Interactions of Glucose Metabolism and Chronic Heart Failure

Authors M. Clodi[1], M. Resl[1], D. Stelzeneder[1], G. Pacini[3], A. Tura[3], D. Mörtl[2], J. Struck[5], N. G. Morgenthaler[5], A. Bergmann[5], M. Riedl[1], M. Anderwald-Stadler[4], A. Luger[1], R. Pacher[2], M. Hülsmann[2]

Affiliations Affiliation addresses are listed at the end of the article

Key words
- cardiovascular incidences
- metabolic features
- obesity

Abstract

Background: We evaluated insulin sensitivity and beta cell function in patients with chronic heart failure (CHF), and investigated a possible correlation of these metabolic parameters with specific biomarkers of heart failure. Additionally, we investigated the effects of two angiotensin receptor blockers (ARBs), namely telmisartan and candesartan, that were administered over a 5 month treatment period, as additional therapy to standard care.

Methods and Results: The study group consisted of 94 CHF patients. Insulin sensitivity (OGIS index) and insulin secretion parameters were investigated by frequently sampled oral glucose tolerance tests and consecutive mathematical modelling. In total, 94.6 % of patients had clinically overt diabetes, impaired glucose tolerance or insulin resistance at the time of enrolment HbA1c was found to correlate to NT-proBNP, MR-proADM, CT-proET-1, and MR-proANP, but not to Copeptin. NT-proBNP correlated inversely to OGIS. None of the metabolic parameters were altered significantly after candesartan or telmisartan treatment in either the patient or standard care group.

Conclusion: Insulin sensitivity and insulin secretion are impaired in CHF and biomarkers ofheart failure and atherosclerotic disease correlate to glucose metabolism.

Introduction

Heart failure (HF) is characterized by depressed left ventricular performance and changes in peripheral tissue, such as impaired peripheral blood flow (Wilson et al. , 1984; Massie et al., 1987; Sullivan et al., 1989), abnormalities of mitochondrial structure and function, alterations in the oxidative metabolism of skeletal muscle and atrophy of predominantly oxidative insulin sensitive slow twitch (type I) fibres (Lillioja et al., 1987; Hambrecht et al., 1995; Hickey et al., 1995; Hambrecht et al., 1997). In fact, whole body insulin resistance is frequently observed in chronic heart failure (CHF) patients (Paolisso et al., 1991; Swan et al., 1997), resulting in a significant risk of either having, or subsequently developing diabetes. It is presently unknown how glucose metabolism is influenced by neurohumoral open loops which play a key role in the pathophysiology of CHF.

Several recent studies, have shown beneficial effects of telmisartan on lipid and glucose metabolism beyond its ability to block angiotensin II receptors (Michel et al., 2004). In diabetics, telmisartan treatment led to a decrease in both serum glucose and serum triglycerides. In hypertensive patients, telmisartan caused a reduction in fasting plasma glucose, fasting insulin resistance (HOMA-IR) and glycosylated hemoglobin (Vitale et al., 2005). Certain in vitro and animal studies have strongly suggested that telmisartan, unlike other angiotensin II receptor blockers, acts as a peroxisome proliferator activated receptor gamma (PPARγ) agonist. Clinical trials suggest that angiotensin receptor blockers (ARBs), such as telmisartan and candesartan, are able to postpone the development of diabetes in chronic heart failure (CHF) patients (Pershadsingh, 2004; Usui et al., 2007). It is currently unknown, whether ARBs are able to reverse abnormal glucose metabolism.

Brain natriuretic peptide (BNP) and atrial natriuretic peptide (MR-proANP) are excellent parameters for determining the severity of heart failure, (Hulsmann et al., 2002) as blood levels of both peptides increase with the grade of left ventricular dysfunction. An association of high values

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Correspondence
R. Pacher, MD,
Associate Professor
Department of Cardiology
Medical University of Vienna
Waehringer Guertel 18-20
1090 Vienna
Austria
Tel.: +43/1/40400 46 14
Fax: +43/1/40400 42 16
richard.pacher@meduniwien.ac.at

Table 1 Patient characteristics, baseline and after therapy

	Standard therapy		Standard therapy + Telmisartan		
	Baseline	**After 5 months**	**Before Therapy**	**p**	**After Therapy**
age (year)	58.12 ± 14.42	–	58.03 ± 8.15	0.942	–
BMI (kg/m^2)	28.43 ± 5.17	28.22 ± 5.47	28.27 ± 4.46	0.957	28.14 ± 4.52
systolic blood pressure (mmHg)	118.62 ± 14.75	112.92 ± 12.15	127.78 ± 12.77	0.152	120.86 ± 17.38*
diastolic blood pressure (mmHg)	78.46 ± 12.81	72.85 ± 9.78	83.33 ± 7.07	0.167	80.14 ± 12.01
Hba1c(%)	6.22 ± 0.96	6.16 ± 0.85	6.43 ± 0.74	0.398	6.49 ± 1.07
waist size (cm)	109.08 ± 12.47	106.15 ± 13.36	114.00 ± 18.13	0.505	110.77 ± 14.97
Hip size (cm)	105.33 ± 11.66	102.44 ± 11.77	108.50 ± 16.64	0.631	106.86 ± 12.62
NT-proBNP (pg/ml))	1729 ± 1981	1515 ± 1679	1238 ± 1744	0.075	1092 ± 2006
metformin	6 patients	–	7 patients	–	–
sulfonylurea	3 patients	–	3 patients	–	–
ACE-inhibitor dose	enalapril 20 mg	enalapril 20 mg	enalapril 20 mg	–	enalapril 20 mg

with a poor prognosis has also been demonstrated (Tsutamoto et al., 1997; Gegenhuber et al., 2006; Gegenhuber et al., 2007). Natriuretic peptides can serve as surrogate parameters for the monitoring of the patients after therapeutic interventions (Tsutamoto et al., 2004). Beside ANP and BNP peptides like Endothelin 1 (ET-1), Adrenomedullin (ADM) and Vasopressin can additionally be linked to severity and prognosis of heart failure. Circulating big ET-1 is a well-recognized marker of atherosclerosis, cardiovascular disease and heart failure (Pacher et al., 1996). Adrenomedullin, another endothelial derived vasoactive factor, was recently shown by its stable surrogate, MR-proADM, which positively correlates with the increasing severity of diabetes (Chi Lim et al., 2007) and heart failure (Gegenhuber, Struck et al., 2007). Copeptin, the C-terminal portion of pro Vasopressin, is a 39-amino acid glycopeptide of unknown function in the circulation. It is a stable surrogate marker for vasopressin and predicts death or heart failure after myocardial infarction. Furthermore Copeptin is an excellent predictor of outcome in advanced heart failure patients (Morgenthaler et al., 2006; Stoiser et al., 2006; Khan et al., 2007).

Elevated levels of proinflammatory cytokines like TNF α, Interleukin 1 and Interleukin 6, which are thought to influence insulin resistance have also been reported (Hotamisligil, 1999; Torre-Amione, 2005). In a study by Doehner and colleagues TNF α and norepinephrine did not correlate with insulin sensitivity (Doehner et al., 2002). Together with BNP, CRP identifies a high risk group with a tendency for poor outcome (Tanner et al., 2007). In patients with Type 2 Diabetes which is closely linked to the metabolic syndrome and to coronary artery disease CRP has also been shown to be a very strong predictor of cardiovascular death. (Diamantopoulos et al., 2006; Linnemann et al., 2006; Zabetian 2008).

Beside the biomarkers sensitive imaging techniques like echocardiography and cardiac MRI are essential for the detection of myocardial changes in diabetic patients (Korosoglou et al., 2007).

Cardiovascular autonomic neuropathy as a manifestation of diabetic neuropathy, causes substantial morbidity and increased mortality (Boulton et al., 2005). The autonomic nervous system modulates the contractility of the heart via the sympathetic and the parasympathetic nervous system (Chow et al., 2001). Clinical manifestations of cardiovascular autonomic neuropathy are tachycardia, orthostatic hypotension, orthostatic tachycardia, bradycardia or silent myocardial ischaemia (Vinik et al., 2007).

In this study we compared the effects of the angiotensin receptor blockers (ARBs) telmisartan and candesartan as add-on therapy to ACE inhibitor and β-blocker on metabolic parameters, to no additional therapy. Furthermore we evaluated the incidence of insulin resistance in our patients and tried to show a possible correlation between biomarkers for cardiovascular disease and glucose metabolism.

Patients and Methods

A prospective, single centre, open, parallel-grouped, randomized controlled 5-month study was conducted. Patients were randomized to either telmisartan, candesartan or standard care for 5 months and assessed at baseline and after 5 months treatment. The study was approved by the ethics committee of the Medical University and General Hospital of Vienna and all patients gave written informed consent.

Patients, up titration of medication and visits

Patients were enrolled between June 2005 and September 2006. Patients, aged 18 years or older, were eligible if they met the following criteria; 1) New York Heart Association functional class I–IV of at least 4 weeks duration, 2) a history of hospital admission for a cardiac reason, 3) chronic heart failure, as proven by echocardiography or Technetium-Scintigraphy, and 4) a left ventricular ejection fraction (LVEF) lower than 45 %. The aetiology of heart failure was ischemic heart disease in 64 of the patients.

Patients were excluded on the following grounds; 1) systemic glucocorticoid treatment, 2) a creatinine level above 1.4 mg/dl, 3) infection, 4) malignant disease, 5) childbearing age and lack of contraception during the study period, 6) HbA1c > 8.5 %, or 7) treatment with insulin sensitizers (glitazones) or insulin.

Ninety four patients (32 In the telmisartan group, 29 in the candesartan group, and 33 in the standard care group) were consecutively recruited from the outpatient service of the division of Cardiology at the Medical University of Vienna. Patients were investigated by frequently sampled oral glucose tolerance tests several days before and 3 months after up-titration of therapy with ARBs (either telmisartan, candesartan or nothing) on top of existing heart failure therapy (standard care according to the ESC 2005 guidelines). Patients consisted of 52 males and 42 females, with an average age of 58 ± 14 years. Patient demographics are shown in **Table 1** and **2**.

After informed consent was obtained and inclusion/exclusion criteria reviewed, patient visits were scheduled as follows;

Visit 1: The experimental protocols started between 0800 h and 0830 h following an overnight fast. Patients firstly underwent an

Table 2 Patient characteristics, baseline and after therapy

	Standard therapy		Standard therapy + Candesartan		
	Baseline	**After 5 months**	**Before Therapy**	**p**	**After Therapy**
age (year)	58.12 ± 14.42	–	57.10 ± 10.45	0.704	–
BMI (kg/m^2)	28.43 ± 5.17	28.22 ± 5.47	29.35 ± 3.39	0.383	29.93 ± 3.58
systolic blood pressure (mmHg)	118.62 ± 14.75	112.92 ± 12.15	120.25 ± 17.24	0.676	113.50 ± 16.94
diastolic blood pressure (mmHg)	78.46 ± 12.81	72.85 ± 9.78	75.50 ± 8.23	0.840	73.20 ± 11.24
Hba1c(%)	6.22 ± 0.96	6.16 ± 0.85	6.24 ± 0.91	0.695	6.20 ± 0.65
waist size (cm)	109.08 ± 12.47	106.15 ± 13.36	113.43 ± 9.64	0.495	110.43 ± 11.77
Hip size (cm)	105.33 ± 11.66	102.44 ± 11.77	110.57 ± 5.03	0.381	109.09 ± 9.04
NT-proBNP (pg/ml)	1729 ± 1981	1515 ± 1679	899 ± 1626	0.042	643 ± 688
metformin	6 patients	–	6 patients	–	–
sulfonylurea	3 patients	–	2 patients	–	–
ACE-inhibitor dose	enalapril 20 mg	enalapril 20 mg	enalapril 20 mg	–	enalapril 20 mg

oral glucose tolerance test (oGTT). Plasma was sampled and frozen at −20° C for determination of natriuretic peptide NT-proBNP, MR-proAdrenomedullin, copeptin, MR-proANP, and CT-proEndothelin-1. Demographic and anthropometric data were then obtained.

After visit 1, patients were randomly assigned to either standard care group, standard care plus candesartan group, or standard care plus telmisartan group. The treatment dose was increased weekly, as tolerated, according to a forced titration protocol, with recommended monitoring of blood pressure, serum creatinine, and potassium. The target dose was 32 mg candesartan and 80 mg telmisartan once daily from 6 weeks onwards. After randomisation, patients were seen at 2, 4, and 6 weeks, and 5 months after baseline. CHF treatment and up titration was performed by three specified physicians from a tertiary care heart failure unit (D.M, R.P M.H).

Visit 2: Visit 2 was scheduled 3 months after optimized dosage of telmisartan or candesartan, or 5 months after visit 1 in the placebo group. Blood sampling and oGTT for determination of the above-mentioned peptides were repeated as per visit 1. Previous therapy of CHF and diabetes (if any) was not altered during the study period.

Medications

At baseline, all patients in all three groups were already taking angiotensin converting-enzyme inhibitors and β-blockers. Along with ACE-inhibitors and beta blockers, concomitant medication consisted of diuretics and spironolactone. The distribution of these medications was similar between the groups: diuretics 58, 63, 63% and spironolactone: 56, 60, and 51% for control, telmisartan and candesartan groups, respectively. New York Heart Association (NYHA) functional class I, II, III, IV for control, telmisartan and candesartan groups were: 24/20/27 %; 59/56/50 %; 14/20/23% and; 3/4/0%, respectively (all not significantly different).

Twenty seven patients (28.7%) participating in the study had known diabetes and were taking oral antidiabetic drugs. In addition, 14 patients(14.9%) were newly diagnosed as having diabetes (DM2) and 23 patients (24.4%) were newly diagnosed as having impaired glucose tolerance (IGT) at entry. Twenty-five patients (26.6%) out of the remaining 30 patients were found to be insulin resistant (IR) according to HOMA. Patients whose HOMA IR exceeded 2,00 were arbitrarily defined as IR. In total, 94.6% of patients had clinically overt DM2, IGT, or IR at the time of enrolment, and less than one third of them were aware of it. HbA1c was 5.8 ± 0.4, 6.0 ± 0.6 and 6.9 ± 0.8 % in the IR, IGT and DM 2 groups, respectively.

Frequently sampled oral glucose tolerance test and mathematical modelling

Following a 10–12 h overnight fast, and after withdrawing blood samples for baseline measurements, the subjects ingested a Roche Glukodrink solution containing 75 g of glucose. Venous blood samples were then drawn for glucose, insulin and C-peptide measurements at 10, 20, 30, 60, 90, 120, 150 and 180 min.

Basal insulin sensitivity indices (QUICKI, HOMA) were calculated from fasting glucose/insulin concentrations (Katz et al., 2000). Dynamic indices of insulin sensitivity from the oGTT (oral glucose insulin sensitivity index, OGIS and Matsuda-DeFronzo index ISIcomp) were determined as described previously (Mari et al., 2001; Pacini et al., 2003). A marker of fasting β cell function was calculated as the ratio of fasting C-peptide concentration to fasting glucose, since C-peptide is not cleared by the liver. Concentration areas under the curve (AUC) were calculated with the trapezoidal rule. Insulin secretion was evaluated from the AUC of C-peptide concentration (AUCCP). Beta cell function was evaluated as the molar ratio AUCCP/AUCG, where AUCG is the area under the glucose concentration curve (Tura et al., 2006) An approximation of the total insulin clearance (hepatic extraction) can be calculated from the C-peptide and insulin measurements obtained during oGTT.

Determination of NT-proBNP, mid regional proAdrenomedullin (MR-proADM), C-terminal proEndothelin-1 (CT-proET-1), mid regional pro-atrial natriuretic peptide (MR-proANP) and Copeptin

Blood samples were immediately placed on ice, then centrifuged and the plasma was transferred into chilled tubes. The plasma was then frozen at −20° C until assayed. Natriuretic peptide was determined using commercially available ELISA kits purchased from Roche Diagnostics for NT-proBNP. CT-proEndothelin-1 was measured with a new sandwich immunoassay (BRAHMS AG, Hennigsdorf, Berlin, Germany) as described elsewhere (Papassotiriou et al., 2006). MR-proADM was measured with a new sandwich immunoassay (BRAHMS AG Hennigsdorf, Berlin, Germany) as described previously (Morgenthaler et al., 2005). MR-proANP (epitopes covering amino acids 53–90) was measured with a new sandwich immunoassay (BRAHMS AG, Hennigsdorf, Berlin, Germany) as described elsewhere in detail (Morgenthaler et al., 2004). Determination of Copeptin (C-terminal pro-Vasopressin) in the chemiluminescence/coated tube format was performed as described recently by Morgenthaler et al., (Morgenthaler, Struck et al., 2006).

Table 3 Patient characteristics, baseline and after therapy

	Standard therapy		Standard therapy + Telmisartan		Standard therapy + Candesartan	
	Baseline	**After 5 month**	**Before therapy**	**After therapy**	**Before therapy**	**After therapy**
basal glucose (mg/dl)	112.4 ± 24.0	112.9 ± 29.7 (+0.5)	117.9 ± 28.4	131.6 ± 56.0 (+13.6)	115.0 ± 23.6	109.9 ± 22.2 (−5.1)
basal insulin (μU/ml)	20.3 ± 19.5	18.2 ± 16.3 (−2)	16.9 ± 11.6	18.1 ± 16.0 (+1.2)	16.1 ± 8.1	15.2 ± 6.5 (−0.9)
basal c-peptide (ng/ml)	5.7 ± 3.3	6.1 ± 3.8 (+0.4)	5.2 ± 1.9	5.5 ± 2.9 (+0.3)	5.1 ± 1.9	4.9 ± 1.7 (−0.2)
AUC glucose (g/ml*180 min)	3503 ± 1351	3373 ± 1435 (−131)	3594 ± 1233	3855 ± 1552 (+261)	3327 ± 1158	3200 ± 1052 (−127)
AUC insulin (U/l*180 min)	13.5 ± 11.4	11.5 ± 7.6 (−1.9)	11.3 ± 5.7	11.4 ± 5.0 (+0.1)	14.4 ± 7.2	15.6 ± 8.8 (+1.2)
AUC c-peptide (mg/l*180 min)	2.7 ± 1.4	2.4 ± 0.9 (−0.3)	2.3 ± 0.6	2.4 ± 0.5 (+0.1)	2.6 ± 0.7	2.6 ± 0.7 (+0.1)
OGIS	327.5 ± 84.4	342.2 ± 111.1 (+14.7)	342.6 ± 89.1	350.1 ± 97.8 (+7.5)	329.5 ± 60.1	335.3 ± 67.2 (+5.8)
insulinogenic	68.2 ± 74.6	70.6 ± 61.0 (+2.5)	66.4 ± 62.4	68.2 ± 63.1 (+1.8)	84.9 ± 67.4	87.8 ± 63.5 (+2.9)
QUICKI	0.37 ± 0.05	0.37 ± 0.05 (+0)	0.37 ± 0.03	0.37 ± 0.05 (+0)	0.37 ± 0.03	0.37 ± 0.03 (+0)
ISIcomp	3.5 ± 2.8	3.6 ± 2.3 (+0.1)	3.0 ± 1.3	3.0 ± 2.0 (+0.1)	2.8 ± 1.3	2.9 ± 1.4 (+0.1)
HOMA	4.9 ± 2.8	5.2 ± 4.8 (−7.9)	6.5 ± 8.8	10.2 ± 16.7 (+3.7)	4.6 ± 2.5	4.2 ± 2.3 (−0.4)
hepatic extraction total	76.0 ± 8.9	76.0 ± 7.7 (+0)	75.0 ± 7.5	75.3 ± 7.2 (+0.3)	72.1 ± 10.5	71.9 ± 11.9 (−0.1)

Statistical methods

SPSS for Windows version 14.0. (SPSS Inc. Chicago, Illinois) was used for statistical analyses. Values were given as means ± SD or as percentages where appropriate. To ensure comparability in baseline characteristics, several unpaired Student's t-tests were performed showing no significant difference between the groups.

Statistical differences of values before versus after therapy were evaluated by paired Student's t-test. Spearman-Rho correlation was used to explore the relationship between plasma concentrations of the biomarkers (NT-proBNP, MR-proADM, CT-proET-1, MR-proANP and Copeptin) and several metabolic factors (HbA1c, age, BMI, blood pressure, fasting glucose, full lipid profile, QUICKI, OGIS, CRP and dynamic indices of oGTT). Subsequent multiple linear regression analysis was carried out thereafter. Results were ranked according to P values. For all analyses, a two tailed p-value <0.05 was considered statistically significant.

Results

ARBs and metabolic parameters

Baseline characteristics of the subjects are presented in **Table 1** and **2**. Mean NT-proBNP entry values were 1729 ± 1981 pg/ml, 1238 ± 744 pg/ml and 899 ± 1626 pg/ml for the standard care, telmisartan and candesartan groups, respectively. These values were not significantly different between the groups. After 5 months, NT-proBNP values tended to be lower, but not significantly lower in all treatment groups (**Table 1, 2**). The effects of telmisartan and candesartan treatment on insulin resistance are shown in **Table 3**. None of the parameters were significantly altered after either candesartan or telmisartan treatment. Similar findings were also observed for the control group (**Table 3**). However, as some of the subjects in this study were taking anti-diabetic drugs, such as sulfonylureas and metformin and these treatments affect insulin sensitivity and other parameters, we compared subjects who were not taking any anti-diabetic medication before and after candesartan or telmisartan treatment. Again, none of the parameters were altered significantly either after candesartan or telmisartan treatment, or in the control group.

Table 4 Baseline values for all subjects

	Baseline values for all subjects N = 94
BMI (kg/m^2)	28.66 ± 4.48
Hba1c(%)	6.27 ± 0.81
NT-proBNP (pg/ml)	1535.6 ± 2484.2
MR-proADM (nmol/l)	0.75 ± 0.373
CT-proET-1 (pmol/l)	82.71 ± 33.38
MR-proANP (pmol/l)	215.8 ± 202.0
copeptin (pmol/l)	21.4 ± 47.0
creatinine (mg/dl)	1.1 ± 0.2

After pooling the data from telmisartan and candesartan groups, we tested the hypothesis that there could be an ARB group effect on insulin and glucose metabolism, but again none of the parameters were altered significantly before or after treatment. All other parameters of glucose metabolism before and after treatment, including HbA1c, were not altered in between groups.

ARBs and obesity, blood pressure and lipid metabolism

No changes were observed in obesity parameters, such as body weight, body mass index (BMI), and waist circumference before and at 5 months after telmisartan or candesartan administration, nor in the control group (**Table 1, 2**). Thus, telmisartan did not induce weight gain. Only telmisartan treatment for 5 months was shown to significantly lower systolic blood pressure from 127.78 ± 12.77 mmHg to 120.86 ± 17.38 mmHg ($P<0.05$).

CHF markers and metabolic parameters

Mean MR-proADM values were 0.75 ± 0. 373 nmol/l, mean CT-proET-1 values were 82.7 ± 33.4 pmol/l, mean MR-proANP values were 215.8 ± 202.0 pmol/l, and Copeptin values were 21.4 ± 47.0 pmol/l. All of these mean values were above the normal values described for the four biomarkers, age 55.59 ± 12.69, HbA1c 6.27 ± 0.81, and BMI (kg/m2) 28.66 ± 4.48 for all 94 patients at entry (**Table 4**). HbA1c correlated with NT-proBNP (**Fig. 1**), MR-proANP (**Fig. 2**) MR-proADM (**Fig. 3**), CT-proET-1 (**Fig. 4**) and, but not to Copeptin (**Table 5**). NT-proBNP

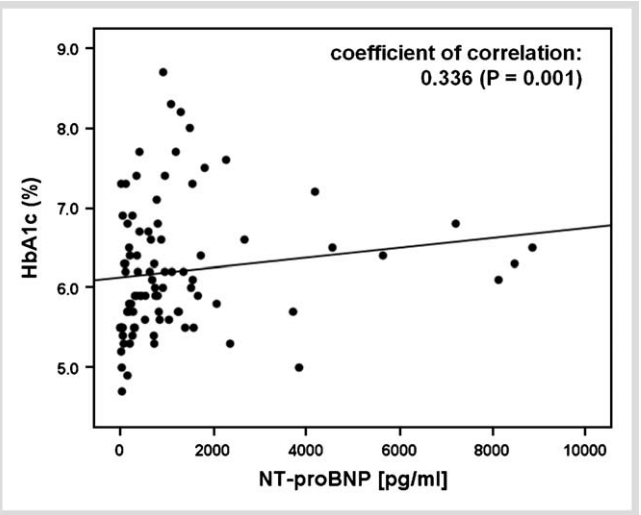

Fig. 1 Significant positive correlation between NT-proBNP and HbA1c NT-proBNP.N-terminal pro b-type natriuretic peptide.

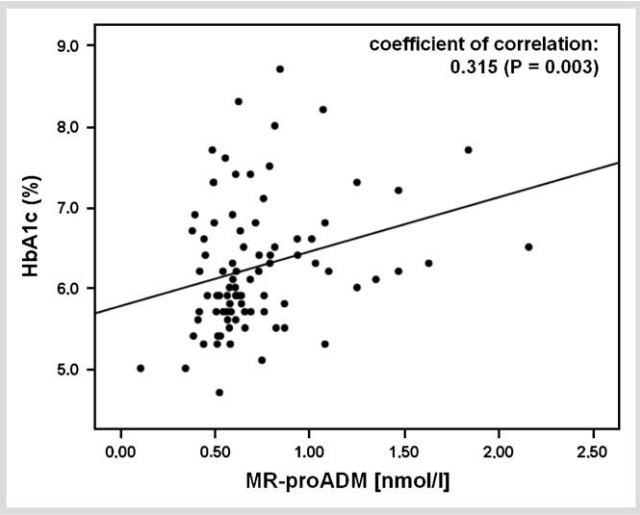

Fig. 3 Significant positive correlation between MR-proADM and HbA1c. MR-proADM.midregional pro adrenomedullin.

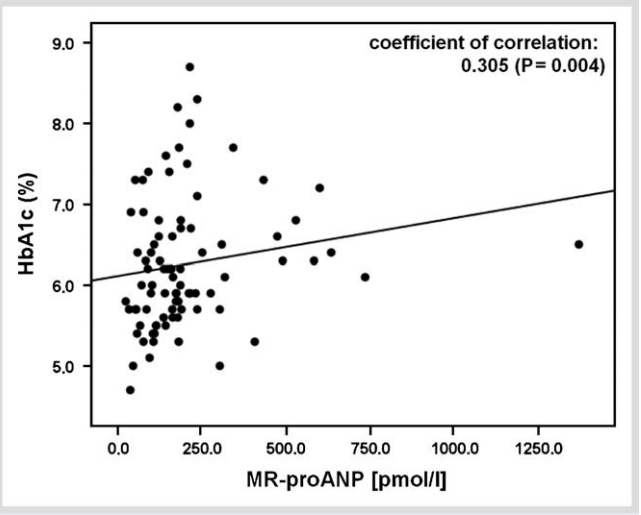

Fig. 2 Significant positive correlation between MR-proANP and HbA1c. MR-proANP.midregional pro atrial natriuretic peptide.

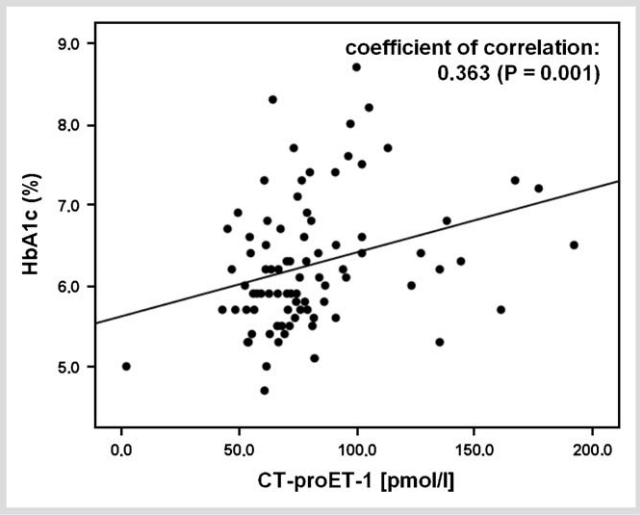

Fig. 4 Significant positive correlation between CT-pro-ET-1 and HbA1c. CT-pro-ET-1.C-terminal pro endothelin 1.

Table 5 Median of the biomarkers, listed by Quartiles of HbA1c

HbA1c Quartile	BNP	MR-proANP	MR-proADM	CT-proET-1	CT-proAVP
Quartile (– 5.7)	429 ± 940.41	107.5 ± 87.68	0.55 ± 0.2	67.3 ± 23.09	8.64 ± 14.28
Quartile (5.71–6.15)	762 ± 1759.82	174 ± 145.55	0.62 ± 0.23	71.9 ± 26.36	10.80 ± 92.76
Quartile (6.16–6.725)	700.5 ± 2623.67	160.5 ± 294.97	0.76 ± 0.43	74.5 ± 36.20	13.80 ± 16.71
Quartile (6.726–8.5)	966 ± 3700.52	187 ± 185.89	0.71 ± 0.43	90.70 ± 36.15	14.4 ± 10.07

inversely correlated with insulin sensitivity (OGIS, P < 0.001). In CHF patients, hepatic extraction inversely correlated with Nt-proBNP.

Multiple regressions

Multiple linear regressions including age, BMI, fasting glucose, QUICKI, OGIS and dynamic indices of oGTT, were performed for the various measured substances.

This analysis revealed that HbA1c, QUICKI, OGIS (inversely), hepatic extraction (inversely), creatinine, and γGT are significant predictors of NT-proBNP (**Table 6**).

HbA1c alone was a significant predictor of NT-proBNP, MR-proADM, MR-proANP, and CT-proET-1, but not to Copeptin (**Table 7**).

Finally, NT-proBNP, MR-proADM, CT-proET-1, MR-proANP, and Copeptin correlated with each other (P < 0.0001 for all). NT-proBNP (P < 0.003), MR-proANP (P < 0.0001), MR-proADM (P < 0.0001), CT-proET-1 (P < 0.0001) and Copeptin (P < 0.020) correlated to age, but only NT-proBNP correlated to BMI (inversely, coefficients of correlation (β) of -0.219 (P = 0.044). In summary the results of the multiple linear regressions highlight the close relationship between biomarkers for heart failure and metabolic parameters like HbA1c, QUICKI and OGIS.

Table 6 Parameters influencing NT-proBNP

HbA1x	0.265 (p = 0.023)
QUICKI	0.424 (p = 0.0001)
OGIS (inversely)	0.198 (p = 0.024)
Hepatic Extraction (inversely)	0.386 (p = 0.0001)
Kreatinin	0.461 (p < 0.0001)
gamma GT	0.492 (p < 0.0001)

Table 7 Parameters influencing HbA1c

NT-proBNP	0.265 (p = 0.023)
MR-proADM	0.289 (p = 0.002)
MR-proANP	0.314 (p < 0.005)
CT-proET-1	0.449 (p < 0.001)

Discussion

The main purpose of this study was the evaluation of possible effects of ARBs on glucose tolerance. In contrast to recently conducted trials which have reported positive effects of ARBs on glucose metabolism (Honjo et al., 2005; Vitale, Mercuro et al., 2005) we could not demonstrate an effect of telmisartan or candesartan on parameters of insulin sensitivity in patients with heart failure. This can probably be explained by the different patient collectives analysed in these studies. In fact, nearly 25 % of all patients participating in major HF clinical trials were diagnosed with diabetes at entry, compared with only 7 % of the general population (Mokdad et al., 2001; Bobbio et al., 2003). During the diagnosis of diabetes 5.8 % of the patients already present with chronic heart failure and diabetics are at increased risk of cardiovascular disease. (Martin et al., 2007; Schwarz et al., 2007). In the RESOLVD HF trial, 43 % of patients had either clinically overt diabetes or preclinical abnormalities of glucose metabolism at the time of enrolment. In our cohort of CHF patients (with a median BNP of 963 pg/ml), 94.6 % had abnormalities in glucose metabolism with clinically overt diabetes in 43.6 %, impaired glucose tolerance in 24.4 % and insulin resistance in 26.6 % at the time of enrolment. Results from the Studies of Left Ventricular Dysfunction (SOLVD), showed that new-onset diabetes developed in 22 % of patients during four years of follow-up, where almost 50 % of patients were overt diabetic (Vermes et al., 2003). A possible reason could be that, in the other studies, telmisartan improved insulin resistance in only the early stages of disease in both diabetic and hypertensive patients. From these studies, it is not clear whether telmisartan has the same beneficial effect in patients with the progression of disease. Although our chronic heart failure patients were clinically stable with 25 % in NYHA functional class I, 50 % in NYHA class II, 20 % in NYHA III, and only 4 % NYHA IV, with a median NT-proBNP value of 963 pg/ml, the disease, i.e. chronic heart failure was already advanced with poor prognosis, and, furthermore, patients were already suitably treated with maximal dosis of ß-blockers and ACE inihibitors. After data from telmisartan and candesartan groups were pooled, we observed a slight, but insignificant decrease in BNP values. No angiotensin receptor blocker effect on insulin and glucose metabolism was observed before and after treatment.

Recently it is not completely understood how chronic heart failure is accompanied by a resistance to the metabolic actions of insulin. Some studies have linked this phenomenon to elevated levels of plasma norepinephrine (NE) and persistent SNS activation (Levine et al., 1982; Marangou et al., 1988; Paolisso, De Riu et al., 1991; Swan et al., 1994; Swan, Anker et al., 1997). Peripheral glucose and insulin delivery in skeletal muscle are mediated by the vascular tone of perfusing arterioles. So glucose utilization decreases when blood flow is shunted away from skeletal muscles by a stimulation of α adrenergic receptors which causes arteriolar vasoconstriction (Pollare et al., 1988).

Furthermore we showed that insulin sensitivity correlates with the degree of heart failure by using NT-proBNP and other biomarkers of heart failure (MR-proANP, CT-proET-1, MR-proADM). In multiple linear regression analysis we proved that HbA1c is a significant predictor of NT-proBNP, MR-proADM, MR-proANP, and CT-proET-1. In contrast to our results Suskin and colleagues found a modest inverse correlation between plasma BNP and insulin resistance among the non-diabetic patients. This can probably be explained by the different calculating models for insulin resistance and the fact that in our study the prevalence of insulin resistance was much higher than in the RESOLVD trial (Suskin et al., 2000).

HbA1c was also a significant predictor of CT-pro ET-1 which serves as a surrogate marker for ET-1. Effects of ET are vasoconstriction, vascular hypertrophy, cell proliferation fibrosis and inflammation. Even slight disturbances in the release or production of ET-1 may have a profound impact on vascular tone and blood flow, therby aggravating peripheral insulin resistance. CT-pro ET-1 was shown to correlate to MR-proADM which is linked to metabolic factors and vascular function in patients with type 2 diabetes (Chi Lim, Morgenthaler et al., 2007). It is recently not fully understood how adrenomedullin production is influenced by hyperglycemia (Hayashi et al., 1999; Kinoshita et al., 2000; Turk et al., 2000). Other mechanisms like acute hyperinsulinemia (Katsuki et al., 2002) increased oxidative stress (Katsuki et al., 2003) angiotensin II and endothelin-1 are thought to increase adrenomedullin expression.(Sugo et al., 1995; Katsuki, Sumida et al., 2003).

In this study, we did not find a relationship between Copeptin and parameters of glucose metabolism. Copeptin is the C-terminal portion of provasopressin which is secreted in equimolar amounts to vasopressin (Struck et al., 2005). It is an excellent predictor of outcome in advanced heart failure patients (Stoiser, Mortl et al., 2006) and its secretion seems to be stimulated by other factors than the secretion of NT-proBNP which might reflect different aspects of cardiovascular homeostasis (Khan, Dhillon et al., 2007).

It has been shown that obesity is significantly connected with the impairment of insulin metabolism even in subjects with normal fasting plasma glucose (Sainaghi et al., 2008). In our cohort mean BMI was 28.34 kg/m^2 which can also have slight effects on insulin sensitivity beside the metabolic changes due to chronic heart failure.

Disclosure

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Conflict of interest: None.

Affiliations
[1] Department of Endocrinology and Metabolism, Medical University of Vienna
[2] Department of Cardiology, Medical University of Vienna
[3] Metabolic Unit, Institute of Biomedical Engineering, CNR, Padua, Italy
[4] 3rd Medical Department of Metabolic Diseases and Nephrology, Hietzing Hospital Vienna
[5] Research & Development, B·R·A·H·M·S AG, Hennigsdorf, Germany

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