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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

Table 1. Clinical and Anthropometric Characteristics of 105 Patients With Chronic Heart Failure and Group Comparison Between Patients Who Died During the Follow-Up Period and Those Who Were Alive at the End of the Follow-Up Period

Parameter	All CHF Patients (n = 105)	Patients Who Died (n = 53)	Patients Alive (n = 52)	p Value
Age (yrs)	62 ± 1	64 ± 1	60 ± 2	0.09
Etiology				
Ischemic cardiomyopathy	66 (63%)	33 (62%)	33 (63%)	
Dilated cardiomyopathy	39 (37%)	20 (38%)	19 (37%)	0.9
NYHA functional class (mean)	2.6 ± 0.08	2.8 ± 0.1	2.3 ± 0.1	**0.003**
Systolic blood pressure (mm Hg)	116 ± 2.0	112 ± 3	120 ± 3	**0.03**
Diastolic blood pressure (mm Hg)	72 ± 1.2	70 ± 2	74 ± 2	0.09
Peak V_{O_2} (ml/kg/min)	18.2 ± 0.7	16.1 ± 0.9	20.3 ± 1.0	**0.004**
Exercise time (s)	424 ± 22	394 ± 26	454 ± 34	0.17
LVEF (%)	28 ± 2	26 ± 2	31 ± 3	0.19
Sodium (mmol/l)	137 ± 0.3	137 ± 0.5	138 ± 0.4	**0.04**
Creatinine (μmol/l)	129 ± 6.2	147 ± 9	110 ± 7	**0.002**
Uric acid (μmol/l)	472 ± 15	531 ± 22	413 ± 17	**<0.0001**
Hemoglobin (g/dl)	13.4 ± 0.1	13.2 ± 0.23	13.6 ± 0.17	0.28
Cholesterol (mmol/l)	5.13 ± 0.11	5.15 ± 0.15	5.10 ± 0.17	0.8
Weight (kg)	73.8 ± 1.6	71.0 ± 2.1	76.8 ± 2.3	0.06
Body mass index (kg/m^2)	24.7 ± 0.4	24.2 ± 0.7	25.2 ± 0.6	0.27
Total body fat tissue (kg)*	18.4 ± 0.86	16.9 ± 1.2	20.0 ± 1.2	0.07
Central fat tissue (kg)*	10.3 ± 0.49	9.58 ± 0.75	11.1 ± 0.59	0.13
Peripheral fat tissue (kg)*	7.08 ± 0.40	6.38 ± 0.52	7.84 ± 0.59	0.06
Ratio central/peripheral fat*	1.56 ± 0.05	1.60 ± 0.07	1.51 ± 0.58	0.3
Total lean tissue (kg)*	52.4 ± 0.53	50.6 ± 1.13	54.4 ± 1.48	**0.04**
Peripheral lean tissue (kg)*	22.1 ± 0.45	21.0 ± 0.53	23.4 ± 0.69	**0.005**
Fasting glucose (mg/dl)	104 ± 3.2	105 ± 4.4	103 ± 4.7	0.7
Fasting insulin (mU/l)	13.0 ± 0.93	14.0 ± 1.37	12.0 ± 1.25	0.2
Incremental insulin area (min · mU/l)	4,081 ± 314	4,707 ± 526	3,443 ± 320	**0.04**
Insulin sensitivity ($min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$)	2.53 ± 0.26	1.87 ± 0.24	3.21 ± 0.43	**0.002**

*Dual-energy X-ray absorptiometric scan in 89 subjects (46 died, 43 survived). Data are presented as the mean value ± SEM or number (%) of subjects. **Bold** values indicate statistically significant results.

CHF = chronic heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; V_{O_2} = oxygen uptake.

(StatView version 4.5, Abacus Concepts Inc., Berkeley, California).

RESULTS

Patient characteristics and follow-up. We studied a total of 105 CHF patients. Patient characteristics at baseline are given in Table 1. The mean follow-up period in these patients was 44 ± 4 months. During this period, 53 patients (50%) died after 4 to 3,319 days (mean 775 ± 106 days, median 527 days). The mean follow-up period of the 52 survivors was 1,905 ± 153 days (range 396 to 3,719 days, median 1,474 days). The cumulative mortality of the patients was 22% at 12 months (95% CI 14% to 30%), 28% at 24 months (95% CI 19% to 36%), and 40% at 36 months (95% CI 30% to 50%).

Patients who died during follow-up had a similar age, BMI, and left ventricular ejection fraction (LVEF) compared with patients who did not die. Patients who died had a smaller regional lean tissue mass at the arms and legs and a trend toward lower total fat mass. These patients had also a higher mean NYHA functional class (+0.5) and lower peak V_{O_2} (−21%, both $p = 0.004$). Insulin sensitivity was lower in these patients compared with the surviving patients (−42%, $p = 0.002$). Detailed clinical and body composition characteristics of both groups are shown in Table 1.

In all patients, mean S_I was 2.53 ± 0.26 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$. According to median S_I (1.82 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$), we dichotomized the CHF patients into two subgroups. Patients with S_I below the median value (n = 52) had a mean S_I of 0.95 ± 0.07 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$), and patients with S_I above the median value (n = 53) had a mean S_I of 4.08 ± 0.40 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$. The main characteristics of both groups are shown in Table 2. Both subgroups were similar in terms of age and NYHA functional class and parameters of body composition (all $p > 0.2$, except for arm lean tissue [$p = 0.08$] and BMI [$p = 0.06$]), but patients with S_I above the median value had a higher LVEF ($p = 0.02$) and peak V_{O_2} ($p = 0.03$).

A comparison of S_I between NYHA functional classes in CHF patients and healthy control subjects is shown in Figure 1. Control values were obtained from healthy subjects (mean age 54.6 years [range 32 to 74 years]) who voluntarily underwent metabolic assessment in our research unit. There was a stepwise decrease of S_I across NYHA functional classes, with the lowest values in class IV ($p = 0.0007$ by analysis of variance). In regression analysis, S_I correlated with LVEF ($r = 0.36$), peak V_{O_2} ($r = 0.23$), BMI ($r = -0.22$), and total ($r = -0.23$) and regional fat mass ($r = -0.27$; all $p < 0.05$). No

Table 2. Group Comparison Between Patients With Chronic Heart Failure Above and Below the Median Insulin Sensitivity Value (1.82 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$)

Parameter	CHF Patients Below Median S_I (n = 52)	CHF Patients Above Median S_I (n = 53)	p Value
Age (yrs)	63 ± 1	61 ± 2	0.5
Etiology			
Ischemic cardiomyopathy	34 (65%)	32 (60%)	
Dilated cardiomyopathy	18 (35%)	21 (40%)	0.6
NYHA functional class (mean)	2.6 ± 0.1	2.5 ± 0.1	0.3
Systolic blood pressure (mm Hg)	116 ± 3	116 ± 3	0.9
Diastolic blood pressure (mm Hg)	71 ± 2	72 ± 2	0.8
Peak Vo_2 (ml/kg/min)	16.8 ± 1.0	19.7 ± 1.0	**0.031**
Exercise time (s)	403 ± 29	447 ± 33	0.3
LVEF (%)	24 ± 2	33 ± 3	**0.019**
Sodium (mmol/l)	137 ± 0.4	138 ± 0.5	0.3
Creatinine (μmol/l)	140 ± 9	117 ± 8	0.06
Uric acid (μmol/l)	484 ± 22	461 ± 21	0.4
Hemoglobin (g/dl)	13.2 ± 0.23	13.5 ± 0.18	0.3
Cholesterol (mmol/l)	5.31 ± 0.16	4.94 ± 0.15	0.10
Weight (kg)	75.7 ± 2.5	71.9 ± 1.8	0.2
Body mass index (kg/m^2)	25.5 ± 0.7	23.8 ± 0.5	0.06
Total body fat tissue (kg)*	19.5 ± 1.3	17.1 ± 1.1	0.2
Central fat tissue (kg)*	10.9 ± 0.7	9.6 ± 0.6	0.2
Peripheral fat tissue (kg)*	7.61 ± 0.6	6.47 ± 0.5	0.15
Ratio central/peripheral fat*	1.55 ± 0.07	1.56 ± 0.06	0.8
Total lean tissue (kg)*	52.7 ± 1.4	52.0 ± 1.2	0.7
Fasting glucose (mg/dl)	108 ± 5	99 ± 4	0.2
Fasting insulin (mU/l)	16.27 ± 1.47	9.76 ± 0.91	**0.0003**
Incremental insulin area (min · mU/l)	5,461 ± 482.4	2,726 ± 309.0	**<0.0001**
Insulin sensitivity ($min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$)	0.95 ± 0.07	4.08 ± 0.40	—

*Dual-energy X-ray absorptiometric scan in 89 subjects (47 below median S_I and 42 above median S_I). Data are presented as the mean value ± SEM or number (%) of subjects. **Bold** values indicate statistically significant results.
Abbreviations as in Table 1.

correlation was found for S_I versus age, mean arterial pressure, lean tissue mass, serum cholesterol, creatinine, uric acid, or hemoglobin (all $p > 0.25$).

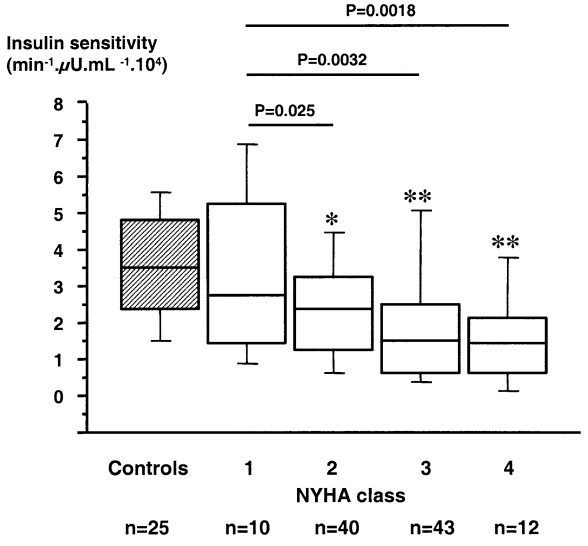


Figure 1. Insulin sensitivity in patients with chronic heart failure according to New York Heart Association (NYHA) functional class, as compared with healthy control subjects. Box plot displaying the 10th, 25th, 50th, 75th, and 90th percentiles. The p values for the Fisher post-hoc test of mean square-root transformed insulin sensitivity. *$p < 0.05$ and **$p < 0.005$ vs. controls.

Insulin sensitivity was not significantly different between patients treated with beta-blockers and those without ($p = 0.13$). Similarly, no difference was found for S_I between patients with and without ACE inhibitor ($p = 0.38$) and diuretic treatment ($p = 0.49$).

Predictors of mortality. In univariate Cox proportional hazard analysis, a higher S_I as a continuous variable significantly predicted lower mortality (RR 0.56, 95% CI 0.35 to 0.89; $p = 0.015$). Fasting glucose and insulin levels and incremental insulin area did not significantly predict mortality (all $p > 0.3$). Low S_I also predicted impaired survival after adjustment for parameters of body composition, such as BMI, total amount of fat tissue, and regional fat distribution ($p < 0.01$; data not shown). When adjusted for the use of beta-blockers, ACE inhibitors, and diuretics, S_I remained a significant predictor of mortality ($p = 0.0080$), with only diuretic treatment significantly contributing to prognosis ($p = 0.018$ vs. $p > 0.3$ for ACE inhibitors and beta-blockers). In addition, age, NYHA functional class, and peak Vo_2 as a continuous variable and as a dichotomized variable (peak Vo_2 <14 ml/kg/min), serum uric acid (all $p < 0.01$), hemoglobin ($p = 0.018$), fat tissue mass, and lean tissue mass (both $p < 0.05$) predicted mortality, but LVEF, BMI, and cholesterol did not (Table 3).

In multivariate analysis including S_I and clinical param-

Table 3. Univariate Cox Proportional Hazards Analyses in Patients With Chronic Heart Failure

Parameter	Univariate Analysis	
	RR (95% CI)	p Value
Insulin sensitivity, continuous ($min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$)	0.56 (0.35–0.89)	**0.015**
Age (yrs)	1.04 (1.01–0.07)	**0.0066**
NYHA functional class	1.62 (1.16–2.26)	**0.006**
Peak Vo_2 (continuous, ml/kg/min)	0.92 (0.87–0.97)	**0.0003**
LVEF (%)	0.98 (0.96–1.01)	0.18
Mean arterial pressure (mm Hg)	0.96 (0.94–0.99)	**0.003**
Diuretic treatment	0.21 (0.051–0.85)	**0.029**
Sodium level (mmol/l)	0.89 (0.83–0.97)	**0.0089**
Creatinine (μmol/l)	1.006 (1.003–1.01)	**0.0003**
Uric acid (μmol/l)	1.004 (1.003–1.006)	**0.0001**
Hemoglobin (g/dl)	0.76 (0.61–0.95)	**0.018**
Cholesterol (mmol/l)	0.87 (0.66–1.15)	0.3
Weight (kg)	0.97 (0.96–0.99)	**0.013**
BMI (kg/m^2)	0.94 (0.88–1.01)	0.07
Total body fat tissue (kg)	0.95 (0.91–0.99)	**0.013**
Central fat tissue (kg)	0.91 (0.85–0.99)	**0.026**
Peripheral fat tissue (kg)	0.88 (0.80–0.97)	**0.014**
Total body lean tissue (kg)	0.96 (0.93–0.99)	**0.028**

Body composition data by dual-energy X-ray absorptiometric scan in 89 patients. **Bold** values indicate statistically significant results.

BMI = body mass index; CI = confidence interval; RR = risk ratio; other abbreviations as in Table 1.

eters (age, NYHA functional class, peak Vo_2, mean arterial pressure, uric acid, hemoglobin, cholesterol, sodium, creatinine, total fat tissue mass, lean tissue mass, and diuretic treatment), S_I remained a significant prognosticator, independent of all other parameters (RR 0.30, 95% CI 0.14 to 0.63; p = 0.0016). In stepwise Cox proportional hazards analysis in three multivariate cumulative models, S_I was an independent predictor of impaired survival (Table 4). The year of recruitment did not contribute to prediction of survival in either univariate or multivariate analyses (data not shown).

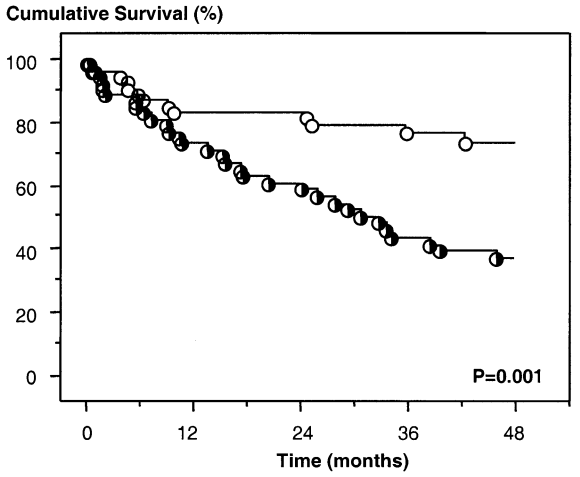
By analyzing S_I as a dichotomized variable, it was found that patients with S_I above the median value had better survival than did patients with S_I below the median value (RR 0.38, 95% CI 0.21 to 0.67; p = 0.001). At two years, survival of patients with S_I above the median was 83% (range 73% to 93%), but in patients with S_I below the median, it was 61% (range 47% to 74%). At three years,

Table 4. Stepwise Cox Proportional Hazard Analysis in Patients With Chronic Heart Failure

Parameter	Model 1			Model 2			Model 3		
	RR	95% CI	p Value	RR	95% CI	p Value	RR	95% CI	p Value
Insulin sensitivity, continuous ($min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$)	0.38	0.21–0.67	**0.001**	0.33	0.17–0.65	**0.001**	0.28	0.14–0.55	**0.0003**
Age (yrs)	1.06	1.026–1.093	**<0.001**	1.065	1.026–1.11	**0.001**	1.068	1.029–1.11	**0.0006**
Mean arterial pressure (mm Hg)	0.96	0.94–0.99	**0.008**			0.06			0.3
NYHA functional class			0.2			0.2			0.17
Peak Vo_2 (continuous, ml/kg/min)			0.14			0.8			0.5
BMI			0.07			0.3			0.6
Etiology			0.15			0.6			0.8
Diuretic treatment			0.7			0.8			0.5
ACE inhibitor treatment			0.9			0.3			0.2
Beta-blocker treatment			0.16			0.5			0.9
Uric acid (μmol/l)				1.003	1.001–1.005	**0.001**	1.003	1.001–1.005	**0.0017**
Creatinine (μmol/l)				1.005	1.000–1.01	**0.038**			0.09
Hemoglobin (g/dl)						0.11			0.3
Sodium level (mmol/l)						0.3			0.6
Total body fat tissue (kg)							0.95	0.90–0.99	**0.036**
Central fat tissue									0.7
Peripheral fat tissue (kg)									0.4
Total body lean tissue (kg)									0.8

Clinical variables (model 1), biochemical variables (model 2), and body composition variables (model 3) were tested in a cumulative approach. Body composition data by dual-energy X-ray absorptiometric scan in 89 patients. In respective analysis using S_I as dichotomized variable (above/below median), the following was found for S_I: model 1: RR 0.21 (95% CI 0.14–0.52); model 2: RR 0.24 (95% CI 0.12–0.49); model 3: RR 0.24 (95% CI 0.11–0.50); all $p < 0.001$. **Bold** values indicate statistically significant results.

ACE = angiotensin-converting enzyme; other abbreviations as in Tables 1 and 3.



	Patients at risk				
S_I above median					
53	44	43	26	21	
S_I below median					
52	38	29	20	16	

Figure 2. Survival in stable, ambulatory chronic heart failure patients (n = 105), classified according to the degree of impairment of insulin sensitivity (S_I) (i.e., above [n = 53] or below [n = 52] median S_I of 1.82 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$). Kaplan-Meier survival curve for four-year survival.

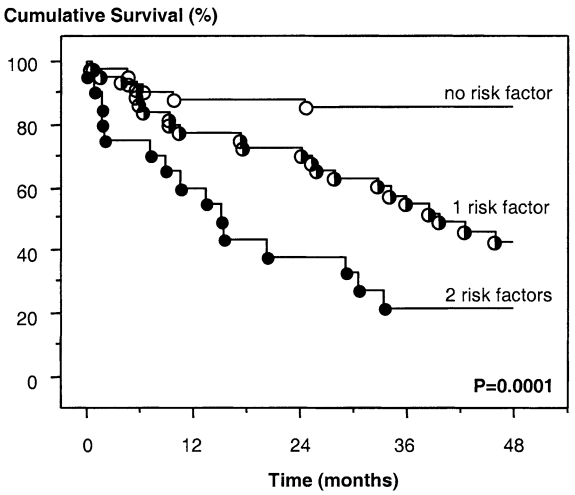
survival was 76% (range 64% to 88%) and 44% (range 30% to 58%), and at four years, survival was 73% (range 60% to 85%) and 37% (range 23% to 51%), respectively (Fig. 2). For illustrative purposes, the prognostic significance of the combination of S_I and peak Vo_2 used as dichotomized variables in a two-risk factor model is shown in Figure 3.

DISCUSSION

This study shows that impaired S_I in patients with CHF is independently associated with impaired prognosis. Insulin resistance provides additional prognostic information independent of well-established prognosticators, such as clinical status, age, LVEF, and exercise capacity, as well as body composition measures. It has previously been shown from our group (3) and others (2) that insulin resistance occurs in CHF independent of ischemic etiology and is associated with the severity of CHF in terms of reduced peak Vo_2 (1), NYHA functional class, or the 6-min walk test (11). In the present study, S_I decreases in parallel with the severity of CHF, as indicated by a stepwise reduction with higher NYHA functional classes.

Insulin resistance is a key precursor and feature of type 2 diabetes. Therefore, information on type 2 diabetes and CHF may provide indirect information on the clinical significance of insulin resistance in CHF (although insulin deficiency may also be a factor in any association between type 2 diabetes and CHF). Diabetes mellitus is a major co-morbidity in patients with CHF, with a prevalence of 20% to 25% (7–10). The Framingham study was the first to show that diabetes mellitus is an independent risk factor for heart failure with a 2.4 times higher risk in men and a 5.1 times higher risk in women, as compared with those without diabetes (18). In more recent, large epidemiologic studies, this association has been confirmed (4,5). In CHF, diabetes independently predicts all-cause mortality in both symptomatic and asymptomatic heart failure patients (RR 1.29, $p < 0.002$), as well as hospitalization due to CHF (RR 1.52, $p < 0.001$) (6). A reciprocal relationship emerges between CHF and type 2 diabetes that suggests impaired S_I being a significant pathophysiologic factor in the metabolic imbalance of the heart failure syndrome. Notably, type 2 diabetes mellitus is only the late consequence of insulin resistance, with the latter preceding frank diabetes for years if not decades (19). The prevalence of diabetes mellitus in CHF, therefore, provides only a minimum indicator of the true prevalence of insulin resistance in these patients. Accordingly, an analysis from the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study has shown that, based on fasting blood glucose criteria, 43% of patients had abnormal glucose metabolism (11).

The present study is in line with previous data by Paolisso et al. (20), who observed impaired S_I as a prognostic marker in CHF. However, in their study, Paolisso at al. (20) excluded about 50% of deaths from their mortality analysis



	Patients at risk				
no risk factor	41	36	35	23	19
1 risk factor	44	34	30	19	14
2 risk factors	20	12	7	4	4

Figure 3. Survival in stable, ambulatory chronic heart failure patients in a two-risk factor model using insulin sensitivity (S_I) and peak oxygen uptake (Vo_2) as dichotomized variables: interaction of impaired S_I (below median of 1.82 $min^{-1} \cdot \mu U \cdot ml^{-1} \cdot 10^4$), with the presence of low peak Vo_2 (peak Vo_2 <14 ml/kg/min) (patients with no risk factor: n = 41, 6 deaths; one risk factor: n = 44, 23 deaths; two risk factors: n = 20, 15 deaths). Kaplan-Meier survival curve for four-year survival.

as non-cardiac events. This might have had the effect of underestimating true mortality in their cohort. Moreover, patients with BMI >28 kg/m^2 were excluded from this study, which may restrict applicability for the general CHF population (21).

Impaired S_I is commonly known to relate to increased BMI, as obesity is a common confounder of type 2 diabetes. Accordingly, we found a correlation between S_I and BMI and fat tissue mass. In our study, however, CHF patients with lower versus higher S_I were not significantly different in terms of body composition. Moreover, when comparing the patients who died with those who were alive at the end of the follow-up period, S_I was 42% lower in the patients who died. These patients were not heavier than the patients who survived, neither did they have more fat or lean tissue. In fact, the surviving patients (i.e., those with a *greater* S_I) had a tendency toward a *higher* fat tissue mass. This is consistent with a previous observation of high BMI being a survival advantage in CHF (22,23). In our study, low S_I predicted impaired survival independent of parameters of body composition, such as weight, BMI, and total and regional fat, as well as lean tissue mass. This is in contrast to the expected association between insulin metabolism and body composition (see above). In CHF patients, impaired S_I is not merely a function of adiposity and may indeed have implications in the pathophysiology of CHF disease progression. Our study confirms and extends previous data showing that the abnormalities in S_I in CHF may occur secondary to heart failure itself (1). Our data also suggest that in CHF, factors causing impaired balance between metabolic pathways and body composition might supersede the physiologic feedback regulation between the aforementioned factors.

To establish the underlying mechanism(s) of insulin resistance in these patients is beyond the scope of this study. Likely, a number of factors, exerting a combined effect, may have contributed, such as reduced peripheral tissue perfusion, impaired oxidative metabolism, lower GLUT4 transport protein amount in skeletal muscle (24), and increased neuroendocrine and immune activation (20). Moreover, changes in diet and reduced physical exercise may be discussed. Beta-blocker treatment has previously been reported to worsen metabolic control, but recent evidence suggests a beneficial effect of carvedilol on S_I in hypertensive type 2 diabetics (25). Data on the metabolic effects of carvedilol in CHF are, however, inconclusive, as studies with no effect on glucose utilization in CHF have been reported (26,27). In our study population, S_I was not dependent on treatment with beta-blockers, diuretics, or ACE inhibitors. When adjusting the Cox model for treatment, S_I remained a significant predictor of mortality. The use of beta-blockers in the present study was low, however, and more work is needed to evaluate the effect of medications such as carvedilol on S_I in CHF. Although medical treatment standards have advanced during the prolonged recruitment period, the predictive value of S_I on survival was not altered when adjusted for the year of recruitment. Whether more complete adherence to modern treatment standards may improve S_I in CHF needs to be tested in the future. Insulin sensitivity is not commonly assessed in patients with CHF during the routine clinical outpatient follow-up and is recognized only when overt diabetes mellitus is diagnosed. The aim of the present study has not been to establish S_I assessment by minimal modeling as another marker for prognostic evaluation in CHF, but to emphasize the importance of metabolic derangement contributing to CHF pathophysiology, which only recently has been gathering growing attention. The time-consuming assessment of S_I by ivGTT may render this method unsuitable to large epidemiologic studies. Simple and easier to apply estimates of S_I such as homeostasis model assessment (using a single time point assessment) may provide a reasonable estimate in large-scale studies. In the setting of smaller epidemiologic evaluations such as the current study, however, the dynamic assessment of S_I within the physiologic range of glucose metabolism may provide a more thorough estimate of pathophysiologic processes.

From the present data, it seems promising to test in future studies whether early detection and therapeutic targeting of insulin resistance in CHF may improve the outcome in these patients. This is indirectly supported from data from long-term exercise studies that show a reduction of mortality in CHF (28,29). Arguably, the well-known beneficial effect of physical exercise on S_I (30) may be involved in the physiologic mechanisms that underlie the beneficial effects of exercise in CHF patients. Whether drug therapy aimed at improved S_I may have a comparable beneficial effect is not known. Thiazolidinediones are selective agonists of peroxisome proliferator-activated receptor-gamma modulating, on a transcriptional level, the insulin-mediated glucose utilization by the skeletal muscle. Insulin sensitizers are, however, controversial in patients with CHF, as they increase fluid retention and may contribute to increased edema in CHF. Interventional studies designed to test whether targeting impaired S_I may be beneficial in patients with CHF are required but need to be done carefully and with great attention to potential adverse effects.

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