Journal of the American College of Cardiology Vol. 53, No. 9, 2009

Published by Elsevier Inc.
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.08.081

Insulin Resistance Is Highly Prevalent and Is Associated With Reduced Exercise Tolerance in Nondiabetic Patients With Heart Failure

Matlooba A. ALZadjali, MD, MPH, Valerie Godfrey, PhD, Faisel Khan, PhD, AnnaMaria Choy, FRCP, FACC, Alexander S. Doney, MD, Aaron K. Wong, MBChB, MRCP, John R. Petrie, MD, FRCP, Allan D. Struthers, MD, FRCP, Chim C. Lang, MD, FACC

Dundee, United Kingdom

Objectives The purpose of this study was to establish the prevalence of insulin resistance (IR) among nondiabetic chronic heart failure (CHF) patients and to seek factors associated with IR in CHF, including the relationship of IR to functional class, exercise capacity, and disease severity in CHF.

Background Several lines of evidence suggest that CHF is an IR state. The prevalence of IR in CHF and its relation to CHF have not been fully defined.

Methods Fasting insulin resistance index (FIRI) was assessed in a cohort of 129 consecutive CHF patients (mean age 69.2 ± 10.4 years; 76% males; body mass index 27.4 ± 4.4 kg/m^2). Patients underwent cardiopulmonary exercise testing and peripheral endothelial function testing by reactive hyperemia peripheral arterial tonometry (RH-PAT).

Results Prevalence of IR as defined by FIRI ≥2.7 was 61% in our cohort of CHF patients. There was a significant correlation between IR and waist circumference ($r = 0.37$; $p < 0.01$), serum triglycerides ($r = 0.34$; $p < 0.01$), high-density lipoprotein cholesterol ($r = -0.22$; $p = 0.02$), and serum leptin ($r = 0.39$; $p = 0.03$). Insulin resistance increased significantly with worsening New York Heart Association functional class ($p < 0.01$). The CHF patients with IR had a significantly lower exercise capacity and peak oxygen consumption than patients with an FIRI <2.7. The RH-PAT ratio was significantly lower in CHF patients with IR compared with CHF patients with an FIRI <2.7 (1.6 ± 0.3 vs. 2.0 ± 0.5; $p < 0.05$).

Conclusions Insulin resistance is highly prevalent among nondiabetic CHF patients and is associated with decreased exercise capacity in patients with CHF. (Insulin Resistance: Heart Failure; NCT00486967). (J Am Coll Cardiol 2009;53: 747–53) © 2009 by the American College of Cardiology Foundation

There are several lines of evidence that suggest that chronic heart failure (CHF) is an insulin resistant (IR) state (1). Clinical studies using hyperinsulinemic-euglycemic clamps have previously demonstrated fasting hyperinsulinemia and IR in patients with both ischemic and nonischemic CHF (2–4). These correlative studies, however, do not exclude the possibility that many such patients may have IR prior to developing left ventricular (LV) systolic dysfunction. Further evidence for CHF as an IR state comes from studies with the pacing heart-failure dog model whereby conscious, chronically instrumented dogs were shown to develop IR and insulin signaling abnormalities during the evolution of CHF (5). The exact mechanisms of IR in CHF are not known. Besides the loss of skeletal muscle bulk and skeletal blood flow, sympathetic overactivity, proinflammatory cytokines, altered adipokines, and endothelial dysfunction have been implicated in the pathophysiology of IR in CHF (6,7).

See page 763

The prevalence of IR in the CHF population has not been fully defined. Neither do we know the clinical associations of IR in patients with CHF. The aim of this study was to investigate the prevalence of IR among nondiabetic CHF patients, utilizing the fasting insulin resistance index (FIRI), which is derived from fasting plasma insulin and glucose levels and has been validated against the hyperinsulinemic-euglycemic clamp (8). We

From the Division of Medicine & Therapeutics, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom. This study was funded in part by grants from the British Heart Foundation (grant number PG/06/143/21897) and DDS Thorntons.

Manuscript received March 13, 2008; revised manuscript received August 14, 2008, accepted August 18, 2008.

JACC Vol. 53, No. 9, 2009
March 3, 2009:747–53

Abbreviations and Acronyms

BMI = body mass index
CHF = chronic heart failure
CI = confidence interval
FIRI = fasting insulin resistance index
HDL = high-density lipoprotein
IR = insulin resistance/resistant
NYHA = New York Heart Association
OR = odds ratio
RH-PAT = reactive hyperemia peripheral arterial tonometry
VO_2 = oxygen consumption

have also sought factors associated with IR in CHF, including the relationship of IR to functional class and exercise capacity.

Methods

Study subjects. CHF patients were identified from inpatients as well as patients attending outpatient clinics and from the general practice in the community. Diagnosis of CHF was based on the European Society of Cardiology guidelines for CHF (i.e., symptoms of CHF and objective evidence of LV systolic dysfunction) (9). All patients with stable CHF were included in the study. Inpatients with CHF who were hospitalized were also included, except patients with acutely decompensated CHF requiring intravenous therapy. CHF patients with a previous diagnosis of diabetes mellitus or with a fasting plasma glucose level ≥7.0 mmol/l or >126 mg/dl as defined by the American Diabetes Association criteria were excluded from the study (10). For comparison, a group of healthy subjects were also studied. They were recruited from the community and were clinically healthy based on history, physical examination, and blood laboratory results and were not taking any medication. All patients and healthy volunteers provided written informed consent for participation in this study, which was approved by the Tayside Committee on Medical Research Ethics.

Study protocol. On the day of study, all subjects were in a fasting state. Following physical examination and determination of their New York Heart Association (NYHA) functional class, anthropometric measurements of fat mass and free fat mass were made. Body fat was measured by recording height, weight, and waist and hip circumference. An estimation of percent body fat and lean body mass was determined from the sum of skin-fold thicknesses measured at 4 sites (biceps, triceps, subscapular, and suprailiac) (11,12). Thereafter, blood was drawn following a 20-min semirecumbent rest for measurement of glucose, insulin (radioimmunoassay kit, INSIK-5, DiaSorin, Berkshire, United Kingdom), plasma catecholamines (ESA Plasma Catecholamine Analysis Kit and HPLC, ESA Analytical Limited, Buckinghamshire, United Kingdom), adiponectin, and leptin (enzyme immunoassay, Quantikine, R&D Systems, Abingdon, United Kingdom).

IR. Insulin resistance was measured by an empirical FIRI, consisting of the product of plasma insulin and glucose (8): FIRI = fasting glucose × fasting insulin/25. On the basis of the plasma glucose concentration upper limit of normal of 6.1 mmol/l and our laboratory's upper limit of normal for plasma insulin of 11.2 mU/l, an FIRI value of 2.7 was determined as the upper limit of normal. An individual with an FIRI ≥2.7 was considered to have IR (8,13).

Cardiopulmonary exercise testing. The CHF patients underwent cardiopulmonary exercise testing utilizing incremental cycle ergometry with continuous expired gas analysis throughout the test with the Innocor System (Innocor rebreathing system, Innovision A/S, Odense, Denmark) as previously described (14). The Innocor system uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) from a 4-l pre-filled anesthesia bag that allows the determination of oxygen consumption (VO_2), metabolic measurements, and cardiac output. After 3 min of data at rest, exercise began at a workload of 0 W and increased every 3 min by 25 W until symptom-limited maximal exercise was reached. Patients were instructed to signal approximately 2 min before peak exercise. Patients performed practice exercise tests on a different day before each actual exercise test. Cardiac output and VO_2 measurements were made at the end of the resting period, at 50 W, and at peak exercise. Peak VO_2 was defined as the highest value of oxygen uptake achieved in the final 20 s of exercise (14).

Endothelial function. Endothelial function was determined by reactive hyperemia-peripheral arterial tonometry (RH-PAT) (Itamar Medical Ltd., Caesarea, Israel). This is a noninvasive technique used to assess peripheral microvascular endothelial function by measuring changes in digital pulse volume during reactive hyperemia (15,16). The RH-PAT ratio was defined as the ratio between the arterial pulse wave amplitude following a 5-min arterial occlusion in the forearm to the pre-occlusion value (15,16). Peripheral endothelial function, as assessed by RH-PAT, has been shown to be highly correlated with coronary endothelial function, and the endothelial function index has been validated against acetylcholine-mediated vasodilatation of coronary arteries, the gold standard in endothelial function testing (16). Although it has not been used in the setting of CHF, the technique has been used in a broad spectrum of patients with cardiovascular disease (15–17). We are not aware of special limitations or reliability problems in the use of this technique in patients with CHF.

Statistical analyses. All results are presented as mean value ± SD. Statistical analyses were performed with SPSS version 14 (SPSS Inc., Chicago, Illinois). Data that were determined to be not normally distributed by histogram and nonparametric test (1-sample Kolmogorov-Smirnov test) were log-transformed before analysis by parametric tests. Independent *t* tests were used to compare mean values between groups, and chi-square analyses were used for categorical variables. When FIRI was modeled as a continuous variable, simple linear regression (least-square method) and multiple linear regression analyses were performed to evaluate the relationship between FIRI and other parameters obtained from anthropometric measurement, NYHA functional class, neurohormone levels, and RH-PAT. Multiple logistic regression was applied when

FIRI was modeled as a categorical variable. One-way analysis of variance was used to test for differences of FIRI between NYHA functional classes. A p value <0.05 was considered statistically significant.

Results

A total of 525 patients were approached to participate in this study. Of these, 281 were excluded because they had a current diagnosis of diabetes, and 115 did not wish to participate in the study. Of the remaining 129 CHF patients, 79 (61%) had an FIRI ≥2.7 and were determined to have IR (Table 1, Fig. 1). Three of 18 healthy participants (16%) had an FIRI ≥2.7; they remained within the healthy subjects group for comparison.

Upon analysis of all patients with CHF for factors associated with the development of IR by univariate logistic regression, we found significant correlations between IR and NYHA functional class, serum triglycerides, body mass index (BMI), leptin, percent fat, waist circumference, ejec-

Table 1 Clinical Characteristics of Study Population

Variables	All CHF (n = 129)	FIRI ≥2.7 (n = 79)	FIRI <2.7 (n = 50)	p Value
Demographic characteristics				
Age (yrs)	69.2 ± 10.4	67.9 ± 9.5	69.9 ± 11.0	NS
Sex				NS
Male	76.0%	79.0%	73.5%	
Female	24.0%	21.1%	26.5%	
SBP	136.6 ± 25.7	135.1 ± 25.5	139.7 ± 25.9	NS
DBP	77.3 ± 12.8	76.8 ± 11.9	78.5 ± 13.9	NS
NYHA functional class				
I	9.3%	2.5%	18.0%	<0.05
II	29.5%	22.7%	40%	
III	54.3%	59.4%	40%	
IV	7.0%	11.3%	0.0%	
Etiology of HF				
Ischemic	82%	80.3%	85.7%	NS
Nonischemic	17.8%	19.7%	14.3%	
Ejection fraction	26.7 ± 6.3%	24.7 ± 6.1%	29.6 ± 5.8%	<0.05
Anthropometric measurement				
BMI (kg/m^2)	27.3 ± 4.4	29.1 ± 4.0	25.4 ± 3.9	<0.05
Waist-hip ratio	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1	NS
% fat	31.3 ± 7.3	33.1 ± 7.4	28.4 ± 6.5	<0.05
% lean body mass	68.6 ± 7.3	66.8 ± 7.2	71.5 ± 6.1	<0.05
Laboratory measurements				
Total cholesterol (mmol/l)	4.0 ± 1.1	3.9 ± 0.9	4.0 ± 1.1	NS
HDL (mmol/l)	1.4 ± 0.4	1.3 ± 0.3	1.5 ± 0.4	<0.05
TG (mmol/l)	1.6 ± 0.9	1.8 ± 0.8	1.3 ± 0.5	<0.05
Fasting blood glucose (mmol/l)	5.0 ± 0.6	5.2 ± 0.7	4.6 ± 0.4	<0.05
Fasting insulin (μU/ml)	20.7 ± 17.8	27.5 ± 18.7	10.3 ± 2.7	<0.05
Neurohormones				
Adiponectin (μg/ml)	10.7 ± 8.1	9.4 ± 6.3	11.8 ± 9.1	<0.05
Leptin (ng/ml)	17.3 ± 27.1	22.1 ± 32.6	8.9 ± 7.2	<0.05
Norepinephrine (ng/ml)	1.1 ± 0.9	0.9 ± 0.7	1.2 ± 1.1	NS
Epinephrine (ng/ml)	0.3 ± 0.8	0.2 ± 0.6	0.3 ± 0.8	NS
Exercise measurement				
Exercise time (s)	428.1 ± 244.5	330.0 ± 162.6	626.2 ± 262.5	<0.01
Peak VO_2 (ml/kg/min)	10.9 ± 4.1	8.0 ± 1.6	15.2 ± 2.3	<0.05
Endothelial function				
RH-PAT	1.7 ± 0.4	1.6 ± 0.3	2.0 ± 0.5	<0.05
Medications				
ACE inhibitors	94%	93%	94%	NS
Beta-blockers	78%	78%	78%	NS
Diuretics	81%	85%	76%	NS
Aldosterone antagonists	24%	30%	14%	<0.05
Digoxin	10%	8%	11%	NS

Data are presented as % or mean value ± SD. p values indicate significant differences between groups.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHF = chronic heart failure; DBP = diastolic blood pressure; FIRI = fasting insulin resistance index; HDL = high-density lipoprotein; HF = heart failure; NYHA = New York Heart Association; RH-PAT = reactive hyperemia-peripheral arterial tonometry; SBP = systolic blood pressure; TG = triglycerides; VO_2 = oxygen uptake.

JACC Vol. 53, No. 9, 2009
March 3, 2009:747–53

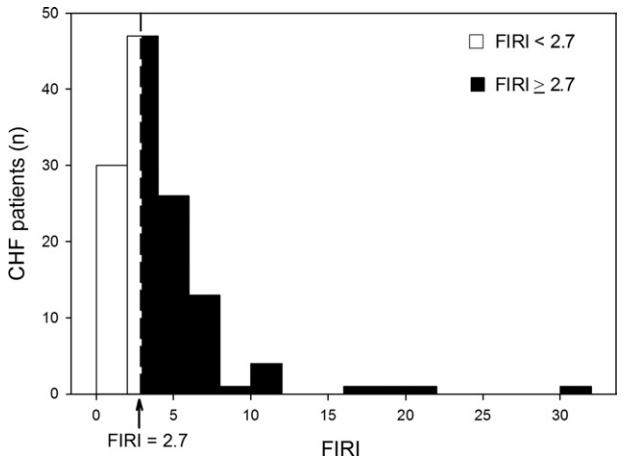

Figure 1 Range of FIRI in Patients With Heart Failure (n = 129)

Patients were considered to be insulin resistant if they had a fasting insulin resistance index (FIRI) ≥2.7. CHF = chronic heart failure.

tion fraction, percent lean body mass, high-density lipoprotein (HDL) cholesterol, and endothelial function as measured by RH-PAT (Table 2). Using multiple logistic regression with the above 11 relevant factors in the patients with CHF, we found that NYHA functional class (odds ratio [OR]: 3.02; 95% confidence interval [CI]: 1.19 to 7.67; $p < 0.001$), triglycerides (OR: 2.81; 95% CI: 1.26 to 6.26; $p < 0.01$), BMI (OR: 1.27; 95% CI: 1.10 to 1.46;

Table 2 Univariate Logistic Regression Analysis of Clinical and Humoral Factors for Prediction of IR in Patients With HF

Variables	Odds Ratio	95% Confidence Interval	p Value
NYHA functional class (severity)	3.37	(1.88–6.04)	<0.01
TG (mmol/l)	2.84	(1.50–5.35)	0.01
BMI (kg/m^2)	1.26	(1.13–1.40)	<0.01
Sex (male)	1.25	(0.55–2.84)	0.58
Leptin (ng/ml)	1.21	(1.07–1.36)	<0.01
Fat (%)	1.15	(1.10–1.21)	<0.01
Waist circumference (cm)	1.02	(1.00–1.03)	0.96
Waist-hip ratio	1.02	(0.41–2.52)	<0.01
Norepinephrine (ng/ml)	1.00	(0.99–1.00)	0.06
Epinephrine (ng/ml)	1.00	(0.99–1.00)	0.53
SBP (mm Hg)	0.99	(0.98–1.01)	0.74
DBP (mm Hg)	0.99	(0.97–1.02)	0.94
Age (yrs)	0.98	(0.94–1.01)	0.13
Alcohol use (yes)	0.93	(0.46–1.85)	0.84
Total cholesterol (mmol/l)	0.87	(0.61–1.23)	0.44
EF (%)	0.87	(0.81–0.93)	<0.01
Adiponectin (ng/ml)	0.75	(0.53–1.05)	0.75
Smoke (yes)	0.57	(0.20–1.57)	0.27
Lean body fat (%)	0.81	(0.82–0.96)	<0.01
HDL (mmol/l)	0.20	(0.07–0.59)	<0.01
RH-PAT ratio	0.12	(0.04–0.36)	<0.01

EF = ejection fraction; IR = insulin resistance; other abbreviations as in Table 1.

Table 3 Multiple Logistic Regression for Each Variable to Predict IR in Patients With HF

Variables	Odds Ratio	95% Confidence Interval	p Value
NYHA functional class	3.02	(1.19–7.67)	<0.01
TG (mmol/l)	2.81	(1.26–6.26)	<0.01
EF (%)	0.82	(0.73–0.92)	<0.01
BMI (kg/m^2)	1.27	(1.10–1.46)	0.01
HDL (mmol/l)	0.15	(0.02–0.92)	<0.05
RH-PAT ratio	0.05	(0.01–0.29)	0.01

Abbreviations as in Tables 1 and 2.

p = 0.01), ejection fraction (OR: 0.82; 95% CI: 0.73 to 0.92; p = 0.001), HDL cholesterol (OR: 0.15; 95% CI: 0.02 to 0.92; $p < 0.05$), and RH-PAT (OR: 0.05; 95% CI: 0.01 to 0.29; p = 0.001) were significant and independent predictors of IR (Table 3).

When FIRI was modeled as a continuous variable, there were significant univariate correlations between IR and NYHA functional class ($r = 0.48$; $p < 0.01$), BMI ($r = 0.46$; $p < 0.01$), percent fat ($r = 0.37$; $p < 0.01$), waist-hip ratio ($r = 0.37$; $p < 0.01$), triglycerides ($r = 0.34$; $p < 0.01$), waist circumference ($r = 0.37$; $p < 0.01$), leptin ($r = 0.39$; p = 0.03), norepinephrine ($r = -0.25$; $p < 0.01$), and HDL ($r = -0.22$; p = 0.02). Multivariate analysis with 9 relevant factors (NYHA functional class, percent fat, BMI, triglycerides, waist-hip ratio, central obesity, norepinephrine, HDL, and leptin) showed that NYHA functional class and BMI were significantly and independently correlated with insulin sensitivity (all $p < 0.05$) in these CHF patients.

Relationship of IR with functional capacity. We found that the mean of FIRI increased significantly with worsening NYHA functional class ($p < 0.01$) (Fig. 2). The degree of IR was also related to the exercise capacity and peak VO_2. A total of 120 patients, 71 patients in the IR group and 49 in the normal insulin-sensitive group, were able to perform the exercise test. The IR patients had a significantly lower exercise duration (330.0 ± 162.6 s vs. 626.2 ± 262.5 s; $p < 0.01$), peak VO_2 (8.0 ± 1.6 ml/kg/min vs. 15.2 ± 2.3

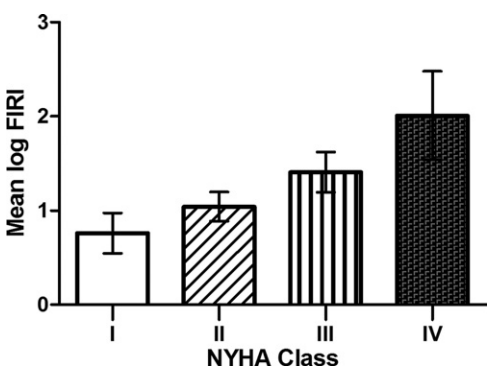

Figure 2 FIRI and NYHA Functional Class

FIRI = fasting insulin resistance index; NYHA = New York Heart Association.

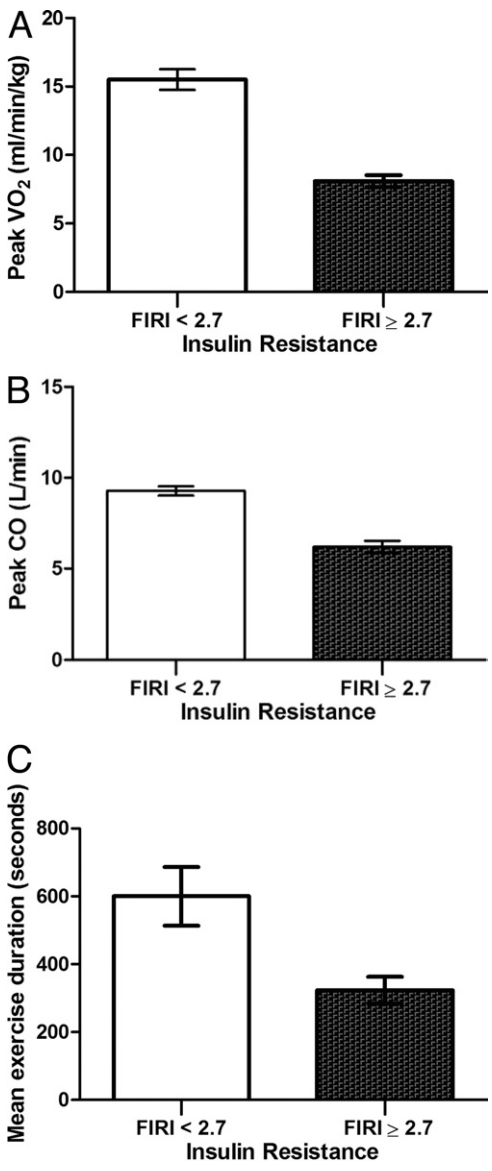

Figure 3 **Relationship Between Insulin Resistance and Exercise Parameters**

The exercise parameters consisted of **(A)** mean peak oxygen consumption (VO_2), **(B)** mean peak cardiac output (CO), and **(C)** mean peak exercise duration. FIRI = fasting insulin resistance index.

ml/kg/min; $p < 0.05$), and peak cardiac output (6.1 ± 1.2 l/min vs. 9.2 ± 0.8 l/min; $p < 0.05$) (Fig. 3). There was a significant correlation between FIRI and peak VO_2 ($r = -0.84$; $p < 0.01$), exercise duration ($r = -0.54$; $p < 0.01$), and peak cardiac output ($r = -0.82$; $p < 0.01$). After adjustment for BMI and NYHA functional class, there was a correlation between FIRI and peak VO_2 ($r = -0.83$; $p < 0.01$), exercise duration ($r = -0.40$; $p < 0.01$), and peak cardiac output ($r = -0.76$; $p < 0.01$).

Healthy volunteer subjects with IR had lower peak VO_2 (16.4 ± 1.1 ml/kg/min vs. 19.8 ± 3.4 ml/kg/min; $p = 0.1$) and peak cardiac output (6.5 ± 0.5 l/min vs. 8.9 ± 2.4 l/min; $p = 0.1$) compared with those with normal insulin sensitivity.

Discussion

This study had 3 main findings. First, IR as assessed by FIRI is highly prevalent (61%) in patients with CHF who do not have a diagnosis of diabetes compared with healthy subjects. Second, IR was associated with increased waist circumference, increased serum leptin levels, and more pronounced endothelial dysfunction in these patients. Finally, IR increased significantly with worsening NYHA functional class and was associated with reduced exercise capacity and exercise duration. Importantly, this was independent from factors associated with increased IR such as BMI and serum triglycerides.

IR in CHF. Previous studies involving much smaller cohorts of patients have investigated IR in CHF, utilizing a hyperinsulinemic-euglycemic clamp, and these have generally demonstrated a reduction in insulin sensitivity and an increase in fasting insulin concentration in patients with CHF (2,4). In this study, we have chosen the simple FIRI equation and have found that IR is highly prevalent in patients with CHF. It should be noted that a previous study by Suskin et al. (13) also utilized FIRI to examine glucose and insulin abnormalities in patients with CHF. They studied CHF patients with diabetes mellitus as well as those who had no diabetes. Like us, they found a high prevalence of patients with an FIRI ≥2.7: 72% among patients with CHF and diabetes and 33% among nondiabetic CHF patients (13). Our somewhat higher prevalence of patients with an FIRI ≥2.7 might be due to our greater proportion of NYHA functional class III to IV patients.

The exact mechanisms of IR in CHF are not known. A number of mechanisms have been proposed, including the loss of skeletal muscle bulk and skeletal blood flow, sympathetic overactivity, pro-inflammatory cytokines, altered adiponectin and leptin levels, and endothelial dysfunction (6,7,18,19). In the present study, we found a significant correlation between IR and BMI, serum triglycerides, HDL, and endothelial function. The significant correlation with BMI and serum lipids was not unexpected as these are well-established characteristics of IR and have been previously reported (6). The correlation with endothelial function is of interest and may suggest a link between endothelial function and IR in CHF (20). We did not see a relationship between IR and sympathetic activation. Paolisso et al. (2) had previously demonstrated an inverse correlation between norepinephrine concentrations and insulin sensitivity. However, this is not a universal finding. In keeping with our finding, Swan et al. (4) did not find a correlation with sympathetic activity. In our study, we found altered adiponectin and leptin levels in patients with IR with significant correlation between FIRI and the plasma levels of leptin and adiponectin. Both leptin and adiponectin are

implicated in the pathophysiology of IR (21,22). This relationship between IR and leptin in CHF has previously been described by Doehner et al. (23). These findings together with our current study may suggest that leptin could be an important regulator of IR in CHF patients. However, it should be emphasized that the presence of correlations between variables does not prove causality. Clearly, further studies are required to define the mechanisms underlying the pathophysiology of IR in CHF.

Functional consequences of IR in CHF. In this study, we found that IR was significantly correlated with peak VO_2, exercise duration, and peak cardiac output, before and after adjustment for BMI and NYHA functional class. The results of our study concur with others that show that the degree of IR is associated with reduced exercise capacity and peak VO_2 in patients with CHF (2–4,13). The underlying mechanism for the decreased exercise capacity caused by IR in CHF has not been defined. The pathophysiology of reduced exercise capacity in CHF is complex and may involve central and peripheral factors (24). The heart is an insulin-responsive organ, and IR may cause cardiac dysfunction and impact on cardiac performance through alterations in cardiac structure, function, and metabolism (25). In our study, the cardiac output at peak exercise was lower in CHF with IR. Baseline cardiac output was not different, which may suggest that cardiac reserve may be altered in CHF patients with IR. With respect to peripheral factors, we found a significant correlation between exercise capacity and endothelial function. This finding was not unexpected, given findings in previous studies in patients with CHF and diabetes showing correlations in these disease states between impaired exercise capacity and reduced endothelial function (26,27). Skeletal abnormalities may also be involved. Previous studies have shown that IR in CHF is closely correlated with a reduction in strength per unit muscle in the quadriceps muscle group and to maximal oxygen uptake per unit muscle (4). Obviously, any evidence that IR causes central cardiac dysfunction or peripheral skeletal muscle abnormalities in patients with CHF must remain speculative and cannot be inferred directly from this study.

Study limitations. First, we did not measure muscle bulk and muscle blood flow. However, we did measure lean body mass, which was significantly lower in IR patients compared with patients with normal insulin sensitivity. Second, measurement of plasma catecholamines is only an indirect measure of sympathetic nervous system activity. Future studies are needed with direct measures of sympathetic activity, including measurement of muscle sympathetic nerve activity, or by determination of norepinephrine turnover utilizing tritiated norepinephrine spillover studies. It should, however, be noted that plasma catecholamine levels do represent the neurohormonal activation in CHF and have consistently been shown to be an important prognostic marker in CHF. We also acknowledge that our healthy group of volunteers was not matched for age, sex, and BMI. Finally, we acknowledge that in this study, we have examined only for the presence of correlations between variables. It should be emphasized that such correlations neither prove causality nor define the manner in which they are related, although we did demonstrate that they were independent from established IR phenotypes such as BMI and serum triglycerides.

Conclusions

Our study suggests that there is a high prevalence of IR in patients with CHF and that IR is independently associated with worsening NYHA functional class, decrease in peak VO_2, decrease in exercise time, and endothelial dysfunction.

Reprint requests and correspondence: Prof. Chim C. Lang, Division of Medicine & Therapeutics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, United Kingdom. E-mail: c.c.lang@dundee.ac.uk.

REFERENCES

1. Coats AJS, Anker S. Insulin resistance in chronic heart failure. J Cardiovasc Pharmacol 2000;35:S9–14.
2. Paolisso G, De Riu S, Marrazzo G, Verza M, Varricchio M, D'Onofrio F. Insulin resistance and hyperinsulinemia in patients with chronic congestive heart failure. Metabolism 1991;40:972–7.
3. Paolisso G, Taglimonte MR, Rizzo MR, et al. Prognostic importance of insulin-mediated glucose uptake in aged patients with congestive heart failure secondary to mitral and/or aortic valve disease. Am J Cardiol 1999;83:1338–44.
4. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure relation to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527–32.
5. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. Cardiovasc Res 2004;61:297–306.
6. Tenenbaum A, Fisman EZ. Impaired glucose metabolism in patients with heart failure: pathophysiology and possible treatment strategies. Am J Cardiovasc Drugs 2004;4:269–80.
7. Kostis JB, Sanders M. The association of heart failure with insulin resistance and development of type 2 diabetes. Am J Hypertens 2005;18:731–7.
8. Duncan MH, Singh BM, Wise PH, Carter G, Alaqhband-Zadeh J. A simple measure of insulin resistance. Lancet 1995;346:120–1.
9. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 Suppl 1:S5–10.
11. Sloan AW. Estimation of body fat in young men. J Appl Physiol 1967;23:311–5.
12. Durnin JVGA, Womersley L. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974;32:77–97.
13. Suskin N, McKelvie RS, Burns RJ, et al. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. Eur Heart J 2000;21:1368–75.
14. Lang CC, Karlin P, Haythe J, Tsao L, Mancini DM. Ease of noninvasive measurement of cardiac output coupled with peak VO2 determination at rest and during exercise in patients with heart failure. Am J Cardiol 2007;99:404–5.
15. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr., Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol 2004;44:2137–41.

16. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol 2003;41:1761–8.
17. Hamburg NM, Keyes MJ, Larson MG, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. Circulation 2008;19:2467–74.
18. Taniguchi A, Fukushima M, Ohya M, et al. Interleukin 6, adiponectin, leptin, and insulin resistance in nonobese Japanese type2 diabetic patients. Metabolism 2006;55:258–62.
19. Rask-Madsen C, Dominguez N, Ihlemann N, et al. Tumor necrosis factor-a inhibits insulin's stimulating effect on glucose uptake and endothelium-dependent vasodilation in humans. Circulation 2003;108: 1815–21.
20. Hsueh WA, Quinones MJ. Role of endothelial dysfunction in insulin resistance. Am J Cardiol 2003;92:10J–7J.
21. Salmenniemi U, Ruotsalainen E, Pihlajamaki J, et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 2004;110: 3842–8.
22. Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274:1185–8.
23. Doehner W, Rauchhaus M, Godsland IF, et al. Insulin resistance in moderate chronic heart failure is related to hyperleptinaemia, but not to norepinephrine or TNF-alpha. Int J Cardiol 2002;83:73–81.
24. Wilson JR, Mancini DM. Factors contributing to the exercise limitation of heart failure. J Am Coll Cardiol 1993;22 Suppl A:93A–8A.
25. Banerjee S, Peterson LR. Myocardial metabolism and cardiac performance in obesity and insulin resistance. Curr Cardiol Rep 2007;9: 143–9.
26. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998;98:2709–15.
27. Maiorana A, O'Driscoll G, Cheetham C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol 2001;38:860–6.

Key Words: heart failure ■ insulin resistance ■ exercise capacity ■ endothelial dysfunction.