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# Insulin Resistance in Chronic Heart Failure: Relation to Severity and Etiology of Heart Failure

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***Objectives.*** **We attempted to assess insulin sensitivity in patients with chronic heart failure (CHF) and its relation to disease severity.**

***Background.*** **Peripheral muscular changes influence the progression of heart failure. This effect may be due to chronic disturbances of insulin and glucose metabolism that affect the energy status of skeletal and myocardial muscle.**

***Methods.*** **We investigated insulin sensitivity in 79 men—38 patients with CHF, 21 patients with angiographic evidence of coronary artery disease without CHF and 20 healthy control subjects—and assessed its relation to disease severity, etiology and hormonal status (all subjects had a similar age and body mass index). Insulin sensitivity was estimated by minimal modeling analysis of the glucose and insulin and profiles during a 0.5-g/kg body weight intravenous glucose tolerance test.**

***Results.*** **Compared with control subjects, patients with CHF had similar mean fasting glucose but increased insulin levels (67 vs. 29 pmol/liter, $p < 0.002$) and a 58% reduced mean insulin sensitivity (2.01 vs. 4.84 $min^{-1}$/pmol/ml × $10^5$, $p < 0.0001$). Peak oxygen consumption ($Vo_2$) ($r = 0.63$), fasting triglycerides ($r = -0.62$) and age ($r = -0.46$, all $p < 0.001$) predicted insulin sensitivity independently. Rest norepinephrine and epinephrine levels, left ventricular ejection fraction and heart failure etiology were not related to insulin sensitivity. Patients with coronary artery disease but no CHF had an intermediate mean insulin sensitivity (3.30 $min^{-1}$/pmol/ml × $10^5$ [−32%, $p = 0.042$ vs. control subjects; +113%, $p = 0.0023$ vs. patients with CHF due to ischemic heart disease]). In multivariate analyses of all 79 subjects, age ($p = 0.0006$), triglycerides ($p = 0.0023$), fasting insulin ($p = 0.0037$) and the presence of CHF ($p = 0.018$) were independent predictors of impaired insulin sensitivity (adjusted joint $R^2 = 0.53$, $p < 0.0001$).**

***Conclusions.*** **CHF is associated with marked insulin resistance, characterized by both fasting and stimulated hyperinsulinemia. Advanced heart failure (in terms of reduced peak $Vo_2$) is related to increased insulin resistance, but this is not directly mediated through ventricular dysfunction or increased catecholamine levels.**

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Insulin resistance is implicated in several potentially adverse metabolic changes, including disturbances in insulin and glucose metabolism, which can affect energy supply and blood flow to both myocardial and skeletal muscle (1,2). A previous pilot study in 10 patients with severe chronic heart failure (CHF) due to ischemic heart disease (3) suggested that these patients were insulin resistant. CHF is a heterogeneous syndrome with an overall adverse prognosis. Insulin resistance in patients with CHF could contribute to both the progressive deterioration of myocardial function and the peripheral clinical features that occur once heart failure has become established.

The purpose of this study was to establish whether insulin resistance is common in CHF. We therefore examined the association between the degree of insulin resistance and both severity and etiology of CHF in 38 patients with a wide range of clinical severity of CHF. Patients with CHF due to coronary artery disease are more likely to have abnormalities in glucose metabolism than are patients with CHF due to idiopathic dilated cardiomyopathy. Therefore, we also studied a control group of patients with coronary artery disease *without* heart failure. We aimed to detect whether the presence of heart failure is an independent risk factor for impaired insulin sensitivity.

## Methods

**Patients with heart failure and control subjects.** The primary study group consisted of 38 white male patients with CHF and 20 healthy male control subjects of similar age and weight. Patients were included in the study if they had stable CHF, due

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**Abbreviations and Acronyms**

ACE = angiotensin-converting enzyme
CHF = chronic heart failure
HDL = high density lipoprotein
LDL = low density lipoprotein
SC = standard coefficient
$Vo_2$ = oxygen consumption

to left ventricular systolic dysfunction, of ≥6 months' duration. Known diabetic patients were excluded from study. On the day of study no patient showed clinical signs of fluid overload, peripheral or pulmonary edema or significant elevation of jugular venous pressure. The diagnosis of ischemic heart disease was based on documentation of previous myocardial infarction, coronary artery bypass surgery or pathologic findings on coronary angiography. Idiopathic dilated cardiomyopathy was diagnosed in the absence of a specific etiology for left ventricular dysfunction and on the basis of normal coronary arteries. All patients were stable with treatment and had had no change in their treatment regimen for ≥6 weeks before the study. The majority of patients were taking furosemide (n = 33) and an angiotensin-converting enzyme (ACE) inhibitor (n = 31). Other pharmacologic drugs in use included aspirin (n = 16), nitrates (n = 13), warfarin (n = 13), amiodarone (n = 11), digoxin (n = 11) and amiloride (n = 9). The mean furosemide equivalent dose in patients was 128 ± 21 mg. None of these agents is known to have a deleterious effect on insulin or carbohydrate metabolism, although ACE inhibitors might improve insulin sensitivity. No patient was receiving antidiabetic treatment before study entry. The patients had not taken medication for ≥12 h before the study.

The 20 control subjects were clinically healthy, asymptomatic volunteers who were seen as part of a routine health screening program. They were taking no medication. All patients and volunteers gave written informed consent, and the protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London as well as by the Ethics Committee of the Wynn Institute of Metabolic Medicine, London.

**Patients with coronary artery disease.** We also present the results of a study in a contemporary group of male patients with angiographically documented coronary artery disease (>50% stenosis of one or more epicardial coronary arteries). Between 1990 and 1992, our group (4) studied 39 such patients. For the present analysis we identified 21 of those patients who were best matched in age and body mass index with the 21 patients with CHF due to coronary artery disease. Ten of these patients had a history of myocardial infarction, but not within 6 months of participating in this study. None of these patients had taken drugs known to affect lipid or carbohydrate metabolism in the previous 6 months, and they presented no symptoms of heart failure.

**Insulin sensitivity.** After an overnight fast, all subjects underwent an intravenous glucose tolerance test with the injection of a single bolus of glucose (0.5 g/kg body weight) over 3 min given as 20% dextrose. Venous blood samples were drawn to measure plasma glucose, insulin and C-peptide concentrations (3) at baseline and at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150 and 180 min. The level of C-peptide characterizes insulin secretion. Incremental glucose, insulin and C-peptide areas (i.e., the area between measured profile and rest level) were calculated by the trapezium rule. Insulin sensitivity was measured by using the minimal model of Bergman et al. (5). The model provides two summary variables: 1) insulin sensitivity (S inversely proportional to insulin resistance), and 2) an index of glucose-dependent glucose elimination (3). The modeling procedure was successful in all but one study subject. We (6) have previously demonstrated a highly significant correlation between insulin sensitivity estimates from the minimal model and the results of the euglycemic clamp reference technique (r = 0.92) in control subjects and patients with CHF. The intravenous glucose tolerance test was preferable in the present study because it is less invasive and requires less fluid loading.

**Evaluation of clinical status.** On the day of study all subjects were physically examined. All patients with CHF and the healthy volunteers performed a maximal treadmill exercise test (modified Bruce protocol, Amis 2000, Odense, Denmark [7]). The maximal oxygen consumption (peak $Vo_2$ in ml/kg per min) and the ventilation/carbon dioxide slope were measured (this was not possible in one control subject). To assess the severity of ventricular dysfunction in patients with CHF, we measured the left ventricular ejection fraction by using radionuclide ventriculography. From the venous blood samples taken at baseline before the glucose tolerance test in healthy control subjects and patients with CHF, hormones were determined that indicate the severity of heart failure: aldosterone (DPC; sensitivity 16 pg/ml), plasma renin activity (Biodata SPA, Italy; sensitivity 0.039 ng/ml per h), epinephrine and norepinephrine. The catecholamines are also known (8) to alter the action of insulin and were measured by using high performance liquid chromatography (sensitivity 0.1 ng/ml for both). Additionally, factors of lipid metabolism were analyzed in all subjects: total cholesterol and low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, and triglyceride concentration.

**Statistical analysis.** All results are presented as mean value ± SEM. Statistical analyses were performed with the StatView 4.5 computer program (Abacus Concepts Inc.). To overcome skewed frequency distributions, parameters were appropriately transformed (9). When analysis of variance showed significant differences, the Fisher post hoc test was applied. When appropriate, Student *t* tests were performed. To analyze relations between variables, simple linear regression (least square method), multivariate analysis (assessment of standard coefficients [SC]) and stepwise regressions (forward, F to enter model: 4.00) were performed. A p value $< 0.05$ was considered statistically significant.

**Table 1.** Clinical Details and Humoral Determinations in 38 Patients With Chronic Heart Failure and 20 Healthy Control Subjects

| | Patients With CHF (n = 38) | Healthy Control Subjects (n = 20) | p Value |
|---|---|---|---|
| Age (yr) | 56 ± 1.5 | 53 ± 2.6 | 0.23 |
| Height (cm) | 174 ± 0.9 | 177 ± 1.3 | 0.06 |
| Weight (kg) | 82.9 ± 2.0 | 82.6 ± 2.5 | 0.91 |
| Body mass index (kg/m$^2$) | 27.4 ± 0.6 | 26.4 ± 0.9 | 0.35 |
| Aldosterone (pmol/liter) | 770 ± 134 | 284 ± 37 | *0.012* |
| Plasma renin activity (ng/ml per h) | 7.70 ± 1.19 | 1.36 ± 0.16 | *0.0002* |
| Norepinephrine (nmol/liter) | 2.50 ± 0.24 | 1.77 ± 0.16 | *0.039* |
| Epinephrine (nmol/liter) | 0.39 ± 0.02 | 0.50 ± 0.04 | *0.012* |
| Total cholesterol (mmol/liter)* | 5.41 (+0.19, −0.18) | 4.91 (+0.20, −0.19) | 0.08 |
| HDL cholesterol (mmol/liter)* | 1.05 (+0.05, −0.05) | 1.24 (+0.06, −0.06) | *0.028* |
| LDL cholesterol (mmol/liter)* | 3.32 (+0.15, −0.14) | 3.11 (+0.19, −0.18) | 0.39 |
| Triglyceride (mmol/liter)* | 1.84 (+0.19, −0.17) | 1.00 (+0.11, −0.10) | *0.0003* |

*Logarithmic transformation results in asymmetric standard errors. Data are presented as mean value ± SEM. p values in italics indicate significant differences between groups. HDL = high density lipoprotein; LDL = low density lipoprotein.

## Results

The clinical details and results of the humoral measurements are given in Table 1. Patients with CHF or coronary artery disease and control subjects had similar age and body mass index. The etiology of heart failure was ischemic heart disease in 21 patients and idiopathic dilated cardiomyopathy in 17. The healthy control subjects had a significantly higher treadmill exercise time (718 ± 37 vs. 475 ± 35 s) and peak $V_{O_2}$ (36.7 ± 1.7 vs. 18.6 ± 1.0 ml/kg per min, both $p < 0.0001$) but a lower ventilation/carbon dioxide slope (25.1 ± 0.8 vs. 36.0 ± 2.5, $p = 0.005$). The patients with CHF had a mean left ventricular ejection fraction of 25.6 ± 2.2%, and 6 were in New York Heart Association class I, 8 in class II, 18 in class III and 6 in class IV. Aldosterone, plasma renin activity and norepinephrine levels were increased in patients with CHF (Table 1). The epinephrine levels of both groups were within normal range and slightly higher in the healthy control group. Total cholesterol and LDL cholesterol were similar in patients with CHF and healthy control subjects, whereas HDL cholesterol was reduced and triglyceride levels were increased in the CHF group (Table 1).

The baseline results of insulin, glucose and C-peptide as well the main results of the minimal model analysis of insulin sensitivity for patients with CHF and healthy control subjects are presented in Table 2. The patients with CHF were markedly insulin resistant, with a 58% reduction in insulin sensitivity ($p < 0.0001$), and they had markedly increased basal insulin and C-peptide levels, as well as increased insulin and C-peptide responses to the glucose load.

Analyzing all patients with CHF and healthy control subjects together for the factors associated with the development of insulin resistance, we found significant *univariate correlations* between insulin sensitivity and peak $V_{O_2}$ ($r = 0.63$) and exercise time ($r = 0.51$), fasting insulin ($r = -0.56$), C-peptide ($r = -0.53$) and triglyceride levels ($r = -0.62$, all $p < 0.0001$), age ($r = -0.46$, $p < 0.0005$), HDL cholesterol ($r = 0.42$) and total cholesterol ($r = -0.39$, both $p < 0.005$), LDL cholesterol ($r = -0.29$) and body mass index ($r = -0.31$, both $p < 0.05$)

**Table 2.** Insulin and Glucose Metabolism Data Assessed in 38 Patients With Chronic Heart Failure and 20 Healthy Control Subjects

| | Patients With Heart Failure (n = 38) | Healthy Control Subjects (n = 20) | p Value* |
|---|---|---|---|
| Fasting insulin (pmol/liter)† | 67 (+10, −9) | 29 (+6, −5) | *0.0011* |
| Fasting glucose (mmol/liter) | 5.47 ± 0.13 | 5.14 ± 0.08 | 0.09 |
| Fasting C-peptide (pmol/liter)† | 746 (+59, −55) | 426 (+42, −38) | *< 0.0001* |
| Incremental insulin area (min·pmol/liter × $10^{-4}$)† | 3.00 (+0.26, −0.24) | 2.10 (+0.22, −0.20) | *0.0092* |
| Incremental C-peptide area (min·$\mu$mol/liter)‡ | 119 (+11, −10) | 77 (+12, −11) | *0.011* |
| Insulin sensitivity ($min^{-1}$/pmol/ml × $10^5$)‡ | 2.01 (+0.33, −0.31) | 4.84 (+0.68, −0.63) | *< 0.0001* |
| $S_G$ ($min^{-1}$ × $10^2$)† | 1.52 (+0.14, −0.12) | 1.45 (+0.21, −0.18) | 0.75 |

*p values in italics indicate significant differences between groups. †Logarithmic and ‡square root transformation results in asymmetric standard errors. Data are presented as mean values ± SEM. $S_G$ = glucose-dependent glucose elimination.

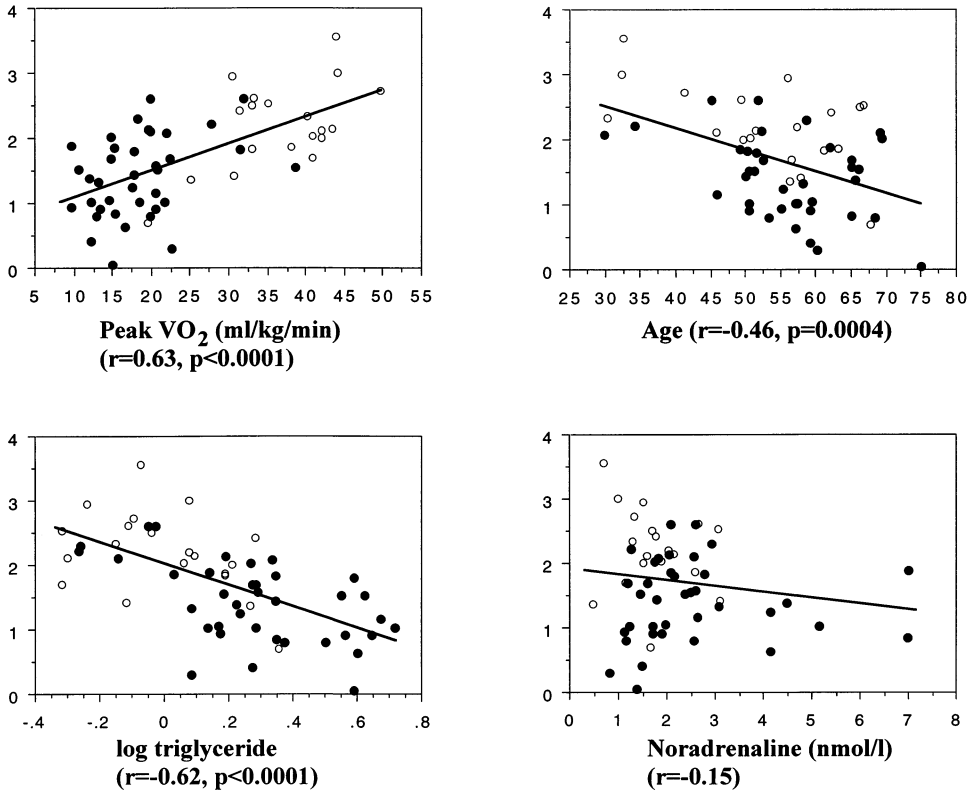


**Figure 1.** Relation between insulin sensitivity and four clinical factors (peak $Vo_2$, patient age [in years], triglyceride level and epinephrine [noradrenaline]) in 38 patients with CHF (**solid circles**) and 20 healthy control subjects (**open circles**). The **y axis** shows insulin sensitivity ($min^{-1}$/pmol/ml $\times 10^5$, square root transformation).

(Fig. 1). Neither epinephrine nor norepinephrine correlated with insulin sensitivity, fasting insulin levels or the insulin and C-peptide response to the glucose bolus in the combined group of patients with CHF and healthy subjects or both groups separately. The left ventricular ejection fraction or the furosemide equivalent dose did also not correlate with insulin sensitivity in the patients with CHF.

In a *multivariate analysis* with seven relevant factors (age, peak $Vo_2$, exercise time, body mass index and fasting triglyceride, insulin and C-peptide levels) in the patients with CHF and healthy control subjects (n = 58), age, peak $Vo_2$ and triglyceride concentration were significantly and independently correlated with insulin sensitivity (all $p < 0.05$). *Stepwise regression* with 15 clinical and humoral factors showed in these subjects that one after another peak $Vo_2$, fasting triglycerides, age and plasma aldosterone contributed significantly to the variation of insulin sensitivity in the 58 study subjects (the variation of all four factors together explained 61.8% of the variation of insulin sensitivity, $p < 0.0001$).

**Influence of coronary artery disease.** Patients with coronary artery disease without CHF were less insulin sensitive than healthy control subjects (−32%, p = 0.042), but their insulin sensitivity was 113% higher than that of patients with CHF due to ischemic heart disease (p = 0.0023) (Fig. 2). The patients with CHF due to ischemic heart disease had the highest triglyceride and fasting insulin levels (Table 3). Patients with CHF due to dilated cardiomyopathy and the patients with coronary artery disease without CHF had similar glucose, insulin, triglyceride and cholesterol levels and similar insulin sensitivity and incremental insulin area (Table 3).

A multivariate analysis of the predictors of insulin sensitivity with age, fasting insulin, triglycerides, presence of CHF and presence of coronary artery disease in all 79 subjects showed that the presence of coronary artery disease did not predict impaired insulin sensitivity. Indeed, in any model that contained fasting insulin or triglyceride levels, the presence of coronary artery disease (with or without heart failure) was not a significant independent predictor of impaired insulin sensitivity ($p > 0.20$). Age (SC = −0.28, p = 0.0006), triglycerides (SC = −0.32, p = 0.0023), fasting insulin (SC = −0.29, p = 0.0037) and presence of CHF (SC = −0.20, p = 0.018) predicted impaired insulin sensitivity independently of each other (adjusted joint $R^2 = 0.53$, $p < 0.0001$).

## Discussion

This study demonstrates that CHF is associated with marked insulin resistance, and is characterized by both fasting and stimulated hyperinsulinemia. The data expand the results of our pilot study (3) considerably, as we studied a larger patient group with a wider range of disease severity and different etiology and included a second control group with patients with coronary artery disease. A high degree of insulin resistance was seen in patients with CHF with a 58% reduction in insulin sensitivity and a 131% increase in fasting insulin concentration compared with values in a healthy control group.

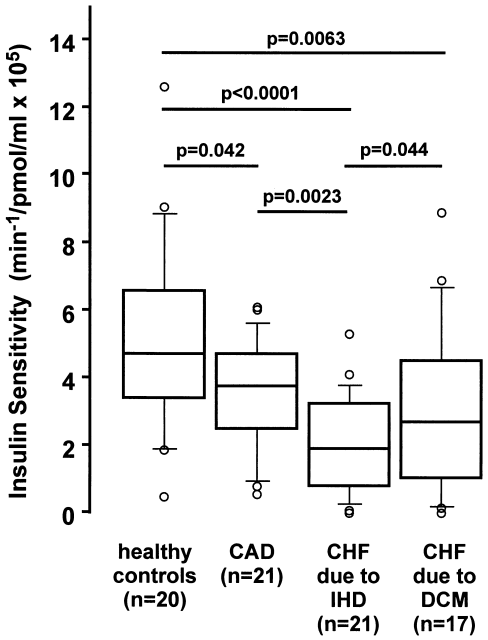


**Figure 2.** Insulin sensitivity in patients with CHF (due to ischemic heart disease [IHD], n = 21; dilated cardiomyopathy [DCM], n = 17), coronary artery disease (CAD, n = 21) and healthy control subjects (n = 20). Box plot displaying the 10th, 25th, 50th, 75th and 90th percentiles. p values for mean square root transformed insulin sensitivity were obtained by Fisher post hoc test.

Increased severity of CHF in terms of peak $Vo_2$ (i.e., functional exercise capacity) was significantly related to increased insulin resistance. CHF is related to the presence of insulin resistance independently of the presence of coronary artery disease.

Although many investigators have assumed that variations in plasma catecholamine levels as a measure of sympathetic activation could cause and hence correlate with insulin resistance in heart failure, we could not demonstrate this hypothesis in our patients. A previous study (10) demonstrated a strong negative correlation between insulin resistance and plasma norepinephrine ($r = -0.82$) in eight patients with mild to moderate heart failure (mainly due to valvular disease). In the present larger study, we could not confirm this negative correlation. Our observations do not exclude a role for sympathetic overactivity at some stage in the establishment of insulin resistance but indicate that it is unlikely to be the sole cause. The interrelation between insulin and catecholamines is complex. In normal subjects infusion of insulin increases sympathetic activity (11), but infusions of either epinephrine or norepinephrine reduce insulin levels (12,13), suggesting a possible negative feedback mechanism. However, some studies (14,15) have implicated increased catecholamine levels as a cause of insulin resistance (and hyperinsulinemia) in patients without heart disease, indicating that a disturbance of the normal feedback mechanism may occur in insulin-resistant states.

The diagnosis of ischemic heart disease or dilated cardiomyopathy was not associated with the abnormalities in insulin metabolism in our study, suggesting that the insulin resistance in CHF is not dependent on the presence of arteriosclerotic disease of the coronary arteries. We found that patients with ischemic heart disease and normal left ventricular function were insulin resistant and hyperinsulinemic but to a significantly lesser degree than patients with CHF due to ischemic heart disease. This finding supports the suggestion that the abnormalities of insulin metabolism occur secondary to the heart failure itself, possibly resulting from circulatory changes or as part of the overall neurohormonal response to heart failure. In this context it is interesting that patients with CHF due to dilated cardiomyopathy and patients with coronary

**Table 3.** Clinical Details and Measures of Carbohydrate Metabolism in Men With Chronic Heart Failure Due to Coronary Artery Disease or Dilated Cardiomyopathy and in Men With Coronary Artery Disease Without Chronic Heart Failure

| | CAD Without CHF (n = 21) | CHF Due to Dilated Cardiomyopathy (n = 17) | CHF Due to CAD (n = 21) |
|---|---|---|---|
| Age (yr) | 55 ± 1.0 | 54 ± 2.7 | 58 ± 1.5 |
| Body mass index (kg/m$^2$) | 26.0 ± 0.3 | 27.1 ± 1.0 | 27.7 ± 0.7 |
| Triglycerides (mmol/liter)‖ | 1.59 (+0.15, −0.11)* | 1.46 (+0.24, −0.21)** | 2.22 (+0.27, −0.24)***†§ |
| Total cholesterol (mmol/liter)‖ | 5.45 (+0.22, −0.21) | 5.23 (+0.36, −0.34) | 5.55 (+0.17, −0.17) |
| Fasting insulin (pmol/liter)‖ | 56 (+9, −8)** | 48 (+14, −11) | 87 (+11, −10)***§ |
| Fasting glucose (mmol/liter) | 5.39 ± 0.12 | 5.28 ± 0.10 | 5.63 ± 0.22 |
| Insulin sensitivity ($min^{-1}$/pmol/ml × $10^5$)¶ | 3.30 (+0.41, −0.38)** | 2.70 (+0.55, −0.50)* | 1.55 (+0.33, −0.30)***††§ |
| Incremental insulin area (min·pmol/liter × $10^{-4}$)‖ | 2.69 (+0.42, −0.37) | 2.48 (+0.36, −0.32) | 3.48 (+0.32, −0.29)* |
| $S_G$ ($min^{-1}$ × $10^2$)‖ | 1.33 (+0.12, −0.11) | 1.63 (+0.24, −0.21) | 1.45 (+0.17, −0.15) |

*$p < 0.05$, **$p < 0.01$ and ***$p < 0.0001$ versus healthy control subjects. †$p < 0.05$ and ††$p < 0.01$ versus patients with coronary artery disease (CAD) without chronic heart failure (CHF). §$p < 0.05$ versus patients with chronic heart failure due to dilated cardiomyopathy. ‖Logarithmic and ¶square root transformation results in asymmetric standard errors. For mean values of healthy control subjects, see Tables 1 and 2. Data are presented as mean value ± SEM. $S_G$ = glucose-dependent glucose elimination.

artery disease without CHF were very similarly metabolically impaired compared to healthy control subjects.

In addition to its effects on catecholamine levels, insulin has a marked antinatriuretic effect (16). Insulin resistance could in the long term also therefore be detrimental to the clinical condition of patients with CHF. This might be reflected by the significant relation between aldosterone and insulin sensitivity after adjusting for the effects of peak $Vo_2$, age and triglycerides. Like increased sympathetic activation, reduced peripheral blood flow has previously been demonstrated (17) to be related to insulin resistance in humans without heart disease. The reduction of skeletal muscle blood flow in heart failure at rest is small and could not alone account for the degree of insulin resistance seen in our study. Resistance to the action of insulin at the myocardial level may reduce the availability of glucose as an energy source for the heart muscle cells. It is possible that this effect plays an important role in patients with CHF, but this hypothesis could not be confirmed by significant relation between left ventricular ejection fraction and measures of insulin resistance.

An important finding of our study was the relation between insulin sensitivity and severity of CHF assessed by measurement of functional exercise capacity, that is, peak $Vo_2$. Peak $Vo_2$ derived from a maximal exercise test is an index of overall integrated cardiopulmonary function and is highly correlated with the prognosis of heart failure (18). In contrast, left ventricular ejection fraction is a measure of ventricular size and the degree of myocardial damage, characteristic of the primary event responsible for the development of CHF. In recent studies including neurohormonal evaluation of patients with CHF, left ventricular ejection fraction was not an independent predictor of prognosis (19,20). Assessment of the severity of heart failure from these two different angles and demonstration that the measures of glucose and insulin metabolism were highly correlated with peak $Vo_2$ suggests also that insulin resistance is a consequence of heart failure rather than a direct result of myocardial dysfunction. One could speculate that 1) the development of insulin resistance may also be associated with a worse prognosis and that 2) in severe CHF and cardiac cachexia, which are characterized by muscle atrophy and neurohormonal abnormalities (21,22), insulin resistance (with reduced availability of glucose as an energy source for the skeletal muscle cells) may be important in reducing skeletal muscle strength and increasing fatigability in these patients (21).

Although the majority of patients were taking furosemide, it is unlikely that this agent affected their insulin sensitivity because we found no relation between the furosemide-equivalent dose and insulin sensitivity. The cause of insulin resistance in heart failure remains unknown and was not directly addressed by this study. Therefore it remains uncertain whether insulin resistance is a primary or secondary phenomenon in heart failure, but our observations strongly support the idea that insulin resistance progresses within the natural course of heart failure and that the development of CHF has an independent additive effect even in the presence of preexisting coronary artery disease. The study was restricted to men; however, it seems unlikely that observations in women with CHF would differ substantially.

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