Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure


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Aims In addition to diabetes mellitus, less severe abnormalities of glucose and insulin metabolism may be related to functional status in patients with heart failure. We examined the relationship of hyperglycaemia (≥6.1 mmol . l⁻¹) and hyperinsulinaemia (≥11.2 mU . l⁻¹) to functional status and cardiac function in patients with heart failure.

Methods and Results Fasting plasma glucose and insulin levels were obtained in 663 heart failure patients. The average left ventricular ejection fraction was 0.28 ± 0.07, 63% were in New York Heart Association Functional Class (NYHA-FC) I/II and 37% were in NYHA-FC III/IV. Twenty seven percent had diabetes mellitus, but an additional 8% had undiagnosed diabetes mellitus (glucose ≥7 mmol . l⁻¹) and 9% had glycemic levels between 6-1 and 7 mmol . l⁻¹, so that a total of 43% (287) of patients had elevated glucose levels (≥6.1 mmol . l⁻¹). In general, more diabetic patients had NYHA-FC III/IV symptoms, shorter 6 min walk distances, but similar left ventricular ejection fractions compared to non-diabetic patients. The non-diabetic patients in NYHA-FC III/IV had higher glucose and insulin levels than patients in NYHA-FC I/II (6·3 ± 0·2 vs 5·6 ± 0·1 mmol . l⁻¹, P<0·001 and 19·6 ± 2·3 vs 10·2 ± 0·6 mU . l⁻¹, P<0·001). Non-diabetic patients with elevated glucose levels had shorter 6 min walk distances compared to those with normal glucose levels (368±8 vs 389±4 m, P=0·02), however, left ventricular ejection fraction was similar.

Conclusion Glucose abnormalities are extremely common in heart failure patients (43% of patients). Diabetes mellitus and hyperglycaemia or hyperinsulinaemia in non-diabetic patients were related to worse symptomatic status but not worsening left ventricular ejection fraction compared to patients with normal glucose and insulin levels.

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Key Words: Glucose, insulin resistance, heart failure.

See page 1293 for the Editorial comment on this article

Introduction

Diabetes mellitus is an independent risk factor for the development of heart failure, and has a prevalence of 20–25% in heart failure patients[1,2,3]. Furthermore, heart failure patients with diabetes mellitus have greater mortality and morbidity than those without[2,3]. Diabetes mellitus may promote the progression of heart failure by accelerating atherosclerosis[4] as well as by other mechanisms[5,6], including excessive interstitial myocardial collagen accumulation which could result in impaired systolic and diastolic function[5].

Elevated cardiovascular risk has been thought to occur only in patients with overt diabetes mellitus. However, there is evidence that plasma glucose concentrations less than accepted for the diagnosis of diabetes mellitus (≤7·0 mmol . l⁻¹) may also represent increased risk of cardiovascular disease[8,9]. Furthermore, heart failure may increase the propensity to insulin resistance, with subsequent increases in fasting plasma glucose
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concentrations in such patients\textsuperscript{[10,11]}.

Patients with heart failure are more insulin resistant compared to patients with coronary artery disease and normal controls\textsuperscript{[12]}. Increased insulin resistance in patients with heart failure may lead to impaired peripheral vasodilation and increased left ventricular afterload, causing further impairment of cardiac performance\textsuperscript{[13]}. Thus, insulin resistance with non-diabetic hyperglycaemia may be associated with increased symptoms of heart failure, and a greater risk of cardiovascular events, including worsening heart failure and hospitalization for heart failure\textsuperscript{[12,13]}.

The prevalence and clinical correlates of increased insulin resistance have not previously been reported in a large group of stable non-diabetic patients with heart failure. The present study specifically examined the relationship of hyperglycaemia, increased insulin resistance and diabetes mellitus to: (1) severity of heart failure symptoms; (2) left ventricular systolic dysfunction; (3) neurohormonal activation; and (4) morbidity and mortality in a cohort of heart failure patients enrolled in a randomized clinical trial\textsuperscript{[15]}.

**Methods**

**Patient selection**

Fasting glucose and insulin concentrations were measured at baseline in 663 participants in the ‘Randomized Evaluation of Strategies for Left Ventricular Dysfunction’ (RESOLVD) Pilot Study. A detailed description of the RESOLVD protocol has been published\textsuperscript{[15]}. Patients were included if they were in NYHA-FC\textsuperscript{[16]} II–IV, with a left ventricular ejection fraction <40, and a 6 min walk distance\textsuperscript{[17]} limited by leg fatigue or shortness of breath to <500 m. Patients less than 21 years of age, with unstable heart failure symptoms, with uncontrolled hypertension (BP >170/100), with significant renal impairment (serum creatinine \(\geq 200\) umol \(l^{-1}\)), with recognized non-cardiac causes of heart failure, or with an anticipated need for cardiac surgery within 3 months were excluded. The clinical diagnosis and duration of diabetes mellitus (diabetic patients) was noted at baseline.

The baseline measurements and blood sampling were made during the final week of the 3 week run-in period during which all patients took enalapril 2.5 mg twice daily. The study was approved by local ethics committees.

**Blood sampling and measurements**

Following a 12 h fast and 30 min of supine rest, blood was drawn for measurement of plasma glucose, insulin and neurohormones. The blood was sampled from a catheter in an antecubital vein, immediately centrifuged, and the plasma was separated and frozen at \(-70^\circ\)C for subsequent analysis at the biochemistry core laboratories of the Montreal Heart Institute, Canada and the Mario Negri Institute in Milano, Italy. All biochemical assays apart from N-terminal pro-atrial natriuretic peptide (pro-ANP) and brain natriuretic peptide (BNP) were performed at the Montreal Heart Institute. Norepinephrine and epinephrine were measured by high pressure liquid chromatography. Pro-ANP and BNP were measured using the method of Sundsfjord et al.\textsuperscript{[19]} in Dr Christian Hall’s laboratory in Oslo, Norway. Glucose was analysed using the GOD-PAP technique (Boehringer-Mannheim, Mannheim, Germany). Insulin was analysed using a micro-particle enzyme immunoassay (MEIA) technique on an IM–2 analyzer (Abbott Diagnostics, Chicago, Illinois, U.S.A.). This assay is highly specific for insulin with essentially no cross reactivity with proinsulin (<0.005%), C-peptide or 32-33 pro peptides. The upper limit of normal for insulin at the Montreal biochemistry core laboratory was 11.2 mU \(l^{-1}\). The degree of insulin resistance was determined by calculating the fasting insulin resistance index, which has been validated against the euglycaemic hyperinsulinaemic clamp\textsuperscript{[18]}. The fasting insulin resistance index is determined by dividing the product of the fasting plasma glucose (mmol \(l^{-1}\)) and insulin (mU \(l^{-1}\)) concentration by 25 (mU \(l^{-1}\) mmol \(l^{-1}\)), in order to have a fasting insulin resistance index value approximating unity, given expected normal plasma glucose and insulin concentrations of 5 mmol \(l^{-1}\) and 5 mU \(l^{-1}\) respectively\textsuperscript{[18]}. Based on the plasma glucose concentration upper limit of normal of 6.1 mmol \(l^{-1}\) and the core laboratory’s upper limit of normal for plasma insulin of 11.2 mU \(l^{-1}\), a fasting insulin resistance index value of 2.7 was accepted as the upper limit of normal. Patients with fasting insulin resistance index values \(\geq 2.7\) were said to have insulin resistance.

**Other measures**

Functional status was determined on all patients using the NYHA-FC and the 6 min walk distance. The 6 min walk test was performed twice in each patient, with an interval of at least 24 h. Measurement of left ventricular volumes and left ventricular ejection fraction were obtained by radionuclide angiography performed locally, utilizing a standard protocol\textsuperscript{[20]} and analysed in the core laboratory at the Toronto Hospital (Western Division). Body weight in kilograms was recorded on all patients. The duration of follow-up was 43 weeks. The clinical outcome used was the composite of any of the following events: death, worsening heart failure, hospitalization due to worsening heart failure, or hospitalization due to any other cardiovascular cause.

**Statistical analyses**

The current analysis was restricted to the 663 patients with insulin and glucose measurements at baseline. Log

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Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic patients (n=487)</th>
<th>Diabetic patients (n=176)</th>
<th>P value non-diabetic vs diabetic patients</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>64 ± 10</td>
<td>63 ± 9</td>
<td>0·14</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>73 (15)</td>
<td>32 (18)</td>
<td>0·32</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>154 (32)</td>
<td>84 (48)</td>
<td>0·001</td>
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<tr>
<td>Heart failure aetiology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>364 (75)</td>
<td>139 (79)</td>
<td>0·26</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>88 (18)</td>
<td>22 (13)</td>
<td>0·09</td>
</tr>
<tr>
<td>Other</td>
<td>35 (7)</td>
<td>15 (9)</td>
<td>0·57</td>
</tr>
<tr>
<td>Glucose (mmol . l⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 1 mmol . l⁻¹, n (%)</td>
<td>111 (23)</td>
<td>151 (86)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>≥7 0 mmol . l⁻¹, n (%)</td>
<td>53 (11)</td>
<td>133 (76)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Insulin (mU . l⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11·2 mU . l⁻¹, n (%)</td>
<td>164 (34)</td>
<td>96 (55)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>≥2·7*, n (%) or insulin resistant</td>
<td>161 (33)</td>
<td>126 (72)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0·28 ± 0·003</td>
<td>0·29 ± 0·005</td>
<td>0·2</td>
</tr>
<tr>
<td>NYHA-FC I/II, n (%)</td>
<td>326 (67)</td>
<td>99 (56)</td>
<td>0·011</td>
</tr>
<tr>
<td>III/IV, n (%)</td>
<td>161 (33)</td>
<td>77 (44)</td>
<td>0·011</td>
</tr>
<tr>
<td>6 MWD§, (m)</td>
<td>385 ± 4</td>
<td>369 ± 7</td>
<td>0·03</td>
</tr>
</tbody>
</table>

*Upper limit of normal; †ADA threshold for diabetes mellitus; §6 min walk distance; ¶no formal comparison performed — see text; FIRI fasting insulin resistance index (glucose × insulin/25).

Results

There was a total of 663 patients, 558 men and 105 women, with a mean age of 64 ± 0·4 years included in this study. Most patients were either NYHA-FC II or III, with only six (0·9%) patients in NYHA-FC I and 11 (1·7%) patients in NYHA-FC IV (Table 1). The mean 6 min walk distance and left ventricular ejection fraction for all patients were 381 ± 3 m and 0·28 ± 0·003, respectively. Ischaemic heart disease was the most frequently reported cause of heart failure (76%), followed by idiopathic dilated cardiomyopathy (17%). Ischaemic heart disease was considered the primary cause of heart failure in a similar proportion of non-diabetic and diabetic patients. Diuretic use was less prevalent among non-diabetic patients (78% vs 88%, P<0·01). Digoxin use was slightly less prevalent among the non-diabetic patients, but calcium channel blocker use was similar between the two groups. More diabetic patients had a diagnosis of hypertension than non-diabetic patients (48% vs 32%, P<0·001). In addition, the mean systolic blood pressure was higher in diabetic patients compared to non-diabetic patients (126 ± 1 mmHg vs 120 ± 1 mmHg, P=0·0001) (Table 1).

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Diabetes, glucose and insulin

A total of 176 patients (27%) had a diagnosis of diabetes mellitus (diabetic patients), including a similar proportion of women and men (30.5% vs 25.8%, P=0.3, Table 1). The mean plasma glucose concentration of the diabetic patients was 9.9 ± 0.3 mmol l\(^{-1}\). The mean plasma glucose concentration of the 487 non-diabetic patients was 5.8 ± 0.1 mmol l\(^{-1}\) (Table 1). A total of 111 (23%) of the non-diabetic patients had elevated fasting glucose concentrations (≥6.1 mmol l\(^{-1}\)) while 53 (11%) of these patients had fasting glucose concentrations in the diabetic range (fasting plasma glucose ≥7.0 mmol l\(^{-1}\)). Overall, 287 (43%) patients (176 diabetic and 111 non-diabetic) had abnormalities of glucose metabolism by fasting blood glucose criteria.

The mean plasma insulin concentration and fasting insulin resistance of the diabetic patients were 28.2 ± 4.6 mU l\(^{-1}\) and 12.1 ± 1.8, respectively. The mean plasma insulin concentration in the non-diabetic patients was 13.3 ± 0.9 mU l\(^{-1}\), and 34% of these patients had elevated (≥11.2 mU l\(^{-1}\)) insulin concentrations. The mean fasting insulin resistance index of the non-diabetic patients was 3.7 ± 0.4, with 34% of these patients having insulin resistance (fasting insulin resistance index ≥2.7) (Table 1).

New York Heart Association functional class

A greater proportion of diabetic compared to non-diabetic patients were in NYHA-FC III/IV (Table 1). In the non-diabetic patients, glucose (6.3 ± 0.2 vs 5.6 ± 0.1 mmol l\(^{-1}\), P<0.005), insulin (19.6 ± 2.3 vs 10.2 ± 0.6 mU l\(^{-1}\), P<0.005), and fasting insulin resistance index (6.2 ± 1.0 vs 2.4 ± 0.2, P<0.005) values were significantly greater in patients with NYHA-FC III/IV than those with NYHA-FC I/II (Fig. 1). Among the non-diabetic patients, significantly more NYHA-FC III/IV patients had elevated fasting values for glucose (≥6.1 mmol l\(^{-1}\); 32% vs 18%, P<0.005), insulin (≥11.2 mU l\(^{-1}\); 45% vs 28%, P<0.005), and fasting insulin resistance index (≥2.7; 44% vs 28%, P<0.005) compared to NYHA-FC I/II patients. Furthermore, more diabetic patients were NYHA-FC III/IV compared to the non-diabetic patients with and without insulin resistance (44% vs 44% vs 28%, chi-square P for trend P=0.005, Fig. 2(a)).

Six minute walk

Diabetic patients had a significantly shorter 6 min walk distance compared to non-diabetic patients overall (Table 1). There was a significant decrease in the 6 min walk distance between non-diabetic patients without insulin resistance compared to non-diabetic patients with insulin resistance and diabetic patients (391 ± 5 m vs 372 ± 7 m vs 369 ± 7 m, ANOVA P<0.005, Fig. 2(a)). Non-diabetic patients with glucose ≥6.1 mmol l\(^{-1}\), insulin concentrations ≥11.2 mU l\(^{-1}\) or a fasting insulin resistance index ≥2.7, had a significantly shorter 6 min walk distance than those with normal values (368 ± 8 m vs 389 ± 4 m, P=0.02; 369 ± 7 m vs...
393 ± 5 m, P<0·005 and 372 ± 7 m vs 391 ± 5 m, P=0·02), respectively (Fig. 2(b)). In addition, plasma glucose concentrations were significantly greater (6·0 ± 0·1 mmol. l⁻¹ vs 5·7 ± 0·1 mmol. l⁻¹, P=0·036) in those non-diabetic patients with a 6 min walk distance less than the median of 398 m compared to those with a 6 min walk distance greater than the median.

Left ventricular ejection fraction, cardiac volumes, and heart rate

There were no significant differences in left ventricular ejection fraction between patients with diabetes mellitus compared to non-diabetic patients with or without insulin resistance (diabetic 0·29 ± 0·01; insulin resistance 0·29 ± 0·01; no insulin resistance 0·27 ± 0·01; P=0·12). However, diabetic patients had smaller end-diastolic (226 ± 7 ml vs 248 ± 9 ml vs 260 ± 6 ml, P<0·005) and end-systolic (166 ± 7 ml vs 183 ± 8 ml vs 195 ± 6 ml, P=0·008) left ventricular volumes, but higher heart rates (77 ± 1 beats. min⁻¹ vs 75 ± 1 beats. min⁻¹ vs 73 ± 1 beats. min⁻¹, P=0·007) compared to non-diabetic patients with and without insulin resistance (Fig. 3).

Neurohormones

Compared to diabetic patients, non-diabetic patients had higher plasma norepinephrine (P<0·01) and epinephrine (P=0·015) levels, with slightly higher plasma Pro-ANP (P=0·086) and BNP (P=0·058) concentrations (Table 2). Those patients with less than the 9 year median duration of diabetes had similar norepinephrine and epinephrine but lower Pro-ANP and BNP levels compared to those with greater than a 9 year duration of diabetes.

Table 2  Neurohormones and diabetic status

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine (pg. ml⁻¹)</th>
<th>Epinephrine (pg. ml⁻¹)</th>
<th>Pro-ANP (pmol. l⁻¹)</th>
<th>BNP (pmol. l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>510 ± 8 ± 13·4</td>
<td>79·2 ± 4·1</td>
<td>1512·4 ± 58·1</td>
<td>57·1 ± 3·1</td>
</tr>
<tr>
<td>Diabetic</td>
<td>441 ± 6 ± 19·2</td>
<td>65·5 ± 3·8</td>
<td>1358·5 ± 68</td>
<td>47·6 ± 3·9</td>
</tr>
<tr>
<td>P for non-diabetic vs diabetic</td>
<td>0·003</td>
<td>0·015</td>
<td>0·086</td>
<td>0·058</td>
</tr>
</tbody>
</table>

Correlations of glucose, insulin, and fasting insulin resistance index with age, weight, blood pressure, heart rate, serum creatinine, left ventricular ejection fraction, and neurohormones

Among the non-diabetic patients there was a significant correlation between weight and plasma glucose (r=0·28, P<0·0001), insulin (r=0·49, P<0·0001), and fasting insulin resistance index (r=0·49, P<0·0001) values. There were modest significant inverse correlations between the 6 min walk distance and glucose (r=−0·11, P<0·05), insulin (r=−0·13, P<0·01), and fasting insulin resistance index (r=−0·13, P<0·01) concentrations. However, body weight was not correlated with NYHA-FC or the 6 min walk distance. Age, blood pressure, heart rate, left ventricular ejection fraction, and serum creatinine were not significantly correlated with plasma glucose, insulin, or fasting insulin resistance index levels. There were modest inverse correlations between plasma glucose and BNP (−0·17, P<0·001) and between fasting insulin resistance index and BNP (r=−0·28, P<0·001). No significant correlations were demonstrated between glucose or fasting insulin resistance index levels and norepinephrine or epinephrine concentrations.

Clinical events during the 43 week follow-up period

Sixty three (35·8%) diabetic patients had an event (death or worsening heart failure or hospitalization due to any other cardiovascular cause including heart failure) compared to 132 (27·1%) of the non-diabetic patients (P=0·03). Diabetes mellitus remained a significant predictor of any clinical event even after adjustment for NYHA-FC and left ventricular ejection fraction (P<0·04). Twenty four (13·6%) diabetic patients were hospitalized due to worsening heart failure compared to 42 (8·6%) non-diabetic patients (P=0·057). In
multivariate analysis after adjustment for age, NYHA-FC and left ventricular ejection fraction for age, diabetes mellitus remained a significant predictor of hospitalizations due to worsening heart failure ($P=0.026$). Those patients with greater than the 9 year median duration of diabetes experienced a slightly greater number of clinical events compared to those with a diabetes duration of less than 9 years, but this did not reach statistical significance.

Among the non-diabetic patients there were no significant differences in the number of heart failure hospitalizations, hospitalizations for any cardiovascular cause, or any combination of these events and death between those with normal compared to elevated plasma glucose (27.4% vs 26.1%, $P=0.8$), or insulin resistance (28.5% vs 24.2%, $P=0.3$).

### Discussion

There were five main findings illustrated by this study. First, hyperglycaemia is much more common in patients with heart failure than was previously recognised and occurred in 43% of patients. Second, the presence of diabetes mellitus or insulin resistance in non-diabetic patients are both associated with more severe symptoms of heart failure and worse functional capacity. Third, this relationship exists despite relative preservation of left ventricular ejection fraction and smaller left ventricular volumes in both diabetic and non-diabetic patients with insulin resistance. Fourth, the presence of diabetes mellitus or insulin resistance in non-diabetic patients was not associated with greater activation of the neurohormonal system. Fifth, diabetic patients more frequently experienced clinical events compared to non-diabetic patients.

Of the 663 heart failure patient cohort, 287 (43%) had elevated fasting glucose concentration or diabetes mellitus. It has been reported that diabetes mellitus occurs frequently in patients with either symptomatic or asymptomatic left ventricular dysfunction [2,21]. Twenty-seven percent of our patients were known to have diabetes mellitus, which is similar to the 26% observed in the SOLVD Treatment Trial [22], and the 27.5% reported by Abbud et al. [3], for individuals presenting with an acute myocardial infarction with left ventricular dysfunction. The present study is unique in that we have demonstrated that hyperglycaemia in patients with heart failure not known to be diabetic is also common, with one quarter of the 487 patients not known to be diabetic having either elevated fasting plasma glucose concentrations or diabetic range hyperglycaemia.

Diabetic patients were 1.6 times (95% CI 1.1–2.2, $P=0.01$) as likely to have NYHA-FC III/IV symptoms than non-diabetic patients and diabetic patients had a significantly lower 6 min walk distance than non-diabetic patients. These data are consistent with the results from the SOLVD Treatment and Prevention Trials. Patients in the SOLVD Treatment Trial of symptomatic patients were 1.9 times (95% CI 1.7–2.2, $P<0.001$) as likely to be diabetic compared to the SOLVD Prevention Trial of asymptomatic patients (calculated from published data from the SOLVD trials [22,21,23]. The results of the present study expand these findings and are the first to demonstrate this type of relationship within a large cohort of diabetic and non-diabetic heart failure patients, as the prevalence of both diabetes mellitus and insulin resistance (in non-diabetic patients) increased with increasing symptoms of heart failure.

In this study, non-diabetic patients with NYHA-FC III/IV symptoms had twice the likelihood (95% CI 1.4–3.1, $P<0.001$) for having insulin resistance compared to patients with NYHA-FC III symptoms. Also, compared to patients whose 6 min walk distance was in the highest tertile, those with a 6 min walk distance in the lowest tertile were 1.6 (95% CI 0.99–2.7, $P=0.04$) times as likely to have elevated plasma insulin concentrations. These findings imply that the mechanism(s) underlying the association of diabetes mellitus to more severe symptoms of heart failure and poorer functional status continue to operate below the diabetic threshold, i.e. in non-diabetic patients with insulin resistance. Variables that may have acted as confounders in this relationship, such as higher blood pressure, lower left ventricular ejection fraction, increasing age, serum creatinine, and weight were found not to correlate with either insulin resistance or functional status. The observed association between diabetic patients or insulin resistance in non-diabetic patients to increased symptoms of heart failure (higher NYHA-FC or lower 6 min walk distance) could be due to a number of mechanisms including a direct cardiomyopathic process and diastolic dysfunction, an impairment of peripheral vasodilation, or skeletal muscle dysfunction [27,28]. The current results do not allow precise determination as to which of these mechanisms are most responsible for this relationship. However, the association between the presence of diabetes mellitus or insulin resistance in non-diabetic patients with increased symptoms of heart failure existed despite the relative preservation of left ventricular ejection fraction. In addition, diabetic patients had significantly smaller left ventricular volumes and higher heart rates compared to non-diabetic patients with and without insulin resistance. This suggests there may be significant ‘diastolic’ abnormalities superimposed on the left ventricular systolic dysfunction in diabetic heart failure patients and non-diabetic heart failure patients with insulin resistance. The diastolic abnormality may be in part related to alterations in glucose and insulin metabolism leading to collagen accumulation and increased myocardial stiffness [4]. Under normal conditions, the very high energy requirements of the myocardium are primarily met by the oxidation of fatty acids. Alterations in fatty acid oxidation can impair contractile function in diabetic and hypertrophied hearts [5]. In particular, oxygen is required for fatty acid metabolism and in diabetic

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patients with concurrent coronary ischaemia, accumulation of fatty acids may occur, which are toxic to the myocardium[25]. There is a growing body of clinical evidence to support the theory that a distinct diabetic cardiomyopathy may exist, which is characterized by diastolic dysfunction and can occur in the absence of known coronary disease[4, 5]. In the SOLVD Prevention and Treatment Trials, left ventricular ejection fraction was similar in diabetic compared to non-diabetic patients[22, 23]. The present study extends this association to non-diabetic patients as there was no relationship found between left ventricular ejection fraction and the degree of insulin resistance. Our findings are in agreement with Swan and colleagues, as they failed to find a significant correlation (although in a smaller number of patients) between the left ventricular ejection fraction and degree of insulin resistance[12].

Diabetic and non-diabetic patients with insulin resistance in this study had increased heart failure symptoms and a shorter 6 min walk distance. Although not investigated in this study, abnormalities of peripheral vascular function may have contributed to this relationship. Endothelial dependent vasodilation due to nitric oxide release from endothelial cells has been shown to be impaired in heart failure patients[26]. Insulin has been shown to stimulate endothelial nitric oxide production through the same signalling pathway that promotes glucose transport, suggesting that nitric oxide production and glucose metabolism may be coupled[13]. In an insulin resistant state such as hypertension, impairment of insulin dependent vasodilation has been observed[13]. Therefore, in heart failure patients with insulin resistance the observed reduction in functional capacity may be the result of increased vascular resistance and reduced peripheral blood flow due to impaired release of nitric oxide from endothelial cells[7].

In this study, the presence of diabetes or insulin resistance among non-diabetic patients were stronger predictors of poor functional status than the well established markers (plasma norepinephrine, epinephrine, and BNP) of poor functional status and prognosis in patients with heart failure, which is intriguing. Diabetic patients had lower plasma norepinephrine, epinephrine, and BNP concentrations compared to non-diabetic patients. Those patients with less than the 9 year median duration of diabetes had similar norepinephrine and epinephrine but lower Pro-ANP and BNP levels compared to those with duration of diabetes greater than 9 years. Among the non-diabetic patients, there was a modest inverse correlation between plasma BNP and insulin resistance. This may in part relate to the diabetic patients having lower left ventricular volumes as ventricular wall stretch is a powerful stimulus for adrenergic stimulation via the vagal afferents from the myocardium[27]. Lower plasma BNP levels were associated with insulin resistance, and insulin resistance was associated with increased heart failure symptoms. This may imply an association between increased heart failure symptoms and lower plasma BNP levels which appears to conflict with some studies which have shown BNP to be a good marker of left ventricular systolic dysfunction[28]. However, BNP may be more closely related to left ventricular ejection fraction once heart failure symptoms develop[29]. In addition, a recent report[30] has linked beta-adrenergic receptor antagonism to augmented levels of plasma BNP, thus augmented plasma levels of BNP may be beneficial in heart failure patients. This is consistent with our data correlating higher plasma levels of BNP with lower insulin resistance and less heart failure symptoms.

This study demonstrated that diabetic patients more frequently experienced clinical events compared to non-diabetic patients, which is consistent with previous studies[22, 23, 24]. In addition, this risk appeared to increase with a greater duration of diabetes. However, the reasons for this relationship remain unclear as diabetic patients had similar left ventricular systolic function, smaller left ventricular volumes and less sympathetic neurohormonal activation compared to non-diabetic patients. Among the non-diabetic patients there were no significant differences in the number of events between those with normal compared to elevated plasma glucose or insulin concentrations or fasting insulin resistance index levels.

There are some potential limitations to the present study. Although the type of diabetes was not specifically noted in the case report forms, this should not have influenced our main results, as it is likely that the majority of the patients were type 2 diabetics. In addition, although all (those known to be diabetic and those not known to be diabetic) patients had blood insulin levels analysed, only those not known to be diabetic had statistical inferences made from these results. Therefore the calculated insulin resistance (glucose and insulin product/25) and the subsequent reported associations with functional status or cardiac function were not influenced by exogenous insulin therapy or none of those patients were receiving any antidiabetic therapy.

Worsening heart failure can be a rather subjective end-point. However, in the RESOLVD main study protocol, worsening heart failure was documented on a case report form, required ancilliary laboratory documentation and was verified by a separate outcome committee. Therefore, although worsening heart failure can be subjective, an effort was made to standardize and make the outcome more objective for this study. In addition, clinical outcomes were not the main focus of the study, and as such any uncertainty relating to clinical outcomes should not have detracted from the main results.

Diabetes mellitus, hyperglycaemia and insulin resistance among non-diabetic patients are common in patients with heart failure. More than 40% of our 663 stable heart failure patients had known diabetes mellitus or hyperglycaemia. Diabetes patients and non-diabetic patients with insulin resistance had more advanced symptoms of heart failure and a shorter 6 min walk distance compared to non-diabetic patients without insulin resistance. This association was not related to the
level of left ventricular systolic dysfunction or the degree of sympathetic neurohormonal activation. This study did not distinguish between whether abnormalities of glucose and insulin metabolism (insulin resistance) were a consequence, or a cause, of worsening symptoms of heart failure, but increases our understanding of these relationships because a substantial number of diabetic and non-diabetic patients were included. Further study is needed, in particular to examine whether interventions to correct insulin resistance in heart failure patients will improve symptoms or outcome.

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References