Effect of selective and non-selective β-blockers on body weight, insulin resistance and leptin concentration in chronic heart failure

Abstract  Background Chronic heart failure (CHF) is characterized by increased insulin resistance and hyperleptinaemia. We aimed to study effects of selective and non-selective β-blockers on body weight, insulin resistance, plasma concentrations of leptin and resistin in patients with CHF. Methods Twenty-six non-cachectic β-blocker-naive patients with CHF were randomized and treated with either carvedilol or bisoprolol. Body weight, plasma concentrations of leptin, resistin, fasting glucose and insulin were measured at baseline and after 6 months of therapy. Insulin resistance was estimated by homeostasis model assessment-estimated insulin resistance (HOMA-IR). Results Body weight increased significantly in the carvedilol group (mean change +2.30 kg, p=0.023) while it did not change in the bisoprolol group (mean change –0.30 kg, p=0.623) (ns between groups). Plasma leptin concentration increased only in the carvedilol group (mean change +4.20 ng/ml, p=0.019) (ns between groups). Fasting glucose and resistin remained unchanged in both groups. After 6 months, mean plasma insulin concentration changed significantly differently (p=0.015) in the bisoprolol (mean change +3.1 μU/ml) compared to the carvedilol group (mean change −6.3 μU/ml) and HOMA-IR was consequently higher in the bisoprolol compared to the carvedilol group (5.2 ±4.2 vs 2.8 ±1.6, p=0.046). Conclusion This study found different metabolic effects of carvedilol and bisoprolol in non-cachectic patients with CHF. With unchanged fasting plasma glucose concentration after 6 months of treatment, carvedilol significantly decreased plasma insulin concentration and insulin resistance compared to bisoprolol.

Key words bisoprolol – carvedilol – chronic heart failure – insulin resistance – leptin – resistin

Introduction

Chronic heart failure (CHF) is a major disorder becoming increasingly prominent as the proportion of elderly in the population increases. The fact that it is also a condition with increased plasma catecholamines led to the hypothesis that sympathetic antagonists might be useful in its management. Today we know that β-adrenergic receptor blockers (β-blockers) are in fact associated with a significant reduction in mortality risk in patients with CHF [22].

CHF is, independent of etiology, a state of increased insulin resistance. The degree of insulin resistance correlates with the degree of heart failure [31]. Diabetes mellitus has been shown to be a pre-
disposing factor for development of CHF [30] and an independent predictor of mortality and morbidity in patients with CHF [7]. Insulin resistance, a condition preceding diabetes mellitus for years to decades, has had a poorly defined clinical significance in patients with CHF in the past. It has been shown lately though that it is independently associated with impaired prognosis in patients with CHF [7, 16]. Gender differences have also been shown in the metabolic syndrome and to play a role in cardiovascular disease [26]. Studies performed on hypertensive populations have shown that treatment with selective β-blockers increased insulin resistance, while with carvedilol a decrease in insulin resistance was observed [13, 14]. Metabolic effects of β-blocker therapy reported in literature include reduced resting energy expenditure, inhibition of lipolysis and decreased insulin sensitivity and weight gain [10, 29, 34]. Beta-blocker therapy remains underused in main diseases predisposing development of heart failure [2, 11, 33].

The aim of our study was to compare effects of selective and nonselective β-blockers on body weight, plasma leptin, resistin, fasting glucose and insulin concentration in non-cachectic patients with CHF. We hypothesized that additional β2 and α adrenergic blocking properties of carvedilol, when compared to the more selective β1 adrenergic receptor blockade by bisoprolol, could result in different metabolic effects when added to the standard therapy of non-cachectic patients with CHF.

Methods

Study population

All consecutive non-cachectic and non-diabetic patients with CHF and echocardiographically measured left ventricular ejection fraction (LVEF) <50% referred to the Department of Cardiology at the General and Teaching Hospital Celje between January 2004 and May 2004 were considered for the study. Eligible patients were β-blocker naive, had stable New York Heart Association Class II–III symptoms for >6 months and were on stable medical regimen for at least 2 months.

Subjects with primary valvular disease, cardiac cachexia (=loss of 5 kg of their dry body weight), acute coronary syndrome within the last 3 months, acute myocarditis, sustained ventricular tachycardia, second- or third-degree atrioventricular block, bradycardia with ventricular frequency <50 beats/min at rest, systolic blood pressure <85 mmHg, liver failure, chronic obstructive pulmonary disease, hypothyreosis or hyperthyreosis, pheochromocytoma, acute infec-

tion, malignancy, psychiatric disorders limiting cooperation, and treatment with β or α adrenergic receptor agonists, and patients on sedatives or phosphodiesterase inhibitors were excluded. A newly diagnosed diabetes mellitus (defined as fasting blood glucose level >6.9 mmol/l) was the most often used exclusion criterion applied in ten of 38 selected patients. Of the remaining 28 patients, seven had a blood glucose level between 6.1 and 6.9 mmol/l (two in the bisoprolol and five in the carvedilol group).

The study protocol was approved by the ethical human research committee at the General and Teaching Hospital Celje. Written informed consent was obtained prior to inclusion in the study.

Study protocol

Patients were randomized in a 1:1 fashion to carvedilol (Dilatrend, Hoffmann-La Roche Ltd, Switzerland) or bisoprolol (Concor, Merck, Germany), which were administered additionally to the established treatment for chronic heart failure. Beta-blocker was titrated in an ambulatory setting to the target dose (25 mg bid for carvedilol and 10 mg od for bisoprolol) or to the maximal dose tolerated by the patient. The dose was titrated in 2-week intervals. If side effects attributed to the study medications developed, increments in dose were delayed or the dose was adjusted to the patient.

Blood samples were taken and body weight was measured on the same balanced scale in the morning after an overnight fast and before the administration of morning medications.

Hormonal measurements

After an overnight fast, we withdrew 42 ml of blood (7 times 6 ml containers – BD Vacutainer Systems Z without added anticoagulant). Plasma was separated by centrifugation at 3000 cycles per min for 5 min and stored at −20 °C.

Plasma insulin was measured with microparticle enzyme immunoassay (MEIA) test with Abbott reagents on Abbott AXSYM analyzer. For the estimation of insulin resistance, homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated using following formula:

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\text{HOMA-IR} = 22.5 \times \frac{\text{fasting plasma glucose concentration (mmol/l)}}{\text{fasting plasma insulin concentration (μU/ml)}}
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