Effect of Beta-Blockers on Insulin Resistance in Patients With Dilated Cardiomyopathy

Yuji Hara, MD; Mareomi Hamada, MD; Yuji Shigematsu, MD; Tomoaki Ohtsuka, MD; Akiyoshi Ogimoto, MD; Jitsuo Higaki, MD

The aim of this study was to evaluate the effect of β-blockers on insulin resistance in patients with dilated cardiomyopathy (DCM). A secondary aim was to determine the effect of this treatment on plasma concentrations of tumor necrosis factor-α (TNF-α) and to investigate the relationships between this adipocytokine and insulin resistance. Insulin resistance determined using the Homeostatic Model Assessment (HOMA), echocardiographic measurements and analysis of plasma TNF-α concentration were carried out in 47 patients with DCM without diabetes mellitus before and after 6 months of β-blocker therapy. A reduction in left ventricular dimensions and an associated increase in ejection fraction occurred with β-blocker. The treatment resulted in a significant decrease in insulin resistance (HOMA index: Baseline, 2.73±3.36 vs Month 6, 1.58±1.33, p=0.0347). Beta-blockade was also associated with a decrease in plasma TNF-α concentration although no significant relationship between this change and the improvement in insulin resistance was observed. Beta-blocker therapy in patients with DCM improved not only cardiac function, but also insulin resistance. The mechanism of the change in insulin function remains unclear, but may be related to improvements in left ventricular function or an attenuation of the inhibitory effect of reduction in TNF-α on insulin signaling. (Circ J 2003; 67: 701–704)

Key Words: Beta-blockers; Dilated cardiomyopathy; Insulin resistance; Tumor necrosis factor-α

It is well established that treatment with a β-blocker results in improvement in cardiac function and prognosis of patients with chronic heart failure. The majority of these patients have increased insulin resistance. Patients with essential hypertension are also insulin resistant but several studies have shown that treatment of essential hypertension with an angiotensin-converting enzyme (ACE) inhibitor improves insulin resistance in contrast to β-blockade that appears to have adverse effect on insulin function in those patients. There is evidence that β-blockers have beneficial hemodynamic effects in patients with dilated cardiomyopathy (DCM), but we are unaware of any other study that has investigated the effects of these agents on insulin resistance. We conducted a prospective 6-month study of the effects of the β-blockers, metoprolol, bevantolol and carvedilol, on insulin resistance in patients with DCM.

Methods

Subjects
We studied 47 patients with DCM (mean age 55±13, range 25–78 years) who had been treated with digitalis, diuretics and an ACE inhibitor for at least 3 months. All patients were diagnosed as having DCM according to the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. All patients underwent coronary angiography, and patients with coronary artery disease were excluded. Patients who had clinical or laboratory evidence of diabetes mellitus were also excluded. Of the 47 patients, 12 were classified as New York Heart Association (NYHA) functional class III, 30 as Class II and 5 as Class I before the administration of β-blocker. Fifteen subjects (mean age 53±15, range 23–74 years) who had no evidence of organic cardiac disease or diabetes mellitus were retrospectively selected as a control group for the measurement of insulin resistance. There were no significant differences in age, gender or body mass index between the DCM group and the control group (Table 1). The study protocol was approved by the Human Investigations Committee of the institution and all patients gave informed consent before participating in the study.

Study Protocol
Following admission to hospital, all patients with DCM had baseline biochemical and echocardiographic assess-
ments carried out. Treatment with a β-blocker was then begun for a period of 6 months, each under the same standard therapy, with 14 patients receiving metoprolol, 13 receiving bevantolol and 20 receiving carvedilol. The initial dosage of metoprolol and bevantolol was 2.5 or 5 mg/day and the initial dosage of carvedilol was 12.5 or 2.5 mg/day. The dose was increased every 5–7 days until a maintenance dose was achieved based on the prior dose being clinically tolerated, heart rate at rest remaining between 50 and 70 beats/min and systolic blood pressure more than 90 mmHg. Mean maintenance doses were 36±10 mg (range 20–60 mg) for metoprolol, 53±32 mg (range 20–150 mg) for bevantolol and 16±6 mg (range 10–30 mg) for carvedilol.

Echocardiographic Study

M-mode and 2-dimensional echocardiographic studies were performed with an Aloka SSD 9000 or SSD 5500 imaging system (Tokyo, Japan) with 2.5- or 3.5-MHz transducers. The M-mode echocardiogram was recorded on a strip-chart recorder at a paper speed of 50 or 100 mm/s. The following conventional variables were obtained from the M-mode measurements according to the criteria of the American Society of Echocardiography:19 left ventricular dimension at end-diastole (LVDd) and end-systole (LVDs), left ventricular volume calculated using Teichholz’s formula, and ejection fraction (EF). Arterial blood pressure was determined in duplicate on the day of the echocardiographic studies using a sphygmomanometer.

Measurement of Insulin Resistance

A blood sample was withdrawn from the antecubital vein on the morning of the investigations after the patient had fasted for 12h. Fasting blood glucose (FBS) and insulin concentrations were measured and used to determine the Homeostatic Model Assessment (HOMA) index of insulin resistance, calculated using the equation: HOMA = FBS×insulin/22.5.20

Measurement of TNF-α (TNF-α)

Blood samples for TNF-α analysis were collected into chilled tubes, immediately centrifuged at 4°C, stored at −80°C and analyzed using an enzyme-linked immunosorbent assay (Immunotech Co, Marseille, France). The average inter- and intra-assay coefficients of variation were <10% for all the assays carried out.

Table 2  Changes in Hemodynamic, Echocardiographic and Plasma TNF-α Concentration Data Before and After Treatment With a β-Blocker in Patients With Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>At baseline</th>
<th>After treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td>2.15±0.60</td>
<td>1.57±0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>76±16</td>
<td>65±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114±12</td>
<td>116±16</td>
<td>0.4942</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>63.6±6.7</td>
<td>59.6±6.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>52.6±8.5</td>
<td>46.5±8.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>35.2±12.0</td>
<td>43.8±12.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>33.9±5.2</td>
<td>15.1±1.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; HR, heart rate; SBP, systolic blood pressure; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; EF, ejection fraction; TNF, tumor necrosis factor.

Statistical Analysis

Data were analyzed using StatView (Abacus Concepts, Inc, Berkeley, CA, USA, 1994) and expressed as mean±SD. The level of significance for comparative analyses was set at p<0.05. Baseline characteristics, except for insulin concentration and HOMA index, were analyzed with an unpaired t test or chi-square test for non-parametrically distributed values. The difference in insulin concentration and the HOMA index between DCM patients and controls was compared using the Mann-Whitney U rank-sum test for unpaired data. Changes in the hemodynamic or echocardiographic variables after β-blocker therapy were analyzed using Student’s paired t test, and changes in NYHA functional class, HOMA index and TNF-α were determined by the Wilcoxon signed rank test. The relationship between HOMA index and hemodynamic or echocardiographic parameters before β-blocker treatment was assessed by linear regression. The relationship between changes in insulin resistance and changes in echocardiography parameters or plasma TNF-α concentration was assessed by linear regression. All calculations were performed on a personal computer with the statistical package StatView (Abacus Concepts, Inc). A value of p<0.05 was considered significant.

Results

Insulin Resistance and Plasma TNF-α Concentration

Insulin resistance at baseline was significantly greater in patients with DCM than in the control subjects (Table 1). The effect of β-blocker treatment on this variable in the DCM group is shown in Fig 1; there was a significant improvement in insulin resistance (mean HOMA index 2.73±3.36 vs 1.58±1.33, p=0.04). The plasma TNF-α concentration was also significantly decreased after 6 months of treatment with the β-blockers (Table 2).

Echocardiography

Table 2 summarizes the changes in echocardiographic parameters, heart rate and systolic blood pressure from baseline to after β-blockade. Although systolic blood pressure remained unchanged, there was a significant decrease in heart rate. As anticipated, both LVDd and LVDs decreased while EF increased.

Relationship Between Insulin Resistance and Hemodynamic, Echocardiographic Parameters or Plasma TNF-α Concentration

There was no relationship between HOMA index and...
hemodynamic or echocardiographic parameters before ß-blocker treatment. There was also no relationship between the improvement in insulin resistance and changes in the echocardiographic parameters or plasma TNF-α concentration.

Discussion

The present study confirms that DCM is associated with insulin resistance and shows that treatment with a ß-blocker attenuated this change in insulin function. However, the mechanism of this apparent improvement in insulin sensitivity remains unclear. In patients with hypertension, ß-blockers reportedly induce insulin resistance, possibly by decreasing the metabolic clearance rate of insulin that in turn results in higher insulin concentrations, impaired glucose disposal and hyperglycemia.14,15 It is possible that the decrease in cardiac output during treatment with a ß-blocker may result in decreased blood flow in skeletal muscles, thereby reducing the availability of glucose to the prime target tissue for glucose disposal.16 However, Malminiemi et al reported that celiprolol, a vaso-dilating ß1-adrenoreceptor antagonist, improved insulin sensitivity in dyslipidemic hypertensive patients; celiprolol had ß2-agonist properties, which can cause vasodilation in muscle tissue.17 Retsgraf et al recently reported that carvedilol is neutral with regard to its influence on insulin sensitivity in patients with congestive heart failure.22 Pietila et al reported that insulin sensitivity was favorably affected by exercise training in chronic heart failure, and that celiprolol augmented this effect.23 The findings of the present study in patients with DCM indicate that the effects of improved cardiac function associated with ß-blockade, such as enhanced exercise capacity and increased peripheral blood flow, may indirectly lead to an increase in insulin sensitivity. Swan et al reached a similar conclusion in a study of patients with heart failure in which it was shown that insulin resistance was a consequence of reduced peak oxygen consumption rather than a result of abnormal ventricular function or changes in norepinephrine activity.10 However, in the present study we were unable to demonstrate an association between changes in left ventricular function and improved insulin resistance and therefore further investigations are warranted in order to better understand the etiologic role of hemodynamic changes on insulin activity.

Our study results also raise the possibility that reductions in plasma TNF-α concentration may be a factor contributing to the increase in insulin sensitivity induced by ß-blockers in DCM. It is well established that TNF-α in combination with norepinephrine has an adverse effect on insulin signaling by inhibiting phosphorylation of the insulin receptor.24–26 The finding of the present study, and that of an earlier investigation27 that ß-blocker treatment markedly reduced the TNF-α concentration raises the possibility that attenuation of the inhibitory effect of this adipocytokine following ß-blockade results in improved insulin sensitivity. However, as with the hemodynamic results we were unable to demonstrate a significant relationship between changes in cytokine concentration and insulin resistance and therefore more comprehensive and larger studies are required in order to validate the role of TNF-α in these beneficial changes associated with ß-blockers.

Study Limitations

The study protocol was not randomized and the researchers were not blinded to treatment. However, measurements of cardiac function, insulin resistance and TNF-α were performed in a blinded manner with regard to treatment groups and time. Another limitation is the small number of study patients. We are aware that a larger number of subjects would have improved the reliability of our results.

Conclusion

Beta-blocker treatment attenuates insulin resistance in patients with DCM and we would suggest that ß-blockers may be a beneficial adjunct to the treatment regimen of patients with DCM, especially those individuals with insulin resistance.

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