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Spironolactone, not furosemide, improved insulin resistance in patients with chronic heart failure ☆

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ABSTRACT

Background/objectives: Insulin resistance plays an important role in the pathophysiology in chronic heart failure (CHF). Diuretics generally have harmful effects on glucose metabolism, however, the effect of mineral corticoid receptor blockers on insulin resistance in CHF is unclear. This study aimed to evaluate the effects of the aldosterone blocker spironolactone, in comparison with furosemide, on insulin resistance in CHF patients.
Methods: The effect of spironolactone (25 mg/day) and furosemide (20 mg/day) on IR for 16 weeks each was analyzed in 16 CHF patients using a double-blind, placebo-controlled, randomized cross-over study design.
Results: Plasma BNP and left ventricular ejection fraction were improved with both treatments (furosemide: $p = 0.02$ and $p = 0.009$, respectively, spironolactone: $p = 0.03$ and $p = 0.007$, respectively). Fasting plasma glucose was not changed; however, plasma insulin levels decreased and insulin sensitivity (by homeostasis model assessment: HOMA-IR) improved with spironolactone as compared to furosemide ($p < 0.0005$). TNF-α, IL-6 and MCP-1 decreased with spironolactone ($p = 0.002$, $p = 0.02$ and $p = 0.02$ vs. baseline, respectively), but not with furosemide. Matrix metalloproteinase (MMP)-2 and MMP-9 were decreased with spironolactone ($p = 0.003$ and $p = 0.04$ vs. baseline, respectively), but not furosemide. Changes in TNF-α, IL-6 and MCP-1 levels after spironolactone treatment were significantly correlated with changes in HOMA-IR ($r = 0.61$, $r = 0.55$ and $r = 0.65$, respectively; $p = 0.01$, $p = 0.03$ and $p = 0.01$, respectively). Furthermore, changes in MMP-2 and MMP-9 levels were significantly correlated with changes in HOMA-IR ($r = 0.58$ and $r = 0.58$, respectively; $p = 0.02$ and $p = 0.02$, respectively).
Conclusions: Spironolactone, not furosemide, improved insulin resistance in CHF patients probably by the inhibition of inflammatory cytokines and MMPs.

1. Introduction

Insulin resistance is common in patients with chronic heart failure (CHF) [1]. Insulin resistance predicted CHF incidence independently of established risk factors including diabetes [2], and is independently associated with impaired prognosis independent of well-established prognostic markers [3]. Beyond mortality, insulin resistance, as a regulating signal of energy utilization, is associated with symptomatic status and exercise capacity in non-diabetic patients with CHF [3,4]. Furthermore, elevated glycosylated hemoglobin (HbA1c) was associated with incident heart failure in a middle-aged population without diabetes [5]. Thus, insulin resistance plays an important role in the pathophysiology in CHF with symptomatic and prognostic implications.

In RALES, the aldosterone antagonist spironolactone improved mortality in severe CHF patients [6]. In addition, eplerenone, a specific mineral corticoid antagonist, improved mortality in patients with myocardial infarction in EPHESUS [7]. Recently, eplerenone was shown to reduce mortality in CHF patients with mild symptoms in EMPHASIS-HF [8]. Clearly, therapeutic interventions to inhibit aldosterone were shown to interfere with CHF pathophysiology to improve mortality in CHF. Notably, aldosterone is closely linked to insulin signaling too. Aldosterone inhibits insulin-induced glucose uptake via degradation of insulin receptor substrate proteins independently of angiotensin II [9]. In addition, spironolactone has been shown in an experimental setting to restore impaired glucose metabolism by ameliorating inflammation [10]. In human, patients with primary aldosteronism were insulin resistant compared with healthy controls, and normal sensitivity to insulin is rapidly restored after treatment with either adrenalectomy or

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aldosterone antagonists [11]. Taken together, elevated aldosterone may be a factor contributing to insulin resistance in CHF.

Diuretics, such as thiazides, generally have harmful effects on glucose metabolism [12,13] although they are routinely used in CHF patients for their symptomatic and hemodynamic effects. However, it is unclear if mineral corticoid receptor blockers improve insulin resistance in CHF patients. In this study, therefore, we aimed to evaluate the effects of spironolactone, an aldosterone blocker, in comparison with furosemide, on glucose metabolism in CHF patients.

2. Methods

In this randomized, double-blinded, controlled study the effect of treatment with spironolactone vs. furosemide on insulin resistance was studied in patients with stable, compensated CHF. A cross-over study design was applied with each patient serving as his or her own control. Sixteen CHF patients (age, 63 ± 4 years; 15 men and 1 woman) were enrolled. Among the 16 patients, 8 had idiopathic dilated cardiomyopathy and 8 had ischemic heart failure after myocardial infarction (New York Heart Association (NYHA) functional classes II: 9, III: 7). Atrial fibrillation, hypertension, and diabetes mellitus were present in 7, 7 and 1 patients, respectively. All patients were in stable, ambulatory conditions with compensated CHF receiving ACE inhibitors and/or angiotensin II receptor blockers; further, 2 patients were on calcium channel blockers, 8 on β-blockers and 2 on nitrates. All patients were in compensated hemodynamic condition, and had no diuretic medication for 8 weeks before enrolment into the study. The medications were not changed during the study.

Patients with renal dysfunction (serum creatinine level >1.5 mg/dl), hyperkalemia (serum potassium level >5 mEq/ml) or under treatment with anti-diabetic agents or diuretics were excluded from this study. After the baseline visit, patients were randomly allocated to spironolactone (25 mg/day) or furosemide (20 mg/day) (8 patients each). After a treatment period of 16 weeks, each patient was switched to the respective opposite treatment group for another 16 weeks following the 4-week wash-out period. At the baseline visit and after each treatment, i.e., 16-week treatment period of spironolactone or furosemide, we performed blood and urine sampling, electrocardiography (ECG), chest X-ray, and echocardiography examinations. No patients were withdrawn from the study during the period.

All blood samples were obtained after overnight fasting and under standardized conditions after at least 15 min of supine resting. We evaluated the total blood count and routine biochemical parameters including brain natriuretic peptide (BNP), and immunoreactive insulin levels. Further, we determined the serum levels of inflammatory cytokines such as TNF-α (Quantikine HS® ELISA kit; R&D system, Minneapolis, MN, USA), IL-6 (CLEIA system, Rumipulse-f®; Fujirebio Inc., Tokyo, Japan), and monocyte chemoattractant protein (MCP)-1 (human MCP-1 immunoassay kit, Quantikine®; R&D system, Minneapolis, MN, USA). Serum matrix metalloproteinase (MMP)-1, 2, 3 and plasma MMP-9 were determined by an immunoassay method using commercially available kits with monoclonal antibodies against each substance according to the manufacturer's instructions (Daiichi Fine Chemical Co., Ltd., Takaoka, Japan). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance index (HOMA-IR) [14]. Echocardiographic analysis was performed by 2 investigators who were blinded to the clinical and treatment status of the patients. Left ventricular (LV) volume (modified Simpson's methods [15]) and LV ejection fraction (LVEF) ([(end-diastolic volume − end-systolic volume) / end-diastolic volume] × 100) were calculated.

All data are expressed as the mean ± standard error of the mean (SEM). The results of the crossover trial were analyzed according to the recommendations of Hills and Armitage for crossover trials [16]. The results for all patients were reported together in the order baseline–furosemide–spironolactone. The results of the 2 groups were compared and the statistical significance was assessed by paired Student's *t*-test; further, the statistical significance of the difference between the values of multiple groups was assessed by analysis of variance (ANOVA) with Fisher's post-hoc test. Univariate linear analyses were performed to determine the correlation between insulin resistance and inflammatory cytokines or MMPs in CHF patients. A p value of <0.05 was considered statistically significant. The primary endpoint of the study was the changes in the parameters of glucose metabolism (fasting blood glucose and insulin levels, and HOMA-IR), and the secondary end points were changes in inflammatory cytokine and MMP levels.

The study protocol conforms to the ethical guidelines of the 1975 Helsinki and was approved by the Ethical Committee of Tottori University Hospital. Written informed consent was obtained from all the patients. The study was registered with ClinicalTrials.gov (identifier: NCT00664222).

3. Results

The changes in clinical parameters with furosemide or spironolactone are shown in Table 1. BNP levels decreased significantly after 16 weeks of treatment with both diuretic drugs by 39% (furosemide, $p = 0.02$) and 43% (spironolactone, $p = 0.03$). NYHA functional classes were improved in 2 NYHA class II patients and 3 class III patients both with furosemide and spironolactone. Body mass index (BMI), heart rate or blood pressure did not change significantly while cardiothoracic ratio from chest radiography significantly reduced after both treatments. In echocardiography, LV fractional shortening and LVEF were improved with both drugs (furosemide; $p = 0.02$ and $p = 0.009$, respectively, spironolactone; $p = 0.02$ and $p = 0.007$, respectively). Serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, or triglyceride levels did not change significantly with both drugs although serum potassium was significantly increased with spironolactone ($p = 0.003$).

Regarding glucose metabolism, fasting plasma glucose was not changed, however, fasting insulin level (baseline: 5.3 ± 0.5 μU/ml, furosemide: 5.9 ± 0.6 μU/ml, spironolactone: 2.8 ± 0.4 μU/ml, $p = 0.001$ vs. baseline and $p = 0.0001$ vs. furosemide) and HOMA-IR (baseline: 1.42 ± 0.17, furosemide: 1.59 ± 0.21, spironolactone: 0.71 ± 0.10, $p = 0.004$ vs. baseline and $p = 0.0005$ vs. furosemide) improved with spironolactone, but not with furosemide treatment (Table 1 and Fig. 1).

TNF-α, IL-6 and MCP-1 decreased with spironolactone ($p = 0.002$, $p = 0.02$ and $p = 0.02$, respectively), but not with furosemide (Fig. 2). Also MMP-2 and MMP-9 were decreased with spironolactone ($p = 0.003$ and $p = 0.04$, respectively), but not with furosemide, however, MMP-1 or MMP-3 was not changed significantly (Fig. 3). Changes in TNF-α, IL-6 and MCP-1 levels were significantly correlated with changes in HOMA-IR ($r = 0.61$ and $p = 0.01$, $r = 0.55$ and $p = 0.03$ and $r = 0.65$ and $p = 0.01$, respectively) (Fig. 4). Furthermore, changes in MMP-2 and MMP-9 levels were significantly correlated with changes in HOMA-IR ($r = -0.58$ and $p = 0.02$ and $r = 0.57$ and $p = 0.02$, respectively) (Fig. 5). The change of serum potassium level was not correlated with HOMA-IR (data not shown), although it was significantly increased by spironolactone.

No side effects of furosemide or spironolactone therapy were reported during the study, and in particular, serum potassium levels increased but remained within the limits of normal range during the treatment of spironolactone.

4. Discussion

In this placebo-controlled, randomized proof-of-concept interventional study, we observed that spironolactone improved insulin resistance (insulin level and HOMA-IR) in CHF patients and decreased pro-inflammatory cytokines and MMP levels. Furthermore, a direct relation between improvement of insulin resistance and change in inflammatory cytokines (TNF-α, IL-6 and MCP-1) and MMPs (MMP-2 and MMP-9) was observed. These results implicate that aldosterone may play a pivotal role in the development of insulin resistance in CHF patients presumably via interaction with inflammatory cytokines and MMPs are involved in this metabolic regulation.

It has previously been reported that there are some relationships between aldosterone and insulin resistance. Primary aldosteronism is associated with impaired glucose metabolism, including hyperglycemia and increased plasma insulin response to an oral glucose load [11,17]. Some possible mechanisms of insulin resistance induced by aldosterone have been considered, such as a low blood potassium concentration and a direct effect of aldosterone on insulin signaling [9,10,18–20].

We demonstrated that spironolactone decreased insulin levels and HOMA-IR in CHF patients while furosemide did not. Both diuretics improved cardiac parameters of echocardiography and BNP similarly. Thus, the improvement of insulin resistance may be mediated not by the improvement of hemodynamic impairment such as peripheral blood flow, but by other mechanisms secondary to the blockade of aldosterone. Yamaji et al. reported that treatment with spironolactone increased plasma HbA1c levels in patients with CHF, while treatment with eplerenone did not [21]. The reason of the differences between the previous data and ours is not fully clear but several aspects need to be addressed. First, the CHF parameters in our patients (NYHA class, LVEF and BNP) revealed a more advanced disease severity and