher. If insulin resistance is pathophysiologically linked with CHF and progresses in parallel with the degree of CHF (1,11), one could hypothesize insulin resistance to be a prognostic factor.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BMI = body mass index
CHF = chronic heart failure
CI = confidence interval
DEXA = dual-energy X-ray absorptiometry
ivGTT = intravenous glucose tolerance test
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RR = risk ratio
S_I = insulin sensitivity
V_{O_2} = oxygen uptake

The aim of present study was to investigate in a cohort of patients with CHF whether the presence of insulin resistance in CHF is an independent risk factor for impaired prognosis. Regional fat and lean tissue composition (important factors in insulin resistance) were also measured.

METHODS

Study population. We prospectively studied 105 male CHF patients with ischemic (63%) or non-ischemic (37%) etiology between May 1993 and February 2001. The diagnosis of CHF was based on clinical evidence of heart failure with shortness of breath, symptomatic exercise limitation, and peripheral edema with a disease history of at least six months. In all patients, evidence of left ventricular functional impairment by radionuclide ventriculography and/or echocardiography was present. All patients were treated as clinically indicated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (85%), diuretics (87%), beta-blockers (20%), digitalis (33%), or aspirin and/or warfarin (75%). Patients were clinically stable at the time of S_I assessment, with no clinical evidence of decompensated heart failure, such as raised jugular venous pressure, ascites, or hepatomegaly. At the time of the study, none of the patients were diagnosed with diabetes (according to World Health Organization criteria) or had antidiabetic treatment. Female patients were excluded from the study to prevent influences from gender and related factors such as hormone replacement therapy.

All patients gave written, informed consent, and the study was approved by our local ethics committees.

Assessment of S_I. All participants underwent intravenous glucose tolerance testing (ivGTT), as previously described (12). The ivGTT was performed under standardized conditions in a metabolic day ward starting in the morning between 8:00 AM and 9:00 AM following overnight fasting after at least 20 min of supine rest. A glucose bolus (50% solution) was administered intravenously at a dose of 0.5 g/kg body weight. All blood samples were immediately processed and stored at −80°C until analysis of glucose and insulin. From the glucose and insulin dynamic profiles, the S_I index was calculated using the minimal model approach according to Bergman et al. (13). The relatively high glucose dose (0.5 vs. 0.3 g/kg) we use enables evaluation of S_I by the minimal model, without the need for augmentation of plasma insulin concentrations by tolbutamide or insulin injection. We have validated S_I estimates derived using this approach in patients with CHF against the euglycemic clamp reference method (14). Insulin sensitivity—the inverse of insulin resistance—is defined as the fraction of the glucose distribution space cleared per minute by insulin-dependent glucose disposal relative to the concentration of insulin and is expressed in $\text{min}^{-1} \cdot \mu\text{U} \cdot \text{ml}^{-1} \cdot 10^4$. Insulin concentrations during ivGTT were expressed as the incremental area under the concentration profile, calculated using the trapezium rule.

Body composition. In all subjects, body mass index (BMI) was calculated as the ratio of weight (kg) and squared height (m^2). For body composition assessment, dual-energy X-ray absorptiometry (DEXA) was performed in 89 of the patients by using a Lunar DPX (Lunar Corp., Madison, Wisconsin). Total body scans were analyzed to obtain total and regional (legs, arms, and trunk) measurements of fat and lean tissue. Precision of total and regional assessments was <2% for lean tissue and <5% for fat tissue (15). Fat mass of the trunk, termed as "central fat mass," includes both visceral and subcutaneous fat of this anatomic region. The sum of fat mass of the legs and arms was termed as "peripheral fat mass." The distribution of fat mass was calculated as the ratio of central fat mass/peripheral fat mass.

Exercise test and follow-up. A maximal cardiopulmonary treadmill exercise test was performed for clinical characterization (modified Bruce protocol), using a respiratory mass spectrometer (Amis 2000, Odense, Denmark) and a standard inert gas dilution technique for assessment of peak oxygen uptake (V_{O_2}), as described previously (16).

All patients received follow-up by the Royal Brompton Hospital Heart Failure and Cardiomyopathy Clinic. Follow-up was by outpatient assessment and from information obtained by the Office of National Statistics, where all patients had been flagged for death. No patient was lost during follow-up.

Statistical analyses. All results are presented as the mean value ± SEM. The unpaired Student *t* test was used to compare mean values between groups. Distributions for biochemical variables were evaluated for normality using the Kolmogorov-Smirnov test, and logarithmic transformation was applied where necessary to allow a parametric statistical approach. Insulin sensitivity was square-root transformed in accordance with our previous analysis of the distribution characteristics of model-derived variables (17). A probability value of <0.05 was considered statistically significant. Cox proportional hazards analysis was employed to assess the association of variables to survival. Stepwise multivariate analysis was performed with all parameters that had a $p \leq 0.1$ in the univariate analysis. The risk ratio (RR) and 95% confidence interval (CI) for risk factors are given. A commercially available statistical software program was used