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TOTAL AND HIGH MOLECULAR WEIGHT ADIPONECTIN LEVELS IN THE RAT MODEL OF POST-MYOCARDIAL INFARCTION HEART FAILURE

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Adiponectin is a protein secreted primarily by adipose tissue. It has been suggested that adiponectin plays a protective role in the early phase following myocardial infarction. Our primary aim was to investigate the effects of post-myocardial infarction heart failure well-characterized by left ventricular hemodynamic parameters on the total and high molecular weight adiponectin concentrations in plasma, fat and cardiac tissue. Eight weeks after myocardial infarction or sham operation, total and high molecular weight adiponectin concentrations in plasma, fat, and cardiac tissues were assayed in rats. In addition, hemodynamic parameters and expression of the genes encoding atrial natriuretic peptide and brain natriuretic peptide in left ventricle were evaluated. Atrial natriuretic peptide and brain natriuretic peptide mRNA levels in left ventricle tissue were higher in rats with myocardial infarction-induced heart failure compared with the controls. Similarly, total adiponectin concentration was increased in left ventricle (but not in right ventricle) in rats with post-myocardial infarction heart failure. In contrast, adiponectin levels in plasma and cardiac adipose tissue in rats with post-myocardial infarction heart failure were lower than in sham-operated animals. Furthermore, there were no significant differences in levels of high molecular weight adiponectin in plasma, cardiac tissue or adipose tissue between these two groups. We conclude that in the rat model of post-myocardial infarction heart failure, adiponectin level is increased in left ventricle tissue. This is accompanied by decreased adiponectin levels in plasma and cardiac adipose tissue.

Key words: *adiponectin, high molecular weight adiponectin, left ventricle, myocardial infarction heart failure, adipose tissue, coronary artery disease, cardiovascular disease*

INTRODUCTION

Accumulating evidence suggests that adipose tissue is not only used for energy storage but it also secretes compounds with important endocrine activity. One of these factors is adiponectin, a 30-kDa protein primarily synthesized by adipocytes and also produced by skeletal muscles, endothelial cells and cardiomyocytes (1). Adiponectin circulates in the bloodstream at high level in three molecular forms: low molecular weight (LMW) trimeric form, medium molecular weight (MMW) hexameric form and high molecular weight (HMW) multimers (2). HMW adiponectin seems to represent the most biologically active oligomeric form (3). Adiponectin mediates beneficial effects on the cardiovascular system by acting directly on the component cells in the heart and blood vessels (4). It was reported that low circulating HMW adiponectin levels of circulating HMW adiponectin are a risk factor for cardiovascular events (5).

Clinical investigations have demonstrated markedly lower plasma total adiponectin levels in patients with coronary artery disease (CAD) (6), as well as in patients with heart failure (7). It was reported that adiponectin is associated with central obesity

and cardiovascular disease (CVD) (8). Animal studies have indicated that adiponectin is a cardiovascular protective molecule. In response to artery ligation followed by reperfusion, adiponectin knockout mice (APN-KO) had a significantly larger infarct size, greater myocardial cell apoptosis and increased tumor necrosis factor- α (TNF- α) expression compared with wild-type controls (9). Although higher adiponectin levels were detected in damaged cardiomyocytes, additional studies have also demonstrated that plasma adiponectin levels rapidly declined after induction of myocardial ischemia-reperfusion injury, supporting the role of adiponectin in cardiac pathologies including myocyte hypertrophy and diastolic dysfunction (8). However, it is still not clear whether adiponectin plays beneficial or detrimental role in the course of heart failure. Thus, detailed studies based on the experimental model are required to explain in details the influence of adiponectin on heart failure. In this regards, the aim of this study was to investigate the effects of myocardial infarction-induced heart failure on total and HMW adiponectin concentrations in plasma, adipose tissue and cardiac tissue in the rat model of chronic heart failure that mimics typical systolic chronic heart failure in humans.

MATERIALS AND METHODS

Animals and treatments

Twenty-four 10-week-old male Wistar rats (Medical University of Bialystok, Poland) weighting 260 – 310 g were used in this study. Animals were housed under controlled condition of temperature 22°C and lighting (10:14 h). Two animals were kept in standard cages with free access to water and standard pelleted food *ad libitum*.

All animal procedures conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH publication No. 85-23, revised 1996) and were approved by the local Ethics Committee.

Myocardial infarction (MI) was induced in 15 rats, as described previously (10). Briefly, the rats were anesthetized with ketamine HCl and xylazine (100 and 5 mg/kg body weight given IP, respectively) and left thoracotomy was performed. The heart was externalized and a suture (5 – 0 silk) was looped around the proximal left coronary artery and tied tightly. The heart was then internalized, the chest closed and pneumothorax was reduced. Nine rats forming the sham-operated group were subjected to the same protocol except that the artery snare was not tied.

During the following 8 weeks, 7 of the rats with MI died. At this point, the 8 surviving MI rats and the 9 sham-operated animals underwent echocardiographic assessment and left ventricle (LV) catheterization. Subsequently, blood samples from the inferior vena cava were collected in sterile tubes containing EDTA (1.6 mg/mL of blood) and aprotinin protease inhibitor (50 KIU/mL of blood) (BD Diagnostics, Plymouth, UK). These samples were centrifuged at 4°C and the plasma was stored in aliquots at –70°C for ELISA. The animals were then euthanized, the heart was removed and the right ventricle (RV) was separated from the LV. Cardiac and adipose tissue depots (subcutaneous, mesenteric, cardiac and epididymal) were collected, frozen in liquid nitrogen and stored at –70°C for further protein analysis.

Echocardiography and left heart catheterization

Echocardiography was performed using a MyLab25 (Esaote, Italy) with 13 MHz linear array transducer. Under light anesthesia (ketamine HCl and xylazine, respectively 75 mg and 3.5 mg/kg body weight, IP) LV end-diastolic and end-systolic diameters, as well as wall thickness were determined from the short-axis view at the midpapillary level. Contractility of 23 wall segments was graded as 1 (normal) or 0 (abnormal) and the WMI (wall motion index) was calculated. Normal hearts had a WMI = 23. Our previous study revealed that WMI is closely correlated with infarct size and that a WMI = 15 corresponds to an infarct size of ~40% (11). The LV ejection fraction (LVEF) was calculated as (LV diastolic area - LV systolic area)/LV diastolic area, both planimetered from the parasternal long-axis view.

Under light anesthesia, a micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted through the right carotid artery into the LV to record LV pressures and the peak rates of the rise and decline of LV pressure (dp/dt_{max} and dp/dt_{min}).

RNA isolation and quantitative real-time PCR

Heart LV samples from rats with post-MI heart failure (n = 5) and the sham-operated group (n = 6) were homogenized using a MagNA Lyser Instrument (Roche Diagnostics GmbH, Mannheim, Germany). Total RNA was then isolated with the

MagNA Pure Compact System (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. cDNA was synthesized using a QuantiTect Reverse Transcription kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. qRT-PCR amplification of fragments of the *Nppa* (natriuretic peptide precursor A; ANP) and *Nppb* (natriuretic peptide precursor B; BNP) genes was performed in a LightCycler 1.5 using LightCycler FastStart DNA Master SYBR Green I (Roche Diagnostics GmbH, Mannheim, Germany). Relative expression levels, corrected for amplification efficiency, were analyzed using REST-MCS©-version 2 software (12). The amplification of a fragment of the constitutively expressed *Gapdh* gene was used as an internal control for data normalization. Primer sequences and parameters of qRT-PCR reactions are available upon request.

Measurement of total and high molecular weight adiponectin concentrations

Frozen adipose and cardiac tissues from rats with post-MI heart failure (n = 8) and sham-operated animals (n = 9) were pulverized in liquid nitrogen and homogenized in cold lysis buffer containing 0.02 M Tris (pH 8.0), 0.137 M NaCl, 10% glycerol (v/v), 1% Nonidet P-40 (v/v), 0.01 M ethylenediaminetetraacetic acid (EDTA), 0.1 M NaF, 0.001 M phenylmethylsulfonyl fluoride (PMSF), 0.25 TIU/mL aprotinin, and 10 µg/mL leupeptin. Homogenates were incubated for 15 min at 4°C and centrifuged at 15,000g for 15 min at 4°C. The supernatants were collected and stored at –70°C until the time of assay.

Total and HMW rat adiponectin levels in plasma, adipose tissue and myocardium homogenates were determined using kits for adiponectin ELISA (Mediagnost, Reutlingen, Germany) and HMW adiponectin ELISA (Shibayagi Co., Ltd., Gunma, Japan), respectively, in accordance with the manufacturer's instructions. The sensitivities of the total adiponectin and HMW adiponectin assays were less than 0.081 ng/ml and 0.021 ng/ml, respectively. Intra-assay and inter-assay precisions were 3% and 5% for total adiponectin assay, and 6% and 5% for HMW adiponectin assessment.

Protein concentrations in adipose tissue and heart homogenates were determined using Bradford Reagent (Sigma-Aldrich, Inc., St. Louis, MO, USA) with bovine serum albumin as the standard.

Statistical analysis

Data are presented as the mean ± S.D. or median and interquartile range (min/max). Statistical analyses were performed using Statistica 10 (StatSoft Inc., Tulsa, OK, USA). Normal data distribution was verified by the Shapiro-Wilk test, while homogeneity of variances was confirmed with the Levene's test. Student's t-test was used to assess statistical significance, whereas the Mann-Whitney U test was performed when non-parametrical testing was required. Spearman's rank correlation coefficients were used to assess the relationship between adiponectin concentration and various covariates. Statistical significance was accepted at $P < 0.05$.

RESULTS

Characteristics of the rat model of post-myocardial infarction heart failure

There was no significant difference between body mass between rats with post-MI heart failure (347 ± 16 g) and sham

Table 1. Hemodynamic parameters in rats with post-myocardial infarction heart failure (MI) and sham-operated rats (Sham) 8 weeks after surgery.

	Sham (n = 9)	MI (n = 8)
WMI	22.2 ± 0.7	12.6 ± 0.9*
LVSP (mmHg)	124.8 ± 9.2	92.0 ± 11.9*
LVEDP (mmHg)	5.9 ± 0.6	21.4 ± 2.6*
dP/dt _{max} (mmHg/s)	6212 ± 300	3249 ± 833*
dP/dt _{min} (mmHg/s)	4325 ± 250	2531 ± 616*
LVDa (mm ²)	41 ± 2	72 ± 9*
EF (%)	51 ± 3	20 ± 6*

dP/dt_{max} and dP/dt_{min} - peak rate of rise and decline of LV pressure; EF - ejection fraction; LVDa - left ventricular diastolic area; LVEDP - left ventricular end-diastolic pressure; LVSP - left ventricular systolic pressure; n-number of rats; WMI - wall motion index. Results are means ± S.D. * P < 0.001 by Mann-Whitney U test between rats with post-MI heart failure vs. sham-operated rats.

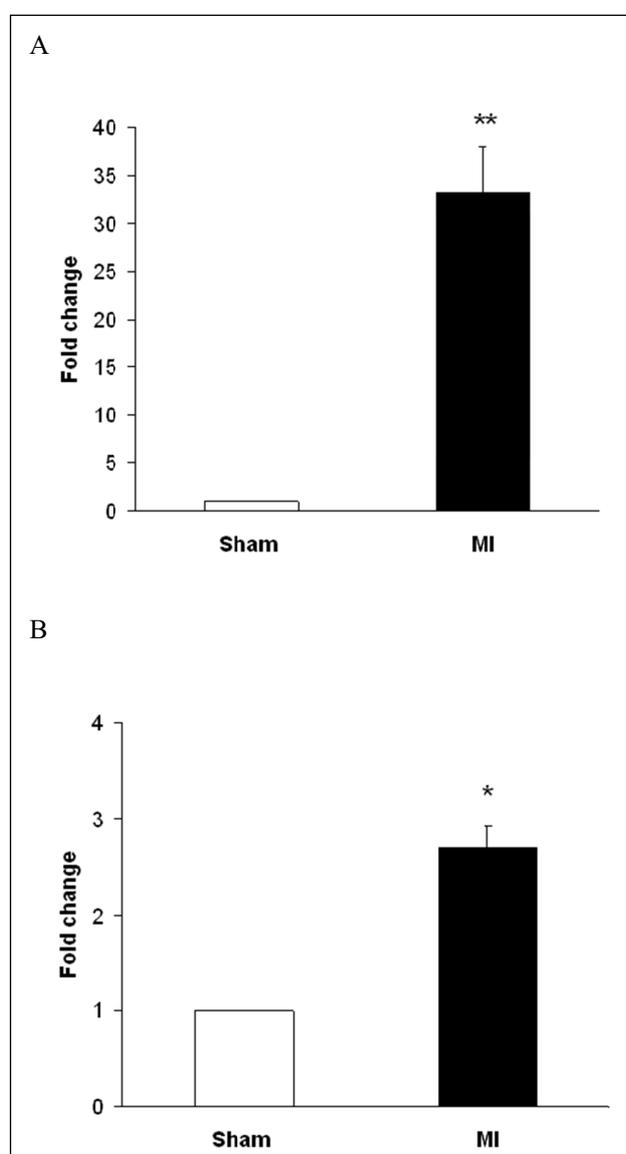


Fig. 1. Changes in left ventricle expression of atrial natriuretic peptide (A) and brain natriuretic peptide (B) mRNAs in rats with post-myocardial infarction heart failure (MI; n = 5) and sham-operated rats (n = 6), 8 weeks after surgery. Results are means ± S.E.M. * P < 0.05, ** P < 0.001.

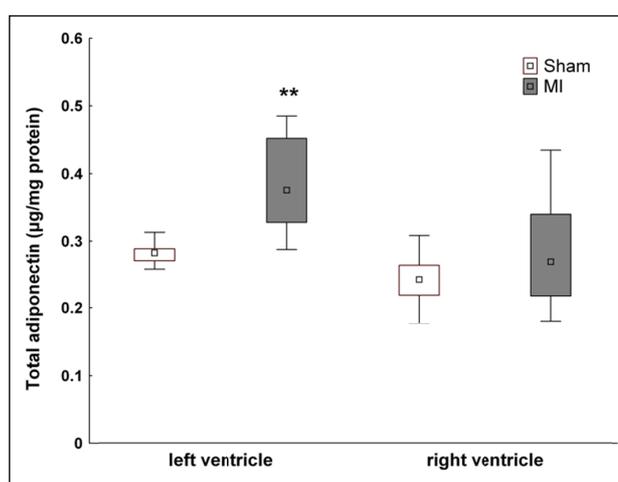


Fig. 2. Total adiponectin concentrations in the left and right ventricle homogenates in rats with post-myocardial infarction heart failure (MI; n = 8) and sham-operated rats (n = 9), 8 weeks after surgery. Results are median and interquartile range (min/max). ** P < 0.005 by the Mann-Whitney U test.

operated animals (366 ± 22 g). Eight weeks after the induction of MI, rat hearts exhibited LV dilation and profound systolic and diastolic dysfunction (Table 1). Quantitative real-time PCR (qRT-PCR) determination of the levels of *Nppa* (ANP) and *Nppb* (BNP) mRNAs in the LV showed that the expression of both genes was significantly higher in rats with post-MI heart failure than in the sham-operated animals (Fig. 1A and 1B). The pronounced increase in left ventricular end-diastolic pressure (LVEDP; Table 1) and increased ANP and BNP genes expression (Fig. 1A and 1B) supported the diagnosis of advanced heart failure in this model.

Total and high molecular weight adiponectin levels in the left and right ventricles in the rat model of post-myocardial infarction heart failure

Eight weeks after the induction of MI, the level of total adiponectin had increased in the LV compared to the controls (Fig. 2). The adiponectin level in the right ventricle (RV) in rats with post-MI heart failure was similar to the concentration found

in the sham-operated group (Fig. 2). Post-MI heart failure had no significant effect on HMW adiponectin levels in either the LV or the RV (data not shown).

In the rat model of post-MI heart failure there was a positive correlation between plasma and LV adiponectin levels ($r =$

0.833, $P < 0.01$) (Fig. 3A). Furthermore, RV adiponectin concentrations correlated with left ventricular diastolic area (LVDa) ($r = 0.783$, $P < 0.02$) (Fig. 3B) and left ventricular systolic area (LVSa) ($r = 0.719$, $P < 0.04$) (Fig. 3C) in rats with post-MI heart failure.

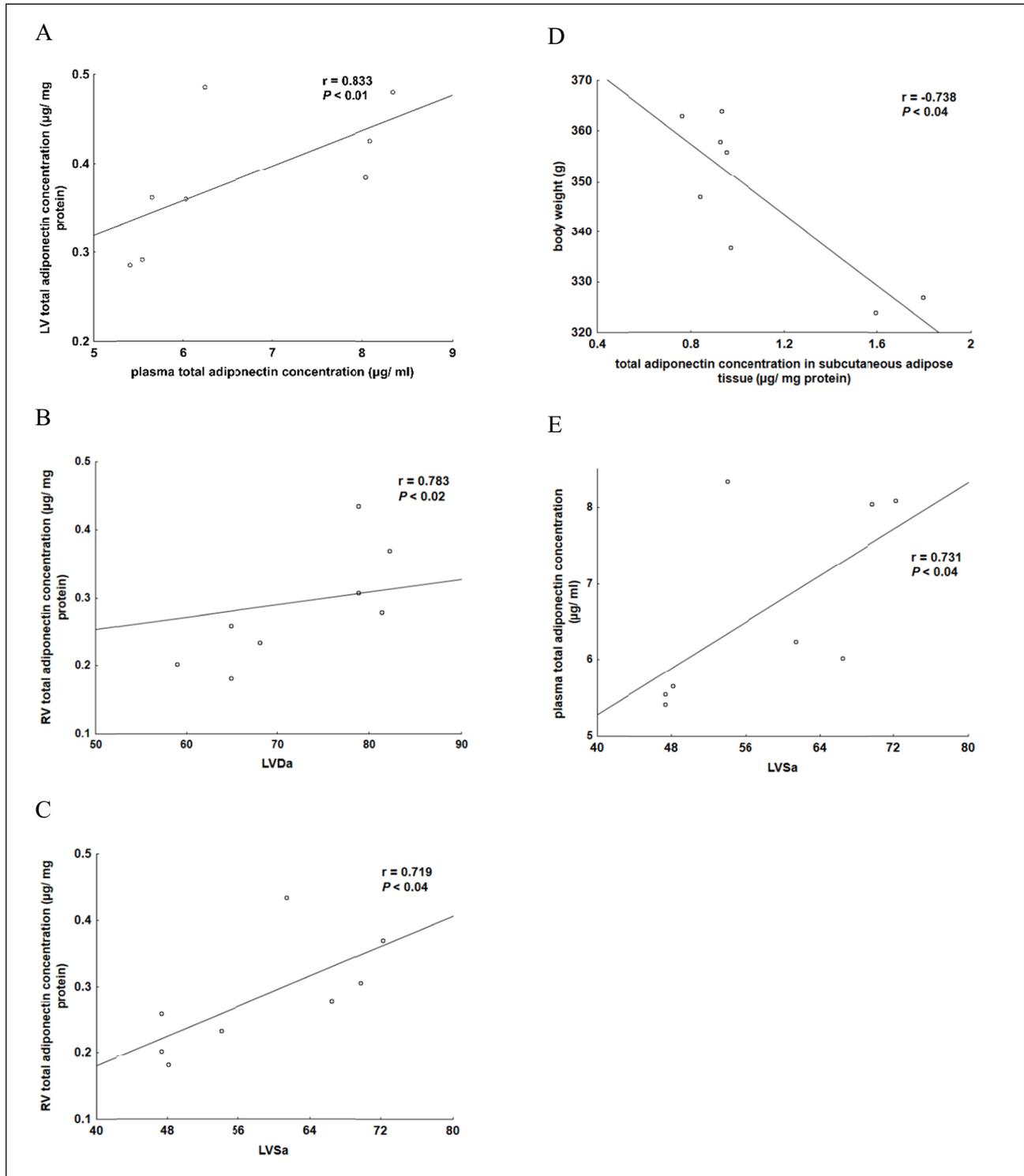


Fig. 3. Correlations between: total adiponectin concentrations in plasma and left ventricle (A), adiponectin concentration in right ventricle and left ventricular diastolic area (B) or left ventricular systolic area (C), adiponectin concentration in subcutaneous adipose tissue and body weight (D), adiponectin plasma levels and left ventricular systolic area (E) in rats with post-myocardial infarction heart failure (MI; $n = 8$), 8 weeks after surgery. Spearman's correlation coefficients and P-values.

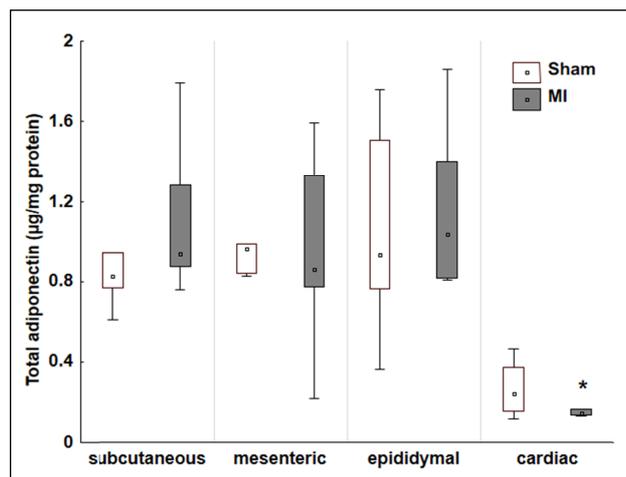


Fig. 4. Total adiponectin concentrations in adipose tissue homogenates in rats with post-myocardial infarction heart failure (MI; $n = 8$) and sham-operated rats ($n = 9$), 8 weeks after surgery. Results are median and interquartile range (min/max). * $P < 0.05$ by the Mann-Whitney U test.

Levels of total and high molecular weight adiponectin in adipose tissue in the rat model of post-myocardial infarction heart failure

The total adiponectin concentration in cardiac fat was found to be markedly reduced in rats with post-MI heart failure compared with the controls (Fig. 4), whereas concentrations of the HMW form did not differ significantly between these two groups (data not shown). There was no significant difference between rats with post-MI heart failure and sham-operated animals in total adiponectin levels in subcutaneous, mesenteric and epididymal adipose tissue depots (Fig. 4), or their respective HMW levels (data not shown).

Adiponectin concentrations in subcutaneous adipose tissue correlated inversely with body weight ($r = -0.738$, $P < 0.04$) (Fig. 3D) in rats with post-MI heart failure.

Plasma levels of total and high molecular weight adiponectin in the rat model of post-myocardial infarction heart failure

Total plasma adiponectin levels were significantly lower in rats with post-MI heart failure compared with the sham-operated animals (Fig. 5A). However, plasma concentrations of HMW adiponectin were not significantly different between these two groups (Fig. 5B). There was no significant difference in HMW to total adiponectin ratio between rats with post-MI heart failure (0.069 ± 0.017) and sham-operated group (0.052 ± 0.031).

A positive correlation was found between plasma adiponectin concentrations and LVSa ($r = 0.731$, $P < 0.04$) (Fig. 3E) in rats with MI-induced heart failure.

DISCUSSION

The present study was designed to examine the effect of post-MI heart failure on total and HMW adiponectin concentrations in the myocardium, adipose tissue in different anatomic locations and plasma. We decided to use the rat model of heart failure two months after MI because this particular stage seems to be appropriate model of chronic heart failure that mimics typical systolic chronic heart failure in humans. We demonstrated that total adiponectin level was increased in the

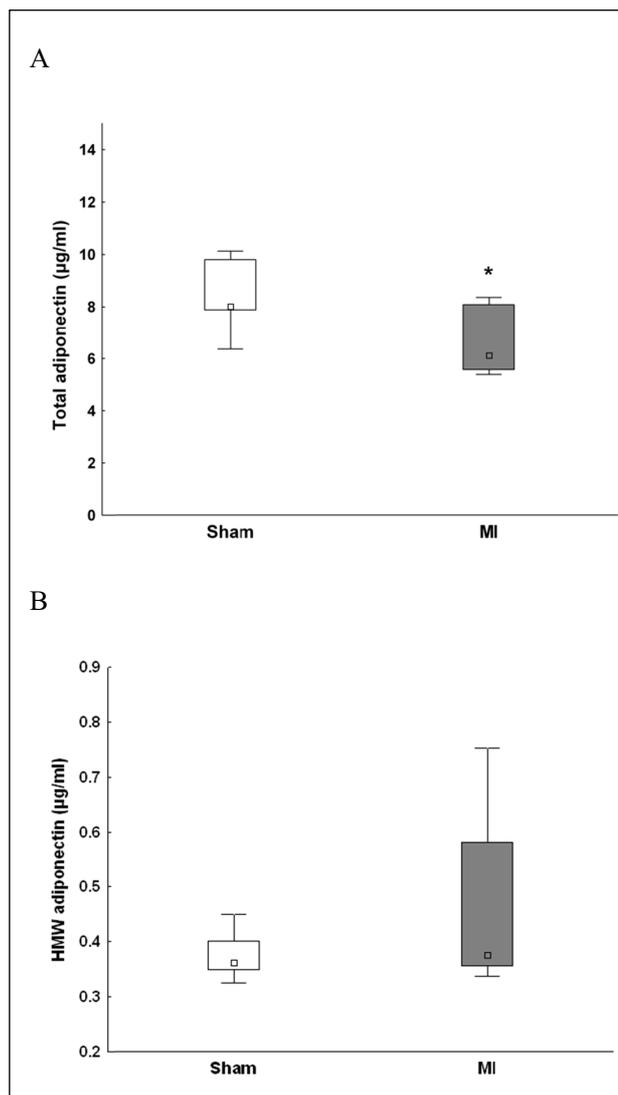


Fig. 5. Total (A) and high molecular weight (B) adiponectin concentrations in plasma in rats with post-myocardial infarction heart failure (MI; $n = 8$) and sham-operated rats ($n = 9$), 8 weeks after surgery. Results are median and interquartile range (min/max). * $P < 0.05$ by the Mann-Whitney U test.

LV tissue, while it was decreased in the plasma and cardiac adipose tissue in rats with MI-induced heart failure.

Local production of adiponectin by cardiomyocytes may permit modulation of cardiac function and metabolism (13). Recent research has been shown that adiponectin has direct anti-inflammatory and anti-oxidant effects, which play a role in its cardioprotective action. Shibata and coworkers (9) observed higher adiponectin levels in damaged cardiomyocytes following ischemia/reperfusion injury, 24 hours after induction of MI. In contrast, a decrease in adiponectin level in the rat myocardium was observed two weeks after acute MI (14).

In the present study we observed for the first time a significant increase of adiponectin in the LV tissue but not in the RV, in post-MI heart failure, which might indicate that this protein contributes to long-term cardioprotection in the LV hypertrophy at the time-point of eight week after induction of MI. In the early phase, 24 hours after MI, it seems that the protective action of adiponectin is mediated by two mechanisms: the stimulation of AMP-activated protein kinase (AMPK) and cyclooxygenase-2 (COX-2) (15).

Adiponectin has been shown to improve glucose metabolism and insulin resistance *via* the AMPK signaling pathway (16). In contrast, insulin inhibits cardiac AMPK activity (17). AMPK is a key regulator of energy metabolism in the heart and its deficiency has been reported to be associated with depressed cardiac function in mice (18). Recently, it was suggested that heart failure may promote metabolic changes in cardiomyocytes such as insulin resistance (19). Thus, an increase of adiponectin concentration in the LV observed in our study may be an adaptive response to left ventricular insulin resistance in the post-MI heart failure.

Adiponectin production by myocardium is markedly lower than that of white adipose tissue (WAT) origin. In addition, the amount of adiponectin locally synthesized by cardiomyocytes is too small to contribute significantly to the plasma concentrations of adiponectin (20). It has been shown that adiponectin is associated with many pathological processes and its synthesis is regulated in different way depending on the fat depot location of this protein (21). Therefore, in the present study we analyzed how different WAT sites respond to post-MI heart failure. We found that post-MI heart failure resulted in a significant decrease in adiponectin levels only in cardiac adipose tissue, which may interact locally with the myocardium. Recent research revealed that these fat tissues expand, become hypoxic and dysfunctional in a course of CVD (22). There are changes in adipocyte size and reduction of the production of protective proteins including adiponectin in favor of detrimental adipocytokines such as leptin, resistin or IL-6. Likewise, recent research revealed that a lower adiponectin concentration in epicardial fat was associated with increased levels of inflammatory molecules in patients with CAD (23). It seems highly possible that these data could explain our findings of adiponectin decrease in cardiac adipose tissue. Fat tissue around the heart may serve as a supportive and mechanical factor and, additionally, it may be a vasocrine and paracrine source of cytokines and adipokines (24). The adiponectin receptor T-cadherin presence on cardiomyocyte surfaces is necessary for binding adiponectin and activating its cardioprotective actions, probably through AMPK signaling. In a clinical study, adiponectin and T-cadherin were detected at the periphery of damaged cardiomyocytes in patients with MI (25). The absence of T-cadherin was found to dramatically increase plasma adiponectin levels (26). There have been reports of reduced total plasma adiponectin levels immediately after acute MI (9, 27), as well as 14 days following MI in animal models (14). Based on our data indicating that plasma adiponectin concentrations were 25% lower in rats with post-MI heart failure than in control rats, we speculate that the plasma adiponectin level might be reduced by binding to T-cadherin. Another possible explanation for the finding of plasma adiponectin levels decline after cardiac injury is that this protein may accumulate in damaged regions of the heart.

Using a mouse model of myocardial ischemia/reperfusion injury, Tao and colleagues (28) observed that adiponectin-deficient mice showed increased myocardial infarct size and apoptosis. These authors also suggested that adiponectin exerts cardioprotective effects by inhibiting oxidative stress (28). In this model, injection of recombinant adiponectin protein caused a reduction in cardiac infarct size and decreased TNF- α production as well as improved LV function (15, 28). Furthermore, recent evidence suggested that adiponectin may play a protective role by reducing the infarct size through an improvement of ischemia-reperfusion injury in the myocardial ischemia preconditioning rat model (29). A recent study demonstrated that swimming exercise improved the ventricular function in rat (30). According to the author, one possible explanation for this effect could be increase cardiac adiponectin mRNA level (30).

Previous study indicated that pro-BNP increased, similar to plasma adiponectin level, depending on the severity of heart failure (31). The increased production of natriuretic peptides, especially BNP, by cardiomyocytes was established as a marker of heart failure in animal models and in clinical practice (32-34). We detected elevations of ANP (33.2-fold) and BNP (2.7-fold) mRNA levels and increased LVEDP in the LV that supported the diagnosis of advanced heart failure in the rat model of MI-induced heart failure. In accordance with the present results, previous reports found that LV ANP and BNP gene expression were significantly increased in the rat model of MI or heart failure compared with sham-operated controls (35-37). Increased cardiac expression of the genes encoding ANP and BNP has been associated with myocardial dysfunction (38) and considered a potential marker of hypertrophic processes in a variety of *in vitro* (39), animal (40) and clinical (41) models.

The report of von Eynatten *et al.* (42) suggested that HMW adiponectin, the most active form of this protein, would be a much more effective and sensitive biomarker than total adiponectin for CAD extent. However, this association was not identified in a subsequent study (43). Moreover, it has been demonstrated that plasma HMW adiponectin levels decreased 24 hours after myocardial ischemia-reperfusion injury in mice (9). However, our results indicated that plasma HMW adiponectin levels did not change in rats with post-MI heart failure compared with the controls. To the best of our knowledge, no other study has examined the HMW adiponectin isoform secretion by different adipose tissue depots and myocardial tissue in the rat model of post-MI heart failure. As we did not observe any differences, we speculate that the decrease of HMW adiponectin levels may be related to early phase of MI rather than post-MI heart failure.

There is a need to investigate new therapeutic tools for the treatment of heart disease. One of the most promising and realistic methods of treating MI is stem cell therapy (44). Another strategy for treatment of cardiovascular disease is consider the potential therapeutic benefits of cardioprotective molecules like adiponectin. Although supplementation with exogenous adiponectin is effective in alleviating CVD in animals, it is still difficult to use adiponectin as a therapeutic agent in humans. This is due to the following facts: 1) high circulating levels of adiponectin are required for its beneficial effects; 2) the extensive post-translational modifications are needed for adiponectin activity; and 3) adiponectin has relatively short half-life. We have shown that adiponectin levels were increased in LV tissue of post-MI failure hearts in the rat model. This effect might be caused by local production of adiponectin by cardiomyocytes and/or transport from the plasma and/or from cardiac adipose tissue. Our present experiments, however, did not examine use of potential cardioprotective drugs in rat model of MI-induced heart failure.

Further research is required to determine an alternative therapeutic approaches focused on regulation of adiponectin synthesis, as well as on inter-cell transport of adiponectin between the heart, cardiac adipose tissue and plasma. In addition, factors enhancing the sensitivity of the cardiomyocytes should be intensively studied. Understanding the mechanisms described above could be useful for treating LV dysfunction following MI.

Acknowledgements: This work was supported by the Centre of Postgraduate Medical Education (CMKP) Grants no. 501-1-31-22-12 and 501-1-21-22-13, and The National Centre for Research and Development Grant N R13 0001 06.

Conflict of interests: None declared.

REFERENCES

- Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; 26: 439-451.
- Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? *Diabetes Care* 2003; 26: 2442-2450.
- Guzik TJ, Mangalat D, Korbust R. Adipocytokines - novel link between inflammation and vascular function? *J Physiol Pharmacol* 2006; 57: 505-528.
- Shibata R, Ouchi N, Ito M, *et al.* Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat Med* 2004; 10: 1384-1389.
- Kintscher U. Does adiponectin resistance exist in chronic heart failure? *Eur Heart J* 2007; 28: 1676-1677.
- Ouchi N, Kihara S, Arita Y, *et al.* Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; 100: 2473-2476.
- Takano H, Obata JE, Kodama Y, *et al.* Adiponectin is released from the heart in patients with heart failure. *Int J Cardiol* 2008; 132: 221-226.
- Barrios V, Gomez-Huelgas R, Rodriguez R, de Pablos-Velasco P. Adiponectin: an emerging cardiovascular risk factor. Reference study. *Rev Esp Cardiol* 2008; 61: 1159-1167.
- Shibata R, Sato K, Kumada M, *et al.* Adiponectin accumulates in myocardial tissue that has been damaged by ischemia-reperfusion injury via leakage from the vascular compartment. *Cardiovasc Res* 2007; 74: 471-479.
- Maczewski M, Mackiewicz U. Effect of metoprolol and ivabradine on left ventricular remodeling and Ca²⁺ handling in the post-infarction rat heart. *Cardiovasc Res* 2008; 79: 42-51.
- Maczewski M, Maczewska J. Hypercholesterolemia exacerbates ventricular remodeling in the rat model of myocardial infarction. *J Card Fail* 2006; 12: 399-405.
- Pfaffl MW, Horgan GW, Dempfle L. Relative expression software tool (REST) for group-wise comparison and statistical analysis of relative expression results in real-time PCR. *Nucleic Acids Res* 2002; 1: 30-36.
- Pineiro R, Iglesias MJ, Gallego R, *et al.* Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett* 2005; 579: 5163-5169.
- Zhang S, He B, Goldstein S, Ge J, Wang Z, Ruiz G. Changes in adiponectin expression in acute myocardial infarction rats and the significance of bisoprolol intervention. *Can J Physiol Pharmacol* 2011; 89: 109-115.
- Shibata R, Sato K, Pimentel DR, *et al.* Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med* 2005; 11: 1096-1103.
- Yamauchi T, Kamon J, Minokoshi Y, *et al.* Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; 8: 1288-1295.
- Gamble J, Lopaschuk GD. Insulin inhibition of 5'-adenosine monophosphate-activated protein kinase in the heart results in activation of acetyl coenzyme A carboxylase and inhibition of fatty acid oxidation. *Metabolism* 1997; 46: 1270-1274.
- Liao Y, Takashima S, Maeda N, *et al.* Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovasc Res* 2005; 67: 705-713.
- Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. *Circulation* 2007; 116: 434-448.
- Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996; 22: 286-289.
- Maury E, Ehala-Aleksejev K, Guiot Y, Detry R, Vandenhooff A, Brichard SM. Adipokines oversecreted by omental adipose tissue in human obesity. *Am J Physiol Endocrinol Metab* 2007; 293: 656-665.
- Zhang H, Zhang C. Regulation of microvascular function by adipose tissue in obesity and type 2 diabetes: evidence of an adipose-vascular loop. *Am J Biomed Sci* 2009; 1: 133-142.
- Zhou Y, Wei Y, Wang L, *et al.* Decreased adiponectin and increased inflammation expression in epicardial adipose tissue in coronary artery disease. *Cardiovasc Diabetol* 2011; 10: 2.
- Iozzo P. Myocardial, perivascular, and epicardial fat. *Diabetes Care* 2011; 34(Suppl. 2): S371-S379.
- Takahashi T, Saegusa S, Sumino H, *et al.* Adiponectin, T-cadherin and tumour necrosis factor-alpha in damaged cardiomyocytes from autopsy specimens. *J Int Med Res* 2005; 33: 236-244.
- Denzel MS, Scimia MC, Zumstein PM, Walsh K, Ruiz-Lozano P, Ranscht B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. *J Clin Invest* 2010; 120: 4342-4352.
- Tao L, Wang Y, Gao E, *et al.* Adiponectin: an indispensable molecule in rosiglitazone cardioprotection following myocardial infarction. *Circ Res* 2010; 106: 409-417.
- Tao L, Gao E, Jiao X, *et al.* Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. *Circulation* 2007; 115: 1408-1431.
- Wang H, Cheng JS, Wu WJ, *et al.* [Ischemia preconditioning attenuated myocardial ischemia via upregulating the expression of adiponectin in rat]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2010; 38: 929-933.
- Sakr HF. Modulation of metabolic and cardiac dysfunctions by swimming in overweight rats on a high cholesterol and fructose diet: possible role of adiponectin. *J Physiol Pharmacol* 2013; 64: 231-240.
- Sokhanvar S, Sheykhi M, Mazlomzade S, Taran L, Golmohammadi Z. The relationship between serum adiponectin and prognosis in patients with heart failure. *Bratisl Lek Listy* 2013; 114: 455-459.
- Langenickel T, Pagel I, Hohnel K, Dietz R, Willenbrock R. Differential regulation of cardiac ANP and BNP mRNA in different stages of experimental heart failure. *Am J Physiol Heart Circ Physiol* 2000; 278: H1500-H1506.
- Hystad ME, Geiran OR, Attramadal H, *et al.* Regional cardiac expression and concentration of natriuretic peptides in patients with severe chronic heart failure. *Acta Physiol Scand* 2001; 171: 395-403.
- Mukoyama M, Nakao K, Hosoda K, *et al.* Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991; 87: 1402-1412.
- Hystad ME, Oie E, Groggaard HK, *et al.* Gene expression of natriuretic peptides and their receptors type-A and -C after myocardial infarction in rats. *Scand J Clin Lab Invest* 2001; 61: 139-150.
- Calderone A, Bel-Hadj S, Drapeau J, *et al.* Scar myofibroblasts of the infarcted rat heart express natriuretic peptides. *J Cell Physiol* 2006; 207: 165-173.
- Yin M, Sillje HH, Meissner M, van Gilst WH, de Boer RA. Early and late effects of the DPP-4 inhibitor vildagliptin in a rat model of post-myocardial infarction heart failure. *Cardiovasc Diabetol* 2011; 10: 85-94.
- de Boer RA, Henning RH, Suurmeijer AJ, *et al.* Early expression of natriuretic peptides and SERCA in mild heart

- failure: association with severity of the disease. *Int J Cardiol* 2001; 78: 5-12.
39. Nakagawa O, Ogawa Y, Itoh H, *et al.* Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy: evidence for brain natriuretic peptide as an 'emergency' cardiac hormone against ventricular overload. *J Clin Invest* 1995; 96: 1280-1287.
40. Tamura N, Ogawa Y, Itoh H, *et al.* Molecular cloning of hamster brain and atrial natriuretic peptide cDNAs: cardiomyopathic hamsters are useful models for brain and atrial natriuretic peptides. *J Clin Invest* 1994; 94: 1059-1068.
41. Hasegawa K, Fujiwara H, Doyama K, *et al.* Ventricular expression of brain natriuretic peptide in hypertrophic cardiomyopathy. *Circulation* 1993; 88: 372-380.
42. von Eynatten M, Humpert PM, Bluemm A, *et al.* High-molecular weight adiponectin is independently associated with the extent of coronary artery disease in men. *Atherosclerosis* 2008; 199: 123-128.
43. Rizza S, Clementi F, Porzio O, *et al.* Adiponectin isoforms are not associated with the severity of coronary atherosclerosis but with undiagnosed diabetes in patients affected by stable CAD. *Nutr Metab Cardiovasc Dis* 2009; 19: 54-60.
44. Ciecierska A, Chodkowska K, Motyl T, Sadkowski T. Myogenic cells applications in regeneration of post-infarction cardiac tissue. *J Physiol Pharmacol* 2013; 64: 401-408.

Received: November 13, 2015

Accepted: July 22, 2015

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